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# Ring opening of 2-acylaziridines by acid chlorides

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**Abstract**—Good nucleophilicity of the ring nitrogen in chiral (2*R*,1′*R*)-2-acyl-(1′-phenylethyl)aziridines initiated the reaction with various acid chlorides to form the corresponding acylaziridinium ion intermediates whose rings were opened by the chloride anion to yield the β-amino-α-chlorocarbonyl compounds. The subsequent displacement of the chloride with the internal oxygen nucleophile originated from methylchloroformate, acetyl chloride, and methyl chlorooxoacetate yielded oxazolidin-2-ones, β-amino-α-acetyloxypropionates, and morpholin-2,3-diones, respectively.


## 1. Introduction

Aziridine, nitrogen containing three-membered ring, is a cousin of oxirane with similar ring strain energy.[1] However, its property including proton affinity is quite different from oxirane when the ring nitrogen has a substituent other than simple hydrogen.[2] Basicity of the ring nitrogen of aziridine is dependent to the substituent whether it is electron donating or electron withdrawing.[3] Its difference would be observed by the comparison of electrostatic potentials of *N*-methyl and *N*-acetyl aziridines shown in Figure 1.[4] Electrostatic potentials of those two examples are very different not only in the nitrogen but carbons of the aziridine ring.

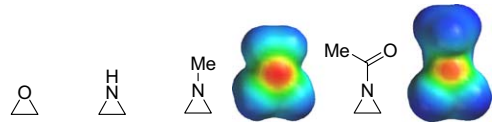
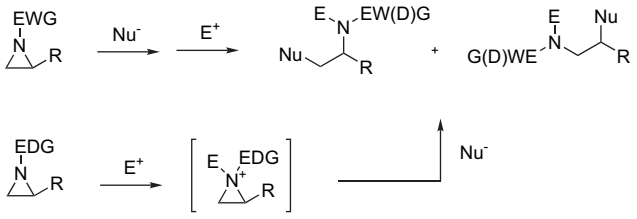



**Figure 1**. The chemical structures of oxirane, aziridine, *N*-methylaziridine, and *N*-acetylaziridine and two electrostatic potential maps of *N*-methylaziridine and *N*-acetylaziridine.

Naturally, the reactivity of aziridine is quite different whether the substituent on the ring nitrogen is electron donating or electron withdrawing.[1] When there is an electron-withdrawing substituent including *N*-sulfonyl, *N*-phosphonyl or *N*-carbonyl, the ring is activated with release of the electron density of the ring nitrogen as shown in *N*-acetyl aziridine in Figure 1. This aziridine reacts with the nucleophile to yield ring-opened products (Scheme 1).[5] However, aziridine with electron-donating substituent such as alkyl is quite inert toward nucleophiles. Ring opening of this aziridine requires the prior activation with a proper electrophile including protic or Lewis acid to form the corresponding azaridinium ion shown in the bracket of Scheme 1 that reacts with coming nucleophiles.[6,7] Regiochemical pathway of the ring-opening reaction is dependent to the substituent of R in Scheme 1. Most of the reactions proceeded in the less hindered position of C-3 to yield α-amino product. When R is allyl, benzyl or acyl substituents, the breakage of the bond between C-2 and the ring nitrogen occurs to give the β-amino product (Scheme 1).[8]




(EWG = Electron-withdrawing group, EDG = Electron-donating group)

**Scheme 1**.

Many examples of aziridine ring openings were disclosed only with electron-withdrawing substituents on the ring

*Keywords*: 2-Acylaziridine; Acid chloride; Ring opening; Morpholin-2,3-dione; Isoserine.
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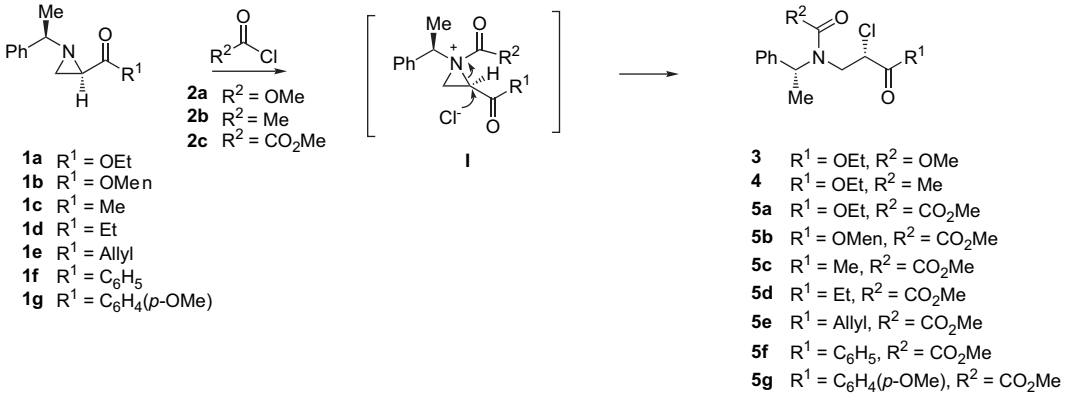
nitrogen such as *N*-sulfonyl, *N*-phosphonyl, and *N*-carbonyl.[1,5] However, they have certain limitations due to the paucity of reliable methodology to accomplish free amine with removal of *N*-substituents under mild condition. A few years ago, we have succeeded multi-kilo scale production of the enantiomerically pure aziridine bearing phenylethyl group at the ring nitrogen.[6] Their synthetic utility have been studied for many years taking advantage of their regio- and stereoselectivities of most reactions due to the rigidity of the aziridine ring.[6,9] Those aziridines represented by (1′*R*)-(1′-phenylethyl)aziridine-2-carboxylates are now commercially available in optically pure forms and are able to provide us many enantiomerically pure α- or β-amino esters and their derivatives.[6] In this report, the reaction of the (1′*R*)-(1′-phenylethyl)aziridine-2-carboxylate with acid chloride for the synthesis of valuable cyclic and acyclic hydroxy amines with important mechanistic implication of the aziridine ring opening reactions is described.

## 2. Results and discussion

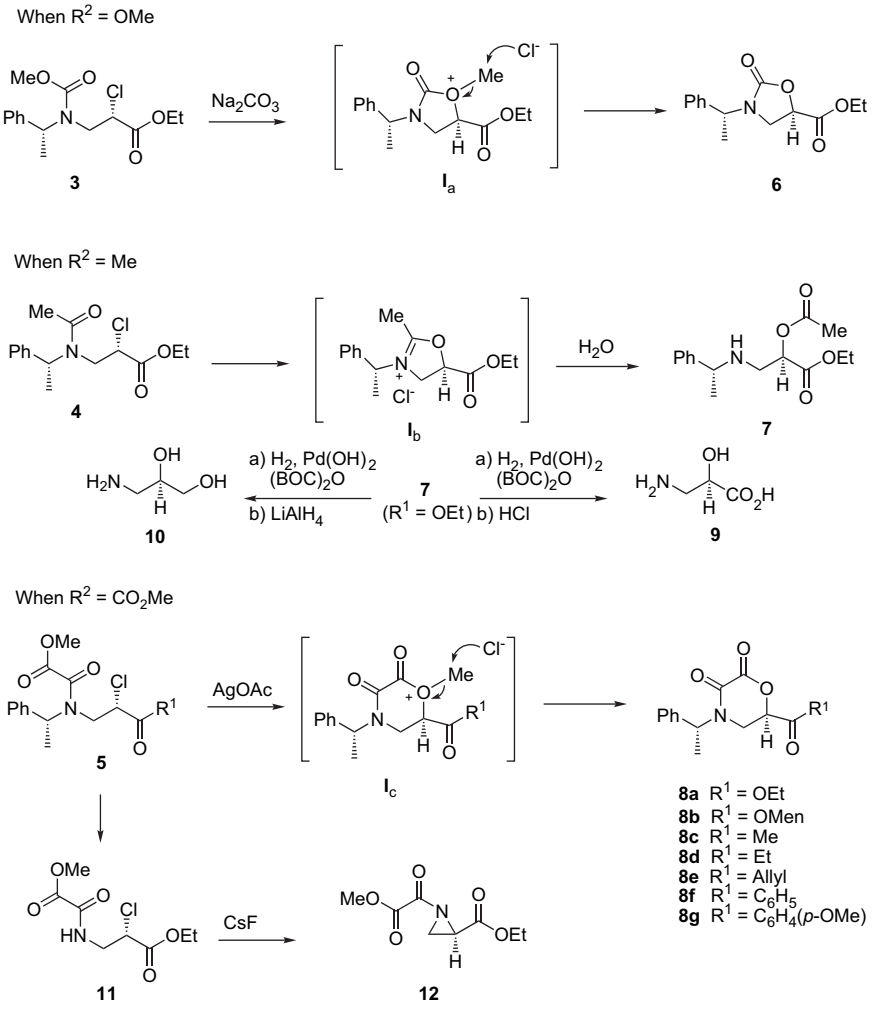
Ring-opening reactions of 2-acylaziridines with phenylethyl group at the ring nitrogen proceed to yield aziridinium ion for initial activation with the assistance of protic acid or Lewis acid as an electrophile followed by nucleophilic attack of the ring. The molecule bearing both characters as an electrophile and a nucleophile is acid chloride that is able to activate the aziridine ring and to provide the nucleophile to lead the ring-opening reactions. At first, the ring nitrogen of (1′*R*)-(1′-phenylethyl)-2-acylaziridines (**1**) is basic enough to react with acid chlorides (**2**) to yield the aziridinium ion (**I**) with the chloride free (Scheme 2). This aziridinium ion shown in the bracket of Scheme 2 is highly activated and ready to react with the coming nucleophile. The nucleophile available in the reaction mixture is the chloride ion liberated originally from the acid chloride during the formation of the aziridinium ion. The acyclic β-amino-α-chlorocarbonyl products (**3**–**5**) were resulted by nucleophilic ring opening of the aziridinium ion intermediate by the chloride. Various acid chlorides were applicable including alkoxychloroformate, acetyl chloride, and methyl chlorooxoacetate. All ring-opening reactions were highly specific without detectable amount of regio- or stereoisomers. This implies that the bond between C-2 and the ring nitrogen was labile as we expected and the reaction proceeded with complete inversion of the configuration during the attack of the coming nucleophile. The reaction was successful at room temperature under mild condition with wide scope of substrates such as aziridine-2-carboxylates (**1a**, **1b**) and 2-acylaziridines (**1c**–**g**) and various acid chlorides including methylchloroformate (**2a**), acetyl chloride (**2b**), and methyl chlorooxoacetate (**2c**) to afford β-amino-α-chloro carbonyl compounds in 53–98% yield (Scheme 2).

Acyclic β-amino-α-chlorocarbonyl compound was further reacted in many ways depending on the characteristics of $R^2$ (Scheme 3). When $R^2$ is OMe originated from methylchloroformate (**2a**), internal nucleophilic reaction by oxygen leads the formation of the oxazolidine-2-one ring (**6**) with removal of the chloride as in $\mathbf{I}_a$. The reaction pathway was disclosed in our early study by the isolation of the acyclic β-amino-α-chlorocarbonyl compound and by the stereochemical outcome of the reaction product.[10] However, the initial product of ethyl (2*R*,1′*R*)-[1-(1′-phenylethyl)]aziridine-2-carboxylate with acetyl chloride (**4**) is readily reacted by the internal oxygen nucleophile with the replacement of the chloride to make the possible dihydrooxazole ring compound as shown in $\mathbf{I}_b$. In the presence of small amount of moisture in the air or in silica gel, the intermediate $\mathbf{I}_b$ was hydrolyzed to yield (2*R*,1′*R*)-1-acetyloxy-2-[*N*-(1′-phenylethyl)]aminopropionate (**7**) in 75% yield. The removal of the phenylethyl group by hydrogenation in the presence of $(BOC)_2O$ and the subsequent hydrolysis provided (+)-(*R*)-isoserine (**9**).[11] Reduction by LAH after debenzylation of α-acyloxy-β-aminopropionate (**7**) afforded (2*R*)-3-amino-1,2-propandiol (**10**). In both of those two cases, the configurations of the stereogenic centers were identified to be '*R*' originated from the C-2 of the aziridine ring with retention of the configuration. This stereochemical outcome supports the double displacements with the inversion of the configuration during the ring opening and the removal of the chloride as we expected from the early observation.[10]

When $R^2$ was methoxycarbonyl originated from methyl chlorooxoacetate all of the acyclic reaction products **5** were stable enough to be isolated bearing the chloride at α-position and to be kept at room temperature under air. Preparation of acyclic β-amino-α-chloro compounds (**5**) was achieved from either aziridine-2-carboxylates or 2-acylaziridines with




**Scheme 2**.




**Scheme 3**.

various substituents of $R^1$ including OEt (**5a**), OMen (**5b**), Me (**5c**), Et (**5d**), allyl (**5e**), phenyl (**5f**), and *p*-methoxyphenyl (**5g**) in high yields. Removal of the phenylethyl from **5a** was successful to yield **11** with methanesulfonic acid and anisole[10] while catalytic hydrogenation did not work. Compound **11** was attempted to be cyclized with the removal of chlorine using several different bases including NaH, $Na_2CO_3$, $Et_3N$, and CsF. Among them, CsF was the best to afford a new (2*R*)-aziridine-2-carboxylate (**12**) as a single isomer judged by chiral GC and HPLC in 62% yield. Its configuration was possibly speculated as '*R*' derived from double inversions as observed in earlier cases for the preparation of **6**, **9**, and **10**. This was further confirmed by the formation of morpholin-2,3-diones in the next series of reactions.

As shown in the cases of oxazolidin-2-one (**6**) and α-acetyloxy-β-aminopropionate (**7**) from the acyclic chloropropanoates (**3** and **4**), cyclization of **5** afforded morpholin-2,3-dione (**8**) via nucleophilic displacement of chlorine by oxygen in the presence of AgOAc. This cyclization proceeded well in 52–86% yield from diverse acyclic compounds **5** originated from the early reactions of 2-acylaziridines (**1**) bearing various substituents. The stereochemistry was identified by the X-ray crystalline structure of morpholin-2,3-dione (**8a**) obtained from ethyl (2*R*)-aziridine-2-carboxylate (**1a**) (Fig. 2).[12]

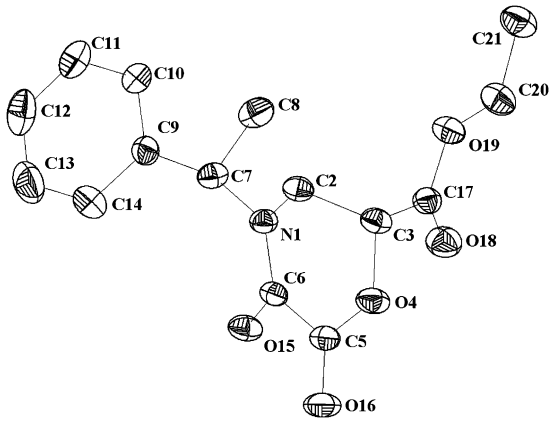



**Figure 2**. The X-ray structure of (6*R*,1′*R*)-6-ethoxycarbonyl-4-(1′-phenylethyl)morpholin-2,3-dione (**8a**).

The configuration '*R*' at C-2 of the starting aziridine was completely retained at C-6 of the final product **8a** whose position was denoted by C3 in Figure 2. This tells us that the reaction proceeds in double inversions during the aziridine ring opening as in Scheme 2 and the internal cyclization to form the morpholin-2,3-dione ring by the oxygen nucleophile as in $\mathbf{I}_c$ in Scheme 3.

In conclusion, good nucleophilicity of the ring nitrogen in the chiral (2*R*,1′*R*)-2-acyl-[1-(1′-phenylethyl)]aziridine initiated the reaction with various acid chlorides to form the acylaziridinium ion intermediates whose rings were opened by the chloride anion released from acid chloride to yield β-amino-α-chlorocarbonyl compounds. The subsequent displacement of the chloride with the internal oxygen nucleophile originated from methylchloroformate, acetyl chloride, and methyl chlorooxoacetate yielded oxazolidin-2-ones, β-amino-α-acetyloxypropionates, and morpholin-2,3-diones, respectively. *This is a new type of aziridine ring-opening reaction based on dual role of acid chlorides as an activator of the aziridine ring and a provider of the nucleophile for the aziridine ring opening*.

## 3. Experimental

### 3.1. General methods

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian 200 (200 MHz for $^1$H and 50.3 MHz for $^{13}$C). Chemical shifts were given in parts per million using TMS as an 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 rotations were measured on Rudolph Research Autopole 3 polarimeter. The silica gel used for column chromatography was Merck 230–400 mesh. Thin layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness.

### 3.2. Reactions of ethyl (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxylate with acetyl chloride

Into the solution of ethyl (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxylate (**1a**, 154 mg, 0.70 mmol) in anhydrous 20 mL $CH_3CN$, acetyl chloride (66 mg, 0.84 mmol) was added drop wise at room temperature. This solution was stirred for 0.5 h at room temperature until all the starting material was consumed. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to yield yellowish hydroscopic solid, which is unstable at room temperature under air. Mp 86 °C (decomposed). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.34–7.65 (m, 5H), 5.59 (d, $J$=10.2 Hz, 1H), 4.17–4.29 (m, 1H), 4.13 (q, $J$=7.2 Hz, 2H), 3.18–3.22 (m, 2H), 2.30 (s, 3H), 1.93 (d, $J$=6.8 Hz, 3H), 1.17 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 170.5, 166.7, 135.4, 129.7, 127.9, 127.1, 67.0, 62.5, 59.0, 44.8, 21.3, 20.6, 14.0. The above solid was dissolved in $CH_2Cl_2$ and was neutralized by $Na_2CO_2$ solution. The resultant organic layer was washed twice with brine and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/*n*-hexane, 1:3) provided 147 mg of analytically pure product (**7**) in 75% yield. Liquid. $[\alpha]_D$ 19.1 (*c* 0.5, $CHCl_3$). $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.26–7.34 (m, 5H), 4.06–4.32 (m, 4H), 3.83 (q, $J$=7.2 Hz, 1H), 3.23–3.28 (m, 1H), 2.05 (s, 3H), 1.39 (d, $J$=7.0 Hz, 3H), 1.27 (t, $J$=7.2 Hz, 3H). $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 173.0, 170.7, 144.7, 128.6, 127.3, 127.0, 66.0, 61.2, 57.8, 56.8, 25.4, 20.9, 14.3. HRMS (EI) calcd for $C_{15}H_{21}NO_4$: 279.1471, found 279.1477. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.58; N, 5.01. Found: C, 64.3; H, 7.66; N, 5.25.

### 3.3. General procedure for reactions of either (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxylate or (2*R*,1′*R*)-2-acyl-(1′-phenylethyl)aziridine with methyl chlorooxoacetate

To the solution of either (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxylate or (2*R*,1′*R*)-2-acyl-(1′-phenylethyl)aziridine (1.25 mmol) in $CH_3CN$ under nitrogen at room temperature was added methyl chlorooxoacetate (184 mg, 1.50 mmol). The mixture was stirred for 1 h at room temperature and concentrated in vacuo. The mixture was extracted with $CH_2Cl_2$ and water. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/*n*-hexane, 1:3) provided analytically pure product.

**3.3.1. Ethyl (2*S*,1′*R*)-2-chloro-3-[2-methoxy-2-oxo-*N*-(1′-phenylethyl)acetamido]propionate (5a).** Yield 89%. Liquid. $[\alpha]_D$ 55.2 (*c*, 1.0 MeOH); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.33–7.58 (m, 5H), 4.96 (q, $J$=8.4 Hz, 1H), 4.57–4.66 (m, 1H), 4.12–4.27 (m, 6H), 3.08–3.20 (m, 1H), 1.70 (d, $J$=6.8 Hz, 3H), 1.15–1.24 (m, 3H). $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 168.1, 163.2, 163.1, 138.0, 129.0, 128.5, 127.3, 62.5, 56.7, 53.1, 53.0, 46.1, 18.0, 13.9. HRMS (EI) calcd for $C_{16}H_{20}ClNO_5$: 341.1031, found 341.1028.

**3.3.2. (−)-Menthyl (2*S*,1′*R*)-2-chloro-3-[2-methoxy-2-oxo-*N*-(1′-phenylethyl)acetamido]-propionate (5b).** Yield 98%. Liquid. $[\alpha]_D$ 18.1 (*c* 1.0, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.19–2.37 (m, 5H), 4.83 (q, $J$=6.8 Hz, 1H), 4.65 (t, $J$=4.0 Hz, 1H), 4.25–4.41 (m, 1H), 3.31–3.48 (m, 2H), 1.90–2.11 (m, 3H), 1.82–0.17 (m, 21H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 168.4, 163.2, 163.0, 137.7, 129.0, 128.5, 127.6, 57.0, 52.8, 52.5, 47.0, 46.1, 40.5, 34.1, 31.4, 26.0, 23.3, 22.1, 20.7, 17.4, 16.1. HRMS (EI) calcd for $C_{24}H_{34}ClNO_5$: 451.2126, found 451.2122.

**3.3.3. *N*-{(2*S*)-Chloro-3-oxobutyl}-*N*-{(1*R*)-phenylethyl}-oxalamic acid methyl ester (5c).** Yield 76%. Liquid. $[\alpha]_D$ 43.4 (*c* 2.5, MeOH); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.28–7.54 (m, 5H), 5.01 (q, $J$=6.8 Hz, 1H), 4.67 (t, $J$=6.6 Hz, 1H), 3.89 (s, 3H), 3.21–3.35 (m, 2H), 2.27 (s, 3H), 1.49–1.65 (m, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 201.6, 163.2, 162.9, 137.5, 129.1, 129.0, 127.6, 58.3, 57.0, 53.0, 44.8, 26.7, 17.3. HRMS (EI) calcd for $C_{15}H_{18}ClNO_4$: 311.0924, found 311.0933.

**3.3.4. *N*-{(2*S*)-Chloro-3-oxopentyl}-*N*-{(1*R*)-phenylethyl}-oxalamic acid menthol ester (5d).** Yield 88%. Liquid. $[\alpha]_D$ 40.1 (*c* 1.0, MeOH); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.19–7.42 (m, 5H), 5.02 (q, $J$=7.2 Hz, 1H), 4.90 (q, $J$=7.0 Hz, 1H), 3.69 (s, 3H), 3.38–3.54 (m, 2H), 2.35–2.47 (m, 2H), 1.52 (d, $J$=7.0 Hz, 3H), 1.01 (t, $J$=6.5 Hz, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 204.3, 163.2, 163.1, 138.0, 129.0, 129.0, 127.3, 57.7, 56.8, 53.0, 45.4, 33.0, 18.0, 7.7. HRMS (EI) calcd for $C_{16}H_{20}ClNO_4$: exact mass: 325.1081, found 325.1085.

**3.3.5. *N*-{(2*S*)-Chloro-3-oxohex-5-enyl}-*N*-{(1*R*)-phenylethyl}oxalamic acid methyl ester (5e).** Yield 84%. Liquid.

$[\alpha]_D$ 44.9 (*c* 1.0, MeOH); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.18–7.43 (m, 5H), 6.86 (q, *J*=7.0 Hz, 1H), 6.24 (d, *J*=15.8 Hz, 2H), 4.84 (q, *J*=8.2 Hz, 1H), 3.85–4.09 (m, 1H), 3.79 (s, 3H), 3.61 (d, *J*=6.6 Hz, 2H), 3.38 (d, *J*=6.2 Hz, 2H), 1.83 (m, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 192.4, 163.3, 163.2, 146.6, 137.7, 129.1, 128.9, 127.9, 127.6, 57.2, 54.9, 53.0, 45.5, 29.0, 18.7. HRMS (EI) calcd for $C_{17}H_{20}ClNO_4$: 337.1081, found 337.0177.

**3.3.6. *N*-{(2*S*)-Chloro-3-oxo-3-phenylpropyl}-*N*-{(1*R*)-phenylethyl}oxalamic acid methyl ester (5f).** Yield 67%. Liquid. $[\alpha]_D$ 59.6 (*c* 0.9, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.89–8.04 (m, 10H), 5.75 (q, *J*=7.4 Hz, 1H), 4.95 (t, *J*=7.2 Hz, 1H), 3.86 (s, 3H), 3.61 (d, *J*=7.6 Hz, 2H), 1.65–1.73 (m, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 193.2, 163.5, 163.2, 137.7, 134.2, 129.1, 128.9, 127.9, 127.5, 57.4, 53.0, 51.4, 46.0, 17.4. HRMS (EI) calcd for $C_{20}H_{20}ClNO_4$: 373.1081, found 373.1088.

**3.3.7. *N*-{(2*S*)-Chloro-3-oxo-3-*p*-methoxylphenylpropyl}-*N*-{(1*R*)-phenylethyl}oxalamic acid methyl ester (5g).** Yield 81%. Liquid. $[\alpha]_D$ 52.2 (*c* 1.0, MeOH); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.26–7.49 (m, 9H), 5.70 (q, *J*=6.2 Hz, 1H), 4.92 (t, *J*=7.0 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.60 (d, *J*=6.6 Hz, 2H), 1.59–1.69 (m, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 191.7, 164.4, 163.5, 163.2, 137.6, 131.6, 131.3, 128.8, 128.6, 127.9, 114.2, 57.4, 55.6, 53.0, 51.3, 46.3, 17.4. HRMS (EI) calcd for $C_{21}H_{22}ClNO_5$: 403.1187, found 403.1179.

### 3.4. (2*R*)-Isoserine (9)

To the solution of ethyl (2*R*,1′*R*)-2-acetyloxy-3-(1′-phenylethyl)aminopropionate (**7**, 450 mg, 1.61 mmol) in MeOH were added $(Boc)_2O$ (530 mg, 2.43 mmol) and 340 mg of Pd/C. The reaction mixture was stirred at room temperature with atmospheric pressure of $H_2$ for 12 h, and then the catalyst was filtered. The solution was concentrated in vacuo. This crude product was dissolved in MeOH containing 2 M HCl. The reaction mixture was stirred for 1 h under reflux. The mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by ion-exchange chromatography on Amberlite® IR-120H ($H^+$ form), eluting first with water and then with 5% $NH_4OH$ to yield 128 mg isoserine in 76% yield. White solid. Mp= 197–198 °C. $[\alpha]_D$ −32.1 (*c* 0.5, $H_2O$); Lit.[11b] $[\alpha]_D$ −32.1 (*c* 0.5, $H_2O$).

### 3.5. (2*R*)-3-Amino-1,2-propandiol (10)

To the solution of **7** (279 mg, 1.0 mmol) in MeOH were added $(BOC)_2O$ (327 mg, 1.50 mmol) and 213 mg of $Pd(OH)_2$. The reaction mixture was stirred at room temperature with atmospheric pressure of $H_2$ for 12 h. Then the catalyst was filtered and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (EtOAc/*n*-hexane, 1:3) provided oil whose solution in THF was added $LiAlH_4$ (95 mg, 2.5 mmol) at 0 °C. The mixture was filtered and concentrated in vacuo. This was dissolved 2 M HCl solution in MeOH and the resultant mixture was stirred for 1 h under reflux. The mixture was cooled to room temperature and concentrated under reduced pressure to afford **10** (29 mg) in 32% yield. Viscous oil. $[\alpha]_D$ 28.5 (*c* 0.5, MeOH); Lit.[13] $[\alpha]_D$ 28 (*c* 4, 5 M HCl). $^1$H NMR ($D_2O$, 200 MHz) $\delta$ 3.45 (br s, 2H), 3.19–3.42 (m, 1H), 2.88 (d, *J*=4.4 Hz, 2H). $^{13}$C NMR ($D_2O$, 50.3 MHz) $\delta$ 70.2, 62.9, 42.2.

### 3.6. Ethyl (2*S*)-2-chloro-3-(2-methoxy-2-oxoacetamido)-propionate (11)

To the solution of **5a** (839 mg, 2.45 mmol) in $CHCl_3$ under nitrogen were added methanesulfonic acid (1.179 g, 12.27 mmol) and anisole (662 mg, 6.13 mmol). The solution was refluxed for 4 h and then cooled to room temperature. The solution was quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic extracts were dried, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/*n*-hexane, 1:2) provided debenzylated product **11** as oil (308 mg, 53% yield). Liquid. $[\alpha]_D$ −22.0 (*c* 1.5, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.39 (t, *J*=6.4 Hz, 1H), 4.14 (q, *J*=7.0 Hz, 2H), 3.85 (s, 3H), 3.73–3.89 (m, 2H), 1.26 (t, *J*=7.2 Hz, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 168.0, 160.6, 156.7, 62.8, 54.0, 53.9, 42.8, 14.0. HRMS (EI) calcd for $C_8H_{12}ClNO_5$: 237.0404, found 237.0397.

### 3.7. Ethyl (2*R*)-1-methoxyoxalylaziridine-2-carboxylate (12)

To the solution of **11** (89 mg, 0.37 mmol) in $CH_3CN$ was added cesium fluoride (70 mg, 0.44 mmol). The solution was refluxed for 3 h and then cooled to room temperature. The mixture was extracted with $CH_2Cl_2$ and water. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/*n*-hexane, 1:2) provided 31 mg **12** in 42% yield. Liquid. $[\alpha]_D$ 34.5 (*c* 0.5, EtOAc); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.31 (q, *J*=7.0 Hz, 2H), 4.23–4.36 (m, 3H), 4.00 (s, 3H), 1.44 (t, *J*=7.0 Hz, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 169.3, 157.1, 156.6, 62.2, 59.3, 53.7, 42.7, 14.0. HRMS (EI) calcd for $C_8H_{11}NO_5$: 201.0637, found 201.0643.

### 3.8. General procedure for the preparation of morpholin-2,3-diones (8) from either (2*S*,1′*R*)-2-chloro-3-{*N*-methoxyoxalyl-(1′-phenylethyl)amino}propionate (5a, 5b) or *N*-{(2*S*)-chloro-3-oxoalkyl}-*N*-{(1*R*)-phenylethyl}oxalamic acid methyl ester (5c–g)

To solution of **5** (0.91 mmol) in $CH_3CN$ was added silver acetate (1.10 mmol). The solution was refluxed for 3 h and then cooled to room temperature. The mixture was extracted with $CH_2Cl_2$ and water. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (EtOAc/*n*-hexane, 1:3) provided **8** as oil.

**3.8.1. (6*R*,1′*R*)-6-Ethoxycarbonyl-4-(1′-phenylethyl)morpholine-2,3-dione (8a).** Yield 84%. Liquid. $[\alpha]_D$ 87.4 (*c* 2.4, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.32–7.58 (m, 5H), 6.01 (q, *J*=7.4 Hz, 1H), 4.91–4.94 (m, 1H), 3.82–4.12 (m, 2H), 3.48–3.72 (m, 2H), 1.47 (d, *J*=7.0 Hz, 3H), 0.97 (t, *J*=6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 50.3 MHz) $\delta$ 167.4, 156.1, 152.7, 138.1, 128.9, 128.5, 127.7, 72.8, 63.1, 51.3, 41.1, 14.8, 13.7. HRMS (EI) calcd for $C_{15}H_{17}NO_5$: 291.1107,

found 291.1115. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.9; H, 5.88; N, 4.81. Found: C, 61.6; H, 5.69; N, 4.87.

**3.8.2. (6*R*,1′*R*)-6-(−)-Menthylcarbonyl-4-(1′-phenylethyl)morpholine-2,3-dione (8b).** Yield 86%. Liquid. $[\alpha]_D$ 7.3 (*c* 2.0, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.24–7.58 (m, 5H), 4.96 (q, *J*=7.2 Hz, 1H), 4.64–4.72 (m, 1H), 3.64–3.82 (m, 1H), 3.32–3.47 (m, 2H), 1.82–0.17 (m, 21H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 169.8, 167.9, 166.9, 138.7, 128.9, 128.8, 127.5, 78.0, 71.6, 52.7, 47.0, 40.5, 34.2, 31.4, 26.4, 23.6, 22.0, 20.7, 20.5, 17.0. HRMS (EI) calcd for $C_{23}H_{31}NO_5$: 401.2202, found 401.2211.

**3.8.3. (6*R*,1′*R*)-6-Acetyl-4-(1′-phenylethyl)morpholine-2,3-dione (8c).** Yield 82%. Liquid. $[\alpha]_D$ 64.2 (*c* 1.5, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.19–7.43 (m, 5H), 4.94 (q, *J*=7.0 Hz, 1H), 4.61–4.74 (m, 2H), 3.48–3.61 (m, 1H), 2.28–2.35 (m, 3H), 1.55 (s, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 202.1, 178.2, 152.8, 137.5, 129.1, 128.7, 127.4, 79.1, 52.0, 40.3, 26.8, 15.1. HRMS (EI) calcd for $C_{14}H_{15}NO_4$: 261.2732, found 261.2736.

**3.8.4. (6*R*,1′*R*)-6-Propionyl-4-(1′-phenylethyl)morpholine-2,3-dione (8d).** Yield 60%. Liquid. $[\alpha]_D$ 85.1 (*c* 1.0, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.16–7.44 (m, 5H), 5.04 (q, *J*=7.4 Hz, 1H), 4.85 (q, *J*=7.0 Hz, 1H), 3.66–3.81 (m, 2H), 2.53 (q, *J*=7.0 Hz, 2H), 1.81 (d, *J*=7.0 Hz, 3H), 0.93 (t, *J*=7.1 Hz, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 206.5, 170.1, 163.4, 138.1, 129.0, 128.8, 127.5, 75.5, 52.9, 42.1, 33.0, 20.5, 7.1. HRMS (EI) calcd for $C_{15}H_{17}NO_4$: 275.2998, found 275.3004.

**3.8.5. (6*R*,1′*R*)-6-But-3-enoyl-4-(1′-phenylethyl)morpholine-2,3-dione (8e).** Yield 52%. Liquid. $[\alpha]_D$ 88.3 (*c* 1.0, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.11–7.32 (m 5H), 5.24 (q, *J*=7.0 Hz, 1H), 571–5.84 (m, 3H), 5.03 (q, *J*=8.2 Hz, 1H), 3.91 (d, *J*=6.2 Hz, 2H), 3.14–3.29 (m, 2H), 1.69–1.86 (m, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 192.4, 160.3, 158.9, 137.1, 132.9, 128.6, 128.3, 127.7, 115.3, 91.8, 50.1, 46.5, 38.0, 21.7. HRMS (EI) calcd for $C_{16}H_{17}NO_4$: 287.1158, found 287.1151.

**3.8.6. (6*R*,1′*R*)-6-Benzoyl-4-(1′-phenylethyl)morpholine-2,3-dione (8f).** Yield 72%. Liquid. $[\alpha]_D$ 65.9 (*c* 1.5, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.93–8.21 (m, 10H), 6.15 (q, *J*=7.0 Hz, 1H), 4.85 (q, *J*=7.0 Hz, 1H), 3.80 (d, *J*=4.0 Hz, 2H), 1.67 (d, *J*=7.2 Hz, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 195.2, 170.0, 163.4, 138.2, 134.0, 129.0, 128.9, 128.8, 128.4, 128.4, 127.9, 127.6, 71.6, 52.9, 43.4, 20.4. HRMS (EI) calcd for $C_{19}H_{17}NO_4$: 323.1158, found 323.1150.

**3.8.7. (6*R*,1′*R*)-6-*p*-Methoxybenzoyl-4-(1′-phenylethyl)-morpholine-2,3-dione (8g).** Yield 81%. Liquid. $[\alpha]_D$ 81.2 (*c* 1.5, $CHCl_3$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.19–7.37 (m, 9H), 5.16 (q, *J*= 7.2 Hz, 1H), 4.91 (q, *J*=7.0 Hz, 1H), 3.79 (s, 3H), 3.34–3.46 (m, 2H), 1.69 (d, *J*=6.8 Hz, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 193.6, 170.1, 164.3, 163.5, 138.3, 131.5, 130.9, 128.8, 128.4, 127.7, 127.5, 71.4, 57.0, 55.6, 53.0, 20.5. HRMS (EI) calcd for $C_{20}H_{19}NO_5$: 353.1263, found 353.1265.

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12. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 295629. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223–336033 or e-mail: deposit@ccdc.cam.ac.uk].
13. Aldrich® catalog for (R)-3-aminopropandiol, No. 09267.