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# Solid-Phase Total Synthesis of 1-β-Methylcarbapenem

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**Abstract:** A 1-β-methylcarbapenem analogue **6** was synthesized on polystyrene-diethylsilane resin (PS-DES) using 2-azetidinone bearing with 2-oxazolidone chiral auxiliary as starting material.

**Keywords:** Solid-phase, synthesis of β-lactam, carbapenem, antibiotics.

Solid-phase organic synthesis (SPOS) is being widely used in combinatorial chemistry in order to prepare libraries for screening against biological systems and enhance the drug discovery effort[1]. The synthesis of carbapenem class of β-lactams antibiotics has attracted considerable attention for their potent and broad-spectrum antibacterial activities[2]. We herein report the first solid-phase synthesis of 1-β-methylcarbapenems derivatives.

As shown in **Scheme 1**, azetidinone **1**, which bears a chiral auxiliary and first synthesized by Kondo and coworkers[2a], was loaded onto the polystyrene-diethylsilane resin (PS-DES) according to Hu's method[3]. The resulting resin **2** condensed with allyl bromoacetate in the presence of sodium bis(trimethylsilyl)amide [$NaN(TMS)_2$] to afford the resin-bound azetidinone **3**. These reactions were monitored by FT-IR, showing characteristic absorptions at 1780, 1758 (β-lactam), 1720 (ester C=O) and 1684 (CONCO) $cm^{-1}$. The resin **3** underwent a TMSCI-promoted Dickmann-type cyclization in the presence of $NaN(TMS)_2$ and diphenyl phosphorochloridate (DPPC) to give the vinyl phosphate resin **4**, a key solid-phase building block in the synthesis of 1-β-methylcarbapenems. This reaction could be monitored by the presence of leaving chiral auxiliary 2-oxazolidone and by FT-IR characteristic absorption at 1785(β-lactam), 1727 (ester C=O) $cm^{-1}$. Resin **4** was then treated with thiophenol[4] to provide resin-bound 1-β-methylcarbapenem **5**. Final cleavage from the resin by treatment with TBAF-AcOH-THF system gave the crude product, which was purified by silica gel column (hexane:AcOEt =1:1,v/v) to gave pure 1-β-methylcarbapenem **6** as an oil[5, 6] (32% overall yield based on initial loading of the PS-DES resin).

The combinatorial solid-phase synthesis of 1-β-methylcarbapenem library will be reported in due course.

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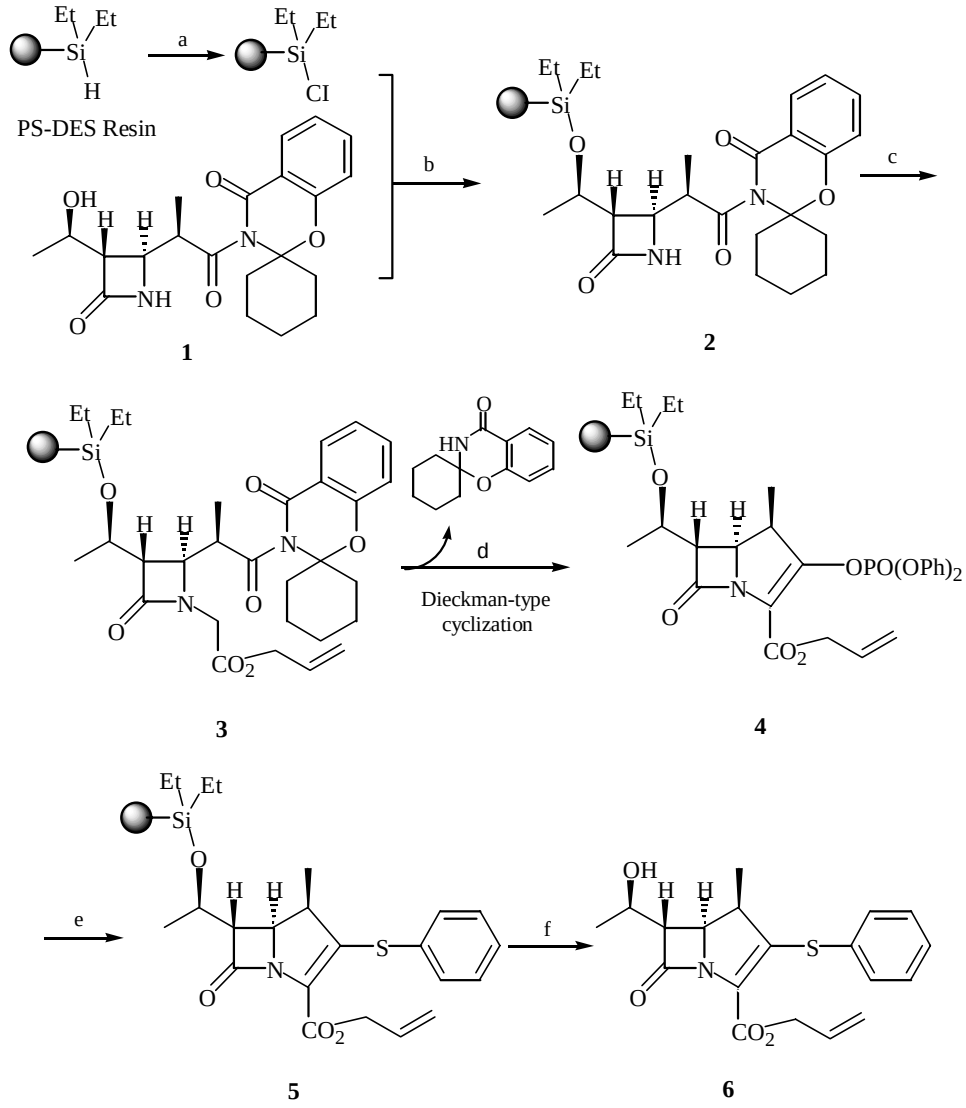
**Scheme 1**




a) trichloroisocyanuric acid, $CH_2Cl_2$, r.t.; b) imidazole, $CH_2Cl_2$, r.t.; c) allyl bromoacetate, $NaN(TMS)_2$, THF, -50°C and then r.t.; d) i. $NaN(TMS)_2$, THF , -20°C; ii. TMSCl, -20°C; iii. DPPC, -20°C; and then r.t.; e) PhSH, THF-MeCN, r.t.; f) TBAF/AcOH, THF, r.t.

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5. Spectral data of compound **6**: IR (Nujol, $cm^{-1}$): 3446, 1771, 1700; MS (*m/z*): 359 ($M^+$); $^1H$ NMR (500 MHz, $CDCl_3$, δ ppm): 7.53-7.38 (m, 5H), 5.99 (m, 1H), 5.49-5.27(m, 2H), 4.88-4.71(m, 2H), 4.19 (m, 1H), 4.13 (dd, 1H, *J*=1.6, 1.8Hz), 3.18 (dd, 1H, *J*=4.5, 2.0Hz), 3.06 (m, 1H), 2.04 (bs, 1H), 1.28 (d, 3H, *J*=6.2Hz), 0.96 (d, 3H, *J*=7.2Hz).
6. The spectral data are correspondent with the following literature data: M. Seki, K. Kondo, T. Kuroda, T. Yamanaka, T. Iwasaki, *Synlett* **1995**, 609.


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