CHEMISTRY LETTERS, pp. 637-640, 1986.

HIGHLY STEREOSELECTIVE ALDOL-TYPE REACTION OF CHIRAL TIN(II) ENOLATE. FORMAL TOTAL SYNTHESIS OF (±)-THIENAMYCIN

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Highly efficient internal chiral induction is achieved in the aldol-type reaction of tin(II) enolate generated from 3-amino-substituted butanoylthiazolidine-2-thione. This reaction is successfully applied to the formal total synthesis of (±)-thienamycin.

The stereoselection of the aldol reaction has been the subject of recent intense study and efficient stereocontrol can now be achieved by the judicious choice of a variety of metal enolates. The most extensive study is focussed on the control of relative stereochemistry (commonly termed as erythro-threo stereoselection), and highly stereoselective reactions have been developed over the past ten years utilizing metal enolates such as boron and tin(II) enolates. On the other hand, the addition reaction of chiral enolates to aldehydes has not been studied extensively except for the enantioselective aldol reaction in which a removable chiral auxiliary is introduced into the enolate molecule beforehand for asymmetric induction.[1)]

In the previous paper, we reported on the generation of tin(II) enolates from functionalized carbonyl compounds, that is, those having an amino functionality at the β-position of the carbonyl group, and also reported the utilization of the produced aldol-type adducts for the stereoselective synthesis of β-lactam derivatives.[2)]

In this communication, we would like to report on the highly efficient internal chiral induction in the addition reaction of chiral tin(II) enolate generated from β-functionalized carbonyl compound having a chiral center at the β-position of the carbonyl group. We also wish to report a highly stereoselective formal total synthesis of (±)-thienamycin using this novel aldol-type reaction.

First, we tried the aldol-type reaction of 3-amino-functionalized butanoylthiazolidine-2-thione (1) with 3-phenylpropanal. According to the previously mentioned procedure,[3)] a CH_2Cl_2 solution of 1 was added dropwise to a CH_2Cl_2 suspension of tin(II) triflate and N-ethylpiperidine, and the mixture was further stirred for an hour to cause enolization. Then, 3-phenylpropanal was added and the mixture was stirred for an additional hour. After usual work-up, the product was purified by silica-gel column chromatography.

A smooth reaction took place when the reaction was carried out at -40 °C, and the desired product was obtained in high yield, however, when the reaction was carried out at -78 °C, only a trace amount of the desired aldol-type product was obtained (<10% yield).

The most noteworthy point is that high stereoselectivity can be realized by the present procedure. In this reaction, there is the possibility of forming up to four diastereomers, and in practice, by using the lithium enolate of the corresponding methyl ester derivative of 1, four diasteromers are formed non-stereoselectively. However, by using the tin(II) enolate, one diastereomer is obtained with high stereoselectivity (≥95% purity).

Next, the reactions with various aldehydes were examined and in every case, both very high yield and high stereoselectivity were realized as summarized in Table 1.

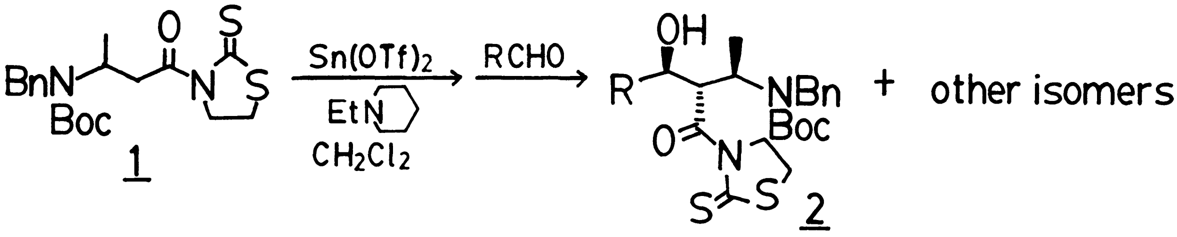


Table 1. Aldol-type Reaction of 3-Amino-functionalized butanoylthiazolidine-2-thione with Aldehydes[a)]

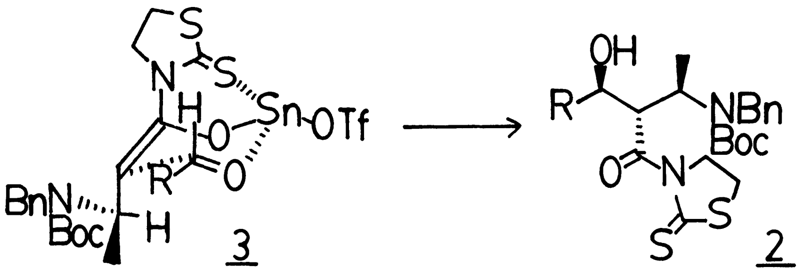
RCHO	Yield/%	Diastereomeric Selectivity/%[b)]
$PhCH_2CH_2CHO$	91	≥95
PhCHO	99	≥95
n-$C_5H_{11}CHO$	91	≥95
n-C_3H_7CHO	98	≥95
CH_3CHO	98	≥95

a) $Sn(OTf)_2$: N-ethylpiperidine : 1 : RCHO = 1.0 : 1.15 : 0.85 : 1.2.

b) In every case, two or three minor products which are assumed to be the epimers of the major isomer are isolated in less than 5% yield. The major isomer is obtained in a diastereomerically pure form judging from the ^{13}C NMR spectrum.

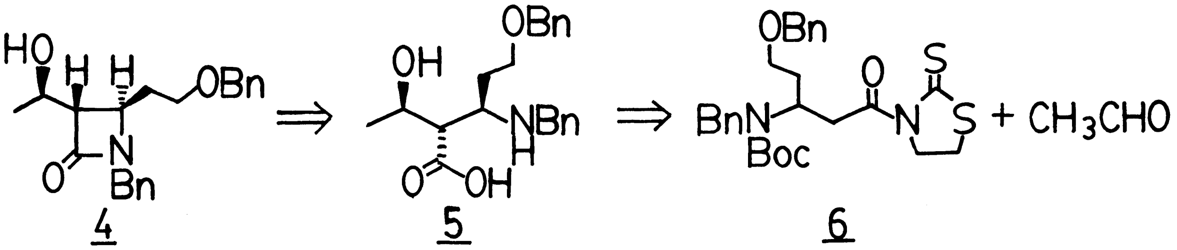
Based on the assumption that the stereoselection of this reaction is comparable with that of the reaction employed in the thienamycin synthesis described below, the major isomer has the relative stereochemistry shown in 2. This can be rationalized as follows; according to Houk's model,[4)] the most energetically favorable transition state is that in which the enolate takes the conformation as shown in 3 and the aldehyde approaches the enolate from the less hindered side, that is, from the side of the Me group. As it is supposed that the reaction proceeds via a chair-type transition state, the aldol-type product with relative stereochemistry as shown in 2 is formed with high stereoselectivity.

Next, the application of this aldol-type reaction to the stereocontrolled synthesis of thienamycin was tried.



Thienamycin is a representative member of the carbapenem antibiotics and due to its unique structure and broad antibacterial activity, a great deal of synthetic study has been carried out over the past ten years, and a number of total syntheses have already been reported based on several conceptually unique approaches. However, there still remains a difficult problem in controlling the relative stereochemistry of the three contiguous chiral centers.$^{5)}$

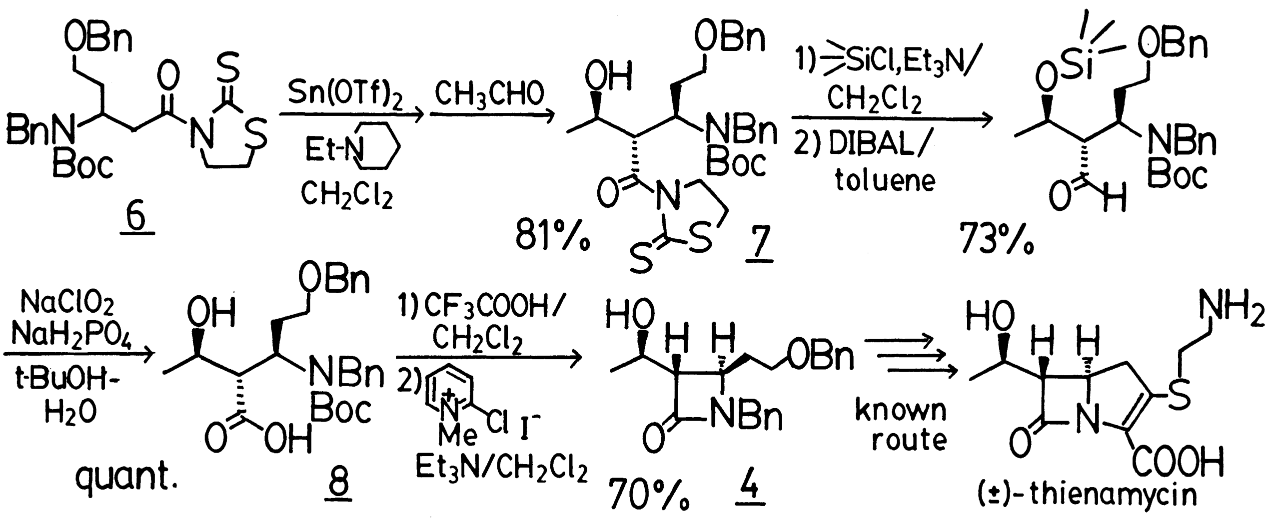
As compound 4 is known as a key-intermediate of thienamycin synthesis,$^{6)}$ we chose this compound as a synthetic target, and a retrosynthetic analysis is shown below. Thus, 4 is cleaved to the corresponding amino acid derivative 5, which is supposed to be synthesized stereoselectively by the tin(II) enolate mediated aldol-type reaction of 6 and acetaldehyde.



Thus, under the standard reaction conditions, tin(II) enolate was generated from 6,$^{7)}$ and the subsequent reaction with acetaldehyde was carried out. As expected the reaction proceeded smoothly, and the aldol-type product 7 was obtained in 81% yield together with three minor diastereomers (total <5% yield) which can be separated easily by column chromatography.

The next step is the conversion of the aldol-type product 7 into the corresponding carboxylic acid. First, we tried this transformation via a two-step procedure as described before;$^{2)}$ (i) methanolysis with K_2CO_3 / MeOH, ii) hydrolysis with LiOH / THF-H_2O), but the yield was disappointingly low. After various examinations, it was found that the desired carboxylic acid 8 can be obtained in a good yield via the following three-step procedure (i) protection of the hydroxy group with TMSCl, Et_3N / CH_2Cl_2, ii) reduction with DIBAL to the aldehyde, iii) oxidation with $NaClO_2$, NaH_2PO_4 / t-BuOH, $H_2O^{8)}$) in an overall 73% yield. Finally, the t-butoxycarbonyl group was deprotected with trifluoroacetic acid in CH_2Cl_2, and after evaporation of the volatile compounds the crude product was treated with 2-chloro-1-methylpyridinium iodide and triethylamine in CH_2Cl_2 under high-dilution conditions (0.01 mol/l).$^{9)}$ The desired β-lactam derivative 4 is obtained stereospecifically in 70% yield.

The NMR and IR spectra of compound 4 and its t-butyldimethylsilyl ether coincide completely with those of the authentic sample.



The authors are grateful to Dr. Masakatsu Shibasaki of Sagami Chemical Research Center for providing NMR and IR spectra of t-butyldimethylsilyl ether of 4 and its diastereomers, and are also thankful to Professor Yoshito Kishi of Harvard University for his kind suggestions on this subject.

References

1) T. Mukaiyama, "Organic Reactions," ed by W. G. Dauben, John Wiley and Sons, Inc., New York (1982), Vol. 28, Chap. 3; D. A. Evans, J. V. Nelson, and T. R. Taber, "Topics in Stereochemistry," ed by N. L. Allinger, E. L. Eliel, and S. H. Wilen, Wiley-Interscience, New York (1982), Vol. 13, Chap. 1; C. H. Heathcock, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1984), Vol. 3, Chap. 2.

2) N. Iwasawa, H. Huang, and T. Mukaiyama, Chem. Lett., 1985, 1045.

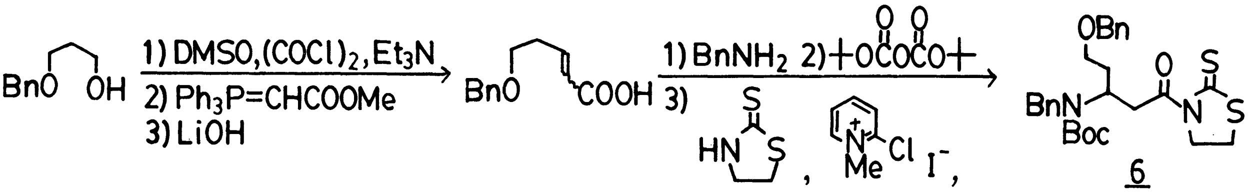
3) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984).

4) M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, J. Am. Chem. Soc., 104, 7162 (1982).

5) R. W. Ratcliffe and G. Albers-Schonberg, "Chemistry and Biology of β-Lactam Antibiotics," ed by R. B. Morin and M. Gorman, Academic Press, New York (1982), Vol. 2, Chap. 4.

6) T. Iimori and M. Shibasaki, Tetrahedron Lett., 26, 1523 (1985).

7) 6 was synthesized easily from 3-benzyloxypropanol as shown below.



8) B. S. Bal, W. E. Childers, Jr., and H. W. Pinnick, Tetrahedron, 37, 2091 (1981).

9) H. Huang, N. Iwasawa, and T. Mukaiyama, Chem. Lett., 1984, 1465.

(Received January 22, 1986)