Synthesis of the Side Chain of a Novel Carbapenem *via* Iodine-Mediated Oxidative Cyclization of (1*R*)-*N*-(1-Aryl-3-butenyl)acetamide

Takashi HASHIHAYATA,* Hiroki SAKOH, Yasuhiro GOTO, Koji YAMADA, and Hajime MORISHIMA

Banyu Tsukuba Research Institute, Okubo-3, Tsukuba, Ibaraki 300–2611, Japan.
Received October 3, 2001; accepted December 19, 2001

A (2*R*,4*S*)-*trans*-disubstituted pyrrolidine ring system was constructed by employing iodine-mediated oxidative cyclization of (1*R*)-*N*-[1-(4-bromophenyl)-3-butenyl]acetamide 3 as a key step. The resulting diastereomeric mixture of (2*R*)-2-aryl-4-acetoxypyrrolidine 4 was stereoselectively converted to the side-chain of a novel ultra-broad-spectrum carbapenem 1, *via* (2*R*,4*R*)-2-aryl-4-hydroxypyrrolidine 7.

Key words 1β-methylcarbapenem; homoallylamine; I_2-mediated oxidative cyclization

We synthesized a novel 1β-methyl carbapenem **1** and reported that **1** had an unusual ultra-broad antimicrobial spectrum that covered clinically important strains including MRSA and *P. aeruginosa*.[1] In the initial approach to the stereoselective preparation of 4-mercapto-2-arylpyrrolidine **9**, a side-chain of **1**, we used D-malic acid as a starting material which was converted to the desired 2,4-disubstituted pyrrolidine system with moderate overall yield *via* addition reaction of aryl metal reagent with the relatively unstable butanal intermediate.[2] We subsequently employed rather expensive (*R*)-4-hydroxy-2-pyrrolidone as a starting material. Although satisfactory selectivity was not obtained to form the 2-position, further improvements in the process for constructing 2,4-disubstituted pyrrolidine system was developed with shortened steps and increased overall yield (Chart 1).[3] In this procedure, a phenyl group was introduced to a protected (*R*)-4-hydroxy-2-pyrrolidone **2** by using aryl-Grignard reagent. Under the basic conditions of Grignard reaction, β-alkoxy carbonyl system of pyrrolidone **2** and adduct were likely to form α,β-unsaturated side products (over 10%). In order to avoid such side reactions, we investigated the construction of a 2-aryl-4-hydroxy pyrrolidine ring system from a benzene derivative having an appropriate carbon chain corresponding to the pyrrolidine ring.

In this paper, we describe oxidative cyclization of the chiral homoallyl acetamide **3**, and subsequent stereoselective conversion to the side-chain of **1**.

Results and Discussion

Homoallylamine is a useful building block of more complex molecules including 3-hydroxypyrrolidine derivative. Taddei and co-workers converted homoallylamine to 3-hydroxypyrrolidine *via* 3,4-epoxybutylamine and subsequent cyclization under alkaline conditions with moderate yield.[4] We applied this procedure to 1-(4-bromophenyl)-3,4-epoxybutylamine; however, 2-aryl-4-hydroxypyrrolidine could not be obtained in an acceptable yield. Takano *et al.* described an efficient method for the stereoselective conversion of homoallylamine to the chiral 2-substituted 4-hydroxypyrrolidine system by benzoylation and subsequent oxidation of the resulting benzamide with iodide in an aqueous-organic solvent.[5] We have found that a 2-aryl-4-hydroxypyrrolidine system could be obtained from the homoallylamine acetamide derivative **3** by the application of this procedure.

Efficient methods for preparing chiral homoallylamine have been developed by several groups.[6] According to the report by Brown and co-workers,[6a] chiral homoallylamine,

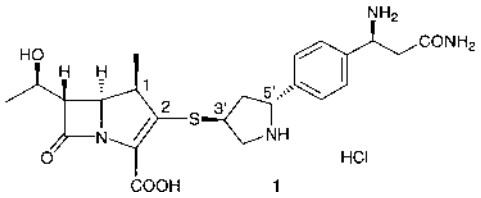


Fig. 1. Structure of **1**

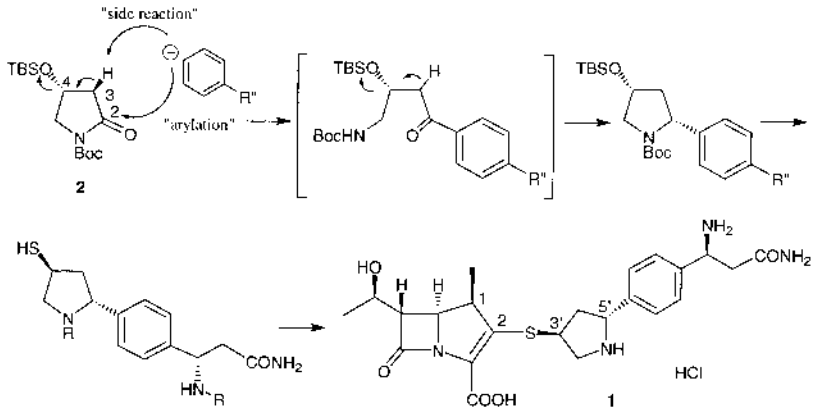
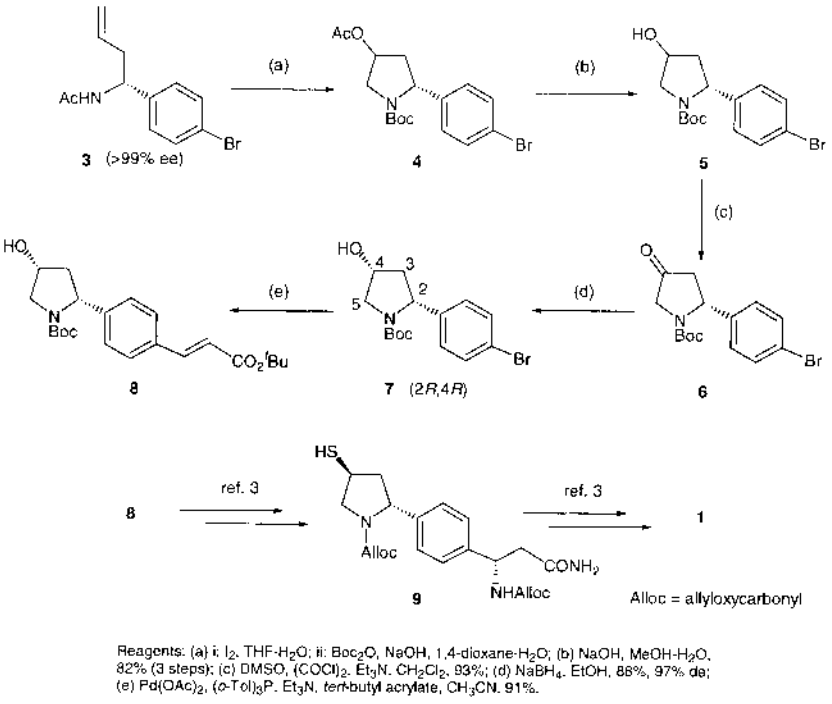


Chart 1. Synthesis of **1** from Pyrrolidone **2**

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



Reagents: (a) i; I_2, THF-H_2O; ii: Boc_2O, NaOH, 1,4-dioxane-H_2O; (b) NaOH, MeOH-H_2O, 82% (3 steps); (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 93%; (d) $NaBH_4$, EtOH, 88%, 97% de; (e) $Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, *tert*-butyl acrylate, CH_3CN, 91%.

Chart 2. Preparation of the Side-Chain

(1*R*)-1-(4-bromophenyl)-3-butenylamine, was prepared and subsequently treated with acetic anhydride and triethylamine to afford acetamide **3** with an acceptable yield (77%) and enantiomeric excess (86% ee). Recrystallization of **3** increased its optical purity (62%, >99% ee).

Oxidative cyclization of homoallylamine acetamide **3** took place smoothly by the action of 3 equivalents of iodine in THF–H_2O (4 : 1) at room temperature. Under these conditions, acetamide **3** was transformed to 4-acetoxy pyrrolidine which was isolated after introduction of a *tert*-butoxycarbonyl (Boc) group, affording *N*-protected pyrrolidine **4** as a diastereomeric mixture [(2*R*,4*R*)/(2*R*,4*S*)=1/2]. Subsequent alkaline hydrolysis of **4** gave 4-hydroxy pyrrolidine **5**.

Swern oxidation of 4-hydroxy pyrrolidine **5** furnished a 4-oxopyrrolidine **6** at a yield of 93%, and subsequent reduction of **6** by $NaBH_4$ provided the desired *cis*-(2*R*,4*R*)-2-aryl-4-hydroxypyrrolidine **7** in good yield (88%) with high diastereoselectivity (97% de).[7] Then, *tert*-butyl acrylate was introduced to bromobenzene **7** by a conventional Heck reaction.[8] The resulting α,β-unsaturated ester **8** was converted to the side-chain **9** according to the procedure reported by our labolatory.[3]

Conclusion

A convenient method for the synthesis of a side-chain of **1** was developed *via* oxidative cyclization of (1*R*)-*N*-[1-(4-bromophenyl)-3-butenyl]acetamide **3**. The resulting 2,4-disubstituted pyrrolidine **5** was successfully converted to the side-chain of **1** *via* stereoselective reduction of 4-oxopyrrolidine **6** to introduce a (4*R*)-carbinol center and using the Heck reaction to install an acrylate unit.

Experimental

General Methods Melting points were measured on a BUCHI B-545 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 JEOL JNM-EX-270. 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. The silica-gel TLC was performed with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300. All reactions involving air-sensitive reagents were performed under nitrogen atmosphere using syringe-septum cap techniques.

(1*R*)-*N*-[1-(4-bromophenyl)-3-butenyl]acetamide 3 A solution of 4-bromobenzaldimine was obtained as follows: To a solution of 4-bromobenzaldehyde (1.00 g, 5.40 mmol) in THF (6 ml) was added lithium bis(trimetylsilyl)amide (1 M in THF, 5.68 ml, 5.68 mmol) at 0 °C, and the mixture was stirred for 15 h at the same temperature. To a solution of $Ipc_2BCH_2CH=CH_2$ in THF, prepared from (+)-DIP-Chloride™ (1.91 g, 5.95 mmol), allylmagnesium chloride (2 M in THF, 2.97 ml, 5.95 mmol) and THF (5.4 ml), were added 4-bromobenzaldimine solution and water (107 μl, 5.95 mmol) in THF (0.54 ml) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature, and then allowed to turn to room temperature. To a solution of aqueous NaOH (1 M, 6.48 ml, 6.48 mmol) and hydrogen peroxide (30% in H_2O, 1.47 g, 13.0 mmol) was added the reaction mixture at the same temperature, and the whole was poured into aqueous hydrochloride. After neutralization by K_2CO_3, the whole was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to afford (1*R*)-1-phenyl-3-butenylamine which was used for the next reaction without further purification.

To a solution of the above in $CHCl_3$ (10 ml) were added triethylamine (934 μl, 6.71 mmol) and acetic anhydride (506 μl, 5.36 mmol) at 0 °C. The mixture was stirred for 30 min at the same temperature and poured into 4% aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (*n*-hexane/EtOAc=4/6) to give **3** (1.12 g, 77%, 86% ee) as a colorless solid. Subsequent recrystallization from $CHCl_3$–*n*-hexane afforded **3** (894 mg, 62%, >99% ee) as a colorless solid. The enantiomeric purity of **3** was determined by HPLC analysis [column, Daicel Chiralcel OJ (4.6ϕ×250 mm); eluent, *n*-hexane : iso-PrOH=95 : 5; flow rate, 1.0 ml/min; detection, UV 250 nm; t_R, (1*R*)-isomer (**3**); 21.0 min, (1*S*)-isomer; 26.8 min]. mp 161—162 °C; $[\alpha]_D^{20}$ +116.8 (c=1.0, $CHCl_3$); IR (KBr) ν_{max} 3292, 1653, 1541, 1371, 1009, 820 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.65 (2H, dd, J=7.0, 7.0 Hz), 5.18 (2H, m), 5.74 (1H, m), 6.42 (1H, d, J=7.3 Hz), 7.21 (3H, m), 7.45 (4H, m), 7.75 (2H, d, J=6.9 Hz) FAB-HR-MS Calcd for $C_{12}H_{15}BrNO$ $(M+H)^+$: 268.0337, Found 268.0344.

***tert*-Butyl (2*R*)-2-(4-bromophenyl)-4-hydroxypyrrolidinecarboxylate 5** To a solution of **3** (>99% ee, 1.00 g, 3.73 mmol) in THF–H_2O (4 : 1, 10 ml) was added iodine (2.84 g, 11.2 mmol) at room temperature. The mixture was stirred for 7.5 h at the same temperature and poured into the mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give (2*R*)-2-(4-bromophenyl)pyrrolidin-4-yl acetate (1.87 g), which was used for the next reaction without further purification.

To a solution of (2*R*)-2-(4-bromophenyl)pyrrolidin-4-yl acetate obtained above (1.81 g) in 1,4-dioxane–H_2O (1 : 1, 30 ml) was added Boc_2O (867 mg, 3.97 mmol) at pH=9, which was maintained using 1 M aqueous NaOH at room temperature. The reaction mixture was poured into the mixture of EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give *tert*-butyl (2*R*)-2-(4-bromophenyl)-4-acetoxypyrrolidinecarboxylate **4** (1.66 g), which was used for the next reaction without further purification.

To a solution of **4** (1.60 g) obtained above in MeOH (10 ml) was added aqueous NaOH (1 M, 2.66 ml, 2.66 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature. The reaction mixture was neutralized by aqueous HCl and poured into EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (*n*-hexane/EtOAc=1/1) to give **5** (978 mg, 82%) as a colorless solid. mp 132—133 °C; IR (KBr) ν_{max} 3425, 2976, 1682, 1423, 1162, 1084, 1009, 770 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.00 (3H, s), 2.65 (2H, dd, *J*=6.9, 6.9 Hz), 5.07 (3H, m), 5.66 (2H, m), 7.15 (2H, d, *J*=6.5 Hz), 7.45 (2H, d, *J*=6.5 Hz); FAB-HR-MS Calcd for $C_{15}H_{20}BrNO_3Na$ $(M+Na)^+$: 364.0524, Found 364.0531.

***tert*-Butyl (2*R*)-2-(4-bromophenyl)-4-oxopyrrolidinecarboxylate 6** To a solution of $(COCl)_2$ (861 mg, 6.78 mmol) in CH_2Cl_2 (14 ml) was added DMSO (1.13 ml, 13.6 mmol) at −78 °C, and the solution was stirred for 10 min at the same temperature. The solution of **5** (909 mg, 2.26 mmol) in CH_2Cl_2 (8 ml) was added to the reaction mixture over 5 min, and the reaction mixture was stirred at the same temperature for 15 min and then at −50 °C for 30 min. The solution was treated with triethylamine (3.33 ml, 20.3 mmol) at the same temperature, and was allowed to warm to room temperature over 30 min. The reaction mixture was poured into the mixture of $CHCl_3$ and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (*n*-hexane/EtOAc=3/1) to give **6** (843 mg, 93%) as a pale yellow solid. mp 93—94 °C; $[\alpha]_D^{20}$ +5.2 (*c*=1.0, $CHCl_3$); IR (KBr) ν_{max} 2978, 1753, 1687, 1406, 1161, 1012, 824, 509 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.38 (9H, br s), 2.53 (1H, dd, *J*=2.8, 18.4 Hz), 3.13 (1H, dd, *J*=10.1, 18.4 Hz), 3.87 (1H, d, *J*=19.4 Hz), 4.08 (1H, d, *J*=19.4 Hz), 5.32 (1H, br s), 7.07 (2H, d, *J*=8.4 Hz), 7.47 (2H, d, *J*=8.4 Hz); FAB-HR-MS Calcd for $C_{15}H_{18}BrNO_3Na$ $(M+Na)^+$: 362.0368, Found 362.0369.

***tert*-Butyl (2*R*,4*R*)-2-(4-bromophenyl)-4-hydroxypyrrolidinecarboxylate 7** To a solution of **6** (165 mg, 4.85 mmol) in EtOH (3 ml) was added $NaBH_4$ (87.0 mg, 2.43 mmol) over 3 min at 0 °C. The mixture was stirred for 10 min at the same temperature and poured into the mixture of aqueous NH_4Cl and $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (*n*-hexane/EtOAc=6/4) to give **7** (146 mg, 88%) as a colorless solid. The enantiomeric purity of **7** (97% de) was determined by HPLC analysis [column, Daicel Chiralcel OJ (4.6ϕ×250 mm); eluent, *n*-hexane : iso-PrOH=95 : 5; flow rate, 1.0 ml/min; detection, UV 250 nm; t_R, (2*R*,4*S*)-isomer; 8.1 min, (2*S*,4*R*)-isomer; 10.3 min, (2*S*,4*S*)-isomer; 12.1 min, and (2*R*,4*R*)-isomer (**7**); 17.1 min]. mp 164—165 °C; $[\alpha]_D^{20}$ +62.2 (*c*=1.0, $CHCl_3$); IR (KBr) ν_{max} 3365, 2978, 1662, 1419, 1126, 1084, 771 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22, 1.43 (each 9H, br s), 1.94 (1H, ddd, *J*=4.3, 4.3, 13.3 Hz), 2.57 (1H, ddd, *J*=5.4, 8.5, 13.3 Hz), 3.55 (1H, dd, *J*=3.7, 11.7 Hz), 3.83 (1H, br s), 4.47 (1H, m), 4.80 (1H, m), 7.16 (2H, d, *J*=8.4 Hz), 7.43 (2H, d, *J*=8.4 Hz); FAB-HR-MS Calcd for $C_{15}H_{20}BrNO_3Na$ $(M+Na)^+$: 364.0524, Found 364.0521.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-[4-[(*E*)-2-(*tert*-butoxycarbonyl)-vinyl]phenyl]-4-hydroxypyrrolidine 8 To a solution of **7** (150 mg, 0.44 mmol) in CH_3CN (5 ml) were added $Pd(OAc)_2$ (5.00 mg, 0.0022 mmol), tris(2-methylphenyl)phosphine (27.0 mg, 0.089 mmol), triethylamine (0.18 ml, 0.13 mmol), and *tert*-butyl acrylate (160 mg, 0.89 mmol) at room temperature. The mixture was stirred at refluxed temperature for 6 h and poured into the mixture of aqueous NH_4Cl and EtOAc. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (*n*-hexane/EtOAc=1 : 1) to give **8** (155 mg, 91%) as a colorless solid. mp 196—197 °C; $[\alpha]_D^{20}$ +71.8 (*c*=1.0, $CHCl_3$); IR (Nujol) ν_{max} 3401, 1693, 1645, 1434, 1324, 987 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (6H, br s), 1.44 (12H, s), 1.94 (1H, m), 2.61 (1H, m), 3.58 (1H, dd, *J*=2.5, 10.3 Hz), 3.87 (1H, m), 4.48 (1H, m), 4.89 (1H, m), 6.33 (1H, d, *J*=16.3 Hz), 7.29 (2H, d, *J*=8.2 Hz), 7.45 (2H, d, *J*=8.2 Hz), 7.57 (1H, d, *J*=16.3 Hz); ^{13}C-NMR (67.5 MHz, $CDCl_3$, major signals) δ: 28.6, 44.3, 55.2, 60.5, 70.1, 80.3, 120.0, 126.6, 128.4, 133.5, 143.7, 154.8, 166.9; FAB-HR-MS Calcd for $C_{22}H_{32}NO_5$ $(M+H)^+$: 390.2280, Found 390.2277; *Anal.* Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60, Found: C, 67.83; H, 8.21; N, 3.53.

Acknowledgment We are grateful to Ms. Kimberley Marcopul and Mr. Dan Johnson, Merck & Co., Inc., for their critical readings of this manuscript.

References and Notes

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) Imamura H., Ohtake N., Sakuraba S., Shimizu A., Yamada K., Morishima H., *Chem. Pharm. Bull.*, **48**, 310—311 (2000).
3) 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).
4) Franciotti M., Mann A., Mordini A., Taddei M., *Tetrahedron Lett.*, **34,** 1355—1358 (1993).
5) *a*) Takano S., Iwabuchi Y., Ogasawara K., *J. Chem. Soc., Chem. Commun.,* **1988**, 1527—1528; *b*) *Idem*, *Heterocycles*, **29**, 1861—1864 (1989).
6) *a*) Chen G. M., Ramachandran P. V., Brown H. C., *Angew. Chem. Int. Ed.*, **38**, 825—826 (1999); *b*) Wu M. J., Pridgen L. N., *Synlett*, **1990**, 636—637; *c*) Basile T., Bocoum A., Savoia D., Umani-Ronchi A., *J. Org. Chem.*, **59**, 7766—7773 (1994).
7) Hanna P. E., *J. Heterocycl. Chem.,* **1973**, 747—753.
8) Kim J. I. I., Patel B. A., Heck R. F., *J. Org. Chem.*, **46**, 1067—1073 (1981).