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SYNTHESIS OF Δ^1-CARBAPENEM DERIVATIVE BY ALDOL CONDENSATION METHOD

Koichi Hirai*, Katsumi Fujimoto, Yuji Iwano, Tetsuo Hiraoka, Tadashi Hata and Chihiro Tamura

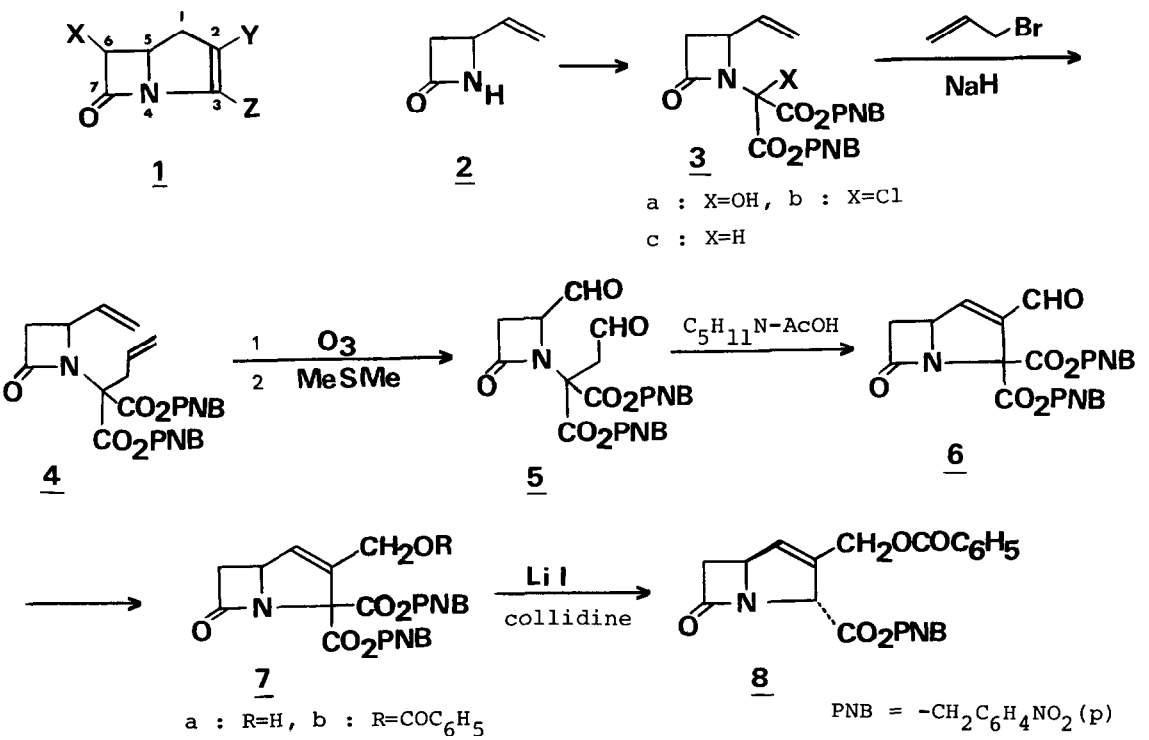
Central Research Laboratories, Sankyo Co., Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan

Summary: The Δ^1-carbapenem derivative(6) was prepared by the aldol condensation of the dialdehydic compound(5) with piperidinium acetate. Careful hydride reduction followed by benzoylation gave 7b, which was successfully decarbalkoxylated to 8. The X-ray structure analysis of 8 showed the C-3 carboxylate group and C-5 H are cis each other.

Current interest for the synthesis of carbapenem derivative(1), which is found in naturally occurring antibiotic thienamycin promoted the synthetic chemists to elaborate the methods for the construction of this unique ring system[1]. Among the reported methods for the construction of the five membered ring attached to the β-lactam ring, the one using intramolecular Wittig type of reaction between C-2 and C-3 to give Δ^2-carbapenem system is widely adapted[2]. In this paper we wish to report a new method of constructing Δ^1-carbapenem system by aldol condensation between C-1 and C-2 positions[3].

Our starting material is the easily accessible 4-vinyl-2-azetidinone(2)[4]. Direct synthesis of diPNB-malonate derivative(3c) under the conditions of phase transfer reported for the synthesis of diethylmalonate derivative[5](3c, Et instead of PNB) failed, but successful path was found in the following steps: condensation with bisPNB-ketomalonate (toluene, reflux, 20 hr) gave the hydroxymalonate derivative(3a), mp 163°(recrystallized from methanol), chlorination of 3a with thionylchloride-pyridine, THF, at -20° gave the

chloromalonate derivative(3b), which was immediately reduced with $P(n\text{-}Bu)_3$ in DMF-H_2O(9:1), K_2HPO_4 to yield the desired diPNB-malonate derivative(3c) in 42 % overall yield[1a]. Rf=0.38 (C_6H_6:AcOEt=4:1)[6], NMR[7] δ: 2.84 (1H, d.d., J=16 and 3 Hz), 3.33 (1H, d.d., J=16 and 5.5 Hz), 4.3-4.7 (1H, m.), 5.29 (1H, s.), 5.1-6.3 (7H), 7.5-8.3 (8H). After treatment of 3c with 1.2 eq. of NaH in DMF-THF (1:1) at r.t. excess allyl bromide was added to the solution to give the allylated product (4), mp 95° in 75 % yield, NMR δ: 2.74 (1H, d.d., J=16 and 3 Hz), 3.26 (1H, d.d., J=16 and 5 Hz), 3.13 (2H, d., J=7 Hz), 4.3-4.7 (1H,m.), 5.39 (4H, s.), 4.9-6.3 (6H), 7.5-8.4(8H). The requisite, labile dialdehydic compound 5 was formed by ozonolysis in CH_2Cl_2 at -20° followed by dimethylsulfide treatment. After removal of the solvent under reduced pressure, the residue was dissolved again in CH_2Cl_2 and then addition of acetic acid and piperidine[8] successively gave the relatively unstable Δ^1-carbapenem derivative(6) in 25 % yield from 4 after preparative TLC purification. The structure of the Δ^1-carbapenem skeleton of 6 was confirmed by the following



physicochemical data. IR $\nu^{liq.}cm^{-1}$: 2850, 1785, 1750, 1695, 1605, 1520, 1348. NMR δ: 3.17 (1H, d.d., J=16 and 3.5 Hz), 3.57 (1H, d.d., J=16 and 6 Hz), 4.7-4.95 (1H, m.), 5.40 (4H, s.), 7.41 (1H, d., J=2 Hz), 7.4-8.4 (8H), 9.99 (1H,s. C<u>H</u>O). The aldehyde group in <u>6</u> was carefully reduced ($LiAl(O^tBu)_3H$, 0°/THF) to the alcohol (<u>7</u>a), which was successively treated benzoyl chloride- NEt_3 to give the benzoyl derivative <u>7</u>b, mp 100-105°, NMR δ: 5.20 (2H,-C<u>H</u>$_2$O). The decarbalkoxylation was smoothly achieved with LiI in collidine at 150° for 20 min. to give the p-nitrobenzyl-2-benzoyloxymethyl-Δ^1-penem-3-carboxylate(<u>8</u>) in 52 % yield. Mp 118° (recrystallized from methanol). IR $\nu^{Nujol}cm^{-1}$: 1768, 1740, 1708, 1610, 1600, 1529. UV $\lambda_{max.}^{EtOH}$ nm: 230.1 (ε 17000), 265.4 (ε 10980). NMR δ: 2.9 (1H, d.d., J=15.5 and 3.0 Hz), 3.4 (1H, d.d., J=15.5 and 5.5 Hz), 4.65 (1H, m.), 5.00 (2H, br. s.), 5.21 (2H, s.), 5.30 (1H), 6.30 (1H), 7.4-8.3 (9H).

It is reasonably assumed that the decarbalkoxylation occurred to yield the more stable product which has the α-orientated carboxylate group (<u>cis</u> to the H at C-5) as depicted in <u>8</u>, but from the NMR it is difficult to say the case unequivocally. Furthermore in connection with the structure-activity relationship our great interest to know how much deviated the pyramidal N in the β-lactam ring from the plane of C-3, C-5 and C-7 prompted us to study the X-ray structure analysis of this compound. The space group is P 2_1/ C, with a = 22.148, b = 7.403, c = 12.288 Å, β = 91.305°, Z = 4. The intensity data for 2480 reflections were collected on a RIGAKU automatic four circle diffractometer using Cu-Kα radiation and the θ-2θ scan technique up to 2θ<128°. The structure was solved by multiple solution techniques and refined to R factor of 5.7 %. A view of the molecule is as shown in Fig.1. The relative stereochemistry of the carboxylate part at C-3 is as expected (α-orientated), and the height of the pyramid formed by C-3, C-5, C-7 and apical N is 0.5 Å. The value is the same as that of thienamycin[9], but the anti-microbial activity of the corresponding carboxylic acid was far less active

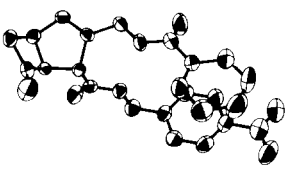


Fig. 1

than thienamycin. The isomerization of the double bond to Δ^2 was unsuccessful.

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