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FROM PENICILLIN TO PENEM AND CARBAPENEM. IV[1] SYNTHESIS OF 2-OXOCARBAPENAM DERIVATIVE

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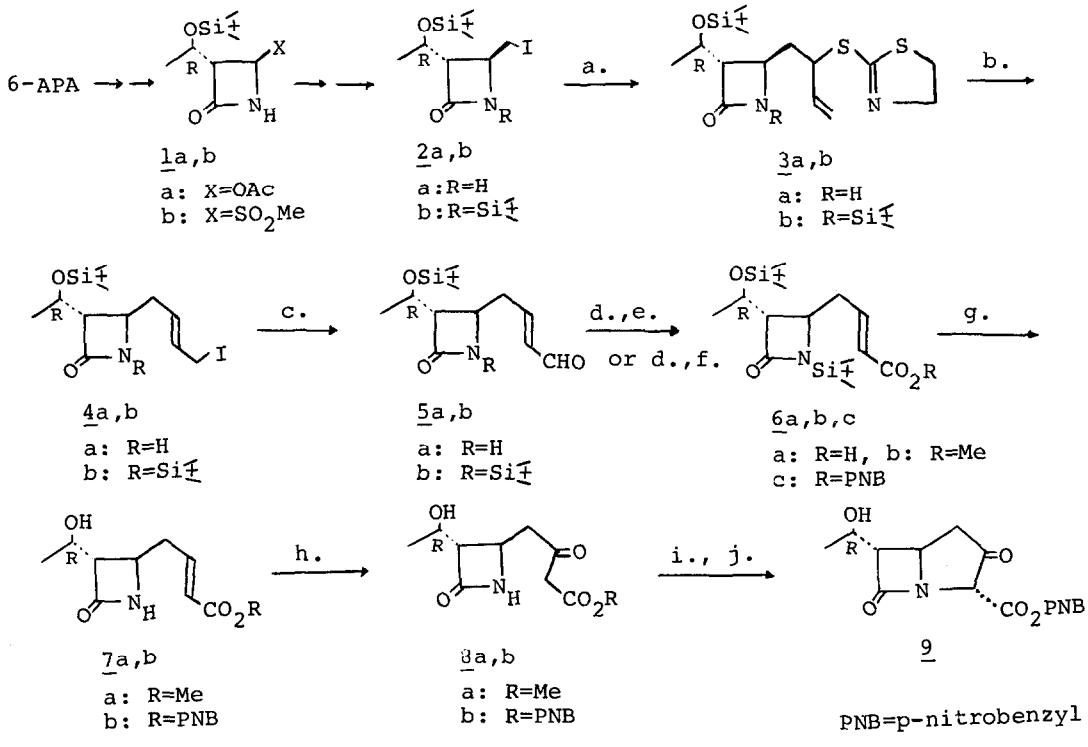
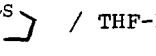
Summary : Previously obtained 4-iodomethylazetidinone derivative (2a) is transformed via the *trans*-iodopropenylation method into the β-keto ester (8), which is thought to be an important precursor for the synthesis of the carbapenem derivatives.

Beside the potent antibacterial and the strong β-lactamase inhibitor activity of the so-called carbapenem compounds (e.g. thienamycin)[2], the unique structural feature of the molecule attracted the chemists to synthesize these compounds from variety of the starting materials[3]. We are also interested in the synthesis of carbapenems from the readily available 6-APA, and have already reported the degradation work of penicillin[4] and C_1-unit introduction at C-4 of azetidinone molecule[1]. In the line of the above work, here we wish to describe the synthesis of 2-oxocarbapenam derivative (9) using our originally developed *trans*-iodopropenylation method.[5]

The iodomethyl azetidinone (2a), prepared by our previously reported procedure[1], was reacted with 3.5 equivalents of lithium salt of allylthiothiazoline in THF (-78°-0°C for 2.5 hr)[5] to afford the desired product(3a) as a diastereomeric mixture (one of which is crystalline, mp 86°C) in 58 % yield. The same reaction was applicable to the N-silylated derivative (2b), mp 70°C (prepared by $ClSiMe_2{}^tBu$/ Et_3N, cat.DMAP in DMF, quantitative yield) in THF-HMPA (5%) solution. The reaction proceeded more cleanly to give the desired product (3b)[6] as a diastereomeric mixture (one of which is crystalline, mp 125°C) in



a.,  / THF-HMPA(5%),-78°-0°; b., excess MeI/DMF ; c., DMSO/ $NaHCO_3$, 130-140°, 3 min.; d., 90% H_2O_2,cat.SeO_2/ ^tBuOH, 50-60°; e., CH_2N_2 ; f., PNBBr, $NaHCO_3$/ DMF ; g., 10% aq.HCl ; h.,Na_2PdCl_4,$^tBuO_2H$/ AcOH-H_2O; i, TsN_3-Et_3N j., $Rh(OAc)_2$/ C_6H_6

72 % yield, and 17 % of 2b was recovered. Next step is rearrangement[7]; each of the azetidinone-thiazoline derivative 3a,b was treated with excess of MeI in DMF in the presence of $CaCO_3$, NaI and Hg(cat.) at 50°C for 5 hr to give the corresponding allylic iodide derivatives 4a and 4b in 75 % and 78 % isolated yields respectively.

The following Kornblum oxidation step was smoothly performed in DMSO at 130°

-140°C (preheated) for 3 minutes in the presence of $NaHCO_3$ to yield the α,β-unsaturated aldehyde 5a (oily, aldehyde H at δ 9.52, d, J=7.5 Hz) and the crystalline 5b (mp71°-73°C) in 69 and 73 % yield respectively. The conversion of the α,β-unsaturated aldehyde 5b to the corresponding carboxylic acid 6a was satisfactorily achieved by the method of Smith and Holm[8] using 90 % H_2O_2 and catalytic amount of SeO_2 in ^tBuOH at 50°-60°C for 1 hr. The crude acid 6a was esterified with diazomethane to give the methyl ester derivative 6b (78 % from the aldehyde 5b), and with p-nitrobenzyl bromide/ $NaHCO_3$ in DMF to give the PNB ester derivative 6c, mp 113°C in 62 % yield from 5b. The desilylation reaction was smoothly effected by adding 10 % aq. HCl to the solution of 6b,c in MeOH-THF for 2 hr at r.t. to give the (R)-hydroxyethyl azetidinones 7a (mp 104°C) and 7b (mp 95°C). Palladium catalyzed oxidation of the ß-position of the α,β-unsaturated ester using Na_2PdCl_4 and ^tBuOOH (Tsuji method)[9] was applicable to both the ester 7a and 7b to afford the ß-keto esters 8a (mp 102°C, soluble in water) and 8b (mp 121°C, $[\alpha]_D^{22}$ +21.3° (c=0.31, $CHCl_3$) in 42 and 54 % yield[9].

The final steps for the formation of the 2-oxocarbapenam derivative (9) were followed to the method of Merck group[10]; the β-keto ester 8b was converted to the α-diazo-β-keto ester (mp 161°C), which was then cyclized to the final 2-oxocarbapenam derivative 9 in high yield. The transformation of 9 to thienamycin and the related compounds were satisfactorily achieved.

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6) Selected Data, 3b (crystalline one): ν(Nujol) 1741, 1570 cm^{-1}; δ($CDCl_3$)0.05 (Me), 0.07(Me), 0.20(Me), 0.25(Me), 0.88(^{t}Bu), 0.95(^{t}Bu), 1.20(Me,d,J=6.5 Hz), 1.7-2.55(2H), 3.03(1H,dd,J=3.5 and 2.5 Hz), 3.32(2H,t,J=7 Hz), 4.15 (2H,t,J=7 Hz), 4.0-4.4(2H), 5.05-6.30(3H, olefinic). 4b: δ($CDCl_3$) 0.07 (Me×2), 0.23(Me×2), 0.89(^{t}Bu), 0.96(^{t}Bu), 1.15(Me,d,J=6 Hz), 2.0-2.65(2H), 2.75(1H,dd,J=5.5 and 2.5 Hz), 3.4-4.3(4H), 5.3-6.2(2H). 5b: ν(Nujol) 1740 1700 cm^{-1} , δ ($CDCl_3$) 0.05(Me×2), 0.07(Me×2), 0.24(Me×2), 0.87(^{t}Bu), 0.96(^{t}Bu), 1.18(Me,d,J=6 Hz), 2.4-2.9(3H), 2.5-2.85(1H), 4.1 (1H, quintet, J=6 Hz), 6.17(1H,dd, J=16 and 8 Hz), 6.76(1H, td, J=6.5 and 16 Hz), 9.51 (1H,d, J=6.5 Hz). 6c: ν(Nujol) 1735, 1665, 1528, 1378 cm^{-1}, δ($CDCl_3$) 0.07 (Me ×2), 0.24(Me×2), 0.86(^{t}Bu), 0.97(^{t}Bu), 1.14(Me,d,J=6.5 Hz), 2.2-2.7 (2H), 2.79(1H,dd,J=5 and 2.5 Hz), 3.5-3.85(1H), 3.9-4.3(1H), 5.20(2H, br s), 5.91 (1H,d,J=16 Hz), 6.9(1H,td,J=7 and 16 Hz), 7.4-8.3 (4H, A_2B_2). 7b: δ($CDCl_3$+D_2O) 1.28(Me,d,J=6 Hz), 2.63(1H,t,J=7 Hz), 2.92(1H,dd, J=5.5 and 2.5 Hz), 3.65-4.1(1H), 4.0-4.45(1H), 5.21(2H,s), 5.95(1H,d,J=16 Hz), 7.0 (1H, td, J=7 and 16 Hz), 7.35-8.35(4H, A_2B_2).

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