Tetrahedron Letters,Vol.26,No.37,pp 4521-4522,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

CYCLIZATION REACTION OF N-PROPARGYL EPOXYAMIDE TO ACETYLENIC 2-AZETIDINONE, A PRECURSOR TO THIENAMYCIN AND RELATED CARBAPENEMS

Hiroshi Maruyama,*[a] Masao Shiozaki, Sadao Oida and Tetsuo Hiraoka

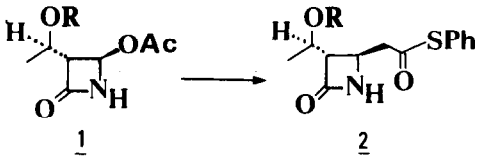
Process Development Laboratories[a] and Chemical Research Laboratories,
Sankyo Co., Ltd., Hiromachi, Shinagawaku, Tokyo, 140, Japan

Summary: Base treatment of N-propargyl epoxyamide 5 afforded the acetylenic 3-(hydroxyethyl)-2-azetidinone 9a, which was subsequently transformed to phenyl thiolester 2, a versatile intermediate for the carbapenem synthesis.

We have recently reported the stereocontrolled synthesis of the (3S,4R)-[(R)-1-hydroxyethyl]-2-azetidinone 1 and related β-lactam compounds starting from L-threonine.[1] Meanwhile, the phenyl thiolester easily derived from 1 has been shown to be a versatile and useful intermediate for the synthesis of (5R, 6S, 8R)-carbapenems.[2] In this paper we report a new short-step synthesis of the phenyl thiolester 2 in the stereocontolled manner which involves, as a key step, a cyclization reaction of phenylthiopropargyl epoxyamide 8 to acetylenic azetidinone 9a. The phenylthiopropargyl epoxyamide 8 was obtained from L-threonine as follows. Phenylthiopropargyl amine 5, prepared by the reaction of the phenylthiopropargyl chloride 3[3] and p-methoxybenzylamine 4 [triethylamine, tetrahydrofurane (THF)] in 64% yield, was condensed with L-threonine-derived (2S,3R)-bromohydroxycarboxylic acid 6[4] (N,N'-dicyclohexylcarbodiimide, CH_2Cl_2) to give the bromohydroxyamide 7 in 86% yield. Dehydrobromination of 7 with lithium hexamethyldisilazide (1.1 equiv) in THF at 0°C provided the requisite epoxyamide 8 in 68% yield.

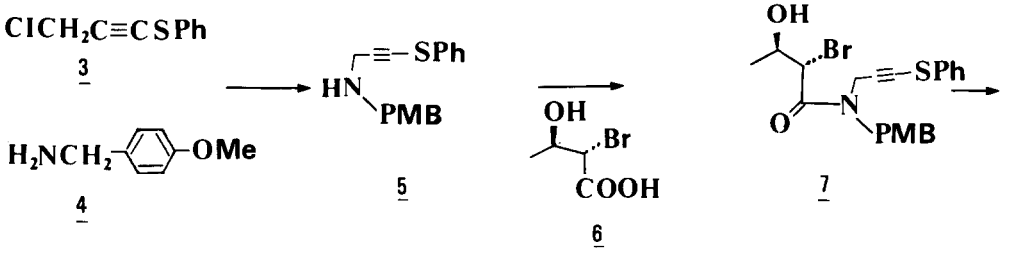
Cyclization of epoxyamide 8 was carried out by treatment with lithium hexamethyldisilazide (1.5 equiv) in THF at 0°C for 5 min to afford a single product, (3S,4S)-1-(p-methoxybenzyl)-3-[(R)-1-hydroxyethyl]-4-phenylthioethynyl-2-azetidinone 9a, in 51% yield; IR ν_{max}^{liquid} cm^{-1} : 3200, 2150, 1760 ; NMR ($CDCl_3$) δ ppm : 1.28 (3H, d, J=6.5 Hz), 3.35 (1H, dd, J=4.5, 3 Hz), 3.75 (3H, s), 4.10 and 4.67 (1H each, ABq, J=15 Hz), 4.25 (1H, m), 4.33 (1H, d, J=3 Hz), 6.80 (2H, d, J=9 Hz), 7.19 (2H, d, J=9 Hz), 7.28 (5H, m). There was no formation of the undesired 3,4-cis azetidinone isomer. In this reaction, the inversion of the configuration at the epoxy ring carbon occurred to form the desired 3α-substituted azetidinones.[1] Hydration of the acetylenic bond was effected after the hydroxy group of 9a was protected with p-nitrobenzyloxycarbonyl (as in 9b) or the t-butyldimethylsilyl (as in 9c). Treatment of 9b

or 9c with trifluoroacetic acid [5] (4 equiv, CH_2Cl_2, rt, 30 min) followed by hydrolysis with moist ethyl acetate gave the phenyl thiolester 10a (32%) and 10b (46%). Removal of the N-p-methoxybenzyl group of 10a and 10b with ceric ammonium nitrate furnished the thiolester 2a and 2b in 70 and 66% yield, respectively.[6] The phenyl thiolester 2a,b could be converted to the variety of thiolesters by the thiolester exchange reaction,[2] whose efficient transformation to carbapenems via an intramolecular Wittig reaction of trialkoxyphosphoran-thiolester has been described.[7] Improvement of this reaction is now under investigation.



1 2

PMB = p-methoxybenzyl
PNZ = p-nitorobenzyloxycarbonyl
TBDMS = t-butyldimethylsilyl



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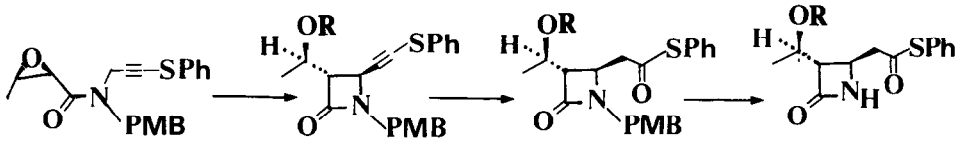

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9a : R=H
b : R=PNZ
c : R=TBDMS

10a : R=PNZ
b : R=TBDMS

2a : R=PNZ
b : R=TBDMS

Acknowlegement. We wish to thank Mr. J. Nakazawa, Mr. N. Ishida, Miss N. Fujino and Mr. H. Masuko for valuable discussion and assistance.

REFERANCES AND NOTE

1. M. Shiozaki, N. Ishida, T. Hiraoka and H. Maruyama, Tetrahedron, 40, 1795 (1984).
2. H. Maruyama, M. Shiozaki and T. Hiraoka, submitted to Bull. Chem. Soc. Jpn.
3. Phenylthiopropargyl chloride 3 was prepared from propargyl chloride and phenylsulfenyl chloride using n-butyllithium as base.
4. Y. Shimohigashi, M. Waki, and N. Izumiya, Bull. Chem. Soc. Jpn., 52, 949 (1979).
5. T. Hiraoka et al., manuscript in preparation.
6. (a) T. Fukuyama, R.K. Frank and C.F. Jewell, Jr., J. Am. Chem. Soc., 102, 2122 (1980) ; D.R. Kronenthal, C.Y. Han and M.K. Taylor, J. Org. Chem., 47, 2765 (1982).
7. A. Yoshida, Y. Tajima, N. Takeda and S. Oida, Tetrahedron Lett., 25, 2793 (1984).

(Received in Japan 20 June 1985)