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A Facile and Highly Stereoselective Reductive Debromination of Anhydro-6- (R)-Hydroxyethyl- 6-Bromopenicillin

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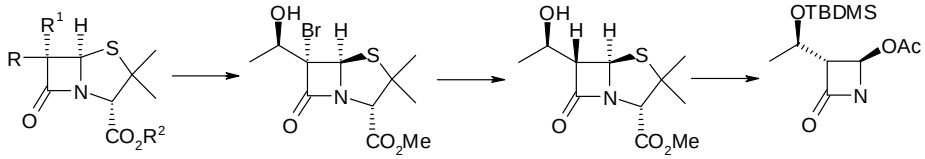
Abstract: Reductive debromination of anhydro-6-(R)-hydroxyethyl-6-bromopenicillin **7** by zinc in ammonium acetate gave **9** in 81% yield with high stereoselectivity of 6-(α):6-(β)=13:1.

Keywords: Reductive debromination, stereoselectivity, anhydro-6-(R)-hydroxyethyl-6-bromo-penicillin.

The title compound, 4-acetoxyazetidinone **5**[1], has been widely used as an important intermediate for penem, carbapenem and trinem synthesis [2a~2f] and several approaches to **5** have been reported [3a~3c].

The semisynthetic approach of 4-acetoxyazetidinone **5** from penicillin **1** reported by DiNinno *et al.*[2b] is a useful one, the debromination of methyl 6-bromo-6-[(R)-1-hydroxy-ethyl]penicillinate **3** by zinc-ammonium acetate afforded the labile compound **4**, 91:9 mixture of *trans* and *cis* isomers, in 92% yield but in the former step the hydroxy-ethylation of the C-6 position of penicillinate **2** suffered from lack of stereospecificity.

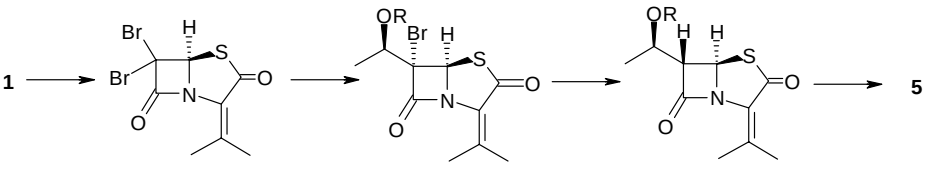


1 R=NH_2, R^1=H, R^2=H **3** **4** **5**

2 R=R^1=Br, R^2=Me

The other useful semisynthetic approach of 4-acetoxyazetidinone **5** from penicillin **1** was developped by Martel *et al.*[3b]. In this method the stereospecific aldol condensation of the enolate derived from anhydro-6,6-dibromopenicillin **6** with acetaldehyde proceeded with only the *cis* 6-(R) derivative **7**. But reduction of **7** with zinc-silver couple at –15℃ gave a mixture of two isomers of **9** from which the *trans* isomer was isolated in only 42% yield. For improvement of stereoselectivity a bulky

group TBDMS should be introduced at the hydroxy group of **7**, when the TBDMS ether **8** was reduced by zinc-silver couple at –45℃ the 6-（R）-hydroxyethyl derivative **10** was formed with α : β ratio 96.8 : 2.5.



6 **7** R=H **9** R=H

8 R=TBDMS **10** R=TBDMS

In our effort to synthesize carbapenem derivatives we found that the reductive debromination of anhydro-6-hydroxyethyl-6-bromopenicillin **7** by zinc-ammonium acetate in THF instead of diethyl ether[2b] at room temperature afforted **9**, a mixture of α / β ratio =13:1[4], in an isolated yield of 81%[5]. In this method the expensive agent tert-butyldimethyl-silyltriflate and the less desirable zinc-silver couple could avoid to be employed, and the reaction can carried out at room temperature.The study of stereocontrol mechanism in the reductive debromination is in progress.

References and notes

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4. The α : β ratio which was determined by ^{1}HNMR on a 500 MHz instrument was that of crude product.
5. A solution of 3. 06 g (10 mmol) of **7** in 100 ml of THF was treated with 50 mL of 1mol/L aqueous NH_4OAc and 2. 62 g (40 mmol) of powder zinc. The resulting mixture was stirred at room temperature for 1 h, and then filtered through a bed of Celite. The organic layer was separated from the aqueous layer, which was extracted twice with methylene chloride. The combined organic extracts were concentrated under reduced pressure. The residue was dissoved in methylene chloride, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. Short- silica-column chromatography gave **9** 1. 83 g (81% yield), mp. 170-171 ℃ (lit. [3b]: m. p. 173-174℃).

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