

A Novel Approach to 1- β -Methylcarbapenem Intermediate Utilizing Lithium Enolate Dianion of 2'-Hydroxypropiophenone

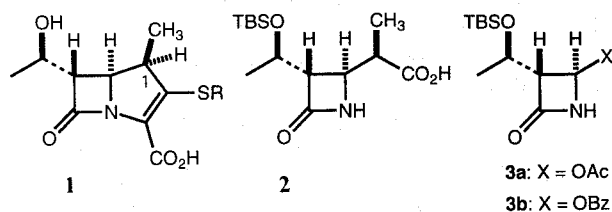
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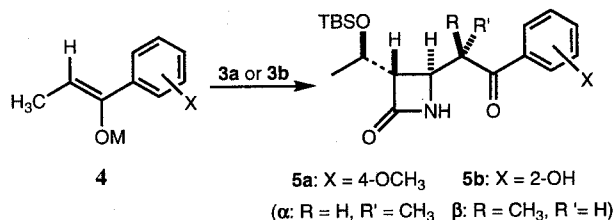
Received August 16, 1995

Since the discovery of thienamycin, intensive efforts have been devoted for the synthesis of chemically and metabolically more stable carbapenem nucleus with enhanced biological activity, and led to the development of 1- β -methylcarbapenems **1**.¹ A number of stereoselective syntheses of **2**, a well-established intermediate of **1**, have been made mainly from commercially available 4-acetoxy-2-azetidinone **3a**.² Conversion of 4-acetoxy group of **3a** into 4-[(R)-1-carboethoxyethyl] group of **2** by aldol-type reactions with metal enolates of propionate derivatives has been a very popular approach. Since the stereoselectivity at the C-1 position depends on the structure of enolate, various chiral and achiral auxiliaries were devised, including 3-thiazolidine-2-thione,³ 2-oxazolidinone,⁴ 2-picolyl thiol,⁵ and 2,3-dihydro-4-*H*-1,3-benzoxazin-4-ones.^{6,7} Although high diastereoselectivities were achieved in introducing the 1-methyl group, these auxiliaries are difficult of access, and such conversion requires expensive reagents, like Sn(OTf)₂ and Et₂BOTf. Thus, a more practical method to provide **2** is still in demand.

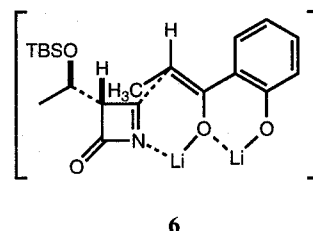


In connection with this, we became interested in the reactions of **3a** or **3b** with metal enolates of readily available 4'-methoxy- and 2'-hydroxypropiophenone. Since the oxygen-substituted benzoyl moiety in the condensation product should be selectively oxidized to the corresponding ester or carboxylic acid, we first studied the stereochemical outcome of this aldol-type condensation of ketone enolate. Trimethylsilyl enol ether of 4'-methoxypropiophenone was reac-

ted **3a** in the presence of ZnI₂ to give **5a** in 97% yield with a dominant α -diastereomer (entry 1, Table 1).⁸ Reaction of **3a** with two equivalents of lithium enolate 4'-methoxypropiophenone, generated with LDA in THF at -78 °C, provided an 1:1.9 mixture of **5a α** and **5a β** in 85% yield (entry 2).⁹ Tin(II) enolate, generated *in situ* from α -bromo-4'-methoxypropiophenone and tin powder, displayed an improved β -selectivity (entry 3).¹⁰ This marginal selectivity could be further



improved by the introduction of enolate dianion of 2'-hydroxypropiophenone. Thus, two equivalents of lithium enolate dianion of 2'-hydroxy propiophenone was reacted with **3a** to give an 1:3.7 mixture of **5b α** and **5b β** in 56% yield (entry 4). These diastereomers were easily separated by recrystallization and SiO₂ chromatography. Even with excess of the dianion, the yield was moderate and unreacted **3a** (about 30%) was recovered. We speculated that the increased basicity of the enolate dianion of 2'-hydroxypropiophenone caused transesterification with **3a** and was responsible for the recovered **3a**. Indeed, when 4-benzyloxy **3b** instead of 4-acetoxy **3a** was used, the yield was improved to 82% (entry 5, Table 1). The enhanced diastereoselectivity in the formation of **5** using the enolate dianion can be explained by the tight coordination in the six-membered transition state, like **6**, between the acylimine generated from **3a** and Z-enolate dianion **4**.¹¹



While the diastereomeric mixture of 4'-methoxyphenyl ketone **5a** was smoothly oxidized to the corresponding ester with *m*-CPBA, the same reaction with diastereomerically pure **5b β** was extremely slow. Direct conversion of 2'-hydroxybenzoyl group of **5b β** to carboxylic acid **2** was accomplished with 30% hydrogen peroxide and 2 N LiOH in THF in 65% yield after reductive work-up with dimethyl sulfide and recr-

Table 1. Condensations of Metal Enolates of 4'-Methoxy- and 2'-Hydroxypropiophenone with **3a** or **3b**

| entry | M | X | 3a/3b | condition | 5a : 5b | yield (%) |
|-------|-------------------|--------------------|--------------|--|-----------------------|-----------|
| 1 | SiMe ₃ | 4-OCH ₃ | 3a | ZnI ₂ , CH ₂ Cl ₂ , rt | 3.5 : 1 | 97 |
| 2 | Li | 4-OCH ₃ | 3a | THF, -78 °C, 1 h | 1 : 1.9 | 85 |
| 3 | SnBr | 4-OCH ₃ | 3a | DMF-CH ₂ Cl ₂ , Sn-AgBF ₄ -I ₂ | 1 : 2.8 | 72 |
| 4 | Li | 2-OLi | 3a | THF, -78 °C, 2h | 1 : 3.7 | 56 |
| 5 | Li | 2-OLi | 3b | THF, -78 °C, 2h | 1 : 3.8 | 82 |

ystallisation.¹²

In summary, we studied diastereoselective reactions between **3a** or **3b** with metal enolates of readily available propiophenone derivatives. Direct oxidative conversion of the resulting 2'-hydroxybenzoyl derivative **5b β** to 1 β -methylcarbapenam intermediate **2** was developed.

Experimental Section

(3S,4R)-3-[(R)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(2-hydroxybenzoyl)]-2-azetidinone (5b β). To a solution of diisopropylamine (1.80 mL, 12.8 mmol) in 30 mL of dry THF at $-78\text{ }^{\circ}\text{C}$ was added 1.6 M *n*-BuLi in hexane (8.0 mL, 12.8 mmol). After 1 h, a solution of 2'-hydroxypropiophenone (0.88 mL, 6.4 mmol) in 5 mL of THF was added to LDA solution *via* cannula and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. A solution of 4-benzoyloxy- β -lactam **3b** (1.04 g, 3.15 mmol) in 5 mL of THF was added to the enolate solution, and the resulting solution was stirred for 2 h at the temperature and quenched by adding 150 mL of sat. NH₄Cl solution. The aqueous layer was extracted twice with 100-mL portions of ethyl acetate and the combined organic layers were washed with 100 mL of brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was flash chromatographed twice (ethyl acetate : hexane = 1 : 4, 1 : 2) to give 203 mg (17%) of **5ba** and 771 mg (65%) of **5b β** . **Isomer 5ba**: mp 165-167 $^{\circ}\text{C}$; R_f = 0.42 (ethyl acetate : hexane = 1 : 1); $[\alpha]_D^{25}$ = +90.3 (c = 1.0, EtOH); IR (KBr) 1762, 1638 cm^{-1} ; ^1H NMR (500 MHz, CDCl₃) δ 0.09 (s, 3H, CH₃Si), 0.10 (s, 3H, CH₃Si), 0.90 (s, 9H, *t*-Bu), 1.29 (d, J = 7 Hz, 3H, CH₃), 1.35 (d, J = 6 Hz, 3H, CH₃), 2.89 (dd, J = 6, 2 Hz, 1H, CHCO), 3.57 (dq, J = 9, 7 Hz, 1H, C(1)H), 3.95 (dd, J = 9, 2 Hz, 1H, CHN), 4.22 (quint., J = 6 Hz, CHOSi), 5.80 (br s, 1H, NH), 6.91-7.75 (m, 4H, ArH), 12.2 (s, 1H, OH); MS m/z (relative intensity) 320 (M^+ -*t*-Bu, 6), 200 (14), 195 (5), 161 (4), 121 (43), 93 (6), 86 (7), 72 (45), 59 (100), 55 (24). **Isomer 5b β** : mp 163 $^{\circ}\text{C}$; R_f = 0.35 (ethyl acetate : hexane = 1 : 1); $[\alpha]_D^{25}$ = -77.1 (c = 1.4, EtOH); IR (KBr) 1761, 1630 cm^{-1} ; ^1H NMR (500 MHz, CDCl₃) δ 0.05 (s, 3H, CH₃Si), 0.07 (s, 3H, CH₃Si), 0.86 (s, 9H, *t*-Bu), 1.15 (d, J = 6 Hz, 3H, CH₃), 1.34 (d, J = 5 Hz, 3H, CH₃), 2.91 (dd, J = 5, 2 Hz, 1H, CHCO), 3.74 (dq, J = 6, 5 Hz, 1H, C(1)H), 3.99 (dd, J = 5, 2 Hz, 1H, CHN), 4.17 (quint., J = 6 Hz, CHOSi), 6.60 (br s, 1H, NH), 6.90-7.76 (m, 4H, ArH), 12.3 (s, 1H, OH); MS m/z (relative intensity) 320 (M^+ -*t*-Bu, 9), 200 (20), 195 (10), 161 (4), 121 (58), 93 (8), 86 (6), 72 (45), 59 (100), 55 (23).

(3S,4R)-3-[(R)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-carboxyethyl]-2-azetidinone (2). To a solution of **5b β** (710 mg, 188 mmol) in 20 mL of THF was added 4 mL of 30% hydrogen peroxide and 4 mL of 2 N LiOH followed by stirring for 2 h at room temperature under atmosphere. Dimethyl sulfide (4 mL) was added, and the resulting mixture was stirred for 2 h at room temperature followed by addition 100 mL of 1 N HCl solution. The aqueous layer was extracted three times with 100-mL portions of ethyl acetate and the combined organic layers were washed with 100 mL of brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was flash chro-

matographed (ethyl acetate : hexane = 1 : 1 and 2 : 1) to give 369 mg (65%) of **2** after recrystallization in ethyl acetate and hexane: mp 142-143 $^{\circ}\text{C}$ (lit. 140-143 $^{\circ}\text{C}$).^{1a} Spectral data (^1H NMR, IR) of **2** are identical with those reported.

Acknowledgment. This study was supported by Korea Science and Engineering Foundation (92-25-00-08) and Korea University. Mass analyses at Organic Chemistry Research Center are also gratefully acknowledged.

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