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Synthesis of (2R, 4R)-2-N-*tert*-Butyloxycarbonyl Amino-4,5-epoxido-valeric Acid Methyl Ester

Xin Rong QIN*, Yu Li XIE, Qiao Ling ZHANG, Hui Bing LUO, Yu Yuan XIE

State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031

Abstract: The stereoselective synthesis of (2R, 4R)-2-N-*tert*-butyloxycarbonyl amino-4, 5-epoxido- valeric acid methyl ester **8**, which is the key intermediate for the synthesis of (2′S, 2R) -3-*trans*-nitrocyclopropyl-alanine, was first accomplished.

Keywords: Amino acid, epoxide, chiral.

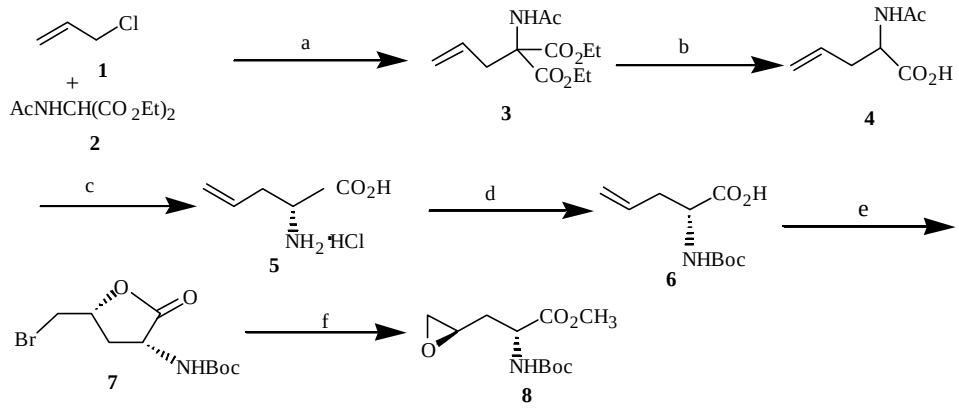
The novel peptide lactone hormaomycin[1] produced by streptomyces griseoflavus is selectively active against some gram-positive bacteria, and influences the secondary metabolic products of certain bacteria. Zeeck elucidated the structure of homaomycin by selective partial hydrolysis, but the absolute configuration of the two molecules of Ala (3-Ncp) remained unknown. Meijere tried to synthesize the enantiopure Ala (3-Ncp), but failed to give full characterization[2]. Recently a novel streptomyces metabolite belactosin **A** exhibiting weak antitumor activity was reported, which contains a novel amino acid (2′S, 2R)-3-*trans*-Ala (3-Acp)[3]. The configuration of 2′-C of (2′S, 2R) -3-*trans*-Ala (3-Acp) leads us to judge that the 2′-C of Ala (3-Ncp) should be S configuration too.

We have recently designed a new strategy for the synthesis of *trans*-(2′S, 2R)-Ala (3-Ncp), in which, (2R, 4R)-2-N-*tert*-butyloxycarbonyl amino-4, 5-epoxido-valeric acid methyl ester **8** was designed as a key intermediate.

Here we reported our preliminary results of synthesis of **8 (Scheme 1)**. After dehydrogenation with NaH, N-acetyl-amino malonate **2** reacted with allyl chlorid **1** to get **3** in 86% yield, which was partially hydrolyzed with sodium hydroxide to give **4** in 87.9% yield. Compound **4** was resoluted by swine kidney acylase to get R-enriched **4**. After recystallization, R-enriched **4** was hydrolyzed to get R-allyglycine hydrochloride **5** in 24% yield, 96% ee. C2-amino group of **5** was protected by *tert*-butyloxycarbonyl to get N-Boc-R-Agl **6** as colorless oil in 92.4% yield, $[\alpha]_D$ -11.1 (c 2.2, CH_3OH)[4], **6** was then bromolactonized by NBS to get compound **7** in 72.8% yield, $[\alpha]_D$ -18.9 (c 1.0, $CHCl_3$). Recrystallization gave enantiopure **7** in 42% yield as a white crystal[5]. Enantiopure **7** reacted with K_2CO_3 in dry methanol afforded the title compound **8** as colorless oil in 91% yield[6].

* E-mail: yyxie@mail.shcnc.ac.cn

Scheme 1



a. NaH, dry DMF; b. 1) NaOH, EtOH, H_2O; 2) 2N HCl; c. 1) swine kidney acylase; 2) 2N HCl; d. Boc_2O; e. NBS,THF; f. K_2CO_3, dry MeOH.

Reference and Notes

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4. A. G. Myers, J. L. Gleason, *Organic Synthesis*, **1999**, *76*, 57. N-Boc-S-Agl $[\alpha]_D^{23}$ 8.6 to 11.4 (C 1.4, CH_3OH).
5. (2R, 4R)– **7**: mp 127 - 128°C; $[\alpha]_D^{20}$ -22.6 (C 1.0, $CHCl_3$); ^{1}HNMR (400Hz, $CDCl_3$, δ ppm): 1.40 (S, 9H, $C(CH_3)_3$), 1.95-2.05, 2.90 - 3.00 (br, 2H, CCH_2C), 3.50 - 3.60, 4.60 - 4.70 (m, 2H, $BrCH_2$), 3.50 - 3.60 (m, 1H, CHO), 4.40 - 4.50 (br, 1H, NCH); IR(KBr/cm^{-1}): 3396, 2979, 1783, 1537, 1355, ESI-MS (*m/z*): 317 $(M+Na)^+$. Anal calcd for $C_{10}H_{16}NO_4Br$: C, 40.82; H, 5.44; N, 4.76. Found: C, 40.87; H, 5.27; N, 4.80.
6. (2R, 4R)– **8**: $[\alpha]_D^{20}$ 1.7 (C 1.0, $CHCl_3$); ^{1}HNMR (400Hz, $CDCl_3$, δ ppm): 1.40 (s, 9H, $C(CH_3)_3$), 1.65 - 1.85, 1.95 - 2.1 0 (br, 2H, CCH_2C), 2.45 - 2.50, 2.75 - 2.80 (br, 2H, OCH_2C), 2.95 - 3.05 (br, 1H, OCH); 3.75 (s, 3H, OCH_3), 4.45 - 4.55 (br, 1H, NCH); IR (KBr/cm^{-1}): 3345, 2979, 1741, 1529, 1236; ESI-MS (*m/z*): 268 $(M+Na)^+$. Anal calcd for $C_{10}H_{15}NO_4$: C, 53.88; H, 7.76; N, 5.71. Found: C 53.91; H, 7.84; N, 5.78.

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