Chinese Chemical Letters Vol. 12, No. 9, pp 767 – 768, 2001
http://www.imm.ac.cn/journal/ccl.html

Synthesis of (s)-(-)-Benzyl-2-tert-butoxycarbonyl amino-4-iodobutyrate

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Abstract: A convenient method to synthesize (s)-(-)-benzyl-2-tert-butoxy carbonylamino-4-iodobutyrate from L-(+)methionine **1** was reported, the enantiomeric purity of the product was established by comparison of optical rotation data with literature values, indicating that the reaction process occurred without racemization.

Keywords: α-Amino acid, chiral.

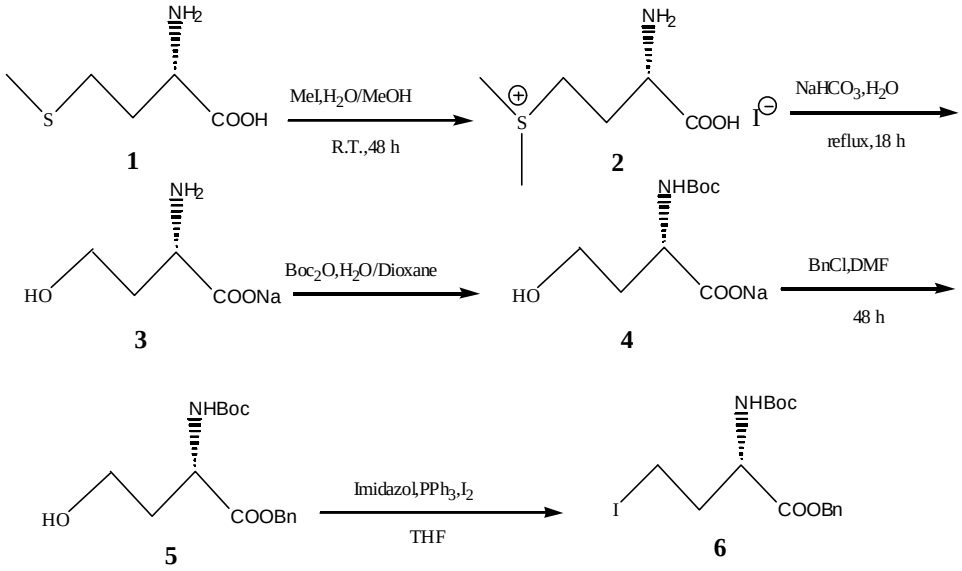
The proteinogenic α-amino acids constitute an important section of the "chiral pool", being inexpensive in the L-form (but available if necessary as the D enantiomers), structurally varied and chemically versatile[1], they are useful starting materials for chiral reagents, auxiliaries and ligands[2]. Any high-yielding transformation of an α-amino acids which proceeds without racemization is thus of potential importance, especially if it generates another reactive center and may be applied to the synthesis of polyfunctional targets.

In the course of our programe on substituted cyclopropyl alanines, the title compound iodohomoalanine derivative **6** was required as an important intermediate. It was clear that compound **6** could be obtained from the decarboxylation of L-glutamic acid derivative[3], however, a convenient synthetic stereoselective preparation suitable for large-scale synthesis has not yet been developed. This letter describes a workable large-scale preparation method of **6** from L-(+)-methionine **1**. The synthesis of **6** is shown in **scheme 1**.

The five step synthesis can be accomplished in two pots using L-(+)-methionine **1** as starting material. The L-(+)-methionine **1** was s-methylated with methyl iodide to give **2**,which was subsequently hydrolyzed to yield L-(-)-homomoserine **3**[4], then, the C2-amino group was protected by tert-butoxycarbonyl to get the sodium salt **4**. The sodium salt was dried thoroughly in vacuum and reacted with benzyl chloride in DMF to get **5** as an orange oil without purification, the hydroxy group in **5** was converted to iodide **6** using triphenylphospine, iodine, and imidazole in THF. The crude product was purified by silica gel columm chromatograph and recrystalized to afford pure (s)-(-)-**6** in 34% yield[5] as a white crystal.mp.56~58°C; $[\alpha]_D^{20}$ –32.3(c 1.0, MeOH)[6]; IR (KBr): ν 3355, 2979, 1754, 1681; ^{1}HNMR (δ ppm, $CDCL_3$): 1.40 (s, 9H,$C(CH_3)_3$), 2.10-2.20 (br, 1H, CH_2), 2.35-2.45 (br, 1H, CH_2), 3.10 (t, 2H, J=8Hz, ICH_2), 4.30-4.40 (br, 1H, NCH), 5.15

(s, 2H, CH_2Ph), 7.30 (s, 5H, ArH). EI-MS (*m/z*): 419 (M+). EA: calcd for $C_{16}H_{22}NO_4$: C 45.83, H 5.29, N 3.34, Found: C 46.08, H 5.25, N 3.38.

Scheme 1



References and notes

1. G. M. Coppola, H. F. Schuster,. *Asymmetric Synthesis: Construction of Chiral Molecules Using a-Amino Acids*, Wiley, New York, **1987**.
2. (a). A. Togni, L. M. Venanzi, *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 497.
   (b). F. J. Sardina, H. Rapoport, *Chem. Rev*., **1996**, *96*, 1825.
3. (a). D. H. R. Barton, Y. Herve, P. Potier, J. Thierry, *Tetrahedron*, **1988**, *44*, 5479.
   (b). R. F. Jackson, N. Wishart, M. J. Wythes, *Synlett*. **1993**, 219.
4. (a). P. H. Boyle, A. P. Davis, K. J. Dempsey, G. D. Hosken, *Tetrahedron: Asymmetry* **1995**, *6*, 2819.
   (b). F. Kich, D. Buchardt, *Synthesis*, **1993**, 1065.
   (c). J. E. Baldwin, M. North, A. Flinn, *Tetrahedron*, **1988**, *44*, 637.
   (d). J. E. Baldwin, A. Flinn, *Tetrahedron lett*. **1987**, *28*, 3605.
5. The yield was calculated according to L-(+)methionine.
6. Literature values (reference 3) mp. 54°C. $[\alpha]_D$ –33.0 (c 1.0, MeOH).

Received 14 February, 2001