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A Convenient Synthesis of Carbapenem Antibiotic Ertapenem Sodium

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A convenient synthesis of ertapenem sodium is described. The starting material, *trans*-hydroxyproline, was converted to *N*-diisopropoxyphosphoryl hydroxyproline (**5**), mesylation of the hydroxyl group and activation of the carboxyl group in **5** by using methanesulfonyl chloride afforded intermediate **6**, aminolysis of the mixed anhydride **6** with allyl 3-aminobenzoate gave compound **8**, treatment of the methanesulfonate (**8**) with potassium thioacetate gave key intermediate compound **4**. The compound **4** was deacetylated and then coupled with enol phosphate **2**, followed by cleavage of protecting groups affording ertapenem in an overall yield of 39.2 %.

Keywords: *N*-Diisopropoxyphosphory, Ertapenem, Carbapenem antibiotic, Mesylation, Walden inversion.

INTRODUCTION

Ertapenem **1** (Fig. 1) is a new broad-spectrum carbapenem antibiotic with a unique efficacy profile against the growing number of cephalosporin-resistant bacteria. Due to its improved pharmacokinetic character in comparison with other carbapenems, ertapenem sodium was approved in the United States as treatment of the most serious upper and lower respiratory tract, urinary tract, skin, obstetric and gynecologic infections[1,2]. While the β-methylcarbapenem clearly represent a significant advance in antibiotic therapy, it challenges existing methods of synthesis. In the convergent approach to this compound, ertapenem can be assembled from protected β-methyl carbapenem enolphosphate **2** and several kinds of side chain **3**[3-6]. The most challenging and interesting part of the preparation for ertapenem is the synthesis of **3** , since compound **2** is now commercially available on a large scale. Here we report our results for an efficient synthesis of ertapenem originated from novel side chain **4**.

All attempts for the synthesis of the side chain are based on a suitably protected 4-hydroxyproline derivative **3** and rely heavily on the use of the protecting groups such as Boc[7], PNZ group[2,5-7]. We placed emphasis on preparation of the side chain **4** starting from the *N*-diisopropoxyphosphoryl-protecting hydroxyproline (**5**)[3]. *N*-diisopropoxyphosphoryl offers particular advantages over the BOC group; diisopropylphosphite is a significantly low cost reagent than di-*tert*-butyl dicarbonate for the protection step, it is economical and only nonvolatile and innocuous cleavage products are generated under mild acidic conditions. Moreover, the mesylate functionality in **6** and **8** performs a pivotal role in our strategy; it not only activates the carbonyl group toward reaction with allyl 3-aminobenzoate, but also allows the stereoselective introduction of a protected thiol group *via* Walden inversion. It is worthy to note that our synthetic strategy for making ertapenem with the amine and carboxyl functionality protected has some advantages in that these protecting groups could be removed efficiently in one-pot with less amount of Pd as well as no hydrogen gas compared with those strategy of PNZ-protections[2,5-7].

EXPERIMENTAL

^{1}H NMR spectra were measured on a Brucker AV 600 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS, which was used as an internal standard. Mass spectra were obtained on an Agilent MS/5975 mass spectrometer. Optical rotation was determined with a Jasco Dip-181 digital polarimeter. IR spectra (KBr) were recorded on a JASCO FT/IR-8400 instrument. Elemental analysis was performed on a CarloErba 1106 instrument and the results of elemental analysis for C, H, N, were within 0.4 % of the theoretical values. All the reactions were monitored by TLC on pre-coated silica gel G plates at 254 nm under a UV lamp. Silica gel chromatography separations were obtained on silica gel (300-400 mesh). All chemicals and solvents were reagent grade purified by standard methods prior to use.

Allyl-3-[(2S,4S)-1-(diisopropoxyphosphoryl)-4-(methylsulfonyloxy)pyrrolidine-2-carboxamino]benzoate (8): To a solution of *N*-(O, O-diisopropylphosphoryl)-*trans*-4-hydroxy-L-proline (**5**) (2 g, 6.80 mmol) and Et_3N (3 g, 29.7 mmol) in

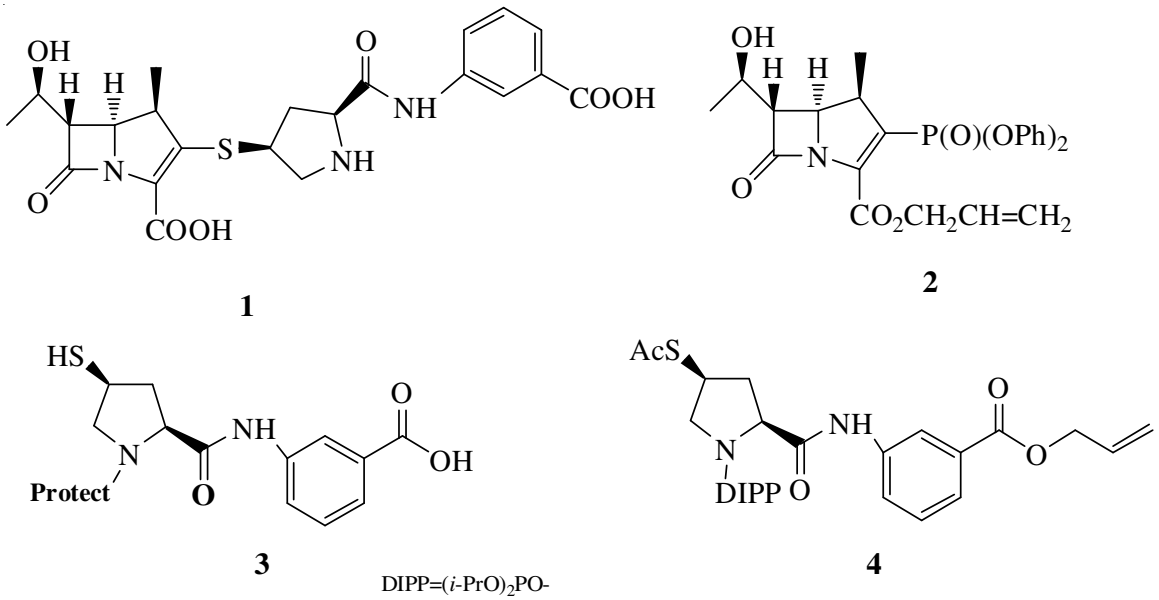
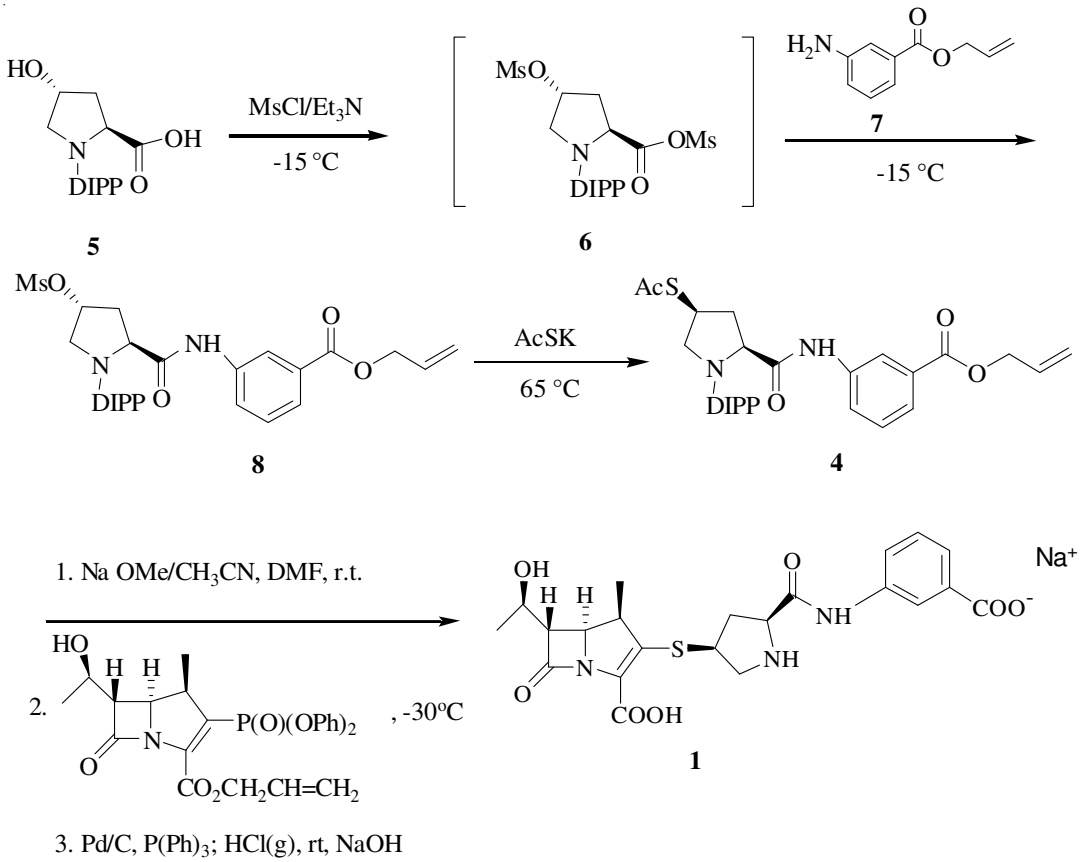


Fig. 1. Structures of related compounds

ethyl acetate (30 mL) was added methanesulfonyl chloride (2 g, 17.5 mmol) dropwise at -15 °C and stirred for 1 h. Then **7** (1.3 g, 7.34 mmol) was added successively and the mixture was stirred at the same temperature for another 1 h. The resulting mixture was partitioned between ethylacetate and water, the organic layer was washed with 1 N HCl, 5 % $NaHCO_3$ and brine, dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography, affording pale yellow oily **8** (3.5 g, 97 % from **5**). $[\alpha]^{22}_{589}$ = -13 (c = 1.00; CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 10.10 (s, 1 H, -CONH-), 8.13 (s, 1 H, ArH), 7.75 (d, *J* = 8.2 Hz, 1 H, ArH), 7.65 (t, *J* = 6.3 Hz, 1 H, ArH), 7.24 (t, *J* = 7.9 Hz, 1 H, ArH), 6.03 (dd, *J* = 16.2 Hz, 1 H, -OCH_2-C*H*=CH_2), 5.48-5.16 (m, 3 H, -OCH_2-C*H*=CH_2, -C(CO)*H*-), 4.79 (d, *J* = 5.6 Hz, 2 H, -O*C*H_2-CH=CH_2), 4.75-4.68 (m, 1 H, -C(S)*H*-), 4.68-4.60 (m, 2 H, -P(O)[O*CH* $(CH_3)_2]_2$), 3.70-3.45 (m, *J* = 5.9 Hz , 2 H, -CH_2-), 3.08 (s, 3 H, -CH_3SO_3-), 2.79-2.39 (m, 2 H, -CH_2-), 1.37 (m, 12 H, -P(O)[OCH(CH_3)$_2$]$_2$). IR (KBr, ν_{max}, cm^{-1}): 3691, 3051, 2987, 2686,2306,1722, 1603, 1551, 1436, 1423, 1373, 1360,1281, 1240, 1166, 992, 780, 660. Anal. ($C_{22}H_{23}N_2O_9SP$) C, 49.62; H, 6.25; N, 5.26; O, 27.04; S, 6.02; P, 5.82. Found: C, 49.68; H, 6.24; N, 5.22; P, 5.79; S. 6.04. EIMS, *m/e*: 532 (M^+).

Allyl-3-[(2S,4S)-4-(acetylthio)-1-(diisopropoxyphosphoryl)pyrrolidine-2-carboxamino] benzoate (4): Potassium thioacetate (2 g, 17.5 mmol) and **8** (4 g, 7.52 mmol) were dissolved in methanol (50 mL), refluxed (65 °C) for 5 h under nitrogen atmosphere. The cooled mixture was filtered; the cake was washed with water, combined the filtrate and was concentrated. The residue was extracted with ethyl acetate, washed with 1 N HCl, 5% $NaHCO_3$ and brine, dried over $MgSO_4$, after removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography to afford a pale yellow oily **4** (3.5 g, 91 % from **8**). $[\alpha]^{22}_{589}$ = -53.6 (c = 1; CH_2Cl_2); ^1H NMR ($CDCl_3$) δ: 9.73 (s, 1H, -CON*H*-), 8.09 (s, 1H, ArH), 7.81 (d, *J* = 7.9 Hz, 1H, ArH), 7.71 (d, *J* = 7.6 Hz, 1H, ArH), 7.30 (t, *J* = 7.9 Hz, 1H, ArH), 5.96 (q, *J* = 5.7 Hz, 1H, -OCH_2-C*H*=CH_2), 5.33 (d, *J* = 17.2 Hz, 1H, -C(CO)*H*-), 5.27-5.17 (m, 2H, -OCH_2-CH=CH_2), 4.74 (d, *J* = 5.3 Hz, 2H, -OCH_2-CH=CH_2), 4.65-4.51 (m, 3H, -P(O)[OCH$(CH_3)_2]_2$, -C(S)*H*-), 3.84-3.71 (m, 2H, -CH_2-), 2.54-2.39 (m, 2H, -CH_2-), 2.23 (d, *J* = 21.5 Hz, 3H, CH_3COS-), 1.34-1.26 (m, 12H, -P(O)[OCH(CH_3)$_2$]$_2$). IR (KBr, ν_{max}, cm^{-1}): 3691, 3051, 2987, 1753, 1693, 1606, 1575, 1457, 1369, 1307, 1234, 1188, 1095, 970, 755, 667, 599. Anal. ($C_{23}H_{33}N_2O_7PS$) C, 53.90, H, 6.49, N, 5.47, O, 21.85, S, 6.26, P, 6.04. Found: C, 53.88, H, 6.52, N, 5.44, S, 6.23, P, 6.07. IR (KBr, ν_{max}, cm^{-1}) : 2871, 1753, 1693,1458, 1307, 917, 705, 599, 543. EIMS *m/z*: 512 (M^+).

Synthesis of entarpenem mono-sodium (1): To a solution of the thioacetate **4** (3 g, 5.9 mmol) in anhydrous THF (30 mL) was added sodium alkoxide (0.5 g, 8.8 mmol) and DMF (10 mL), the mixture was stirred under nitrogen at room temperature overnight[8]. The solution was cooled to -30 °C; diisopropylethylamine (1.6 g, 12.3 mmol) was added, after aged at -30 °C for 40 min, **2** (3.5 g, 7.23 mmol) was added in one portion and the mixture was allowed to react for 24-48 h at the same temperature. The reaction was complete as determined by HPLC analysis (Kromasil ODS; UV 298 nm; 0.1 M phosphate buffer/methanol from 80:10 to 50:50; pH 6.8)[9], then dichloro *bis*(triphenylphosphine)palladium (0.6 g, 0.9 mmol) and triphenylphosphine (1.1 g, 4.8 mmol) were added and the reaction mixture was stirred at room temperature for 5 h under nitrogen[10], the resulting mixture was flushed with HCl gas (saturated in THF) while keeping stirring for 0.5 h. The catalyst was removed by filtration and the pH of the filtrate was adjusted to 5.5 with NaOH in ice bath, evaporation of the filtrate in vacuo to remove THF, the residue was extracted with 30 mL of isoamyl alcohol to give an aqueous solution[3], which was purified by diaion CHP20P resin, freeze drying to obtain resultant product ertapenem as white yellow (1.2 g, 25 m mol, 44 % from **4**). $[\alpha]^{22}_{589}$ = -15 (C=1.0 in H_2O). ^1H NMR (D_2O) δ: 7.86 (m, 1H), 7.71 (m, 1H), 7.65 (m, 1H), 7.47 (t, 1H, *J* = 8 Hz), 4.62 (t, 1H, *J* = 8.3 Hz), 4.21 (m, 1H), 4.18 (dd, 1H, *J* = 9.5, 2.4 Hz), 4.07 (m, 1H), 3.82 (dd, 1H, *J* = 12.3, 6.8 Hz), 3.47 (dd, 1H, *J* = 12.3, 5.6 Hz), 3.42 (dd, 1H, *J* = 6.0, 2.4 Hz), 3.31 (m, 1H), 3.02 (m, 1H), 2.20 (m, 1H), 1.27 (d, 3H, *J* = 6.4



Scheme-I: Synthesis of ertapenem

Hz), 1.17 (d, 3H, J = 6.8 Hz); IR (KBr, ν_{max}, cm^{-1}): 3420, 2971, 1749, 1692, 1562, 1386, 1296, 775. EIMS *m/z*: 497 (M^+).

RESULTS AND DISCUSSION

A formal total synthesis of the title compound is outlined in **Scheme-I**. It first required us to make *N*-diisopropoxyphosphoryl-protected hydroxyproline **5** according to the procedure described in the literature[4]. Reaction of the *N*-diisopropoxyphosphoryl-protected hydroxyproline **5** with excess of methanesulfonyl chloride at -15 °C in the presence of triethylmine provided the mesylate **6**, which underwent aminolysis with allyl 3-aminobenzoate at -15 °C to yield the compound **8**. Treatment of **8** with potassium thioacetate at 65 °C in methanol gave the compound **4**. This novel intermediate was deacetylated under nitrogen atmosphere affording the free thiol derivate **3** and condensed immediately with **2** using a moderate excess of diisopropylethylamine in a THF and DMF mixed solvent at -30 °C to give the coupling product, which was hydrogenlized upon treatment of 5 % Pd/C and $P(Ph)_3$ to remove the allyl group, without purification, hydrolysis upon HCl gas associated with deprotection of the *N*-diisopropoxyphosphoryl group at 20 °C led to ertapenem. The mesylate displacement using potassium thioacetate allows stereoselective introduction of a protected thiol in compound **4** to avoid disulfide[1a]. The optical rotation of sodium salt ertapenem sodium suggests that the stereoselectivity of this displacement is accessible. In addition, this process allowed preparation of thiol substrate for the coupling reaction with protecting groups both at the carboxylic acid and amine, which could avoid competing reactions, as well as improve the organic solubility. The projection that transformation leading from **4** and **2** to **1** in an overall yield of 39.2 % could be performed in the same pot promised to make our approach practical and economical.

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REFERENCES

1. (a) K.M.J. Brands, R.B. Jobson, K.M. Conrad, J.M. Williams, B. Pipik, M. Cameron, A.J. Davies, P.G. Houghton, M.S. Ashwood, I.F. Cottrell, R.A. Reamer, D.J. Kennedy, U.H. Dolling and P.J. Reider, *J. Org. Chem.*, **67**, 4771 (2002); (b) E. Boselli, D. Breilh, M.C. Saux, J.B. Gordien and B. Allaouchiche, *Intensive Care Med.*, **32**, 2059 (2006).
2. W.G. Song, Y. Xia and H. Fang, *Zhongguo Yaoye*, **18**, 87 (2009).
3. J.M. Williams, K.M.J. Brands, R.T. Skerlj, R.B. Jobson, G. Marchesini, K.M. Conrad, B. Pipik, K.A. Savary, F.R. Tsay, P.G. Houghton, D.R. Sidler, U.H. Dolling, L.M. DiMichele and T.J. Novak, *J. Org. Chem.*, **70**, 7479 (2005).
4. K.M.J. Brands, K. Wiedbrauk, J.M. Williams, U.H. Dolling and P.J. Reider, *Tetrahedron Lett.*, **39**, 9583 (1998).
5. M. Sunagawa, H. Matsumura and T. Bando, *Heterocycles*, **41**, 147 (1995).
6. (a) Y. F. Zhang, H. Chen, J. H. Peng, R. C. Gao, G. M. Zhang, *J. Chin. Pharm. Univ.*, **38**, 305 (2007); (b) Y. Shi, K. Li, X.B. Zhao, J. Lu and X.W. Sun, *Zhongguo Kangshengsu Zazhi*, **36**, 519 (2011).
7. K.M.J. Brands, G. Marchesini, J.M. Williams, U.H. Dolling and P.J. Reider, *Tetrahedron Lett.*, **37**, 2919 (1996).
8. J.H. Chapman and L.N. Owen, *J. Chem. Soc.*, 579 (1950).
9. T. Legrand, S. Chhun, E. Rey, B. Blanchet, J.R. Zahar, F. Lanternier, G. Pons and V. Jullien, *J. Chromatogr. B*, **875**, 551 (2008).
10. J.P. Huang, X.X. Chen, S.X. Gu, L. Zhao, W.X. Chen and F.E. Chen, *Org. Process Res. Dev.*, **14**, 939 (2010).