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New synthesis and ring opening of *cis*-3-alkylaziridine-2-carboxylates☆

Kwang-Deuk Lee,[a] Jang-Min Suh,[a] Jae-Hoon Park,[a] Hyun-Joon Ha,[a,*] Hwan Gun Choi,[b] Chan Sun Park,[b] Jae Won Chang,[b] Won Koo Lee,[b,*] Yongkwan Dong[c] and Hoseop Yun[c]

[a]*Department of Chemistry, Hankuk University of Foreign Studies, Yongin, Kyunggi-Do 449-791, South Korea*
[b]*Department of Chemistry, Sogang University, Seoul 121-742, South Korea*
[c]*Department of Molecular Science and Technology, Ajou University, Suwon 442-749, South Korea*

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Abstract—Syntheses of *cis*-3-alkylaziridine-2-carboxylates including *cis*-3-benzyl- and *cis*-3-phenylaziridine-2-carboxylates were achieved from the reaction of α-aminonitrile and alkyldiazoacetate in the presence of a Lewis acid. Asymmetric version of this reaction with the chiral α-methylbenzylamine was also successful for the preparation of chiral aziridines that were used for the synthesis of various amino acids including homophenylalanine, β-amino-α-hydroxy acid, α,β-diamino acid, and α-amino-β-hydroxy acid via regioselective aziridine ring openings.

1. Introduction

Aziridine-2-carboxylates and their derivatives are useful intermediates for the synthesis of various amine-containing molecules by stereospecific ring opening reactions with several different nucleophiles.[1] Nucleophiles for the ring opening reactions include not only heteroatoms such as halide, oxygen, nitrogen but also carbanions as alkylcuprates and phosphorus ylides.[1,2] Aziridine ring could also be transformed into five-membered heterocycles such as oxazoline-2-ones and imidazolidin-2-ones.[3]

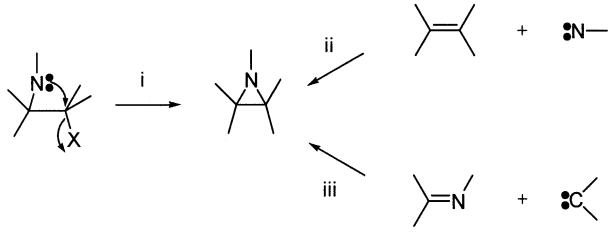
Ample examples of their synthesis were reported in the literature based on three different approaches as shown in Scheme 1, (i) nucleophilic displacement by nitrogen with removal of the leaving group at the α-position, (ii) 1,2-addition of a nitrene to olefins, and (iii) 1,2-addition of a carbene to imines.

Among the methods (iii) was most extensively investigated with success of its catalytic versions with various imines.[4] A new version of three-components reactions with aldehydes, amines, and diazoacetates were also achieved by Kobayashi group with lathanide triflate as a catalyst.[5] However, one great limitation in the method (iii) is that no reaction is possible with phenylacetaldimines so far. Phenylacetaldimine is an unstable and non-isolable imine due to its possible conversion to more stable enamine, 2-phenylethenamine, under the reaction condition for its preparation.[6] Therefore, no direct synthesis of 3-benzylaziridine-2-carboxylate was available up to now. However, we found the synthetic possibility from our recent success utilizing phenylacetaldimine equivalent[7] generated in situ from 2-amino-3-phenylpropanenitrile in the presence of a Lewis acid.

In this paper we would like to describe the first direct synthesis of *cis*-3-benzylaziridine-2-carboxylates and its expanded version for a general synthesis of *cis*-3-alkylaziridine-2-carboxylates, including *cis*-3-phenylaziridine-2-carboxylate, from the reaction of α-aminonitriles for the synthetic precursors of the corresponding imines and alkyldiazoacetate in the presence of a Lewis acid.

2. Results and discussion

Though several synthetic methods are available for the



Scheme 1.

☆ This paper is part 16 in the series of 'Lewis acid induced synthetic equivalents of imines and iminum ions'. For part 15 see Ref. 26.

Keywords: aziridine-2-carboxylate; homophenylalanine; β-amino-α-hydroxy acid; α,β-diamino acid; α-amino-β-hydroxy acid.

* Corresponding authors. Tel.: +82-335-30-4369; fax: +82-335-333-1696. Fax: +82-2-7010967; e-mail: hjha@hufs.ac.kr; wonkoo@sogang.ac.kr

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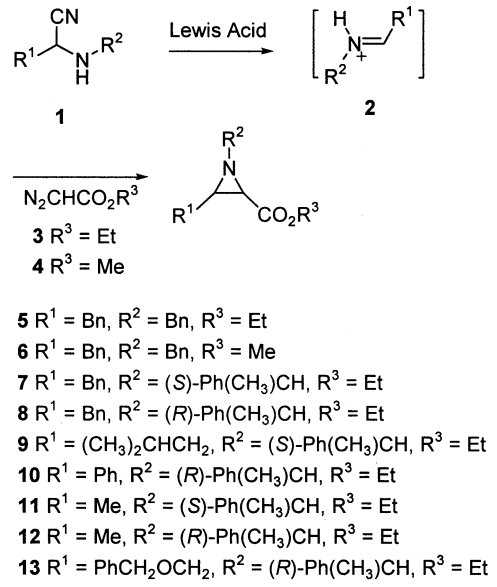


Scheme 2.

preparation of 3-alkylaziridine-2-carboxylates from imines and alkyl diazoacetates in high yields, no direct synthesis of 3-benzylaziridine-2-carboxylates was reported due to the instability of the corresponding phenylacetaldimine. Therefore, 3-benzylaziridine-2-carboxylate (**5**) was the first synthetic target based on the possible reaction of the phenylacetaldimine generated in situ from its precursor with ethyl diazoacetate. We generated the phenylacetaldimine equivalent (**2**, R^1=Bn) in situ from 2-amino-3-phenylpropanenitrile (**1**, R^1=Bn) in the presence of a Lewis acid, TMSOTf, and subsequently utilized it for the aldimine coupling reaction with (*Z*)-α-methoxy trimethylsilyl ketene acetal to afford 3-amino-2-hydroxy-4-phenylbutanoate.[7] This observation suggested us the possible direct synthetic method toward 3-benzylaziridine-2-carboxylate (**5**) from 2-amino-3-phenylpropanenitrile (**1**) and alkyldiazoacetate (**3**, **4**) with the assistance of a proper Lewis acid (Scheme 2).

The reactions starting form 2-benzylamino-3-phenylpropanenitrile (**1**, R^1=R^2=Bn) and ethyl diazoacetate (**3**) were not successful with several different Lewis acids[8] including $TiCl_4$, $AlCl_3$, $MgBr_2$, TMSOTf, $BF_3{\cdot}OEt_2$, TiF_4, $AgBF_4$, and $Yb(OTf)_3$ until $ZnCl_2$ and $SnCl_4$ were found to be effective (entries 1–10) (Table 1).

With one mole equivalent of $SnCl_4$, reactions with either ethyl- or methyl diazoacetate (**3**, **4**) proceed smoothly in CH_2Cl_2 at room temperature to afford the expected product 3-benzylaziridine-2-carboxylate (**5**, **6**) in 51 and 48 % yields, respectively, with the only *cis* stereochemistry between benzyl at C-3 and carboxylate at C-2 (entry 10 and 12).[9] Cutting the mole ratio of $SnCl_4$ to the half of α-aminonitrile, lowered the reaction yield to 42% (entry 11). Neither changing the solvent nor the reaction temperature could improve the reaction yield.

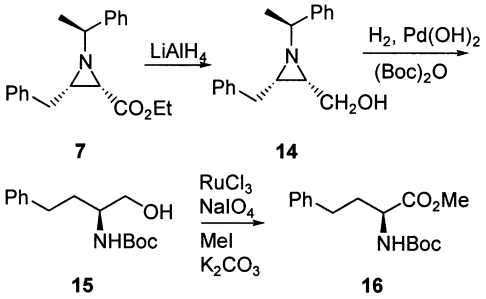
Once the reaction condition was established we carried out the reaction with a chiral substrate, 3-phenyl-2-[(*S*)-1-phenylethylamino]propanenitrile (**1**, R^1=Bn, R^2=(*S*)-Ph-(CH_3)CH), considering the additional factor of diastereofacial selectivity. The standard Strecker synthesis[10] from phenylacetaldehyde and (*S*)-1-phenylethylamine provides 3-phenyl-2-[(*S*)-1-phenylethylamino]propanenitrile as a diastereomeric mixture of 2*S* and 2*R* with 4:1 ratio.[7,10] This diastereomeric mixture was used for the next coupling reaction without further purification or isolation because each isolated isomer yielded the same stereochemical outcome possibly due to the same iminium ion intermediate. With one mole equiv. of $SnCl_4$ the expected product ethyl *cis*-3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate was obtained as a diastereomeric mixture (**7** and **7′**) with the ratio of 58:42 in 47% yield after chromatography (Scheme 3).

The major isomer 3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (**7**) was reduced by $LiAlH_4$ to give hydroxymethylaziridine **14**. Hydrogenolysis of **14** with a catalyst $Pd(OH)_2$ in the presence of $(Boc)_2O$ gave the ring-opened

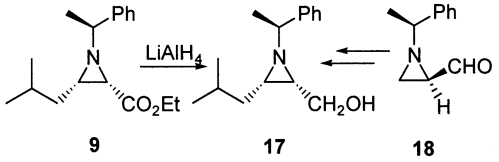
Table 1. Reactions of α-aminonitriles (**1**) and alkyldiazoacetate (**3**, **4**) in CH_2Cl_2 at room temperature in the presence of Lewis acids (LA)

Entry	R^1	R^2	R^3	LA (equiv.)	Yield[a] (%)	(2*S*,3*S*)/(2*R*,3*R*)
1	$PhCH_2$	$PhCH_2$	Et	$TiCl_4$ (1.0)	No rxn	
2	$PhCH_2$	$PhCH_2$	Et	$AlCl_3$ (1.0)	No rxn	
3	$PhCH_2$	$PhCH_2$	Et	$MgBr_2$ (1.0)	No rxn	
4	$PhCH_2$	$PhCH_2$	Et	TMSOTf (1.0)	No rxn	
5	$PhCH_2$	$PhCH_2$	Et	TiF_4 (1.0)	No rxn	
6	$PhCH_2$	$PhCH_2$	Et	$AgBF_4$ (1.0)	No rxn	
7	$PhCH_2$	$PhCH_2$	Et	$Yb(OTf)_3$ (1.0)	No rxn	
8	$PhCH_2$	$PhCH_2$	Et	$BF_3{\cdot}OEt_2$ (1.0)	No rxn	
9	$PhCH_2$	$PhCH_2$	Et	$ZnCl_2$ (1.0)	**5** (21)	
10	$PhCH_2$	$PhCH_2$	Et	$SnCl_4$ (1.0)	**5** (51)	
11	$PhCH_2$	$PhCH_2$	Et	$SnCl_4$ (0.5)	**5** (42)	
12	$PhCH_2$	$PhCH_2$	Me	$SnCl_4$ (1.0)	**6** (48)	
13	$PhCH_2$	(*S*)-Ph(CH_3)CH	Et	$SnCl_4$ (1.0)	**7** (47)	58/42
14	$PhCH_2$	(*R*)-Ph(CH_3)CH	Et	$SnCl_4$ (1.0)	**8** (42)	61/39
15	$(CH_3)_2CHCH2$	(*S*)-Ph(CH_3)CH	Et	$SnCl_4$ (1.0)	**9** (71)	73/27
16	Ph	(*R*)-Ph(CH_3)CH	Et	$SnCl_4$ (0.5)	**10** (39)	75/25
17	CH_3	(*S*)-Ph(CH_3)CH	Et	$SnCl_4$ (0.5)	**11** (50)	66/34
18	CH_3	(*R*)-Ph(CH_3)CH	Et	$SnCl_4$ (0.5)	**12** (54)	63/37
19	$PhCH_2OCH_2$	(*S*)-Ph(CH_3)CH	Et	$SnCl_4$ (1.0)	**13** (25)	71/29[b]
20	$PhCH_2OCH_2$	(*S*)-Ph(CH_3)CH	Et	$ZnCl_2$ (1.0)	**13** (63)	53/47[b]

[a] More than >98% of *cis* was observed.
[b] The absolute stereochemistry was not confirmed.



Scheme 3.



Scheme 4.

product 4-phenyl-2-*t*-butyloxycarbonylaminobutanol (**15**) exclusively without formation of its regioisomer. Selective ring opening between N-1 and C-3 of 3-benzyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridines can be explained by possible coordinated association of amine and oxygen pended in aziridine via hydrogen bond or metal-mediated coordination to result for the bond between N-1 and C-3 of the aziridine ring to be weak. Oxidation of the aminobutanol (**15**) by $RuCl_3$ and $NaIO_4$ followed by methylation with CH_3I with K_2CO_3 to afford *N*-Boc-homophenylalanine methyl ester (**16**) with $[\alpha]_D^{24}$ as -14.2 that is corresponding to 2*S* isomer.[11] Therefore, the major isomer of the aziridine was assigned as (2*S*,3*S*)-3-benzyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridines (**7**). The same reaction with 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile [**1**, R^1=Bn, R^2=(*R*)-Ph(CH_3)CH] yielded a set of diastereomers of 3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylates (**8**) in 42% yield. Those were reduced by $LiAlH_4$ to give (2*S*,3*S*)- and (2*R*,3*R*)-3-benzyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridines in 88% yield. X-ray structure of its major isomer (2*R*,3*R*)-3-benzyl-2-hydroxymethyl-1-[(*R*)-1-phenylethyl]aziridine (*ent*-**14**) was determined as shown in Fig. 1.[12] An intramolecular hydrogen bond was observed between the hydrogen of the hydroxy group and the nitrogen of aziridine with the length of 2.808 Å and the dihedral angle of 174°.

The values of chiral aziridines prompted us to expand this synthetic method with diverse α-cyanoalkylamines as substrates prepared from the Strecker reaction of aldehydes and amines at ease. *cis*-3-Isobutyl-, 3-phenyl-, and 3-methyl-aziridine-2-carboxylates (**9**, **10**, **11** and **12**) bearing either (*S*)-1-phenylethyl or (*R*)-1-phenylethyl as a chiral auxiliary were elaborated in 71, 39, 50 and 54% yield with the diastereomeric ratio of 73:27, 75:25, 66:34, and 63:37, respectively (entries 15, 16, 17 and 18). For all of these reactions $SnCl_4$ was effective as a Lewis acid. However, $SnCl_4$ was not a very effective Lewis acid for the same reaction with the substrate (**1**, R^1=CH_2OCH_2Ph) to attain the aziridine in better yield than 25% with the diastereomeric ratio 71:29 (entry 19). In this case $ZnCl_2$ was effective to yield the corresponding aziridine (**13**) in much better yield of 63%. However, the diastereomeric ratio was poor as 53:47 (entries 19 and 20).

The major isomer (**9**) from the entry 15 was reduced by $LiAlH_4$ in quantitative yield to give 3-*iso*-butyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridines (**17**) whose configurations were confirmed as 2*S* and 3*S* by comparison of the authentic compound synthesized from (2*R*)-1-[(*S*)-1-phenylethyl]aziridine-2-carboxaldehyde.[13] (Scheme 4)

(2*R*,3*R*)-3-Benzyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (**8**) was reduced by DIBAL and reacted with a phosphorus ylide in one pot to give (2*R*,3*R*)-2-benzyl-3-vinyl-1-[(*R*)-1-phenylethyl]aziridine (**19**) in 64% yield. Ring opening was carried out with AcOH in CH_2Cl_2 to afford 3-acetyloxy-4-[(*R*)-1-phenylethyl]amino-5-phenyl-pent-1-ene (**20**) exclusively due to the allylic activation. The ring opening product **20** was transformed by the

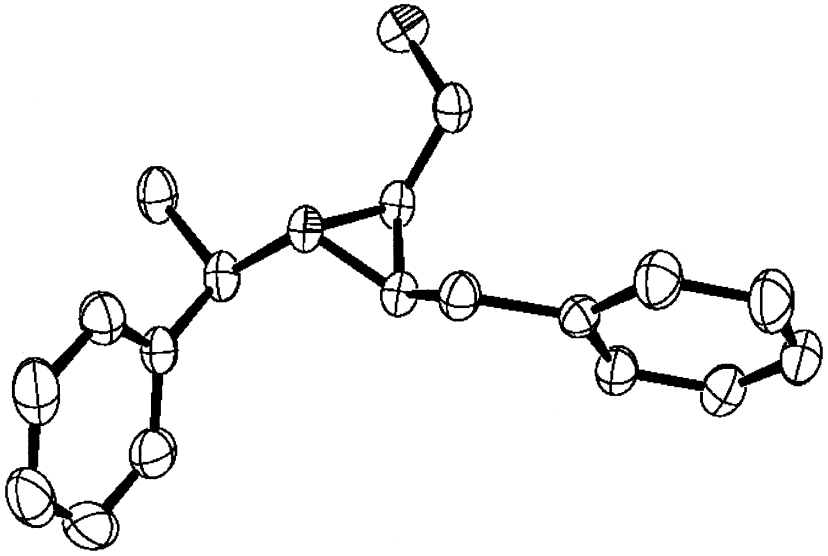
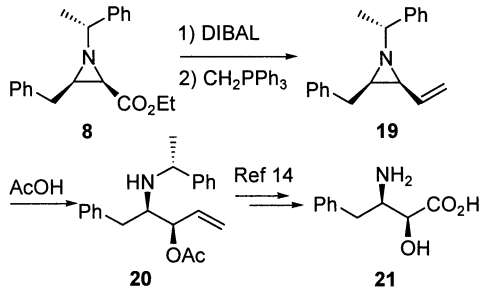


Figure 1. X-ray structure of (2*R*,3*R*)-3-benzyl-2-hydroxymethyl-1-[(*R*)-1-phenylethyl]aziridine (*ent*-**14**).

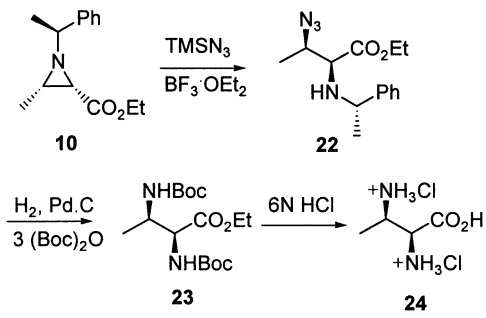


Scheme 5.

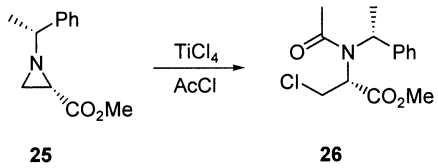
known method[14] to (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid (**21**) as a key component of natural product bestatin[15] (Scheme 5).

Ring opening of aziridine-2-carboxylates with azide would produce α,β-diamino acids which can be used widely as a synthetic precursors and chiral ligands.[1a] When $TMSN_3$ was added to the solution of ethyl (2*S*,3*S*)-3-methyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (**10**) in CH_2Cl_2, no reaction occurred even under reflux. This was contrasted to the early observation that the substrate ethyl (2*R*)-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (*ent*-**25**) was known to be reacted.[16] Addition of the Lewis acid $BF_3{\cdot}OEt_2$ promoted the reaction to proceed at room temperature to give ethyl (2*S*,3*R*)-3-azido-2-[(*S*)-1-phenylethyl]aminopropionate (**22**) in 67% yield as shown in Scheme 6. The absolute stereochemistry and the exact location of the azide in the product **22** could not be confirmed by spectral data. If the ring opening by the azide occurs at C-2 of the aziridine, (2*R*,3*S*)-2-azido-3-[(*S*)-1-phenylethyl]amino-propionate would have been produced with the similar spectral data. The ring-opened product was further transformed to 2,3-diaminobutanoic acid by sequential reaction of hydrogenation with Pd/C in the presence of 3.0 mol equiv. $(Boc)_2O$ and the subsequent acid hydrolysis to yield (2*S*,3*R*)-2,3-diaminobutanoatic acid (**24**){HCl disalt, $[\alpha]_D^{22}=+34.7$ (*c* 0.2, 6N HCl); lit.[17] $[\alpha]_D^{20}=+33.4$ (*c* 1.0, 6N HCl)}. Retrospectively the stereochemical course of aziridine ring opening by $TMSN_3$ in the presence of $BF_3{\cdot}OEt_2$ occurred with breakage of the bond between N-1 and C-3.

The origin of the regioselectivity in the ring opening stems from the electronic effect because the size difference between methyl at C-3 and ethoxycarbonyl at C-2 in the



Scheme 6.



Scheme 7.

aziridine is not big enough to discriminate for the reaction to proceed in one direction. Electronic characteristics in the aziridin-2-carboxylate governs the ring opening reaction with breakage between N-1 and C-3 selectively.[16] Coordination of the Lewis acid to the nitrogen of the aziridine develops positive charge that is dispersed through the aziridine ring with concomitant weakening the C–N bonds. The bond accommodating positive charge better becomes weaker. Between two carbon–nitrogen bonds of the aziridine ring, the bond between N-1 and C-3 gets weaker with better accommodation of the developing positive charge with concomitant bond-breakage toward the coming nucleophile. This observation is consistent with the early report. Ring opening reaction of aziridine-2-carboxylates with simple halide such as NaBr occurred with breakage of the bond between N-1 and C-2 while the reaction with a Lewis acid $MgBr_2$ resulted the bond breaking at N-1 and C-3 of the aziridine ring.[18]

The same regiochemical outcome was observed in the ring opening reaction of ethyl (2*S*)-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (**25**) by AcCl in the presence of $TiCl_4$ as a Lewis acid to afford (2*R*)-2-{*N*-acetyl-*N*-[(*R*)-1-phenylethyl]amino}-3-chloro-propionic acid methyl ester (**26**) in 64% yield (Scheme 7), whose X-ray structure[19] is in Fig. 2. Note that the apparent inversion (2*S*) to (2*R*) is only due to a switch in the CIP-priority.

In the same manner (2*R*,3*R*)-3-benzyl-1-[(*R*)-1-phenylethyl]-aziridine-2-carboxylate (**8**) and (2*R*,3*R*)-3-methyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (**12**) were reacted with AcCl and $TiCl_4$ to produce (2*R*,3*R*)-3-acetoxy-4-phenyl-2-[(*S*)-1-phenylethyl]aminobutanoate (**27**) and (2*R*,3*R*)-3-acetoxy-2-[(*S*)-1-phenylethyl]aminobutanoate (**28**) in 54 and 75% respectively. Their configurations were determined by the corresponding 2-amino-3-hydroxy-4-phenylbutanoic acid {$[\alpha]_D^{22}=-5.5$ (*c* 5.0, 1N HCl); lit.[20], $[\alpha]_D^{22}=+9.1$ (*c* 1.0, 1N HCl) for its enantiomer} and D-*allo*-threonine {$[\alpha]_D^{22}=-8.7$ (*c* 0.9, H_2O); lit.[21], $[\alpha]_D=+9.7$ (*c* 1.0, H_2O) for its enantiomer}that were obtained by the sequential reactions of hydrogenolysis with $(Boc)_2O$ toward **29** and **30** and the subsequent hydrolysis.

These streochemical results of the ring opening reactions with retention of configuration at β-position bearing acetoxy could be explained by double displacements by chloride and by oxygen to replace chlorine with formation of oxazoline ring that was subsequently hydrolyzed to the products **27** and **28** as shown in Scheme 8. All of these observations make it possible to predict that most Lewis acid mediated nucleophilic ring opening reactions of *cis*-3-alkylaziridine-2-carboxylates occur with concomitant breakage of the bond between N-1 and C-3 of the aziridine ring.

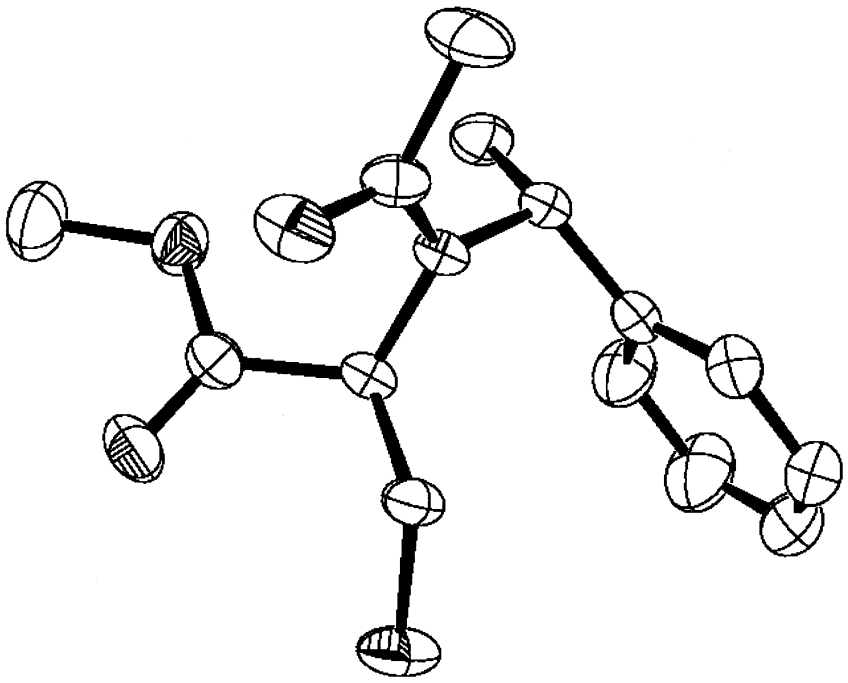
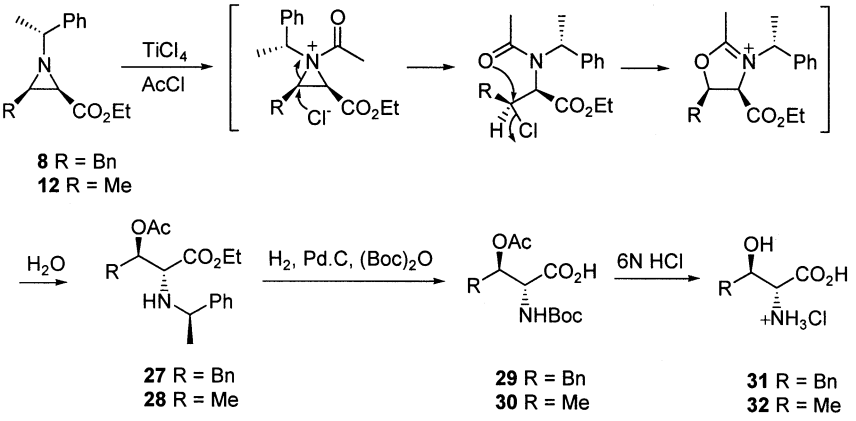


Figure 2. X-Ray structure of (2*R*)-2-{*N*-acetyl-*N*-[(*R*)-1-phenylethyl]amino}-3-chloro-propionic acid methyl ester (**26**).



Scheme 8.

3. Conclusion

This work describes a new synthesis of *cis*-3-alkylaziridine-2-carboxylates from the reaction between α-aminonitrile and alkyldiazoacetate in the presence of a Lewis acid including the first direct preparation of *cis*-3-benzylaziridine-2-carboxylate. Asymmetric version of this reaction with the chiral α-methylbenzylamine was also successful for the preparation of chiral aziridines that were used for the synthesis of various amino acids including homophenylalanine, β-amino-α-hydroxy acid, α,β-diamino acid and α-amino-β-hydroxy acid via regioselective aziridine ring openings. We also have found that Lewis acid mediated nucleophilic ring opening reactions occur with concomitant breakage of the bond between N-1 and C-3 of the aziridine ring.

4. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 200 or 400 (200 and 400 MHz for ^{1}H and 50.3 and 100.6 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as the internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analysis was taken on a Perkin–Elmer 240 DS elemental analyzer. Melting point was measured by Mel-II capillary melting point apparatus. Optical rotation was measured with Rudolph Research Autopole 3 polarimeter. The silica gel used for column chromatography was Merck 200–230 mesh. Thin layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness.

4.1. General synthesis of *cis*-3-alkylaziridine-2-carboxylates (2–10)

Anhydrous $SnCl_4$ (1.2 mmol) and alkyldiazoacetate (1.8 mmol) was added at room temperature under nitrogen atmosphere to the solution of the α-aminonitrile (**1**) (1.2 mmol) that was prepared from the corresponding aldehyde

and amine in CH_2Cl_2 (30 mL). The resultant solution was stirred for 8 h until all the starting nitrile was consumed on TLC. The reaction mixture was poured into ice–water and the resulting solution was neutralized with cold sat. $NaHCO_3$ solution. The reaction product was extracted with EtOAc (50 mL×3) and the organic layer was washed with 100 mL of water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give product. Product for chemical analysis was obtained as colorless oil by short path vacuum distillation except **10** and **10′**.

4.1.1. Ethyl *cis*-3-benzyl-1-benzylaziridine-2-carboxylate (5). ^{1}H NMR δ 1.28 (3H, t, J=7.2 Hz), 2.21 (1H, q, J=6.4 Hz), 2.33 (1H, d, J=7.0 Hz), 2.87 (1H, dd J=4.6, 5.7 Hz), 3.18 (1H, dd, J=6.6, 14.4 Hz), 3.63 (2H, dd, J=13.6, 20.0 Hz), 4.24 (2H, q, J=7.2 Hz), 7.15–7.42 (10H, m); ^{13}C NMR δ 14.2, 33.9, 42.3, 47.3, 60.9, 63.5, 126.2, 127.1, 127.9, 128.2, 128.3, 128.6, 137.6, 138.6, 169.6. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.17; N, 4.74. Found: C, 77.6; H, 7.24; N, 4.89.

4.1.2. Methyl *cis*-3-benzyl-1-benzylaziridine-2-carboxylate (6). ^{1}H NMR δ 2.09 (1H, q, J=6.2 Hz), 2.26 (1H, d, J=7.0 Hz), 2.72 (1H, dd J=4.8, 5.4 Hz), 2.95 (1H, dd, J=6.2, 14.2 Hz), 3.55 (2H, dd, J=13.6, 20.0 Hz), 3.70 (3H, s), 7.05–7.24 (10H, m); ^{13}C NMR δ 34.0, 42.2, 47.3, 52.1, 63.6, 126.3, 127.2, 128.0, 128.3, 128.4, 128.6, 137.5, 138.6, 170.1. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.81; N, 4.98. Found: C, 76.6; H, 6.77; N, 4.79.

4.1.3. Ethyl (2*S*,3*S*)-3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (7) and ethyl (2*R*,3*R*)-3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (7′). R_f (*n*-Hex/Ether, 3:1) 0.56 for **7** and 0.63 for **7′**. For **7**, $[\alpha]_D^{24}$=−36.8 (c=5.0 in CH_2Cl_2), 1.30 (3H, t, J=7.0 Hz), 1.48 (3H, d, J=6.6 Hz), 2.11 (1H, q, J=6.6 Hz), 2.32 (1H, d, J=6.6 Hz), 2.68 (1H, q, J=6.6 Hz), 2.89 (2H, m), 4.26 (2H, q, J=7.0 Hz), 6.95–7.37 (10H, m); ^{13}C NMR δ 14.10, 22.45, 33.75, 42.42, 46.71, 60.77, 69.50, 125.88, 126.79, 127.01, 128.05, 128.09, 128.34, 138.40, 142.98, 169.63. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.6; H, 7.49; N, 4.53. Found: C, 77.4; H, 7.44; N, 4.59. For **7′** $[\alpha]_D^{24}$=+9.1 (c=5.0 in CH_2Cl_2) ^{1}H NMR δ 1.11 (3H, t, J=7.0 Hz), 1.20 (3H, d, J=6.2 Hz), 2.02–2.13 (2H, m), 2.54 (1H, q, J=6.6 Hz), 2.75–3.02 (2H, m), 3.96–4.13 (2H, m), 7.03–7.29 (10H, m); ^{13}C NMR δ 14.1, 23.6, 34.4, 42.2, 48.3, 60.7, 69.4, 126.3, 126.4, 126.9, 128.2, 128.4, 128.8, 138.8, 143.5, 169.4. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.6; H, 7.49; N, 4.53. Found: C, 77.3; H, 7.56; N, 4.32.

4.1.4. Ethyl (2*S*,3*S*)-3-*iso*-butyl-1-[(*S*)-1-phenylethyl]-aziridine-2-carboxylate (9) and ethyl (2*R*,3*R*)-3-*iso*-butyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (9′). R_f (*n*-Hex/Ether, 1:2) 0.56 for **9** and 0.65 for **9′**. For **9** $[\alpha]_D^{24}$=−36.8 (c=5.0 in CH_2Cl_2), 1.30 (3H, t, J=7.0 Hz), 1.48 (3H, d, J=6.6 Hz), 2.11 (1H, q, J=6.6 Hz), 2.32 (1H, d, J=6.6 Hz), 2.68 (1H, q, J=6.6 Hz), 2.89 (2H, m), 4.26 (2H, q, J=7.0 Hz), 6.95–7.37 (10H, m); ^{13}C NMR δ 14.1, 21.4, 22.7, 28.4, 36.0, 42.7, 44.8, 60.5, 69.5, 126.8, 127.0, 128.0, 143.3, 170.0. [HREIms. Found: 275.1889. $C_{17}H_{25}NO_2(M^+)$ requires: 275.1885]. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.15; N, 5.09. Found: C, 73.7; H, 8.96; N, 5.32. For **9′** $[\alpha]_D^{24}$=9.1 (c=5.0 in CH_2Cl_2) ^{1}H NMR δ 1.11 (3H, t, J=7.0 Hz), 1.20 (3H, d, J=6.2 Hz), 2.02–2.13 (2H, m), 2.54 (1H, q, J=6.6 Hz), 2.75–3.02 (2H, m), 3.96–4.13 (2H, m), 7.03–7.29 (10H, m); ^{13}C NMR δ 14.1, 23.6, 34.4, 42.2, 48.3, 60.7, 69.4, 126.3, 126.4, 126.9, 128.2, 128.4, 128.8, 138.8, 143.5, 169.4. [HREIms. Found: 275.1891. $C_{17}H_{25}NO_2(M^+)$ requires: 275.1885].

4.1.5. Ethyl (2*R*,3*R*)-3-phenyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (10) and ethyl (2*S*,3*S*)-3-phenyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (10′). R_f (*n*-Hex/Ether, 2:1) 0.40 for **10** and 0.52 for **10′**. For **10**, solid, mp 87–89°C, $[\alpha]_D^{24}$=−51.0 (c=5.0 in CH_2Cl_2), ^{1}H NMR δ 1.00 (3H, t, J=7.0 Hz), 1.57 (3H, d, J=6.6 Hz), 2.64 (1H, d, J=7.0 Hz), 2.86 (1H, q, J=6.6 Hz), 3.01 (1H, d, J=6.6 Hz), 3.99 (2H, q J=7.0 Hz), 7.17–7.50 (10H, m); ^{13}C NMR δ 13.9, 22.9, 46.0, 47.3, 60.6, 69.7, 126.9, 127.1, 127.2, 127.6, 127.7, 128.3, 135.1, 143.2, 168.2. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.17; N, 4.74. Found: C, 77.6; H, 7.41; N, 4.69. For **10′**, solid, mp 64–66°C, ^{1}H NMR δ 1.13 (3H, t, J=7.0 Hz), 1.52 (3H, d, J=6.5 Hz), 2.55 (1H, d, J=6.9 Hz), 2.93 (1H, q, J=6.6 Hz), 3.13 (1H, d, J=6.9 Hz), 3.87–4.15 (2H, m), 7.03–7.29 (10H, m). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.17; N, 4.74. Found: C, 77.4; H, 7.37; N, 4.66.

4.1.6. Ethyl (2*S*,3*S*)-3-methyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (12) and ethyl (2*R*,3*R*)-3-methyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (12′). R_f (*n*-Hex/Ether, 1:2) 0.64 for **12′** and 0.54 for **12**. For **12**, $[\alpha]_D^{24}$=−56.8 (c=5.0 in CH_2Cl_2), ^{1}H NMR δ 1.15 (3H, t, J=5.4 Hz), 1.27 (3H, t, J=7.0 Hz), 1.42 (3H, d, J=6.6 Hz), 1.85 (1H, q, J=6.6 Hz), 2.21 (1H, d, J=6.6 Hz), 2.61 (1H, q, J=6.6 Hz), 4.14 (2H, q, J=6.6 Hz), 7.18–7.39 (5H, m); ^{13}C NMR δ 13.0, 14.2, 22.8, 40.9, 42.9, 60.6, 69.6, 126.5, 126.8, 128.1, 143.6, 169.6. [HREIms. Found: 233.1421. $C_{14}H_{19}NO_2(M^+)$ requires: 233.1416]. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.21; N, 6.00. Found: C, 72.4; H, 8.38; N, 5.84. For **12′** $[\alpha]_D^{24}$=+21.1 (c=5.0 in CH_2Cl_2) ^{1}H NMR δ 1.18 (3H, t, J=7.0 Hz), 1.33 (3H, d, J=7.0 Hz), 1.42 (3H, d, J=6.6 Hz), 1.95–2.09 (2H, m), 2.62 (1H, q, J=6.6 Hz), 4.04–4.20 (2H, m), 7.18–7.39 (5H, m); ^{13}C NMR δ 13.4, 14.1, 23.5, 42.0, 42.3, 60.5, 69.4, 126.3, 126.8, 128.1, 143.5, 169.3. [HREIms. Found: 233.1427. $C_{14}H_{19}NO_2(M^+)$ requires: 233.1416]. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.21; N, 6.00. Found: C, 72.2; H, 8.25; N, 5.72.

4.1.7. Ethyl (2*S*,3*S*)-3-benzyloxymethyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (13) and ethyl (2*R*,3*R*)-3-methoxymethyl-1-[(*S*)-1-phenylethyl]-aziridine-2-carboxylate (13′). R_f (*n*-Hex/Ether, 1:2) 0.63 for **13** and 0.56 for **13′**. For **13**, ^{1}H NMR δ 1.30 (3H, t, J=7.0 Hz), 1.48 (3H, d, J=6.6 Hz), 2.11 (1H, q, J=6.6 Hz), 2.32 (1H, d, J=6.6 Hz), 2.68 (1H, q, J=6.6 Hz), 2.89–2.95 (2H, m), 4.26 (2H, q, J=7.0 Hz), 6.95–7.37 (12H, m); ^{13}C NMR δ 14.1, 22.5, 33.8, 42.4, 46.7, 60.8, 69.5, 125.9, 126.8, 127.0, 128.1, 128.1, 128.3, 138.4, 143.0, 169.6. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.3; H, 7.42; N, 4.13. Found: C, 74.1; H, 7.52; N, 4.29. For **13′**, ^{1}H NMR δ 1.11 (3H, t, J=7.0 Hz), 1.20 (3H, d, J=6.2 Hz), 2.02–2.13 (2H, m,), 2.54 (1H, q, J=6.6 Hz), 2.75–3.02 (2H, m), 3.96–4.13 (2H, m), 7.03–

7.29 (12H, m); ^{13}C NMR δ 14.1, 23.6, 34.4, 42.2, 48.3, 60.7, 69.4, 126.3, 126.4, 126.9, 128.2, 128.4, 128.8, 138.8, 143.5, 169.4. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.3; H, 7.42; N, 4.13. Found: C, 74.6; H, 7.29; N, 4.14.

4.1.8. (2*S*,3*S*)-3-Benzyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridine (14). To a suspension of $LiAlH_4$ (228 mg, 6 mmol) in 30 mL of Et_2O at 0°C was added slowly ethyl 3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (**7**, 464 mg, 1.5 mmol) in 15 mL of Et_2O. The mixture was stirred at 0°C and then quenched with sat. $KHSO_4$ solution. The mixture was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product as a diastereomeric mixture was purified and each isomers was separated by flash column chromatography to give 353 mg of the product in 88% yield. R_f (*n*-Hex/Ether, 1:1) 0.30 for **14** and 0.59 for its diastereomer as white solid. The same products were formed from the separated isomers of aziridine-2-carboxylates. (2*S*,3*S*)-3-Benzyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridine (**14**) Mp 79–81°C, ^{1}H NMR δ 1.47 (3H, d, J=6.6 Hz), 1.38–1.94 (m, 2H), 2.53–2.80 (3H, m), 3.80–3.88 (2H, m), 4.25 (1H, br s), 6.91–7.30 (10H, m); ^{13}C NMR δ 22.8, 34.3, 44.2, 45.1, 59.7, 69.6, 125.8, 126.7, 126.9, 128.1, 128.1, 128.2, 138.9, 143.7. $[\alpha]_D^{20}=-0.15$ (c=6.0 in CH_2Cl_2). [HREIms. Found: 267.1626. $C_{18}H_{21}NO_2(M^+)$ requires: 267.1623]. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 80.9; H, 7.92; N, 5.24. Found: C, 80.7; H, 7.74; N, 5.36. For (2*R*,3*R*)-3-benzyl-2-hydroxymethyl-1-[(*S*)-1-phenylethyl]aziridine, ^{1}H NMR δ 1.19 (3H, d, J=6.6 Hz), 1.74 (1H, q, J=6.2 Hz), 1.88 (1H, q, J=6.1 Hz), 2.53 (1H, q, J=6.6 Hz), 2.68 (1H, br s), 2.83 (2H, d, J=6.6 Hz), 3.58 (2H, d, J=5.6 Hz), 7.15–5.38 (10H, m); ^{13}C NMR δ 22.6, 34.5, 43.6, 45.9, 59.6, 69.2, 126.0, 126.4, 126.9, 128.2, 128.6, 139.4, 144.0. $[\alpha]_D^{20}=-26.5$ (c= 2.5 in CH_2Cl_2).

4.1.9. (2*S*)-2-*N*-*t*-Butyloxycarbonylamino-4-phenylbutanol (15). To a solution of **14** (780 mg, 2.92 mmol) was added $(Boc)_2O$ (956 mg, 4.39 mmol) with 180 mg $Pd(OH)_2$ on carbon. This solution was charged with H_2 gas in a balloon and the mixture was stirred at room temperature until all the starting material was consumed on TLC for 8 h. The mixture was filtered and concentrated under reduced pressure. This crude reaction product was purified by flash chromatography to give 564 mg (73%) of the product. ^{1}H NMR δ 1.49 (9H, s), 1.95(1H, m), 1.81–1.86 (2H, m), 2.69 (1H, bs), 2.71–2.88 (2H, m), 3.62–3.74 (2H, m), 4.75 (1H, bs), 7.21–7.34 (5H, m). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.9; H, 8.74; N, 5.28. Found: C, 67.7; H, 8.46; N, 5.03.

4.1.10. (2*S*)-*N*-Boc-homophenylalanine methyl ester (16). To a vigorously stirred solution of the aminoalcohol **15** (190 mg, 0.72 mmol) in 1.1 mL of a mixed solvent (CCl_4,/ CH_3CN/H_2O, 2:2:3) were added sodium periodate (192 mg, 0.90 mmol) and ruthenium chloride (9 mg, 0.02 mmol). The reaction mixture was stirred for 8 h, the acidic material was carefully extracted into diethyl ether. The ethereal solution was briefly dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. To a solution of the crude acid in *N*,*N*-dimethylformamide were added K_2CO_3 (61 mg, 0.22 mmol) and methyl iodide (27 μL, 0.44 mmol). The resultant mixture was stirred at room temperature for 6 h and quenched by adding water. The reaction product was extracted with CH_2Cl_2 (10 mL×3) and the organic layer was washed with 20 mL each of water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 130 mg of the product **16** in 62% yield. $[\alpha]_D^{24}=-14.2$ (c 2.0, MeOH); lit.[11], $[\alpha]_D^{20}=-14.7$ (c 1.2, MeOH).

4.1.11. (2*S*,3*S*)-2-hydroxymethyl-3-isobutyl-1-[(*S*)-1-phenylethyl]aziridine (17). To a suspension of $LiAlH_4$ (152 mg, 4 mmol) in 25 mL of Et_2O at 0°C was added slowly ethyl (2*S*,3*S*)-3-*iso*-butyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (**6**, 275 mg, 1.0 mmol) in 15 mL of Et_2O. The mixture was stirred at 0°C and then quenched with sat. $KHSO_4$ solution. The mixture was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 228 mg of the product in 98% yield. ^{1}H NMR δ 1.18–1.30 (3H, m), 1.33–1.40 (3H, m), 2.01 (1H, br s), 2.96 (1H, d, J=4.0 Hz), 3.50–3.78 (5H, m), 7.23–7.33 (5H, m); ^{13}C NMR δ 16.2, 25.2, 51.2, 56.7, 59.1, 62.7, 127.0, 128.3, 128.3, 144.5, 173.6. $[\alpha]_D^{22}=-75.5$ (c 6.0, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.2; H, 9.93; N, 6.00. Found: C, 77.1; H, 9.77; N, 5.89.

4.1.12. (2*S*,3*R*)-2-Benzyl-1-[(*S*)-1-phenylethylamino]-3-vinylaziridine (19). To a stirred solution of methyltriphenylphosphonium bromide (502 mg, 1.40 mmol) was added dropwisely *n*-BuLi in hexane (1.12 mmol). After stirring the solution for 30 min was added ethyl (2*S*,3*S*)-3-benzyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (**8**, 290 mg, 93.8 mmol) in THF and then a solution of DIBAL (1.03 mmol) in toluene. The resulting solution was stirred for 6 h at −78°C prior to warming to room temperature. The reaction mixture was poured into water and the resulting solution was extracted with EtOAc (100 mL×3). The organic layer was washed with 100 mL each of water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 158 mg of the product in 64% yield. ^{1}H NMR δ 0.67 (3H, d, J=6.3 Hz), 0.76 (3H, d, J=6.3 Hz), 1.15–1.79 (1H, m), 1.32–1.38 (1H, m), 1.49 (3H, d, J=6.59 Hz), 1.66 (1H, q, J=6.6 Hz), 1.84–1.94 (1H, m), 2.61 (1H, q, J=6.59 Hz), 3.02 (1H, br), 3.61 (1H, dd, J=7, 11.54 Hz), 3.85 (1H, dd, J=4.81, 11.54 Hz), 7.34–7.44 (1H, m). $[\alpha]_D^{22}=-23.9$ (c 1.1, $CHCl_3$). Anal. Calcd for $C_{19}H_{21}N$: C, 86.7; H, 8.04; N, 5.32. Found: C, 86.6; H, 8.17; N, 5.09.

4.1.13. (3*S*,4*R*)-3-Acetyloxy-5-benzyl-4-[(*S*)-1-phenylethylamino]pentene (20). To a stirred solution of (2*S*,3*R*)-2-Benzyl-1-[(*S*)-1-phenylethylamino]-3-vinylaziridine (**19**, 138 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) was added acetic acid (0.15 mL, 2.6 mmol). The reaction mixture was stirred at room temperature and quenched with sat. $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The organic layer was washed with 20 mL each of water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 138 mg of the product in 82% yield. ^{1}H NMR δ 1.16 (3H, d, J=6.6 Hz), 1.95 (3H, s),

2.71 (2H, m), 3.79 (1H, q, J=6.6 Hz), 5.24–5.39 (3H, m), 5.93–6.01 (1H, m), 6.78–7.12 (11H, m). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.0; H, 7.79; N, 4.33. Found: C, 77.7; H, 7.64; N, 4.42.

4.1.14. Ethyl (2*S*,3*R*)-3-azido-2-[(*S*)-1-phenylethylamino]-butanoate (22). $BF_3{\cdot}OEt_2$ (298 mg, 2.10 mmol) was added at room temperature to ethyl (2*S*,3*S*)-3-methyl-1-[(*S*)-1-phenylethyl]aziridine-2-carboxylate (**10**) (976 mg, 4.19 mmol) dissolved in CH_2Cl_2 (30 mL). This solution was stirred for 10 min before adding $TMSN_3$ (2.42 g, 21.0 mmol). The resultant reaction mixture was stirred for 18 h and the reaction mixture was poured into water with EtOAc. The resulting solution was extracted with EtOAc (50 mL×3) and the organic layer was washed with 100 mL each of water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 1.01 g of the product in 87% yield. ^{1}H NMR δ 1.06–1.17 (9H, m), 2.04 (1H, s), 2.94 (1H, d, J=4.0 Hz), 3.12–3.72 (2H, m), 4.12 (2H, q, J=7.4 Hz), 7.09–7.29 (5H, m); ^{13}C NMR δ 14.2, 16.4, 25.3, 56.8, 59.2, 61.1, 62.9, 127.1, 127.2, 128.4, 144.7, 173.2. $[\alpha]_D^{22}$=−90.8 (c 6.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.9; H, 7.30; N, 20.3. Found: C, 60.7; H, 7.42; N, 20.1.

4.1.15. Ethyl (2*S*,3*R*)-2,3-bis-*N*-*tert*-butoxycarbonyl-amino butanoate (23). Ethyl (2*S*,3*R*)-3-azido-2-[(*S*)-1-phenylethylamino]butanoate (**22**) (474 mg, 1.72 mmol) and $(Boc)_2O$ (788 mg, 3.61 mmol) were dissolved in EtOH (20 mL). Into this solution was added Pd/C (150 mg) and the solution was charged with H_2 gas in a balloon and the mixture was stirred at room temperature until all the starting material was consumed on TLC for 20 h. The mixture was filtered and concentrated under reduced pressure and the crude product was purified by flash chromatography to give 357 mg of the product in 60% yield. ^{1}H NMR δ 1.11 (3H, d, J=5.4 Hz), 1.28–1.52 (18H, br s), 3.66 (3H, s), 4.02–4.30 (2H, br s), 4.85 (1H, br s), 5.52 (1H, br s); ^{13}C NMR δ 18.2, 28.1, 48.3, 57.8, 79.3, 79.7, 155.1, 155.7, 171.4. $[\alpha]_D^{22}$=+45.2 (c 4.6, $CHCl_3$). Anal. Calcd for $C_{16}H_{30}N_2O_6$: C, 55.5; H, 8.73; N, 8.09. Found: C, 55.8; H, 8.59; N, 8.13.

4.1.16. (2*S*,3*R*)-2,3-Diaminobutanoic acid 2HCl (24). The substrate **23** (195 mg, 0.56 mmol) in 6N HCl solution (10 mL) was refluxed for 6 h for the reaction to be completed. The reaction mixture was concentrated under reduced pressure to give yellowish crude product that was recrystallized from acetone to give 123 mg of white solid in 95% yield. $[\alpha]_D^{22}$=+34.7 (c 0.2, 6N HCl); lit.[17], $[\alpha]_D^{22}$=+33.4 (c 1.0, 6N HCl). ^{1}H NMR δ 1.15–1.22 (3H, m), 3.60–3.77 (1H, m), 3.85–3.90 (1H, m); ^{13}C NMR δ 10.3, 43.8, 51.6, 167.9.

4.1.17. Ethyl (2*R*)-2-[*N*-acetyl-*N*-(*R*)-1-phenylethyl-amino]-3-chloropropionate (26). $TiCl_4$ (588 mg, 3.1 mmol) was added at room temperature to (2*S*)-1-[(*R*)-1′-phenylethyl]aziridine-2-carboxylate (**25**) (1.70 g, 7.76 mmol) dissolved in CH_2Cl_2 (50 mL). This solution was stirred for 10 min before adding acetyl chloride (1.5 mL, 20 mmol). The resultant reaction mixture was stirred for 8 h and the reaction mixture was poured into water (150 mL) with EtOAc (150 mL). The aqueous layer was extracted with EtOAc (60 mL×2) and the combined organic layer was washed with brine (200 mL), dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 1.60 g of the target product in 69% yield. $[\alpha]_D^{22}$=+67.5 (c 4.6, $CHCl_3$). ^{1}H NMR δ 1.64 (1H, dd, J=6.6 Hz), 2.26 (3H, s), 2.86–2.94 (1H, m), 3.63–3.71 (1H, m), 3.71 (3H, s), 4.08–4.19 (1H, m), 5.14 (1H, q, J=6.6 Hz), 7.17–7.38 (5H, m); ^{13}C NMR δ 17.1, 21.9, 42.8, 52.4, 57.0, 58.8, 127.4, 128.4, 128.8, 138.7, 169.5, 170.2. Anal. Calcd for $C_{15}H_{20}ClNO_3$: C, 60.5; H, 6.77; N, 4.70. Found: C, 60.6; H, 6.69; N, 4.84.

4.1.18. Ethyl (2*R*,3*R*)-3-acetyloxy-4-phenyl-2-[(*R*)-1-phenylethylamino]butanoate (27). $TiCl_4$ (131 mg, 0.69 mmol) was added at room temperature to ethyl (2*R*,3*R*)-3-benzyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (**8**) (534 mg, 1.73 mmol) dissolved in CH_2Cl_2 (30 mL). This solution was stirred for 10 min before adding acetyl chloride (0.33 mL, 4.58 mmol). The resultant reaction mixture was stirred for 8 h and the reaction mixture was poured into water (60 mL) with EtOAc (90 mL). The resulting solution was neutralized by adding $NaHCO_3$. This solution was stirred for two days until no change was observed based on TLC. The aqueous layer was extracted with EtOAc (30 mL×2) and the combined organic layer was washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 338 mg of the product in 53% yield. ^{1}H NMR δ 1.29 (3H, t, J=7.0 Hz), 1.39 (3H, d, J=5.4 Hz), 1.88 (3H, s), 2.11 (1H, br s), 2.84 (1H, dd, J=13.8, 8.2 Hz), 3.07 (1H, dd, J=13.8, 5.2 Hz), 3.24 (1H, d, J=5.8 Hz), 3.72 (1H, q, J=6.2 Hz), 4.19 (2H, q, J=7.0 Hz), 5.15–5.24 (1H, m), 7.18–7.35 (10H, m); ^{13}C NMR δ 14.2, 20.7, 22.5, 36.7, 56.8, 61.0, 61.1, 75.1, 126.4, 127.0, 127.1, 128.1, 128.2, 129.2, 136.8, 144.2, 169.7, 172.7. $[\alpha]_D^{22}$=−67.5 (c 6.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.37; N, 3.79. Found: C, 71.4; H, 7.16; N, 3.63.

4.1.19. Ethyl (2*R*,3*R*)-3-acetyloxy-2-[(*R*)-1-phenylethyl-amino]butanoate (28). The same reaction as for **25** with the different substrate (2*R*,3*R*)-3-methyl-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (**11**) (919 mg, 3.94 mmol) was carried out to obtained 1.06 g of the target product in 79% yield. $[\alpha]_D^{22}$=+10.2 (c 4.6, $CHCl_3$). ^{1}H NMR δ 1.13–1.38 (9H, m), 1.93 (3H, s), 3.08 (1H, d, J=6.0 Hz), 3.66 (1H, q, J=6.6 Hz), 4.17 (2H, q, J=6.6 Hz), 4.94 (1H, quin, J=6.2 Hz), 7.16–7.31 (5H, m); ^{13}C NMR δ 14.2, 16.3, 20.8, 25.2, 56.7, 60.8, 62.5, 71.2, 126.9, 127.0, 128.2, 144.5, 169.9, 173.0. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.90; N, 4.77. Found: C, 65.4; H, 7.83; N, 4.62.

4.1.20. Ethyl (2*R*,3*R*)-3-acetyloxy-2-*N*-*tert*-butoxycarbonylamino-4-phenylbutanoate (29). Methyl (2*R*,3*R*)-3-aceryloxy-4-phenyl-2-[(*S*)-1-phenylethylamino]butanoate (**27**) (194 mg, 0.53 mmol) and $(Boc)_2O$ (194 mg, 0.89 mmol) were dissolved in MeOH (10 mL). Into this solution was added Pd/C (80 mg) and the mixture was charged with H_2 in a balloon and stirred at room temperature until all the starting material was consumed on TLC for 20 h. The mixture was filtered and concentrated under

reduced pressure. This crude product was purified by flash chromatography to give 145 mg of the product in 75% yield. $[\alpha]_D^{22}=-26.8$ (*c* 2.0, CH_2Cl_3). ^{1}H NMR δ 1.28 (3H, t, *J*=6.8 Hz), 1.42 (9H, s), 1.94 (3H, s), 2.90–3.00 (2H, m), 4.17 (2H, q, *J*=7.0 Hz), 4.61–4.66 (1H, m), 5.26–5.34 (1H, m), 5.40 (1H, d, *J*=8.6 Hz), 7.18–7.29 (5H, m); ^{13}C NMR δ 14.4, 20.8, 28.2, 36.5, 55.3, 61.7, 74.6, 80.0, 126.7, 128.4, 129.3, 136.4, 155.2, 169.4, 170.4. Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.5; H, 7.45; N, 3.83. Found: C, 62.4; H, 7.31; N, 3.72.

4.1.21. Ethyl (2*R*,3*R*)-3-acetyloxy-2-*N*-*tert*-butoxycarbonylaminobutanoate (30). The same reaction as for **29** with the different substrate methyl (2*R*,3*R*)-3-acetyloxy-2-[(*S*)-1-phenylethylamino]butanoate (**28**) (530 mg, 1.81 mmol) was carried out to obtained 439 mg of the target product in 84% yield. $[\alpha]_D^{22}=+10.2$ (*c* 5.0, $CHCl_3$). ^{1}H NMR δ 1.09–1.24 (6H, m), 1.34 (9H, s), 1.93 (3H, s), 4.13 (2H, q, *J*=7.2 Hz), 4.45–4.51 (1H, m), 5.01–5.12 (1H, m), 5.31 (1H, d, *J*=8.8 Hz); ^{13}C NMR δ 14.0, 15.5, 20.8, 28.0, 56.2, 61.5, 70.2, 79.8, 155.1, 169.4, 170.2. Anal. Calcd for $C_{13}H_{23}NO_6$: C, 54.0; H, 8.01; N, 4.84. Found: C, 53.8; H, 7.89; N, 4.67.

4.1.22. (2*R*,3*R*)-2-Amino-3-hydroxy-4-phenylbutanoic acid (31). Methyl (2*R*,3*R*)-3-acetyloxy-2-*N*-*tert*-butyloxyamino-4-phenylbutanoate (**29**, 99 mg, 0.27 mmol) in 6N HCl solution (10 mL) was refluxed for 6 h for the reaction to be completed. The reaction mixture was concentrated under reduced pressure to give yellowish crude product that was recrystallized from acetone to give 58 mg of a white solid in 95% yield. $[\alpha]_D^{22}=-5.5$ (*c* 5.0, 1N HCl); lit.[14], $[\alpha]_D^{22}=+9.1$ (*c* 1.0, 1N HCl) for its enantiomer. ^{1}H NMR δ 2.72–2.94 (2H, m), 3.94–4.02 (1H, m), 4.08–4.22 (1H, m), 7.02–7.38 (5H, m); ^{13}C NMR δ 36.4, 54.5, 68.9, 124.8, 126.6, 127.2, 135.0, 167.0.

4.1.23. (D)-*allo*-Threonine (32). The same reaction as for **31** with the different substrate methyl (2*R*,3*R*)-3-acetyloxy-2-*N*-*tert*-butyloxyaminobutanoate (**30**) (36 mg, 0.12 mmol) was carried out to obtained 16 mg of the target product as cystalline solid in 84% yield. $[\alpha]_D^{22}=-8.7$ (*c* 0.9, H_2O); lit.[21], $[\alpha]_D=+9.7$ (*c* 1.0, H_2O) for its enantiomer. ^{1}H NMR δ 1.12 (3H, d, *J*=4.6 Hz), 3.84 (1H, d, *J*=4.4 Hz), 4.12–4.26 (1H, m), 4.66 (4H, bs); ^{13}C NMR δ 15.3, 55.4, 63.2, 167.5. Mp 275°C (decomp.).

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