Regio- and Stereoselective Generation of Enolates from Aminohydroxyacetone Derivatives

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Key Words: Aminohydroxyacetone, Aldol reaction, Silyl enol ether, Dihydroxyacetone

1-Amino-3-hydroxyacetone (AHA, 1) is the deoxyamino-derivative of 1,3-dihydroxyacetone (DHA, 2). Nature utilizes dihydroxyacetone phosphate (DHAP), a phosphorylated form of DHA, as the donor substrate in enzymatic aldol reactions for the synthesis of ketose sugars. Although DHAP-dependent aldolases possess an almost perfect ability to control the stereochemistry of aldol products, they are relatively unstable and do not accept many useful aldehydes as acceptor substrates. The chemical aldol reaction of protected DHAs with aldehydes, therefore, attracted a great deal of attention as a useful supplement or alternative to the enzymatic aldol reaction of DHAP. Since the first report on the chemical aldol reaction of protected DHAs with aldehydes by our laboratory, there have been numerous reports on diastereoselective and enantioselective aldol reactions of DHA derivatives with various aldehydes. Consequently, the DHA unit is now well recognized as a versatile building block in organic synthesis.

Aldol reactions of AHA derivatives with aldehydes, on the other hand, would provide useful aminoketose sugars or precursors for other important natural products containing the amino group. However, neither enzymatic nor chemical aldol reactions of AHA derivatives have been explored although a few AHA derivatives have been synthesized before. Aldol reactions of AHA derivatives are inherently more complex than those of symmetric DHA derivatives: there would be two stereoisomeric enolates, Z- and E-enolates, possible by the deprotonation of DHA derivatives whereas four isomeric enolates possible from AHA derivatives due to additional regioisomers. In order to establish the reliable enantioselective chemical aldol reactions of AHA derivatives with aldehydes, the development of the method for the regio- and stereoselective generation of enolates from appropriately protected AHAs is essential. Herein we describe the synthesis of new protected AHAs and reveal the method for the regioselective and stereoselective generation of their enolates.

This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

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and a nitrogen atom would make the of the potassium ion to two oxygen atoms or to an oxygen enolates. The five-membered ring chelates by coordination chelation of the metal ion with the heteroatoms in the

TBDMSCI (1.5 equiv) at −78 °C for 2 h provided Z-enolate 12 in 69% yield as shown in Scheme 3. The reaction was completely regioselective and stereoselective, providing enol ether 12 exclusively and no other isomeric enol ethers were detected in the reaction mixture. Based on 1H/13C/ COSY/HSQC/HMBC NMR data, the location of the double bond in 12 was determined while the stereochemistry of the double bond in 12 was assigned by examining its NOESY spectrum. Thus, strong NOE cross-peaks between H-1 and H-3 and between H-3 and benzylic H of 12 were observed and their intensity are almost same. It is known that the NOE between H-1 and H-3 is observed in the Z-silyl enol ether obtained from dibenzyl-DIA but not in the E-silyl enol ether.1 Similarly, the regiochemistry and stereochemistry of the double bond in enol ethers 10 and 11 were also determined based on their HSQC, HMBC, and NOSEY NMR data.

The preferred formation of Z-silyl enol ethers from all three ketones 5, 7, and 9 could be explained by assuming the chelation of the metal ion with the heteroatoms in the enolates. The five-membered ring chelates by coordination of the potassium ion to two oxygen atoms or to an oxygen and a nitrogen atom would make the Z-enolates more stable.

Because the azido and phthalimido groups are probably more electron-withdrawing and the dibenzylamino group is less electron-withdrawing than the benzyloxy group,12 the protons at C-1 near the nitrogen are more acidic than those at C-3 in both 5 and 7 while the protons at C-3 near the oxygen has the higher acidity than that at C-1 in 9. In addition, the sterically demanding dibenzylamino group might also reduce the kinetic acidity of the C-1 protons of the ketone 9.

The result indicates that Z-enolates are formed stereoselectively from AHA derivatives by the chelation-controlled reaction and that the regiochemistry of the enolates from the AHA derivatives can be controlled by the simple choice of the appropriate protecting group for the amino group. Further studies are underway to explore the catalytic asymmetric synthesis of aminoketose sugars from AHA derivatives.

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References