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DIASTEREOSELECTIVE SYNTHESIS OF 6-BROMO-6-(1-HYDROXYETHYL)PENICILLANATE BY CROSS-COUPLING OF 6,6-DIBROMOPENICILLANATE AND ACETALDEHYDE PROMOTED WITH GRIGNARD REAGENTS: ROLE OF AMINE LIGANDS

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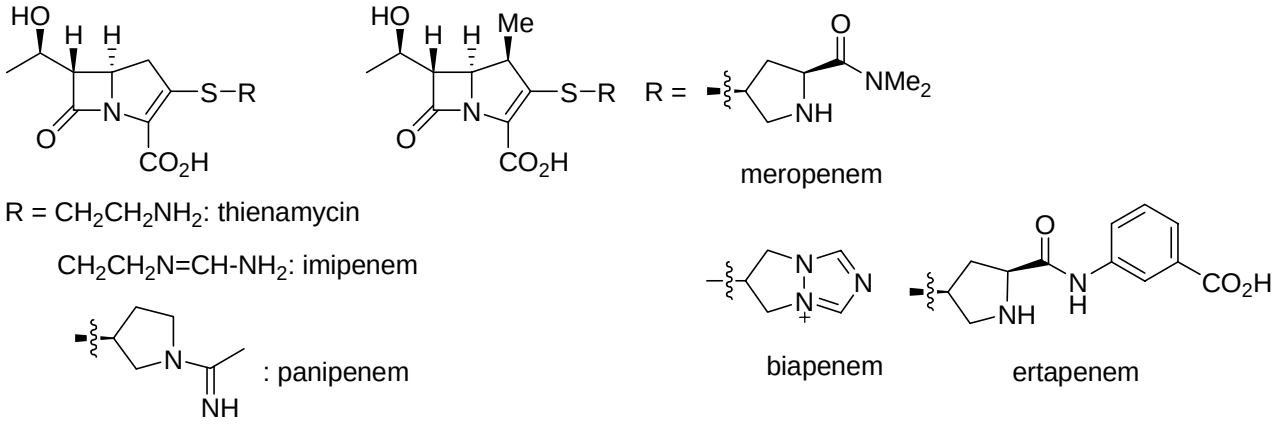
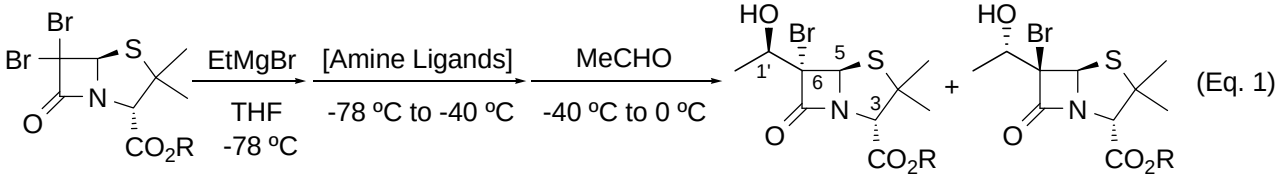
Abstract – Grignard reagent-promoted coupling reaction of diphenylmethyl 6,6-dibromopenicillanate **1b** with acetaldehyde in the presence of *N*,*N*,*N'*,*N"*,*N"*-pentamethyldiethylenetriamine took place in a highly diastereoselective manner to give diphenylmethyl (1'*R*,3*S*,5*R*,6*S*)-6-bromo-6-(1'-hydroxyethyl)penicillanate **2b** effectively, which is a potent intermediate for the synthesis of carbapenem antibiotics.

β-Lactam antibiotics are widely prescribed antibiotics in medicine. They have potent and broad antibacterial activities, low toxicity as well as excellent metabolic stability.[1] In the past decades, research on β-lactam, especially on synthesis of penicillin and cephalosporin derivatives, has widely spread. Most of the β-lactam antibiotics of these categories become, however, ineffective against microorganisms which can produce β-lactamase. In 1976, thienamycin was discovered as a member of new class of β-lactam antibiotics commonly called carbapenems.[2] Research has focused on the carbapenem antibiotics because they possess potent antibacterial activities against a wide range of gram-positive and gram-negative bacteria, and high resistance to bacterial β-lactamases. However, thienamycin itself could not be marketed due to its chemical and biological instability. To overcome these problems, many groups have been seeking more stable derivatives of carbapenems, and carbapenem derivatives such as imipenem,[3] meropenem,[4] biapenem,[5] panipenem,[6] and ertapenem[7] have been developed and marketed (Scheme 1).

Scheme 1. Carpapenems



As a structural feature, these carbapenems have 1-hydroxyethyl group at C-6 position of carbapenem framework. Stereoselective introduction of the 1-hydroxyethyl group must be an indispensable task in the syntheses of these carbapenems. A few methodologies have been developed, such as intramolecular cyclization of 2-(1'-hydroxyethyl)-3-aminopropanoic acid,[8] aldol reaction of 2-azetidinones and acetaldehyde,[9] stereoselective reduction of 3-acetyl-2-azetidinones,[10] and intramolecular cyclization of *N*-2-oxapropyl 2,3-epoxypropanamide.[11] Yoshida and his co-workers reported[12] Grignard reagents-promoted cross-coupling of benzyl 6,6-dibromopenicillanate **1a** and acetaldehyde affording a mixture of benzyl (1'*R*,3*S*,5*R*,6*S*)-6-bromo-6-(1'-hydroxyethyl)penicillanate **2a** and its (1'*S*,6*R*)-isomer **3a** in totally 91% yield. We executed a similar reaction with diphenylmethyl 6,6-dibromopenicillanate **1b**,[13] resulting in the formation of a mixture of the desired isomer **2b** and the undesired **3b** in a ratio of 1.6:1 in totally 60% yield (*vide infra*). The stereoselectivity was not satisfactory in a practical sense.



1a (R = CH_2Ph)
1b (R = $CHPh_2$)

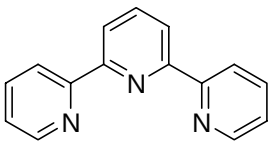
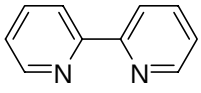
2a (R = CH_2Ph)
2b (R = $CHPh_2$)
(desired)

3a (R = CH_2Ph)
3b (R = $CHPh_2$)
(undesired)

In our continuing studies on potent intermediates for the synthesis of carbapenem antibiotics, we reinvestigated the Grignard reagent-promoted reaction of diphenylmethyl 6,6-dibromopenicillanate **1b** with acetaldehyde in the presence of various amine ligands (Eq. 1), and found that the stereoselectivity was significantly improved by the presence of the amine ligands. In this paper we describe the remarkable effects of the amine ligands on the improvement of stereoselectivity of the coupling reaction.

A typical procedure is as follows (Table 1, Entry 2): Into a THF solution (2.5 mL) of diphenylmethyl 6,6-dibromopenicillanate **1b** (0.30 mmol) was added a THF solution of ethylmagnesium bromide (0.98 M, 0.49 mmol) dropwise at -78 ºC. After the mixture was stirred at -78 ºC for 30 min., *N,N,N',N",N"*-pentamethyldiethylenetriamine (PMDTA, 0.51 mmol) was added. The mixture was gradually warmed up to -40 ºC and stirred for additional 2 h at this temperature. To the mixture was added THF solution (2 mL) of acetaldehyde (1.5 mmol) at -40 ºC, and stirring was continued at 0 ºC for 3 h. Usual work-up followed by column chromatography (SiO_2, toluene/AcOEt = 10/1) afforded the desired compound **2b** (0.26 mmol, 86%) and its isomer **3b** (0.02 mmol, 6%).

Table 1. EtMgBr-Promoted Aldol-type Coupling of Dibromopenam **1b** and Acetaldehyde

Entry	Ligand		**2b**[a]	**3b**[a]	**2b** + **3b**	Ratio
		equiv.[b]	/%	/%	/%	of **2b**/**3b**
1	none	-	37	23	60	1.6
2	$Me_2N(CH_2)_2NMe(CH_2)_2NMe_2$	1.7	86	6	92	14.3
3	$Me_2N(CH_2)_2NMe_2$	1.2	62	13	75	4.8
4	$Me_2N(CH_2)_2NMe_2$	2.2	63	18	81	3.5
5	$Et_2N(CH_2)_2NEt_2$	1.2	51	17	68	3.0
6	NEt_3	1.2	37	13	50	2.8
7	NEt_3	2.2	41	8	49	5.1
8	NEt_3	3.2	50	8	58	6.3
9	*i*-Pr_2NEt	3.2	52	11	63	4.2
10	NPh_3	3.2	54	17	71	3.2
11		1.7	56	26	82	2.2
12		1.2	61	22	83	2.8
13	pyridine	3.2	42	19	61	2.2

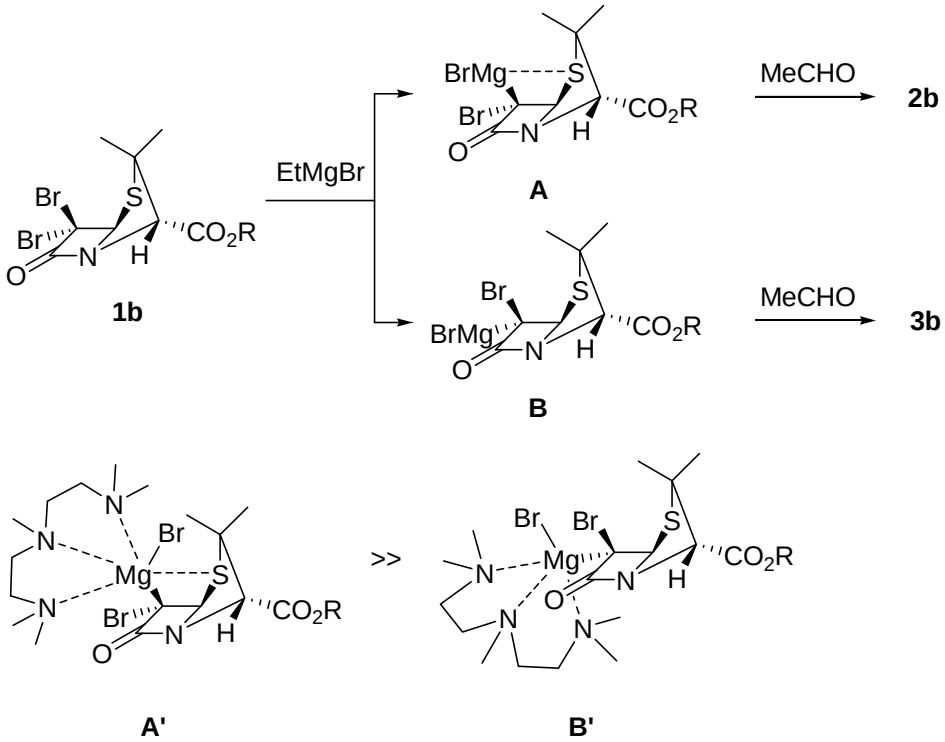
[a]Isolated yield after column chromatography. [b]Mol equivalent *vs*. **1b**.

The effect of amines on the stereoselectivity is summarized in Table 1. When a similar reaction was carried out in the absence of amine ligand (Entry 1), the stereoselectivity of the 6-(1'-hydroxyethyl) moiety was poor, yielding a mixture of the desired (1'*R*,6*S*)-isomer **2b**:and the undesired (1'*S*,6*R*)-isomer

3b (**2b**/**3b** = 1.6) in 60% yield. The remarkable increase of the total yield (**2b + 3b)** as well as the selectivity (**2b** vs. **3b**) by addition of PMDTA prompted us to investigate the reaction of **1b** with acetaldehyde in the presence of various amines. Aliphatic amines, such as *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA, Entries 3-4), *N*,*N*,*N*',*N*'-tetraethylethylenediamine (TEEDA, Entry 5), triethylamine (Entries 6-8), and ethyldiisopropylamine (Entry 9) were effective in improving the **2b**/**3b** ratio The stereoselectivity varied in the range of 2.8 to 6.3 depending on the choice of amine. The yields and the ratio **2b**/**3b** were also dependent on the amount of amine: indeed, 1.2 equivalents of triethylamine gave a mixture of **2b** and **3b** in a ratio of 2.8/1, and the ratio **2b**/**3b** significantly increased to 6.3/1 with 3 equivalent of triethylamine. Among amines examined thusfar, trivalent amine PMDTA was the best choice for the stereoselective coupling reaction. Heteroaromatic amines, such as 2,2';6',2"-terpyridyl, 2,2'-bipyridyl, and pyridine, were also examined, but they were less effective than the corresponding aliphatic amines (**2b**/**3b** = 2.2-2.8) (Entries 11-13).

Upon treatment of the 6,6-dibromopenicillanate **1b** with ethylmagnesium bromide, the corresponding C-enolate **A** and **B** would be formed. Subsequently, enolates **A** and **B** would react with acetaldehyde to give (1'*R*,6*S*)-6-bromo-6-(1'-hydroxyethyl)penicillanate **2b** and its (1'*S*,6*R*)-isomer **3b**, respectively. It is likely that addition of PMDTA would favor the formation of amine-ligated enolate **A'** [14] rather than the isomer **B'**, resulting in the significantly enhanced stereoselectivity in formation of the desired isomer **2b**.

Scheme 2. Plausible Intermediates of the Coupling Reaction of 6,6-Dibromopenicillanate **1b** and Acetaldehyde with Grignard Reagent/PMDTA



In conclusion, Grignard reagent-promoted coupling reaction of diphenylmethyl 6,6-dibromopenicillanate **1b** with acetaldehyde in the presence of *N,N,N',N",N"*-pentamethyldiethylenetriamine proceeded smoothly in highly stereoselective manner to afford the desired (1'*R*,3*S*,5*R*,6*S*)-6-bromo-6-(1'-hydroxyethyl)penicillanate **2b** efficiently.

EXPERIMENTAL

IR spectra were obtained on JASCO FT/IR VALOR-III spectrometer and JASCO FT/IR-4100 spectrometer. ^{1}H NMR spectra were determined with a VARIAN Gemini 200 (200 MHz) and a VARIAN VXR-500 (500 MHz) spectrometer. ^{13}C NMR spectra were determined with a VARIAN VXR-500 (125 MHz) spectrometer.

Grignard reagent-promoted coupling reaction of diphenylmethyl 6,6-dibromopenicillanate 1b with acetaldehyde Diphenylmethyl 6,6-dibromopenicillanate **1b** (156 mg, 0.30 mmol) and THF (2.5 mL) were placed into a 20 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a three-way cock, and a rubber septum. To the solution was added THF solution of EtMgBr (0.98 mol·L^{-1}, 0.50 mL, 0.49 mmol) dropwise at -78 ºC, and the resultant was stirred at -78 ºC for 30 min. After the addition of PMDTA (0.11 mL, 0.51 mmol) at -78 ºC, the mixture was gradually warmed up to -40 ºC and stirred at this temperature for 2 h. Then, a supernatant of a mixture of acetaldehyde (0.080 mL, 1.5 mmol), molecular sieves 3A powder (102 mg), and THF (2.0 mL) was added dropwise at -40 ºC. The mixture was gradually warmed up to 0 ºC, and stirred at 0 ºC for 3 h before aq. sat. NH_4Cl (4.5 mL) were added. The whole mixture was filtrated through celite. The organic layer was separated and the aqueous layer was extracted with AcOEt (10 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (toluene/AcOEt = 10/1) to afford the desired compound **2b** (126 mg, 0.26 mmol, 86%) and its isomer **3b** (9 mg, 0.02 mmol, 6%).

Diphenylmethyl (1'*R*,3*S*,5*R*,6*S*)-6-bromo-6-(1'-hydroxyethyl)penicillanate (**2b**):[12c] colorless solids; R_f = 0.13 (toluene/AcOEt : 10/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.28 (d, J = 4.0 Hz, 3H), 1.63 (s, 3H), 2.40 (d, J = 5.2 Hz, 1H), 4.08-4.30 (m, 1H), 4.61 (s, 1H), 5.63 (s, 1H), 6.94 (s, 1H), 7.30-7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.96, 25.60, 33.52, 64.89, 67.17, 68.06, 71.87, 74.69, 78.54, 127.06, 127.34, 128.17, 128.28, 128.38, 128.59, 128.61, 128.98, 138.88, 138.95, 165.89, 169.03; IR (KBr) 3471, 3063, 3033, 2978, 2931, 1783, 1746, 1496, 1455, 1373, 1256, 1179, 1020 cm^{-1}.

Diphenylmethyl (1'*S*,3*S*,5*R*,6*R*)-6-bromo-6-(1'-hydroxyethyl)penicillanate (**3b**):[12c] colorless solids; R_f = 0.20 (toluene/AcOEt : 10/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.44 (d, J = 6.4 Hz, 3H), 1.65 (s, 3H), 2.17 (d, J = 5.2 Hz, 1H), 4.15-4.28 (m, 1H), 4.60 (s, 1H), 5.51 (s, 1H), 6.93 (s, 1H), 7.33-7.36 (m, 10H); IR (KBr) 3426, 3065, 3031, 2978, 2931, 1784, 1739, 1454, 1373, 1261, 1181, 1020 cm^{-1}.

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