

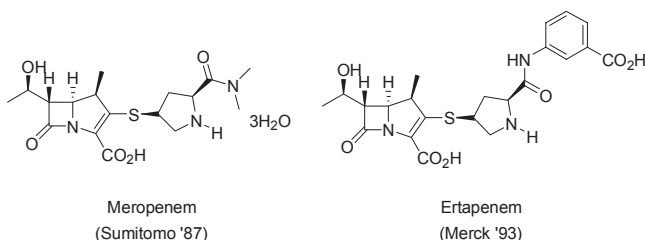
Stereocontrolled Crotylation of 4-Acetoxy-2-azetidinone for the Synthesis of 1 β -Methylcarbapenem Precursor

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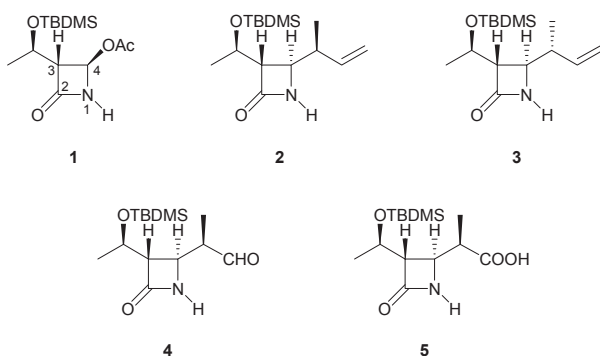
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The 1 β -methylcarbapenems are one of the important β -lactam antibiotics and become the object of ongoing pharmaceutical development.¹ For example, meropenem² and ertapenem³ have excellent spectrum of antibiotic activities and good resistance to renal dehydropeptidase I (DHP-I).⁴



One of the main problems for the synthesis of 1 β -methylcarbapenems from commercially available starting material such as (3*R*,4*R*)-4-(acetoxy)-3-[(1*R*)-1-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-2-azetidinone **1** is the introduction of carbon substituent at the C-4 position of the azetidinone moiety.⁵ Although a number of Reformatsky type enolate additions to azetidinones have been described,⁶ only a few examples regarding crotylation of azetidinone were reported with low or moderate yields, poor stereoselectivity or non-practical applicability.⁷



Several crotylation methods involving crotyl bromide with zinc powder^{7a,7b} and indium powder^{7c} are reported to give **2** and **3** as a 1:1 mixture of diastereomers. These methods are simple and practical, however, they are not stereoselective. Other methods using organometallic tri-*n*-butyl crotylstannane^{7d,7e} and (*Z*)-2-butenylchlorodimethylsilane^{7f} have been reported. Although the use of tri-*n*-butylcrotylstannane gives a good β to α

ratio (5:1) of diastereomers with the desired **2** as major component, the yield of **2** from **1** is low (35%). Also the use of stannyl and silyl derivatives are non-practical in industrial process. These are the reasons why a facile and efficient method for the stereoselective crotylation at C4 position should be developed. In the actual industrial process of carbapenems, compound **2** is converted directly into aldehyde **4**⁸ or carboxylic acid **5**⁹ followed by further functionalization.

We report herein an extremely simple and stereoselective, and therefore industrially feasible synthesis of **2** from the commercially available acetoxyazetidinone **1**. In order to find the optimum conditions for stereocontrolled syntheses of **2**, acetoxyazetidinone **1** was reacted with crotyl bromide and metals in the presence of ligands and Lewis acids. The control experiments with various metals in the absence of chiral ligands exhibited no stereoselectivity in all cases. The amount of tested ligands and Lewis acids varies from 0.0125 to 1.0 mole equivalents. The kinds of tested Lewis acids are AgCl, PdCl₂, AgOTf, CuCl, CuCN, Cu(OAc)₂, InCl₃, PbBr₂, GaCl₃, Ti(OPr)₄, CeCl₃, Sc(OTf)₃, ZnCl₂ and ZnBr₂. The kinds of tested chiral ligands are cinchonine, cinchonidin, quinine, quinidine, norephedrin, (*R*)-(+)-BINAP, (*S*)-(-)-BINAP, (*S*)-(-)-amino-3-phenyl-1-propanol, (*R*)-(-)-2-phenylglycinol, amino-2-indanol, (*S*)-(+)-amino-1-butanol, *O*-acetylquinine, *O*-acetylquinidine, (*R*)-BINOL, (*S*)-BINOL, (*S*)-2-aminopropanol, (*R*)-2-aminopropanol, *O*-acetylquinine and *O*-acetylquinidine. The kinds of tested metals are zinc, aluminum, gallium and indium. Common solvents such as diethyl ether, dioxane, THF, DMF, DME and IPE are tested. After numerous trials, excellent results are obtained with zinc as a metal, InCl₃ as a Lewis acid, and cinchonine as a ligand in diethyl ether. When the reaction was performed with catalytic amount of InCl₃ (0.025 equiv), Zn (2.0 equiv) and cinchonine alkaloids (0.025 equiv) in diethyl ether at 25 ~ 30 °C, best results were obtained with reasonably good β to α ratio (5.0 : 1.0) in 98% isolated yield. All ratios were observed from the ¹H-NMR after work-up. The selected results of this approach are summarized in Table 1.

Interestingly, it is found that the β to α ratios are reversed by simply using indium instead of zinc under same conditions (entry **9** ~ **12**). The typical procedure is as follows. To a mixture of **1** (2.874 g, 10.0 mmol), cinchonidine (0.074 g, 0.025 equiv), InCl₃ (0.044 g, 0.025 equiv) in ether (240 mL) was added crotyl bromide (2.0 mL, 2.0 equiv) at 25 ~ 30 °C and the mixture was stirred for 30 min. Zinc (0.654 g, 2.0 equiv) granule purchased from Aldrich without further activation was added therein and

Table 1. Barbier-type crotylation of 4-acetoxy-2-azetidinone

entry ^a	ligand	equiv of ligands	equiv of InCl ₃	metal	isolated yield	ratio (β : α)
1	cinchonidine	0.025	0.025	Zn	98	5.0 : 1.0
2	quinine	0.025	0.025	Zn	89	3.6 : 1.0
3	quinidine	0.025	0.025	Zn	80	2.6 : 1.0
4	cinchonine	0.025	0.025	Zn	91	4.9 : 1.0
5 ^b	quinine	0.025	0.025	Zn	86	2.2 : 1.0
6	quinidine	0.05	0.05	Zn	88	2.6 : 1.0
7	quinidine	0.0125	0.0125	Zn	93	3.1 : 1.0
8	cinchonine	0.0125	0.0125	Zn	91	3.9 : 1.0
9	cinchonine	0.025	0.025	In	91	1.0 : 2.1
10	cinchonidine	0.025	0.025	In	94	1.0 : 1.9
11	quinine	0.025	0.025	In	97	1.0 : 1.6
12	quinidine	0.025	0.025	In	95	1.0 : 2.0

^aThe reactions were run with zinc or indium (2.0 equiv) and crotyl bromide (2.0 equiv) in Et₂O at 25 ~ 30 °C. ^bThe reaction was run at 0 ~ 5 °C.

stirred for 2 h. The reaction mixture was poured into saturated ammonium chloride solution (40 mL), extracted with ether (30 mL × 2). The organic layer was dried over anhydrous Na₂SO₄, evaporated in vacuo and chromatographed on a silica gel column to give white solid of **2** and **3** (2.780 g, 98%). The product ratio was determined to be 5.0 : 1.0 by 400 MHz ¹H-NMR analysis.^{7b} Chromatographic separation of β-isomer from α-isomer was not effective at this stage. The separation of the mixture of α,β-isomers was well documented in the literature after desilylation followed by chromatography.^{7b}

To our knowledge, this is the best stereoselective synthesis of (4R)-4[(1S)-1-methylallyl]-2-azetidinone **2** with high yields. Some parts of these results are applied for the patent.¹⁰ We anticipate that this methodology will be useful in the industrial process for the synthesis of 1β-methylcarbapenems from commercially available azetidinone **1**.

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