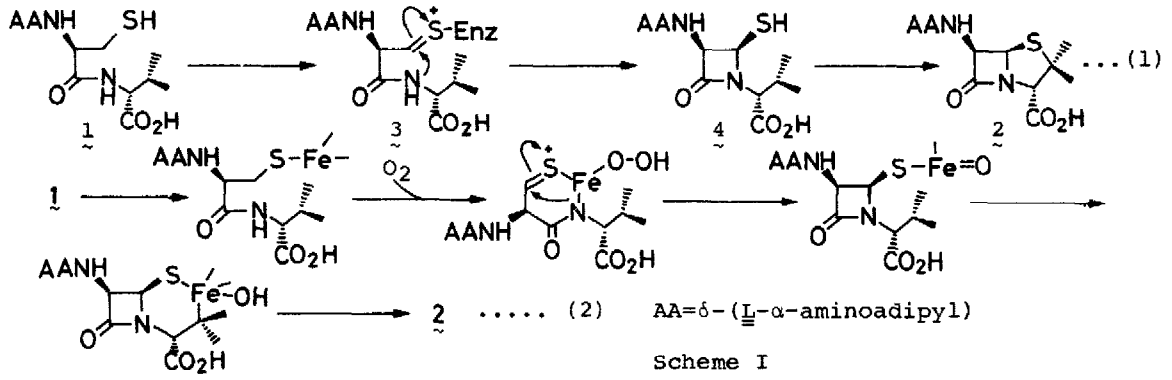
Tetrahedron Letters, Vol.30, No.6, pp 729-730, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CHEMISTRY OF O-SILYLATED KETENE ACETALS: BIOMIMETIC SYNTHESIS OF CIS-β-LACTAMS

Yasuyuki Kita,* Osamu Tamura, Takashi Miki, Hideyuki Tono,
Norio Shibata, and Yasumitsu Tamura
Faculty of Pharmaceutical Sciences, Osaka University
1-6, Yamada-oka, Suita, Osaka 565, Japan

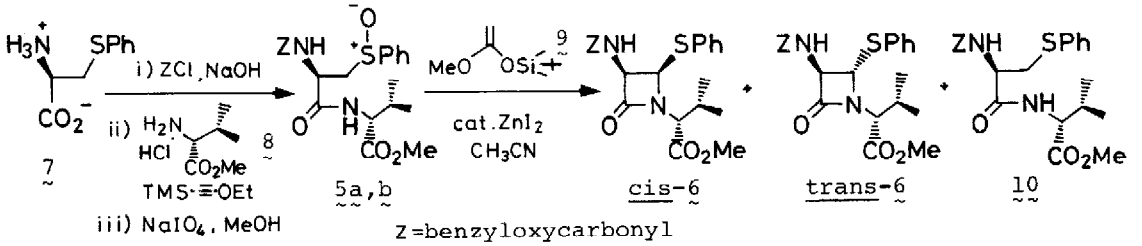
Summary; The first successful biomimetic conversion of an Arnstein tripeptide analogue into the cis-β-lactam via a silicon-induced Pummerer-type rearrangement is described.

Since the antibiotic family of penicillins and cephalosporins was discovered, the biosynthesis of these compounds has been studied extensively.[1] Many experiments led to the conclusion that L-cysteine and L-valine are incorporated intact into the Arnstein tripeptide, δ-(L-α-aminoadipyl)-L-cysteinyl-D-valine (LLD-ACV, 1), which is isolated from Penicillium chrysogenum.[2] Although the exact mechanism of formation of penams and cephems is still obscure, β-lactam ring has been shown to form first during the enzymatic conversion of 1 into isopenicillin N, 2.[3] There are three possible mechanisms for the conversions.[4] One of them involving sulfonium intermediate (3) is represented by eq 1. Chemically, the transformation of β-lactam (4) to 2 finds some support in the studies reported by Wolfe[5] and by Cooper,[6] in which cyclization to penicillins of species related to 4 has been envisaged. On the contrary, despite numerous efforts,[7] no evidence has been found for the conversion of 3 to 4. In connection with this biomimetic conversion of 1 to 2 by isopenicillin N synthetase[8] and proposed a similar mechanism involving sulfonium intermediate represented by eq 2.[3,9] Recently, Kaneko reported a conversion of simple 3-(phenylsulfinyl)propionamides into β-lactams involving sulfonium intermediates.[10] We communicate here a successful biomimetic conversion of a tripeptide analogue (5) into β-lactam (6) by our silicon-induced Pummerer-type rearrangement.[11]



Scheme I

Treatment of sulfide (7) with benzyloxycarbonyl chloride followed by coupling with D-valine derivative (8) using (trimethylsilyl)ethoxyacetylene[12] afforded a condensed product, which was oxidized with $NaIO_4$ to furnish 5 (a mixture of diastereomers, 5a:5b=37:63) in 50% overall yield. The mixture was treated with 6 eq of ketene methyl t-butyldimethylsilyl acetal (9) at r.t. in the presence of a catalytic amount of ZnI_2 in dry CH_3CN for 22h to give cis-6 [40% yield, $[\alpha]_D^{20}$ -134.7° (c 0.39, $CHCl_3$)] and trans-6 [15% yield, $[\alpha]_D^{20}$ +19.9° (c 0.096, $CHCl_3$)] accompanied by 5 (10%) and the deoxygenated 10 (11%). It should be noted that cis-6 was obtained preferentially, since most of the naturally occurring β-lactams have cis-substituent at C_5 and C_6 (in the penicillin numbering system). To clarify the preferential formation of cis-6, the mixture (5) was separated by column chromatography on silica gel with ethyl acetate/hexane. The polar isomer, 5a [mp 123-5°C, $[\alpha]_D^{28}$ +66.5° (c 0.87, $CHCl_3$)] was treated with 9 to give cis-6 predominantly (cis:trans=4.2:1), although the less polar isomer, 5b [mp 156-7°C, $[\alpha]_D^{30}$ -114.3° (c 0.41, $CHCl_3$)] gave a 1:1.8 mixture of cis- and trans-6. The relationship between the absolute configuration of the sulfoxides and the stereochemistry at C_5 and C_6 was found to be important and is now currently under investigation.



Scheme II

References

1) (a) D. J. Aberhart, Tetrahedron, 33, 1545 (1977); (b) In "Topics in Antibiotic Chemistry", P. G. Sammes, Ed.; Ellis Horwood Limited; England, 1980; Vol. 4, pp 13-21.
2) S. W. Queener, N. Neuss, In "Chemistry and Biology of β-lactam Antibiotics", R. B. Morin, M. Gorman Eds.; Academic Press; New York, 1982; Vol. 3, pp 2-81.
3) J. E. Baldwin, R. M. Adlington, M. J. C. Crabbe, T. Nomoto, C. J. Schofield, Tetrahedron, 43, 4217 (1987) and references cited therein.
4) References 2, pp 19.
5) S. Wolfe, R. N. Bassett, S. M. Caldwell, F. I. Wasson, J. Am. Chem. Soc., 91, 7205 (1969).
6) R. D. G. Cooper, J. Am. Chem. Soc., 94, 1018 (1972).
7) E. P. Abraham, In "Recent Advances in the Chemistry of β-lactam Antibiotics", J. Elks, Ed., Chemical Society Special Publication No. 28, 1977, pp 1.
8) J. E. Baldwin, R. M. Adlington, N. G. Robinson, H. -H. Ting, J. Chem. Soc., Chem. Commun., 1986, 409.
9) J. E. Baldwin, In "Selectivity-a Goal for Synthetic Efficiency", W. Bartmann, B. M. Trost Eds.; Verlag Chemie GmbH, Weinheim, 1984, pp 391-409.
10) T. Kaneko, J. Am. Chem. Soc., 107, 5490 (1985).
11) Y. Kita, O. Tamura, T. Miki, Y. Tamura, Tetrahedron Lett., 28, 6479 (1987) and references cited therein.
12) Y. Kita, S. Akai, N. Ajimura, M. Yoshigi, T. Tsugoshi, H. Yasuda, Y. Tamura, J. Org. Chem., 51, 4150 (1986).

(Received in Japan 15 November 1988)