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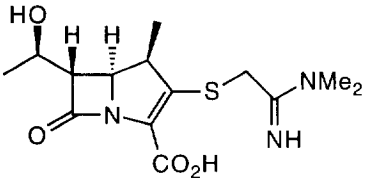
A New Synthetic Method of 1β-Methylcarbapenems Utilizing the Ketene Dithioacetal-Terminated Cyclization

Osamu Sakurai and Hiroshi Horikawa*

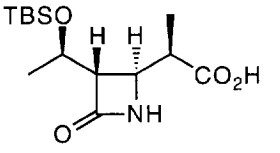
Lead Generation Research Laboratory, Tanabe Seiyaku Co., Ltd.,
3-16-89, Kashima, Yodogawa, Osaka 532, Japan

Abstract: Cyclization of alcohols **5** with the ketene dithioacetal terminator into carbapenams **6** was accomplished via the acyliminium ion generated from the corresponding mesylates. Carbapenams **6** were transformed into carbapenem **7** through $^1O_2$-mediated cleavage of the ketene dithioacetal portion, enolphosphorylation, and addition-elimination processes. Copyright © 1996 Elsevier Science Ltd

1β-Methylcarbapenems (e.g. **1**) have received much attention as new β-lactam antibiotics because of their excellent properties (broad-spectrum, strong antibacterial activities, resistance to β-lactamases, and metabolic stability to renal dehydropeptidase-I).[1] Furthermore, in addition to their potentials as β-lactam agents, their intriguing molecular structures (strained bicyclic β-lactams with four contiguous stereogenic centers and abundant functionalities) have stimulated extensive efforts to the synthetic studies.[2-4] In the syntheses of 1β-methylcarbapenems, the construction of 1-azabicyclo[3,2,0]heptane skeletons with the functionalities which are necessary for the "full-functionalized" carbapenems[4] has been as crucial a process as the stereocontrolled synthesis of the optically active carboxylic acid **2**.[2,3] In the context of our studies on the synthesis of carbapenems,[4g,5] we wish to report herein a new efficient synthesis of 1β-methylcarbapenems based on the cationic cyclization of the acyliminium ion with a ketene dithioacetal terminator via the novel intermediate **4**.



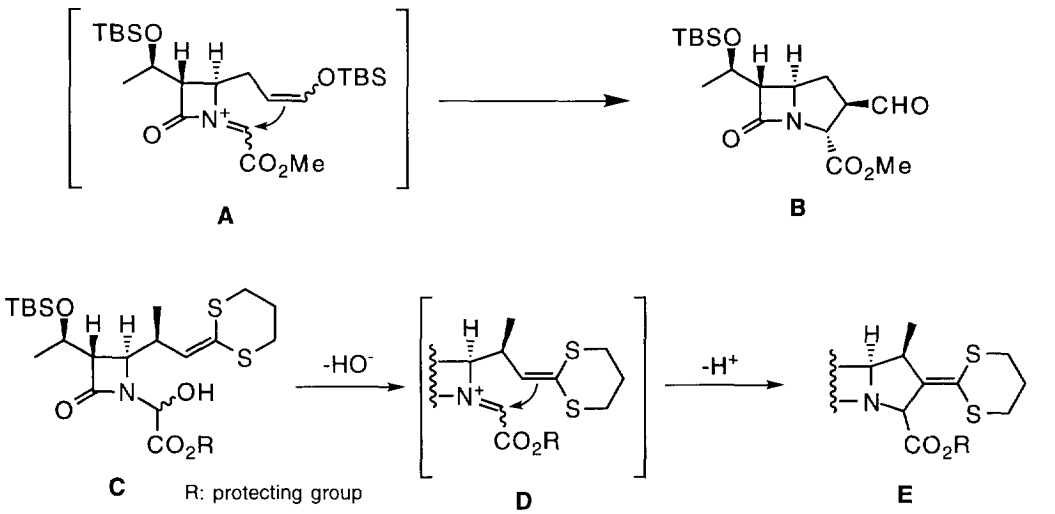
1



2 TBS: *t*-$BuMe_2Si$

Iminium ion- or acyliminium ion-mediated cyclization with electron-rich alkenes or alkynes is one of the most effective C-C bond-forming reactions and has been widely used for the syntheses of alkaloids and the related compounds.[6] We previously reported the synthesis of carbapenems utilizing aza-Cope-Mannich cyclization and demonstrated therein the cyclization of the 1-alkoxycarbonylmethylene acyliminium ion such as **A** indeed proceeded to give carbapenam **B**.[5b] We therefore thought that the acyliminium ion **D** generated from

easily accessible alcohols **C**, having a ketene dithioacetal moiety to secure the selective formation of the five-membered ring,[7] would lead to carbapenam **E**, which could then be transformed into the carbapenems.

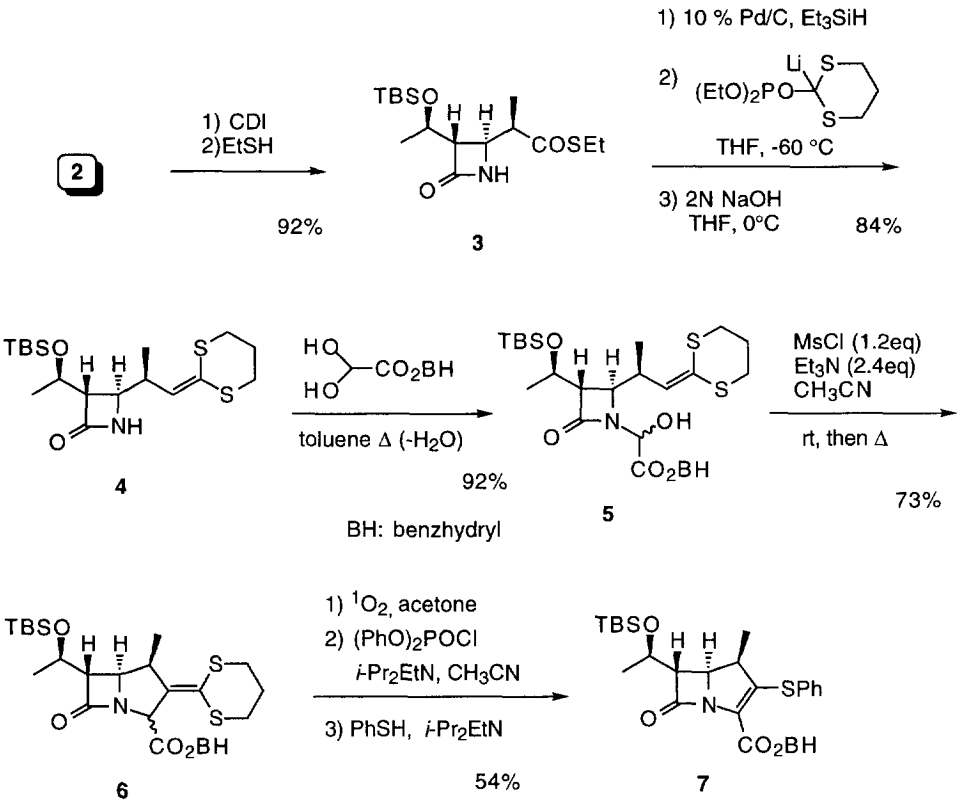


The precursor for the critical cyclization, alcohols **5**, was prepared in a straightforward fashion. Thioester **3**, derived from carboxylic acid **2** in an usual way, was subjected to the Fukuyama's reaction[8] to reduce to the corresponding aldehyde. Under these conditions, a concomitant protection of the lactam nitrogen with a triethylsilyl group proceeded presumably by the action of the resultant ethyl triethylsilyl sulfide as a silylating agent. The *N*-silylated aldehyde thus obtained was reacted with the lithium salt of 2-diethylphosphoryl-1,3-dithiane[9] followed by the selective *N*-desilylation[10] to afford ketene dithioacetal **4** in good yield.[11,12] Ketene dithioacetal **4** was next condensed with benzhydryl glyoxylate in refluxing toluene (azeotropical removal of water) to give an epimeric mixture of alcohols **5**.

With the desired precursor in hand, we turned our attention to the key reaction: the ketene dithioacetal-terminated cationic cyclization. In the related reactions used for the syntheses of alkaloids,[7a,13] it was reported that CH_3CN was a suitable solvent for the generation of the acyliminium ion from the mesylate intermediate and the subsequent cyclization. Thus, we employed the similar conditions: mesylate formation from **5** was performed in CH_3CN at room temperature (MsCl 1.2 eq, Et_3N 2.4 eq, ~1hr) followed by reflux of the reaction mixture. Under these conditions the desired carbapenams **6** were obtained as an epimeric mixture at C3 in good yield.[14]

Carbapenams **6** were transformed into carbapenem **7** in the following way. The ketene dithioacetal portion of **6** was oxidatively cleaved[7c,15] by $^1O_2$ to afford the corresponding β-ketoester. Without isolation, the β-ketoester was treated with $(PhO)_2POCl$ in the presence of *i*-Pr_2EtN in CH_3CN to form the enol phosphate, which was converted to carbapenem **7**[16] via the addition-elimination process.[1]

In summary, we established a new effective method for the synthesis of 1β-methylcarbapenems based on the cationic cyclization with a ketene dithioacetal terminator via the novel intermediate **4**. Research is in progress to investigate the scope of this process, the results of which will be disclosed in due course.



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11. Full crystal data for **4** has been deposited at the Cambridge Crystallographic Data Centre.
12. Characteristics of **4**: mp=115-116°C (from AcOEt-*n*-hexane); $[\alpha]_D^{25}$=+28.9° (*c* 1.0, $CHCl_3$); IR(KBr) 3250, 3100, 1754, 1711cm^{-1}; ^{1}H NMR(200MHz, $CHCl_3$) δ 0.07(6H,S), 0.88(9H, S), 1.04(3H, d, *J*=6.7Hz), 1.16(3H, d, *J*=6.3Hz), 2.15(2H, quintet, *J*=6.0Hz), 2.77-3.01(6H, m), 3.52(1H, dd, *J*=7.9, 2.1Hz), 4.19(1H, m), 5.69(1H, d, *J*=9.9Hz), 5.82(1H, br-s); ^{13}C NMR(200MHz, CD_3OD) δ -4.75, -4.06, 17.36, 18.80, 23.29, 26.05, 26.35, 30.35, 30.79, 39.85, 55.51, 62.96, 65.93, 130.1, 134.3, 171.7.
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14. A typical procedure is as follows: To a stirring solution of **5** (1.10g, 1.75mmol) in dry CH_3CN (20ml) with ice-cooling under N_2 atmosphere was added methanesulfonyl chloride (0.162ml, 2.10mmol) and triethylamine (0.585ml, 4.20mmol). After the reaction mixture was stirred for 30 min, the reaction temperature was raised to room temperature and stirring was continued for another 30 min to complete the corresponding mesylate formation. The reaction mixture was then refluxed until the mesylate intermediate was consumed (~4h). The reaction mixture was evaporated to remove CH_3CN. AcOEt and H_2O was added to the reaction mixture and the organic layer was separated. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel (elution with *n*-hexane:AcOEt = 7:1) to afford **6** (777mg, 73%) as a gummy syrup.
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16. Characteristics of **7**: IR(film) 1777, 1709cm^{-1}; ^{1}H NMR(200MHz, $CHCl_3$) δ 0.07(3H,s), 0.10(3H,s), 0.86(9H, s), 0.93(3H, d, *J*=7.3Hz), 1.15(3H, d, *J*=6.2Hz), 3.01(1H, m), 3.17(1H, dd, *J*=4.3, 2.9Hz), 4.20(1H, dd, *J*=9.7, 2.8Hz), 4.28(1H, m), 6.98(1H, s), 7.17-7.62(15H, m).

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