ORGANIC LETTERS

2000
Vol. 2, No. 18
2889−2892

Stereoselective Reduction of α-Bromopenicillanates by Tributylphosphine

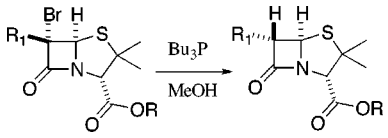
Akihiro Ishiwata, Lakshmi P. Kotra, Kazuyuki Miyashita, Tsuyoshi Nagase, and Shahriar Mobashery*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

som@mobashery.chem.wayne.edu

Received July 12, 2000

ABSTRACT

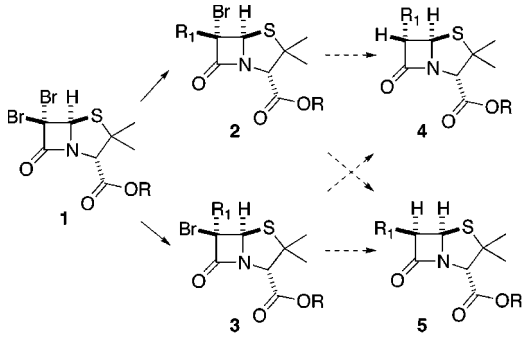


Diastereoselective reduction of 6-bromo-6-substituted penicillanate esters has been achieved by treatment with tributylphosphine to give 6-substituted penicillanate esters. This reaction would appear to proceed through a phosphonium β-lactam enolate species, followed by a diastereoselective protonation. This method has the advantage of being simple to carry out and it is mild, gives high diastereoselectivity, and should tolerate a number of functional groups in the substrates. Implications of these observations are discussed.

We have described recently the use of 6α-hydroxyalkylpenicillanates as effective mechanism-based inhibitors for class A β-lactamases, the most common bacterial resistance enzymes for β-lactam antibiotics.[1−4] These molecules acylate the active site serine of these drug resistance enzymes readily, and the 6α-hydroxyalkyl moiety of the acyl−enzyme species becomes poised to prevent the travel of the hydrolytic water to the ester carbonyl, resulting in a considerable longevity to the species, which accounts for enzyme inhibition. Furthermore, carbapenem antibiotics possess the 6α-1*R*-hydroxyethyl moiety, which renders them resistant to the action of β-lactamases.[5] Recent findings indicate that the pocket where the hydrolytic water fits in the active sites of class A β-lactamases has undergone some evolutionary restructuring to give rise to a novel group of these enzymes which are capable of turning over the carbapenem antibiotics.[3,6,7] Therefore, there is considerable interest in 6α-hydroxyalkylpenicillanates, and we are currently in the process of investigating the properties of a series of these inhibitors with different 6α-hydroxyalkyl groups in inhibition of β-lactamases.

α,α-Dibromopenicillanate ester **1**[1,8] is conveniently converted to derivatives **2** and **3**.[1,9] A good approach for syntheses of 6-substituted penicillanates is reduction of α-bromo-β-lactams (Scheme 1). This type of reductive

Scheme 1

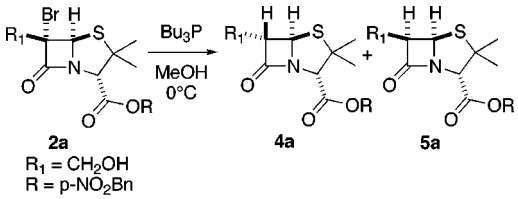


(1) Miyashita, K.; Massova, I.; Taibi, P.; Mobashery, S. *J. Am. Chem. Soc.* **1995**, *117*, 11055−11059.
(2) Maveyraud, L.; Massova, I.; Birck, C.; Miyashita, K.; Samama, J. P.; Mobashery, S. *J. Am. Chem. Soc.* **1996**, *118*, 7435−7440.
(3) Mourey, L.; Miyashita, K.; Swarén, P.; Bulychev, A.; Samama, J. P.; Mobashery, S. *J. Am. Chem. Soc.* **1998**, *120*, 9383−9385.
(4) Golemi, D.; Maveyraud, L.; Vakulenko, S.; Tranier, S.; Ishiwata, A.; Kotra, L. P.; Samama, J. P.; Mobashery, S. *J. Am. Chem. Soc.* **2000**, *122*, 6132−6133.
(5) Hashizume, T.; Yamaguchi, A.; Hirata, T.; Sawai, T. *Antimicrob. Agents Chemother*. **1984**, *25*, 149. Kropp, H.; Gerckens, L.; Sundelof, J. G.; Kahan, F. M. *Rev. Inf. Dis.* **1985**, *7*, Suppl 3, S389.

10.1021/ol000185e CCC: $19.00
Published on Web 08/17/2000

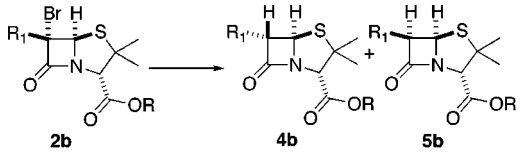
chemistry may be achieved by the use of tributytin hydride,[10] zinc-mediated reduction,[9,11] or hydrogenolysis over Pd−C.[12] These reactions afford the desired products; however, they go through relatively harsh conditions, often give poor yields, and suffer from low stereoselectivity. In the present report we disclose a convenient and stereoselective reduction of α-bromo-6-hydroxyalkylpenicillanates by tributylphosphine, a reaction that affords the corresponding debrominated *β*-lactams in good yields. We provide mechanistic insight into the stereoselectivity that is found in this reaction.

Reduction of α-bromocarbonyl compounds with triphenylphosphine in a protic solvent, such as methanol, is a useful and convenient reaction.[13] Chern and co-workers have reported that in the case of either benzyl or allyl α-bromopenicillanate reduction with tributylphosphine in methanol gave the corresponding penicillanate esters without loss of the ester moiety.[14] Our previous investigation of the reduction of 6α-bromo-6*β*-(hydroxylmethyl)penicillanate (**2a**) with tributylphosphine in methanol[1] suggested that this reaction would provide the desired *β*-lactam derivatives under mild conditions. The use of tributylphosphine in methanol resulted predominantly in the stereoselective formation of 6α-(hydroxylmethyl)penicillanate (**4a**), with inversion of stereochemistry.

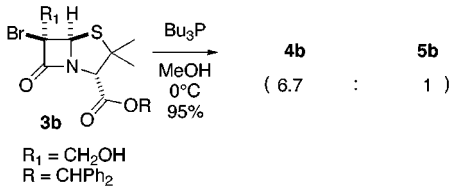


We have investigated the scope of this reaction further (Scheme 2). The reaction of **2b** with tributylphosphine in methanol gave the corresponding 6α-substituted penicillanate ester (**4b**) predominantly (0 °C for 30 min).[15] However, the use of triphenylphosphine, even at room temperature for 6 h, gave no reaction. A likely explanation here is that tributylphosphine is a more nucleophilic reagent than triphenylphosphine, since the model for the reactive intermediate (vide infra) does not implicate sterics as a likely reason for this large difference. The reaction with tributylphosphine was then carried out in 2-propanol and in *tert*-butyl alcohol (Scheme 2). In contrast to the case in methanol, the reaction of **2b** with tributylphosphine in 2-propanol gave a predominance of ester **5b** over **4b** (2.3:1). Treatment in a bulkier solvent, *tert*-butyl alcohol, improved the ratio of **5b** over **4b** (3.9:1). However, as stereoselectivity improved in favor of **5b** as the size of the alcohol increased from 2-propanol to *tert*-butyl alcohol, the yield suffered. The reaction in *tert*-butyl alcohol did not go to completion. It is interesting to note that treatment of the epimeric 6*β*-bromo-6α-(hydroxylmethyl)penicillanate ester **3b** with tributylphosphine in methanol gave the 6α-substituted penicillanate ester in nearly the same ratio of isomers as that for the reaction with 6α-bromopenicillanate (Scheme 2). The reduction of **3b** took place with retention of stereochemistry, which was opposite to the case of the reduction of **2b** in methanol.

Scheme 2



Run	Reagent	solvent	Yield / %	ratio (**4b** : **5b**)
1	Bu_3P	MeOH	93	(5.9 : 1)
2	Ph_3P	MeOH	0	——
3	Bu_3P	*i*-PrOH	69	(1 : 2.3)
4	Bu_3P	*t*-BuOH	26	(1 : 3.9)



The results of the reaction of tributylphosphine in methanol with a number of 6-bromopenicillanate ester derivatives are summarized in Table 1. In all cases, the α-substituted

(6) Rasmussen, B. A.; Bush, K. *Antimicrob. Agents Chemother.* **1997**, *41*, 223−232.

(7) Bush, K.; Mobashery, S. How *β*-Lactamases Have Driven Pharmaceutical Drug Discovery: from Mechanistic Knowledge to Clinical Circumvention. In *Resolving the Antibiotic Paradox: Progress in Understanding Drug Resistance and Development of New Antibiotics*; Rosen, B. P., Mobashery, S., Eds.; Plenum Press: New York, 1998; pp 71−98.

(8) (a) Clayton, J. P. *J. Chem. Soc. C* **1969**, 2123−2127. (b) Sacripante, G.; Just, G. *J. Org. Chem.* **1987**, *52*, 3659−3661.

(9) For examples, see: (a) Yoshida, A.; Hayashi, T.; Takeda, N.; Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1981**, *10*, 2899−2909. (b) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilening, R. R.; Wildonger, K. J.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2505−2513. (c) Fujimoto, K.; Iwano, Y.; Hirai, K.; Sugawara, S. *Chem. Pharm. Bull.* **1986**, *34*, 999−1014.

(10) For examples, see: (a) Ziegler, C. B., Jr.; Fields, T. L. *Tetrahedron* **1993**, *49*, 3919−3932. (b) Hanessian, S.; Alpegiani, M. *Tetrahedron* **1989**, *45*, 941−950. (c) Foulds, C. D.; Kosmirak, M.; Sammes, P. G. *J. Chem. Soc., Perkin. Trans. 1* **1985**, 963−968. (d) Hirai, K.; Iwano, Y.; Fujimoto, K. *Tetrahedron Lett.* **1982**, *23*, 4021−4024.

(11) For examples, see: (a) DiNinno, F.; Beattie, T. R.; Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960−2965. (b) Quallich, G. J.; Bordner, J.; Elliott, M. L.; Morrissey, P.; Volkmann, R. A.; Wroblewska-Adams, M. M. *J. Org. Chem.* **1990**, *55*, 367−370. (c) Altamura, M.; Bedeschi, A.; Marchi, M.; Visentin, G.; Francalanci, F. *Heterocycles* **1991**, *32*, 1671−1679.

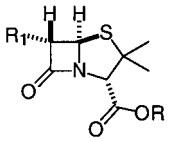
(12) For examples, see: (a) Girijavallabhan, V. M.; Ganguly, A. K.; McCombie, S. W.; Pinto, P.; Rizvi, R. *Tetrahedron Lett.* **1981**, *22*, 3485−3488. (b) Rossi, R. L.; Kapilani, L. V.; Morrissey, P.; Retsema, J. A. *J. Med. Chem.* **1990**, *33*, 291−297.

(13) (a) Borowitz, I. J.; Brossman, L. I. *Tetrahedron Lett.* **1962**, 471−474. (b) Borowitz, I. J.; Virkhaus, R. *J. Am. Chem. Soc.* **1963**, *85*, 2183−2184. (c) Borowitz, I. J.; Kibby, K. C.; Virkhaus, R. *J. Org. Chem.* **1966**, *42*, 4031−4037.

(14) Chern, J.-W.; Huang, M.; Tien J−H.; Pai, S.-H. *Heterocycles* **1988**, *27*, 1349−1351.

(15) **Typical experimental procedure**: Tri-*n*-butylphosphine (95%, 332 μL, 1.27 mmol) was added to a solution of bromide **3b** (386 mg, 0.810 mmol) in methanol (20 mL) at 0 °C, and the reaction mixture was stirred for 30 min. After concentration under reduced pressure, the residual oil was purified by silica gel column chromatography using a gradient solvent system (hexane/ethyl acetate = 10/1 to 5/1 to 1/1 to 1/3) to give a mixture of the two isomers (307 mg, 95%). The ratio was determined by ^{1}H NMR of the crude product (α:*β* = 6.7:1).

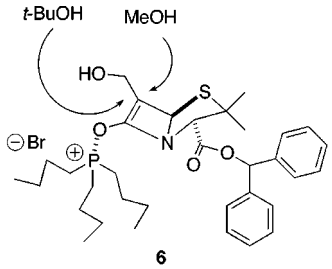
Table 1. Reaction of Tributylphosphine in Methanol with 6-Bromopenicillanate Ester Derivatives



compd	R_1	R	yield/%	ratio (α:β)
4c	(*R*)-$CH_3CH(OH)$	*p*-NO_2Bn	95	(100% α)
4d	(*R*)-$CH_3CH_2CH(OH)$	*p*-NO_2Bn	98	(9.4:1)
4e	$(CH_3)_2C(OH)$	*p*-NO_2Bn	93	(7.0:1)
4a	CH_2OH	*p*-NO_2Bn	95	(7.8:1)
4b	CH_2OH	$CHPh_2$	95	(6.7:1)
4f	$CH_2OTBDMS$	$CHPh_2$	80	(10:1)

penicillanate ester was obtained stereoselectively. In the case of the 6-bromo-6-(1*R*-hydroxyethyl)penicillanate ester, the reaction gave exclusively the α isomer. In addition, protection of the hydroxyl group as a *tert*-butyldimethylsilyl (TBDMS) ether in the side chain at C6 also gave 6α-substituted penicillanate ester predominantly, without cleavage of the TBDMS ether.

These results indicate that the reactions of both 6α- and 6β-bromopenicillanate esters with tributylphosphine must go through the same intermediate. The effect of the size of the alcohol (Scheme 2) suggests that the β-selective protonation should not be an intramolecular process via the hydroxyl groups in the various side chains at C6 but an intermolecular one by an electrophile. Also, the outcome of the reaction with the TBDMS ether at the C6 substituents (to give **4f**), which obviously cannot donate the proton, indicates that the reaction mechanism involves a diastereoselective intermolecular protonation by the solvent. We propose that the key intermediate is the phosphonium β-lactam enolate **6**. It has



6

previously been reported that several types of β-lactam enolates (e.g., lithium, sodium, magnesium, and zinc) can be generated,[9,11,16] and when treated with an electrophile (e.g., carbonyl compounds or proton), the addition occurred predominantly from the β-face. These findings are consistent with our results for the reaction of tributylphosphonium β-lactam enolates in methanol. However, the reason for the diastereoselectivity has not been made clear, although it would appear to be influenced by both electrostatic[17] and steric factors. The favorable electrostatic contribution to the reaction applies in the case of the small electrophile, when it would approach from the more electron rich β-face of enolate. However, when a bulkier electrophile is used, this trajectory for approach is not possible because of considerable steric encumbrance. The computational model for the structure of compound **6** (Figure 1) shows that there is an

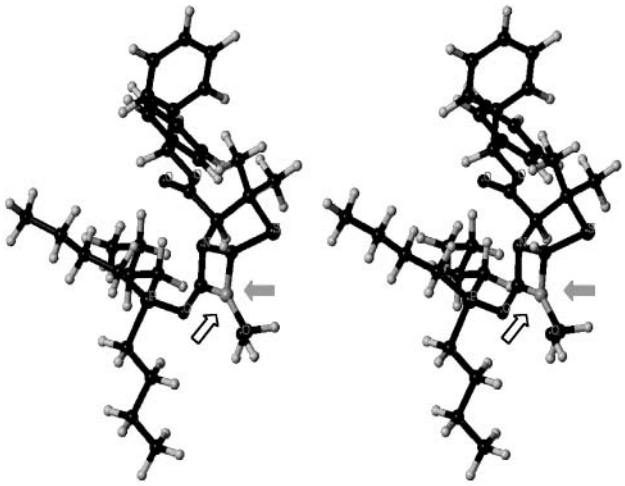


Figure 1. Stereoview of the time-averaged structure from 85 ps of dynamics simulations performed on the energy-minimized species **6**. The gray arrow shows the direction for β-attack at C6 and the white arrow indicates that for α-attack.

increasing steric constraint on the β-face of the compound (indicated by the gray arrow) as the side chain at C6 varies from hydroxymethyl to hydroxyisopropyl. Because of this reason, when the solvent, which also serves as the proton source for the reaction, is changed from methanol to 2-propanol to *tert*-butyl alcohol, the approach of the alcohol from the β-face (for protonation) becomes less favored, giving a diminished yield for the 6α-product. As shown in the molecular model of compound **6** (Figure 1), the α-face of the molecule (indicated by a white arrow) is also sterically hindered, although to a lesser extent than the corresponding β-face (due to the bulk at the C6 substituent). Hence, the approach of a bulky proton donor such as *tert*-butyl alcohol from either the α- or β-face of **6** will be difficult, but less so in the former case. This effect translates into a low yield for the reaction with bulkier proton donors but gives considerably greater selectivity for the formation of the 6β-hydroxyalkylated penicillanate product.

We have shown in this Letter that the tributylphosphine-mediated reduction of 6-bromo-6-substituted penicillanate esters gives diastereoselectivity that can be controlled to give the predominance of one isomer over the other on the basis

(16) For examples, see: (a) Durst, T.; LeBelle, M. J. *Can. J. Chem.* **1972**, *50*, 3196−3201. (b) Kuhlein, K.; Jensen, H. *Liebigs Ann. Chem.* **1974**, 369−402. (c) Durst, T.; Van Den Elzen, R.; Legault, R. *Can. J. Chem.* **1974**, *52*, 3206−3208. (d) Mukerjee, A. K.; Singh, A. K. *Synthesis* **1975**, 547−589.

(17) Karn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663.

of the reaction conditions. This reduction is excellent for the preparation of 6α-substituted penicillanate esters from 6α-bromopenicillanates. The likely intermediate for this reaction is the tributylphosphonium β-lactam enolate, which is readily protonated from the β-face. The protonation occurs from this face mainly because of the electrostatic interaction between the intermediate and proton donor, a process that is influenced by the size of the latter. This method has the advantage of being simple to carry out and it is mild, gives high diastereoselectivity, and should tolerate a number of functional groups in the substrates. We have also provided a mechanistic and structural rationale for the outcome of the reactions. This reaction and the principles delineated herein for its diastereoselectivity should find applications in other systems in the immediate future.

Acknowledgment. This research was supported by the National Institutes of Health.

Supporting Information Available: Experimental procedures, characterization of compounds **2b**, **3b**, **2d**, **3f**, **4b**, **5b**, **4d**, and **4f**, and computational protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000185E