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Synthesis of alkyl 2-(bromomethyl)aziridine-2-carboxylates and alkyl 3-bromoazetidine-3-carboxylates as amino acid building blocks

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ABSTRACT

A short synthesis of alkyl 2-(bromomethyl)aziridine-2-carboxylates and alkyl 3-bromoazetidine-3-carboxylates was developed involving amination, bromination, and base-induced cyclization of alkyl 2-(bromomethyl)acrylates. These new small ring azaheterocyclic α- and β-amino acid derivatives are promising synthons as demonstrated by their transformation to 2-(aminomethyl)aziridine-2-carboxylates and 3-aminoazetidine-3-carboxylates.

Aziridine-2-carboxylic acid derivatives are biologically and synthetically important amino acid derivatives useful for the preparation of proteinogenic, non-proteinogenic amino acids, and a variety of biologically active nitrogen-containing compounds, due to the fact that these strained heterocycles undergo regio- and stereoselective ring opening reactions with nucleophiles.[1] On the other hand, derivatives of azetidine-3-carboxylic acid disclose gametocidal activity,[2] and have been used for the preparation of a variety of pharmaceutically active compounds.[3] In view of the biological and synthetic importance of the aforementioned classes of amino acids and the continuous need of new lead compounds in agrochemical and pharmaceutical industry, the synthesis of new three- and four-membered azaheterocyclic α- and β-amino acid derivatives is an important research field in modern synthetic chemistry. As broadly demonstrated by our research group and others, the presence of a halogenated carbon atom and ring strain in 2-(halomethyl)aziridines,[4,5] and in the related isomeric 3-haloazetidines,[5a,6] allows synthetic elaboration of these azaheterocycles via nucleophilic displacement reactions, ring opening reactions, and ring transformations. In the present Letter, results are described on the synthesis of alkyl 2-(bromomethyl)aziridine-2-carboxylates and alkyl 3-bromoazetidine-3-carboxylates, as new promising azaheterocyclic amino acid derivatives, the structures of which incorporate the biologically interesting aziridine-2-carboxylate or azetidine-3-carboxylate moiety as well as the synthetically important 2-(halomethyl)aziridine or 3-haloazetidine structural feature. To the best of our knowledge, if trifluorinated derivatives are excluded, only one report has been published on the synthesis of related alkyl 2-(halomethyl)aziridine-2-carboxylates, that is, substituted dialkyl 2-(bromomethyl)aziridine-1,2-dicarboxylates obtained via addition of diazomethane across N-protected β-bromo α-imino acids.[7] 1,2,2,4-Tetrasubstituted 3-bromo- and 3-chloroazetidine-3-carboxylic esters have been prepared via reaction of azomethine ylides derived from aziridines with sulfur ylides,[8] and more interestingly, ring opening of *tert*-butyl 1-azabicyclo[1.1.0]butane-3-carboxylate, obtained from the unstable *tert*-butyl 1-chloroazetidine-3-carboxylate, with *p*-toluenesulfonyl chloride resulted in the synthesis of *tert*-butyl 3-chloro-1-(*p*-toluenesulfonyl)azetidine-3-carboxylate.[9] However, no further reactivity studies were performed on these aziridines or azetidines.

Allylamines are suitable substrates for the synthesis of 2-(bromomethyl)aziridines and/or 3-bromoazetidines via bromination to the corresponding β,γ-dibromo amines followed by intramolecular ring closure,[4a–c,10] or via electrophile-induced bromocyclization.[11] This ring closure usually has high selectivity toward the formation of aziridines instead of azetidines. N-Substituted alkyl 2-(aminomethyl)acrylates are useful functionalized allylamines, used as monomers for anionic polymerization,[12] in case of *N*-acyl-substituted derivatives for iodocyclization to the corresponding dihydro-1,3-oxazoles as intermediates in the synthesis of functionalized analogues of *N*-benzoyl-*syn*-phenylisoserine,[13] and for

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the synthesis of β-lactams.[14] It was envisaged that the hitherto unreported bromocyclization or bromination of N-substituted alkyl 2-(aminomethyl)acrylates could provide a convenient entry toward alkyl 2-(bromomethyl)aziridine-2-carboxylates **6** and alkyl 3-bromoazetidine-3-carboxylates **7**.

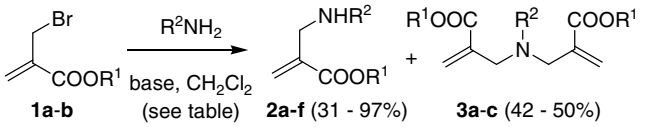
The synthesis of alkyl 2-(aminomethyl)acrylates **2a–f** via substitution reactions of alkyl 2-(bromomethyl)acrylates **1** with primary amines was performed under optimized conditions adapted from literature procedures (Table 1).[12,15] Addition of alkyl 2-(bromomethyl)acrylates **1** to 1.02 equiv of primary amine and 1.04 equiv of triethylamine in dichloromethane at 0 °C afforded ethyl and methyl 2-[(alkylamino)methyl]acrylates **2a–d**,**f** in good yields (Table 1, entries 1–4 and 6),[16] or diesters **3b–c** in moderate yields resulting from undesired *N*,*N*-diallylation of the less sterically demanding amines (Table 1, entries 7 and 8). The synthesis of ethyl 2-[(tosylamino)methyl]acrylate **2e**, in which an electron-withdrawing group is present on nitrogen, was achieved in moderate yield together with the formation of diallylation compound **3a**, through reaction of 2-(bromomethyl)acrylate **1a** with *p*-toluenesulfonamide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) (Table 1, entry 5).

Inspired by the aforementioned iodocyclization reaction,[13] ethyl 2-[(*tert*-butylamino)methyl]acrylate **2a** was treated with NBS in chloroform at room temperature, which, unfortunately, led to a complex reaction mixture. Alternatively, following a typical procedure for the bromination of allylamines,[17] the amino group of alkyl acrylates **2a–c** was protected by treatment with aqueous hydrobromic acid in dichloromethane to the corresponding hydrobromide salts which were subsequently reacted with bromine. Bromination at room temperature for 4–14 h efficiently afforded the desired hydrobromide salts **4a–c** in 84–98% yield (Table 2, entries 1–3).[18] These hydrobromide salts **4** could be spectroscopically characterized from the crude reaction mixtures, but they are hygroscopic, unstable, and bromine elimination was observed upon heating. In order to obtain more stable reaction products, the bromination was followed by neutralization of the reaction mixture with $NaHCO_3$ efficiently affording the desired dibromopropanoates **5a–d** (entries 4–7).[19] Bromination of ethyl 2-[(tosylamino)methyl]acrylate **2f** proceeded uneventfully using 1.1 equiv of bromine in dichloromethane and afforded ethyl dibromopropanoate **5e** in 57% yield (entry 8). With the targeted dibromo amino esters **4** and **5** in hand, their ring closure was studied under different basic conditions (Table 3).

Initial cyclizations were performed on the hydrobromide salts **4** with excess of base. Upon using rather apolar conditions (Et_3N, CH_2Cl_2) no cyclization of **4a** was observed and only the neutralized amine **5a** was isolated (entry 1). In a polar system (KOH, THF/H_2O), only neutralization to **5a** was achieved at room temperature (entry 2), while azetidine **7a** could be isolated in 32% yield when the reaction was done under reflux for 24 h (entry 3). The use of Hunig's base in acetonitrile under reflux resulted in cyclization of hydrobromide salts **4a** and **4b** allowing the isolation of azetidine **7a** after a reaction time of 4 h (entry 4), and neutralized amine **5b**, aziridine **6b** and azetidine **7b** in low yields after a shorter reaction time (entry 5). In view of the moderate results obtained with the hydrobromide salts **4**, further optimization of the reaction conditions was performed on the free dibromo amines **5**. The use of harsher reaction conditions (K_2CO_3, *i*PrOH, heat or *t*BuOK, THF, heat) resulted in decomposition of dibromo amine **5a** (entries 6 and 7), while a clean conversion of dibromo amines **5** was possible under milder conditions with K_2CO_3 in acetone or acetonitrile (entries 8–16). A complete conversion to the aziridines **6** as major products together with the azetidines **7** as minor compounds was achieved by extension of the reaction time and by the use of 1.5 equiv of K_2CO_3 in acetonitrile at 60 °C. However, the isolated yields of the aziridines **6** and azetidines **7** were low after purification by column chromatography on silica gel as, apparently, these azaheterocycles partly decompose on column. To our satisfaction, acceptable isolated yields of the targeted aziridines **6a–d** (36–54%) and azetidines **7a–d** (17–26%) were obtained via separation by preparative TLC up to 1 g scale (entries 12–15).[20] Interestingly, reaction of the dibromopropanoate **5e** with an electron-withdrawing substituent (R^2 = *p*-Tos) on nitrogen resulted in the very efficient and selective cyclization to aziridine **6e** (95% yield, entry 16).

An attempt was also made to perform the bromination and cyclization in a one-pot reaction. Bromination of ethyl 2-[(1-phenylethylamino)methyl]acrylate **2f** was executed using the aforementioned conditions after which dichloromethane was evaporated and replaced by acetonitrile. Upon adding 2.5 equiv of K_2CO_3, a selective cyclization of the intermediate hydrobromide salt **4f** to the aziridines **6f**, as an inseparable mixture of diastereomers, occurred without difficulties, resulting in an excellent overall isolated yield of 81% (Scheme 1). It is worth mentioning that from the dibromopropanoates **4f** and **5e** with a sterically demanding substituent (R^2 = PhMeCH) or an electron-withdrawing substituent (R^2 = *p*-Tos), only the corresponding aziridines **6** were formed in excellent yields (see Table 3, entry 16 and Scheme 1). This might be explained by the fact that aziridines **6** are the kinetic cyclization products, while azetidines **7** result from a thermodynamical equilibration. The isomerization of 2-(halomethyl)aziridines to 3-haloazetidines, although only observed in some cases, was explained

Table 1
Synthesis of alkyl 2-(aminomethyl)acrylates **2**

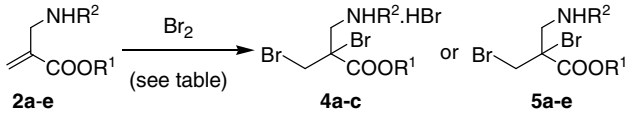


1a-b **2a-f** (31 - 97%) **3a-c** (42 - 50%)

Entry	R^1	R^2	Reaction time	Result (%)
1	Et	*t*-Bu	30 min	**2a** (97)[a]
2	Et	*t*-Amyl	30 min	**2b** (91)[a]
3	Me	*t*-Bu	30 min	**2c** (80)[a]
4	Me	*t*-Amyl	30 min	**2d** (91)[a]
5	Et	*p*-Tos	2 h	**2e** (31)[b] + **3a** (50)[b]
6	Et	PhMeCH	1 h	**2f** (76)[a]
7	Et	*n*-Bu	30 min	**3b** (42)[a]
8	Et	Bn	30 min	**3c** (46)[a]

[a] Reaction conditions: 1.02 equiv R^2NH_2, 1.04 equiv Et_3N, CH_2Cl_2, 0 °C.
[b] Reaction conditions: 1.2 equiv *p*-$TosNH_2$, 1.33 equiv DABCO, CH_2Cl_2, rt.

Table 2
Bromination of alkyl 2-(aminomethyl)acrylates **2**

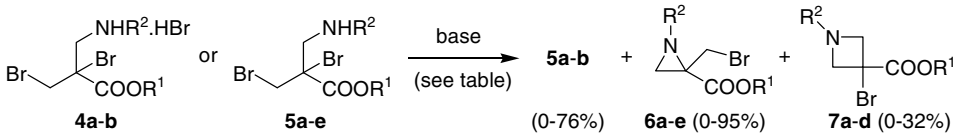


2a-e **4a-c** (84 - 98%) **5a-e** (57 - 98%)

Entry	R^1	R^2	Reaction time	Result (%)
1	Et	*t*-Bu	4 h	**4a** (98)[a]
2	Et	*t*-Amyl	14 h	**4b** (86)[a]
3	Me	*t*-Bu	4 h	**4c** (84)[a]
4	Et	*t*-Bu	14 h	**5a** (98)[b]
5	Et	*t*-Amyl	14 h	**5b** (97)[b]
6	Me	*t*-Bu	6 h	**5c** (78)[b]
7	Me	*t*-Amyl	5 h	**5d** (61)[b]
8	Et	*p*-Tos	4.5 h	**5e** (57)[c]

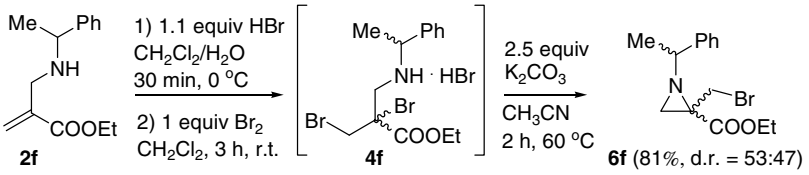
[a] Reaction conditions: (1) 1.1 equiv HBr, CH_2Cl_2/H_2O, 30 min, 0 °C; (2) 1 equiv Br_2, CH_2Cl_2, 4–14 h, rt.
[b] Reaction conditions: (1) 1.1 equiv HBr, CH_2Cl_2/H_2O, 30 min, 0 °C; (2) 1 equiv Br_2, CH_2Cl_2, 5–14 h, rt; (3) $NaHCO_3$, EtOAc.
[c] Reaction conditions: 1.1 equiv Br_2, CH_2Cl_2, 4.5 h, rt.

Table 3
Optimization of the ring closure reactions of alkyl 2-[(amino)methyl]-2,3-dibromopropanoates **4** and **5**



Entry	Substrate	R^1	R^2	Reaction conditions	Result (%)[a,b]
1	**4a**	Et	*t*-Bu	3 equiv Et_3N, CH_2Cl_2, Δ, 6 d	**5a** (76)
2	**4a**	Et	*t*-Bu	2 equiv KOH, THF/H_2O 1/1, r.t., 20 h	**5a** (not isolated)
3	**4a**	Et	*t*-Bu	2 equiv KOH, THF/H_2O 1/1, Δ, 24 h	**7a** (32)
4	**4a**	Et	*t*-Bu	2.5 equiv *i*Pr_2NEt, CH_3CN, Δ, 4 h	**6a** (not isolated)/**7a** (22) 1:1.3
5	**4b**	Et	*t*-Amyl	2.5 equiv *i*Pr_2NEt, CH_3CN, Δ, 45 min	**5b** (30)/**6b** (15)/**7b** (8)
6	**5a**	Et	*t*-Bu	1 equiv K_2CO_3, *i*-PrOH, 60 °C, 48 h	full decomposition of **5a**
7	**5a**	Et	*t*-Bu	1 equiv *t*-BuOK, THF, 40 °C, 4 h + 55 °C, 3 h	partial decomposition of **5a**
8	**5a**	Et	*t*-Bu	1 equiv K_2CO_3, acetone, Δ, 18 h	**5a**/**6a**/**7a** 1:4.3:2.5
9	**5a**	Et	*t*-Bu	1 equiv K_2CO_3, CH_3CN, 60 °C, 2 h	**5a**/**6a**/**7a** 1:4:2.1
10	**5a**	Et	*t*-Bu	1.5 equiv K_2CO_3, acetone, Δ, 39 h	**6a** (7)/**7a** (11)
11	**5a**	Et	*t*-Bu	1.5 equiv K_2CO_3, CH_3CN, 60 °C, 19 h	**6a** (19)/**7a** (13)
12	**5a**	Et	*t*-Bu	1.5 equiv K_2CO_3, CH_3CN, 60 °C, 19 h	**6a** (36)[c]/**7a** (26)[c]
13	**5b**	Et	*t*-Amyl	1.5 equiv K_2CO_3, CH_3CN, 60 °C, 12 h	**6b** (54)[c]/**7b** (24)[c]
14	**5c**	Me	*t*-Bu	1.5 equiv K_2CO_3, CH_3CN, 60 °C, 8 h	**6c** (41)[c]/**7c** (17)[c]
15	**5d**	Me	*t*-Amyl	1.5 equiv K_2CO_3, CH_3CN, 60 °C, 18 h	**6d** (54)[c]/**7d** (26)[c]
16	**5e**	Et	*p*-Tos	1.5 equiv K_2CO_3, CH_3CN, 60 °C, 1 h	**6e** (95)[c]

[a] Parentheses indicate isolated yields after purification by column chromatography.
[b] Ratio of reaction products determined via ^1H NMR ($CDCl_3$, 300 MHz) analysis of the crude reaction mixtures.
[c] Parentheses indicate isolated yields after purification by preparative TLC.

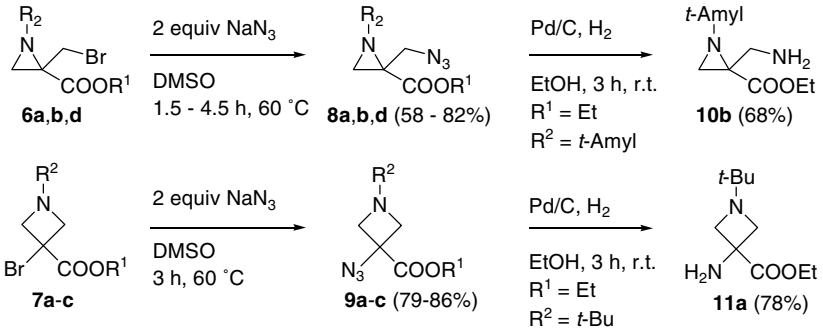


Scheme 1.

via ionization to the corresponding carbenium ion, followed by rapid isomerization to a bicyclic azonia[1.1.0]bicyclobutane intermediate and recombination with the initially expelled halide to give 3-haloazetidines or 2-(halomethyl)aziridines.[5a] In the assumption that a strained bicyclic ion is involved in the formation of alkyl 3-bromoazetidine-3-carboxylates **7**, a sterically demanding or electron-withdrawing group at nitrogen destabilizes this bicyclic ion and therefore stabilizes the initially formed alkyl 2-(bromomethyl)aziridine-2-carboxylates **6**. Experimental support for this slow isomerization process was obtained by heating ethyl 1-*t*-butyl-2-(bromomethyl)aziridine-2-carboxylate **6a** under different conditions. Heating aziridine **6a** in acetonitrile at 60 °C for 3 h gave no reaction, while prolonged heating in acetonitrile in the presence of 1 equiv of KBr at 60 °C resulted in decomposition to unidentified compounds after 24 h. Nevertheless, a rather clean isomerization of aziridine **6a** to azetidine **7a** was observed upon heating in DMSO, giving a mixture of **6a** and **7a** in a 2:1 ratio (^1H NMR analysis) after 24 h at 55 °C. The latter mixture further isomerized to **6a** and **7a** in a 1:2.8 ratio after additional heating at 65 °C for 6 h.

Introduction of new functional groups in aziridines **6** and azetidines **7** would highly enrich the chemistry of these important classes of α- and β-amino acid derivatives as the combination of a strained ring, functional group, and ester function in the same molecule could provide access to a broad variety of highly functionalized aziridines and azetidines with a wide range of potential biological and synthetic applications. Alkyl 2-(azidomethyl)aziridine-2-carboxylates **8a**,**b**,**d** and 3-azidoazetidine-3-carboxylates **9a**–**c** were prepared in good to excellent yield by reaction with 2 equiv of sodium azide in DMSO at 60 °C (Scheme 2).[6a,21] All attempts to prepare ethyl 2-(azidomethyl)-1-tosylaziridine-2-carboxylate under similar conditions (1.1–6 equiv NaN_3, DMSO, 3–72 h, 60 °C) as in the synthesis of aziridines **8a**,**b**,**d**, by reaction of *N*-tosylaziridine **6e** failed, leading to inseparable mixtures of azido compounds resulting from ring opening and substitution, similar as to the reported failure to synthesize 2-(azidomethyl)-1-tosylaziridine from 1-tosyl-2-(bromomethyl)aziridine.[4d] Using simple hydrogenolysis, ethyl 1-*tert*-pentyl-2-(azidomethyl)aziridine-2-carboxylate **8b** and 1-*tert*-butyl-3-azidoazetidine-3-carboxylate **9a** were converted into the corresponding ethyl 2-(aminomethyl)aziridine-2-carboxylate **10b** and 3-aminoazetidine-3-carboxylate **11a** upon stirring the reaction mixture in ethanol under hydrogen atmosphere for 3 h in the presence of Pd/C catalyst at room temperature.[22,23] The only reported alkyl 2-(aminomethyl)aziridine-2-carboxylate entails the *N*-phthalimidoaziridine formed via aziridination of methyl 2-[(*p*-tosylamino)(phenyl)methyl]acrylate with *N*-aminophthalimide.[24] N-substituted 3-aminoazetidine-3-carboxylic acid derivatives are important for the synthesis of series of active compounds used in SAR, as exemplified for EGF receptor tyrosine kinase inhibitors,[25] CB1 receptor antagonists,[26] and modulators of the NMDA receptor complex.[27] 3-Aminoazetidines have been frequently investigated also as antibacterial agents.[28]

In conclusion, several alkyl 2-(bromomethyl)aziridine-2-carboxylates and alkyl 3-bromoazetidine-3-carboxylates were synthesized via an unreported stepwise bromocyclization strategy on alkyl 2-(aminomethyl)acrylates. These novel strained azaheterocyclic α- and β-amino acid derivatives constitute promising amino acid building blocks as demonstrated by their conversion



Scheme 2.

into alkyl 2-(aminomethyl)aziridine-2-carboxylates and alkyl 3-aminoazetidine-3-carboxylates with potential biological activities.

Acknowledgments

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16. Methyl 2-[(*tert*-pentylamino)methyl]acrylate **2d**. Yellow oil, yield 91%, R_f = 0.50 (petroleum ether/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.43 Hz, CH_2CH_3), 1.07 (6H, s, $C(CH_3)_2$), 1.44 (2H, q, J = 7.43 Hz, CH_2CH_3), 3.35 (2H, s, CH_2NH), 3.77 (3H, s, OCH_3), 5.81 (1H, d × t, J = 1.65 Hz, 1.38 Hz, C=C*H*(H)), 6.23 (1H, d, J = 1.38 Hz, C=CH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.3, 26.7, 33.2, 43.2, 51.9, 52.8, 125.7, 139.9, 167.5. IR (neat, cm^{-1}): ν_{NH} = 3336 (weak), $\nu_{C=O}$ = 1718, $\nu_{C=C}$ = 1634. MS (ES, pos. mode): *m/z* (%): 186 (M+H$^+$, 100).
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18. Ethyl 2,3-dibromo-2-[(*tert*-butylamino)methyl]propanoate hydrobromide salt **4a**. Yield 98%, orange viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.15 Hz, CH_2CH_3), 1.67 (9H, s, $C(CH_3)_3$), 3.72–3.91 (2H, m, NCH_2), 4.30 (1H, d, J = 11.01 Hz, C*H*(H)Br), 4.52 (1H, d, J = 11.01 Hz, CH(*H*)Br), 4.35–4.45 (2H, m, OCH_2), 8.94 (2H, br s, NH·HBr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 26.4, 34.6, 47.1, 53.0, 61.9, 64.3, 167.6. IR (NaCl, cm^{-1}): ν_{NH} = 3408, $\nu_{C=O}$ = 1732. MS (ES, pos. mode): *m/z* (%): 344/346/348 (M−HBr+H$^+$, 75).
19. Ethyl 2-((*tert*-pentylamino)methyl)-2,3-dibromopropanoate **5b**. Colorless oil, yield 97%, R_f = 0.71 (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.4 Hz, CCH_2CH_3), 1.04 (3H, s, $CCH_3(CH_3)$), 1.05 (3H, s, $CCH_3(CH_3)$), 1.34 (3H, t, J = 7.15 Hz, OCH_2CH_3), 1.40 (2H, q, J = 7.3 Hz, CCH_2CH_3), 3.15 (1H, d, J = 13.76 Hz, NC*H*(H)), 3.20 (1H, d, J = 13.76 Hz, NCH(*H*)), 4.06 (1H, d, J = 9.63 Hz, CBr*H*(H)), 4.22 (1H, d, J = 9.63 Hz, CBrH(*H*)), 4.28 (1H, d × q, J = 7.15 Hz, 10.66 Hz, OC*H*(H)), 4.32 (1H, d × q, J = 7.15 Hz, 10.73 Hz, OCH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.2, 13.9, 26.8, 27.0, 33.6, 34.4, 45.9, 52.4, 62.4, 62.7, 168.2. IR (NaCl, cm^{-1}) ν_{NH} = 3327 (weak), $\nu_{C=O}$ = 1742. MS (ES, pos. mode): *m/z* (%): 358/360/362 (M+H$^+$, 100).
20. Synthesis of alkyl 2-(bromomethyl)aziridine-2-carboxylates **6** and alkyl 3-bromoazetidine-3-carboxylates **7**. As a representative example, the synthesis of methyl 1-*tert*-pentyl-2-(bromomethyl)aziridine-2-carboxylate **6d** and methyl 1-*tert*-pentyl-3-bromoazetidine-3-carboxylate **7d** is described here. To a solution of methyl 2-[(*tert*-pentylamino)methyl]-2,3-dibromopropanoate **5d** (618 mg, 1.79 mmol, 1 equiv) in CH_3CN (30 mL) was added powdered K_2CO_3 (371 mg, 2.69 mmol, 1.5 equiv) and the reaction mixture was stirred at 60 °C for 18 h. Then the solvent was removed under reduced pressure and Et_2O (30 mL) was added. The resulting solution was filtered and the filter cake was washed with small portions of Et_2O. Evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/Et_2O 7:3) afforded analytically pure samples. Methyl 1-*tert*-pentyl-2-(bromomethyl)aziridine-2-carboxylate **6d**. Light yellow oil, yield 54%, R_f = 0.48 (petroleum ether/Et_2O 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 7.60 Hz, CH_2CH_3), 0.94 (3H, s, CCH_3), 0.96 (3H, s, CCH_3), 1.36–1.58 (2H, m, CH_2CH_3), 1.85 (1H, s, NC*H*(H)), 2.59 (1H, s, NCH(*H*)), 3.05 (1H, d, J = 9.91 Hz, BrC*H*(H)), 3.77 (3H, s, OCH_3), 4.07 (1H, d, J = 10.18 Hz, BrCH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 24.1, 24.4, 33.9, 36.5, 36.9, 44.3, 52.7, 57.4, 170.4. IR (neat, cm^{-1}): $\nu_{C=O}$ = 1732. MS (ES, pos. mode): *m/z* (%): 264/266 (M+H$^+$, 100). Methyl 1-*tert*-pentyl-3-bromoazetidine-3-carboxylate **7d**. Yellow oil, yield 26%, R_f = 0.31 (petroleum ether/Et_2O 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (3H, t, J = 7.43 Hz, CH_2CH_3), 0.88 (6H, s, $C(CH_3)_2$), 1.24 (2H, q, J = 7.43 Hz, CH_2CH_3), 3.59–3.62 (2H, m, C*H*(H)NC*H*(H)), 3.83 (3H, s, OCH_3), 3.89–3.92 (2H, m, CH(*H*)NCH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6, 20.1, 31.6, 45.3, 53.4, 54.8, 59.5, 171.0. IR (neat, cm^{-1}): $\nu_{C=O}$ = 1742. MS (ES, pos. mode): *m/z* (%): 264/266 (M+H$^+$, 100).
21. Ethyl 1-*tert*-butyl-2-(azidomethyl)aziridine-2-carboxylate **8a**. Yellow oil, yield 58%, R_f = 0.47 (petroleum ether/EtOAc 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s, $C(CH_3)_3$), 1.33 (3H, t, J = 7.15 Hz, CH_2CH_3), 1.88 (1H, d, J = 1.65 Hz, NC*H*(H)), 2.47–2.48 (1H, m, NCH(*H*)), 3.26 (1H, d, J = 12.66 Hz, C*H*(H)N_3), 3.68 (1H, d, J = 12.66 Hz, CH(*H*)N_3), 4.19 (1H, d × q, J = 10.73 Hz, 7.15 Hz, OC*H*(H)CH_3), 4.26 (1H, d × q, J = 10.73 Hz, 7.15 Hz, OCH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 28.3, 32.0, 43.1, 54.6, 55.8, 61.8, 170.4. IR (neat, cm^{-1}): ν_{N3} = 2101, $\nu_{C=O}$ = 1734. MS (ES, pos. mode): *m/z* (%): 227 (M+H$^+$, 100). Anal. Calcd for $C_{10}H_{18}N_4O_2$: C, 53.08; H, 8.02; N, 24.76. Found: C, 52.77; H, 8.17; N, 24.45. Ethyl 1-*tert*-butyl-3-azidoazetidine-3-carboxylate **9a**. Yellow oil, yield 86%, R_f = 0.18 (petroleum ether/Et_2O 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, J = 7.15 Hz, CH_2CH_3), 3.32 (2H, d, J = 7.43 Hz, C*H*(H)NC*H*(H)), 3.70 (2H, d, J = 7.43 Hz, CH(*H*)NCH(*H*)), 4.29 (2H, q, J = 7.15 Hz,

OCH_2CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.2, 24.0, 52.2, 54.4, 59.3, 62.4, 170.0. IR (neat, cm^{-1}): ν_{N3} = 2109, $\nu_{C=O}$ = 1737. MS (ES, pos. mode): *m/z* (%): 227 (M+H$^+$, 100).

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23. Ethyl 1-*tert*-pentyl-2-(aminomethyl)aziridine-2-carboxylate **10b**. Yellow oil, yield 68%, R_f = 0.27 (CH$_2$Cl$_2$/MeOH 9:1). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.92 (3H, t, *J* = 7.60 Hz, CCH$_2$CH_3), 0.94 (3H, s, CCH_3), 0.98 (3H, s, CCH_3), 1.30 (3H, t, *J* = 7.15 Hz, OCH$_2$CH_3), 1.48 (1H, d × q, *J* = 13.62 Hz, 7.43 Hz, CC*H*(H)CH$_3$), 1.51 (1H, d × q, *J* = 13.35 Hz, 7.43 Hz, CCH(*H*)CH$_3$), 1.78 (1H, d, *J* = 1.10 Hz, C*H*(H)N), 1.86 (2H, br s, NH_2), 2.41 (1H, d, *J* = 1.38 Hz, CH(*H*)N), 2.87 (1H, d, *J* = 13.76 Hz, C*H*(H)NH$_2$), 2.89 (1H, d, *J* = 13.76 Hz, CH(*H*)NH$_2$), 4.16 (1H, d × q, *J* = 10.73 Hz, 7.15 Hz, OC*H*(H)CH$_3$), 4.22 (1H, d × q, *J* = 10.73 Hz, 7.15 Hz, OCH(*H*)CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 8.9, 14.1, 23.8, 24.5, 31.4, 36.7, 46.9, 56.5, 61.3, 172.1. IR (neat, cm^{-1}): ν_{NH_2} = 3381 (weak), $\nu_{C=O}$ = 1724. MS (ES, pos. mode): *m/z* (%): 215 (M+H$^+$, 100). Ethyl 1-*tert*-butyl-3-aminoazetidine-3-carboxylate **11a**. Yellow oil, yield 78%, R_f = 0.10 (petroleum ether/EtOAc 1:1). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.99 (9H, s, C(CH_3)$_3$), 1.31 (3H, t, *J* = 7.15 Hz, CH$_2$CH_3), 2.37 (2H, br s, NH_2), 3.10 (2H, d, *J* = 8.26 Hz, NC*H*(H)), 3.72 (2H, d, *J* = 8.26 Hz, NCH(*H*)), 4.22 (2H, q, *J* = 7.15 Hz, OCH_2CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.3, 24.0, 52.2, 53.1, 57.7, 61.5, 173.9. IR (neat, cm^{-1}): ν_{NH_2} = 3376 (weak), $\nu_{C=O}$ = 1730. MS (ES, pos. mode): *m/z* (%): 201 (M+H$^+$, 100).
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