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Practical, Stereocontrolled Synthesis of 2-Functionalized-methyl-1β-methylcarbapenems

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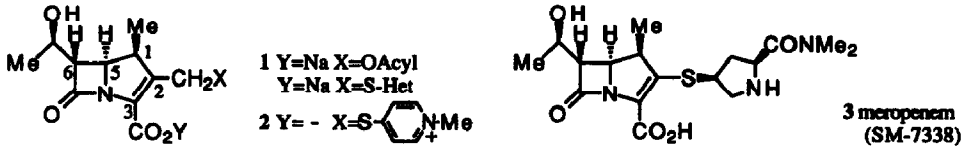
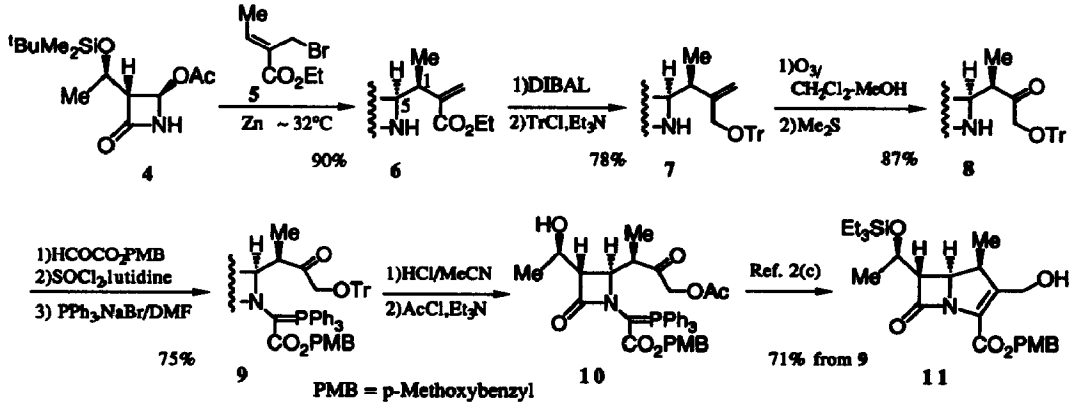
Abstract: Reaction of acetoxy-azetidinone **4**, (*Z*)-crotylbromide **5** and Zn selectively gave **6**, which was converted to 1β-methyl-2-(hydroxymethyl)carbapenem **11**, a key intermediate in synthesis of antibiotic **2**, in high overall yield.

2-Functionalized-methyl-1β-methylcarbapenem antibiotics **1**[1,2], which can be clearly distinguished from conventional-type 1β-methylcarbapenems represented by meropenem (SM-7338) **3** [3], have recently attracted much attention because of their high therapeutic potential. In the course of our project to develop carbapenem antibiotics, we have found that 2-(N-methyl-4-pyridinio)thiomethyl derivative **2** showed excellent *in vivo* as well as *in vitro* activity against both Gram-positive and -negative bacteria [4].



We report herein a highly stereocontrolled and practical synthesis of **2**, which allowed us to carry out further evaluation of this and related compounds as potential therapeutic agents.

The commercially available acetoxy-azetidinone **4** [5] was reacted with ethyl (*Z*)-2-(bromomethyl)-but-2-enoate **5** [6] (1.5 eq.) and Zn dust (1.5 eq.) in DMF at 25~32°C for 4 h. to give, after usual work-up and recrystallization, a single isomer **6** in 90% yield. The 1*S*,5*R* stereochemistry (carbapenem structure numbering) of **6** was proved by its successful conversion to the known derivatives **10** and **11** (*vide infra*). The 1*R* diastereoisomer, the only



other isomer which could be isolated for characterization, was detected by HPLC in less than 5% of the crude product. Reduction of **6** (DIBAL-toluene, -40 °C) followed by tritylation (TrCl-Et_3N, CH_2Cl_2, rt) gave the protected allylic alcohol **7** in 78% yield, which on ozonolysis (CH_2Cl_2-MeOH, -70 °C, then Me_2S, rt) provided the ketone **8** in 87% yield. The stable ylid **9** was then prepared by the standard procedure {1)$HCOCO_2PMB$, cat. Et_3N,THF, rt 2)$SOCl_2$-lutidine, THF, -40°C 3)PPh_3-lutidine, NaBr} in 75% yield. All the above intermediates including the ylid **9** are easy-to-purify crystalline materials which are suitable for large-scale synthetic operations. The two protective groups were removed by acid treatment (HCl-MeCN) and the primary OH group was selectively acetylated to give the monoacetoxy-ylid **10**. This synthesis of **10** is much more efficient and practical than our previous ones [7], and **10** was converted to **11**, the key intermediate in the synthesis of the antibiotic **2**. The overall yield of **11** from the ylid **9** was 71%.

The application of this method to the preparation of various 1β-(functionalized-)alkylcarbapenems of this type is now being investigated in our laboratories [8,9].

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9. Selected physical data: **6**; mp 92-93.5 °C. ^{1}H-NMR(200MHz $CDCl_3$) δ: 0.06 (6H, s), 0.87 (9H, s), 1.14 (3H, d, *J*=6.2Hz), 1.15 (3H, d, *J*=7Hz), 1.31 (3H, t, *J*=7.2Hz), 2.83 - 2.86 (1H, m), 2.97 - 3.11 (1H, m), 3.76 (1H, dd, *J*=6Hz, 2.2Hz), 4.11 - 4.25 (1H, m), 4.22 (2H, q, *J*=7.2Hz), 5.63 (1H, s), 5.88 (1H, s), 6.31(1H, s). **7**; mp147-148 °C. ^{1}H-NMR(200MHz $CDCl_3$) δ: 0.03 (6H, s), 0.83 (9H, s), 1.03 (3H, d, *J*=7Hz), 1.07 (3H, d, *J*=6.2Hz), 2.22 - 2.36 (1H, m), 2.69 (1H, dd, *J*=4.3Hz, 2.2Hz), 3.58(1H, dd, *J*=5.8Hz, 2.2Hz), 3.51 and 3.61 (2H, ABq, *J*=13Hz), 4.02- 4.14 (1H, m), 5.01 (1H, s), 5.41 (1H, s), 5.65(1H, s), 7.26 - 7.47(15H, m). **8** mp133-134 °C. ^{1}H-NMR(200MHz $CDCl_3$) δ : 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 1.09 (3H, d, *J*=7Hz), 1.15(3H, d, *J*=6.2Hz), 2.83 (1H, dd, *J*=5Hz, 2.2Hz), 3.09 - 3.22 (1H, m), 3.79 (1H, dd, *J*=4.4Hz, 2.2Hz), 3.84 (2H, s), 4.07 - 4.19 (1H, m), 5.75(1H, s), 7.26 - 7.46(1H, m). **9**; mp178-179 °C.

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