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Aziridines derived from amino acids as synthons in pseudopeptide synthesis

Laidong Song, Vincent Servajean and Josiane Thierry*

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

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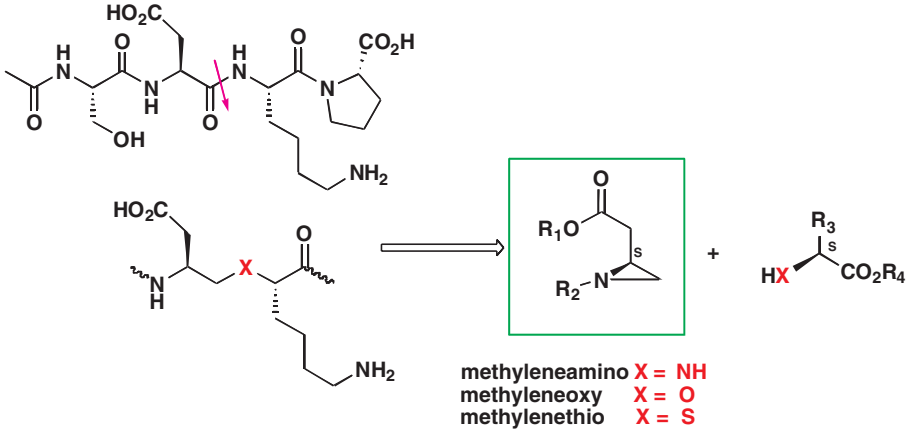
Abstract—The reactivity of the *Z*-protected aziridine derived from aspartic acid has been studied with various *N*- and *O*-nucleophiles. The optimized reaction conditions allow quick and easy access to 1, 2-diamines or amino alcohols. In the case of opening with *N*-nucleophiles, very good regioselectivity was observed. Use of an α-amino ester as the nucleophile yielded a methyleneamino pseudodipeptide.

1. Introduction

During the course of our ongoing study concerning the tetrapeptide Ac-Ser-Asp-Lys-Pro-OH extracted from bone marrow,[1] we were interested in preparing various analogues, which would be stable towards proteolysis.[2] A common approach to achieve this goal is to replace the hydrolyzable peptide bond by a surrogate bond.[3] Among the number of possibilities reported in the literature, the methyleneamino, methyleneoxy and methylenethio pseudopeptides have retained our attention. Of the three, only the former has been extensively used since a fully described methology is available for its preparation.[4] Examples of the two other surrogates are scarce as there is no general methodology for their synthesis. In principle, these three pseudopeptides could be obtained from a common precursor, namely an aziridine, which could be opened by amino acids or peptide esters or analogues (α-hydroxy or α-thio esters) as shown in Scheme 1. A preliminary report exploring the reactivity of the aziridine derived from an aspartic acid derivative with amines has shown the feasability of this approach with respect to the methyleneamino analogue.[5]

Aziridines as reactive intermediates have drawn considerable interest in the last decade.[6] They can be opened by



Scheme 1. Preparation of pseudodipeptides through opening of an aziridine by an α-amino, α-hydroxy or α-thio ester.

Keywords: Methyleneamino pseudopeptide; *Z*-Substituted aziridine opening; Microwaves; β-Amino alcohols; β-Amino acids.
* Corresponding author. Fax: +33 1 69 07 72 47; e-mail: josiane.thierry@icsn.cnrs-gif.fr

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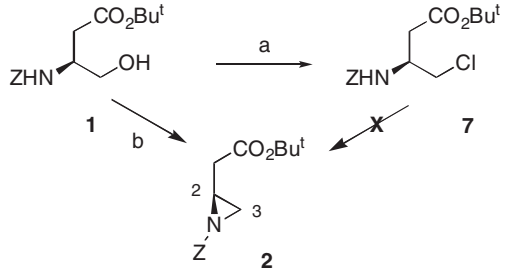
a variety of amine, alcohol, thiol or carbon nucleophiles. Their reactivity depends greatly on the nature of the substituent on the nitrogen. Thus, *N*-sulfonylaziridines react very readily with nucleophiles.[7] Using the chiral pool, optically active aziridines can be easily obtained from α-amino alcohols and many reports deal with aziridines derived from serine. There are, however, fewer papers dealing with aziridines derived from other amino acids.[8] Our purpose was to prepare derivatives, which could be used directly for peptide synthesis from amino acids having common protecting groups such as *t*-butyl and benzyl via the use of aziridines (Scheme 1).

We first addressed the question of the reactivity of *N*-benzyloxycarbonyl protected aziridines by studying aziridine **2** obtained from *Z*-Asp(OBu^t)-ol. This molecule bearing a *tert*-butyl ester on the side chain was reacted with various *N*-nucleophiles after screening of different mild reaction conditions. The reaction of **2** with oxygenated and sulfur nucleophiles was studied afterwards.

2. Results

2.1. Preparation of aziridine 2

Aziridine **2** was synthesized from the amino alcohol *Z*-L-Asp(OBu^t)-ol **1**.[9] This alcohol, obtained from commercial *Z*-L-Asp(OBu^t)-OH was treated either under Mitsunobu conditions (PPh_3, DEAD, THF) or with methanesulfonyl chloride in the presence of diisopropylethylamine (Scheme 2).[8] Only the Mitsunobu reaction yielded aziridine **2**. The mesylation of alcohol **1** followed by reflux with DIPEA gave the chloride **7** as the sole product. This chloride resisted further treatment with various bases (K_2CO_3, $KHCO_3$, $NaHSO_3$, AgO, KF, NaH), which gave either no reaction or decomposition.



Scheme 2. Synthesis of aziridine **2** (a): MsCl, DIPEA, THF, reflux, 20 h, 90%; (b): PPh_3, DEAD, THF, 0 °C, 30 min, rt, 18 h, 60–90%.

2.2. Ring opening of aziridine 2 with *N*-nucleophiles

2.2.1. With simple amines. We first applied conditions taken from the literature.[10] All the reactions were run in refluxing acetonitrile with 1.2 equiv of nucleophile and 1 equiv of $LiClO_4$[†] (Method A, entries 1, 3, 5). Most of the reactions were completed in 22–29 h and were quite regioselective yielding an approximately 1:10 ratio of **4**:**3** along with some tertiary amine **5** resulting from the attack of secondary amine **3** on aziridine **2** as shown in Table 1 (entries 1, 3, 4). In order to avoid the formation of **5**, we used an excess of nucleophile (3 equiv) in the following reactions.

Microwave-assisted organic synthesis has proven very efficient in shortening reaction times and increasing yields of sluggish reactions.[11] We used microwave irradiation to accelerate the reaction of **2** with amines and sealed tubes, which allowed reaction temperatures higher than the solvent or reagent boiling points. The screening of other reactions conditions (different solvents (toluene, THF) or catalysts ($Yb(OTf)_3$,[12] $MgClO_4$, $LiBF_4$, $Sc(OTf)_3$[13]) did not provide any benefit. However, the amount of $LiClO_4$ could be reduced to 0.5 equiv without reduction of yield whereas the use of 0.2 equiv decreased the rate of the reaction. Finally, the best reaction conditions were found to be 3 equiv of nucleophile in acetonitrile at 100 °C with 0.5 equiv $LiClO_4$[†] as catalyst in sealed tubes under microwave irradiation (Method B).

The aziridine opening reaction with simple amines (Table 1, entries 1–8) displayed very good regioselectivity except for benzylhydroxylamine (entry 5) where **3** and **4** were obtained in a ratio of 4:1, respectively. In all cases, the attack took place on the less substituted carbon. In some cases (entries 7 and 8), no product **4** resulting from attack at C-2 was isolated. Microwave activation gave satisfactory results considerably increasing the rate of the reactions (entries 1 and 2 and entries 3 and 4) while giving better yields. The reactions were generally completed within 1 h (entries 4, 7–8). The tertiary amine **5** was not obtained when a larger excess of nucleophile (3 equiv) was used (entries 7 and 8).

The 1, 2-diamino compounds **3** and **4** are valuable synthetic intermediates as their various protecting groups may be selectively cleaved before further elaboration.

2.2.2. Opening of 2 with other *N*-nucleophiles and amino acid esters (entries 9–11). When **2** was treated with the free bases of glycine *tert*-butyl ester or lysine methyl ester, **3** was obtained in good yield as the only regioisomer in the case of the latter (entry 10) whereas a slight amount of **4** could be isolated in the case of the former nucleophile (entry 9).

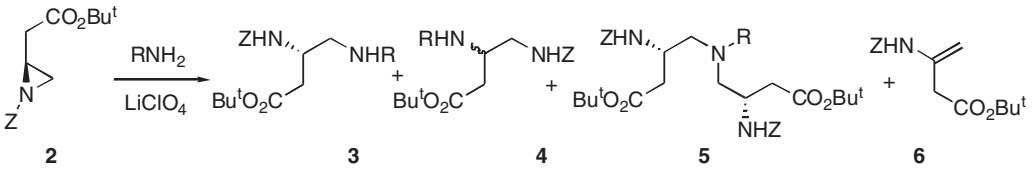
Treatment of **2** with NaN_3 (2 equiv) in CH_3CN/H_2O yielded only one regioisomer **3**, along with some elimination product **6** (29%) (entry 11).

2.3. Ring opening of aziridine 2 with *O*-nucleophiles

2.3.1. With alcohols (Scheme 3). Whereas, a wealth of catalysts is known to promote the opening of aziridines with *N*-nucleophiles, there are only a few described for their opening with *O*-nucleophiles, namely Lewis acids.[6] The most widely used catalyst is boron trifluoride etherate ($BF_3 \cdot OEt_2$), though $Yb(OTf)_3$[14] and $Sn(OTf)_2$[15] have also been reported for cases in which the alcohol nucleophile is used as the solvent. More recently, CAN[7b] has been used to catalyze the opening of tosyl aziridines also when using the alcohol as the solvent.

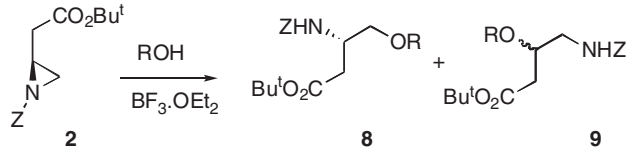
[†] Lithium perchlorate in organic solvents is a potential explosive hazard. It must be handled in small amounts and with appropriate care.

Table 1. Reaction of **2** with *N*-nucleophiles



Entry	Nucleophile (equiv)	Method[a]	Time (h)	Yield (**3**+**4**) (%)[b]	Ratio **4**:**3**	Yield **5** (%)[b]
1	$PhCH_2NH_2$ (1.1)	A	22	60	1:11	3
2	$PhCH_2NH_2$ (3)	B	0.5	85	1:14	
3	CH_2=CH–CH_2–NH_2 (1.5)	A	29	60	1:11	6
4	CH_2=CH–CH_2–NH_2 (1.5)	A[c]	2	70	1:8	10
5	$PhCH_2$–ONH_2 (1.2)	A	22	76	1:4	
6	$PhCH_2OCONHNH_2$ (2.4)	A	8 days	67	1:14	2
7	$(OEt)_2CHCH_2NH_2$ (3)	B	0.5	82	[d]	
8	*p*-MeO–$PhCH_2NH_2$ (3)	B	0.3	88	[d]	
9	$H_2NCH_2CO_2Bu^t$ (3)	B	1	80	1:26	
10	H-Lys(Boc)-OMe (1.2)	A	18	82	[d]	5
11	NaN_3 (2)	B	1.1	47	[d,e]	

[a] Method A: aziridine **2** (0.3 mmol), amine (1.2 equiv) and $LiClO^4$ (1 equiv) in refluxing acetonitrile (1.5 mL). Method B: aziridine **2** (0.2 mmol), amine (3 equiv) and $LiClO_4$ (0.5 equiv) in acetonitrile (1 mL) in sealed tubes under microwave irradiation T=100 °C, power: 40 W.
[b] Yields of purified products.
[c] Same conditions as entry 3, except that the reaction mixture in sealed tubes was subjected to microwave irradiation T=80 °C, power: 40 W.
[d] No product **4** was isolated.
[e] Elimination product **6**: 29%.

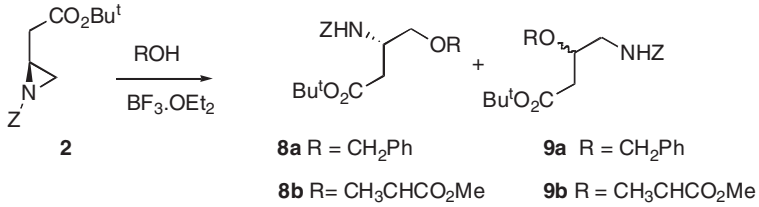


Scheme 3. Ring opening of **2** with alcohols.

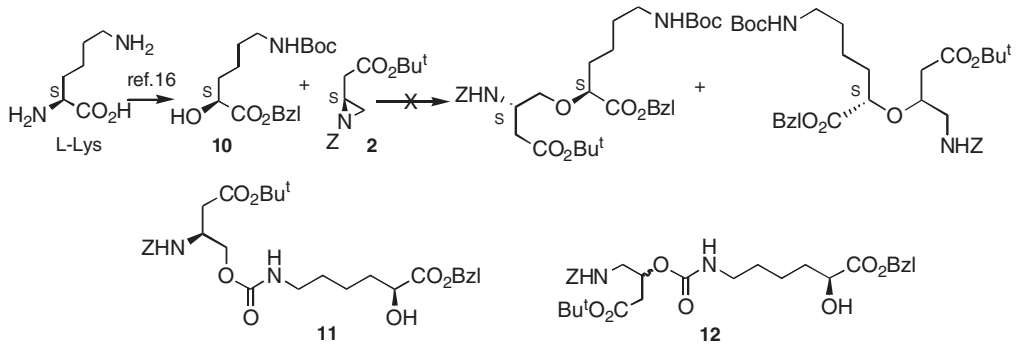
2.3.1.1. Reaction of 2 with benzyl alcohol. A first experiment run with 2 equiv of benzyl alcohol and 0.5 equiv of $BF_3 \cdot OEt_2$ catalyst at 0 °C for 1 h and at room temperature overnight provided a 46% yield of **8a** and **9a** in a 1:1 ratio. A additional experiment run at −30 °C with only 0.1 equiv of $BF_3 \cdot OEt_2$ improved the yield (74%) while giving the same ratio of regioisomers. Different sets of conditions were then investigated aiming to achieve better regioselectivity in favor of **8**. The use of bentonite yielded modest overall yields (40%) of **8a** and **9a** in a 1:1 ratio for reactions run at 130 °C in toluene or 100 °C without solvent under microwave activation. Montmorillonite KSF or K10 were not useful as catalysts either at room temperature in CH_2Cl_2 or in refluxing CH_3CN. Silica gel under solvent free conditions was totally inefficient.

2.3.1.2. With secondary alcohols. We then used methyl lactate as a model of an α-hydroxy ester nucleophile. In the presence of $BF_3 \cdot OEt_2$ (0.2 equiv) as the catalyst (Scheme 4), the two regioisomers **8b** and **9b** were obtained in 56% yield and in a 1.5:1 ratio. Keeping in mind our goal of preparing methyleneoxypseudodipeptides, we also used as nucleophile the benzyl ester of (2*S*)-6-(*tert*-butylcarboxylamino)-2-hydroxy-hexanoic acid **10** obtained through nitrous deamination of L-lysine followed by protection of the amino and carboxylic functions with the corresponding protecting groups (Scheme 5).[16] Using the same conditions as described above, no product corresponding to the expected mass could be isolated. Numerous attempts to improve these reaction conditions by varying the ratios of the reagents or the reaction temperature consistently gave the same results, that is, a reaction mixture the mass and NMR spectra of which indicated the loss of a *t*-butyl group. Careful HPLC analysis indicated a 7:3 ratio of two products and allowed the isolation of sufficient amounts for their identification. 2D NMR analysis established their structures as being two regioisomers **11** (major) and **12** (minor) as shown in Scheme 5. Although the Boc group is known to react in an intramolecular fashion with aziridines,[19] there is no literature precedence for such an intermolecular reaction to the best of our knowledge.

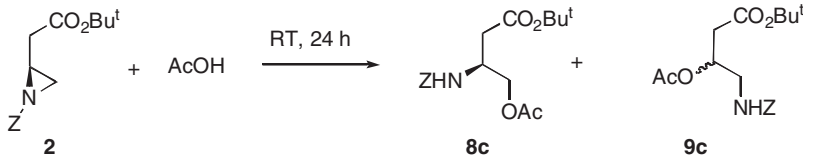
2.3.2. With acetic acid.[17] The opening of aziridine **2** with AcOH (5 equiv) at room temperature for 24 h yielded two compounds **8c** and **9c**, which could not be easily separated on silica gel. Acetylation of the alcohol **1** with acetic anhydride and DMAP allowed identification of **8c** in the



Scheme 4. Ring opening of **2** with primary and secondary alcohols.



Scheme 5. Opening of **2** with (2*S*)-2-hydroxy 6-amino hexanoic acid derivative **10**.

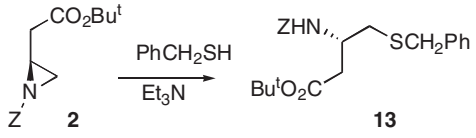


Scheme 6. Opening of **2** with acetic acid.

HPLC chromatogram of the mixture. The reaction gave the two regioisomers **8c** and **9c** in 81% yield and 3:1 ratio (Scheme 6).

2.4. Ring opening of aziridine 2 with *S*-nucleophiles

There are several reports of such a reaction.[7a,18,19] One describes the opening of a *Z*-protected serine-derived aziridine with various thiols used in large excess.[18a] The reaction, catalyzed by boron trifluoride etherate, required severals days to reach completion and was very regioselective. Crotti et al.[18b] used thiophenol (3 equiv) under metal assisted ($LiClO_4$) or basic (Et_3N) conditions in aprotic (CH_3CN) or protic (MeOH) solvents to open activated bicyclic tosyl aziridines. They also observed very good regioselectivity as did Dauban et al.[18c] in their study of a Ac or *Z*-protected bicyclic aziridine.



Scheme 7. Opening of **2** with benzyl mercaptan.

Thus, **2** was treated with benzyl mercaptan under the conditions described by Maligres[7a] and Crotti.[18b] The best results were obtained under basic conditions with Et_3N (5 equiv) in methanol and benzylmercaptan (3 equiv) at room temperature or Et_3N (0.2 equiv) in THF and benzylmercaptan (1.05 equiv) at 30 °C. In both cases, the thioether **13** was obtained after 5 days in 65% yield as a single regioisomer (Scheme 7).

The present study shows that benzyloxycarbamate-protected aziridines, although less activated than tosylaziridines, are sufficiently reactive to be easily and regioselectively opened by *N*-nucleophiles giving 1, 2-diamino compounds suitably protected for further transformations. The opening of **2** with the methyl ester of H-Lys(Boc)-OMe (entry 10, Table 1) provided the methyleneaminopseudopeptide *Z*-Asp(OBut)Ψ[CH_2-NH]Lys(Boc)-OMe with a good yield and excellent regioselectivity thereby affording a new route to this kind of compound. Treatment of **2** with alcohol in presence of boron trifluoride etherate gave mixtures of regioisomers whereas the use of a thiol as nucleophile gave only the product of C-3 attack. The synthesized compounds are presently being explored as building blocks in pseudopeptide synthesis.

3. Experimental

3.1. General

Protected amino acids are from Novabiochem (VWR) and Senn Chemicals. L-Lysine was purchased from Sigma. Commercially available reagents were used as received. Solvents were dried on dry basic alumina prior to use. Analytical TLC was conducted on Merck 60F-254 silica gel on precoated aluminum sheets; compounds were visualized with UV-light or with ninhydrine.

Flash column chromatography was performed using Merck silica gel 60 (40–63 μ). Infrared spectra were recorded on a Perkin–Elmer Spectrum BX instrument. Optical rotations were measured on a Jasco polarimeter using a cell of 1 dm-length path. Mass spectra were obtained using LCT Micromass (low and high resolution ES^+) spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a AM300, AVANCE 300 Bruker 300 MHz. Chemical shifts are expressed in ppm referenced to the peak of $CDCl_3$, defined at $\delta=77.1$ (^{13}C). Microanalyses were performed by the analytical laboratory in Gif. HPLC analysis was performed on a Waters apparatus consisting of Alliance gradient controller, an automatic 717 injector, a multi-wavelength UV detector and a chromatogram analyser. Analyses were carried out on a *C*18-Symmetry column

(5 μ, 4.6×250 mm). The eluent was a mixture of H_2O and acetonitrile both containing 0.1% trifluoroacetic acid at a 1 mL/min flow rate. The mass spectrometer connected to the HPLC apparatus was a Waters Micromass ZQ with an ESI probe. The microwave oven was a Discover™ monomodal apparatus from CEM μWaves (Orsay, France). Experimental parameters were: power: 40 W, temperature: 100 °C.

3.1.1. (2*R*)-2-*tert*-Butoxycarbonylmethyl-aziridine-1-carboxylic acid benzyl ester 2. To a solution of triphenylphosphine (2.62 g, 10 mmol) in THF (25 mL) cooled in an ice-water bath was added DEAD (1.6 mL, 10 mmol) over 30 min. A solution of *Z*-Asp(OBu^t)-ol[9b] (1.55 g, 5 mmol) in THF (12.5 mL) was added dropwise over 1 h at the same temperature. After 1 h at 0 °C, the reaction mixture was stirred at room temperature for 19 h. After evaporation of the solvents, the residue was taken up in CH_2Cl_2 and separated by column chromatography on silica gel. Elution with CH_2Cl_2 gave 0.667 g of pure aziridine and further elution with CH_2Cl_2–MeOH (99/1) gave 0.468 g of a less pure fraction, which was further purified on a silica gel column with heptane–EtOAc (85/15) yielding 0.344 g of pure product as a clear oil. Overall yield: 69%. R_f 0.53 (heptane/EtOAc, 7:3); R_f 0.67 (CH_2Cl_2/ether, 95:5).

$[\alpha]_D$ +23.7 (*c* 0.76, MeOH). MS (EI): *m*/*z* 292 ($M^{+\cdot}$), 236 ($M^{+\cdot}-56$), 192 ($M^{+\cdot}-100$), 107, 91, 57. ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.08 (d, *J*=3.6 Hz, 1H), 2.27 (dd, *J*=6.6, 16 Hz, 1H), 2.43 (d, *J*=6 Hz, 1H), 2.58 (dd, *J*=6, 16 Hz, 1H), 2.80 (M, 1H), 5.14 (S, 2H), 7.35 (s, 5H); ^{13}C NMR (75 MHz): δ 28.14, 31.57, 34.16, 38.88, 68.32, 81.30, 128.29, 128.41, 128.63, 135.82, 163.06, 169.74. Anal. Calcd for $C_{16}H_{21}NO_4$ C, 65.96, H, 7.27, N, 4.81. Found: C, 66.09, H, 7.17, N, 4.69.

3.1.2. (3*S*)- *tert*-Butyl-3-benzyloxycarbonylamino-4-chloro-butyrate 7. *Z*-L-Asp(OBu^t)-ol **1**[9b] (3.21 g, 10 mmol) was dissolved in THF (20 mL), DMAP (25 mg, 0.2 mmol) and DIPEA (4 mL, 23 mmol) were added, the mixture was cooled to −20 °C and then CH_3SO_2Cl (1 mL, 12 mmol) was added dropwise. The resulting suspension was warmed gradually to room temperature and then refluxed at 90 °C for 20 h. The mixture was cooled to room temperature; EtOAc (30 mL) and NaCl solution (20 mL) were added; the organic phase was isolated, dried over Na_2SO_4 and evaporated under vacuum to leave a syrup, which was purified by chromatography (EtOAc/pentane, 1:8–1:4) to give 2.61 g (90%) of the chloride derivative R_f 0.51 (EtOAc/heptane, 1:2). $[\alpha]_D$ −2.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz): 1.38 (s, 9H), 2.28–2.37 (q, 1H), 2.63–2.69 (q, 1H), 4.05–4.10 (q, 1H), 4.26–4.36 (m, 1H), 4.47–4.53 (t, 1H), 5.15 (s, 2H), 7.25–7.33 (m, 5H); ^{13}C NMR (75 MHz): 28.1, 42.1, 60.2, 72.3, 73.8, 81.0, 128.1, 128.4, 135.2, 163.1, 170.4. IR (neat) 3325, 2977, 1697, 1529, 1367, 1246, 1149, 1043, 955, 840, 737. MS (ES): *m*/*z* 350 (MNa^+), 294 (MNa^+-56); HRMS $C_{16}H_{22}ClNO_4Na$. Found: 350. 1126; calcd: 350.1135.

3.2. General procedure for opening of 2 with *N*-nucleophiles

Method A. Aziridine **2** (0.3 mmol) was dissolved in acetonitrile (1.5 mL). $LiClO_4$ (31 mg, 0.3 mmol) followed by the nucleophile (0.45 mmol or as described in Table 1) were added to the solution. The reaction mixture was refluxed (except in the case of entry 4 where it was heated at 50 °C) and monitored by TLC. At the end of the reaction period, the mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography.

Method B. Aziridine **2** (0.2 mmol) was dissolved in acetonitrile (1 mL) in a heavy-walled tube. $LiClO_4$ (10 mg, 0.1 mmol) followed by the nucleophile (0.6 mmol) were added to the solution. The tube was sealed with a teflon cap. The reaction mixture was submitted to microwave irradiation at *T*=100 °C and *P*=40 W under magnetic stirring for at least 20 min in the Discover microwave apparatus. The reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was washed with brine and dried with Na_2SO_4. Alternatively, the reaction mixture was evaporated under vacuum. In both cases, the crude product was purified by silica gel column chromatography.

3.2.1. With benzylamine (Method A).

3.2.1.1. (3*S*)-*tert*-Butyl-4-benzylamino-3-benzyloxycarbonylamino-butyrate 3a. Yield: 55%, R_f 0.17 (EtOAc/heptane, 4:6). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 1.51 (br s, 1H), 2.50 (m, 2H), 2.75 (m, 2H), 3.79 (s, 2H), 4.10 (m, 1H), 5.12 (s, 2H), 5.48 (m, 1H), 7.31, 7.36 (s, 10H); ^{13}C NMR (75 MHz): 28.0, 38.4, 48.2, 51.8, 53.7, 66.6, 81.1, 127.0, 128.1, 128.4, 128.5, 136.5, 140.1, 155.9, 170.8. MS: MH^+: 399, MH^+-56: 243; HRMS Found: $C_{23}H_{31}N_2O_4$ 399.2272; calcd: 399. 2284; IR (neat): 3330, 2976, 1721, 1249, 1156, 741.

3.2.1.2. 3(*R*)-3-Benzylamino-4-benzyloxycarbonylamino-butyric acid-*tert*-butyl ester 4a. Yield: 5%, R_f 0.30 (EtOAc/heptane, 4:6). ^{1}H NMR (300 MHz): 1.45 (s, 9H), 1.75 (br s, 1H), 2.42 (d, 2H), 3.14 (m, 1H), 3.26 (m, 1H), 3.35 (m, 1H), 3.80 (s, 2H), 5.12 (s, 2H), 5.31 (m, 1H), 7.32, 7.38 (s, 10H); ^{13}C NMR: 28.1, 38.3, 43.4, 50.9, 53.9, 66.7, 67.0, 81.1, 127.1, 128.2, 128.5, 128.6, 136.4, 139.9, 156.3, 171.2. MS: MNa^+: 421, MH^+: 399, MH^+-56: 343; HRMS $C_{23}H_{31}N_2O_4Na$. Found: 421.2096; calcd: 421.2103.

3.2.2. With allylamine (Method B).

3.2.2.1. (3*S*)-*tert*-Butyl-4-allylamino-3-benzyloxycarbonylamino-butyrate 3b. Yield: 62%. $[\alpha]_D$ −5 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 1.67 (br s, 1H), 2.51 (m, 2H), 2.73 (m, 2H), 3.25 (br s, 2H), 4.06 (m, 1H), 5.10 (br s+m, 4H), 5.50 (m, 1H), 5.86 (m, 1H), 7.37 (s, 5H); ^{13}C NMR (75 MHz): 28.0, 38.4, 48.2, 51.6, 52.1, 66.6, 81.1, 116.1, 128.0, 128.3, 128.5, 128.6, 136.5, 155.8, 170.8. IR (neat): 3338, 2978, 1722, 1537, 1253, 1158, 1054, 919, 919, 738, 697. MS: MNa^+: 371, MH^+: 349, MH^+-56: 293; HRMS $C_{19}H_{29}N_2O_4$. Found: 349.2132; calcd: 349.2127.

3.2.2.2. (3*R*)-*tert*-Butyl-3-allylamino-4-benzyloxycarbonylamino-butyrate 4b. Yield: 8%, R_f 0.54 (EtOAc/heptane, 4:6). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.39 (d, 2H), 2.96–3.40 (m, 4H), 5.03–5.31 (br s+m, 5H), 5.85

(m, 1H), 7.37 (s, 5H); ^{13}C NMR (75 MHz): 28.1, 38.3, 41.3, 49.3, 53.7, 66.7, 81.1, 116.5, 128.1, 128.5, 136.5, 157, 171.2. MS: MNa^+: 371, MH^+: 349, MH^+-56:293; IR (neat): 3338, 1722.

3.2.3. With *O*-benzylhydroxylamine (Method A).

3.2.3.1. (3*S*)-*tert*-Butyl-4-benzyloxyamino-3-benzyloxycarbonylamino-butyrate 3c. Yield: 60%, R_f 0.25 (EtOAc/heptane, 3:7). $[\alpha]_D$ +18 (*c* 1.1, $CHCl_3$). ^{1}H NMR: 1.43 (s, 9H), 2.56 (d, 2H), 3.08 (m, 2H), 4.20 (m, 1H), 4.69 (s, 2H), 5.11 (s, 2H), 5.47 (m, 1H), 5.74 (br s, 1H), 7.34, 7.37 (s, 10H); ^{13}C NMR (75 MHz): 28.0, 38.1, 46.9, 54.3, 66.6, 76.1, 81.1, 128.0, 128.1, 128.4, 128.5, 136.5, 137.5, 155.8, 170.7. MS: MK^+: 453, MNa^+: 437, MH^+: 415, MNa^+-56: 381, MH^+-56: 359; HRMS (ES) $C_{23}H_{30}N_2O_5Na$. Found: 437.2028; calcd: 437.2052

3.2.3.2. (3*R*)-3-Benzyloxyamino-4-benzyloxycarbonylamino-butyric acid-*tert*-butyl ester 4c. Yield: 16%. ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.34 (m, 1H), 2.46 (m, 1H), 3.21 (m, 1H), 3.33 (m, 1H), 4.55 (s, 2H), 4.96 (br s, 1H), 5.10 (s, 2H), 6.04 (br s, 1H), 7.36, 7.37 (s, 10H); ^{13}C NMR (75 MHz): 28.1, 35.2, 42.2, 56.9, 66.7, 76.6, 81.1, 128.0, 128.1, 128.4, 128.5, 128.6, 136.5, 137.6, 155.8, 171.1. MS: MK^+: 453, MNa^+: 437, MH^+: 415, MNa^+-56: 381, MH^+-56: 359.

3.2.4. With *N*-benzyloxycarbonylhydrazine (Method A).

3.2.4.1. 3(*S*)-4-(*N*-Benzyloxycarbonyl-hydrazino)-3-benzyloxycarbonylamino-butyric acid-*tert*-butyl ester 3d. Yield: 63%, R_f 0.25 (EtOAc/heptane, 4:6). $[\alpha]_D$ +53 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz): 1.42 (s, 9H), 2.32–2.61 (dd, 2H), 2.75–3.06 (m, 2H), 4.12 (m, 2H), 5.13 (m, 5H), 5.52 (m, 1H), 6.83 (m, 1H), 7.37 (10H); ^{13}C NMR (75 MHz): 28.1, 38.0, 46.3, 54.1, 54.6, 66.8, 67.0, 81.3, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 136.1, 136.4, 156.6, 157.2, 170.7; HRMS (ES) $C_{24}H_{31}N_3O_6Na$. Found: 480.2134; calcd: 480.2111.

3.2.5. With 2,2-diethoxyethylamine (Method B).

3.2.5.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-(2,2-diethoxy-ethylamino)-butyrate 3e. Yield: 82%, R_f 0.22 (EtOAc/heptane, 3:1). $[\alpha]_D$ +2.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz): 1.22 (t, 6H, *J*=7.1 Hz), 1.43 (s, 9H), 2.49 (m, 2H), 2.76 (m, 4H), 3.53 (m, 2H), 3.68 (m, 2H), 4.08 (m, 1H), 4.54 (t, 1H), 5.10 (s, 2H), 5.45 (br, 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz): 15.4, 28.0, 38.3, 48.3, 52.1, 52.3, 62.3, 66.6, 81.01, 102.0, 128.0, 128.5, 136.6, 155.9, 170.7. MS (m/z): 425.2 (MH^+); IR (neat): 3332, 2976, 2930, 1725, 1530, 1455, 1368, 1250, 1157, 1061, 844, 738

3.2.6. With *p*-methoxybenzylamine (Method B).

3.2.6.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-(4-methoxy-benzylamino)-butyrate 3f. Yield: 88%, R_f 0.31 (EtOAc/heptane, 5:2). $[\alpha]_D$ −0.6 (*c* 1.5, $CHCl_3$). ^{1}H NMR (300 MHz): 1.43 (s, 9H), 2.50 (m, 2H), 2.74 (m, 2H), 3.74 (s, 2H), 3.82 (s, 3H), 4.09 (m, 1H), 5.11 (s, 2H), 5.44 (br, 1H), 6.79 (d, 2H, *J*=8.6 Hz), 7.15 (d, 2H, *J*=8.6 Hz), 7.38 (m, 5H); ^{13}C NMR (75 MHz): 28.0, 38.4, 48.1, 51.7, 53.1, 55.2, 66.6, 81.0, 113.8, 128.0, 128.5, 129.2, 132.3, 136.6, 155.9, 158.7, 170.8. MS (m/z): 451 (MNa^+), 429 (MH^+), 373 (MH^+-56); HRMS $C_{24}H_{31}N_2O_5Na$. Found: 451.2217; calcd: 451.2209; IR (neat): 3335, 2977, 2836, 1723, 1611, 1513, 1247, 1157, 1037, 843, 739.

3.2.7. With glycine *tert*-butyl ester (Method B).

3.2.7.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-(*tert*-butoxycarbonylmethyl-amino)-butyrate 3g. Yield: 77%, R_f 0.23 (EtOAc/heptane, 3:1). $[\alpha]_D$ +5.7 (*c* 1.9, $CHCl_3$). ^{1}H NMR (300 MHz): 1.4 (s, 9H), 1.43 (s, 9H), 2.48 (m, 2H), 2.76 (m, 2H), 3.35 (AB s, 2H, *J*=17 Hz), 4.03 (m, 1H), 5.11 (s, 2H), 5.50 (br, 1H), 7.36 (m, 5H); ^{13}C NMR (75 MHz): 28.0, 28.1, 38.3, 48.3, 51.6, 52.0, 66.6, 81.0, 81.2, 128.0, 128.4, 136.6, 155.9, 170.7, 171.6. MS (m/z): 445 (MNa^+), 423 (MH^+), 389 (MNa^+-tBu), 367 (MH^+-tBu), 311 (MNa^+-Z); HRMS $C_{22}H_{34}N_2O_6Na$. Found: 445.2351; calcd: 445.2315; IR (neat): 3338, 2978, 1728, 1530, 1368, 1247, 1157, 1054, 846, 752.

3.2.8. With sodium azide (Method B).

3.2.8.1. (3*S*)-*tert*-Butyl-4-azido-3-benzyloxycarbonylamino-butyrate 3h. Yield: 47%, R_f 0.41 (EtOAc/heptane, 1:2). $[\alpha]_D$ −3.0 (*c* 1.2, $CHCl_3$). ^{1}H NMR (300 MHz): 1.45 (s, 9H), 2.54 (d, 2H), 3.51 (m, 2H), 4.16 (m, 1H), 5.13 (s, 2H), 5.45 (m, 1H), 7.38 (br s, 5H); ^{13}C NMR (75 MHz): 28.0, 37.2, 47.9, 53.7, 66.9, 81.7, 128.1, 128.2, 128.5, 136.2, 155.6, 170.1. MS (m/z): 357 (MNa^+), 301 (MNa^+-56); HRMS $C_{16}H_{22}N_4O_4Na$. Found: 357.1549; calcd: 357.1539; IR (neat): 3328, 2979, 2103, 1727, 1532, 1454, 1368, 1255, 1157, 1055, 961, 843, 738.

3.2.9. With H-Lys(Boc)-OMe (Method B).

3.2.9.1. (2*S*)-Methyl-2-(2-benzyloxycarbonylamino-3-*tert*-butoxycarbonyl-propylamino)-6-*tert*-butoxycarbonylamino hexanoate 3i. Yield: 83%, R_f 0.23 (EtOAc/heptane, 4:6); R_f 0.28 (CH_2Cl_2/MeOH, 98:2). ^{1}H NMR (300 MHz): 1.46 (s, 9H), 1.47 (s, 9H), 2.37 (d, 2H, *J*=6.3 Hz), 3.08 (m, 1H), 3.25 (m, 2H), 3.33 (s, 2H), 5.12 (s, 2H), 5.49 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (75 MHz): 28.0, 38.8, 43.5, 49.1, 54.5, 66.6, 81.0, 81.4, 128.1, 128.5, 136.6, 156.6, 170.7, 171.6. IR (neat): 3342, 2975, 2928, 1728, 1530, 1366, 1236, 1145, 843, 751. MS (m/z): 574 (MNa^+), 552 (MH^+); HRMS $C_{28}H_{46}N_3O_8Na$. Found: 552.3286; calcd: 552.3285.

3.3. General procedure for opening of aziridine 2 with *O*-nucleophiles.

3.3.1. With benzyl alcohol. $BF_3\cdot OEt_2$ (6 μL, 0.1 equiv) was added to a solution of **2** (146 mg, 0.5 mmol) and benzyl alcohol (104 μL, 2 equiv) in dry $CHCl_3$ (6 mL) cooled to −30 °C. After 3 h 30 min stirring at this temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was then washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (217 mg) containing **8a**, **9a** and benzyl alcohol, which was separated on a silica gel column. Elution with heptane/EtOAc 8:2 gave pure **8a** (19 mg), a mixture of **8a** and **9a** (107 mg) and pure **9a** (27 mg). Overall yield: 74%.

3.3.1.1. (3*S*)-*tert*-Butyl-3-benzyloxycarbonylamino-4-benzyloxy-butyrate 8a. R_f 0.53 (heptane/EtOAc, 7:3). $[\alpha]_D$ −8 (*c* 1.1, MeOH).^{1}H NMR (300 MHz): 1.38 (s, 9H), 2.53 (d, 2H, *J*=6.3 Hz), 3.51 (m, 2H), 4.19 (m, 1H), 4.48 (s, 2H), 5.07 (s, 2H), 5.38 (br d, 1H), 7.32 (br s, 10H); ^{13}C NMR

(75 MHz): 28.1, 37.5, 48.1, 66.8, 71.1 73.3, 81.1, 127.8, 127.7, 128.5, 128.2, 128.6, 136.6, 138.0, 155.8, 170.7. MS (m/z): 438 (MK^+), 422 (MNa^+), 366 (MNa^+-56), 266 (MH^+-134); IR (neat): 3335, 2977, 1732, 1538, 738, 697.

3.3.1.2. (3*S*)-*tert*-Butyl-3-benzyloxy-4-benzyloxycarbonylamino-butyrate 9a. R_f 0.45 (heptane/EtOAc, 7:3). $[\alpha]_D$ +1 (*c* 1.1, MeOH). ^1H NMR (300 MHz): 1.41 (s, 9H), 2.50 (AB s, 2H, $J=6.3$ Hz), 3.25 (m, 1H), 3.39 (m, 1H), 3.94 (m, 1H), 4.58 (AB s, 2H, $J=11$ Hz), 5.05 (s, 3H), 7.31 (br s, 10H); ^{13}C NMR (75 MHz): 28.2, 39.0, 43.9, 66.8, 72.0 75.1, 81.1, 127.9, 128.2, 128.6, 136.6, 138.1, 156.6, 170.4. MS (m/z): 438 (MK^+), 422 (MNa^+), 400 (MH^+), 366 (MNa^+-56), 344 (MH^+-56), 266 (MH^+-134); IR (neat): 3343, 2976, 1718, 1540, 737, 697.

3.3.2. With (*S*)-methyl lactate. To a cold solution of $BF_3\cdot OEt_2$ (9 μL, 0.2 equiv) in $CHCl_3$ (0.4 mL) was added methyl lactate (72 μL, 2 equiv) followed by a solution of **2** (111 mg, 0.4 mmol) in $CHCl_3$ (1.2 mL). After 1 h stirring in the ice bath, the reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was then washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (157 mg) containing **8b** and **9b**. MS-HPLC analysis of the crude product indicated that the 2 regioisomers were present ($t_R=$ 11.79 and 12.35 min) in a 1.5–1 ratio. The analysis was performed on a Waters Symmetry column. The eluent was a gradient of H_2O and acetonitrile both containing 0.1% TFA starting from 35% acetonitrile to 100% over 20 min at a 1 mL/min flow rate.

3.3.3. With acetic acid. Acetic acid (86 μL, 5 equiv) was added to a solution of aziridine **2** (87 mg, 0.3 mmol) in CH_2Cl_2 (0.9 mL). The solution was stirred under argon during 24 h. The reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure afforded 102 mg of a yellow oil. The crude product was separated by flash chromatography. Elution with heptane/EtOAc 75/25 did not allow separation of the two regioisomers and gave 95 mg of a mixture of **8c** and **9c**. ^1H NMR analysis showed a of 3:1 ratio of **8c**:**9c**. A second flash chromatography using petroleum ether–acetone (9:1) gave pure **8c** (8 mg) and a mixture of **8c** and **9c**.

3.3.3.1. (3*S*)-4-Acetoxy-3-benzyloxycarbonylamino-butyric acid *tert*-butyl ester 8c. R_f 0.31 (EtOAc/heptane, 3:7). ^1H NMR (300 MHz): 1.43 (s, 9H), 2.05 (s, 3H), 2.52 (d, $J=5.9$ Hz, 2H), 4.15 (m, 2H), 4.28 (m, 1H), 5.11 (s, 2H), 5.41 (d, $J=9$ Hz, 1H), 7.35 (s, 5H); ^{13}C NMR (75 MHz): 20.7, 28.0, 37.1, 47.2, 65.1, 66.8, 81.5, 127.1, 128.1, 128.5, 136.3, 155.3, 155.6, 170.0, 170.7. MS (m/z): 390 (MK^+), 374 (MNa^+), 318 (MNa^+-56).

3.3.4. With benzyl (2*S*)-6-(*tert*-butyloxycarbonylamino)-2-hydroxy-hexanoate 10. $BF_3\cdot OEt_2$ (52 μL, 0.2 equiv) in dry $CHCl_3$ (0.2 mL) was added to a solution of **2** (65 mg, 0.22 mmol) and alcohol **10** (151 mg, 2 equiv) in dry $CHCl_3$ (0.6 mL) cooled to 0 °C. After 15 min stirring at this temperature and 4 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with a 5% $NaHCO_3$ solution. The organic layer was then washed with H_2O, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (207 mg). The residue was purified by flash chromatography with heptane–EtOAc (7/3) to remove excess **10**. Elution with methanol and evaporation of methanol fractions gave a mixture of **11** and **12** (79 mg) as a transparent oil, which could only be separated by HPLC. Analysis of the mixture showed a 7:3 ratio of **11** and **12**. Elution on a *C*18-symmetry column was isocratic with a mixture of H_2O and acetonitrile (1/1) both containing 0.1% trifluoroacetic acid at a 1 mL/min flow rate. t_R (**11**)= 23.0 min, t_R (**12**)=24.1 min.

Chromatography under the same conditions provided each compound as a pure sample (2 mg) allowing 2D NMR analysis. Both compounds had an identical ESI mass spectum corresponding to MNa^+-56: 595.

Compound **11**. ^{13}C NMR (100 MHz) in DMSO-d_6: 21.9, 28.0, 29.4, 33.7, 38.4, 40.7, 44.3, 66.8, 67.3, 70.2, 81.2, 128.1, 124.4, 128.5, 128.6, 128.7, 135.1, 136.4, 155.7, 156.5, 155.7, 169.2, 174.9.

3.4. Opening of 2 with benzyl mercaptan.

3.4.1. (2*S*)-*tert*-Butyl 3-(benzyloxycarbonylamino)-4-(benzylthio) butyrate propanoate 13. (a) Benzyl mercaptan (37 μL, 1.05 equiv) was added to a solution of aziridine **2** (87 mg, 0.3 mmol) and Et_3N (8 μL, 0.2 equiv) in THF (0.3 mL). The reaction was run under argon for 5 days at 30 °C. The reaction mixture was diluted with ether and the organic phase was washed with water, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (121 mg). The residue was purified by flash chromatography with heptane–EtOAc (8/2) to give **13** (81 mg) as an oil.

(b) Benzylmercaptan (105 μL, 3 equiv) was added to a solution of aziridine **2** (87 mg, 0.3 mmol) and Et_3N (208 μL, 5 equiv) in methanol (0.3 mL). The reaction was run under argon for 5 days at room temperature. The reaction mixture was diluted with ether and the organic phase was washed with water, brine and dried on Na_2SO_4. Evaporation under reduced pressure yielded an oil (176 mg). The residue was purified by flash chromatography with heptane–EtOAc (8/2) to give **13** (82 mg).

R_f 0.53 (EtOAc/heptane, 3:7). $[\alpha]_D$ +10.8 (*c* 1.6, $CHCl_3$). ^1H NMR (300 MHz): 1.43 (s, 9H), 2.49–2.69 (m, 4H), 4.74 (br s, 2H), 4.14 (m, 1H), 5.12 (s, 2H), 5.42 (1H), 7.36 (m, 10H); ^{13}C NMR (75 MHz): 28.0, 35.4, 36.5, 38.6, 47.6, 66.7, 81.3, 127.1, 128.0, 128.1, 128.5, 128.9, 136.5, 138.0, 155.6, 170.5. MS (m/z): 438 (MNa^+), 382 (MNa^+-56); HRMS $C_{23}H_{29}NO_4NaS$. Found: 438.1675; calcd: 438.1715.

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