Chemistry of Heterocyclic Compounds, Vol. 34, No. 11, 1998

RESEARCH ON THE CORRELATION BETWEEN THE PUMMERER REACTION AND PENICILLIN BIOSYNTHESIS (REVIEW)

Norio Shibata and Yasuyuki Kita

Research on the correlation between the Pummerer reaction mechanism and β-lactam formation during penicillin biosynthesis is discussed based on our silicon-induced asymmetric Pummerer type reaction.

INTRODUCTION

During the biosynthesis of penicillin, when a precursory tripeptide δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine (ACV) is converted to isopenicillin N in both fungi and bacteria, one of the hydrogen atoms at C-(3) of the cysteine residue of ACV is perfectly discriminated by removing the enzyme isopenicillin N synthase (IPNS) to form a β-lactam ring which has 5,6-*cis* stereochemistry. How can such a complete stereoselection be achieved by the enzyme *in vivo*? To answer this question, we have started model studies for the biosynthesis of penicillin using the Pummerer type reaction of sulfoxides. Despite our many experiments carried out *in vitro* for this purpose, and some interesting results have already been reported, the accurate mechanism of β-lactam ring formation is still obscure. However, just recently, Professor Baldwin has finally solved the question by X-ray crystallographic analysis of IPNS in the presence of Fe(II) and ACV [1], in addition to the information gained from their vast substrate analog studies. The unquestionable chemical mechanism of IPNS has been answered. Their findings have put to rest the problem which has long been full of mystery.

We have been carrying out the development of the asymmetric Pummerer reaction [2] in parallel with the biomimetic synthesis of penicillin using the silicon-induced Pummerer reaction as a key step. Prior to the publication of this paper, we have carried out partial research studies. Here, we summarize our project on penicillin studies in more detail centering on our silicon-induced Pummerer type reaction, since we feel that it is time to wind up the project.

PENICILLIN BIOSYNTHESIS

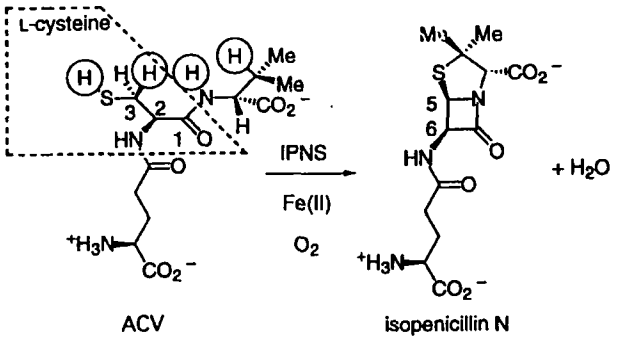
A key step in the biosynthesis of penicillin is the cyclization of ACV to isopenicillin N, catalyzed by the iron-dependent enzyme IPNS (Scheme 1). The mechanism of the reaction has no counterpart in the standard repertoire of organic chemical reactions, proceeding by stereoselective removal of four hydrogen atoms from the substrate [3].

The investigation of the biosynthesis of penicillin was started for the purpose of introducing unnatural side chains into penicillins in the 1940s [4]. The pathway of penicillin biosynthesis exhibits several interesting chemical reactions, especially β-lactam ring formation, thiazolidine ring formation, and ring expansion from penicillins to cephalosphorins, with which many scientists have been fascinated. Revealing the intimate details of the ring closures has been the main subject in investigations of penicillin biosynthesis. Despite extensive investigation by many biochemists, organic chemists, and inorganic chemists, even the sequence of ring closure could not be elucidated. This

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan. Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1463-1474, November, 1998. Original article submitted August 4, 1998.

0009-3122/98/3411-1237$20.00

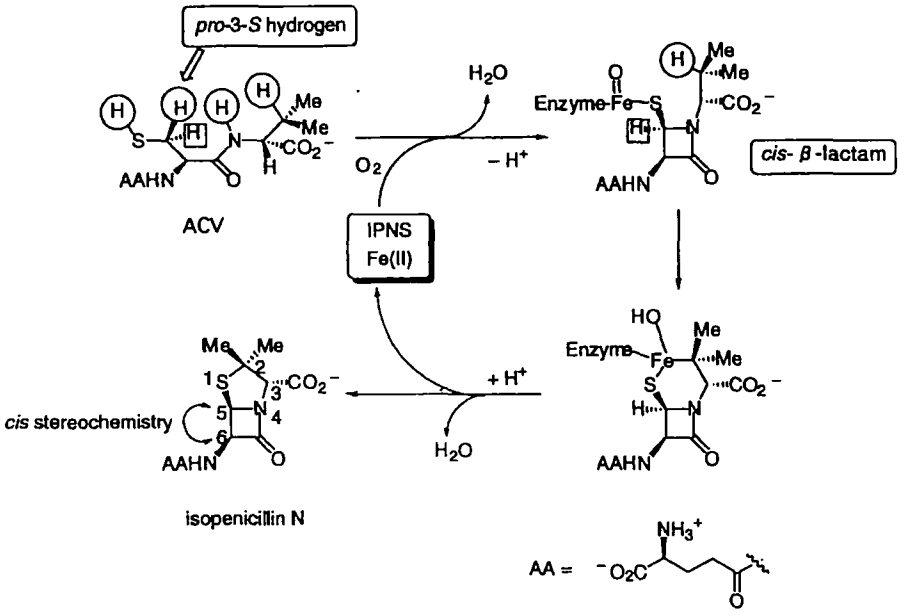
Scheme 1

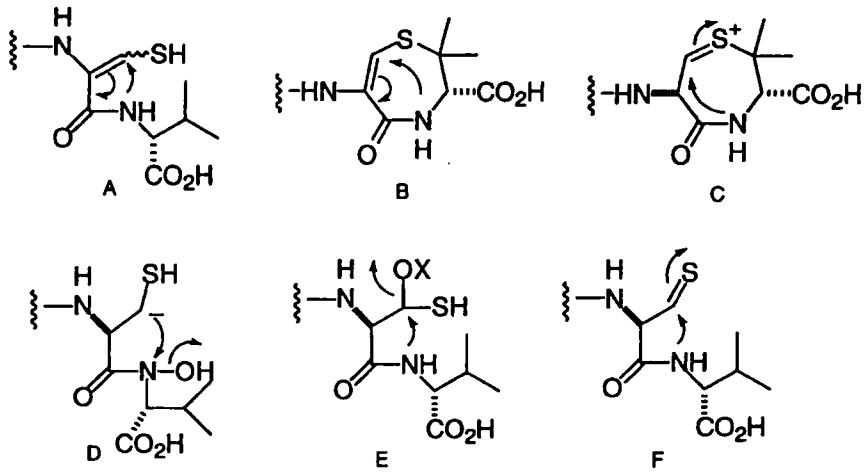


was apparently due to the fact that the detection of the intermediates on the pathway from ACV to isopenicillin N had never been successful. Although it seemed impossible to experimentally establish the chemical mechanism, a powerful study for the elucidation of penicillin biosynthesis by Baldwin, with his theory based upon a bold hypothesis and with excellent enzymatic techniques, has gradually thrown light on it [5]. He and his co-workers probed the fact that the β-lactam ring is formed first by using isotopic competition experiments [6]. Furthermore, the mechanism of the second ring closure, i.e., thiazolidine ring formation, was explained in terms of his novel and unconventional idea that the participation of highly reactive ferryl species in the reaction is a key feature of IPNS [5]. They even demonstrated that the second ring closure may be effected in a biomimetic way in the absence of the enzyme, by treatment of a β-lactam thiol with oxygen, iron(II), and appropriate co-factors (Scheme 2) [7]. In spite of their great efforts, the first step in the biosynthesis of penicillin, β-lactam formation, was still a fascinating mechanistic problem.

Historically, several mechanisms have been proposed [3]. Earlier, two hypothetical intermediates involving 2,3-dehydrocysteinyl structures A, B were ruled out by labelling experiments. Other proposed intermediates including thiazepine C [8] and hydroxamic acid D [9] were discredited based on the results of experiments on transformation of ACV analog into penicillin under incubation conditions. Two mechanisms called the activated alcohols E theory [3] and thioaldehyde F theory [10] still remain because no negative results against them have been reported.

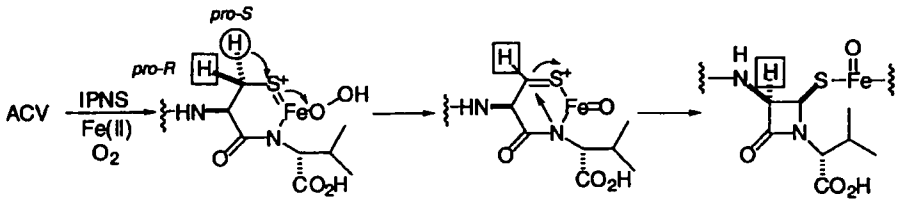
Scheme 2





Baldwin proposed the latter type of mechanism involving the iron-bound thioaldehyde formation route (Scheme 3) as the most likely biosynthetic prospect [5]. However, the intermediate for this mechanism had not been identified yet, and hence a model study was required.

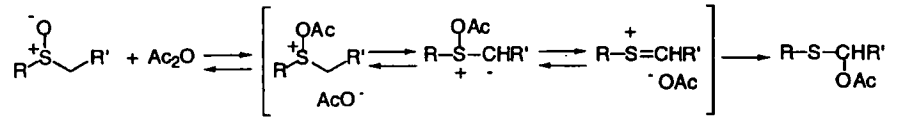
Scheme 3



PUMMERER REARRANGEMENT

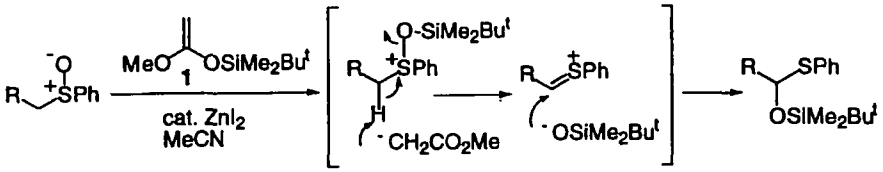
The Pummerer rearrangement of sulfoxides is a useful method for the synthesis of α-substituted sulfides and has attracted considerable attention from both synthetic and mechanistic points of view [11]. The first reaction reported by Pummerer was the conversion of phenylsulfinylacetic acid to glyoxylic acid and thiophenol *via* α-substituted sulfides under elevated temperatures in the presence of mineral acids [12]. Any reaction of sulfoxides with acids *via* a similar reaction pathway is now generally known as the Pummerer rearrangement. A generalized mechanism for the Pummerer rearrangement consisting of four sequential elemental reactions can be considered (Scheme 4).

Scheme 4

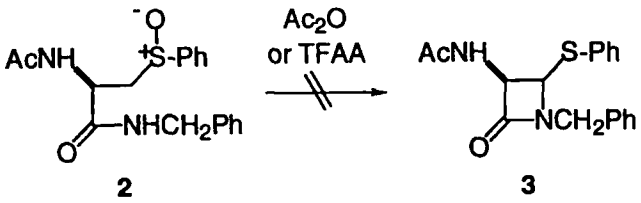


In 1984, we examined the use of an effective silylating reagent, O-methyl-O-*tert*-butyldimethylsilyl ketene acetal (**1**), for the Pummerer type rearrangement of sulfoxides and found a new methodology which led to α-siloxysulfides under mild conditions [13]. Our Pummerer type rearrangement of sulfoxides with **1** proceeds smoothly in the presence or absence of a catalytic amount of zinc iodide in acetonitrile to give the α-siloxysufides in good yields. The reaction

Scheme 5



Scheme 6

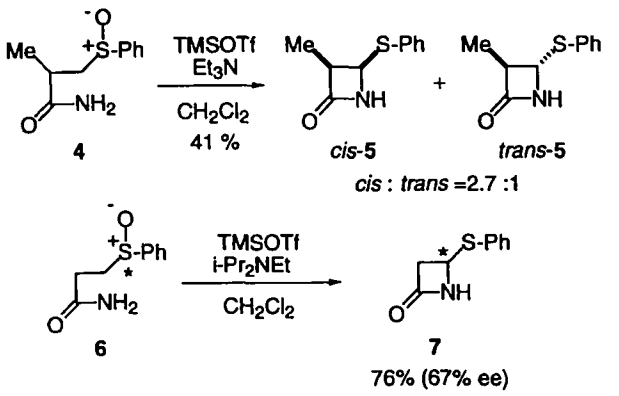


of sulfoxides with **1** presumably occurs *via* the sulfonium intermediate shown in Scheme 5 with initial silicon transfer from **1** to the sulfoxides and subsequent abstraction of the α-hydrogen by the generated ester enolate anion, possibly giving a sulfonium intermediate, which then rearranges by the usual Pummerer pathway to give α-siloxy sulfides.

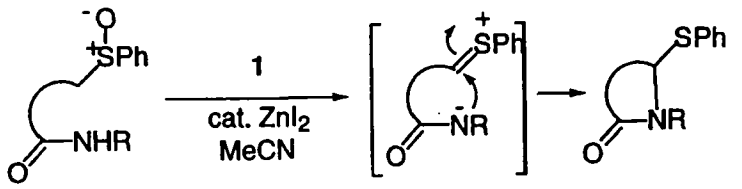
BIOMIMETIC SYNTHESIS OF PENICILLIN [14]

A Pummerer reaction of an appropriate sulfoxide was considered to generate a chemical equivalent of the enzymatic iron-bound sulfonium ion intermediate suggested by Baldwin. The idea of using the Pummerer reaction for the mimic synthesis of the β-lactams was not new, but a little work had been done before our participation in this field. A pioneering study for the biomimetic β-lactam formation using the Pummerer reaction was reported by Wolfe and his co-workers in 1979 [15]. They attempted (Scheme 6) to form a β-lactam **3** from S-phenylcystineamide sulfoxide **2** under various Pummerer conditions using acetic anhydride or trifluoroacetic anhydride, *etc.*, however, no evidence was obtained for the formation of **3**. They explained the results that the β-lactam **3** formed from **2** might undergo rapid destruction under these Pummerer conditions, since it was observed, as a comparative study, that methyl ester of phenylpenicillin did not survive under the same Pummerer conditions [15].

Scheme 7



Scheme 8



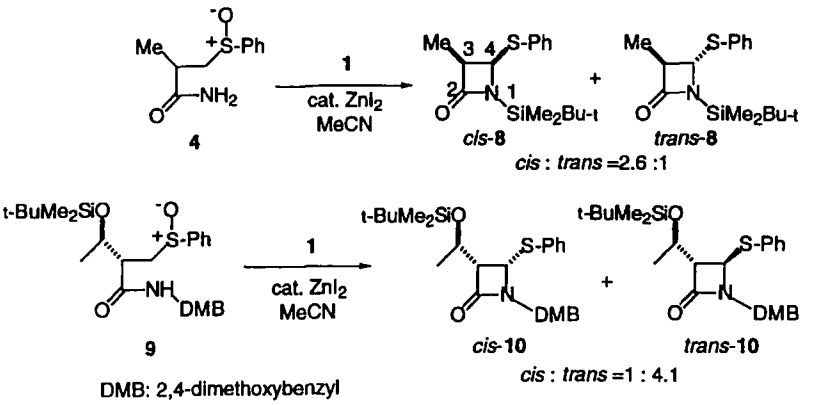
In 1984, the first successful mimic conversion from sulfoxides to β-lactams was reported by Kaneko using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a novel Pummerer reagent [16]. Thus when 2-methyl-3-phenylsulfinylpropionamide (**4**) was treated with TMSOTf in the presence of triethylamine at 20°C, β-lactam **5** was obtained as a 2.7:1 mixture of *cis:trans* isomers in 41% yield (Scheme 7). Though it was a very simple model reaction for mimic cyclization, he pointed out that the major product of this reaction was the *cis* isomer, since most of the naturally occurring β-lactams have *cis*-arranged substituents. Kaneko and co-workers applied the new Pummerer system to the asymmetric synthesis of a β-lactam. Treatment of an enantiopure sulfoxide **6** separated by an HPLC chiral column with TMSOTf and diisopropylethylamine in dichloromethane gave chiral β-lactam **7** in 76% yield with 67% ee [17]. The reaction mechanism could not precisely be discussed because the absolute stereochemistry of the sulfoxide was not determined.

Independently, we developed a new Pummerer reaction, the so-called silicon-induced Pummerer rearrangement reaction using sulfoxides with ketene silyl acetals as described above [2], as a part of our research program directed towards novel silyl transfer reaction [18].

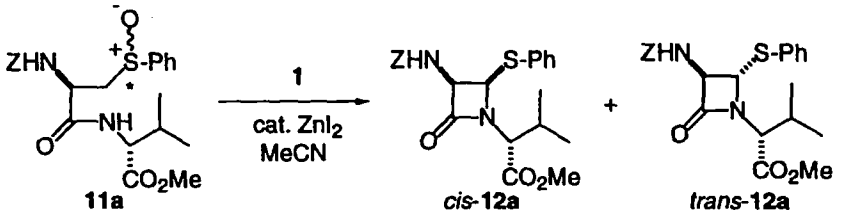
Thus we applied this system to the intramolecular Pummerer reaction. When ω-carbamoylsulfoxides were used for our silicon-induced Pummerer reaction, 5~7 membered α-sulfenyl lactams were obtained in good to excellent yields under nearly neutral conditions (Scheme 8) [19].

It was thought that the system was mild enough not to destroy the β-lactam ring. Therefore, we next applied the intramolecular Pummerer reaction to the preparation of β-lactams. β-Amidosulfoxides reacted with **1** to give 4-phenylthioazetidin-2-ones. In this cyclization reaction 3,4-*cis* β-lactams were predominantly produced although the *trans* ones were obtained selectively when bulky substituents were present at position 3 of the produced β-lactams. For instance, reaction of 2-methyl-3-phenylsulfinylpropionamide **4** with **1** furnished *cis* β-lactam **8** (*cis:trans* = 2.6:1) [20], whereas, in the case of 3-*tert*-butyl- dimethylsilyloxy-2-phenylsulfinylmethylbutanamide (9), *trans* isomer 10 was formed predominantly (*trans:cis* = 4.1:1) (Scheme 9) [21]. The phenomena were consistent with the result reported by Kaneko shown in Scheme 8.

Scheme 9



Scheme 10



Z: benzyloxycarbonyl

In order to demonstrate the mimetic synthesis of penicillin, we extended our method to ACV analog. First, dipeptide **11** was treated with **1** in the presence of a catalytic amount of zinc iodide in acetonitrile at room temperature to give a mixture of *cis* (40%) and *trans* β-lactams **12** (15%) (Scheme 10) [22]. It should be noted that the *cis* isomer was preferentially obtained even when the ACV analog was used.

To clarify the preferential formation of the *cis* isomer, the stereoisomers caused by the chiral sulfoxide were separated and used for our silicon-induced Pummerer reaction. Thus the R-sulfoxide **11a** when treated with **1** predominantly gave the cis isomer **12a** (*cis*:*trans* = 5.2:1) and S-sulfoxide **11a** with **1** afforded a mixture of *cis* and *trans* isomers (*cis*:*trans* = 1:2.2). Next, we examined the reaction of the more closely related ACV analog **11b** with **1** [23]. Similar results were observed as in the case of dipeptides **11a**. The reaction of R-**11b** with **1** predominantly gave the *cis* β-lactam **12b** (up to 11:1) and S-**11b** gave a mixture of the cis and trans β-lactams (*cis*:*trans* = 1:1.1) (Scheme 11).

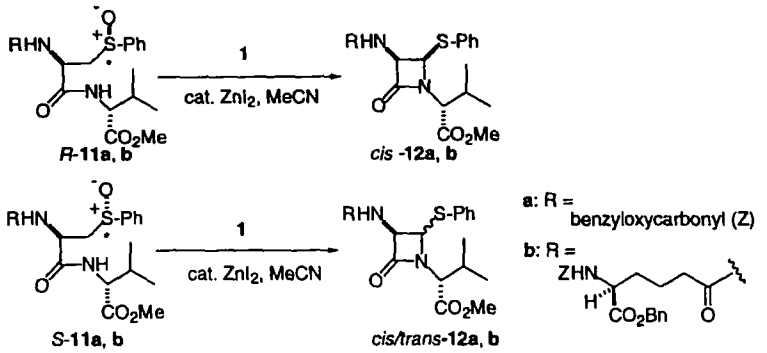
We were very pleased with the results obtained such that our Pummerer type cyclization of the ACV tripeptide analog *R*-**11** furnished the *cis* β-lactam **12** which has the same configuration as that of penicillin even though a long substituent, the aminoadipoyl side chain, was present at the C-3 position of the β-lactam. This result supports the hypothesis that the penicillin nucleus could be constructed *via* the thionium ion intermediate *in vivo*.

In order to discuss the mechanism of *cis* stereoselection in our silicon-induced Pummerer reaction of ACV analog, we needed to investigate the Pummerer reaction of the chiral sulfoxides which did not have amino substituents at the β-carbon of the sulfur atom. The Pummerer cyclization of the *R*- and *S*-sulfoxides **13** with **1** in acetonitrile gave a mixture of the *R*- and *S*-β-lactams **14**, respectively (Scheme 12).

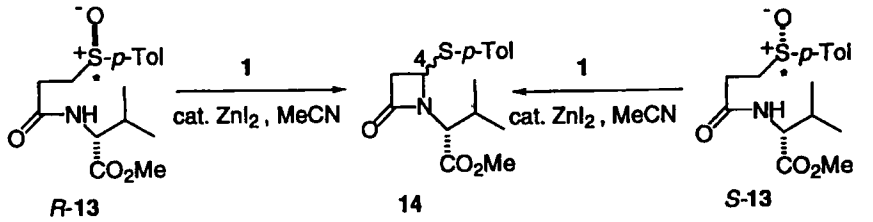
There was no *cis* (*i. e.* 4*R*) selectivity in the deaminosulfoxides **13**. These results explain that the *cis* selectivity is strongly influenced by the cysteinyl amino group as well as the absolute stereochemistry of the sulfoxide.

A working hypothesis of the *cis* selectivity in the reaction of *R*-**11** with **1** is shown in Scheme 13. The initial silicon transfer from **1** to *R*-**11** could result in the chelated structure A. The subsequent removal of the α-hydrogen by the generated ester enolate anion and elimination of the siloxy ligand would lead to the *E*-type thionium intermediate B. The amido moiety may be forced to attack the α-position resulting in the formation of *cis*-**12**. However,

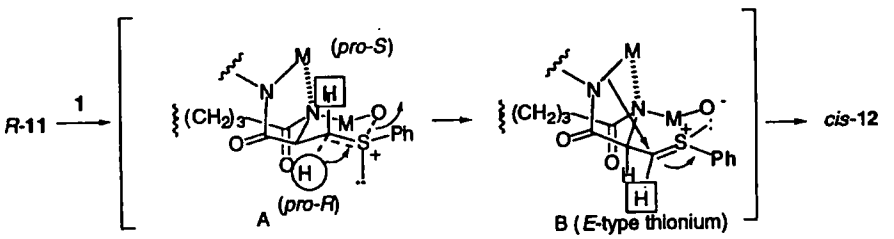
Scheme 11



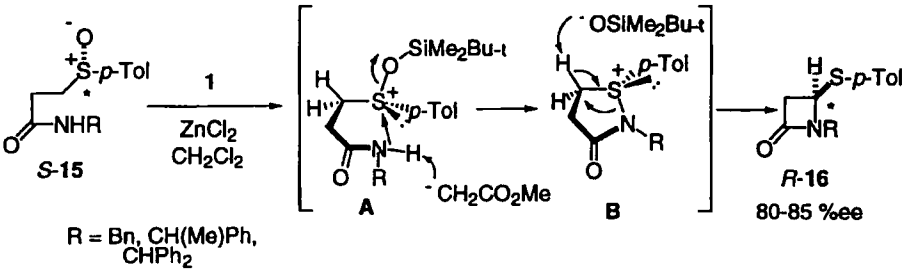
Scheme 12



Scheme 13



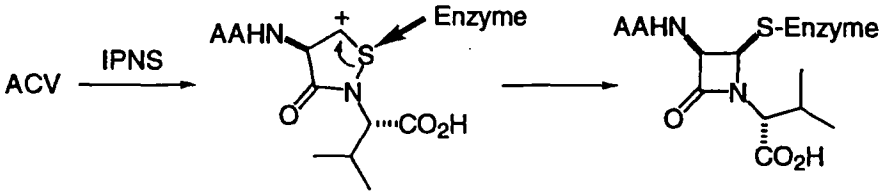
Scheme 14



the mechanism mentioned here includes a contradiction. Our Pummerer reaction presumably proceeds with the loss of the cysteinyl α-*pro*-3-*R* hydrogen.

Since Baldwin proposed that a complex of enzyme Fe with the thiolate of substrate ACV was initially formed before the cyclization to penicillins, the surroundings of the sulfur atom of ACV in the transition state should have a chiral environment. In order to let the surroundings of the sulfur atom of the model compound be chiral, optically active sulfoxides might be considered to be the best substrate. Moreover, the chiral substrate should be more simple than **11** for understanding the net effect of sulfur chirality. Hence we carried out our Pummerer type cyclization reaction using chiral β-amidosulfoxides **15** which did not include the chiral center other than sulfur atom. Thus, *S*-**15** were treated with **1** in the presence of a catalytic amount of zinc iodide in methylene dichloride to give predominantly the corresponding 4*R*-β-lactams **16** in more than 80% ee [24]. These results showed that the stereoinduction was influenced by the absolute configuration of the sulfoxides and the reaction mechanism is as follows. The silylation of *S*-**15** with **1** affords an intermediate A which may then yield a chiral pseudo isothiazolone derivative B through axial attack of the amido anion generated by proton abstraction with the ester anion and elimination of the siloxy ligand. The hydrogen neighboring the sulfur atom is then removed by the siloxy anion and the amido ligand migrates from the α-face to give the β-lactam *R*-**16** (Scheme 14).

Scheme 15



It is interesting to note that this mechanism is similar to another hypothesis, the proposed isothiazolidinone route (Scheme 15) [25]. However, we were a bit confused about the obtained results. The *S*-sulfoxide **15** was converted to the 4*R*-β-lactam **16** having the same configuration corresponding to that of natural penicillin. On the contrary, the *R*-sulfoxides **11** predominantly gave the *cis* β-lactam **12** in the case of the ACV analog as shown in Scheme 11.

We then started to work out the final stage in question: to attempt the elucidation of the mechanism of the selective removal of the *pro-S* hydrogen at the C-3 cysteinyl residue of ACV.

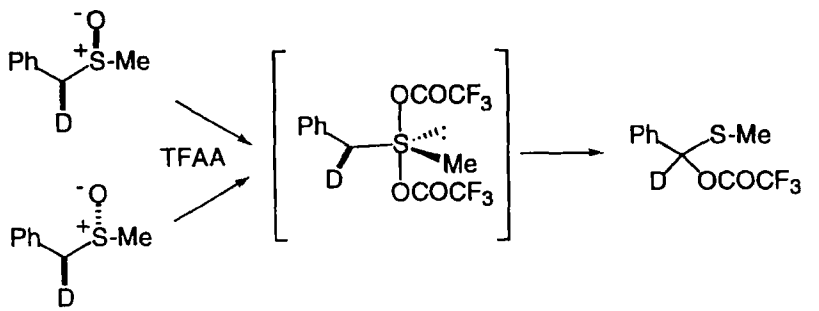
STEREOSELECTIVE REMOVAL OF *PRO*-S HYDROGEN

As a preparatory experiment to discuss the mechanism of the selective deprotonation of the cysteinyl *pro-S* hydrogen at the C-3 position during the conversion of ACV to isopenicillin N, we first needed to clarify the relationship between the stereospecific deprotonation and sulfur chirality in the Pummerer rearrangement in acyclic sulfoxides.

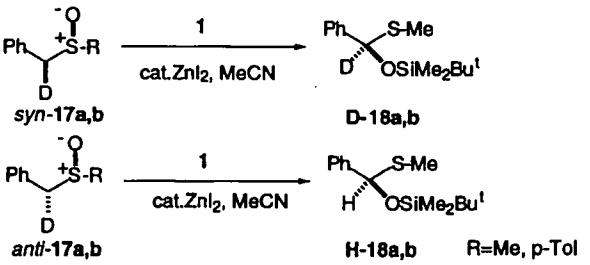
Historically, Wolfe and Kazmaier attempted to study the diastereoselectivity of deprotonation step in the Pummerer rearrangement of deuterated benzyl methyl sulfoxides (Scheme 16). According to the paper, they could not discuss it at all because of the competing epimerization at the sulfur atom *via* the sulfurane intermediate under acid anhydride conditions [26].

We investigated the Pummerer type rearrangement of racemic α-deuteriobenzyl methyl sulfoxides and chiral *R*-α-deuterobenzyl tolylsulfoxides with **1** and found that removal of the α-proton occurred with high diastereoselectivity, *i. e.*, the Pummerer rearrangement proceeded with preferential loss of the sulfinyl *pro-R*-α-hydrogen in the R-sulfoxides (Scheme 17) [27]. The following mechanism is proposed to explain these results. The silylation of sulfoxides **17** with the acetal **1** affords **A**. Thus, **A** may yield an anion intermediate **B** through abstraction of the *pro-R* hydrogen (antiperiplanar hydrogen) with an ester enolate generated from the opposite face of the sulfoxide oxygen, and the siloxy group may be forced to attack the α-position as soon as the anion intermediate **B** undergoes *anti*-elimination resulting in the production of the α-siloxy sulfide which has *R* stereochemistry at the newly generated chiral center (Scheme 18).

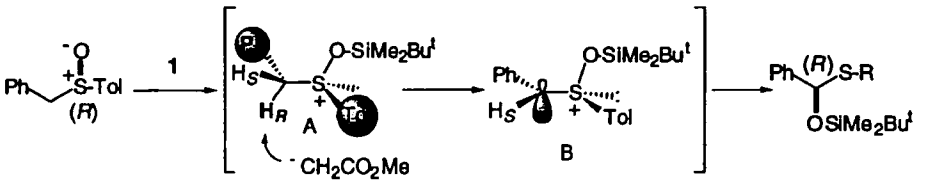
Scheme 16



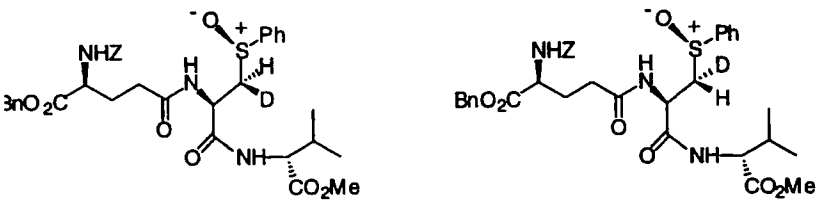
Scheme 17



Scheme 18



So far, we could clearly understand the relationship between the sulfoxide chirality, the abstraction of the α-hydrogen, and the stereochemistry of products in the Pummerer rearrangement of the acyclic sulfoxides. We would finally attempt to elucidate the mechanism of the α-deprotonation of sulfoxides in the Pummerer type cyclization reaction.



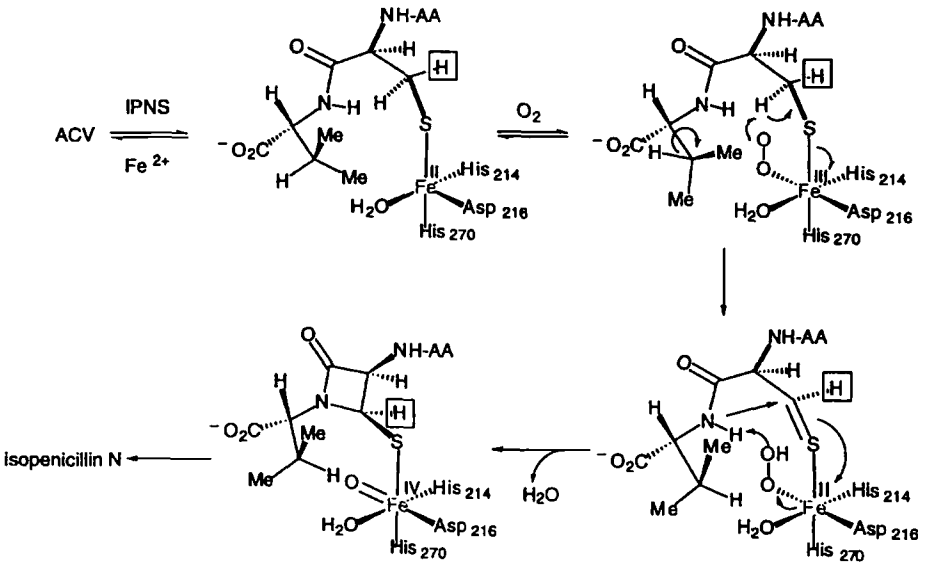
19a 19b

However, during our trial of synthesizing deuteriosubstrates **19a,b**, Baldwin and his co-workers have unraveled the intimate details of the penicillin biosynthesis using the substrate-bound crystal structure of IPNS [1], which was enough to put an end to our project of the biomimetic synthesis of penicillin. There is no ambiguity in the overall pathway shown in Scheme 19 [1, 28]. The original literature can be read for details of the answer.

CONCLUSION

Our interest in "*Why penicillin has cis stereochemistry*?" and "*How IPNS discriminates one of the two cysteinyl C-3 hydrogens of ACV*?" started more than ten years ago. These questions let us start the project. At that time, we were developing the original, silicon-induced Pummerer type rearrangement. We postulated that there must be a clue to solve them using the Pummerer reaction. Consequently, we have developed the asymmetric Pummerer type rearrangement, asymmetric additive Pummerer type rearrangement, and asymmetric Pummerer type cyclization of

Scheme 19



chiral, nonracemic sulfoxides and we now understand the intimate details of the reaction mechanism of the Pummerer reaction. We did not reach the goal of the project, but our findings have greatly contributed to the improvement in the chemistry of the Pummerer reaction. We are very pleased to know the exact answer by Baldwin, mechanism for the selective removal of the *pro*-3-*S* hydrogen by the enzyme IPNS which was unimaginable and very unique.

REFERENCES

1. (a) P. L. Roach, I. J. Clifton, C. M. H. Hensgens, N. Shibata, C. J. Schofield, J. Hajdu, and J. E. Baldwin, Nature (London), **387** (June), 827 (1997).
   (b) P. L. Roach, I. J. Clifton, C. M. H. Hensgens, N. Shibata, A. J. Long, R. W. Strange, S. S. Hasnain, C. J. Schofield, J. E. Baldwin, and J. Hajdu, Eur. J. Biochem., **242**, 736 (1996).
   (c) P. L. Roach, I. J. Clifton, V. Fulop, K. Harlos, G. J. Barton, J. Hajdu, I. Andersson, C. J. Schofield, and J. E. Baldwin, Nature (London), **375** (June), 700 (1995).
   (d) N. Shibata, Chemistry Today (Gendai Kagaku), No. 324, 23 (1998).
2. (a) Y. Kita and N. Shibata, Synlett., 289 (1996).
   (b) Y. Kita and N. Shibata, Yuki Gosei Kagaku Kyokai-Shi, **52**, 746 (1994).
   (c) Y. Kita, Phosphorus, Sulfur, Silicon, **120** & **121**, 145 (1997).
3. (a) S. W. Queener and N. Neuss, in: Chemistry and Biology of β-Lactam Antibiotics, R. B. Morin and M. Gorman (eds.), Academic Press, New York (1982), pp. 22-81.
   (b) D. J. Aberhart, Tetrahedron, **33**, 1545 (1977).
4. O. K. Behrens, J. Corse, J. P. Edwards, L. Garrison, R. G. Jones, Q. P. Soper, F. R. van Abeele, and C. W. Whotehead, J. Biol. Chem., **175**, 793 (1948).
5. (a) J. E. Baldwin, J. Heterocyclic Chem., **27**, 71 (1990).
   (b) J. E. Baldwin and M. Bradley, Chem. Rev., **90**, 1079 (1990).
   (c) J. E. Baldwin and Sir E. Abraham, Natural Product Reports, 129 (1988).
6. J. E. Baldwin, R. M. Adlington, S. E. Moroney, L. D. Field, and J.-H. Ting, J. Chem. Soc. Chem. Commun., 984 (1984).
7. J. E. Baldwin, R. M. Adlington, and R. Bohlmann, J. Chem. Soc. Chem. Commun., 357 (1985).
8. (a) S. Wolfe, R. J. Bowers, S. K. Hasan, and P. M. Kazmaier, Can. J. Chem., **59**, 406 (1981).
   (b) G. Bahadur, J. E. Baldwin, T. Wan, and M. J. Jung, Chem. Soc. Chem. Commun., 1146 (1981).

9. (a) A. J. Birch and H. Smith, in: Amino Acids and Peptides with Antimetabolic Activity (Chiba Foundation Symposium), G. E. W. Wolstenholme and C. M. O'Conner (eds.), Churchill, London (1958), pp. 243-263.
(b) A. I. Scott, S. E. Yoo, S.-K. Chung, and J. A. Lacadie, Tetrahedron Lett., 1137 (1976).
(c) R. L. Baxter, G. A. Thomson, and A. I. Scott, J. Chem. Soc., Chem. Commun., 32 (1984).
10. H. R. V. Arnstein and J. C. Crawhall, Biochem. J., **67**, 180 (1957).
11. (a) T. Numata and S. Oae, Yuki Gosei Kagaku Kyokai-Shi., **35**, 726 (1977).
(b) T. Numata, Yuki Gosei Kagaku Kyokai-Shi., **36**, 845 (1978).
(c) S. Oae and T. Numata, Isot. Org. Chem., **5**, 45 (1980).
(d) S. Oae, T. Numata, and T. Yoshimura, in: The Chemistry of the Sulphonium Group, C. J. M. Stirling and S. Patai (eds.), John Wiley, New York (1981), p. 571.
(e) O. D. Lucchi, U. Miotti, and G. Modena, Organic Reactions, **40**, 157 (1991).
(f) D. S. Grierson and H.-P. Husson, in: Comprehensive Organic Synthesis, Vol. 6, B. M. Trost and I. Fleming (eds.), Pergamon Press, Oxford (1991), p. 910.
12. (a) R. Pummerer, Chem. Ber., **42**, 2282 (1909).
(b) idem, ibid., **43**, 1401 (1910).
13. (a) Y. Kita, H. Yasuda, O. Tamura, F. Itoh, and Y. Tamura, Tetrahedron Lett., **25**, 4681 (1984).
(b) idem, Chem. Pharm. Bull., **35**, 562 (1987).
14. (a) N. J. Leonard and R. Y. J. Ning, Org. Chem., **32**, 677 (1967).
(b) R. D. G. Cooper, J. Am. Chem. Soc., **94**, 1018 (1972).
(c) R. B. Morin, E. M. Gordon, T. McGrath, and R. Shuman, Tetrahedron Lett., 2159 (1973).
(d) R. B. Morin, E. M. Gordon, and J. R. Lake, Tetrahedron Lett., 5213 (1973).
(e) J. E. Baldwin, S. B. Haber, and J. J. Kitchin, Chem. Soc. Chem. Commun., 790 (1973).
(f) J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, J. Chem. Soc. Chem. Commun., 47 (1974).
(g) J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, J. Chem. Soc. Perkin Trans. I, 986 (1974).
(h) S. Nakatsuka, H. Tanio, and Y. Kishi, J. Am. Chem. Soc., **97**, 5008, 5010 (1975).
(i) J. E. Baldwin, A. Au, M. Christie, S. B. Haber, and D. Hesson, J. Am. Chem. Soc., **97**, 5957 (1975).
(j) J. E. Baldwin, M. Christie, S. B. Haber, and L. I. Kruse, J. Am. Chem. Soc., **98**, 3045 (1976).
(k) J. E. Baldwin and M. Jung, J. Chem. Soc. Chem. Commun., 609 (1978).
(l) A. L. J. Beckwith and C. J. Easton, Tetrahedron, **39**, 3995 (1983).
(m) N. Shibata, J. E. Baldwin, and M. E. Wood, Bioorgan. & Med. Chem. Lett., **7**, 413 (1997).
(n) N. Shibata, J. E. Baldwin, A. Jacobs, and M. E. Wood, Tetrahedron, **52**, 12839 (1996).
(o) N. Shibata, J. E. Baldwin, A. Jacobs, and M. E. Wood, Synlett., 519 (1996).
15. (a) S. Wolfe, P. M. Kazmaier, and H. Auksi, Can. J. Chem., **57**, 2417 (1979).
(b) S. Wolfe, R. J. Bowers, S. K. Hasan, and P. M. Kazmaier, ibid., **59**, 406 (1981).
16. T. Kaneko, J. Am. Chem. Soc., **107**, 5409 (1985).
17. T. Kaneko, Y. Okamoto, and K. Hatada, J. Chem. Soc. Chem. Commun., 1511 (1987).
18. (a) Y. Kita, O. Tamura, and Y. Tamura, Yuki Gosei Kagaku Kyokai-Shi, **44**, 1118 (1986).
(b) Y. Kita, Yakugaku Zasshi., **106**, 269 (1986).
(c) Y. Kita, J. Haruta, T. Fujii, J. Segawa, and Y. Tamura, Synthesis, 451 (1981).
(d) Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, Tetrahedron Lett., 4311 (1979).
19. (a) Y. Kita, O. Tamura, T. Miki, and Y. Tamura, Tetrahedron Lett., **28**, 6479 (1987).
(b) Y. Kita, O. Tamura, N. Shibata, and T. Miki, Chem. Pharm. Bull., **38**, 1473 (1990).
20. (a) Y. Kita, O. Tamura, N. Shibata, and T. Miki, J. Chem. Soc. Perkin Trans. I, 1862 (1989).
(b) Y. Kita, N. Shibata, O. Tamura, and T. Miki, Chem. Pharm. Bull., **39**, 2225 (1991).
21. (a) Y. Kita, N. Shibata, T. Miki, Y. Takemura, and O. Tamura, J. Chem. Soc. Chem. Commun., 727 (1990).
(b) idem, Chem. Pharm. Bull., **40**, 12 (1992).
22. Y. Kita, O. Tamura, T. Miki, H. Tono, N. Shibata, and Y. Tamura, Tetrahedron Lett., **30**, 729 (1989).
23. Y. Kita, N. Shibata, N. Kawano, T. Tohjo, C. Fujimori, and H. Ohishi, J. Am. Chem. Soc., **116**, 5116 (1994).
24. Y. Kita, N. Shibata, N. Kawano, T. Tohjo, and K. Matsumoto, Tetrahedron Lett., **36**, 115 (1995).
25. (a) J. E. Baldwin, A. L. J. Becwith, A. P. Davis, G. Procter, and K. A. Singleton, Tetrahedron, **37**, 2181 (1981).
(b) C. J. Easton, J. Chem. Soc. Chem. Commun., 1349 (1983).

26. S. Wolfe and P. M. Kazmaier, Can. J. Chem., **57**, 2388, 2397 (1979).
27. (a) Y. Kita, N. Shibata, N. Yoshida, S. Fukui, and C. Fujimori, Tetrahedron Lett., **35**, 2569 (1994).
(b) Y. Kita, N. Shibata, N. Yoshida, S. Fukui, N. Kawano, C. Fujimori, N. Yoshikawa, and S. Fujita, J. Chem. Soc. Perkin Trans. I, 3335 (1994).
(c) Y. Kita, N. Shibata, and N. Yoshida, Tetrahedron Lett., **34**, 4063 (1993).
(d) Y. Kita, N. Shibata, S. Fukui, and S. Fujita, Tetrahedron Lett., **35**, 9733 (1994).
(e) Y. Kita, N. Shibata, N. Yoshida, and S. Fujita, J. Chem. Soc. Perkin Trans. I, 3335 (1994).
(f) Y. Kita, N. Shibata, N. Kawano, S. Fukui, and C. Fujimori, Tetrahedron Lett., **35**, 3575 (1994).
28. C. J. Rowe, C. P. Shorrock, T. DW. Claridge, and J. D. Sutherland, Chemistry & Biology, **5**, 229 (1998).