SYNTHESIS OF (6S, 8R)-6-(1'-HYDROXYETHYL)CARBAPENEM, A THIENAMYCIN TYPE

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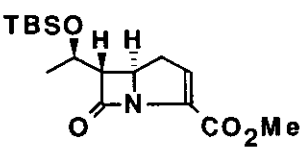
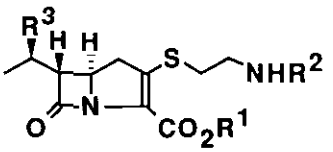
Abstract - Title carbapenem (**1**) having thienamycin-type of side chain at C-6 was synthesized from L-glutamic acid. Chirospecific oxymercuration of 6-vinylcarbapenam (**12a**) successfully induced 8R-hydroxyl.

Carbapenem antibiotic thienamycin (**2**) consists of azabicyclo[3.2.0]heptene ring as a basic skeleton which is assembled from two rings, a β-lactam and a pyrrolidine ring. Its potent and broad antibiotic spectrum as well as chemical lability has attracted numerous microbiological and organochemical interests for the production or the synthesis of thienamycin and its analogues.[1] We reported a synthesis of the PNB ester (**3**) of carbapenem antibiotic PS-5, in which the effective use of L-pyroglutamate was demonstrated.[2] In conjunction with our interest of making effective synthetic chirons from L-pyroglutamate (**4**), we planned to synthesize an appropriately substituted pyrrolidine such as **9** as a synthetic intermediate which could be transformed to a carbapenem. In this communication we wish to describe the synthesis of the carbapenem (**1**) having thienamycin-type of side chain at C-6.



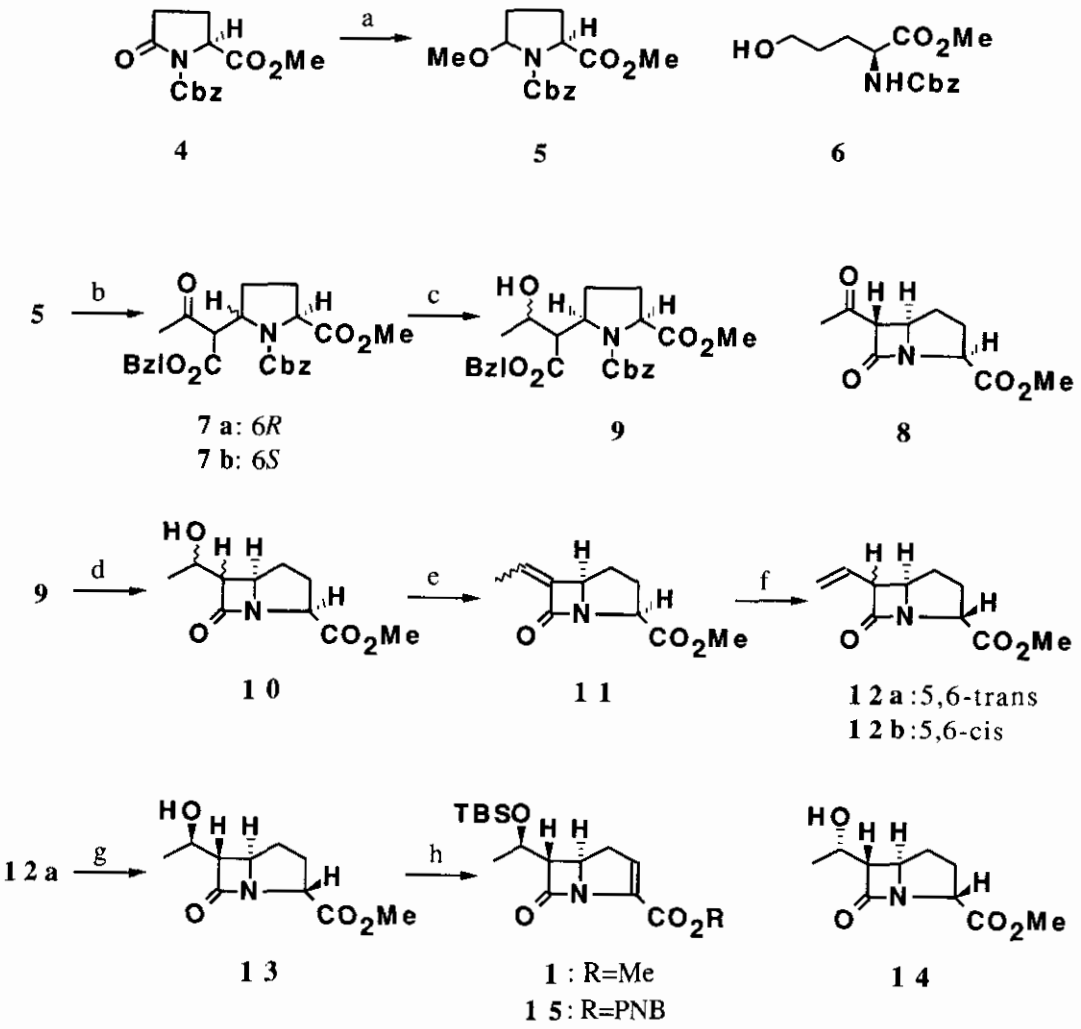
1



2 : R^1=R^2=H, R^3=OH

3 : R^1=PNB, R^2=Ac, R^3=H

Scheme 1



a): $NaBH_4$, MeOH, -30 °C, 0.5 h; HCl/MeOH, 0 °C, 0.5 h. b): $MeCOCH_2CO_2Bzl$, $TiCl_4$, 0 °C, 2 h. c): $NaBH_4$, MeOH, -15 °C, 0.5 h. d): H_2, Pd-C, MeOH, 1 h; DCC, MeCN, room temp., 20 h. e): MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; DBU, room temp., 1 h. f): LDA-HMPA, THF, -78 - -10 °C; aq. NH_4Cl. g): $Hg(OAc)_2$, THF-H_2O (1:1), room temp., 2 h; $NaBH_4$, 0 °C, 10 min. h): TBSCl, MeIm, CH_2Cl_2, room temp., 2 d; $LiN[Si(Me)_3]_2$, THF, -78 °C, 1 h; Ph_2Se_2, 15 min; 30% H_2O_2, pyridine, CH_2Cl_2, 0 °C, 0.5 h.

The N-carbamoyl-L-pyroglutamate (**4**) derived from L-glutamic acid was first reduced regioselectively with sodium borohydride to afford the 5-methoxypyrrolidine (**5**) after a treatment with methanolic hydrogen chloride. Regioselectivity may come from the high reactivity of C-5 carbonyl of the lactam (**4**).[3] The reduction at 0 °C or at higher temperature produced mostly the primary alcohol (**6**). Over reduction was prevented when the reaction was done under lower temperature, at -30 °C, and quenched with methanolic hydrogen chloride.[4] 5-Methoxypyrrolidine (**5**) was condensed with benzyl acetoacetate under Lewis acidic conditions giving 5-substituted prolinate (**7**) in 94% yield.[5] The ratio of the 2,5-cis (**7a**) to the 2,5-trans derivative (**7b**) was 5:1. The keto ester (**7**) was thought to be transformed to the ketocarbapenam (**8**) which could be stereocontrolled at C-6. Because hydrogenolytic deprotection of the benzyl ester of **7** accompanied decarboxylation at the same time, the keto ester (**7a**) was reduced with sodium borohydride to the alcohol (**9**). Protective groups were removed and the resulting β-amino acid was lactamized to the carbapenam (**10**) in moderate yield, 69%. The carbapenam (**10**), however, could not be oxidized to the desired ketocarbapenam (**8**) probably because of steric hindrance around the β-lactam. Stereocontrol at this stage was then suspended. Dehydration of the alcohol (**10**) and stereoselective reintroduction of a hydroxyl into an olefinic side chain in a compound such as the vinylcarbapenam (**12**) was considered to be a promising alternative. Mesylation of **10** and the following basic treatment gave the ethylidene carbapenam (**11**) in 96% yield. In order to obtain an appropriate stereochemistry at C-6 position, stereospecific protonation procedure as described earlier was applied to the ethylidene derivative (**11**) with minor modification.[2] Treatment of **11** with lithium diisopropylamide-hexamethylphosphoramide (LDA-HMPA)[6] at -78 °C and protonation at -10 °C gave 63% yield of the 6-vinylcarbapenam (**12a** and **12b**) in the ratio of 2.6:1. The stereochemistry at C-6 of the carbapenams (**12**) was determined with coupling constant (J) between H-5 and H-6. The trans product (**12a**), $[\alpha]_D^{22}$ +271.3° (c 0.91, $CHCl_3$), showed smaller $J_{5,6}$ of 2.0 Hz in contrast with the cis derivative (**12b**), $J_{5,6}$=7.9 Hz. Oxymercuration of the 5,6-trans-carbapenam (**12a**) at room temperature followed by demercuration with excess sodium borohydride gave two products in the ratio of 9:1. The observed stereocontrol implies a crowded steric environment around the β-lactam of **12a**. The major alcohol (**13**), $[\alpha]_D^{22}$ +160.9° (c 0.77, $CHCl_3$), was given in 79% yield. Because of showing no distinguishable chemical shift or coupling constant in ^1H nmr spectra of both of the alcohols (**13** and **14**), we could not determine the stereochemistries at this stage. Hence the 2-selenylation and deselenoxide process were applied to the major alcohol (**13**) after silylation.[2] The carbapenem (**1**),[7] $[\alpha]_D^{25}$ +64.0° (c 0.025, $CHCl_3$),

thus obtained in 61% yield, showed closely similar hydrogen signal parameters for H-5 through H-9 to those of the carbapenem (**15**).[8] Therefore the carbapenem (**1**) was determined to have 6S,8R-stereochemistry. It may be feasible to convert the carbapenem (**1**) into thienamycin according to a similar procedure as described earlier.[2]

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7. **15**: ν (neat) 1780, 1720, 1610 cm^{-1}. δ ($CDCl_3$, 500 MHz) 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.26 (3H, d, J=5.9 Hz), 2.77 (1H, ddd, J=2.9, 7.8, 19.1), 2.91 (1H, ddd, J=2.9, 10.3, 19.1 Hz), 3.14 (1H, dd, J=2.9, 6.3 Hz), 3.82 (3H, s), 4.21 (1H, dq, J=5.9, 6.3 Hz), 4.23 (1H, ddd, J=2.9, 7.8, 10.3 Hz), 6.45 (1H, t, J=2.9 Hz). m/z (EI) 326.1780 (M^++1, $C_{16}H_{28}NO_4Si$, Δ -0.6 mmu).
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