This article was downloaded by: [York University Libraries] On: 31 December 2014, At: 05:09 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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

Jiang Yao Zhong  $^{\rm a}$  , Liu Guilan  $^{\rm a}$  , Zhou Changyou  $^{\rm a}$  , Piao Hauri  $^{\rm a}$  , Wu Lanjun  $^{\rm a}$  & Mi Aiqiao  $^{\rm a}$ 

<sup>a</sup> Chengdu Institute of Organic Chemistry, Academia Sinica, Chengdu, 610015, P. R. China Published online: 23 Sep 2006.

To cite this article: Jiang Yao Zhong , Liu Guilan , Zhou Changyou , Piao Hauri , Wu Lanjun & Mi Aiqiao (1991) Asymmetric Synthesis XIII: The Stereocontrolled Synthesis of (R)– $\alpha$ –Amino Acids via a Double Chiral Induction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:8-9, 1087-1090, DOI: <u>10.1080/00397919108019799</u>

To link to this article: http://dx.doi.org/10.1080/00397919108019799

### PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and

are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

### ASYMMETRIC SYNTHESIS X II : THE STEREOCONTROLLED SYNTHESIS OF (R)−α−AMINO ACIDS VIA A DOUBLE CHIRAL INDUCTION

Jiang Yao zhong', Liu Guilan, Zhou Changyou, Piao Huri, Wu Lanjun, Mi Aiqiao chengdu Institute of organic Chemistry, Academia Sinica Chengdu 610015, P. R. China

Abstract: The stereocontrolled synthesis of (R) - a - amino acids via a double chiral induction in alkylation of the ketimine derived from (+) - campbor and (+) - menthyl glycinate which is a chiral match pair has been studied. (R) - a - 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 abtain the higher diastereoselectivity for the stereocontrolled synthesis.

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

Copyright © 1991 by Marcel Dekker, Inc.

<sup>.</sup> Also spelling as Yao-Chung Chiang. To whom correspondence should be addressed.



In this paper we would like to report the stereocontrolled synthesis of  $(R) - \alpha$ 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°C affords the alkylated intermediates 5 which are refluxed with 6N HCl to offer (R)— $\alpha$ —amino acids 6 in good chemical yield (60-85)%. The optical yield of (R)— $\alpha$ —amino acids is determined by chiral gas chromatography or by comparison with the specific rotation of the optical pure  $\alpha$ —amino acids.

The results are summarized in the Table

From the table, it is noteworthy that the diastereosclectivity 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)- $\alpha$ -amino acids.

From the Table, it can be seen, six (R)  $-\alpha$ -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-

Entry	menthyl*	RX	amino acid 6	chemical yield %*)	e • e <sup>0</sup> /0 <sup>b)</sup>
1	(+)-men	phCH <sub>2</sub> Br	phenylalanine	85	99
2	(—)-men	phCH <sub>2</sub> Br	phenylalanine	73	7.3
3	(+)-men	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> Br	n-leucine	75	84.7
4	(—)-men	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> Br	n—leucine	77	26.1
5	(+)-men	CH <sub>2</sub> =CHCH <sub>2</sub> Br	allylglycine	74	85.0
6	(—)-men	CH <sub>2</sub> =CHCH <sub>2</sub> Br	allylglycine	70	3.0
7	(+)-men	(CH <sub>3</sub> ) <sub>2</sub> CHBr	Valine	68	95.3
8	(+)-men	CH=CCH <sub>2</sub> Br	Propargylglycine	57	80. 0°)
9	(+)-men	3. $4 - (MeO)_2$ -phCH <sub>2</sub> Br	3. 4—dimethoxy —phenylalanine	76	84. 9"

Table optical yield of  $(R) - \alpha$ -amino acids 6

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<sup>[2-5]</sup></sup>

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<sup>[1]</sup>.

Allkylation of 3: A solution of 3 (4mmol) in THF added to a stirred solution of LDA(4.8mmol) in THF at -78°C 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°C, the solution was warmed to room temperature. 10-

15mL of aqueous saturated NaCl was added, extracted with ether( $3 \times 20$ mL). The combined ether layers were washed with aqueous saturated NaCl and dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed under reduced pressure to give 5.  $[\alpha]_{5}^{5} = +92.8^{\circ}(C=1,EtOH)$ , IR(neat): 1739(C=O), 1687(C=N), 1179(C=O), 750, 700(C<sub>6</sub>H<sub>5</sub>)cm<sup>-1</sup>. H<sup>1</sup>-NMR(CDCl<sub>3</sub>): 0.56-1.09(18H,m,6CH<sub>3</sub>), 1.13-2. 45(16H,CH<sub>2</sub>,CH), 3.15-3.24(2H,m,CH<sub>2</sub>), 3.82-4.13(1H,m,=N-CH-), 4.16-4.83(1H,m,COCH), 7.05-7.35(5H,m,C<sub>6</sub>H<sub>5</sub>)ppm. m/z: 438(M<sup>+</sup>+1)

Hydrolysis of 5 to  $\alpha$ -amino acid 6: 5 (3 mmol) in 20ml 6NHCl was directly refluxed for 6h under N<sub>2</sub>. After suitable treatment, 6 (phenylalanine) was obtained in 89% chemical yield and 99% e.e. (by chiral GC)  $[\alpha]_{6}^{1}+33.8^{\circ}(c=1,H_{2}O)$ . IR: 2400 - 3200((NH $_{7}^{+}$ ), 1574, 1410(COO), 745, 700(C<sub>6</sub>H<sub>5</sub>) cm<sup>-1</sup>. H<sup>1</sup> - NMR (D<sub>2</sub>O): 3.15 - 3.35(2H,m,CH<sub>2</sub>), 3.95 - 4.12(1H,m,CH), 7, 25 - 7.55(5H, m,C<sub>6</sub>H<sub>5</sub>)ppm. (Found: C, 64.86, H, 6.80, N, 8.38, Calc for C<sub>9</sub>H<sub>10</sub>NO<sub>2</sub>, C, 65.38, H, 6. 67, N, 8.48)

Acknowledgment: We are grateful to National Science Foundation of China and Humboldt Foundation of F. R. Germany for supportion this research work.

#### 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

(Received in USA 11 March, 1991)