Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1771-1772, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00207-4

A Highly Stereoselective Synthesis of (2*S*, 3*S*)-β-Hydroxyleucine

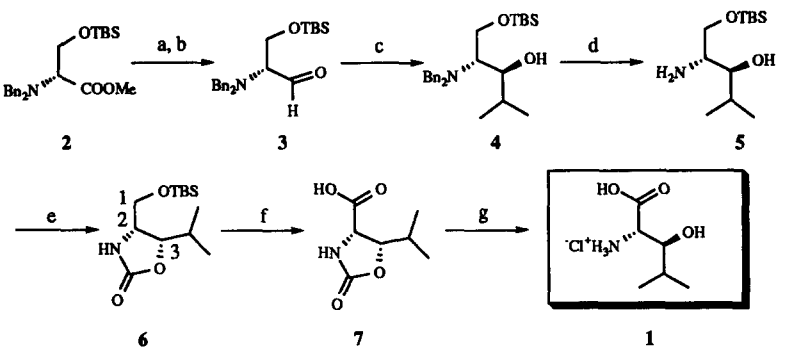
Taoues Laïb, Jacqueline Chastanet, Jieping Zhu*[1]

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-Sur-Yvette, France

Abstract: A highly diastereoselective nucleophilic addition of Grignard reagent to *N,N*-dibenzyl-*O*-TBS-serinal **3** was the key step in the present synthesis of (2*S*, 3*S*)-β-hydroxyleucine **1**.

β-Hydroxy-α-amino acids have been found in many bioactive naturally occurring peptides.[1] In connection with our work on the total synthesis of cyclopeptide alkaloids,[2] we required an efficient and general synthesis of *erythro* (2*S*, 3*S*)-β-Hydroxyleucine **1** and other related (2*S*, 3*S*)-β-Hydroxy-α-amino acids. While a number of elegant asymmetric appoaches have been described,[3] we thought to develop an alternative and more convenient synthesis using proteinogenic amino acid as chiral starting material.

As chiral building blocks, *N*-protected amino aldehydes have been found very useful in the synthesis of a wide variety of compounds.[4] Very recently, Joullié and co-workers[5] reported a diastereoselective addition of Grignard reagents to modified Garner's aldehyde[6] as a new route to β-Hydroxy-α-amino acids. Though moderate to good selectivity was obtained, the facial selectivity was found to be reagent dependent making prediction of stereochemical outcome tenuous. We wish to describe herein an efficient synthesis of **1** with predictable high diastereoselectivity based on the chemistry of *N,N*-dibenzyl amino aldehyde developed by Reetz *et al.*[7]



Reagents and Conditions: a) $LiBH_4$, Et_2O-MeOH, reflux, 86%; b) Swern; c) ^iPrMgCl, Et_2O, -78°C, 77%; d) $Pd(OH)_2$, H_2, MeOH, 100%; e) CDI, DMAP (catalytic), THF; f) KF, Jones, 72% g) conc. HCl, 85%

Scheme 1

[1] Fax: 33-1-69823131; e-mail: zhu@icsn.cnrs-gif-Fr

N,N-dibenzyl-*O*-TBS-serine methyl ester **2** was prepared from D-serine in good overall yield. Reduction of methyl ester with $LiBH_4$ (Et_2O, MeOH) gave the corresponding primary alcohol which was submitted to Swern oxidation affording *N,N*-dibenzyl-*O*-TBS-serinal **3**.[8] Addition of isopropylmagnesium chloride to the crude aldehyde at -78°C afforded *anti* adduct **4** as a single detectable diastereoisomer (NMR). The stereoselectivity of this reaction could be explained on the basis of a non-chelated transition state and is in line with Felkin-Anh model.[9] It is worthy noting that selectivity observed in this study was complimentary to Joullié's observation where *syn* product was formed predominantly when the same Grignard reagent was used. Hydrogenolysis of **4** on Pearlman's catalyst gave amino alcohol **5** which was transformed into oxazolidinone **6** by treatment with carbonyl diimidazole (CDI). An NOE was observed between H-2 and H-3 (in C_6H_6-D_6) indicating a cis relationship of these two protons and thus confirming the 2*S*, 3*S* stereochemistry of adduct **4**.[10] One-pot deprotection-Jone's oxidation[11] led to oxazolidinone carboxylic acid **7** in 72% yield. Finally, removal of carbamate function under acidic conditions gave hydrochloride salt of (2*S*, 3*S*)-β-hydroxy leucine **1** in 85% yield.

In summary, we have described an efficient asymmetric synthesis of (2*S*, 3*S*)-β-hydroxyleucine **1**. The stategy should be applicable to the synthesis of other related β-hydroxy amino acids. Moreover, by using either L or D-serine as starting material and by exploiting the reduction of the corresponding dibenzylamino ketone, all other diastereoisomers should be available.

Acknowledgement. Financial support from the CNRS and a doctoral fellowship from "Ligue nationale contre le cancer" to T. Laib are gratefully acknowledged.

References and Notes

1 For recent general reviews, see: a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539-1650; b) Durand, J. O.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 612-619.

2 Zhu, J.; Laïb, T.; Chastanet, J.; Beugelmans, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2517-2519.

3 For the synthesis of (2*S*, 3*S*)-3-hydroxyleucine, see: a) Caldwell, C. G.; Bondy, S, S. *Synthesis* **1990**, 34-36; b) Corey, E, J.; Lee, D. -H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735-38; c) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637-6640; d) Kanemasa, S.; Mori, T.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 8293-8296; e) Sunazuka, T.; Nagamitsu, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A. Smith, A. B. *Tetrahedron Lett.* **1993**, *34*, 4447-4448; f) Hale, K. J.; Manaviazar, S.; Delisser, V. M; *Tetrahedron* **1994**, *50*, 9181-9188; g) Schmidt, U.; Respondek, M; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256-261.

4 Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149-164.

5 Willams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673-11694; see also: Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021-5030.

6 Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361-2364.

7 Reetz, M. T. *Angew. Chem., Int. ed; Engl.* **1991**, 30, 1531-1546.

8 This compound was mentionned in Professor Reetz's review (ref 7) based on his unpublished results.

9 Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199-2204; b) Chérest, M.; Felkin, H., *Tetrahedron Lett.* **1968**, 2204-2208.

10 Wagner, B.; Beugelmans, R. Zhu, J. *Tetrahedron Lett.* **1996**, *37*, 6557-6560.

11 Liu, H. T.; Han, I. S. *Synthetic Chemmun.* **1985**, *15*, 759-764.

(*Received in France* 17 *January* 1997; *accepted* 28 *January* 1997)