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

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

Key words 1β-methylcarbapenem; homoallylamine; I2-mediated oxidative cyclization

Results and Discussion

Homoallylamine is a useful building block of more complex molecules including 3-hydroxy-2-pyrrolidine derivative. Taddei and co-workers converted homoallylamine to 3-hydroxy-2-pyrrolidine 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-hydroxy-2-pyrrolidine 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-hydroxy-2-pyrrolidine 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-hydroxy-2-pyrrolidine 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,7) chiral homoallylamine, 3

Fig. 1. Structure of 1

Chart 1. Synthesis of 1 from Pyrrolidine 2

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(1R)-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–H2O (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 [(2R,4R)/(2R,4S)=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 NaBH4 provided the desired cis-(2R,4R)-2-aryl-4-hydroxyoxypyrrolidine 7 in good yield (88%) with high diastereoselectivity (97% de). Then, tert-butyl acrylate was introduced to bromobenzene 7 by a conventional Heck reaction. The resulting α,β-unsaturated ester 8 was converted to the side-chain 9 according to the procedure reported by our laboratory.1

Conclusion
A convenient method for the synthesis of a side-chain of 1 was developed via oxidative cyclization of (1R)-N-[1-(4-bromophenyl)-3-buteny]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 (4R)-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 1H-NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane (TMS) as an internal standard. The 13C-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 F254 pre-coated 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.

(1R)-N-[1-(4-bromophenyl)-3-buteny]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(trimethylsilyl)amide (1 η 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 1-[4-bromophenyl]CH=CH2 in THF, prepared from (+)-DIP-ChlorideTM (1.91 g, 9.59 mmol), allylmagnesium chloride (2 η THF, 2.97 ml, 5.95 mmol) and THF (5.4 ml), were added 4-bromobenzaldimine solution and water (1 07 ml, 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 η, 6.48 ml, 6.48 mmol) and hydrogen peroxide (30% in H2O, 1.47 g, 13.0 mmol) was added the reaction mixture at the same temperature, and the whole was poured into aqueous hydrochloric acid. After neutralization by K2CO3, the whole was extracted with EtO. The organic layer was washed with brine, dried over MgSO4, and evaporated under reduced pressure to afford [1R]-1-phenyl-3-buteny]acetamide 3 as a colorless solid. The enantiomeric purity of 3 was determined by HPLC analysis [column, Daicel Chiralcel OJ (4.6×250 mm); eluent, n-hexane/EtOH=4/6] to give 3 (1.12 g, 77%, 86% ee) as a colorless solid. Subsequent recrystallization from CHCl3–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 OD (4.6×250 mm); eluent, n-hexane:iso-ProOH=95:5; flow rate, 1.0 ml/min; detection, UV 250 nm; tR (1R)-isomer (3): 21.0 min, (1S)-isomer: 26.8 min]. mp 161−162°C; [α]D20 +116.8 (c=1.0, CHCl3); IR (KBr) νmax 3292, 1653, 1541, 1371, 1009, 820 cm−1; 1H-NMR (300 MHz, CDCl3) 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-MS Calcd for C18H12BrNO (M+H)+: 268.0337, Found 268.0344.
**tert-Butyl (2R)-2-(4-bromophenyl)-4-hydroxyproplyridinecarboxylate 5**

To a solution of 3 (3.97 mmol) at pH 7.0, tert-butyl (2R)-2-(4-bromophenyl)-4-hydroxyproplyridinecarboxylate 4 (1.66 g), which was used for the next reaction without further purification.

**tert-Butyl (2R)-2-(4-bromophenyl)-4-oxopyrrolidin-4-yl acetate 6**

To a solution of tert-butyl (2R)-2-(4-bromophenyl)-4-oxopyrrolidin-4-yl acetate (1.87 g), 1,4-dioxane-H2O (1:1, 30 ml) was added Boc2O (867 mg, 3.97 mmol) at pH = 9, which was used for the next reaction without further purification.

**tert-Butyl (2R,2R)-4-oxopyrrolidin-4-yl acetate 6**

To a solution of tert-butyl (2R,2R)-4-oxopyrrolidin-4-yl acetate (150 mg, 91%) as a colorless solid. mp 196—197 °C; [α]D 20 +71.8 (c = 1.0, CHCl3); IR (KBr) νmax 3401, 1693, 1645, 1434, 1324, 987 cm⁻¹; 1H-NMR (300 MHz, CDCl3) δ: 1.22, 1.43 (each 9H, br s), 1.94 (2H, m), 7.45 (2H, d, J=6.5 Hz); FAB-HR-MS Calcd for C15H20BrNO3Na (M+Na⁺): 364.0524, Found 364.0521.

**References and Notes**


