Diastereoselective Allylation of a Chiral Imine with Allylzinc Reagents: Diastereoselective Synthesis of a Novel Broad Spectrum Carbapenem

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Abstract: Diastereoselective allylation of chiral imine with allylmetal reagents was applied to prepare β-amino acid derivative as a key intermediate for the synthesis of a novel carbapenem **1**. Combination of the allylzinc reagents and chiral imine, which was derived from L-valine methyl ester as a chiral auxiliary afforded a homoallylamine in good yield with excellent diastereoselectivity.

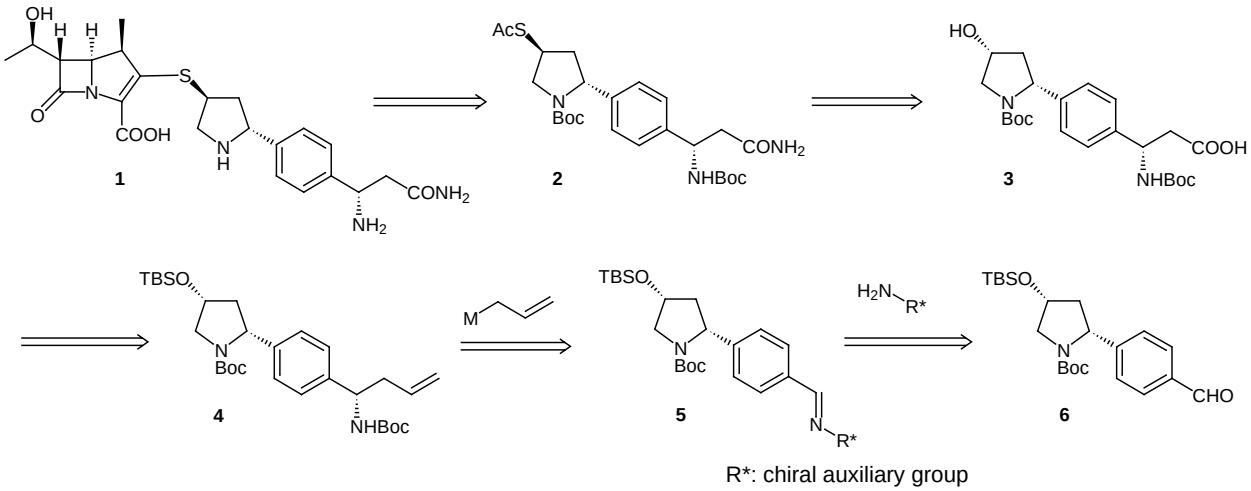
Key words: diastereoselective allylation, chiral imine, homoallylamine, 1-β-methylcarbapenem

Recently, we reported that a novel 1-β-methylcarbapenem **1**[1] has an ultra-broad antimicrobial spectrum covering methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Although the known carbapenems such as meropenem,[2] S-4661,[3] E1010 (ER-35786),[4] ertapenem[5] and lenapenem[6] have *cis*-3,5-disubstituted pyrrolidin-3-ylthio side chains at the C-2 position of the carbapenem nucleus, **1** has a *trans*-3,5-disubstituted pyrrolidin-3-ylthio side-chain which afforded such unique biological activities.

In order to stereoselectively construct the β-alanine moiety of the side chain of **1**, we previously described two strategies as follows: 1) asymmetric Michael addition of chiral amine to cinnamate ester[7] and 2) enzymatic resolution of diastereomeric mixture of 3-aryl-3-hydroxy propionate ester.[8] These methods were effective and practical, however, cost-effectiveness of these were low because considerable amounts of expensive chiral amine was used in the Michael addition, half of the substrate used was lost in enzymatic resolution, and so on. Accordingly, we investigated an alternative approach using diastereoselective allylation of chiral imine[9a,b] to construct the β-alanine moiety of the side chain of **1**. Herein, we disclose a highly diastereoselective allylation of chiral imine derived from α-amino acid[9c–h] and following conversion to **1**.

Retrosynthetic analysis of **1** is outlined in Scheme 1. Conversion of protected thiol intermediate **2** to the final product **1** was reported in our previous paper.[7] Carbamoyl function of **2** was formed from carboxylic acid **3**, which was obtained by oxidative cleavage of homoallylamine **4**. Diastereoselective allylation of chiral aldimine **5** and replacement of the substituent on nitrogen gave chiral homoallylamine **4**.

There are many efficient asymmetric allylmetalation procedures using N-masked aldimines with chiral allylmetal reagents,[9l–n] however, we initially examined the addition reaction of allylmetal reagents with aldimines bearing chiral auxiliary such as α-amino acid,[9c–k] since high stereoselectivity would be expected by convenient procedures. In this paper, our attention was focused on the development of an efficient method for the construction of



Scheme 1

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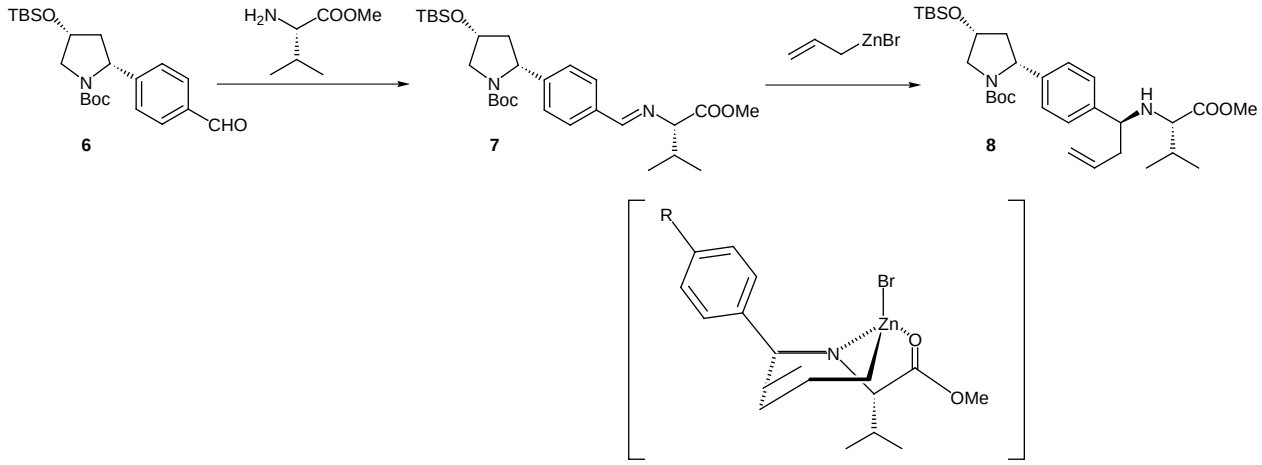


Scheme 2

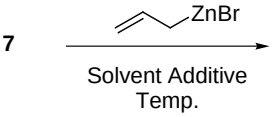
(*S*)-homoallylamine **4** using valine as a chiral auxiliary, which is inexpensive and can be supplied in bulk quantities.

The Schiff base **7** was readily derived from aldehyde **6**[10] and L-valine methyl ester. First, allylation of imine **7** by the allyl Grignard reagent was carried out, and afforded the desired homoallylamine with excellent diastereoselectivity (> 99% diastereomeric excess).[11] However, chemical yield was moderate (48%), and byproducts formed were unseparable by column chromatography. On the other hand, Barbier-type allylation using allyl bromide and zinc powder combination resulted in acceptable yield and selectivity[9c–h] (Table). Althoug the Zn-promoted reaction of allyl bromide did not proceed below ambient temperature (entry 1, 2), allylation product was obtained at 60 °C in THF (entry 3). The yield was significantly increased by using DMF as a solvent (entry 11),[12] while the presence of $CeCl_3$ did not influence the yield (entry 4, 5). The reason why the reaction readily proceeds using DMF as a solvent is not clear. We propose that the reaction proceeds through a plausible cyclic chair transition state (Scheme 2), where Zn is coordinated by ester group and the bulky isopropyl group is disposed externally.[9f] Under the optimized conditions, Zn-promoted allylation took place smoothly to provide multi grams of the desired (*S*,*S*) diasteromer **8** (77%, Scheme 3).[13]

Stereoselectivities of the diastereoselective allylation reaction were determined after conversion of **8** to the protected primary homoallylamine **4** by sequential manipulation. According to the reported procedures,[9f] **8** was reduced with $LiAlH_4$ (85%), and the resulting amino alcohol **9**[14] was oxidatively cleaved by using HIO_4 to form a primary amino group which was then protected with a Boc group to afford **4** in quantitative yield. Enantiomeric purity of **4** (> 98% diastereomeric excess)[15] was determined by HPLC analysis with comparison of a standard sample.[16]

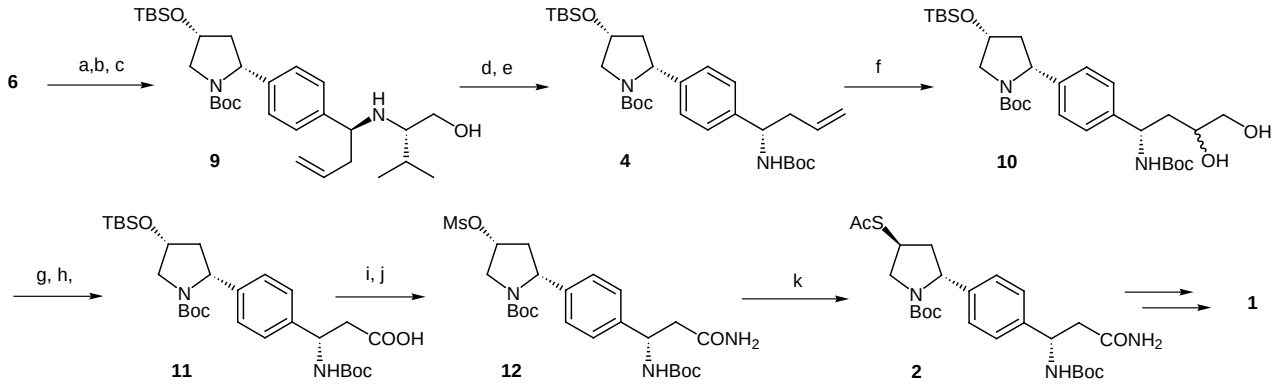
Oxidation of homoallylamine **4** by the combination of osmium tetroxide and 4-methylmorpholine *N*-oxide (NMO) at room temperature afforded vicinal diol **10** (74%), which was oxidized with sodium periodate forming aldehyde and sequentially with sodium chlorite[17] to provide *N*-Boc-β-aryl-β-amino acid **11**. After removal of the *t*-butyldimethylsilyl (TBS) group by using tetrabutylammonium fluoride (TBAF), hydroxy acid **3** was treated with methanesulfonyl chloride (MsCl) in the presence of Et_3N at –20 °C, and successively with ammonia water to form carbamoyl derivative **12** (46% from diol **10**). Finally, a thiol function was introduced by the substitution reaction

Table Reaction of Allylzinc Reagent under various Conditions.[a]



Entry	Solvent	Additive	Temp.	Yield[c]
1	THF	none	0 °C → r.t.	n.r.[d]
2	THF	$CeCl_3 \cdot 7\ H_2O$ (x 0.1)	0 °C → r.t.	n.r.[d]
3	THF	none	60 °C	~ 40%
4	THF	$CeCl_3$[b] (x 0.8)	60 °C	20%
5	THF	$CeCl_3 \cdot 7\ H_2O$ (x 0.8)	60 °C	39%
6	Et_2O	none	reflux	n.r.[d]
7	CH_2Cl_2	none	reflux	trace
8	Benzene	none	60 °C	n.r.[d]
9	Dioxane	none	60 °C	n.r.[d]
10	MeCN	none	60 °C	n.r.[d]
11	DMF	none	60 °C	69%
12	DMSO	none	60 °C	n.r.[d]

[a] Conditions: **7** 50 mg (0.096 mmol), Zn 60 mg (10 equiv), Allylbromide 170 mL (20 equiv), solvent 3 mL.
[b] Anhydrous beads, purchased from ALDRICH.
[c] Isolated yield.
[d] No reaction.



Scheme 3 Reagents and conditions: (a) L-Val-OMe·HCl, Et_3N, $MgSO_4$, THF, r.t., quant.; (b) Allyl bromide, Zn, DMF, 60 °C, 77%; (c) LAH, THF, 0 °C, 85%; (d) H_5IO_6, $MeNH_2$, MeOH–H_2O, 0 °C; (e) Boc_2O, NaOH, Dioxane–H_2O, 0 °C, quant. in 2 steps; (f) OsO_4, NMO, Acetone–H_2O, r.t., 74%; (g) $NaIO_4$, THF–H_2O, r.t.; (h) $NaClO_2$, NaH_2PO_4, 2-metyl-2-butene, *t*-BuOH–H_2O, rt.; (i) TBAF, THF, r.t.; (j) MsCl, Et_3N, THF, –20 °C → –10 °C then NH_4OH, r.t., 46% in 4 steps; (k) AcSK, DMF, 70 °C, 67%.

of mesylate **12** with potassium thioacetate in DMF to yield enantiomerically pure thioacetate **2** (67%, > 99% diastereomeric excess).[18] No appreciable decrease of the enantiomeric purity was observed in the above transformation of **4** to **2**.

In conclusion, aldehyde **6** was converted to the enantiomerically pure **2** in 11 steps and the overall yield was 15% with > 99% diastereomeric excess. These procedures were practical by using economical reagents without cryogenic conditions and provided complete stereoselectivity. Thus, we successfully demonstrated the efficiency of diastereoselective allylation of valine-derived aldimine for constructing the β-alanine amide structure of side chain of 1-β-methylcarbapenem **2**.

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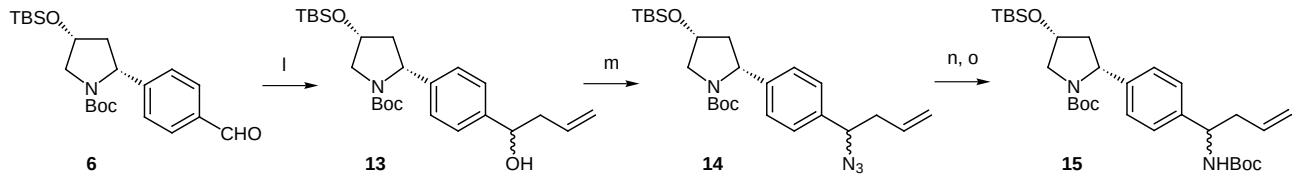

Scheme 4 Reagents and conditions: (l) Allylmagnesium bromide, THF, 0 °C, 92%; (m) MsCl, Et_3N, THF, –50 °C → –30 °C then NaN_3, DMF, r.t., 46%; (n) PPh_3, H_2O, THF, 60 °C; (o) Boc_2O, NaOH, Dioxane–H_2O, 0 °C, 72% in 2 steps.

(11) The diastereomeric excess (de) of **8** was determined by HPLC analysis after converting to the corresponding **4**. See ref[15] about the HPLC condition of **4**.

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(13) A typical experimental procedure for the synthesis of **8** is as follows: To a mixture of **7** (6.57 g, 12.67 mmol)and Zn powder (8.06 g, 123.3 mmol) in DMF (100 mL) was added allyl bromide (21.3 mL, 246.1 mmol) at r.t. The reaction mixture was stirred at 60 °C overnight (ca. 12–18 h). The mixture was poured into H_2O and the whole was extracted EtOAc. The organic layer was washed with brine, dried over anhyd $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 10:1) to give **8** (5.47 g, 77%) as a pale yellow oil; $[\alpha]^{25}_D$ –39.4 (*c* 1.0, $CHCl_3$); IR (KBr): 2931, 1734, 1697, 1396, 1157, 1092, 837, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ = –0.04 (3 H, s), 0.05 (3 H, s), 0.82 (9 H, s), 0.83 (3 H, d, *J* = 7.0 Hz), 0.88 (3 H, d, *J* = 7.0 Hz), 1.14 (9 H, s), 1.80 (2 H, m), 1.92 (1 H, m), 2.35 (2 H, m), 2.51 (1 H, m), 2.77 (1 H, m), 3.47 (2 H, m), 3.70 (3 H, s), 3.87 (1 H, m), 4.38 (1 H, m), 4.69 (1 H, m), 5.08 (2 H, m), 5.71 (1 H, m), 7.17 (2 H, d, *J* = 8.4 Hz), 7.20 (2 H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.0, 17.9, 18.6, 19.4, 25.6, 28.1, 28.4, 31.7, 43.8, 44.6, 51.2, 54.7, 60.1, 60.5, 64.3, 70.0, 79.3, 117.5, 125.9, 127.2, 135.3, 141.5, 143.8, 154.5, 176.2; HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{31}H_{53}N_2O_5Si$, 561.3724; found 561.3736.

(14) Selected data for compound **9**: $[\alpha]^{25}_D$ +16.8 (*c* 1.0, $CHCl_3$); IR (KBr): 3047, 2926, 1684, 1404, 1092, 837, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ = –0.04 (3 H, s), 0.05 (3 H, s), 0.81 (9 H, s), 0.81 (3 H, d, *J* = 6.6 Hz), 0.86 (3 H, d, *J* = 6.6 Hz), 1.15 (9 H, s), 1.69 (1 H, ddd, *J* = 6.6, 6.6, 20.2 Hz), 1.91 (1 H, ddd, *J* = 5.9, 7.0, 12.7 Hz), 2.08 (1 H, br s), 2.23 (1 H, m), 2.40 (1 H, m), 2.48 (2 H, m), 3.39 (1 H, dd, *J* = 3.3, 10.6 Hz), 3.46 (1 H, dd, *J* = 4.9, 10.4 Hz), 3.61 (1 H, dd, *J* = 3.9, 10.8 Hz), 3.69 (1 H, t, *J* = 7.0 Hz), 3.83 (1 H, m), 4.39 (1 H, m), 4.72 (1 H, m), 5.02 (2 H, m), 5.68 (1 H, m), 7.15 (2 H, d, *J* = 8.1 Hz), 7.21 (2 H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.1, 17.7, 18.7, 19.4, 25.5, 27.9, 29.2, 29.5, 42.6, 44.4, 54.6, 59.4, 59.7, 59.9, 61.0, 69.9, 79.2, 117.0, 125.9, 126.5, 135.2, 141.6, 143.7, 154.3; HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{30}H_{53}N_2O_4Si$, 533.3774; found 533.3759.

(15) Selected data for compound **4**: $[\alpha]^{25}_D$ –4.8 (*c* 1.0, $CHCl_3$); IR (KBr): 2931, 2347, 1697, 1508, 1396, 1173, 1093, 837, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ = –0.03 (3 H, s), 0.04 (3 H, s), 0.81 (9 H, s), 1.14 (9 H, s), 1.40 (9 H, s), 1.89 (1 H, m), 2.50 (3 H, m), 3.42 (1 H, m), 3.82 (1 H, m), 4.37 (1 H, m), 4.69 (2 H, m), 4.87 (1 H, br s), 5.07 (2 H, m), 5.65 (1 H, m), 7.16 (2 H, d, *J* = 8.1 Hz), 7.21 (2 H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = –5.1, 17.7, 25.5, 27.9, 28.2, 29.5, 41.1, 44.5, 53.6, 54.5, 59.9, 69.8, 79.3, 117.9, 125.7, 126.0, 133.8, 143.6, 154.3; HRMS–FAB: *m/z* $[M + Na]^+$ calcd for $C_{30}H_{50}N_2O_5SiNa$, 569.3386; found 569.3365. Analytical HPLC condition: column, Chiralcel OD-H (Daicel, 4.6 mm I. D. × 250 mm); eluent, *n*-hexane:*i*-PrOH = 98:2; flow rate, 0.5 mL/min; column temp., 40 °C; detection, UV 230 nm; retention time, 10.9 min [**4**, (*S*)-isomer] and 12.2 min [(*R*)-isomer].

(16) Diastereomeric mixture of homoallylamine **15** was prepared as illustrated above (Scheme 4). Allylation of aldehyde **6** with allylmagnesium bromide afforded homoallyl alcohol **13** (92%). Mesylation of **13** with MsCl and Et_3N at –50 °C, followed by treatment with NaN_3 gave azide **14** (46%). Reduction of **14** with triphenylphosphine in the presence of water and subsequent protection with Boc_2O provided the mixture of (*R*)- and (*S*)-homoallylamine (ca. 1:1, 72%) **15**.

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(18) Compound **2** was in agreement with all reported analytical data and the enantiomeric purity was determined by HPLC analysis. See ref[7].