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A highly diastereoselective synthesis of a 1-β-methylcarbapenem intermediate using titanium enolate of 2′-hydroxypropiophenone

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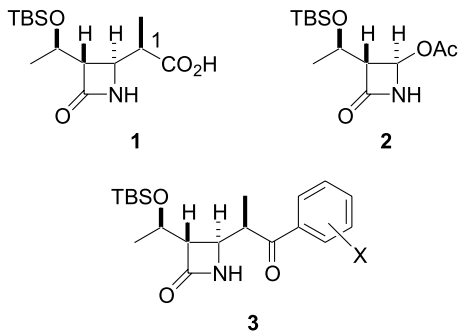
Abstract—A key 1-β-methylcarbapenem intermediate is synthesized from a highly diastereoselective condensation between the titanium enolate of 2′-hydroxypropiophenone with 4-acetoxy-β-lactam followed by ozonolysis of the resulting ketone to the carboxylic acid.

1. Introduction

In the synthesis of 1-β-methylcarbapenems with increased chemical and metabolic stability retaining the potent antibacterial activity of thienamycin, β-lactam **1** is serving as a key intermediate.[1] Most of the efforts for the synthesis of **1** have been devoted to the stereoselective introduction of 2-propionic acid moiety to the C(4) position of the commercially available 4-acetoxy-β-lactam **2**.[2] Diverse metal enolates of propionic acid derivatives having chiral and achiral auxiliaries were devised, including 2-oxazolidinones,[3a] 2-picolyl thiols,[4] and 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones,[5] for the improved β-selectivity of **1**. But, still more easily accessible auxiliary and convenient reaction conditions have to be devised for more stereoselective and economic introduction of 2-propionic acid unit to **1**.



In our earlier study, we used lithium enolates of the readily available propiophenone derivatives for an aldol-type condensation with **2** followed by Baeyer–Villiger oxidation of the resulting ketone **3** with hydrogen peroxide under basic condition to generate **1**.[6] The β-selectivity in this condensation was low (<4:1), and, the transenolization between the enolate of the propiophenone and the acetate group of **2** caused about 30% of recovered **2**. Also, the oxidation of **3** with H_2O_2/NaOH provided unpredictable yield of **1** due to the β-lactam ring cleavage with a prolonged exposure of the reaction mixture to the basic media. Thus, an alternative approach has been pursued for more selective condensation between **2** and enolates of the propiophenone derivatives, together with a more reliable method for the oxidative conversion of the resulting ketone to **1**.[7]

2. Results and discussion

We used hydroxy- and methoxy-substituted propiophenones **4a–c**, which are commercially available in low cost, as a synthon for 2-propionic acid in expectation that the electron-rich aroyl group of **3** could be oxidized to the corresponding carboxylic acid in **1**. The titanium enolate of 2′-hydroxypropiophenone (**4a**), generated from **4a**, titanium tetrachloride and tri-*n*-butylamine, was condensed with **2** in high β-selectivity (Table 1). The yield of this reaction depends heavily on the amount of the enolate used. With the use of less than 2 equiv. of the enolate, the yields were sharply decreasing (entries 1 and 2). The reaction was best optimized with the use of 2.3 equiv. of the Ti(IV)-enolate to give 82% of **3a** after SiO_2 chromatography with 98:2 β/α diastereselectivity (entry 3). Conveniently, the crude mixture after the aqueous workup was directly recrystallized in ethyl acetate-hexanes to provide 78% of **3a** with

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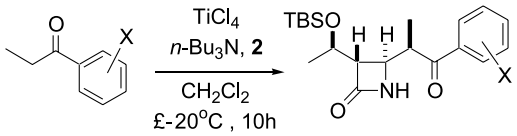
Table 1. Condensation of titanium enolate of propiophenones **4a–c** with **2**

Entry	Ketone (equiv.)[a]	$TiCl_4$ (equiv.)[a]	n-Bu_3N (equiv.)[a]	Product	Yield[b] (%)	De[c] (%)
1	**4a** (1.0)	1.0	3.0	**3a**	28	91
2	**4a** (1.8)	1.8	4.6	**3a**	63	93
3	**4a** (2.3)	2.3	5.6	**3a**	82 (78)[d]	96 (98)[d,e]
4	**4a** (3.0)	3.0	7.0	**3a**	32	96
5	**4b** (2.3)	2.3	3.3	**3b**	44	75
6	**4c** (2.3)	2.3	3.3	**3c**	57	85

[a] Equivalence relative to the amount of **2** used.
[b] Yields after SiO_2 chromatography.
[c] The diastereomeric excess was determined by ^1H NMR of the crude product.
[d] Yield and diastereomeric excess in the parenthesis refer to those after recrystallization of the crude product.
[e] Determined by HPLC analysis.

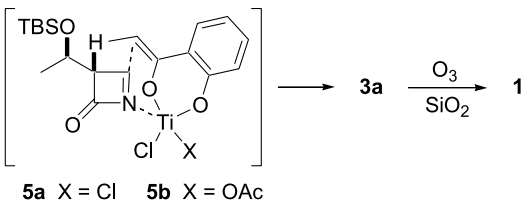
99:1 β-selectivity. The reaction did not proceed with the use of $Ti(O^iPr)_4$ or $TiCl_2(O^iPr)_2$, and, also, with the use of triethylamine instead of tri-*n*-butylamine.[8] Methoxypropiophenones, **4b** and **4c**, provided the corresponding **3b** and **3c** with much lower yields and diastereoselectivities than the use of **4a** under the same condition (entries 5 and 6). Unexpectedly, 2′-methoxy derivative **4b** showed a lower diastereoselectivity than 4′-methoxy derivative **4c**. Lack of an intramolecular chelation of the poorly basic phenyl ether oxygen in **4b** with the titanium enolate and the resulting tilt of the 2′-methoxyphenyl ring from the plane of the enolate may be the reason for the decreased selectivity in the condensation (Scheme 1).

The enhanced stereoselectivity in the formation of **3a** can be explained with the selective *Z*-enolate formation from **4a** through the bidentated Ti(IV)-enolate, and a tight coordination in the six-membered transition state of the resulting enolate with the acylimine generated from **2**, as shown in **5a**. The need for more than 2 equiv. of Ti(IV)-enolate of **4a** for an improved result may be due to the presence of less reactive acetoxy-substituted enolate **5b**.



Scheme 1.

Since the oxidation of **3a** with *m*-CPBA was too slow to be a practical method, and the use of H_2O_2/NaOH provided unpredictable yield of **1**, decomposition of 2-hydroxybenzoyl group of **3a** using ozone into a carboxyl group of **1** had been studied. Among the ozonolysis conditions studied, dry ozonation method was found to be most successful.[9] Passing a stream of ozone at −78 °C through the silica gel pre-adsorbed with **3a**, warming the mixture to ambient temperature followed by washing the silica gel with ethyl acetate provided conveniently the acid **1** in 60% yield in a reproducible manner (Scheme 2).



Scheme 2.

3. Conclusions

In conclusion, we developed a new practical method for the synthesis of a key 1-β-methylcarbapenem intermediate using a highly diastereoselective condensation of 4-acetoxy-β-lactam with a titanium enolate of 2′-hydroxypropiophenone and oxidative conversion of the resulting ketone to the carboxylic acid with a dry ozonation method. Eventually, 2-hydroxyphenyl group of the cheaply available 2′-hydroxypropiophenone served as an excellent achiral auxiliary for the highly diastereoselective introduction of 2-propionic acid needed for a 1-β-methylcarbapenem synthesis.

4. Experimental

4.1. General

IR spectra were recorded on a Bomem MB-104 spectrophotometer. Optical rotations were measured with a Rudolph Research Autopol III polarimeter. ^1H NMR spectra were recorded on a Varian Germini 300 (300 MHz) with TMS as an internal reference. ^{13}C NMR spectra were recorded on a Bruker AMX 400 (100 MHz) with TMS or $CDCl_3$ as an internal reference. Elemental analyses were obtained from Sogang Organic Chemistry Research Center, Seoul. Chiral HPLC analysis was performed on a Jasco LC-1500 Series HPLC system with a UV detector. TLC was performed on Merck silica gel 60 F_{254} precoated glass backed plates. Dichloromethane and tri-*n*-butylamine were dried by distillation over CaH_2 before use. All reactions were carried out in oven-dried glassware under an argon atmosphere.

4.1.1. (3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsiloxy)ethyl]-4-[(*R*)-1-(2-hydroxybenzoyl)ethyl]-2-azetidinone (3a). To a solution of 2′-hydroxypropiophenone **4a** (1.29 mL, 9.37 mmol) in 20 mL of dichloromethane at −78 °C was added slowly titanium tetrachloride (1.00 mL, 9.37 mmol) followed by tri-*n*-butylamine (5.50 mL, 23.0 mmol). The mixture was stirred for 30 min at the temperature and another 30 min at −40 °C. A solution of **2** (1.17 g, 4.07 mmol) in 14 mL of dichloromethane was added to the mixture dropwise, and the resulting solution was stirred at −20 °C for 10 h. The mixture was quenched with 80 mL of sat. NH_4Cl and extracted three times with 100 mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was recrystallized in ethyl acetate and hexanes to give 1.20 g (78%, β/α=99:1) of **3a** as a white solid: 98% de by HPLC analysis (Chiralpak CAPCELL PAK C_{18}, 4:6 H_2O/CH_3CN, 1 mL/min, 254 nm UV detector), t_R=11.6 min for **3a** β-form, and t_R=13.8 min

for α-form; R_f=0.35 (1:1 ethyl acetate/hexanes); $[\alpha]_D^{25}=-79.8$ (*c* 1.4, EtOH); mp=170–171 °C; IR (KBr) 1760, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.15 (d, *J*=6 Hz, 3H), 1.34 (d, *J*=5 Hz, 3H), 2.92 (dd, *J*=5, 2 Hz, 1H), 3.75 (dq, *J*=6, 5 Hz, 1H), 4.00 (dd, *J*=5, 2 Hz, 1H), 4.12 (m, 1H), 6.00 (br s, 1H), 6.93–7.74 (m, 4H), 12.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.77, −4.00, 13.67, 18.17, 22.65, 25.98, 42.82, 52.01, 62.17, 65.56, 118.34, 119.27, 119.41, 130.00, 137.32, 163.60, 168.45, 209.00; Anal. Calcd for $C_{20}H_{31}NO_4Si$: C, 63.62; H, 8.28; N, 3.71. Found: C, 63.63; H, 8.42; N, 3.67.

4.1.2. (3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsiloxy)ethyl]-4-[(*R*)-1-(2-methoxybenzoyl)ethyl]-2-azetidinone (3b). To a solution of 2′-methoxypropiophenone **4b** (340 mg, 2.07 mmol) in 5 mL of dichloromethane at −78 °C was added slowly titanium tetrachloride (0.22 mL, 2.07 mmol) followed by tri-*n*-butylamine (0.71 mL, 3.0 mmol). The mixture was stirred for 30 min at the temperature and another 30 min at −40 °C. A solution of **2** (260 mg, 0.90 mmol) in 2.5 mL of dichloromethane was added to the mixture dropwise, and the resulting solution was stirred at −20 °C for 10 h. The mixture was quenched with 20 mL of sat. NH_4Cl and extracted three times with 30-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual white solid was purified by silica gel flash chromatogaphy (1:2 ethyl acetate/hexanes) to give 154 mg (44%, β/α=7:1) of **3b** as a chromatographically inseparable diastereomeric mixture. The ratio of α and β diastereomers was determined by integration of the ^1H NMR signals of C(3)/H at 2.81 ppm (α-isomer) and 2.93 ppm (β-isomer). Spectral data for major β-isomer: R_f=0.25 (1:2, EtOAc/hexanes); IR (KBr) 1759, 1672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 1.20 (d, *J*=6 Hz, 3H), 1.21 (d, *J*=5 Hz, 3H), 2.93 (dd, *J*=5, 2 Hz, 1H), 3.78 (dq, *J*=6, 5 Hz, 1H), 3.90 (s, 3H), 4.04 (dd, *J*=5, 2 Hz, 1H), 4.12 (quint, *J*=5 Hz, 1H), 5.89 (br s, 1H), 6.96–7.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.15, −4.31, 12.07, 17.83, 22.42, 25.65, 47.52, 51.71, 55.41, 61.30, 65.50, 111.38, 120.81, 127.80, 130.33, 133.60, 158.01, 168.54, 205.55; Anal. Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found: C, 64.33; H, 8.67; N, 3.36.

4.1.3. (3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsiloxy)ethyl]-4-[(*R*)-1-(4-methoxybenzoyl)ethyl]-2-azetidinone (3c). To a solution of 4′-methoxypropiophenone **4c** (0.165 mL, 0.937 mmol) in 2 mL of dichloromethane at −78 °C was added slowly titanium tetrachloride (0.10 mL, 0.94 mmol) followed by tri-*n*-butylamine (0.32 mL, 1.35 mmol). The mixture was stirred for 30 min at the temperature and another 30 min at −40 °C. A solution of **2** (117 mg, 0.407 mmol) in 1 mL of dichloromethane was added to the mixture dropwise, and the resulting solution was stirred at −20 °C for 10 h. The mixture was quenched with 20 mL of sat. NH_4Cl and extracted three times with 20-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual white solid was purified by silica gel flash chromatography (1:2 ethyl acetate/hexanes) to give 92 mg (57%, β/α=12.3:1) of **3c** as a chromatographically inseparable diastereomeric mixture. The ratio of α and β diastereomers was determined by integration of the ^1H NMR signals of Ar/H doublets at 8.07 ppm (α-isomer) and 7.94 ppm (β-isomer). Spectral data for major β-Isomer: R_f=0.17 (1:2, EtOAc/hexanes); IR (KBr) 1757, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.15 (d, *J*=6 Hz, 3H), 1.27 (d, *J*=5 Hz, 3H), 2.88 (dd, *J*=5, 2 Hz, 1H), 3.66 (dq, *J*=6, 5 Hz, 1H), 3.88 (s, 3H), 3.97 (dd, *J*=5, 2 Hz, 1H), 4.16 (quint, *J*=5 Hz, 1H), 6.06 (br s, 1H), 6.95 (d, *J*=9 Hz, 2H), 7.94 (d, *J*=9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.10, −4.33, 13.07, 17.84, 22.34, 25.66, 42.50, 51.97, 55.44, 61.65, 65.37, 113.93, 128.63, 130.62, 163.79, 168.41, 201.09; Anal. Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found: C, 64.46; H, 8.44; N, 3.32.

4.1.4. (3*S*,4*R*)-3-[(*R*)-1-(*t*-Butyldimethylsiloxy)ethyl]-4-[(*R*)-1-carboxyethyl]-2-azetidinone (1). A solution of **3a** (206 mg, 0.546 mmol) in 50 mL of dichloromethane was added 5.4 g of silica gel (70–130 mesh) followed by the removal of the solvent under reduced pressure. The silica gel pre-adsorbed with **3a** in 500 mL Erlenmeyer flask was passed with ozone at −78 °C for 10 min followed by warming the flask to room temperature. The silica gel was washed with ethyl acetate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3:2 hexanes/ethyl acetate) to give **1** as a white solid (98 mg, 60%): mp 140–143 °C. Spectral data (^1H NMR, IR) of **1** are identical with those reported.[1]

Acknowledgements

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References and Notes

1. (a) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29–40. (b) Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871–880.
2. Berks, A. H. *Tetrahedron* **1996**, *52*, 331–375, and references cited therein.
3. (a) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675–4676. (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673–4675.
4. Martel, A.; Daris, J.-P.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1537–1539.
5. (a) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 2877–2884. (b) Kondo, K.; Seki, M.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1096–1097.
6. Ha, D.-C.; Kim, H.-S.; Park, N.-S.; Choi, J.-K. *Bull. Korean Chem. Soc.* **1996**, *17*, 76–77.
7. (a) Humphrey, G. R.; Miller, R. A.; Pye, P. J.; Rossen, K.; Reamer, R. A.; Maliakal, A.; Ceglia, S. S.; Grabowski, E. J. J.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1999**, *121*,

11261–11266. (b) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722–5728. (c) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135–4138.
8. (a) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727–8730. (b) Evans, D. A.; Reiger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049.
9. (a) Klein, H.; Steinmetz, A. *Tetrahedron Lett.* **1975**, *16*, 4249–4250. (b) Cohen, Z.; Keinan, E.; Mazur, Y.; Varkony, T. H. *J. Org. Chem.* **1975**, *40*, 2141–2142.