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FROM PENICILLIN TO PENEM AND CARBAPENEM. VI[1)]

SYNTHESIS OF DETHIATHIENAMYCIN

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Summary : A new C_3-unit substitution reaction at C-4 position of 4-acetoxyazetidinone derivative (1 and 5) by tetraallyltin (2) in the presence of 1/10 eq. of BF_3-ether in methylene chloride is described. From 4-allylazetidinone derivative (3) via ylid intermediate (14) dethiathienamycin (16) was synthesized.

One of the fundamental problems for the synthesis of carbapenem derivative from the azetidinone derivative such as 1, which is easily prepared from penicillin derivative[2)], is how to introduce carbon substituent at the C-4 position of the azetidinone molecule. Along this line several C-C bond formation methods at the C-4 position have been elaborated, and they are divided into the following three categories:

1. Utilization of the organometalic reagents[3)]
2. Utilization of silyl derivatives[4)]
3. Utilization of KCN[5)]

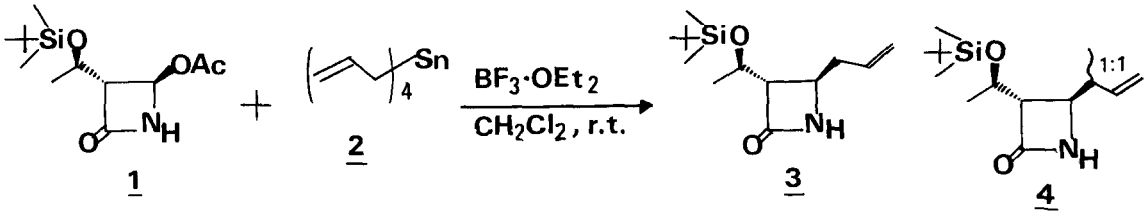
The common intermediate for the above substitution reactions is reasonably considered to be the azetinone (or azetinonium) one.

By the mechanistic speculation and the analogous reactivity of silicon[6)] and tin we took advantage of allyltin-reagent[7)] and succeeded in finding a very mild and convenient method for the introduction of the allyl substituent at the C-4 position of the azetidinone molecule[4)], and applied this to the synthesis of dethiathienamycin (16). The tetraallyl- or tributylallyltin is used in our method as the sourse of the allylic part.

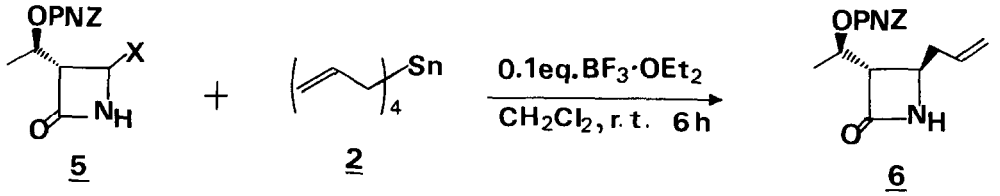
The following procedure is representative.

To a solution of (3R,4R)-4-acetoxy-3-[(R)-1'-(t-butyldimethylsilyloxy)-ethyl] azetidin-2-one (1)(1 g) and 1.46 g of tetraallyltin in 20 ml of methylene chloride was added 0.1 g of BF_3-ether at rt. The whole mixture was stirred overnight at rt. Methylene chloride was added and the solution was washed with water three times and dried over $MgSO_4$. After the evaporation of the solvent the residue was chromatographed on silica gel column to afford 800 mg of

(3S,4R)-4-allyl-3-[(R)-1'-(t-butyldimethylsilyloxy)ethyl]azetidin-2-one (3),mp 70-77°C, Rf = 0.25 (c-Hex.:AcOEt=2:1), which is identical with the authentic sample prepared from the corresponding 4-phenylsulfonyl azetidinone derivative and allylmagnesium chloride under the reported conditions[8]. The same product 3 was also obtained using tributylallyltin under the same conditions.



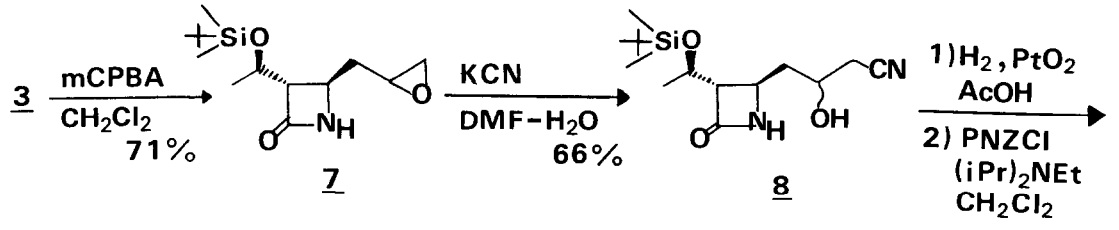
When tributylcrotyltin was used the 4-(1'-methyl)allyl substituted product 4 was obtained as a 1:1 mixture (δ 1.17, 1/2 CH_3, d, J=6 Hz and 1.21, 1/2 CH_3, d, J=6 Hz) in 80 % yield. It is well known that BF_3-ether in chloroform is one of the conditions for the desilylation of the silyl ether[9], so the PNZ (p-nitrobenzyloxycarbonyl) protected azetidinone derivatives 5 which are stable to the above conditions were subjected to the same reaction, and the progress of the reaction was monitored on silica gel TLC (UV detected). It was proved that regardless of the configurations of the C-4 acyloxy groups the reaction was completed in 6 hr and the same allyl substituted azetidinone product 6 was obtained in 93 % isolated yield. The Lewis acid catalysts such as $TiCl_4$ or $SnCl_4$ were also effective, but 1/10 eq. BF_3-ether was most practical, and the reaction proceeded very cleanly.

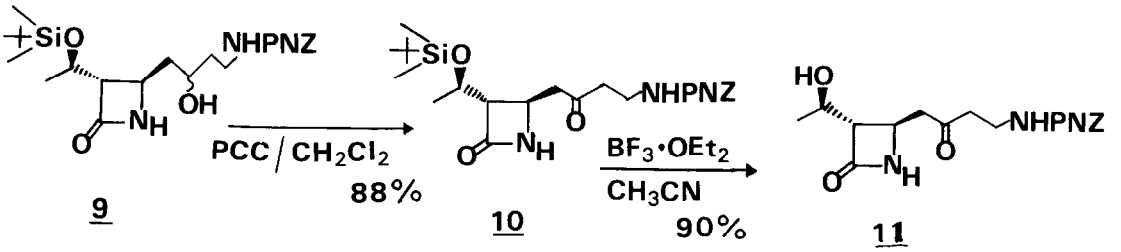


X = α-AcO , β-AcO OR α-PhCO (O) Isolated Yield 93 %

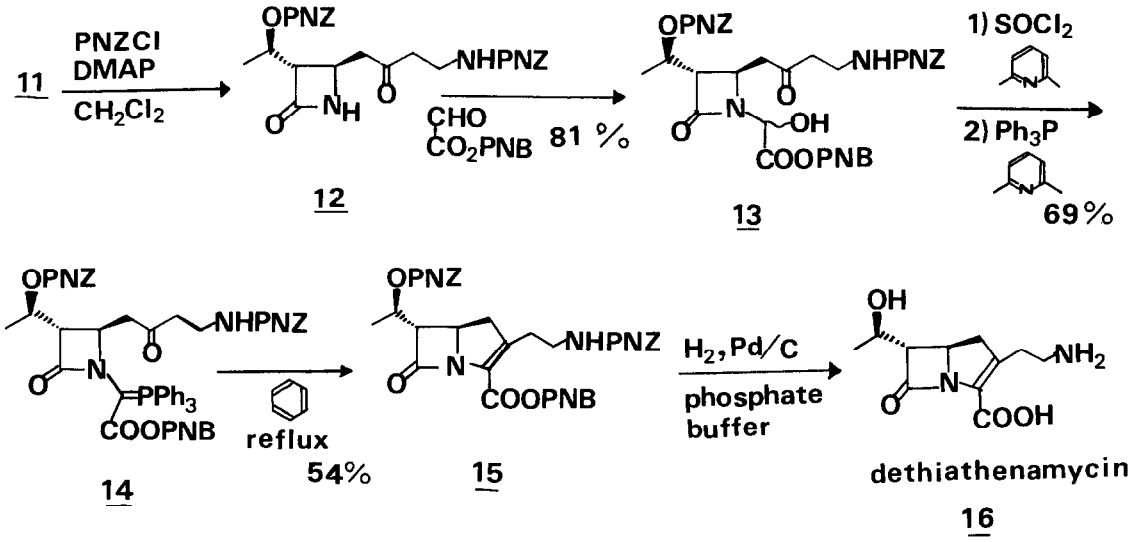
At this stage from the interest to know the antibacterial activity we turned our attention to the synthesis of dethiathienamycin 16 in which the sulfur atom is missing from the thienamycin molecule. The allyl substituted derivative 3 was oxidized with mCPBA in methylene chloride to the epoxides 7 as a mixture of two diastereomers, one of which crystallized : mp 83.5°C $[\alpha]_D^{24}$ -18° (c=1, $CHCl_3$). The oxirane ring was opened regiospecifically to the cyanoalcohol derivatives 8, one of the diastereomers crystallized, mp 120-125°C IR(Nujol) ν: 3330, 2240, 1700 cm^{-1}, by KCN in DMF:H_2O (3:1) at rt for 15 hr. The cyano group was then hydrogenated to the amino group using PtO_2 in AcOH conditions, and the successive protection of the amino group by PNZCl gave the compound 9 in 50 % yield. The hydroxy group in 9 was effectively oxidized to the ketonic compound 10 with PCC in methylene chloride. The desilylation condi-

tions, BF_3-ether in CH_3CN[4b] were effectively applied to the compound 10 to give the hydroxyethyl compound 11, mp 115-116°, IR (KBr) ν: 3340, 1755, 1700, 1680cm^{-1}, NMR (CD_3COCD_3) δ: 1.18(3H, d, J=6.2 Hz), 2.5-3.0 (4H), 3.1-3.6 (2H), 3.6-4.2 (3H), 5.14 (2H, s), 7.3-8.4 (4H, A_2B_2). The hydroxy group in 11 was reprotected by PNZ group using PNZCl-DMAP in methylene chloride in 70 % isolated yield. The aminal formation reaction between 12 and p-nitrobenzyl glyoxylate (water was removed azeotropically before use) was smoothly performed in benzene in the presence of a catalytic amount of triethylamine at 40°C for 5 min to give





the expected compound 13. Chlorination and the ylide formation were performed under the standard conditions[10] to afford the ylid 14. The intramolecular Wittig reaction was successfully applied to the ylid 14 by refluxing in benzene for 5 hr to give the desired carbapenem derivative 15, Rf = 0.2 (CH_2Cl_2: ether = 20 : 1), IR (neat) ν: 3400, 1775, 1745, 1720 cm^{-1}, NMR ($CDCl_3$) δ: 1.46 (3H, d, J=6.2 Hz), 2.5-3.7 (7H), 3.7-4.5 (1H), 4.9-5.4 (8H), 7.1-7.8 (6H), 7.8-8.4 (6H). The final stage of the synthesis ; the deprotection of the PNZ and PNB group of the carbapenem derivative 15, was achieved hydrogenetically by 10 % Pd/C in phosphate buffer (PH 7.0) and the purification of the crude product was performed carefully on HP-20 AG chromatography (water elution) to give the desired dethiathienamycin 16. The antibacterial activity of dethiathienamycin 16 thus obtained was about the half of that of thienamycin.



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