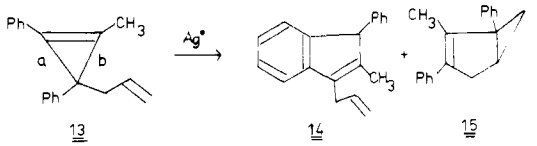
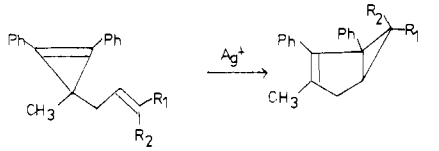


13 14 15

The products obtained from the silver-induced reactions are derived from exclusive cleavage of the cyclopropene bond attached to the phenyl group (bond a). This stands in marked contrast to the direct irradiation of **13**, which results in predominant bond b cleavage.[6]

At this stage of our studies we decided to investigate the stereochemical course of the silver-induced intramolecular cycloaddition reaction. Treatment of (*E*)-1-(1-methyl-2,3-diphenyl-2-cyclopropen-1-yl)-2-butene (**16**) with 2 mol % of silver perchlorate in benzene gave a 96% yield of *exo*-3,6-dimethyl-1,2-diphenylbicyclo[3.1.0]hex-2-ene (**17**). Similarly, the reaction of the corresponding *Z*-isomer **18** with silver ion gave *endo*-bicyclohexene **19** as the sole product in 97% yield. These results indicate that complete retention of stereochemistry about the π system has occurred in the silver-catalyzed cycloaddition reaction.

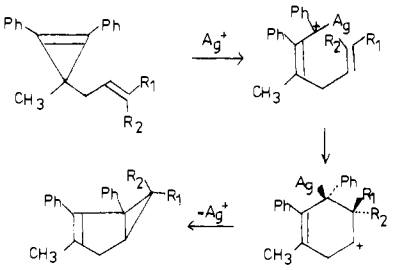


16 ; R_1=CH_3 ; R_2=H 17 , R_1 = CH_3 ; R_2 = H

18 , R_1 = H ; R_2 = CH_3 19 ; R_1 = H , R_2 = CH_3

In line with earlier evidence for the intermediacy of a metal-bonded carbonium ion–metal complexed carbene hybrid intermediate in the transition metal promoted rearrangement of strained ring systems,[8,9] it is tempting to suggest the involvement of a related species in the silver-induced rearrangements of the above systems. Thus, we propose that silver ion behaves as a very specific Lewis acid which attacks the cyclopropene ring to yield argentocarbonium ion **20**.[10] Electrocyclization of this intermediate followed by loss of silver ion nicely rationalizes the formation of the indene ring. The clean conversion of **6** in the presence of Ag^+ into **7** and **8** in methanol can be explained in terms of an oxidation–reduction reaction.[11] The reduction of Ag(I) to the metallic state is somewhat reminiscent of results reported by Koser and Faircloth.[12] These workers found that quadricyclane was oxidized and silver ion was reduced to silver metal in the reaction between silver trifluoroacetate and quadricyclane in methanol.[13] The above results also suggest that the crucial step which dictates the regioselectivity of bond cleavage of the cyclopropene ring is strongly dependent upon relative carbonium ion stabilities. Breakage of bond a would be expected to give rise to the more energetically favorable benzylic argentocarbonium ion.[14]

The intramolecular trapping of the ring-opened species by the neighboring double bond provides additional evidence for the carbenoid character of the intermediate. A reasonable mechanistic option for the intramolecular cycloaddition involves a stepwise attack of the terminal double bond on the argentocarbonium ion so as to generate a six-membered ring. As long as the loss of silver ion occurs simultaneously with bond making, the cycloaddition will proceed with retention of configuration.



We are continuing to investigate the more intriguing synthetic and mechanistic aspects of these interesting silver ion promoted reactions.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation.

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(9) Paquette, L. A. *Acc. Chem. Res.* **1971**, *4*, 280.

(10) Formation of the argentocarbonium ion may occur via attack on the cyclopropene π bond followed by a rapid ring opening of the transient cyclopropyl cation. Alternatively, silver ion attack could occur on the σ bond to give the argentocarbonium ion directly.

(11) In this case, a full equivalent of silver ion was used.

(12) Koser, G. F.; Faircloth, J. N. *J. Org. Chem.* **1976**, *41*, 583.

(13) It should be pointed out that the production of metallic silver in the conversion of **6** to **7** also leads to the formation of perchloric acid. Control experiments established, however, that the cyclopropene ring system is stable to perchloric acid in methanol under the experimental conditions used. Furthermore, the reaction of **6** in methanol with Ag(I) ion readily occurs in the presence of an excess of triethylamine. These observations indicate that the conversion of **6** to **7** does not proceed via an acid-induced pathway.

(14) The regioselectivity of bond cleavage encountered in the direct irradiation of unsymmetrical cyclopropenes has been attributed to a funneling of the excited state of the cyclopropene to the energy surface of the higher lying vinyl carbene state.[6,7]

Synthesis of (*S*)- and (*R*)-4-[(Methoxycarbonyl)methyl]-2-azetidinone by Chemicoenzymatic Approach

Masaji Ohno,* Susumu Kobayashi, Takamasa Iimori, Yi-Fong Wang, and Toshio Izawa†

Faculty of Pharmaceutical Sciences, University of Tokyo Bunkyo-ku, Tokyo 113, Japan

Received November 10, 1980

Naturally occurring β-lactam antibiotics which belong to the group carbapenem are still increasing in number[1] and have attracted a great deal of synthetic study because of their unique structure and interesting biological activity.[1a] However, most of them lead to racemic carbapenem derivatives,[2,3] and even the chiral synthesis of thienamycin and (−)-homothienamycin consists of multistep reactions to get the azetidinone moiety in low overall yields starting from L-aspartic acid.[4] The requirements for a simple and high-yielding synthesis of 4-substituted-2-azetidinones having desired absolute configuration[5] at C-4 are indeed demanding in the exploitation of such highly potential β-lactam antibiotics. We wish to report here an efficient methodology for the preparation of (*S*)- and (*R*)-4-[(methoxycarbonyl)methyl]-

† Visiting scientist from Institute of Microbial Chemistry, Shinagawa-ku, Tokyo, Japan.

(1) (a) For thienamycin, olivanic acid, and their analogues, see: "Topics in Antibiotic Chemistry"; Sammes, P., Ed.; Ellis Horwood: New York, 1980; pp 101–138. (b) For PS-5, see: Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamoto, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiot.* **1980**, *33*, 796. (c) For carpetimycins, see: Nakayama, M.; Iwasaki, A.; Kimura, S.; Mizoguchi, T.; Tanabe, S.; Murakami, A.; Watanabe, I.; Okuchi, M.; Itoh, H.; Saino, Y.; Kobayashi, F.; Mori, T. *J. Antibiot.* **1980**, *33*, 1388.

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(3) An efficient synthesis of *dl*-thienamycin has recently been reported: Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.

(4) (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193. (b) Ikota, N.; Shibata, H.; Koga, K. *Heterocycles* **1980**, *14*, 1077 and references cited therein.

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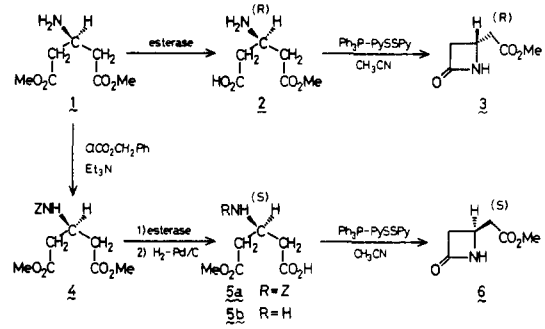
Scheme I



2-azetidinones by chemicoenzymatic approach starting from citric acid derivative as shown in Scheme I.

4-[(Methoxycarbonyl)methyl]-2-azetidinone was considered to be a versatile intermediate of the carbapenem nuclei on the basis of previous studies,[2-4] and a combination of enzymatic and chemical procedures was taken as our synthetic strategy. Cohen and Khedouri showed that α-chymotrypsin hydrolyzes the pro-*S* ester group of diethyl β-acetamidoglutarate.[6] However, the acetamido compound was considered not a good candidate for our purpose, since it may cause difficulty in further hydrolysis of the acetyl amino group followed by formation of the β-lactam ring. Dimethyl β-aminoglutarate (**1**) has been chosen as our starting material. It was prepared in excellent yield by reductive amination of dimethyl β-oxoglutarate[7] according to Borch's method[8] ($CH_3CO_2NH_4/NaBH_3CN$). The rate of hydrolysis of **1** with α-chymotrypsin was found to be extremely slow, and a large amount of the enzyme seemed necessary for synthetic purposes. Therefore, pig liver esterase was employed as shown in the case of β-hydroxy-β-methyl dimethyl glutarate by Sih and his coworkers.[9] Pig liver esterase[10] hydrolyzed **1** very efficiently and (3*R*)-half-ester **2** was formed in low optical yield. In a typical experiment, **1** (346 mg) in 0.1 M phosphate buffer (pH 8.0) (7 mL) was incubated with the esterase (400 units) at 25 °C for 1.5 h. Following usual workup, half-ester **2**, $[\alpha]^{22}_D$ +2.36° (*c* 4.23, H_2O), was obtained in 94% yield. The β-amino acid ester **2** was converted to 2-azetidinone **3**, $[\alpha]^{25}_D$ -26.03° (*c* 1.26, $CHCl_3$), with a Ph_3P-$(PyS)_2$-CH_3CN system[11] in 82% yield, and its absolute configuration and optical purity were determined by comparison with an authentic sample,[12] (*S*)-4-[(methoxycarbonyl)methyl]-2-azetidinone (**6**), prepared from L-aspartic acid.[4a] The results showed that pig liver esterase cleaved the pro-*S* methyl ester group of **1** more selectively giving **2**. However, it was also shown that the substrate **1** was partly hydrolyzed at the reaction condition even in the absence of the enzyme (about 30%), explaining the low optical yield (about 40% ee). It was assumed that the free amino group participates in the chemical hydrolysis through hydrogen bonding with a carbonyl group of the ester. Therefore, the amino group was protected by the benzyloxycarbonyl (Z) group with ZCl, affording **4** in 90% yield. Surprisingly, incubation of **4** with pig liver esterase at the same reaction condition afforded (3*S*)-half-ester **5a**, mp 97-97.5 °C, $[\alpha]^{25}_D$ +0.69° (*c* 7.45, $CHCl_3$), in 93% yield. Hydrogenolysis (H_2, Pd-C in MeOH) of **5a** afforded quantitatively **5b**, mp 175-177 °C, $[\alpha]^{25}_D$ -5.52° (*c* 3.26, H_2O). It was converted to monocyclic β-lactam **6** with Ph_2P-$(PyS)_2$-CH_3CN[11] in 84% yield, affording (*S*)-4-[(methoxycarbonyl)-methyl]-2-azetidinone in high optical purity, $[\alpha]^{25}_D$ +65.34°[12] (*c* 1.11, $CHCl_3$). In the absence of the enzyme, essentially no hydrolysis took place for **4**. This confirms that the esterase stereospecifically cleaved the pro-*R* methyl ester group of **4** giving **5a** and **5b**. It is worthy of note that the protection with ZCl of the amino group at the prochiral center in **1** reversed the chirality of the product with the same enzyme by hydrolyzing selectively one of the enantiotopic (methoxycarbonyl)methyl groups. *tert*-Butyloxycarbonyl- and benzylamino derivatives of **1** both afforded the corresponding half-esters with *S* configuration upon enzymatic hydrolysis, but the acetyl derivative afforded the corresponding half-ester with *R* configuration. These findings are synthetically useful and important, since formation of β-amino acid with desired configuration can be selectively chosen at the stage of enzymatic hydrolysis.

The key features of the present methodology include the following: (1) dimethyl β-aminoglutarate (**1**) and dimethyl β-[(benzyloxycarbonyl)amino]glutarate (**4**) were efficiently hydrolyzed with pig liver esterase to (*R*)- and (*S*)-half-esters, **2** (40% ee) and **5a** (>96% ee), respectively; (2) the half-esters were converted to optically active 2-azetidinone **3** and **6** with Ph_3P-$(PyS)_2$-CH_3CN system in high yields; (3) (*S*)-azetidinone **6** having the desired absolute configuration is now easily available in quantity as a versatile synthon for carbapenem nuclei; (4) **2** and **5a** or **5b** are useful for the synthesis of chiral β-amino acids of biological interest.

Further investigation of the enzymatic process and the synthetic work to carbapenem β-lactam antibiotics will be reported in due course.

Acknowledgment. We express our gratitude to Professor H. Umezawa of Institute of Microbial Chemistry for his interest and support of this work and also Dr. H. Nakai for the preparation of the authentic sample **6**.

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(10) This was purchased from Sigma Co.
(11) After a systematic investigation of the condensing reagents for β-lactam formation from β-amino acids, this excellent system has been found and is the subject of the following publication.
(12) (*S*)-4-(Iodomethyl)-2-azetidinone[4a] was converted into **6**, $[\alpha]^{25}_D$ +63.95° (*c* 1.34, $CHCl_3$), in the following procedures: (a) silylation with $ClSi(Me)_2Bu$-*t* (94%), (b) tris(ethylthio)methane/*n*-BuLi (82%), (c) esterification with MeOH-$HgCl_2$ (43%), (d) desilylation with aqueous MeOH-HCl (46%).
(13) All materials described here gave MS, IR, and NMR (^{13}C and ^1H) spectra consistent with their structures.

Ph_3P-$(PyS)_2$-CH_3CN as an Excellent Condensing System for β-Lactam Formation from β-Amino Acids

Susumu Kobayashi, Takamasa Iimori, Toshio Izawa,† and Masaji Ohno*

Faculty of Pharmaceutical Sciences, University of Tokyo Bunkyo-ku, Tokyo 113, Japan

Received November 10, 1980

In the preceding publication[1] we reported that the enzymatic hydrolysis of dimethyl β-aminoglutarate afforded (*R*)-3-amino-4-(methoxycarbonyl)butyric acid selectively and that the protection of the amino group at the prochiral center with benzyloxycarbonyl chloride reversed the chirality of the product, affording the corresponding (*S*)-β-amino acid ester (**1a**) in excellent yield and with remarkable optical purity. This communication describes a new and efficient methodology for the formation of β-lactam compounds from β-amino acids by using triphenylphosphine and 2,2′-dipyridyl disulfide in acetonitrile.

A great deal of synthetic work has been already carried out in the formation of β-lactam compounds from β-amino acids.[2,3]

† Visiting scientist from Institute of Microbial Chemistry, Shinagawa-ku, Tokyo.
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