Notes

Synthesis of the 1β-Methylcarbapenem Key Intermediate

Yang Mo Goo[†], Min Hyo Seo, and Youn Young Lee[*]

Department of Chemistry and [†]Department of Pharmacy, Seoul National University, Seoul 151-742, Korea
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1β-Methylcarbapenem (1)[1] was developed as a derivative of thienamycin (2)[2,3] which shows good antimicrobial activity but less susceptibility to renal dehydropeptidase-I. In the course of synthetic studies on the derivatives of thienamycin, we developed a new method for the synthesis of 1β-methylcarbapenem key intermediate. Our recent paper[4] covered the synthesis of 3-[1-(t-butyldimethylsilyloxy)ethyl]-4-(1-carboxy-1-methylethyl)-2-azetidinone (3). Further examination of this compound, we were able to convert it to a 4-isopropenyl-2-azetidinone derivative and further to 3-[1-(t-butyldimethylsilyloxy)ethyl]-4-(1-carboxyethyl)-2-azetidinone (4) which is the key intermediate for the synthesis of 1β-methylcarbapenem.[5] We wish to report the result in this paper.

Treatment of compound 3 with lead tetracetate in DMF-acetic acid converted the carboxy group to an acetoxy group. Since the silyl protecting group was removed during the reaction, the product was treated with t-butyldimethylchlorosilane in the presence of imidazole to give a product (6) in which both the hydroxy group and the NH group of β-lactam ring were silylated simultanously. Refluxing of the compound, 6 in toluene with DBU did not give elimination of the acetoxy group. So, we reduced the acetoxy group with DIBAL to give a hydroxy compound 7. After conversion of compound 7 to a methanesulfonyl derivative and further treatment of one more equivalent of triethylamine gave an eliminated product 8 in good yield. Compound 8 was then reacted with borane-dimethyl sulfide complex and followed by oxidation of the borane complex with hydrogen peroxide gave the alcohol derivative, 9 in 62% yield. The spectral data of 9 were identical with those reported.[6] It has already been established that oxidation of 9 with pyridinium dichromate can produce 4 in high yield.[7]

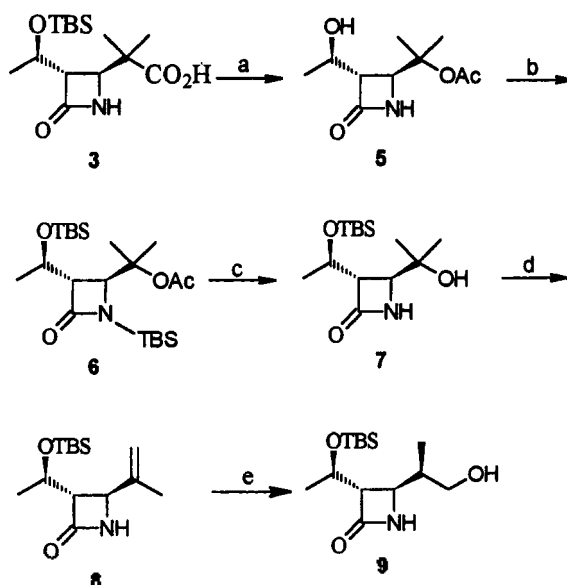### Experimental

IR spectra were recorded with Perkin-Elmer 735-B IR or
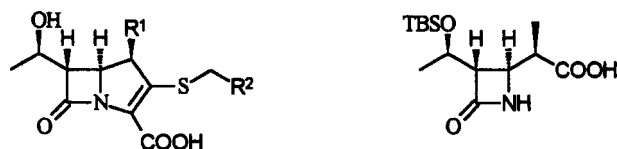
1 : R[1]=Me, R[2]=C(=NH)NMe₂
2 : R[1]=H, R[2]=CH₂NH₂

Figure 1.

(a) Pb(OAc)₄, DMF-AcOH (1:1), rt, 1h, 68%. (b) TBDMSCl, Imidazole, DMF, rt, 12h, 92%. (c) DIBAL, Et₂O, 1.5h, 74%. (d) MsCl, Et₃N, CH₂Cl₂, rt, 2h, 86%. (e) BH₃-SMe₂, THF, rt, 2h, NaOAc, H₂O₂, rt, 2h, 62%.

Scheme 1.

Jasco J-0068 FT IR spectrophotometer. 1H NMR spectra were obtained with Varian EM-360 (60 MHz), Bruker AC 80 (80 MHz) or Varian VXR-200S (200 MHz) NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ (ppm). Melting points were obtained with digital melting point measurement instrument made by Electrothermal Co. without correction. THF and ethyl ether were distilled in the presence of sodium and benzophenone. Benzene was washed with concentrated sulfuric acid and distilled over sodium. DMF was dried over KOH pellets before use. Other solvents are first grade and distilled before use. All the chemicals were purchased from Aldrich Chemical Co. or Merck Co.

4-(1-Acetoxy-1-methylethyl)-1-(t-butyldimethylsilyl)-3-[1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone (6). Lead tetracetate (0.71 g, 1.6 mmol) in DMF-acetic acid (1:1, 3 mL) was added slowly to the solution of 3-[1-(t-butyldimethylsilyloxy)ethyl]-4-(1-carboxy-1-methylethyl)-2-azetidinone (0.48 g, 1.5 mmol) in DMF-acetic acid (1:1, 10 mL) which was cooled in ice-water bath to 0 °C and stirred under nitrogen gas. The mixture was stirred at the same temperature for 1 h and further at room tem-

perature for 1 h. The reaction mixture was poured into crushed ice (50 g) and extracted with ethyl acetate (20 mL). The extract was washed with 5% sodium bicarbonate solution and with 10% sodium chloride solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a colorless oil (5). Yield, 0.22 g (68%).

The solution of compound 5, triethylamine (0.29 mL, 2.2 mmol), and *t*-butyldimethylchlorosilane (0.35 g, 2.3 mmol) in DMF (10 mL) was stirred at room temperature for 12 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (20 mL×2). The extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent and chromatography of the residue over silica gel with hexane-ethyl acetate (8:1) gave the product. Yield, 0.42 g (92%); ^{1}H NMR (CDCl$_3$) δ 0.00 (s, 6H, Si(CH$_3$)$_2$) 0.02 (s, 6H, Si(CH$_3$)$_2$), 0.87 (s, 9H, C (CH$_3$)$_3$), 0.91 (s, 9H, C(CH$_3$)$_3$), 1.23 (d, 3H, *J*=6.0 Hz, CH$_3$), 1.26 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 2.12 (s, 3H, CH$_3$CO), 3.00 (dd, 1H, *J*=5.2, 2.1 Hz, 3-H), 4.09 (d, 1H, *J*=2.1 Hz, 4-H), 4.25 (m, 1H, OCH); IR (neat) 2980, 1755, 1735, 1255, 1095, 840, 780 cm^{-1}.

3-[1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(1-hydroxy-1-methylethyl)-2-azetidinone (7).

DIBAL (THF, 1.0 M, 1.0 mL, 1.0 mmol) was added to the solution of compound 6 (0.40 g, 0.90 mmol) in ether (10 mL) which was cooled in dry-ice acetone bath and stirred under nitrogen gas slowly. After stirring for 2 h at the same temperature the mixture was warmed up to room temperature slowly. The mixture was stirred for 1.5 h at room temperature. The reaction was stopped by adding hydrochloric acid (0.1 N, 10 mL) and the ether layer was separated. The aqueous layer was further extracted with ethyl acetate (10 mL). The combined organic layer was washed with 10% sodium chloride solution (50 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and chromatography of the residue with hexane-ethyl acetate (4:1) gave a colorless oily product. Yield, 0.19 g (74%); ^{1}H NMR (CDCl$_3$) δ 0.02 (s, 6H, Si(CH$_3$)$_2$), 0.87 (s, 9H, C(CH$_3$)$_3$), 1.23 (d, 3H, *J*=6.0 Hz, CH$_3$), 1.26 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 2.20 (br s, 1H, OH), 3.00 (dd, 1H, *J*=5.2, 2.1 Hz, 3-H), 4.09 (d, 1H, *J*=2.1 Hz, 4-H), 4.25 (m, 1H, OCH), 5.99 (br s, 1H, NH); IR (neat) 3450-2760, 1755, 1255, 1095, 840, 780 cm^{-1}.

3-[1-(*t*-Butyldimethylsilyloxy)ethyl]-4-isopropenyl-2-azetidinone (8).

To the mixture of compound 7 (0.18 g, 0.62 mmol) and triethylamine (0.10 mL, 0.75 mmol) in methylene chloride (10 mL) which was cooled in ice-salt-water bath to -10 °C was added methanesulfonyl chloride (86 mg, 0.75 mmol) slowly. The solution was stirred for 1 h at the same temperature and for 2 h at room temperature. After evaporation of the solvent the residue was dissolved with triethylamine (0.1 mL, 0.75 mmol) in benzene (10 mL) and refluxed for 6 h. After addition of water (10 mL) and ethyl ether (10 mL) with stirring, the organic layer was separated, washed with 10% sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a colorless liquid. A colorless liquid was obtained by chromatography over silica gel with hexane-ethyl acetate (6:1). Yield, 0.143 g (86%); ^{1}H NMR (CDCl$_3$) δ 0.04 (s, 6H, Si(CH$_3$)$_2$), 0.87 (s, 9H, C(CH$_3$)$_3$), 1.35 (d, 3H, *J*=6.0 Hz, CH$_3$), 1.87 (s, 3H, =

CCH$_3$), 3.06 (dd, 1H, *J*=4.5, 2.1 Hz, 3-H), 3.98 (d, 1H, *J*= 2.1 Hz, 4-H), 4.13 (m, 1H, OCH), 4.94 (s, 1H, =CH), 5.10 (s, 1H, =CH), 6.46 (br s, 1H, NH); IR (neat) 3300, 2980, 1755, 1255, 1095, 840, 780 cm^{-1}.

3-[1-(*t*-Butyldimethylsilyloxy)ethyl]-4-(2-hydroxy-1-methylethyl)-2-azetidinone (9).

Borane-dimethyl sulfide (THF, 2.0 M, 0.24 mL, 0.48 mmol) was added to the solution of compound 8 (0.13 g, 0.48 mmol) in THF (5 mL) which was cooled to 0 °C under nitrogen gas. After stirring for 30 min at the same temperature, the mixture was further stirred at room temperature for 2 h. Then, anhydrous sodium acetate (40 mg, 0.48 mmol) and hydrogen peroxide (35%, 0.50 mL) was added. After stirring for 2 h at room temperature, ethyl acetate (10 mL) and hydrochloric acid solution (0.1 M, 10 mL) was added. The reaction mixture was stirred for 30 min at the same temperature and the ethyl acetate layer was separated. After washing the ethyl acetate solution with 10% sodium bicarbonate solution and water, it was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a solid residue. Purified product was obtained by chromatography over silica gel with hexane-ethyl acetate (1:1). Yield, 85 mg (62%); mp 87-88 °C (lit[6] 90-91 °C); ^{1}H NMR (CDCl$_3$), δ 0.04 (s, 6H, Si(CH$_3$)$_2$), 0.87 (s, 9H, C(CH$_3$)$_3$), 0.90 (d, 3H, *J*=6.8 Hz, CH$_3$), 1.35 (d, 3H, *J*=6.0 Hz, CH$_3$), 1.86 (m, 1H, CH$_3$CHCH$_2$O), 2.96 (m, 1H, OH), 3.15 (dd, 1H, *J*=9.0, 2.2 Hz, 4-H), 3.30 (dd, 1H, *J*=8.8, 2.2 Hz, 3-H), 3.53 (m, 2H, CH$_2$O), 4.13 (m, 1H, OCH), 5.99 (br, s, 1H, NH); IR (KBr) 3450-2760, 1755, 1255, 1095, 840, 780 cm^{-1}.

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Synthesis of p-Phenylcalix[5]arene

Kwanghyun No*, Kyoung Mee Kwon, and Bo Hyung Kim

Department of Chemistry, Sookmyung Women's University, Seoul 140-742, Korea
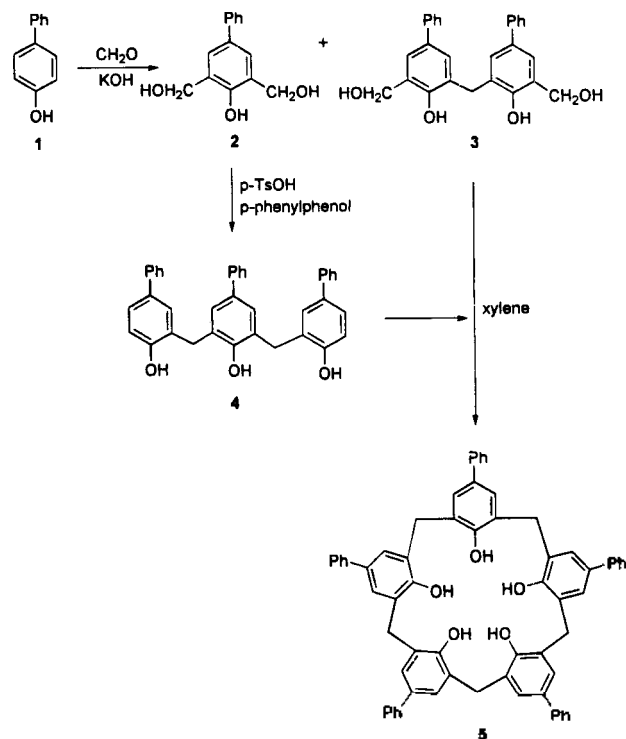*Received May 6, 1997*

Calixarenes are macrocyclic compounds available in a variety of ring sizes and are of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures.[1-3] From the standpoint of constructing an enzyme model the p-phenylcalix[n]arenes are specially attractive because not only do the phenyl groups increase the size of the calixarene cavity by considerable amount but they also provide potential sites at the 4' positions for the addition of functional groups. However, the chemistry of the deep-cavity calix[n]arenes has been slow to develop because of the lack of high-yield synthetic pathways. The direct base-induced condensation of p-phenylphenol with formaldehyde only afforded the p-phenylcalix[6]arene and p-phenylcalix[8]arene in low yields.[4] The p-phenyl-calix[4]arene was first synthesized by Gutsche and No using stepwise route in low overall yield[5,6] and an improved synthesis was reported by our laboratory[7] using the fragmentation condensation reaction between p-phenylphenol dimer and 2,2'-bishydroxymethylated p-phenylphenol dimer in the presence of TiCl₄. Recently, limited number of p-phenylcalix[4]arene derivatives were synthesized starting from the O-alkylation of the de-*tert*-butylated calix[4]arene followed by halogenation, metallation and then coupling with substituted benzene.[8-11]

On the other hand, the chemistry of calix[5]arenes is still unexplored even though they may possess a greater propensity to completely include small organic molecules than analogous calix[4]arenes due to their larger cavity size.[12-14] In 1982 Ninagawa and Matsuda[15] reported for the first time the one-step synthesis of p-*tert*-butylcalix[5]arene with ca. 6% yield. The yield was recently increased to 15% by Steward and Gutsche[16] to allow its chemistry to be investigated with relative ease. In 1992 Souley and coworkers[17] reported the synthesis of p-benzylcalix[5]arene from the reaction of p-benzylphenol and formaldehyde in 33% yield. However, p-phenylcalix[5]arene which has the deeper and larger hydrophobic cavity, was not reported and here we describe the first synthesis of p-phenylcalix[5]arene.

Results and Discussions

As shown in Scheme, p-phenylcalix[5]arene was synthesized by '3+2' fragmentation condensation reaction bet-

ween p-phenylphenol trimer and bishydroxy-methylated p-phenylphenol dimer. When the mixture of p-phenylphenol and 35% formaldehyde was stirred for 4 days at 40 °C in the presence of potassium hydroxide, the mixture of monomer diol 2 and dimer diol 3 was resulted as white solid from which 2 and 3 could be separated in 35 and 55% yield respectively using the published procedure.[5,7,18] p-Phenylphenol trimer was prepared by the acid catalyzed condensation reaction between 2,6-bishydroxymethyl-4-phenylphenol 2 and p-phenylphenol. A solution of compound 2, p-phenylphenol and p-toluenesulfonic acid in dioxane was refluxed to yield trimer 4 in 82% yield. Compound 4 can also be prepared in ca. 10% yield by the direct reaction of p-phenylphenol with paraformaldehyde.[20] A mixture of p-phenylphenol and paraformaldehyde in xylene was heated

Scheme