

## A Novel Approach to 1- $\beta$ -Methylcarbapenem Intermediate Utilizing Lithium Enolate Dianion of 2'-Hydroxypropiophenone

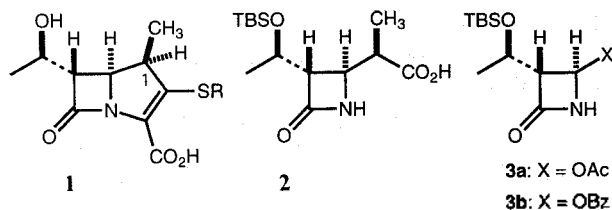
Deok-Chan Ha,\* Hyun-Seok Kim, No-Sang Park<sup>†</sup>,  
and Joong-Kwon Choi<sup>†</sup>

Department of Chemistry, Korea University,  
Seoul 136-701, Korea

<sup>†</sup>Division of Medicinal Chemistry, KRICT,  
Taejeon 305-600, Korea

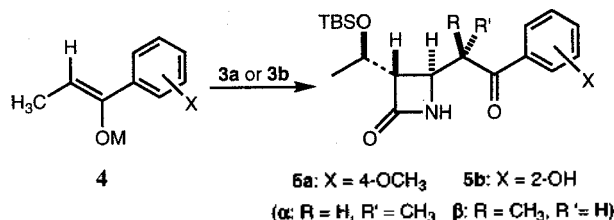
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Since the discovery of thienamycin, intensive efforts have been devoted for the synthesis of chemically and metabolically more stable carbapenem nucleus with enhanced biological activity, and led to the development of 1- $\beta$ -methylcarbapenems 1.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3</sup> 2-oxazolidinone,<sup>4</sup> 2-picolyl thiol,<sup>5</sup> and 2,3-dihydro-4-*H*-1,3-benzoxazin-4-ones.<sup>6,7</sup> 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)<sub>2</sub> and Et<sub>2</sub>BOTf. Thus, a more practical method to provide 2 is still in demand.

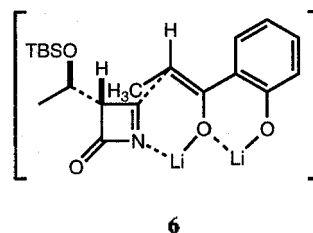


In connection with this, we became interested in the reactions of 3a or 3b with metal enolates of readily available 4'-methoxy- and 2'-hydroxypropiophenone. Since the oxygen-substituted benzoyl moiety in the condensation product should be selectively oxidized to the corresponding ester or carboxylic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

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



improved by the introduction of enolate dianion of 2'-hydroxypropionophenone. Thus, two equivalents of lithium enolate dianion of 2'-hydroxypropionophenone was reacted with 3a to give an 1 : 3.7 mixture of 5b $\alpha$  and 5b $\beta$  in 56% yield (entry 4). These diastereomers were easily separated by recrystallization and SiO<sub>2</sub> 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'-hydroxypropionophenone caused transesterification with 3a and was responsible for the recovered 3a. Indeed, when 4-benzoyloxy 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.<sup>11</sup>



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 $\beta$  was extremely slow. Direct conversion of 2'-hydroxybenzoyl group of 5b $\beta$  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'-Hydroxypropionophenone with 3a or 3b

entry	M	X	3a/3b	condition	5a : 5 $\beta$	yield (%)
1	SiMe <sub>3</sub>	4-OCH <sub>3</sub>	3a	ZnI <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , rt	3.5 : 1	97
2	Li	4-OCH <sub>3</sub>	3a	THF, -78 °C, 1 h	1 : 1.9	85
3	SnBr	4-OCH <sub>3</sub>	3a	DMF-CH <sub>2</sub> Cl <sub>2</sub> , Sn-AgBF <sub>4</sub> -I <sub>2</sub>	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.<sup>12</sup>

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 **5bβ** to 1β-methylcarbapenam intermediate **2** was developed.

### Experimental Section

**(3S,4R)-3-[(R)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(R)-1-(2-hydroxybenzoyl)]-2-azetidione (5bβ).** 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.  $\text{NH}_4\text{Cl}$  solution. The aqueous layer was extracted twice with 100-mL portions of ethyl acetyl acetate and the combined organic layers were washed with 100 mL of brine, dried over  $\text{MgSO}_4$  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 **5bβ**. **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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.09 (s, 3H,  $\text{CH}_3\text{Si}$ ), 0.10 (s, 3H,  $\text{CH}_3\text{Si}$ ), 0.90 (s, 9H, *t*-Bu), 1.29 (d,  $J$  = 7 Hz, 3H,  $\text{CH}_3$ ), 1.35 (d,  $J$  = 6 Hz, 3H,  $\text{CH}_3$ ), 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 ( $\text{M}^+$ -*t*-Bu, 6), 200 (14), 195 (5), 161 (4), 121 (43), 93 (6), 86 (7), 72 (45), 59 (100), 55 (24). **Isomer 5bβ**: 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.05 (s, 3H,  $\text{CH}_3\text{Si}$ ), 0.07 (s, 3H,  $\text{CH}_3\text{Si}$ ), 0.86 (s, 9H, *t*-Bu), 1.15 (d,  $J$  = 6 Hz, 3H,  $\text{CH}_3$ ), 1.34 (d,  $J$  = 5 Hz, 3H,  $\text{CH}_3$ ), 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 ( $\text{M}^+$ -*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-azetidione (2).** To a solution of **5bβ** (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 2h 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  $\text{MgSO}_4$ . 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  $^{\circ}\text{C}$ ).<sup>1a</sup> Spectral data ( $^1\text{H}$  NMR, IR) of **2** are identical with those reported.

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