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An Efficient Synthesis of 3-(*E*)-Hydroxypropenyl Cephem Derivatives, Key Intermediates for 3-(*E*)-Ammoniopropenylcephalosporin Antibiotics

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An efficient synthesis of 3-(*E*)-hydroxy- and 3-(*E*)-acetoxypropenylcephem derivatives, key intermediates for the synthesis of 3-(*E*)-propenylcephalosporins was achieved *via* Stille coupling reaction of 3-trifloxycephem with 3-(*E*)-tributylstannylallylic alcohol.

Key words : Ammoniopropenyl, 3-(*E*)-Propenylcephem, Cephalosporins, Antibacterial, Stille coupling

INTRODUCTION

Recently, 3-(*E*)-propenylcephalosporin antibiotics (Hanaki *et al.*, 1996; Iimura *et al.*, 1993; Kamachi *et al.*, 1992) have been a great deal of interest among β-lactam antibiotics because of their potent and wide-spectrum antibacterial activity. We (J. Y. Lee *et al.*, 1996) also have reported the synthesis of quaternary 3-(*E*)-ammoniopropenylcephalosporins with hydroxylated alicyclic or aliphatic amines possessing potent and well-balanced antibacterial activities against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. In general, 3-(*E*)-hydroxy- and 3-(*E*)-acetoxypropenylcephem (**1**, **2**) have been served as potential intermediates for the synthesis of various 3-(*E*)-propenylcephalosporin antibiotics (Kamachi *et al.*, 1992).

In connection with our continued research program on the synthesis of quaternary 3-ammoniocephalosporins, we needed large quantities of 3-(*E*)-hydroxy- and 3-(*E*)-acetoxypropenylcephems (**1**, **2**). However, the known synthetic strategies to 3-(*E*)-acetoxypropenylcephem derivatives are rather less efficient. During the Wittig reaction of acetoxyacetaldehyde with a ylide derived from 3-iodomethylcephems, 3-(*Z*)-acetoxypropenylcephem was generated (Kamachi *et al.*, 1992). It required an additional thermal isomerization in toluene for 2 days to obtain a desired 3-(*E*)-isomer. On the other hand, the allylic rearrangement approach (Beeby *et al.*, 1977) requires lengthy reaction sequence and starts from expensive 3-formyl-2-cephem derivative. This prompted us to investigate an alternative efficient route to 3-(*E*)-hydroxypropenylcephems (**1**). Herein we report an expeditious synthesis of **1** and **2** *via* palladium-catalyzed Stille coupling reaction.

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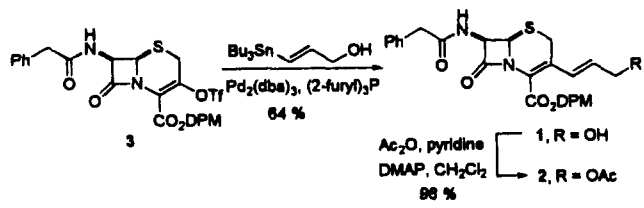
RESULTS AND DISCUSSION

3-Trifloxycephem (**3**) has extensively used for the synthesis of C-C and C-S bonds at C-3 position of the cephalosporin nucleus. While several cephalosporin derivatives containing olefinic side chain or heterocycle at C-3 position have been prepared (Farina *et al.*, 1989; Kant, 1993; Y. S. Lee *et al.*, 1996), the synthesis of 3-(*E*)-hydroxypropenylcephem (**1**), a potential intermediate for the synthesis of various 3-(*E*)-propenylcephalosporins, was not reported unexpectedly starting from 3-trifloxycephem (**3**). Based on these findings, we envisaged that 3-(*E*)-hydroxypropenylcephem (**1**) can be readily synthesized by the palladium-catalyzed coupling reaction of **3** with 3-(*E*)-tributylstannylallylic alcohol.

The requisite 3-trifloxycephem **3** (Kant, 1993) and 3-(*E*)-tributylstannylallylic alcohol (Jung *et al.*, 1982) were



Scheme 1.

prepared by known methods. The coupling reaction of **3** and 3(*E*)-tributylstannylallylic alcohol proceeded cleanly in the presence of $ZnCl_2$ (2 equiv.), tris(2-furyl) phosphine (4 mol %), and $Pd_2(dba)_3$ (2 mol %) in *N*-methylpyrrolidone at room temperature to afford 3-(*E*)-hydroxypropenylcephem (**1**) in 64% yield. The ^1H NMR spectrum of **1** showed one of the vinylic protons at 6.97 ppm with a coupling constant of 16.2 Hz indicating that olefin configuration of the product was E-geometry.

3-(*E*)-Hydroxypropenylcephem (**1**) has been used as a potential intermediate for the synthesis of 3-carbamoyl or 3-acyloxypropenylcephalosporins (Kamachi *et al.*, 1992). Furthermore, compound **1** can be transformed readily to another intermediate, 3-(*E*)-acetoxypropenylcephem (**2**), which also can be useful for the synthesis of various 3-propenylcephalosporin antibiotics. Upon treatment of **1** with pyridine (1.1 equiv.) and a catalytic amount of 4-dimethylaminopyridine in acetic anhydride-dichloromethane at room temperature for 2.5h, 3-(*E*)-acetoxypropenylcephem (**2**) was obtained in 96% yield.

To demonstrate the utility of 3-(*E*)-acetoxypropenylcephem (**2**) as a potential intermediate for the synthesis of 3-(*E*)-propenylcephalosporins, **2** was transformed to a quaternary 3-(*E*)-ammoniopropenylcephalosporin derivative (**6**) as shown in Scheme 2.

Removal of the phenylacetyl group of **2** by an imino-chloride method (PCl_5, pyridine, methanol) followed by acylation of the resulting free amines with aminothiazole active ester (**4**) and deprotection of diphenylmethyl group with trifluoroacetic acid (TFA) afforded 7-aminothiazolyl cephalosporin **5** as a TFA salt in overall 66% yield. Quaternization of **5** at C-3 position was carried out by the standard method (Walker *et al.*, 1988) to provide **6** in 18% yield. The spectral data of **6** were identical to those which was prepared from 3-(*E*)-chloropropenylcephem in our laboratory (J. Y. Lee *et al.*, 1996).

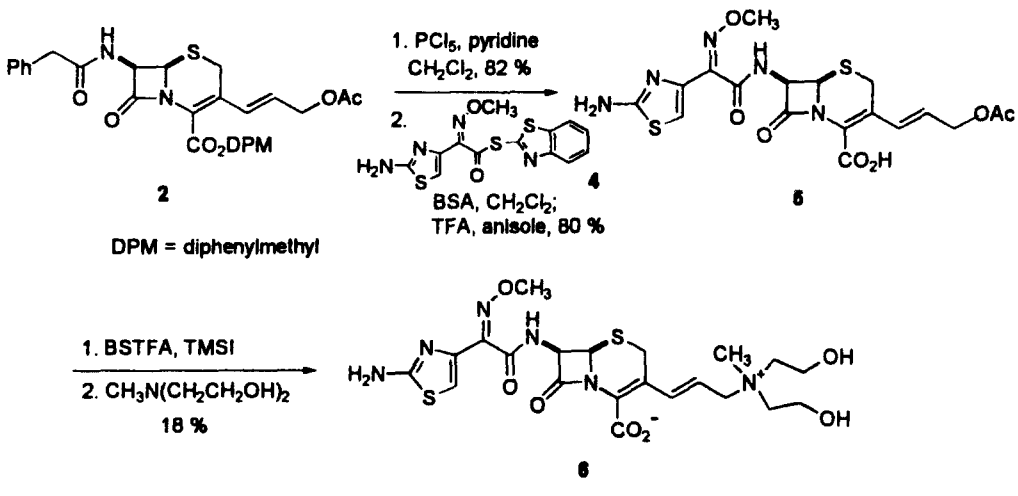
EXPERIMENTAL SECTION

General

Melting points (mp) were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. ^1H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Gemini Varian-300 (75 MHz) spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer 16F-PC FT-IR and MIDAC 101025 using a potassium bromide pellet. Optical rotations were determined on a Autopol III automatic polarimeter (Rudolph Research Co.) using the sodium D line (λ=589 nm) at the temperature indicated.

Diphenylmethyl 7-phenylacetamido-3-[3-(*E*)-hydroxy-1-propen-1-yl]-3-cephem-4-carboxylate (1)

To a stirred solution of diphenylmethyl 7-phenylacetamido-3-trifluoromethanesulfonyloxy-3-cephem-4-carboxylate (**6**, 14.3 g, 22.6 mmol), $ZnCl_2$ (6.2 g, 45.2 mmol), tris(dibenzylideneacetone)dipalladium (0) (412 mg, 0.45 mmol), and tris(2-furyl)phosphine (210 mg, 0.9 mmol) in 80 ml of *N*-methyl-pyrrolidinone (NMP) was added (*E*)-tributylstannylallylic alcohol (10.7 g, 30.7 mmol) under nitrogen. The reaction mixture was stirred at room temperature overnight and poured into a mixture of ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane:ethyl acetate=1:1) to afford a 3-(*E*)-hydroxypropenylcephem **1** (7.8 g, 64%) as a yellow solid. mp 163-165°C; $[\alpha]_D^{22}$ -98.2 (*c* 1.00, $CHCl_3$); IR (KBr): ν 3414, 3067, 1774, 1721, 1652 cm^{-1};



Scheme 2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.25 (15H, m, 3× Ph), 6.97 (1H, d, *J*=16.2 Hz, CH=CH-CH_2), 6.92 (1H, s, Ph_2CH), 6.50 (1H, d, *J*=9.0 Hz, CO-NH), 5.90 (1H, dt, *J*=16.2, 5.4 Hz, CH=CH-CH_2), 5.77 (1H, dd, *J*=9.0, 4.7 Hz, C7-H), 4.97 (1H, d, *J*=4.7 Hz, C_6-H), 4.15 (2H, br s, CH=CH-CH_2), 3.64 (2H, d, *J*=3.0 Hz, Ph-CH_2), 3.46 & 3.24 (2H, ABq, *J*=17.3 Hz, 2×C_2-H), 1.61 (1H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.75, 166.06, 160.97, 139.61, 136.16, 135.17, 134.15, 129.55-126.88 (16C), 124.54, 122.65, 79.04, 63.04, 59.67, 58.93, 43.34, 24.70.

Diphenylmethyl 7-phenylacetamido-3-[3-(*E*)-acetoxy-1-propen-1-yl]-3-cephem-4-carboxylate (2)

To a stirred solution of 3-(*E*)-hydroxypropenylcephem **1** (1.0 g, 1.85 mmol) and a catalytic amount of 4-dimethylaminopyridine in a mixture of 10 ml of acetic anhydride and 10 ml of CH_2Cl_2 was added pyridine (161 mg, 2.03 mmol) at room temperature. After stirring for 2.5 h, the reaction mixture was poured into a mixture of ethyl acetate (50 ml) and water (50 ml). The separated organic layer was washed with water, saturated $NaHCO_3$ solution, and brine successively. After drying over $MgSO_4$, the organic layer was concentrated and purified by flash column chromatography (hexane:ethyl acetate=2:1) to afford 3-(*E*)-acetoxypropenylcephem 2 (1.03 g, 96%) as a yellow solid. mp 154-155°C; $[\alpha]_D^{22}$-136.5 (*c* 1.06, $CHCl_3$); IR (KBr) ν 3300, 3028, 1768, 1755, 1730, 1668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (15H, m, 3×Ph), 6.97 (1H, s, Ph_2CH-) 6.93 (1H, d, *J*=16.2 Hz, CH=CH-CH_2), 6.35 (1H, d, *J*=9.0 Hz, CO-NH), 5.89 (1H, dt, *J*= 16.2, 6.1 Hz, CH=CH-CH_2), 5.83 (1H, dd, *J*=9.0, 5.0 Hz, C_7-H), 4.97 (1H, d, *J*=5.0 Hz, C_6-H), 4.54 (2H, d, *J*=6.1 Hz, CH=CH-CH_2), 3.63 (2H, d, *J*=3.0 Hz, Ph-CH_2), 3.53 & 3.42 (2H, ABq, *J*=14.7 Hz, C_2-2H), 2.03 (3H, s, OAc); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.35, 170.59, 165.00, 161.00, 139.35, 139.13, 133.90, 129.49-127.05 (18C), 124.48, 79.43, 64.52, 59.37, 57.82, 43.26, 24.56, 20.82.

7-[2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetamido]-3-[3-(*E*)-(*N,N*-bis(2-hydroxyethyl)-*N*-methylammonio)-1-propen-1-yl]-3-cephem-4-carboxylate (6)

A quaternary 3-(*E*)-ammoniopropenylcephalosporin **6** was synthesized from **2** as an amorphous solid by using a standard method (Walker *et al.*, 1988). The spectral data of **6** were identical to those of **6** prepared from 3-(*E*)-chloropropenylcephem (J. Y. Lee *et al.*, 1996). IR (KBr) ν 3382, 1766, 1608 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 7.02 (1H, s, aminothiazole-H), 6.93 (1H, d, *J*=15.6 Hz, -CH=CH-CH_2), 5.95 (1H, dt, *J*=15.6, 6.6 Hz, -CH=CH-CH_2), 5.83 (1H, d, *J*=4.5 Hz, C_7-H), 5.27 (1H, d, *J*=4.5 Hz, C_6-H), 4.17 (2H, d, *J*=6.6 Hz, CH=CH-CH_2-N^+), 4.06 (4H, br s, 2×N^+-CH_2CH_2OH), 3.73 & 3.63 (2H, ABq, *J*=16.8 Hz, 2×C_2-H), 3.55 (4H, br d, *J*=5.1 Hz, 2×N^+-CH_2CH_2OH), 3.13 (3H, s, N^+-CH_3); ^{13}C NMR (75 MHz, D_2O) δ 171.08, 168.78, 164.99, 163.11, 148.24, 140.61, 139.16, 133.20, 115.89, 115.43, 113.54, 66.05, 63.55, 63.24, 62.91, 62.85, 59.30, 57.62, 55.41, 48.99, 23.82.

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REFERENCES CITED

Beeby, P. J. and Edwards, J. A., 3-(3-Substituted prop-1-enyl)cephalosporins. *J. Med. Chem.*, 20, 1665 (1977).

Farina, V., Baker, S. R. and Hauck, S. I., Palladium catalysis in cephalosporin chemistry: General methodology for the synthesis of cephem side chains. *J. Org. Chem.*, 54, 4962 (1989).

Hanaki, H., Akagi, H., Nomura, S., Unemi, N. and Hiramatsu, K., Structure-activity relationships of cephalosporin derivatives against methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*. *J. Antibiotics*, 49, 402 (1996).

Iimura, S., Imae, K., Hasegawa, T., Okita, T., Tamaoka, M., Murata, S., Kamachi, H. and Kamei, H., Cephalosporins having a heterocyclic catechol in the C3 side chain, II. Improvement of pharmacokinetic profile. *J. Antibiotics*, 46, 850 (1993).

Jung, M. E. and Light, L. A., Preparation of iodoallylic alcohols via hydrostannylation: Spectroscopic proof of structures. *Tetrahedron Lett.*, 23, 3851 (1982).

Kamachi, H., Okita, T., Hoshi, H., Okuyama, S. and Naito, T., Synthesis of geometrical isomers of 3-(3-acetoxy and 3-carbamoyl-1-propenyl)cephalosporins and their structure-activity relationship. *J. Antibiotics*, 45, 998 (1992).

Kant, J. A., Synthetic approach to 3-substituted cephalosporins: Carbon-carbon bond formation at C-3 of the cephem via organocuprate chemistry. *J. Org. Chem.*, 58, 2296 (1993).

Lee, J. Y., Lee, Y. S., Suk, D. W., Woo, E.-R., Chung, B. Y. and Park, H., Synthesis and biological activity of quaternary ammoniopropenylcephalosporins with hydroxylated alicyclic or aliphatic amines. *J. Antibiotics*, 49, 1286 (1996).

Lee, Y. S., Lee, Y. S. and Park, H., Synthesis and biological activities of C-3 heterocyclylcarbon-substituted novel cephalosporins. *J. Antibiotics*, 49, 405 (1996).

Walker, D. G., Brodfuehrer, P. R., Shih, K. M. and Sapino, Jr., C., Use of bistrimethylsilylated intermediate in the preparation of semisynthetic 7-amino-3-substituted-cephems. Expedient synthesis of a new 3-[(1-methyl-1-pyrrolidino)methyl]cephalosporin. *J. Org. Chem.*, 53, 983 (1988).