Diastereoselective Synthesis of (2*R*,4*R*)-2-Aryl-4-hydroxypyrrolidine: Preparation of the Side Chain of Novel Carbapenem

Takashi HASHIHAYATA,* Hiroki SAKOH, Yasuhiro GOTO, Masaaki HIROSE, Shunji SAKURABA, Hideaki IMAMURA, Yuichi SUGIMOTO, Koji YAMADA, and Hajime MORISHIMA

Banyu Tsukuba Research Institute, Okubo-3, Tsukuba, Ibaraki 300–2611, Japan.
Received July 24, 2001; accepted August 29, 2001

Improved synthesis of the *trans*-3,5-disubstituted pyrrolidin-3-ylthio side-chain of the novel carbapenem 1 was achieved *via* stereoselective reduction of the 1-aryl-1-butanone derivative 5 and successive intramolecular cyclization of the resulting chiral alcohol 6. The 1-aryl-1-butanone derivative 5 was obtained by a coupling reaction of protected 4-hydroxy-2-pyrrolidone with aryl-Grignard reagent.

Key words diastereoselective reduction; 1-aryl-1-butanone; 1β-methylcarbapenem

Our recent report demonstrated that **1** is a novel 1β-methylcarbapenem with good safety profiles and an unusual ultra-broad antimicrobial spectrum covering clinically important strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.[1] We also reported the synthesis of **1** by employing two procedures for the construction of the *trans*-3,5-disubstituted pyrrolidin-3-ylthio side-chain.[2] One of these procedures employed (*R*)-4-hydroxy-2-pyrrolidone as the starting material and provided hundreds of grams of **1**[2a]; however, the step that introduced a chiral center at C-2 of the *trans*-2,4-disubstituted pyrrolidine ring proceeded with moderate selectivity, producing poor overall yield (Chart 1). In this report, we describe the improved method of constructing the *trans*-2,4-disubstituted pyrrolidine system *via* stereoselective reduction of 1-aryl-1-butanone **5** formed by a coupling reaction of the protected 4-hydroxy-2-pyrrolidone **3** with aryl-Grinard reagent **4**.

Results and Discussion

According to our reported procedure, the addition reaction of protected (*R*)-4-hydroxy-2-pyrrolidone **3** and aryl-Grignard reagent **4** was carried out to form 1-aryl-1-butanone **5** and its cyclic aminal form **5′**, which was converted to (1*S*)-butanol **6** with moderate selectivity by an *in situ* reduction with $NaBH_4$. The selectivity of such an *in situ* reduction could not be improved despite using several reducing agents. In order to investigate diastereoselective reduction, the ketone **5** was isolated by treating aminal **5′** with sodium hydroxide for complete conversion to the ketone **5** and by subsequent silica gel chromatography.

The reduction of isolated **5** with $NaBH_4$ proceeded with similar diastereoselectivity (46% de) compared with the '*in situ*' reduction described in our previous paper. Improved selectivities were observed when trialkylborohydrides were used (Table 1). The reduction of **5** with lithium triethylborohydride (Super-Hydride®) and lithium 9-borobicyclo[3.3.1]-

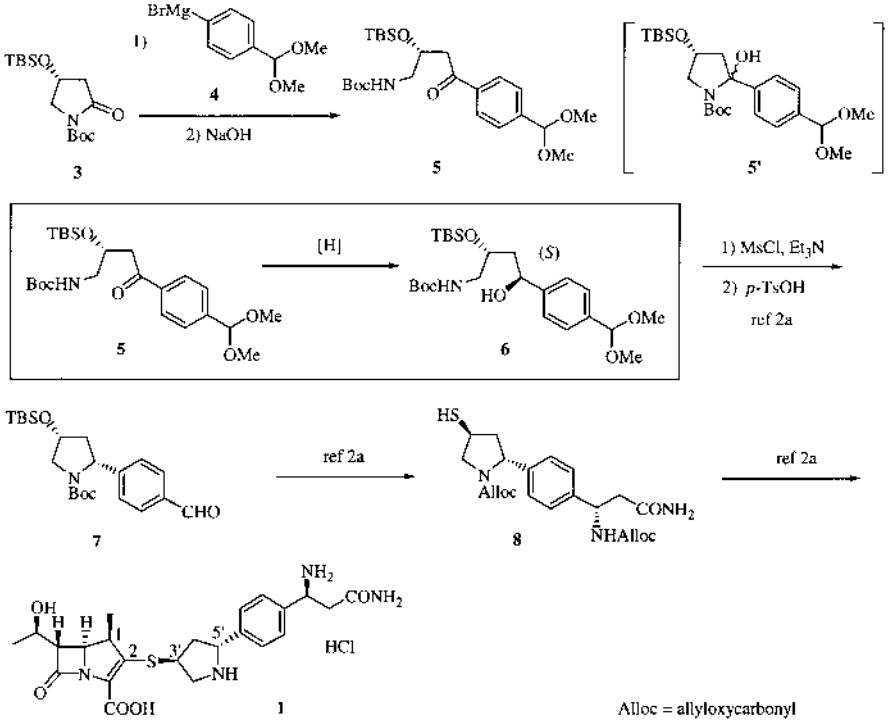


Chart 1

* To whom correspondence should be addressed. e-mail: hshytatk@banyu.co.jp

Table. 1. Diastereoselective Reduction of Ketone **5**

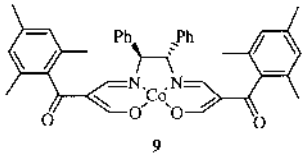
5 —(Reductant / Solvent)→ **6**

Entry	Reductant	Solvent	Temperature (°C)	**6** % de (yield: %)
1	$NaBH_4$	MeOH	−40	46 (90)
2	LS-Selectride	THF	−70	60 (49)[a]
3	Super-Hydride	THF	−70	78 (95)
4	Lithium 9-BBN hydride	THF	−70	80 (99)

a) 46% of **5** was recovered.

Table. 2. Diastereoselective Reduction of Ketone **5** Using Chiral β-Ketonato Cobalt(II) Complex **9**

5 —(Co(II) complex **9** / coreductant / $CHCl_3$)→ **6**



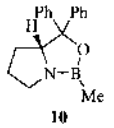
9

Entry	Catalyst (mol%)	Coreductant[a]	Temperature (°C)	**6** % de (yield: %)
1	1	A	−60	84 (95)
2	2	A	−60	82 (91)
3	2	A	−20	86 (95)
4	2	B	−20	82 (96)

a) Preparation of coreductant A: $NaBH_4$/EtOH/THFA = 1/3/14, rt, 20 min. B: $NaBH_4$/EtOH/THFA = 1/1/14, 0 °C, 3 h.

Table. 3. Diastereoselective Reduction of Ketone **5** Using Chiral Oxazaborolidine **10**

5 —(oxazaborolidine **10** / BH_3-Me_2S / THF)→ **6**



10

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	**6** % de (yield: %)
1	10	20	2	76 (96)
2	20	20	0.3	97 (95)
3	20	0	19	95 (95)

nonane (9-BBN) hydride resulted in acceptable selectivities with 78% de and 80% de, respectively, while the use of lithium trisiamylborohydride (LS-Selectride®) resulted in moderate selectivity (60% de).

Subsequently, diastereoselective reductions of ketone **5** by chiral reducing agents were carried out. The combination of the commercially available β-diketonato cobalt(II) complex derived from (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine, $NaBH_4$, EtOH, and tetrahydrofurfuryl alcohol (THFA) reduced **5** smoothly to produce **6** (Table 2).[3] Acceptable selectivity (86% de) and good yield (95%) were obtained by using 2 mol% of Co(II) complex **9** at −20 °C (entry 3).

Chiral oxazaborolidine was also effective, and (*R*)-oxazaborolidine **10** formed the desired (*S*) configuration to yield **6** (Table 3). The reduction of **5** with BH_3–Me_2S complex in the presence of 20 mol% of **10** at 20 °C resulted in excellent selectivity (97% de) and good yield (95%) (entry 2).[4]

Intramolecular cyclization of the carbinol **6** produced the 2,4-disubstituted pyrrolidine **7** *via* the corresponding mesylate, which was formed by methanesulfonyl chloride (MsCl) in the presence of Et_3N. After removing dimethylacetal with *p*-toluenesulfonic acid (TsOH) in aqueous tetrahydrofuran (THF), the product was crystallized, resulting in the 2,4-disubstituted pyrrolidine **7** with increased purity (>99% de), which was converted to the side-chain thiol **8** as in our previous report.[2a]

Conclusion

Diastereoselective reduction of the ketone **5** with Super-Hydride® or lithium 9-BBN hydride provided increased selectivity (78—80% de) compared with the $NaBH_4$ reduction (46% de). Further improvement of the selectivity was achieved by diastereoselective reduction of **5** using chiral β-diketonato cobalt(II) complex **9** or chiral oxazaborolidine **10** (up to 97% de). Intramolecular cyclization of the resulting chiral alcohol **6** yielded the 2,4-disubstituted pyrrolidine **7**, the purity of which was increased to >99% de by crystallization.

Experimental

General Methods Melting points were measured on a METTLER FP62 melting point apparatus and were not corrected. The ^{1}H-NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane (TMS) as an internal standard. The ^{13}C-NMR spectra were recorded on a JOEL JNM-A500. IR absorption spectra were recorded on a Horiba FT-200 spectrometer. Specific rotations were measured on a Jasco DIP-370 polarimeter. Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. Silica gel TLC was performed with Merck Kieselgel F_{254} precoated plates, and the silica gel used for column chromatography was WAKO gel C-300. All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere using syringe-septum cap techniques.

(3R)-4-*tert*-Butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-1-(4-dimethoxymethylphenyl)butanone 5 The solution of 4-bromobenzaldehyde dimethylacetal (5.50 g, 26.2 mmol) in THF (10 ml) was added dropwise to a mixture of Mg turning (636 mg, 26.2 mmol) in THF (20 ml) under a nitrogen atmosphere maintained over 70 °C. After the addition was complete, the reaction mixture was allowed to cool at room temperature. Formed Grignard reagent was added to a solution of (*R*)-4-*tert*-butyldimethylsiloxy-1-*tert*-butoxycarbonyl-2-pyrrolidone **3** (2.63 g, 8.34 mmol) in THF (30 ml) under a nitrogen atmosphere at −30 °C. After being stirred for 30 min at the same temperature, the mixture was poured into saturated aqueous NH_4Cl, and the whole was extracted with EtOAc. To the organic layer (200 ml) was added 1 N aqueous NaOH (45 ml) at room temperature, and the mixture was stirred for 1.5 h at the same temperature. The organic layer was separated and washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc/Et_3N = 90/10/0.1—80/20/0.1) to yield **5** (2.80 g, 72%) as a colorless oil. $[\alpha]_D^{20}$ +31.2 (*c* = 1.0, $CHCl_3$); IR (KBr) ν_{max} 3701, 2956, 1699, 1511, 1101, 1054, 835, 777 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ −0.05 (3H, s), 0.08 (3H, s), 0.81 (9H, s), 1.42 (9H, s), 3.14 (2H, m), 3.32 (6H, s), 4.46 (1H, m), 4.80 (1H, br s), 5.44 (1H, s), 7.54 (2H, d, *J* = 8.3 Hz), 7.95 (2H, d, *J* = 8.3 Hz); FAB-high resolution (HR)-MS *m*/*z* Calcd for $C_{24}H_{41}NO_6SiNa$ $(M+Na)^+$: 490.2601, Found 490.2604.

(1*S*,3*R*)-4-*tert*-Butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-1-(4-dimethoxymethylphenyl)butanol 6. I) Reduction of 5 Using Lithium 9-BBN Hydride Lithium 9-BBN hydride (1 M in THF, 321 μl, 0.321 mmol) was added to a solution of **5** (100 mg, 0.214 mmol) in THF (2.0 ml) under a nitrogen atmosphere at −70 °C. After being stirred for 1 h at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. $NaBO_3$–$4H_2O$ (98.8 mg, 0.642 mmol) was added to the suspension of the residue in THF–H_2O (2.4 ml, 1 : 2) at room temperature, and the mixture was stirred for 18 h at the same temperature. The mixture was poured into

water, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc/Et_3N=90/10/0.1—70/30/0.1) to yield **6** (100 mg, 99%, 80% de) as a colorless oil. The enantiomeric purity of **6** was determined by HPLC analysis [column, YMC ProC18 AS-303 (4.6ϕ×250 mm); eluent, 10 mM $(NH_4)_2HPO_4$/CH_3CN=30/70; flow rate, 1.0 ml/min; detection, UV 230 nm; t_R, (1*R*)-isomer; 28.6 min, (1*S*)-isomer (**6**); 30.9 min].

II) Reduction of 5 Using β-Diketonato Cobalt(II) Complex 9 as a Catalyst EtOH (97.6 μl, 1.67 mmol) and tetrahydrofurfuryl alcohol (757 μl, 7.81 mmol) were added to a mixture of $NaBH_4$ (21.1 mg, 0.558 mmol) in $CHCl_3$ (10 ml) under a nitrogen atmosphere at room temperature, and the mixture was stirred for 20 min at the same temperature. The resulting mixture and (1*S*,2*S*)-*N*,*N*′-bis[3-oxo-2-(2,4,6-trimethylbenzoyl)butylidene]-1,2-diphenylethylenediaminato cobalt(II) (2.9 mg, 4.16 mmol) were added to the solution of **5** (120 mg, 0.257 mmol) in $CHCl_3$ (4.0 ml) under a nitrogen atmosphere at −20 °C. After being stirred for 1.5 h at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc/Et_3N=90/10/0.1—70/30/0.1) to yield **6** (115 mg, 95%, 86% de) as a colorless oil.

III) Reduction of 5 Using Oxazaborolidine 10 BH_3–Me_2S (2 M in THF, 214 μl, 0.428 mmol) was added to a solution of (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (11.9 mg, 42.8 mmol) in THF (1.0 ml) under a nitrogen atmosphere at 20 °C, and the mixture was stirred for 15 min at the same temperature. A solution of **5** (100 mg, 0.214 mmol) in THF (1.0 ml) was added to the mixture under a nitrogen atmosphere at 20 °C. After being stirred for 20 min at the same temperature, the reaction mixture was poured into the solution MeOH–brine, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. $NaBO_3$–$4H_2O$ (98.8 mg, 0.642 mmol) was added to the suspension of the residue in THF–H_2O (2.4 ml, 1 : 2) at room temperature, and the mixture was stirred for 18 h at the same temperature. The mixture was poured into water, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc/Et_3N=90/10/0.1—70/30/0.1) to yield **6** (95.7 mg, 95%, 97% de) as a colorless oil. $[\alpha]_D^{20}$ −15.2 (*c*=1.0, $CHCl_3$); IR (Nujol) ν_{max} 1712, 1693 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.91 (9H, s), 1.44 (9H, s), 1.84 (2H, m), 3.21 (1H, m), 3.31 (6H, s), 4.08 (1H, m), 4.80 (1H, m), 4.91 (1H, m), 5.37 (1H, s), 7.35 (2H, d, *J*=8.4 Hz), 7.42 (2H, d, *J*=8.4 Hz); FAB-HR-MS *m*/*z* Calcd for $C_{24}H_{43}NO_6SiNa$ $(M+Na)^+$: 492.2757, Found 492.2745.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsiloxy-2-(4-formylphenyl)pyrrolidine 7 Triethylamine (71.1 μl, 0.510 mmol) and MsCl (14.5 μl, 0.187 mmol) were added to a solution of **6** (80.0 mg, 0.17 mmol, 97% de) in CH_2Cl_2 (1.6 ml) under a nitrogen atmosphere at −60 °C. After being stirred for 30 min, the reaction mixture was poured into H_2O, and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in THF (1 ml) and H_2O (0.2 ml), and was treated with *p*-TsOH–H_2O (3.2 mg, 17 mmol) for 1 h at room temperature. The mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was crystallized from *n*-hexane, collected by filtration, and dried to yield **7** (51.0 mg, 74%, >99% de) as colorless plate crystals. The enantiomeric purity of **7** was determined by HPLC analysis [column, YMC ODS-AQ AQ-303 (4.6ϕ× 250 mm); eluent, 10 mM $(NH_4)_2HPO_4$/CH_3CN=20/80; flow rate, 1.0 ml/min; detection, UV 254 nm; t_R, (2*R*)-isomer (**7**); 14.2 min, (2*S*)-isomer; 14.8 min]. Mp 102—103 °C; $[\alpha]_D^{20}$ +49.0 (*c*=1.0, $CHCl_3$); IR (KBr) λ_{max} 1708, 1673, 1606 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.72 (9H, s), 1.18 (6H, s), 1.43 (3H, s), 1.88 (1H, m), 2.48 (1H, m), 3.43 (1H, m), 3.80 (1H, m), 4.40 (1H, m), 4.79 (0.34H, m), 4.81 (0.66H, m), 7.40 (2H, d, *J*=7.0 Hz), 7.78 (2H, d, *J*=7.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$, major signals) δ −5.2, −5.1, 17.7, 25.4, 28.0, 44.1, 55.1, 60.2, 70.1, 79.7, 126.6, 129.5, 134.9, 152.1, 191.9; FAB-HR-MS *m*/*z* Calcd for $C_{22}H_{36}NO_4Si$ $(M+H)^+$: 406.2414, Found 406.2390; *Anal*. Calcd for $C_{22}H_{35}NO_4Si$: C, 65.15; H, 8.70; N, 3.45, Found: C, 65.11; H, 8.84; N, 3.52.

Acknowledgments We are grateful to Ms Jocelyn Winward, Merck & Co., Inc. for her critical reading of this manuscript.

Reference

1) Imamura H., Ohtake N., Shimizu A., Sato H., Sugimoto Y., Sakuraba S., Nagano R., Nakano M., Abe S., Suzuki-Sato C., Nishimura I., Kojima H., Tsuchiya Y., Yamada K., Hashizume T., Morishima H., *Bioorg. Med. Chem*., **8**, 1969—1982 (2000).
2) *a*) Imamura H., Shimizu A., Sato H., Sugimoto Y., Sakuraba S., Nakajima S., Abe S., Miura K., Nishimura I., Yamada K., Morishima H., *Tetrahedron,* **56**, 7705—7713 (2000); *b*) Imamura H., Ohtake N., Sakuraba S., Shimizu A., Yamada K., Morishima H., *Chem. Pharm. Bull*., **48**, 310—311 (2000).
3) Nagata T., Sugi D. K., Yamada T., Mukaiyama T., *Synlett*, **1996**, 1076—1078.
4) *a*) Itsuno S., Sakurai Y., Ito K., Nakayama S., *Bull. Chem. Soc. Jpn*., **60**, 395—398 (1987); *b*) Corey E. J., Bakshi R. K., Shibata S., *J. Am. Chem. Soc*., **109**, 5551—5553 (1987).