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FROM PENICILLIN TO PENEM AND CARBAPENEM. II[1)]
SYNTHESIS OF 3,4-DISUBSTITUTED AZETIDINONE DERIVATIVES FROM 6,6-BIS(PHENYLSELENYL)PENICILLANATE

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Summary 6,6-Bis(phenylselenyl)penicillanate 2a was converted into 6-1'-(R)-hydroxyethyl substituted penicillanate 5 in high yield. Compound 5 was deselenylated to 10. Oxidation, and then the basic epimerization of the cis sulfone 11 gave trans sulfone derivative 12. The trans sulfone 12 was degraded to the monocyclic β-lactams 14, 15 which are important precursors for the carbapenem syrthesis.

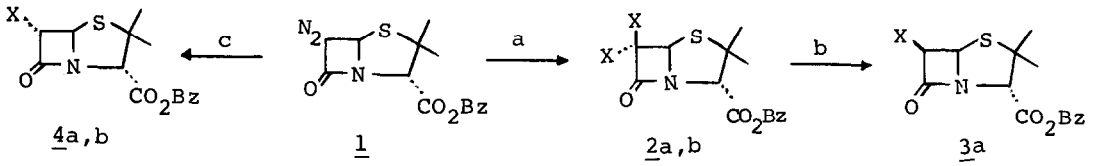
After the discovery of thienamycin the intense study about the synthesis and the structure-activity relationship of this and the related compounds revealed that a part of their potent antibacterial properties is concerned with the presence of the 1'-(R)-hydroxyethyl substituent in the 6-position of the molecule[2)].

Our interest in the synthesis of the so-called carbapenem derivatives from penicillin prompted us to elaborate the method for the synthesis of the monocyclic β-lactam such as 15 which has the (R)-hydroxyethyl group and the suitable leaving group at 3 and 4 positions in the azetidinone molecule.

During the course of our study of the degradation of the penicillin molecule we have already reported the efficient method for the construction of such a molecule like 15 (X=OAc)[1)], but our continuing interest in developing new method prompted us to seek another road to the compound of the general formula depicted 15 utilizing benzyl 6,6-bis(phenylselenyl)penicillanate 2a.

The starting materials 2a, 3a and 4a which have phenylseleno substituents were prepared from the known diazo compound 1[3)] by the reported method[4)] as shown in scheme 1. 2a NMR ($CDCl_3$) δ 1.31 (Me,s) and 1.70 (Me,s). 3a δ : 1.40 (Me,s) and 1.70 (Me,s). 4a δ 1.33 (Me,s) and 1.57 (Me,s).

The corresponding phenylthio derivatives 2b, 4b were prepared analogously, but the 6α-phenylthio derivative corresponded to 3b could not be obtained by the procedure b in scheme 1. 2b, mp 100-103°C, 4b, mp 84-86°C.



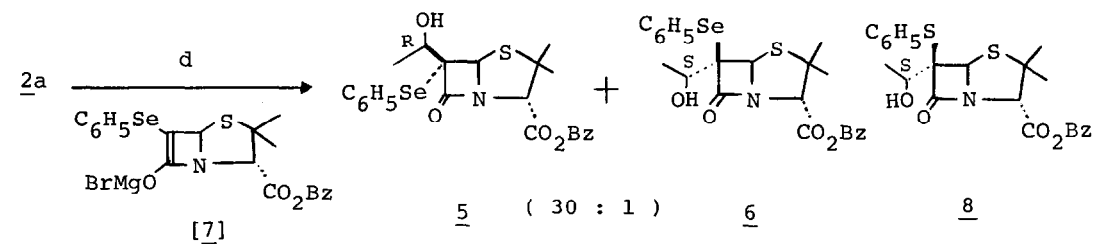
4a,b 1 2a,b 3a

a : X = C_6H_5Se b : X = C_6H_5S

a, $(C_6H_5Se)_2$ or $(C_6H_5S)_2$-BF_3etherate/CH_2Cl_2 ; b, $^nBu_3SnH$-AIBN/THF ;
c, C_6H_5SeH or C_6H_5SH-BF_3etherate/CH_2Cl_2 Scheme 1

It is well known that the selenoacetal generates carbanion by releasing one of the seleno part as a cation on base treatment, but this is not the case in the thioacetal[5]. So at first 2a was treated with MeMgBr in THF, and then was reacted with excess of acetcaldehyde to yield 5 (oily) and 6 (mp 195°C) in 78 % isolated yield in a ratio of 30 : 1. When n-BuLi was used instead of MeMgBr the ratio changed to 2 : 3[6]. The NMR signals of the dimethyl group in 5 appeared at δ 1.28 and 1.55, and in the case of 6 they appeared at δ 1.45 and 1.78. These data strongly suggested that compound 5 has α-orientated phenylseleno group at C-6 (4a type) and 6 has β-orientated phenylseleno group (3a type) and furthermore the structure were confirmed by the comparison of a standard sample (vide infra). By treating with n-BuLi and CH_3CHO 4a gave 5 and 6 in a ratio of 1 : 2[6], but 3a did not give any of 5 or 6, but gave phenylselenol (hence diphenyl diselenide). These results show cleanly that the enolate [7] is involved in this aldol condensation.

In the case of bis(phenylthio) derivative 2b no products corresponded to 5 or 6 were formed as anticipated, but the reaction of 4b with n-BuLi and CH_3CHO gave the 1'-(S)-hydroxylated product 8 as crystal, mp 179°C.

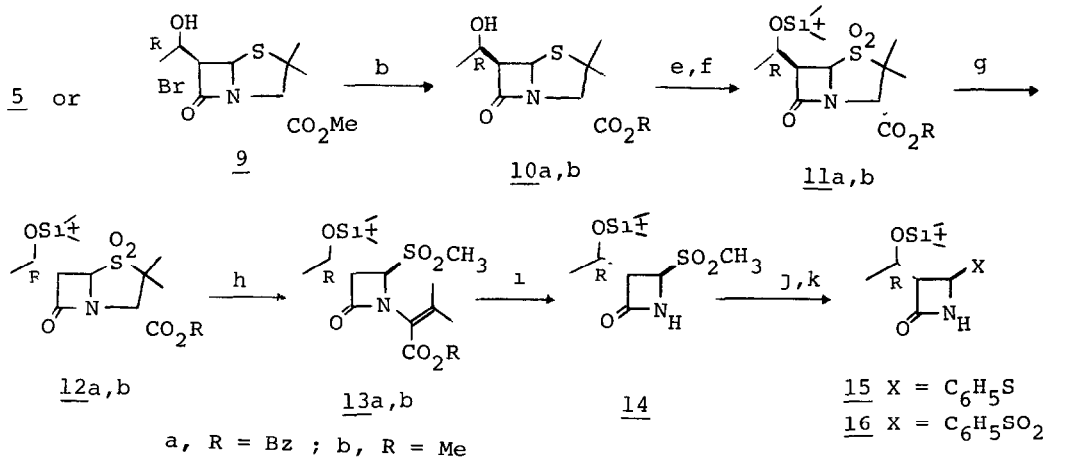


2a [7] 5 (30 : 1) 6 8

d, MeMgBr, -60°C CH_3CHO

Scheme 2

Now the desired product 5 in hand new convertion method from 5 into 3,4-trans disubstituted azetidinone derivative was strongly elaborated. By tin hydride reduction the phenylselenyl part in 5 was removed to give 6β-1'-(R)-hydroxyethylated product 10a in 95 % isolated yield[7]. The coupling constant between the protons on the β-lactam ring is 4.4 Hz and the structure was confirmed as 10a by the comparison of the authentic sample prepared from the known benzyl 6α-bromo,6β-1'-(R)-hydroxyethyl penicillanate[1] by the tin hydride reduction. After the protection of the hydroxy group the product was oxidized with 2.5 eq. of m-Cl perbenzoic acid to afford the cis sulfone derivative 11a, mp 118°C. NMR ($CDCl_3$) δ 0.1 (3H,s), 0.15 (3H,s), 0.91 (9H,s), 1.26 (3H,s), 1.52 (3H,s), 1.28 (3H,d, J=7 Hz), 3.80 (1H, dd, J= 10 and 5.5 Hz), 4.46 (1H,s), 4.59 (1H,d, J=5.5 Hz), 4.85 (1H, m), 5.20 (2H, br.s), 7.40 (5H,s). IR (Nujol) ν cm^{-1} 1810, 1750. The crucial step for the isomerization of cis (11a) to trans (12a) was satisfactorily achieved by adding a catalytic amount of DBN to a solution of 11a in CH_2Cl_2 at r.t.. The isomerization occured within 30 min to yield the trans product 12a, NMR ($CDCl_3$) δ 0.1 (6H,s), 0.91 (9H,s), 1.26 (3H,d, J=7 Hz), 1.31 (3H,s), 1.55 (3H,s), 3.66 (1H,dd, J=3.8 and 2.0 Hz), 4.2-4.55 (1H,m), 4.39 (1H,s), 4.61 (1H,d, J=2 Hz), 5.22 (2H,s), 7.42 (5H,s). The ring opening of the trans sulfone 12a was smoothly achieved by excess CH_3I and KO^tBu (2.5 eq.) in THF · DMF (1 2) to yield the monocyclic β-lactam 13a. In this ring opening reaction NaH was not effective. The N-substituent in 13a was oxidatively removed by $KMnO_4$ or ozonolysis to give the desired monocyclic β-lactam 14, mp



Scheme 3

100°C, $[\alpha]_D^{20}$ -12.8 (c=1, $CHCl_3$), NMR ($CDCl_3$) δ : 0.09 (6H,s), 0.88 (9H,s), 1.28 (3H,d, J=6 Hz), 2.94 (3H,s), 3.54 (1H, t, J=2 Hz), 4.1-4.5 (1H, m), 4.7 (1H, d, J=2 Hz), 6.95 (NH). IR (Nujol) ν cm^{-1} : 3350, 1795, 1780, 1737. The sequence of the reactions in scheme 3 was successfully applicable to methyl 6α-bromo-6β-1'-(R)-hydroxyethyl penicillanate 9[1] to afford the same monocyclic β-lactam 14. The methylsulfonyl part in 14 was transformed into phenylthio derivative 15, which was oxidized to the phenylsulfone derivative 16 by the reported procedure[8].

The utility of the monocyclic β-lactams, 14 and 16 as versatile starting materials for the synthesis of the carbapenem derivative will be described in the following communication.

REFERENCES AND FOOTNOTE

1) Part I, K. Hirai, Y. Iwano, and K. Fujimoto, Heterocycles 17 201 (1982).
2) W.J. Leanza, K.J. Wildonger, J. Hannah, D.H. Shih, R.W. Ratcliffe, L. Barash, E. Walton, R.A. Firestone, G.F. Patel, F.M. Kahan, J.S. Kahan, and B.G. Christensen, "Recent Advances in the Chemistry of β-lactam Antibiotics" second international symposium (1980, London). Abst. Paper p. 240.
3) J.C. Sheehan, Y.S. Lo, J. Lölinger, and C.C. Podewell, J. Org. Chem. 39 1444 (1974).
4) P.J. Giddings, D.I. John, and E.J. Thomas, Tetrahedron Lett. 995 (1978). Idem, ibid, 399 (1980).
5) D. Seebach, and N. Peleties, Chem. Ber. 105 511 (1972). P. Bayet, and A. Krief, Angew. Chem. (Int. Ed.) 13 804 (1974).
6) Actually 6α-1'-(R)-hydroxyethylated product corresponded to 6 was obtained in a ratio of 2 (in the case of 2a) and 1 (in the case of 4a) respectively.
7) J.A. Aimetti, E.S. Hamanaka, D.A. Johnson, and M.S. Kellog, Tetrahedron Lett. 4631 (1979).
8) K. Clauβ, D. Grimm, and G. Prossel, Liebig's Ann. Chem. 539 (1974).

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