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Conjugate addition of amines to chiral 3-aziridin-2-yl-acrylates

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ABSTRACT

Conjugate addition of benzylamine to chiral methyl *cis*-3-aziridin-2-yl-acrylates was successfully proceeded to yield 3-aziridin-2-yl-3-benzylaminopropionates in high yield with high stereoselectivity. The addition products were used for the asymmetric synthesis of vicinal diamine derivatives including 4-amino-5-methylpyrrolidin-2-one, 3,4-diaminopentanoate, and 5-chloromethyl-4-alkoxycarbonylmethylimidazolidin-2-one.

Synthesis of stereochemically well-defined 1,2-diamines is still a great challenge to many organic chemists due to their vast utilities as catalysts, metal-ligands, and sub-unit of some natural products.[1] Especially β,γ-diamino acids and their cyclic forms like 4-aminopyrrolidin-2-one and imidazolidin-2-one have unique properties as peptidomimetics[2] and as constituents of biologically active molecules including renin-inhibitory statin analogs,[3] antifungal and cytotoxic microsclerodermins,[4] and antipsychotic nemonapride.[5] Furthermore, the reduced form of 4-aminopyrrolidin-2-one provides an entry into the 3-aminopyrrolidine family of alkaloids (Fig. 1).[6]

Considering the vast utilities of these compounds, limited methods are available and most of which is based on α-amino acids as starting material through homologations followed by introducing one more amine functionality.[7] These known methods were suffered from the limited sources of starting substrates and the multi-reaction steps including low yield. In this Letter is described a general and facile synthetic method to access enantiomerically pure anti β,γ-diamino acids and their cyclic forms using chiral aziridine.

During last several years we have shown that enantiomerically pure aziridine-2-carboxylate is a configurationally stable surrogate of α- or β-amino acids.[8] Homologation and proper functionalization of carboxylate followed by aziridine ring opening provided many valuable compounds such as unnatural amino acids,[9] sphinganine,[10] phytosphingosine,[11] ceramide analogs,[12] and terminal 1,2-diamines.[13] Homologation by two carbons and introduction of one more amino group adjacent to the aziridine-ring will be able to provide a good synthetic intermediate toward the targeted β,γ-diamino acids and their cyclic forms.

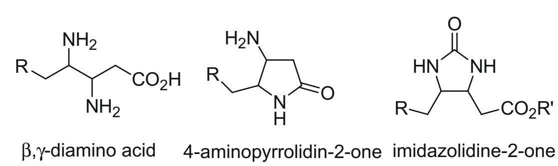

Figure 1. β,γ-Diamino acids, 4-aminopyrrolidin-2-ones, and imidazolidine-2-ones.

At first *trans*- and *cis*-3-[{(1′*R*)-phenylethylaziridine}-(2*R*)- and (2*S*)-yl]-acrylates were selectively prepared from aziridine-2-carboxaldehyde.[8] The reaction of [(1*R*)-phenylethylaziridine]-(2*R*)-carboxaldehyde with $(EtO)_2POCH_2CO_2R$ yielded *trans*-3-[{(1′*R*)-phenylethylaziridin}-(2*S*)-yl]-acrylate in more than 95% yield with the ratio of 98:2 regardless of R (methyl and ethyl). The same reaction with $Ph_3PCH_2CO_2R$ leading to alkyl *cis*-3-[{(1′*R*)-phenylethylaziridin}-(2*R*)- and (2*S*)-yl]-acrylates, **1** and **2**, was also successfully provided in more than 93% yield with the ratio of 88:12 (R = Me) and 86:14 (R = Et). Interestingly, only the cis and trans isomers bearing methyl ester were chromatographically

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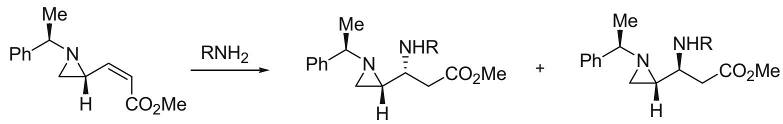
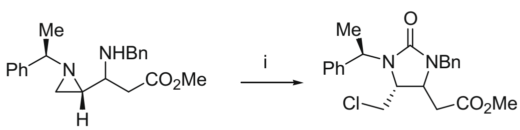
Table 1
Addition of benzylamines to methyl *cis*-3-[{(1′*R*)-phenylethylaziridin}-(2*R*)-yl]-acrylate (**1**)



1 **3A** (*erythro*) **3B** (*threo*)

Entry	RNH_2	Temp (°C)	Time[a] (h)	Yield[b] (%)	Ratio[c] (**3A**:**3B**)
1	$PhCH_2NH_2$ (**a**)	rt	14	95	2.9:1
2	$PhCH_2NH_2$ (**a**)	0	24	91	2.9:1
3	$PhCH_2NH_2$ (**a**)	−40	20	98	4.0:1
4	(*R*)-$Ph(CH_3)CHNH_2$ (**b**)	50	7	95	3.3:1
5	**(*S*)-$Ph(CH_3)CHNH_2$ (c)**	**50**	**7**	**97**	**>99:1**

[a] The reaction was carried out with amine in MeOH.
[b] Yields, not optimized.
[c] Ratios, determined by ^1H NMR.



3Aa, **3Ba** **5**, **6**

Scheme 1. Reagents and conditions: (i) (1) NaH, $Cl_3COCOOCCl_3$, −10 °C, THF, 3 h.

separable (R_f values, 0.75 and 0.70 for cis and trans, hexane/EtOAc, 1:1 (v/v)).

Conjugate addition of benzylamine (**a**) to methyl *trans*- and *cis*-3-[{(1′*R*)-phenylethylaziridin}-(2*R*)-yl]-acrylate in MeOH showed the big difference on the reactivity and stereoselectivity between two substrates. The *cis* isomer **1** is much more reactive to yield the expected diastereomeric mixture **3Aa** and **3Ba** in a 2.9:1 ratio at room temperature while *trans* is quite sluggish with no selectivity (Table 1, entry 1) The ratio obtained of **3Aa** was changed by lowering the reaction temperature to 0 °C and −45 °C as 2.9:1 and 4.0:1, respectively (Table 1, entries 2 and 3). Addition of chiral amines for the possible improvement of diastereoselectivity was succeeded with (*R*)- and (*S*)-α-methylbenzylamine (**b** and **c**) to yield addition products. In case of (*R*)-α-methylbenzylamine (**b**) not much improvement was observed in terms of selectivity to give 3.3:1 (**3Ab**:**3Bb**) (entry 4). However, the addition of (*S*)-α-methylbenzylamine (**c**) yielded a single isomer **3Ac** as a sole product judged by NMR and HPLC analyses (entry 5). This high selectivity arisen from the right match between 2*R* configuration of the phenylethyl group of the aziridine ring and (*S*)-α-methylbenzylamine nucleophile.

The inseparable diastereomeric mixture of **3Aa** and **3Ba** obtained from entry 2 in Table 1 was further reacted with triphosgene and NaH to yield 4-chloromethyl-5-methoxycarbonylmethylimdazolidin-2-ones **5** and **6** (Scheme 1).[14]

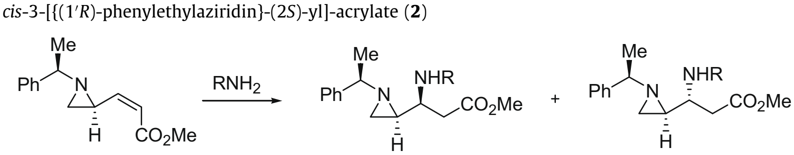
The coupling constants of two vicinal hydrogens at C4 and C5 of compounds **5** (major) and **6** (minor) were 7.5 and 3.0 Hz, respectively. On the basis of these values we could determine the stereochemistry of **3Aa** and **3Ba** as *erythro* and *threo*, respectively.[14,15]

A similar selectivity was observed with methyl *cis*-3-[{(1′*R*)-phenylethylaziridin}-(2*S*)-yl]-acrylate (**2**) as the starting substrate and benzylamine (**a**) to give a *erythro* (**4Aa**) and *threo* (**4Ba**) mixture with the ratio as 2.3:1 and 2.6:1 (entries 1–3 of Table 2). Both the chiral nucleophiles (*R*)-α-methylbenzylamine (**b**) and (*S*)-α-methylbenzylamine (**c**) with **2** yielded addition products with poor selectivities as 1.2:1 and 2.1:1, respectively (entries 4 and 5 of Table 2).

The drastic difference in the stereoselectivity was observed during the addition reaction of the chiral nucleophiles (*R*)-α-methylbenzylamine (**b**) and (*S*)-α-methylbenzylamine (**c**) to either **1** or **2** (entries 4 and 5 in Table 1 and Table 2). This implies the participation of the α-methylbenzyl group at the ring nitrogen and the coming nucleophile resulted the 'matched' (entry 5 in Table 1) and 'mismatched' cases (entry 4 in Table 1, and entries 4 and 5 in Table 2) in the transition state during the course of the reaction.[16]

The possible transition state stems from the most stable conformer of 2-substituted aziridine with two substituents X and Y

Table 2
Addition of benzylamines to methyl *cis*-3-[{(1′*R*)-phenylethylaziridin}-(2*S*)-yl]-acrylate (**2**)



2 **4A** (*erythro*) **4B** (*threo*)

Entry	RNH_2	Temp (°C)	Time[a] (h)	Yield[b] (%)	Ratio[c] (**4A**:**4B**)
1	$PhCH_2NH_2$ (**a**)	rt	14	96	2.3:1
2	$PhCH_2NH_2$ (**a**)	0	24	91	2.3:1
3	$PhCH_2NH_2$ (**a**)	−40	30	95	2.6:1
4	(*R*)-$Ph(CH_3)CHNH_2$ (**b**)	50	8	82	1.2:1
5	(*S*)-$Ph(CH_3)CHNH_2$ (**c**)	50	8	95	2.1:1

[a] The reaction was carried out with amine in MeOH.
[b] Yields, not optimized.
[c] Ratios, determined by ^1H NMR.

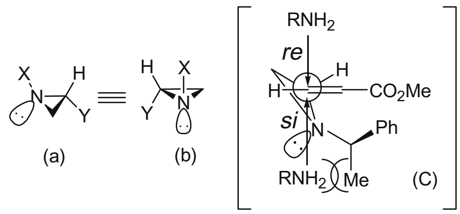
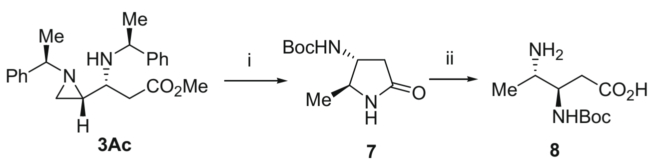


Figure 2. (a), (b) Front and side views of the aziridine with two substituents X and Y at N1 and C2. (c) View of methyl *cis*-3-[{(1′*R*)-phenylethylaziridin}-(2*R*)-yl]-acrylate (**1**) and the possible approaching faces of the amine nucleophile in the transition state model.



Scheme 2. Reagents and conditions: (i) (1) H_2 (1 atm), $Pd(OH)_2$, rt. 4 h, (2) $(Boc)_2O$, MeOH, rt, two steps 89%. (ii) LiOH, $EtOH/H_2O$ = 5:1 (v/v) 50 °C, 8 h, rt, ion-exchange column, 82%.

situated in *trans*-relationships as shown in Figure 2 (a) and (b). This *trans*-relationship was also observed in many crystalline structures of aziridines.[17] Putting both substituents of phenylethyl (X) and methoxycarbonylethenyl (Y) groups generates the structure (c) in Figure 2 with possible two faces, *re* and *si*, for the nucleophile to come.

Among two possible directions *re* face attack is more favorable rather than *si* face away from the steric hindrance, which is the controlling factor to yield the *erythro* adduct as the major product along with the additional stereodifferentiation by (*R*)-α-methylbenzylamine. This stereochemical pathway is opposite to the reaction with chelation-controlled transition state to yield the *threo* product.[14]

The addition product **3Ac** was further treated with an atmospheric pressure of hydrogen in the presence of $Pd(OH)_2$ catalyst followed by reaction with $(Boc)_2O$ to yield (4*R*,5*S*)-4-*t*-butyloxycarbonylamino-5-methylpyrrolidin-2-one (**7**) in a 89% yield. Hydrolysis of **7** followed by anion exchange column afforded the known (3*R*,4*S*)-4-amino-3-*t*-butyloxycarbonylaminopentanoic acid (**8**) in a 82% yield (Scheme 2).[18] The addition product **3Ac** will be served as a synthetic intermediate for the preparation of various chiral diamines through aziridine ring opening with various nucleophiles.[8]

In conclusion, the conjugate addition of benzylamine to chiral methyl *cis*-3-[{(1′*R*)-phenylethyl-aziridin}-(2*R*)- and (2*S*)-yl]-acrylates provides the *erythro* adduct, 3-(aziridin-2-yl)-3-benzylaminopropionate as the major product. Additional stereodifferentiation by (*S*)-α-methylbenzylamine to the substrate (2*R*)-acrylates yielded a single enantiomeric adduct in high yield which was used as the precursor for the substituted nitrogen-containing heterocycles and enantiomerically pure β,γ-diaminoacids.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.087.

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