Synthesis of new functionalized aziridine-2- and azetidine-3-carboxylic acid derivatives of potential interest for biological and foldameric applications

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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. The aziridines are the kinetically favored cyclization products and could be transformed into 3-bromoazetidine-3-carboxylic acid derivatives via thermal isomerization. The new small-membered azaheterocyclic *α*- and *β*-amino acid derivatives contain a bromo-substituted carbon center as a useful moiety for functionalization. Transformation of these functionalized azaheterocycles via nucleophilic substitution with carbon, sulfur, oxygen and nitrogen nucleophiles and via elaboration of the amino and carboxyl group provided a broad range of new conformationally constrained aziridine-2- and azetidine-3-carboxylic acid derivatives which are of interest from a biological point-of-view as well as for applications in the field of foldamers.

Keywords *Aziridine-2-carboxylic acids, Azetidine-3-carboxylic acids, β-Amino acids, α-Amino acids, Conformational constraint*

Introduction

Aziridine-2-carboxylic acid derivatives are biologically important constrained amino acid derivatives and versatile building blocks in the preparation of proteinogenic and non-proteinogenic amino acids and biologically active nitrogen-containing compounds (Cardillo et al. 2003, 2006; Lee and Ha 2003;

Lucarini and Tomasini 2001; Ide et al. 2005; Vicik et al. 2006). The latter is nicely exemplified by the ring opening of (2*R*)-*N*-(acetyl)aziridine-2-carboxylates **1** in the synthesis of lacosamide (**2**, Vimpat®; UCB), approved in 2008 for the adjunctive treatment of partial onset seizures in patients with epilepsy (Figure 1) (Morieux et al. 2008; Hughes 2009b). The different isomers of 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylate **3** (AziDAP) are irreversible inhibitors and substrate mimics of diaminopimelate (DAP) epimerase, a key enzyme for the biosynthesis of lysine in plants (Pillai et al. 2006, 2009). In view of the analogy with constrained $\beta^{2,2}$-amino acids such as β^2-HAib **5**, 3_{14}-helix- and sheet-breaking in β-peptides (Seebach and Gardiner 2008; Cheng et al. 2001), and 1-(aminomethyl)cyclopropanecarboxylic acid **6**, which forms β-oligopeptides with a ribbon- or stair-like structure (Abele et al. 1999), the unknown 2-(aminomethyl)aziridine-2-carboxylic acids **4** are of significant interest as potential foldameric building blocks. Alternatively, derivatives of azetidine-3-carboxylic acid disclose gametocidal activity (Zhang et al. 2004; Verbrugge and De Waal 1989; Orr and Clifford 1984; Devlin 1981), have found application as *β*-proline analogues (Mazzini et al. 1997), and have been used for the preparation of a variety of pharmaceutically active compounds (Miller et al. 2003). More specifically, a 3-aminoazetidine-3-carboxylic acid derivative has been incorporated in CE-178,253 (**7**, Pfizer), a CB_1 antagonist for the treatment of obesity (Brandt et al. 2009). Furthermore, 3-aminoazetidine-3-carboxylic acid derivatives **8** also represent interesting conformationally constrained functionalized C^{α}-tetrasubstituted α-amino acids, which have not been studied in the foldameric field. Related C^{α}-tetrasubstituted α-amino acids such as Aib (**9**) and 1-aminocyclobutane-1-carboxylic acid (**10**, Ac_4c) are known to form short peptides with a conformational preference for β-turns and 3_{10}-helices (Toniolo et al. 2006; Maity and König 2008; Soloshonok and Sorochinsky 2010).

In view of the importance of the aforementioned classes of amino acids, the development of pathways to new three- and four-membered azaheterocyclic α- and β-amino acid derivatives is a challenging research field in modern synthetic chemistry at the biological interface (Hughes 2009a; Kiss and Fülöp 2010; Fülöp et al. 2006; Kuhl et al. 2005; Miller and Nguyen 2005; Cativiela and Ordóñez 2009; Komarov et al. 2004; Cowell et al. 2004; Gelmi and Pocar 2003; Park and Kurth 2002).

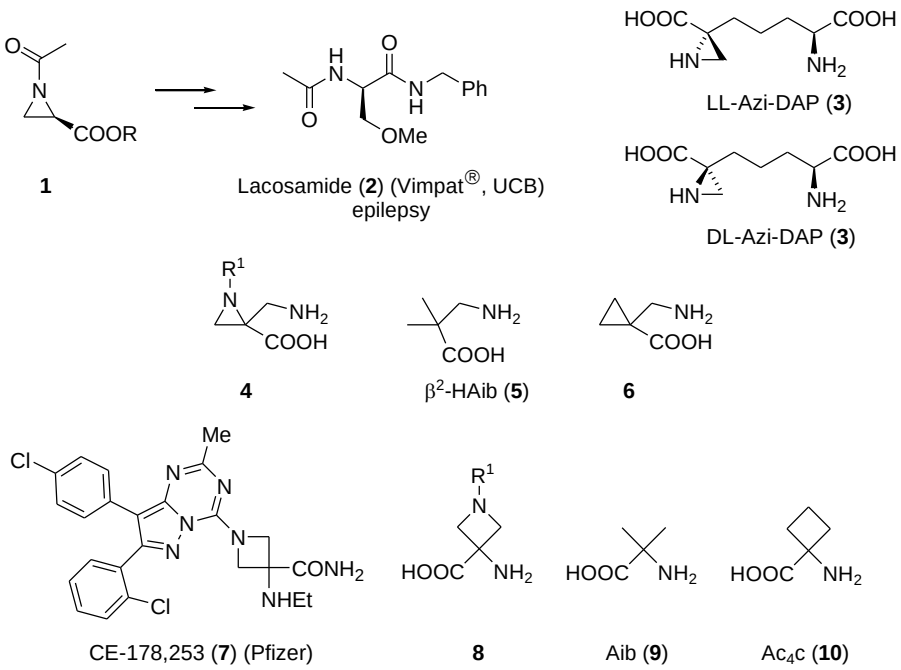


Fig. 1 Several aziridine-2- and azetidine-3-carboxylic acid derivatives and related compounds with biological or foldameric applications

Following a preliminary communication (Mangelinckx et al. 2008), in the present paper, in-depth results are described on the synthesis and study of the reactivity of 2-(bromomethyl)aziridine-2-carboxylic esters and 3-bromoazetidine-3-carboxylic esters, the structures of which incorporate the synthetically important 2-(halomethyl)aziridine (Abbaspour Tehrani et al. 2002; De Smaele et al. 1998; De Kimpe et al. 1997; D'hooghe et al. 2006a; Mangelinckx et al. 2009; Vervisch et al. 2010), or 3-haloazetidine structural motif (Van Driessche et al. 2006; Van Brabandt et al. 2009). The bromo-substituted carbon atom can be advantageously used as a moiety for functionalization. Allylamines have proven to be suitable substrates for the synthesis of 2-(bromomethyl)aziridines and/or 3-bromoazetidines via bromination of the C-C double bond to the corresponding *β*,*γ*-dibromo amines followed by intramolecular ring closure (Abbaspour Tehrani et al. 2002; De Smaele et al. 1998; De Kimpe et al. 1997; Hayashi et al. 2004; Gensler 1948), or via electrophile-induced bromocyclization (Robin and Rousseau 2000, 2002). This ring closure usually has high selectivity towards the formation of aziridines instead of azetidines.

Material and methods

Reagents and solvents were purchased from commercial suppliers and used without further purification, unless indicated otherwise. Dichloromethane was distilled from calcium hydride before use. The purification of reaction mixtures was performed through flash chromatography using a glass column with silica gel (0.035-0.070 nm, pore diameter ca. 6 nm) or by preparative thin layer chromatography on silica gel (silica gel GF preparative layer with UV 254, 2 mm). Solvent systems were evaluated via TLC analysis (silica gel 2 – 25 μm, thickness 0.25 mm, medium pore diameter 60 Å with UV 254). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded on a JEOL ECLIPSE FT 300 NMR spectrometer at room temperature. The compounds were dissolved in deuterated solvents as indicated for each compound. Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer in neat form with an ATR (Attenuated Total Reflectance) accessory. Alternatively, IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. Mass spectra were recorded on an Agilent 1100 series mass spectrometer using either a direct inlet system (electron spray, 4000V) or LC-MS coupling (UV detector).

Synthesis of alkyl 2-[(alkylamino)methyl]acrylates **12a-d**

As a representative example, the synthesis of methyl 2-[(*tert*-pentylamino)methyl]acrylate (**12d**) is described here. To a solution of *tert*-pentylamine (175 mg, 2 mmol) and triethylamine (210 mg, 2.08 mmol) in CH_2Cl_2 (10 mL), a solution of methyl 2-(bromomethyl)acrylate (**11b**) (358 mg, 2 mmol) in CH_2Cl_2 (5 mL) was added dropwise while stirring at 0 °C. After the reaction was stirred for 30 min at 0 °C, water (20 mL) was added to the reaction mixture, which was extracted with CH_2Cl_2 (3 × 20 mL). Drying ($MgSO_4$), filtration and evaporation of the solvent under reduced pressure afforded methyl 2-[(*tert*-pentylamino)methyl]acrylate (**12d**) in 98% yield which was used without further purification.

*Ethyl 2-[(tert-butylamino)methyl]acrylate (**12a**)*

Yellow oil, yield 97%, R_f = 0.50 (petroleum ether/EtOAc 7/3). The ^{1}H NMR data were in good agreement with reported data (Habaue et al. 1997). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (9H, s, $C(CH_3)_3$), 1.31 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.40 (2H, s, NCH_2), 4.22 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.78 (1H, dt, J = 1.3 Hz, 1.5 Hz, C=C*H*(H)), 6.23 (1H, s, C=CH(*H*)). Anal. Calcd for $C_{10}H_{19}NO_2$ (%): C, 64.83; H, 10.34; N, 7.56. Found (%): C, 64.58; H, 10.56; N, 7.41.

*Ethyl 2-[(tert-pentylamino)methyl]acrylate (**12b**)*

Colorless oil, yield 91%, R_f = 0.51 (petroleum ether/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.4 Hz, CCH_2CH_3), 1.06 (6H, s, $C(CH_3)_2$), 1.31 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.44 (2H, q, J = 7.4 Hz, CCH_2CH_3), 3.34 (2H, s, NCH_2), 4.22 (2H, q, J = 7.2 Hz, OCH_2CH_3), 5.79 (1H, dt, J =1.4 Hz, 1.4 Hz, C=C*H*(H)), 6.23 (1H, d, J = 0.8 Hz, C=CH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.2, 14.2, 26.6, 33.1, 43.2, 52.7, 60.6, 125.4, 140.0, 166.9. IR (NaCl, cm^{-1}) υ_{NH} = 3328, $\upsilon_{C=O}$ = 1717, $\upsilon_{C=C}$ = 1635. MS (ES, pos. mode): *m/z* (%): 200 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{21}NO_2$ (%): C, 66.29; H, 10.62; N, 7.03. Found (%): C, 66.12; H, 10.37; N, 7.22.

*Methyl 2-[(tert-butylamino)methyl]acrylate (**12c**)*

Colorless oil, yield 94%, R_f = 0.48 (petroleum ether/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (9H, s, $C(CH_3)_3$), 3.41 (2H, br s, NCH_2), 3.77 (3H, s, $COOCH_3$), 5.80 (1H, dt, J = 1.5 Hz, 1.7 Hz, C=C*H*(H)), 6.23 (1H, d, J = 1.1 Hz, C=CH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.1, 43.8, 50.6, 51.8, 125.5, 139.9, 167.4. IR (NaCl, cm^{-1}): υ_{NH} = 3327, $\upsilon_{C=O}$ = 1719, $\upsilon_{C=C}$ = 1635. MS (ES, pos. mode): *m/z* (%): 172 ($M+H^+$, 100). Anal. Calcd for $C_9H_{17}NO_2$ (%): C, 63.13; H, 10.01; N, 8.18. Found (%): C, 63.35; H, 10.34; N, 7.96.

*Methyl 2-[(tert-pentylamino)methyl]acrylate (**12d**)*

Yellow oil, yield 98%, R_f = 0.50 (petroleum ether/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.07 (6H, s, $C(CH_3)_2$), 1.44 (2H, q, J = 7.4 Hz, CH_2CH_3), 3.35 (2H, s, CH_2NH), 3.77 (3H, s, OCH_3), 5.81 (1H, dt, J = 1.7 Hz, 1.4 Hz, C=CH(H)), 6.23 (1H, d, J = 1.4 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}): υ_{NH} = 3336 (weak), $\upsilon_{C=O}$ = 1718, $\upsilon_{C=C}$ = 1634. MS (ES, pos. mode): *m/z* (%): 186 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{19}NO_2$ (%): C, 64.83; H, 10.34; N, 7.56. Found (%): C, 64.60; H, 10.41; N, 7.34.

Bromination of alkyl 2-[(alkylamino)methyl]acrylates **12a-d**

As a representative example, the synthesis of methyl 2-[(*tert*-pentylamino)methyl]-2,3-dibromopropanoate (**13d**) is described here. To a solution of methyl 2-[(*tert*-pentylamino)methyl]acrylate (**12d**) (330 mg, 1.78 mmol) in CH_2Cl_2 (30 mL), a 48% aqueous solution of hydrobromic acid (332 mg, 1.96 mmol) was added dropwise at 0 °C and the reaction mixture was stirred for 30 min. Then, a solution of Br_2 (285 mg, 1.78 mmol) in CH_2Cl_2 (15 mL) was added dropwise and the reaction mixture was left stirring upon warming to room temperature for 5 h. Subsequently, the resulting reaction mixture was neutralised by pouring into saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 20 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by flash chromatography on silica gel (petroleum ether/EtOAc 9/1) afforded dibromo ester **13d** in 97% yield.

*Ethyl 2-[(tert-butylamino)methyl]-2,3-dibromopropanoate (**13a**)*

Colorless oil, yield 98%, R_f = 0.50 petroleum ether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.24 (1H, d, J = 13.8 Hz, NCH(H)), 3.30 (1H, d, J = 13.8 Hz, NCH(H)), 4.08 (1H, d, J = 9.9 Hz, CH(H)Br), 4.23 (1H, d, J = 9.9 Hz, CH(H)Br), 4.22-4.39 (2H, m, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 28.5, 34.6, 46.6, 54.0, 59.8, 63.0, 168.0. IR (NaCl, cm^{-1}): υ_{NH} = 3327, $\upsilon_{C=O}$ = 1739. MS (ES, pos. mode): *m/z* (%): 344/346/348 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{19}Br_2NO_2$ (%): C, 34.81; H, 5.55; N, 4.06. Found (%): C, 34.48; H, 5.32; N, 3.84.

*Ethyl 2-[(tert-pentylamino)methyl]-2,3-dibromopropanoate (**13b**)*

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 = 7.2 Hz, OCH_2CH_3), 1.40 (2H, q, J = 7.3 Hz, CCH_2CH_3), 3.15 (1H, d, J = 13.8 Hz, NCH(*H*)), 3.20 (1H, d, J = 13.8 Hz, NC*H*(H)), 4.06 (1H, d, J = 9.6 Hz, CBrH(*H*)), 4.22 (1H, d, J = 9.6 Hz, CBr*H*(H)), 4.28 (1H, dq, J = 7.2 Hz, 10.7 Hz, OCH(*H*)), 4.32 (1H, dq, J = 7.2 Hz, 10.7 Hz, OC*H*(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}): υ_{NH} = 3327 (weak), $\upsilon_{C=O}$ = 1742. MS (ES, pos. mode): m/z (%): 358/360/362 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{21}Br_2NO_2$ (%): C, 36.79; H, 5.89; N, 3.90. Found (%): C, 36.62; H, 6.12; N, 3.81.

*Methyl 2-[(tert-butylamino)methyl]-2,3-dibromopropanoate (**13c**)*

Yellow oil, yield 90%, R_f = 0.53 (petroleum ether/EtOAc 9/1). Spectroscopically characterized as the hydrobromide before neutralization. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.37 (9H, s, $C(CH_3)_3$), 3.69 (2H, br s, NCH_2), 3.84 (3H, s, OCH_3), 4.27 (1H, d, J = 11.0 Hz, BrC*H*(H)), 4.41 (1H, d, J = 10.7 Hz, BrCH(*H*)), 8.58 and 8.65 (2H, 2×br s, NH·HBr). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.8, 35.3, 46.2, 54.1, 55.6, 59.0, 166.7. IR (NaCl, cm^{-1}): υ_{NH} = 3445, $\upsilon_{C=O}$ = 1740. MS (ES, pos. mode): *m/z* (%): 330/332/334 ($M-HBr+H^+$, 100). Anal. Calcd for $C_9H_{17}Br_2NO_2$ (%): C, 32.65; H, 5.18; N, 4.23. Found (%): C, 32.29; H, 5.36; N, 4.07.

*Methyl 2-[(tert-pentylamino)methyl]-2,3-dibromopropanoate (**13d**)*

Yellow oil, yield 97%, R_f = 0.50 (petroleum ether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.04 (3H, s, CH_3CCH_3), 1.05 (3H, s, CH_3CCH_3), 1.40 (2H, q, J = 7.4 Hz, CH_2CH_3), 1.56 (1H, br s, NH), 3.16 (1H, d, J = 13.5 Hz, NHC*H*(H)), 3.20 (1H, d, J = 13.8 Hz, NHCH(*H*)), 3.84 (3H, s, OCH_3), 4.06 (1H, d, J = 9.6 Hz, C*H*(H)Br), 4.22 (1H, d, J = 9.6 Hz, CH(*H*)Br).

^{13}C NMR (75 MHz, $CDCl_3$): δ 8.4, 26.9, 27.0, 33.7, 34.5, 46.1, 52.5, 53.4, 62.6, 168.9. MS (ES, pos. mode): *m/z* (%): 344/346/348 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{19}Br_2NO_2$ (%): C, 34.81; H, 5.55; N, 4.06. Found (%): C, 34.69; H, 5.75; N, 3.80.

Synthesis of alkyl 2-(bromomethyl)aziridine-2-carboxylates **14a-d** and alkyl 3-bromoazetidine-3-carboxylates **15a-d**

As a representative example, the synthesis of methyl 1-*tert*-pentyl-2-(bromomethyl)aziridine-2-carboxylate (**14d**) and methyl 1-*tert*-pentyl-3-bromoazetidine-3-carboxylate (**15d**) is described here. To a solution of methyl 2-[(*tert*-pentylamino)methyl]-2,3-dibromopropanoate (**13d**) (618 mg, 1.79 mmol) in CH_3CN (30 mL) was added powdered K_2CO_3 (371 mg, 2.69 mmol) 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 aziridine **14d** in 54% yield and azetidine **15d** in 26% yield.

*Ethyl 1-tert-butyl-2-(bromomethyl)aziridine-2-carboxylate (**14a**)*

Light yellow oil, yield 50%, R_f = 0.48 (petroleum ether/Et_2O 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s, $(CH_3)_3$), 1.33 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.83 (1H, d, J = 1.1 Hz, NC*H*(H)), 2.55 (1H, dd, J = 1.1 Hz, 1.1 Hz, NCH(*H*)), 3.03 (1H, d, J = 9.9 Hz, BrC*H*(H)), 4.05 (1H, dd, J = 9.9 Hz, 1.1 Hz, BrCH(*H*)), 4.21 (1H, dq, J = 10.7 Hz, 7.2 Hz, C*H*(H)CH_3), 4.26 (1H, dq, J = 11.0 Hz, 7.15 Hz, CH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 28.2, 33.6, 37.0, 45.2, 55.1, 61.8, 169.6. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1732. MS (ES, pos. mode): *m/z* (%): 264/266 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{18}BrNO_2$ (%): C, 45.47; H, 6.87; N, 5.30. Found (%): C, 45.41; H, 6.98; N, 5.19.

*Ethyl 1-tert-butyl-3-bromoazetidine-3-carboxylate (**15a**)*

Yellow oil, yield 33%, R_f = 0.20 (petroleum ether/Et_2O 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (9H, s, $C(CH_3)_3$), 1.32 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.62 (2H, d, J = 9.9 Hz, C*H*(H)NC*H*(H)), 3.93 (2H, d, J = 9.9 Hz, CH(*H*)NCH(*H*)), 4.28 (2H, q, J = 7.2 Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 24.1, 45.2, 52.4, 59.6, 62.4, 170.4. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1739. MS (ES, pos. mode): *m/z* (%): 264/266 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{18}BrNO_2$ (%): C, 45.47; H, 6.87; N, 5.30. Found (%): C, 45.38; H, 7.06; N, 5.41.

*Ethyl 1-tert-pentyl-2-(bromomethyl)aziridine-2-carboxylate (**14b**)*

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 = 7.4 Hz, CCH_2CH_3), 0.95 (3H, s, $CCH_3(CH_3)$), 0.97 (3H, s, $CCH_3(CH_3)$), 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.45 (1H, qd, J = 7.3 Hz, 13.5 Hz, CC*H*(H)CH_3), 1.49 (1H, qd, J = 7.6 Hz, 13.6 Hz, CH(*H*)CH_3), 1.84 (1H, d, J = 1.1 Hz, NC*H*(H)), 2.59 (1H, dd, J = 1.2 Hz, 1.2 Hz, NCH(*H*)), 3.03 (1H, d, J = 9.9 Hz, BrC*H*(H)), 4.07 (1H, dd, J = 1.2 Hz, 10.0 Hz, BrCH(*H*)), 4.21 (1H, dq, J = 7.0 Hz, 10.7 Hz, OC*H*(H)), 4.26 (1H, dq, J = 7.1 Hz, 10.6 Hz, OCH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 14.0, 24.0, 24.4, 33.7, 36.4, 37.0, 44.4, 57.4, 61.6, 169.7. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1736. MS (ES, pos. mode): *m/z* (%): 278/280 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{20}BrNO_2$ (%): C, 47.49; H, 7.25; N, 5.04. Found (%): C, 47.24; H, 7.41; N, 4.82.

*Ethyl 1-tert-pentyl-3-bromoazetidine-3-carboxylate (**15b**)*

Yellow oil, yield 24%, R_f = 0.48 (petroleum ether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (3H, t, J = 7.6 Hz, CCH_2CH_3), 0.88 (6H, s, $C(CH_3)_2$), 1.24 (2H, q, J = 7.4 Hz, CCH_2CH_3), 1.32 (3H, t, J = 7.0 Hz, OCH_2CH_3), 3.60 (2H, d, J = 9.6 Hz, C*H*(H)NC*H*(H)), 3.90 (2H, d, J = 9.6 Hz, CH(*H*)NCH(*H*)), 4.28 (2H, q, J = 7.1 Hz, OCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.5, 13.9, 20.1, 31.5, 45.5, 54.7, 59.3, 62.2, 170.4. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1739. MS (ES, pos. mode): *m/z* (%): 278/280 ($M+H^+$, 90). Anal. Calcd for $C_{11}H_{20}BrNO_2$ (%): C, 47.49; H, 7.25; N, 5.04. Found (%): C, 47.41; H, 7.36; N, 4.84.

*Methyl 1-tert-butyl-2-(bromomethyl)aziridine-2-carboxylate (**14c**)*

Light yellow oil, yield 44%, R_f = 0.45 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, $(CH_3)_3$), 1.84 (1H, d, J = 1.1 Hz, NC*H*(H)), 2.55 (1H, dd, J = 1.1 Hz, 1.0 Hz, NCH(*H*)), 3.06 (1H, d, J = 9.9 Hz, BrC*H*(H)), 3.78 (3H, s, OCH_3), 4.05 (1H, dd, J = 10.2 Hz, 1.1 Hz, BrCH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 33.6, 36.7, 45.0, 52.7, 55.1, 170.2. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1732. MS (ES, pos. mode): *m/z* (%): 250/252 ($M+H^+$, 100). Anal. Calcd for $C_9H_{16}BrNO_2$ (%): C, 43.22; H, 6.45; N, 5.60. Found (%): C, 43.06; H, 6.69; N, 5.34.

*Methyl 1-tert-butyl-3-bromoazetidine-3-carboxylate (**15c**)*

Yellow oil, yield 25%, R_f = 0.16 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (9H, s, $C(CH_3)_3$), 3.60-3.64 (2H, m, C*H*(H)NC*H*(H)), 3.83 (3H, s, OCH_3), 3.91-3.95 (2H, m, CH(*H*)NCH(*H*)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 44.9, 52.4, 53.5, 59.7, 170.9. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1736. MS (ES, pos. mode): *m/z* (%): 250/252 ($M+H^+$, 100). Anal. Calcd for $C_9H_{16}BrNO_2$ (%): C, 43.22; H, 6.45; N, 5.60. Found (%): C, 42.83; H, 6.61; N, 5.41.

*Methyl 1-tert-pentyl-2-(bromomethyl)aziridine-2-carboxylate (**14d**)*

Light yellow oil, yield 54%, R_f = 0.48 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 7.6 Hz, CH_2CH_3), 0.94 (3H, s, CH_3CCH_3), 0.96 (3H, s, CH_3CCH_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 = 9.9 Hz, BrC*H*(H)), 3.77 (3H, s, OCH_3), 4.07 (1H, d, J = 10.2 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}): $\upsilon_{C=O}$ = 1732. MS (ES, pos. mode): *m/z* (%): 264/266 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{18}BrNO_2$ (%): C, 45.47; H, 6.87; N, 5.30. Found (%): C, 45.38; H, 6.98; N, 5.02.

*Methyl 1-tert-pentyl-3-bromoazetidine-3-carboxylate (**15d**)*

Yellow oil, yield 26%, R_f = 0.31 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (3H, t, J = 7.4 Hz, CH_2CH_3), 0.88 (6H, s, $C(CH_3)_2$), 1.24 (2H, q, J

= 7.4 Hz, C*H*$_2$CH$_3$), 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}): $\upsilon_{C=O}$ = 1742. MS (ES, pos. mode): *m/z* (%): 264/266 (M+H$^+$, 100). Anal. Calcd for $C_{10}H_{18}BrNO_2$ (%): C, 45.47; H, 6.87; N, 5.30. Found (%): C, 45.12; H, 7.08; N, 5.42.

Isomerisation of alkyl 2-(bromomethyl)aziridines **14a-d** to alkyl 3-bromoazetidines **15a-d**

As a representative example, the synthesis of methyl 1-*tert*-pentyl-3-bromoazetidine-3-carboxylate (**15d**) is described here. Methyl 1-*tert*-pentyl-2-(bromomethyl)aziridine-2-carboxylate (**14d**) (100 mg, 0.38 mmol) was dissolved in DMSO (2 mL) and heated at 70 °C for 5 h. After cooling, the reaction mixture was poured into water (2 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (hexane/EtOAc 9/1) afforded azetidine **15d** in 50% yield.

Synthesis of alkyl 2-(cyanomethyl)aziridine-2-carboxylates **16a-c**

As a representative example, the synthesis of methyl 1-*tert*-butyl-2-(cyanomethyl)aziridine-2-carboxylate (**16c**) is described here. A solution of methyl 1-*tert*-butyl-2-(bromomethyl)aziridine-2-carboxylate (**14c**) (118 mg, 0.47 mmol) and potassium cyanide (31 mg, 0.47 mmol) in DMSO (2 mL) was heated at 60 °C for 4 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/EtOAc 8/2) afforded 2-(cyanomethyl)aziridine **16c** in 57% yield.

*Ethyl 1-tert-butyl-2-(cyanomethyl)aziridine-2-carboxylate (**16a**)*

Pink oil, yield 47%, R_f = 0.26 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.95 (1H, d, J = 1.4 Hz, NC*H*(H)), 2.60 (1H, d, J = 1.1 Hz, NCH(*H*)), 2.65 (1H, d, J = 17.1 Hz, C*H*(H)CN), 2.81 (1H, d, J = 16.8 Hz, CH(*H*)CN), 4.21 (1H, dq, J = 11.0 Hz, 7.2 Hz, C*H*(H)CH_3), 4.87 (1H, dq, J = 10.9 Hz, 7.2 Hz, CH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 25.4, 28.4, 33.6, 39.9, 54.9, 62.2, 117.3, 169.7. IR (neat, cm^{-1}): υ_{CN} = 2253 (weak), $\upsilon_{C=O}$ = 1733. MS (ES, pos. mode): *m/z* (%): 211 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{18}N_2O_2$ (%): C, 62.83; H, 8.63; N, 13.32. Found (%): C, 62.95; H, 8.78; N, 13.17.

*Ethyl 1-tert-pentyl-2-(cyanomethyl)aziridine-2-carboxylate (**16b**)*

Pink oil, yield 54%, R_f = 0.29 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.4 Hz, CCH_2CH_3)), 1.00 (3H, s, CCH_3), 1.01 (3H, s, CCH_3), 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.39-1.56 (2H, m, CCH_2CH_3)), 1.97 (1H, d, J = 1.7 Hz, NC*H*(H)), 2.63 (1H, d, J = 1.4 Hz, NCH(*H*)), 2.66 (1H, d, J = 16.8 Hz, C*H*(H)CN), 2.84 (1H, d, J = 16.8 Hz, CH(*H*)CN), 4.21 (1H, dq, J = 10.7 Hz, 7.2 Hz, OC*H*(H)CH_3), 4.26 (1H, dq, J = 10.7 Hz, 7.2 Hz, OCH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 14.0, 23.9, 24.6, 25.3, 33.8, 37.0, 39.2, 57.2, 62.2, 117.3, 169.9. IR (neat, cm^{-1}): υ_{CN} = 2253 (weak), $\upsilon_{C=O}$ = 1734. MS (ES, pos. mode): *m/z* (%): 225 ($M+H^+$, 100). Anal. Calcd for $C_{12}H_{20}N_2O_2$ (%): C, 64.26; H, 8.99; N, 12.49. Found (%): C, 64.01; H, 8.84; N, 12.61.

*Methyl 1-tert-butyl-2-(cyanomethyl)aziridine-2-carboxylate (**16c**)*

Yellow oil, yield 57%, R_f = 0.24 (petroleum ether/EtOAc 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (9H, s, $(CH_3)_3$), 1.96 (1H, d, J = 1.4 Hz, NC*H*(H)), 2.60 (1H, d, J = 1.4 Hz, NCH(*H*)), 2.67 (1H, d, J = 16.8 Hz, C*H*(H)CN), 2.81 (1H, d, J = 17.1 Hz, CH(*H*)CN), 3.79 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 28.4, 33.7, 39.7, 53.0, 54.8, 117.2, 170.2. IR (neat, cm^{-1}): υ_{CN} = 2253 (weak), $\upsilon_{C=O}$ = 1728. MS (ES, pos. mode): *m/z* (%): 197 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{16}N_2O_2$ (%): C, 61.20; H, 8.22; N, 14.27. Found (%): C, 61.14; H, 8.43; N, 14.25.

Synthesis of alkyl 2-(thiocyanomethyl)aziridine-2-carboxylates **17a-b**

As a representative example, the synthesis of ethyl 1-*tert*-butyl-2-(thiocyanomethyl)aziridine-2-carboxylate (**17a**) is described here. A solution of ethyl 1-*tert*-butyl-2-(bromomethyl)aziridine-2-carboxylate (**14a**) (132 mg, 0.5 mmol) and potassium thiocyanate (97 mg, 1 mmol) in DMF (2 mL) was heated at 70 °C for 2 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/Et_2O 7/3) afforded 2-(thiocyanomethyl)aziridine **17a** in 48% yield.

*Ethyl 1-tert-butyl-2-(thiocyanomethyl)aziridine-2-carboxylate (**17a**)*

Yellow oil, yield 48%, R_f = 0.31 (petroleum ether/Et_2O 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s, $(CH_3)_3$), 1.33 (3H, t, J = 7.2 Hz, CH_2CH_3), 2.05 (1H, d, J = 1.2 Hz, NCH(*H*)), 2.64 (1H, s, NC*H*(H)), 3.28 (1H, d, J = 12.9 Hz, C*H*(H)SCN), 3.39 (1H, d, J = 12.9 Hz, CH(*H*)SCN), 4.20 (1H, dq, J = 11.0 Hz, 7.2 Hz, C*H*(H)CH_3), 4.28 (1H, dq, J = 10.7 Hz, 7.2 Hz, CH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 28.3, 33.4, 40.2, 42.7, 54.9, 62.2, 113.1, 169.7. IR (neat, cm^{-1}): υ_{SCN} = 2154, $\upsilon_{C=O}$ = 1735. MS (ES, pos. mode): *m/z* (%): 243 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{18}N_2O_2S$ (%): C, 54.52; H, 7.49; N, 11.56. Found (%): C, 54.69; H, 7.61; N, 11.37.

*Ethyl 1-tert-pentyl-2-(thiocyanomethyl)aziridine-2-carboxylate (**17b**)*

Yellow oil, yield 44%, R_f = 0.30 (petroleum ether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.7 Hz, CCH_2CH_3), 0.98 (3H, s, CCH_3), 1.01 (3H, s, CCH_3), 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.37-1.58 (2H, m, CCH_2CH_3), 2.07 (1H, s, NCH(*H*)), 2.66 (1H, s, NCH(*H*)), 3.32 (1H, d, J = 12.9 Hz, C*H*(H)SCN), 3.43 (1H, d, J = 13.2 Hz, CH(*H*)SCN), 4.19 (1H, dq, J = 10.7 Hz, 7.2 Hz, OC*H*(H)CH_3), 4.27 (1H, dq, J = 11.0 Hz, 7.2 Hz, OCH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 14.0, 23.9, 24.7, 33.4, 36.8, 40.3, 42.0, 57.3, 62.2, 113.1,

169.9. IR (neat, cm^{-1}): υ_{SCN} = 2155, $\upsilon_{C=O}$ = 1735. MS (ES, pos. mode): *m/z* (%): 257 ($M+H^+$, 100). Anal. Calcd for $C_{12}H_{20}N_2O_2S$ (%): C, 56.22; H, 7.86; N, 10.93. Found (%): C, 55.98; H, 8.02; N, 10.68.

Synthesis of alkyl 2-(azidomethyl)aziridine-2-carboxylates **18a-d**

As a representative example, the synthesis of methyl 1-*tert*-butyl-2-(azidomethyl)aziridine-2-carboxylate (**18c**) is described here. Methyl 1-*tert*-butyl-2-(bromomethyl)aziridine-2-carboxylate (**14c**) (250 mg, 1 mmol) and sodium azide (130 mg, 2 mmol) were heated in DMSO (5 mL) at 60 °C for 3 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). Drying with $MgSO_4$, filtration of the drying agent, evaporation of the solvent under reduced pressure and purification by flash chromatography on silica gel (Hexane/Et_2O 9/1 - 7/3) afforded 2-(azidomethyl)aziridine **18c** in 91% yield.

*Ethyl 1-tert-butyl-2-(azidomethyl)aziridine-2-carboxylate (**18a**)*

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* = 7.2 Hz, CH_2CH_3), 1.88 (1H, d, *J* = 1.7 Hz, NC*H*(H)), 2.47-2.48 (1H, m, NCH(*H*)), 3.26 (1H, d, *J* = 12.7 Hz, C*H*(H)N_3), 3.68 (1H, d, *J* = 12.7 Hz, CH(*H*)N_3), 4.19 (1H, dq, *J* = 10.7 Hz, 7.2 Hz, OC*H*(H)CH_3), 4.26 (1H, dq, *J* = 10.7 Hz, 7.2 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}): υ_{N3} = 2101, $\upsilon_{C=O}$ = 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-pentyl-2-(azidomethyl)aziridine-2-carboxylate (**18b**)*

Yellow oil, yield 93%, R_f = 0.50 (petroleum ether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.4 Hz, CCH_2CH_3), 0.97 (3H, s, CCH_3), 0.99 (3H, s, CCH_3), 1.32 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.46 (1H, dq, *J* = 13.8 Hz, 7.3

Hz, CC*H*(H)CH_3), 1.51 (1H, dq, *J* = 13.6 Hz, 7.5 Hz, CCH(*H*)CH_3), 1.90 (1H, d, *J* = 1.1 Hz, NC*H*(H)), 2.50-2.51 (1H, m, NCH(*H*)), 3.26 (1H, d, *J* = 12.7 Hz, C*H*(H)N_3), 3.70 (1H, d, *J* = 12.7 Hz, CH(*H*)N_3), 4.19 (1H, dq, *J* = 11.0 Hz, 7.2 Hz, OC*H*(H)CH_3), 4.25 (1H, dq, *J* = 10.7 Hz, 7.2 Hz, OCH(*H*)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 14.0, 24.0, 24.6, 32.1, 36.6, 42.5, 55.7, 57.0, 61.7, 170.7. IR (neat, cm^{-1}): υ_{N3} = 2101, $\upsilon_{C=O}$ = 1734. MS (ES, pos. mode): *m/z* (%): 241 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{20}N_4O_2$ (%): C, 54.98; H, 8.39; N, 23.32. Found (%): C, 54.61; H, 8.53; N, 23.14.

*Methyl 1-tert-butyl-2-(azidomethyl)aziridine-2-carboxylate (**18c**)*

Light yellow oil, yield 91%, R_f = 0.53 (hexane/Et_2O 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s, $C(CH_3)_3$), 1.90 (1H, d, *J* = 1.1 Hz, NC*H*(H)), 2.47 (1H, s, NCH(*H*)), 3.29 (1H, d, *J* = 12.7 Hz, C*H*(H)N_3), 3.67 (1H, d, *J* = 12.7 Hz, CH(*H*)N_3), 3.77 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 32.0, 42.9, 52.7, 54.6, 55.6, 61.8, 171.0. IR (neat, cm^{-1}): υ_{N3} = 2105, $\upsilon_{C=O}$ = 1740. MS (ES, pos. mode): *m/z* (%): 213 ($M+H^+$, 100). Anal. Calcd for $C_9H_{16}N_4O_2$ (%): C, 50.93; H, 7.60; N, 26.40. Found (%): C, 50.64; H, 7.47; N, 26.51.

*Methyl 1-tert-pentyl-2-(azidomethyl)aziridine-2-carboxylate (**18d**)*

Yellow oil, yield 64%, R_f = 0.25 (petroleum ether/Et_2O 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.6 Hz, CCH_2CH_3), 0.96 (3H, s, CCH_3), 0.98 (3H, s, CCH_3), 1.45 (1H, dq, *J* = 13.6 Hz, 7.3 Hz, CC*H*(H)CH_3), 1.50 (1H, dq, *J* = 13.6 Hz, 7.7 Hz, CCH(*H*)CH_3), 1.92 (1H, d, *J* = 1.4 Hz, NC*H*(H)), 2.50-2.51 (1H, m, NCH(*H*)), 3.28 (1H, d, *J* = 12.7 Hz, C*H*(H)N_3), 3.69 (1H, d, *J* = 12.7 Hz, CH(*H*)N_3), 3.77 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 23.9, 24.5, 32.1, 36.6, 42.2, 52.6, 55.6, 56.9, 171.3. IR (neat, cm^{-1}): υ_{N3} = 2100, $\upsilon_{C=O}$ = 1732. 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, 52.85; H, 8.24; N, 24.59.

Synthesis of alkyl 2-(phenoxymethyl)aziridine-2-carboxylates **19a-b**

As a representative example, the synthesis of ethyl 1-*tert*-butyl-2-(phenoxymethyl)aziridine-2-carboxylate (**19a**) is described here. Ethyl 1-*tert*-butyl-2-(bromomethyl)aziridine-2-carboxylate (**14a**) (80 mg, 0.3 mmol) was added to a mixture of phenol (57 mg, 0.6 mmol) and K_2CO_3 (168 mg, 1.2 mmol) in DMSO (4 mL) and the reaction mixture was heated at 60 °C for 8 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), saturated NaOH (aq.) solution (2 × 10 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/EtOAc 9/1) afforded 2-(phenoxymethyl)aziridine **19a** in 60% yield.

*Ethyl 1-tert-butyl-2-(phenoxymethyl)aziridine-2-carboxylate (**19a**)*

Yellow oil, yield 60%, R_f = 0.33 (petroleum ether /EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (9H, s, $(CH_3)_3$), 1.25 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.92 (1H, d, J = 1.1 Hz, NC*H*(H)), 2.49 (1H, s, NCH(*H*)), 3.72 (1H, d, J = 9.4 Hz, CC*H*(H)O), 4.18 (1H, dq, J = 10.7 Hz, 7.2 Hz, OC*H*(H)CH_3), 4.22 (1H, dq, J = 10.7 Hz, 7.2 Hz, OCH(*H*)CH_3), 4.60 (1H, d, J = 9.6 Hz, CCH(*H*)O), 6.86-6.97 (3H, m, 3×CH_{arom}), 7.23-7.30 (2H, m, 2×CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 28.2, 31.7, 43.6, 54.6, 61.5, 72.1, 114.9, 121.1, 129.5, 158.7, 170.4. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1730. MS (ES, pos. mode): *m/z* (%): 278 ($M+H^+$, 100). Anal. Calcd for $C_{16}H_{23}NO_3$ (%): C, 69.29; H, 8.36; N, 5.05. Found (%): C, 69.43; H, 8.61; N, 4.76.

*Ethyl 1-tert-pentyl-2-(phenoxymethyl)aziridine-2-carboxylate (**19b**)*

Yellow oil, yield 67%, R_f = 0.19 (petroleum ether/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, J = 7.4 Hz, CCH_2CH_3), 0.97 (3H, s, CCH_3), 1.00 (3H, s, CCH_3), 1.25 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.45-1.59 (2H, m, CCH_2CH_3), 1.93 (1H, d, J = 1.4 Hz, NC*H*(H)), 2.53 (1H, s, NCH(*H*)), 3.70 (1H, d, J = 9.4 Hz, CC*H*(H)O), 4.18 (1H, dq, J = 10.7 Hz, 7.2 Hz, OC*H*(H)CH_3), 4.21 (1H, dq, J = 11.0 Hz, 7.2 Hz, OCH(*H*)CH_3), 4.61 (1H, dd, J = 9.4 Hz, 0.8 Hz, CCH(*H*)O), 6.85-6.97 (3H, m, 3×CH_{arom}), 7.23-7.30 (2H, m, 2×CH_{arom}). ^{13}C NMR (75 MHz,

$CDCl_3$): δ 8.8, 14.1, 24.0, 24.5, 31.9, 36.4, 42.8, 56.9, 61.4, 72.1, 114.9, 121.1, 129.5, 158.8, 170.7. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1730. MS (ES, pos. mode): *m/z* (%): 292 ($M+H^+$, 100). Anal. Calcd for $C_{17}H_{25}NO_3$ (%): C, 70.07; H, 8.65; N, 4.81. Found (%): C, 69.91; H, 8.83; N, 4.54.

Synthesis of ethyl 1-*tert*-butyl-3-cyanoazetidine-3-carboxylate (**21a**)

A solution of ethyl 1-*tert*-butyl-3-bromoazetidine-3-carboxylate (**15a**) (132 mg, 0.5 mmol) and potassium cyanide (65 mg, 1 mmol) in DMSO (2 mL) was heated at 60 °C for 4 h. After cooling, the reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/EtOAc 8/2) afforded 3-cyanoazetidine **21a** in 79% yield. Yellow oil, R_f = 0.43 (petroleum ether/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.62 (2H, d, *J* = 7.2 Hz, C*H*(H)NC*H*(H)), 3.72 (2H, d, *J* = 7.4 Hz, CH(*H*)NCH(*H*)), 4.30 (2H, q, *J* = 7.2 Hz, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 23.8, 34.6, 52.2, 54.3, 63.2, 119.0, 167.0. IR (neat, cm^{-1}): υ_{CN} = 2246 (weak), $\upsilon_{C=O}$ = 1742. MS (ES, pos. mode): *m/z* (%): 211 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{18}N_2O_2$ (%): C, 62.83; H, 8.63; N, 13.32. Found (%): C, 62.91; H, 8.79; N, 13.01.

Synthesis of alkyl 3-thiocyanoazetidine-3-carboxylates **22a-b**

As a representative example, the synthesis of ethyl 1-*tert*-butyl-3-thiocyanoazetidine-3-carboxylate (**22a**) is described here. A solution of ethyl 1-*tert*-butyl-3-bromoazetidine-3-carboxylate (**15a**) (94 mg, 0.36 mmol) and potassium thiocyanate (52 mg, 0.53 mmol) in DMSO (2 mL) was heated at 60 °C for 3 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/Et_2O 7/3) afforded 3-thiocyanoazetidine **22a** in 59% yield.

*Ethyl 1-tert-butyl-3-thiocyanoazetidine-3-carboxylate (**22a**)*

Yellow oil, yield 59%, R_f = 0.17 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (9H, s, $C(CH_3)_3$), 1.35 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.44 (2H, d, J = 8.8 Hz, C*H*(H)NC*H*(H)), 3.83 (2H, d, J = 8.8 Hz, CH(*H*)NCH(*H*)), 4.32 (2H, q, J = 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 24.0, 47.4, 52.4, 55.7, 63.0, 109.9, 169.2. IR (neat, cm^{-1}): υ_{SCN} = 2157, $\upsilon_{C=O}$ = 1736. MS (ES, pos. mode) *m/z* (%): 243 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{18}N_2O_2S$ (%): C, 54.52; H, 7.49; N, 11.56. Found (%): C, 54.27; H, 7.64; N, 11.64.

*Ethyl 1-tert-pentyl-3-thiocyanoazetidine-3-carboxylate (**22b**)*

Yellow oil, yield 83%, R_f = 0.21 (petroleum ether/Et_2O 7/3). ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, J = 7.4 Hz, CCH_2CH_3), 0.90 (6H, s, $C(CH_3)_2$), 1.25 (2H, q, J = 7.7 Hz, CCH_2CH_3), 1.35 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.43 (2H, d, J = 8.8 Hz, C*H*(H)NC*H*(H)), 3.82 (2H, d, J = 9.4 Hz, CH(*H*)NCH(*H*)), 4.31 (2H, q, J = 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.5, 14.1, 20.2, 31.4, 47.9, 54.8, 55.6, 63.0, 110.0, 169.3. IR (neat, cm^{-1}): υ_{SCN} = 2157, $\upsilon_{C=O}$ = 1736. MS (ES, pos. mode) *m/z* (%): 257 ($M+H^+$, 100). Anal. Calcd for $C_{12}H_{20}N_2O_2S$ (%): C, 56.22; H, 7.86; N, 10.93. Found (%): C, 56.09; H, 8.01; N, 10.64.

Synthesis of alkyl 3-azidoazetidine-3-carboxylates **23a-c**

As a representative example, the synthesis of ethyl 1-*tert*-pentyl-3-azidoazetidine-3-carboxylate (**23b**) is described here. A solution of ethyl 1-*tert*-pentyl-3-bromoazetidine-3-carboxylate (**15b**) (111 mg, 0.4 mmol) and sodium azide (52 mg, 0.8 mmol) in DMSO (2 mL) was heated at 60 °C for 3 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL) and water (10 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/Et_2O 8/2) afforded 3-azidoazetidine **23b** in 98% yield.

*Ethyl 1-tert-butyl-3-azidoazetidine-3-carboxylate (**23a**)*

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 = 7.2 Hz, CH_2CH_3), 3.32 (2H, d, J = 7.4 Hz, C*H*(H)NC*H*(H)), 3.70 (2H, d, J = 7.4 Hz, CH(*H*)NCH(*H*)), 4.29 (2H, q, J = 7.2 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}): υ_{N3} = 2109, $\upsilon_{C=O}$ = 1737. 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, 52.74; H, 8.31; N, 24.90.

*Ethyl 1-tert-pentyl-3-azidoazetidine-3-carboxylate (**23b**)*

Yellow oil, yield 98%, R_f = 0.24 (petroleum ether/Et_2O 8/2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, J = 7.4 Hz, CCH_2CH_3), 0.91 (6H, s, $C(CH_3)_2$), 1.27 (2H, q, J = 7.4 Hz, CCH_2CH_3), 1.34 (3H, t, J = 7.2 Hz, OCH_2CH_3), 3.30 (2H, dd, J = 7.2 Hz, 1.4 Hz, C*H*(H)NC*H*(H)), 3.70 (2H, dd, J = 7.3 Hz, 1.4 Hz, CH(*H*)NCH(*H*)), 4.28 (2H, q, J = 7.2 Hz, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.6, 14.2, 20.0, 31.5, 54.3, 54.6, 59.7, 62.3, 170.0. IR (neat, cm^{-1}): υ_{N3} = 2108, $\upsilon_{C=O}$ = 1738. MS (ES, pos. mode): *m/z* (%): 241 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{20}N_4O_2$ (%): C, 54.98; H, 8.39; N, 23.32. Found (%): C, 54.59; H, 8.53; N, 23.64.

*Methyl 1-tert-butyl-3-azidoazetidine-3-carboxylate (**23c**)*

Yellow oil, yield 79%, R_f = 0.22 (petroleum ether/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (9H, s, $C(CH_3)_3$), 3.33 (2H, d, J = 7.4 Hz, C*H*(H)NC*H*(H)), 3.70 (2H, d, J = 7.4 Hz, CH(*H*)NCH(*H*)), 3.84 (3H, s, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0, 52.2, 53.2, 54.5, 59.4, 170.5. IR (neat, cm^{-1}): υ_{N3} = 2109, $\upsilon_{C=O}$ = 1740. MS (ES, pos. mode): *m/z* (%): 213 ($M+H^+$, 100). Anal. Calcd for $C_9H_{16}N_4O_2$ (%): C, 50.93; H, 7.60; N, 26.40. Found (%): C, 50.79; H, 7.69; N, 26.21.

Synthesis of alkyl 3-phenoxyazetidine-3-carboxylates **20a-b**

As a representative example, the synthesis of ethyl 1-*tert*-pentyl-3-phenoxyazetidine-3-carboxylate (**20b**) is described here. Ethyl 1-*tert*-pentyl-3-bromoazetidine-3-carboxylate (**15b**) (83 mg, 0.3 mmol) was added to a mixture of phenol (70 mg, 0.75 mmol) and K_2CO_3 (206 mg, 1.5 mmol) in DMSO (2 mL) and the reaction mixture was heated at 60 °C for 8 h. After cooling, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 15 mL), saturated NaOH (aq.) solution (2 × 10 mL) and water (15 mL). Drying ($MgSO_4$), filtration, evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/Et_2O 7/3) afforded 3-phenoxyazetidine **20b** in 81% yield.

*Ethyl 1-tert-butyl-3-phenoxyazetidine-3-carboxylate (**20a**)*

Yellow oil, yield 36%, R_f = 0.25 (petroleum ether/Et_2O 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (9H, s, $C(CH_3)_3$), 1.15 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.51 (2H, d, J = 9.1 Hz, C*H*(H)NC*H*(H)), 3.88 (2H, d, J = 9.1 Hz, CH(*H*)NCH(*H*)), 4.21 (2H, q, J = 7.2 Hz, OCH_2CH_3), 6.65-6.69 (2H, m, 2×CH_{arom}), 6.93-6.98 (1H, m, CH_{arom}), 7.20-7.27 (2H, m, 2×CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 24.1, 52.2, 55.0, 61.9, 73.8, 115.2, 121.5, 129.6, 155.4, 171.4. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1736. MS (ES, pos. mode): *m/z* (%): 278 ($M+H^+$, 100). Anal. Calcd for $C_{16}H_{23}NO_3$ (%): C, 69.29; H, 8.36; N, 5.05. Found (%): C, 69.02; H, 8.59; N, 4.83.

*Ethyl 1-tert-pentyl-3-phenoxyazetidine-3-carboxylate (**20b**)*

Yellow oil, yield 81%, R_f = 0.27 (petroleum ether/Et_2O 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, J = 7.4 Hz, CCH_2CH_3), 0.92 (6H, s, $C(CH_3)_2$), 1.15 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.30 (2H, q, J = 7.4 Hz, CCH_2CH_3), 3.51 (2H, d, J = 8.0 Hz, C*H*(H)NC*H*(H)), 3.86 (2H, d, J = 8.0 Hz, CH(*H*)NCH(*H*)), 4.21 (2H, q, J = 7.2 Hz, OCH_2CH_3), 6.66-6.69 (2H, m, 2×CH_{arom}), 6.93-6.98 (1H, m, CH_{arom}), 7.21-7.26 (2H, m, 2×CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.7, 14.1, 20.0, 31.5, 54.7, 54.8, 61.8, 74.1, 115.2, 121.5, 129.6, 155.5, 171.4. IR (neat, cm^{-1}): $\upsilon_{C=O}$ = 1736. MS (ES, pos. mode): *m/z* (%): 292 ($M+H^+$, 100). Anal. Calcd for

$C_{17}H_{25}NO_3$ (%): C, 70.07; H, 8.65; N, 4.81. Found (%): C, 70.34; H, 8.40; N, 4.60.

Synthesis of ethyl 1-*tert*-pentyl-2-(aminomethyl)aziridine-2-carboxylate (**24b**)

To a solution of ethyl 1-*tert*-pentyl-2-(azidomethyl)aziridine-2-carboxylate (**18b**) (70 mg, 0.29 mmol) in EtOH (7 mL), Pd (7 mg, 10 wt% on carbon) was added and the reaction mixture was stirred under H_2 atmosphere (4 bar) at room temperature for 3 h. Subsequently, the reaction mixture was filtered over Celite® and the filter cake was washed with small portions of EtOH. Evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (CH_2Cl_2/MeOH 100/5) afforded 2-(aminomethyl)aziridine **24b**. Yellow oil, yield 68%, R_f = 0.27 (CH_2Cl_2/MeOH 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.6 Hz, CCH_2CH_3), 0.94 (3H, s, CCH_3), 0.98 (3H, s, CCH_3), 1.30 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.48 (1H, dq, J = 13.6 Hz, 7.4 Hz, $CCH(H)CH_3$), 1.51 (1H, dq, J = 13.4 Hz, 7.4 Hz, $CCH(H)CH_3$), 1.78 (1H, d, J = 1.1 Hz, $CH(H)N$), 1.86 (2H, br s, NH_2), 2.41 (1H, d, J = 1.4 Hz, $CH(H)N$), 2.87 (1H, d, J = 13.8 Hz, $CH(H)NH_2$), 2.89 (1H, d, J = 13.8 Hz, $CH(H)NH_2$), 4.16 (1H, dq, J = 10.7 Hz, 7.2 Hz, $OCH(H)CH_3$), 4.22 (1H, dq, J = 10.7 Hz, 7.2 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}): υ_{NH2} = 3381 (weak), $\upsilon_{C=O}$ = 1724. MS (ES, pos. mode): *m/z* (%): 215 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{22}N_2O_2$ (%): C, 61.65; H, 10.35; N, 13.07. Found (%): C, 61.27; H, 10.62; N, 12.91.

Synthesis of alkyl 2-(*tert*-butoxycarbonylaminomethyl)aziridine-2-carboxylates **25b-c**

As a representative example, the synthesis of methyl 1-*tert*-butyl-2-(*tert*-butoxycarbonylaminomethyl)aziridine-2-carboxylate (**25c**) is described here. To a solution of methyl 1-*tert*-butyl-2-(azidomethyl)aziridine-2-carboxylate (**18c**) (65 mg, 0.31 mmol) in degassed CH_3CN (8 mL), Pd (6.5 mg, 10 wt% on carbon) and di-*tert*-butyl dicarbonate (334 mg, 1.53 mmol) were added and the reaction mixture was stirred under H_2 atmosphere (10 bar) at room temperature for 3 h. Subsequently, the reaction mixture was filtered over Celite® and the filter cake

was washed with small portions of CH_3CN. Evaporation of the solvent under reduced pressure and purification by flash chromatography on silica gel (hexane/EtOAc 9/1) afforded aziridine **25c** in 76% yield.

*Ethyl 1-tert-pentyl-2-(tert-butoxycarbonylaminomethyl)aziridine-2-carboxylate (**25b**)*

Light yellow oil, yield 49%, R_f = 0.13 (hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.7 Hz, CCH_2CH_3), 0.96 (3H, s, $NCCH_3$), 0.97 (3H, s, CCH_3), 1.29 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.40-1.50 (2H, m, CCH_2CH_3), 1.43 (9H, s, $NCCH_3$), 1.86 (1H, d, J = 1.1 Hz, NC*H*(H)), 2.39 (1H, s, NCH(*H*)), 3.30 (1H, dd, J = 13.8 Hz, 4.4 Hz, C*H*(H)NH), 3.60 (1H, d, J = 13.8 Hz, 7.7 Hz, CH(*H*)NH), 4.18 (2H, m, OCH_2CH_3), 4.90 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.8, 14.0, 24.2, 24.6, 28.5, 31.0, 36.7, 42.3, 43.5, 56.6, 61,4, 79.3, 155.9, 171.6. IR (neat, cm^{-1}): υ_{NH} = 3382, $\upsilon_{C=O}$ = 1717. MS (ES, pos. mode): *m/z* (%): 315 ($M+H^+$, 100). Anal. Calcd for $C_{16}H_{30}N_2O_4$ (%): C, 61.12; H, 9.62; N, 8.91. Found (%): C, 61.39; H, 9.51; N, 8.86.

*Methyl 1-tert-butyl-2-(tert-butoxycarbonylaminomethyl)aziridine-2-carboxylate (**25c**)*

Light yellow oil, yield 76%, R_f = 0.07 (hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, $NC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 1.87 (1H, d, J = 1.1 Hz, NC*H*(H)), 2.34 (1H, s, NCH(*H*)), 3.33 (1H, dd, J = 13.8 Hz, 4.4 Hz, C*H*(H)NH), 3.57 (1H, dd, J = 13.8 Hz, 7.2 Hz, C*H*(H)NH), 3.72 (3H, s, OCH_3), 4.93 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 28.5, 31.0, 42.9, 43.6, 52.4, 54.3, 79.3, 155.9, 172.0. IR (neat, cm^{-1}): υ_{NH} = 3382, $\upsilon_{C=O}$ = 1718. MS (ES, pos. mode): *m/z* (%): 287 ($M+H^+$, 100). Anal. Calcd for $C_{14}H_{26}N_2O_4$ (%): C, 58.72; H, 9.15; N, 9.78. Found (%): C, 58.59; H, 9.38; N, 9.59.

Synthesis of ethyl 1-*tert*-butyl-3-aminoazetidine-3-carboxylate (**26a**)

To a solution of ethyl 1-*tert*-butyl-3-azidoazetidine-3-carboxylate (**23a**) (52 mg, 0.23 mmol) in EtOH (5 mL), Pd (5.2 mg, 10 wt% on carbon) was added and the

reaction mixture was stirred under H_2 atmosphere (4 bar) at room temperature for 3 h. Subsequently, the reaction mixture was filtered over Celite® and the filter cake was washed with small portions of EtOH. Evaporation of the solvent under reduced pressure and purification by preparative TLC on silica gel (petroleum ether/EtOAc 1/1) afforded 3-aminoazetidine **26a** in 78% yield. Yellow oil, 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 = 7.2 Hz, CH_2CH_3), 2.37 (2H, br s, NH_2), 3.10 (2H, d, J = 8.3 Hz, NC*H*(H)), 3.72 (2H, d, J = 8.3 Hz, NCH(*H*)), 4.22 (2H, q, J = 7.2 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}): υ_{NH2} = 3376 (weak), $\upsilon_{C=O}$ = 1730. MS (ES, pos. mode): *m/z* (%): 201 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{20}N_2O_2$ (%): C, 59.97; H, 10.07; N, 13.99. Found (%): C, 59.61; H, 10.17; N, 13.64.

Synthesis of alkyl 3-azidoazetidine-3-carboxylic acids **27a-b**

As a representative example, the synthesis of 1-*tert*-butyl-3-azidoazetidine-3-carboxylic acid (**27a**) is described here. To a solution of ethyl 1-*tert*-butyl-3-azidoazetidine-3-carboxylate (**23a**) (96 mg, 0.42 mmol) in MeOH (3 mL), 2N NaOH (aq.) solution (3 mL) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was acidified with 1N HCl aq. solution till pH=7 and the solvents were evaporated under reduced pressure. The residue was dissolved in H_2O and purified by means of ion-exchange chromatography on Dowex H^+ (50 × 8–100) by sequential elution with H_2O and 1N NH_4OH aq. solution. The eluted aqueous solution of the ammonium salt was neutralized with 2N HCl aq. solution and the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered and evaporated under reduced pressure to afford carboxylic acid **27a** in 90% yield.

*1-tert-Butyl-3-azidoazetidine-3-carboxylic acid (**27a**)*

Yellow viscous oil, yield 90%, R_f = 0.15 (CH_2Cl_2/MeOH 9/1). ^{1}H NMR (300 MHz, CD_3OD): δ 1.34 (9H, s, $C(CH_3)_3$), 4.05 (2H, d, J = 11.0 Hz, C*H*(H)NC*H*(H)), 4.51 (2H, d, J = 11.6 Hz, CH(*H*)NCH(*H*)). ^{13}C NMR (75 MHz, CD_3OD): δ 24.2, 53.5, 55.6, 62.2, 176.5. IR (neat, cm^{-1}): υ_{OH} = 3425, υ_{N3} = 2121,

$\upsilon_{C=O}$ = 1623. MS (ES, pos. mode): *m/z* (%): 199 ($M+H^+$, 100). Anal. Calcd for $C_8H_{14}N_4O_2$ (%): C, 48.47; H, 7.12; N, 28.26. Found (%): C, 48.09; H, 6.98; N, 28.07.

*1-tert-Pentyl-3-azidoazetidine-3-carboxylic acid (**27b**)*

Yellow viscous oil, yield 76%, R_f = 0.21 (CH_2Cl_2/MeOH 9/1). ^{1}H NMR (300 MHz, CD_3OD): δ 0.98 (3H, t, *J* = 7.7 Hz, CCH_2CH_3), 1.30 (6H, s, $C(CH_3)_2$), 1.27 (2H, q, *J* = 7.7 Hz, CCH_2CH_3), 4.07 (2H, d, *J* = 11.0 Hz, CH(H)NCH(H)), 4.54 (2H, d, *J* = 11.6 Hz, CH(H)NCH(H)). ^{13}C NMR (75 MHz, CD_3OD): δ 8.6, 20.0, 31.5, 54.3, 54.6, 59.7, 170.0. IR (neat, cm^{-1}): υ_{OH} = 3417, υ_{N3} = 2102, $\upsilon_{C=O}$ = 1604. MS (ES, pos. mode): *m/z* (%): 213 ($M+H^+$, 100). Anal. Calcd for $C_9H_{16}N_4O_2$ (%): C, 50.93; H, 7.60; N, 26.40. Found (%): C, 50.74; H, 7.78; N, 26.29.

Synthesis of alkyl 3-aminoazetidine-3-carboxylic acids **28a-b**

As a representative example, the synthesis of 1-*tert*-pentyl-3-aminoazetidine-3-carboxylic acid (**28b**) is described here. To a solution of 1-*tert*-pentyl-3-azidoazetidine-3-carboxylic acid (**27b**) (60 mg, 0.3 mmol) in MeOH (12 mL), Pd (6 mg, 10 wt% on carbon) was added and the reaction mixture was stirred under H_2 atmosphere (3 bar) at room temperature for 3 h. Subsequently, the reaction mixture was filtered over Celite® and the filter cake was washed with small portions of MeOH. The solvent was evaporated under reduced pressure. The residue was dissolved in H_2O and purified by means of ion-exchange chromatography on Dowex H^+ (50 × 8–100) by sequential elution with H_2O and 1N NH_4OH aq. solution. The eluted aqueous solution of the ammonium salt was neutralized with 2N HCl aq. solution and the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2, filtered and evaporated under reduced pressure to afford amino acid **28b** in 80% yield.

*1-tert-Butyl-3-aminoazetidine-3-carboxylic acid (**28a**)*

Brown viscous oil, yield 76%, R_f = 0.02 (CH_2Cl_2/MeOH 9/1). ^{1}H NMR (300 MHz, CD_3OD): δ 1.21 (9H, s, $C(CH_3)_3$), 3.75 (2H, d, *J* = 10.5 Hz,

C*H*(H)NC*H*(H)), 4.25 (2H, d, *J* = 10.5 Hz, CH(*H*)NCH(*H*)). ^{13}C NMR (75 MHz, CD_3OD): δ 23.5, 54.2, 59.1, 59.3, 176.4. IR (neat, cm^{-1}): $\upsilon_{OH,NH2}$ = 3379, $\upsilon_{C=O}$ = 1650. MS (ES, pos. mode): *m/z* (%): 173 ($M+H^+$, 100). Anal. Calcd for $C_8H_{16}N_2O_2$ (%): C, 55.79; H, 9.36; N, 16.27. Found (%): C, 55.51; H, 9.52; N, 16.39.

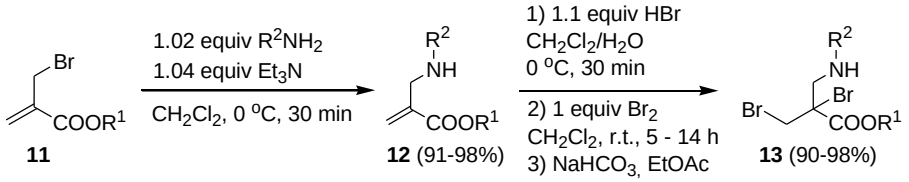
*1-tert-Pentyl-3-aminoazetidine-3-carboxylic acid (**28b**)*

Brown viscous oil, yield 80%, R_f = 0.03 (CH_2Cl_2/MeOH 9/1). ^{1}H NMR (300 MHz, CD_3OD): δ 0.96 (3H, t, *J* = 7.4 Hz, CCH_2CH_3), 1.21 (6H, s, $C(CH_3)_2$), 1.56 (2H, q, *J* = 7.4 Hz, CCH_2CH_3), 3.72 (2H, d, *J* = 10.5 Hz, C*H*(H)NC*H*(H)), 4.24 (2H, d, *J* = 9.9 Hz, CH(*H*)NCH(*H*)). ^{13}C NMR (75 MHz, CD_3OD): δ 8.6, 20.0, 30.8, 54.8, 59.3, 61.5, 176.8. IR (neat, cm^{-1}): $\upsilon_{OH,NH2}$ = 3338, $\upsilon_{C=O}$ = 1625. MS (ES, pos. mode): *m/z* (%): 187 ($M+H^+$, 100). Anal. Calcd for $C_9H_{18}N_2O_2$ (%): C, 58.04; H, 9.74; N, 15.04. Found (%): C, 57.85; H, 9.87; N, 14.83.

Results and discussion

The synthesis of *N*-substituted alkyl 2-(aminomethyl)acrylates **12** via substitution reactions of alkyl 2-(bromomethyl)acrylates **11** with primary amines was performed under optimized conditions in analogy with literature procedures (Baraki et al. 1999; Habaue et al. 1997). Addition of alkyl 2-(bromomethyl)acrylates **11** to a solution of primary amine and triethylamine in dichloromethane at 0 °C afforded ethyl and methyl 2-[(alkylamino)methyl]acrylates **12** in excellent yields (Table 1). Subsequently, following a typical procedure for the bromination of functionalized allylamines (De Smaele et al. 2001), the amino group of alkyl 2-[(alkylamino)methyl]acrylates **12** was protected by treatment with aqueous hydrobromic acid in dichloromethane to the corresponding hydrobromide salts. Subsequent bromination followed by neutralization of the reaction mixture with an aqueous $NaHCO_3$ solution afforded the desired dibromopropanoates **13** in excellent yields (Table 1).

Table 1 Synthesis and bromination of alkyl 2-(aminomethyl)acrylates **12**



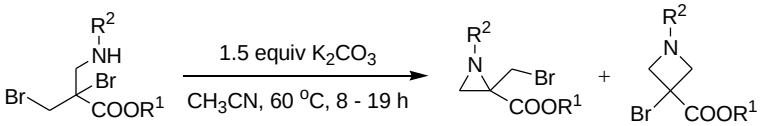
Entry	Substrate	R^1	R^2	**12** (%)	**13** (%)[a]
1	**11a**	Et	*t*-Bu	**12a** (97)	**13a** (98)
2	**11a**	Et	*t*-Pentyl	**12b** (91)	**13b** (97)
3	**11b**	Me	*t*-Bu	**12c** (94)	**13c** (90)
4	**11b**	Me	*t*-Pentyl	**12d** (98)	**13d** (97)

[a] Values between parentheses indicate yields of isolated products

With the targeted dibromo amino esters **13** in hand, their ring closure upon treatment under basic conditions to the desired aziridines **14** and/or azetidines **15** was investigated. After extensive screening of different bases, solvents, reaction temperatures and reaction times, it was found that a clean conversion of dibromo amines **13** to the aziridines **14** as major products together with the azetidines **15** as minor compounds could be achieved by using K_2CO_3 in acetonitrile at 60 °C. However, the yields of the isolated aziridines **14** and azetidines **15** were low after purification by flash chromatography on silicagel as, apparently, these azaheterocycles partly decompose on column (Table 2, entry 1). To our satisfaction, good overall yields of the targeted isolated aziridines **14** (44-54%) and azetidines **15** (24-33%) were obtained via separation by preparative TLC up to 1 g scale (Table 2, entries 2-5).

It was envisioned that aziridines **14** are the kinetic cyclization products, while azetidines **15** result from a thermodynamical equilibration. The isomerization of 2-(halomethyl)aziridines to 3-haloazetidines, although only in some cases observable for 2-(chloromethyl)aziridines which lack a second substituent at the 2-position, was explained via the intermediacy of a bicyclic azonia[1.1.0]bicyclobutane **I** and eventually the corresponding carbenium ion **II**, followed by recombination with the initially expelled halide to give 3-haloazetidines or 2-(halomethyl)aziridines (Gaertner 1970; Higgins and Kidd 1998). In order to experimentally prove this isomerization of aziridine **14** to azetidine **15**, alkyl 2-(bromomethyl)aziridine-2-carboxylates **14** were heated under several conditions similar to the reaction conditions used in the preparation of azetidines **15** from acyclic dibromo amino esters **13** (Table 3).

Table 2 Synthesis of alkyl aziridine-2-carboxylates **14** and alkyl azetidine-3-carboxylates **15**



13a (R^1 = Et, R^2 = *t*-Bu)
13b (R^1 = Et, R^2 = *t*-Pentyl)
13c (R^1 = Me, R^2 = *t*-Bu)
13d (R^1 = Me, R^2 = *t*-Pentyl)

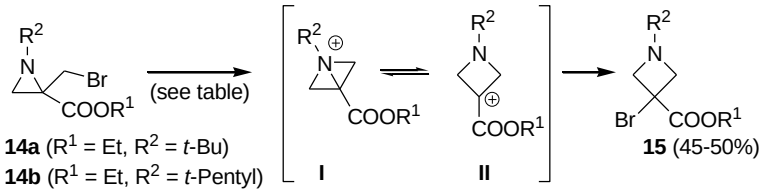
14 (44-54%) **15** (24-33%)

Entry	Substrate	Reaction time (h)	Result (%)[a,b]
1	**13a**	19	**14a** (19)[a] + **15a** (13)[a]
2	**13a**	19	**14a** (50)[b] + **15a** (33)[b]
3	**13b**	12	**14b** (54)[b] + **15b** (24)[b]
4	**13c**	8	**14c** (44)[b] + **15c** (25)[b]
5	**13d**	18	**14d** (54)[b] + **15d** (26)[b]

[a] Values between parentheses indicate yields of isolated products after purification by flash chromatography

[b] Values between parentheses indicate yields of isolated products after purification by preparative TLC

Table 3 Isomerization of 2-(bromomethyl)aziridines **14** to 3-bromoazetidines **15**



14a (R^1 = Et, R^2 = *t*-Bu)
14b (R^1 = Et, R^2 = *t*-Pentyl)
14c (R^1 = Me, R^2 = *t*-Bu)
14d (R^1 = Me, R^2 = *t*-Pentyl)

15 (45-50%)

Entry	**Substrate**	**Reaction conditions**	**Result**
1	**14a**	CH_3CN, 60 ºC, 3 h	No reaction
2	**14a**	CH_3CN, Δ, 15 h	Decomposition
3	**14a**	1 equiv KBr, CH_3CN, 60 ºC, 24 h	Decomposition
4	**14a**	DMSO, 55 ºC, 24 h	**14a**:**15a** = 2:1[a]
5	**14a**	DMSO, 55 ºC, 24 h + 65 ºC, 6 h	**14a**:**15a** = 1:2.8[a]
6	**14a**	DMSO, 70 ºC, 18 h	**15a** (45%)[b]
7	**14b**	DMSO, 70 ºC, 45 h	**15b** (45%)[b]
8	**14c**	DMSO, 70 ºC, 5 h	**15c** (45%)[b]
9	**14d**	DMSO, 70 ºC, 5 h	**15d** (50%)[b]
10	**14a**	1 equiv KBr, DMSO, 70 °C, 18 h	**15a** (26%)[b]
11	**14a**	DMSO/H_2O 1/1, 70 °C, 48 h	Decomposition
12	**14a**	1 equiv KBr, DMSO/H_2O 1/1, 70 °C, 48 h	Decomposition

[a] Ratio determined by ^{1}H NMR analysis

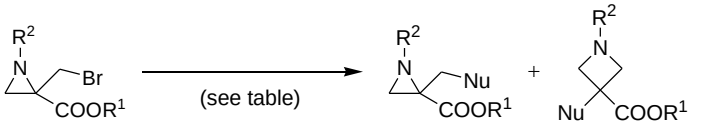
[b] Values between parentheses indicate yields of isolated products

Heating of aziridine **14a** in acetonitrile at 60 °C for 3 h gave no reaction (entry 1), while prolonged heating in acetonitrile at 60 °C in the presence of KBr, which is formed *in situ* during the cyclization of **13**, resulted in decomposition to unidentified compounds after 24 h (entry 3). Nevertheless, a satisfactory isomerization of aziridine **14a** to azetidine **15a** was observed upon heating in DMSO, giving a mixture of **14a** and **15a** in a 2:1 ratio (^{1}H NMR analysis) at 55 °C after 24 h. The latter mixture further isomerized to **14a** and **15a** in a 1:2.8 ratio after additional heating at 65 °C for 6 h. After raising the temperature to 70 °C, full isomerization of aziridines **14a-d** to azetidines **15a-d** was obtained within 45 h with 45–50% yield (Table 3, entries 6-9). Attempts to improve the outcome of the isomerization reaction by adding KBr resulted in a lower yield of 26% of azetidine **15a**, while addition of water to the reaction (Table 3, entries 11-12) slowed down the isomerization and eventually led to total decomposition.

Introduction of new functional groups in alkyl aziridine-2-carboxylates **14** and alkyl azetidine-3-carboxylates **15** in particular, would highly enrich the chemistry of these important classes of α- and β-amino acid derivatives. Therefore, the potential of the synthesized alkyl 2-(bromomethyl)aziridine-2-carboxylates **14** and alkyl 3-bromoazetidine-3-carboxylates **15** for further functionalization via substitution reactions with *C*-, *S*-, *N*- and *O*-nucleophiles was investigated (Tables 4 and 5). Treatment of alkyl 2-(bromomethyl)aziridine-2-carboxylates **14a-c** with potassium cyanide in DMSO at 60 °C for 3 – 4 h uneventfully afforded the corresponding alkyl 2-(cyanomethyl)aziridine-2-carboxylates **16a-c** in 47 – 57% yield (Table 4, entries 1-3). Few 2-(cyanomethyl)aziridines can be found in the literature (Gaertner 1970; Subbaraj et al. 1989; Antunes et al. 2007; Vedejs et al. 2003; Krasnova et al. 2005), and some have been used recently for the synthesis of biologically relevant *N*-(2-cyanocyclopropyl)benzimidates (D'hooghe et al. 2006a), 2-aminocyclopropanecarbonitriles (Mangelinckx et al. 2009), 4-amino-2-butenenitriles (D'hooghe et al. 2007a, 2007b), 3,4-diaminobutanenitriles (D'hooghe et al. 2007a), and 2-aminopentanedinitriles (D'hooghe et al. 2008). Ethyl 2-(thiocyanomethyl)aziridine-2-carboxylates **17a-b** were synthesized in moderate yield (44 – 48%) utilizing potassium thiocyanate in DMF at 70 °C due to the formation of some unidentified reaction products which were present in the crude reaction mixture (Table 4, entries 4-5). Only one report on the synthesis of

2-(thiocyanomethyl)aziridines, which were used for an intramolecular cyclisation to 2-iminothiazolidines, has been made (D'hooghe et al. 2005b).

Table 4 Reactions of alkyl 2-(bromomethyl)aziridines **14** with different nucleophiles



14a (R^1 = Et, R^2 = *t*-Bu)
14b (R^1 = Et, R^2 = *t*-Pentyl)
14c (R^1 = Me, R^2 = *t*-Bu)
14d (R^1 = Me, R^2 = *t*-Pentyl)

16 (Nu = CN)
17 (Nu = SCN)
18 (Nu = N_3)
19 (Nu = OPh)

20 (Nu = OPh)

Entry	Substrate	Reaction conditions	Result (%)[a]
1	**14a**	1 equiv KCN, DMSO, 60 ºC, 3 h	**16a** (47)
2	**14b**	1 equiv KCN, DMSO, 60 ºC, 4 h	**16b** (54)
3	**14c**	1 equiv KCN, DMSO, 60 ºC, 4 h	**16c** (57)
4	**14a**	2 equiv KSCN, DMF, 70 ºC, 2 h	**17a** (48)
5	**14b**	2 equiv KSCN, DMF, 70 ºC, 6 h	**17b** (44)
6	**14a**	2 equiv NaN_3, DMSO, 60 ºC, 1.5 h	**18a** (58)
7	**14b**	2 equiv NaN_3, DMSO, 60 ºC, 2 h	**18b** (93)
8	**14c**	2 equiv NaN_3, DMSO, 60 ºC, 3 h	**18c** (91)
9	**14d**	2 equiv NaN_3, DMSO, 60 ºC, 3 h	**18d** (64)
10	**14a**	2.2 equiv PhOH, 5 equiv K_2CO_3 acetone/DMF 1/1, Δ, 125 h	**19a** (10)
11	**14b**	2.2 equiv PhOH, 5 equiv K_2CO_3 acetone/DMF 1/1, Δ, 160 h	-
12	**14a**	2 equiv PhOH, 4 equiv K_2CO_3 DMSO, 60 ºC, 8 h	**19a** (60) + **20a** (5)
13	**14b**	2 equiv PhOH, 4 equiv K_2CO_3 DMSO, 60 ºC, 5 h	**19b** (34) + **20b** (4)
14	**14b**	3 equiv PhOH, 6 equiv K_2CO_3 DMSO, 60 ºC, 16 h	**19b** (67)

[a] Values between parentheses indicate yields of isolated products

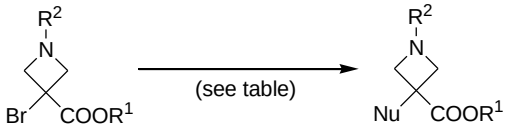
Alkyl 2-(azidomethyl)aziridine-2-carboxylates **18a-d** were prepared in good to excellent yield by reaction with sodium azide in DMSO at 60 °C (Table 4, entries 6-9). 2-(Azidomethyl)aziridines are also scarcely reported in the literature (Jamookeeah et al. 2008; Han et al. 2008; D'hooghe et al. 2005a). Methyl (2*R*,3*R*)-1-benzyl-3-(azidomethyl)-2-aziridinecarboxylate has been used in routes towards the synthesis of aziridinomitosenes as antitumor antibiotics (Shaw et al. 1985). Upon reaction of ethyl 2-(bromomethyl)aziridine-2-carboxylates **14a-b**

with phenol and K_2CO_3 in a mixture of acetone and DMF (1/1) under reflux, no satisfactory results were obtained even after prolonged reaction time (Table 4, entries 10-11). However, treating ethyl 2-(bromomethyl)aziridine-2-carboxylates **14a-b** with phenol and K_2CO_3 in DMSO at 60 °C for 5 to 16 hours afforded ethyl 1-*tert*-butyl-2-(phenoxymethyl)aziridine-2-carboxylate **19a** and ethyl 1-*tert*-pentyl-2-(phenoxymethyl)aziridine-2-carboxylate **19b** in 60 – 67% yield (Table 4, entries 12-14). Noteworthy, besides the aziridines **19** as major compounds, the rearranged compounds, i.e. ethyl 1-*tert*-butyl-3-phenoxyazetidine-3-carboxylate **20a** and ethyl 1-*tert*-pentyl-3-phenoxyazetidine-3-carboxylate **20b**, were isolated in small amounts (4-5%) from this reaction. 2-(Aryloxymethyl)aziridines have recently been used for the synthesis of biologically relevant 2-amino-1-aryloxy-3-methoxypropanes (D'hooghe et al. 2006b), and for the synthesis of 1*H*-tetrazole-1-alkanenitriles as potent orally bioavailable growth hormone secretagogues (Hernández et al. 2008).

In analogy with the reactions of aziridines **14**, treatment of the 3-bromoazetidines **15** with potassium cyanide, potassium thiocyanate, sodium azide and potassium phenoxide in DMSO at 60 °C for 3 to 4 hours afforded the corresponding 3-cyano-, 3-thiocyano-, 3-azido- and 3-phenoxyazetidine-3-carboxylic esters **20**-**23** in 36-98% yield (Table 5). 3-Substituted azetidines are frequently used in structure-activity relationship (SAR) studies for the preparation of libraries of bioactive compounds, e.g. bronchodilating and anti-inflammatory drugs (Provins et al. 2007), antibacterial agents (Murphy et al. 2007), and antidepressant agents (Melloni et al. 1979).

In order to extend the potential applicability of the synthesized constrained amino acid derivatives as building blocks for the synthesis of foldamers, the deprotection of several amino acid derivatives was studied as well. Using simple hydrogenolysis, ethyl 1-*tert*-pentyl-2-(azidomethyl)aziridine-2-carboxylate **18b** and 1-*tert*-butyl-3-azidoazetidine-3-carboxylate **23a** were converted into the corresponding ethyl 2-(aminomethyl)aziridine-2-carboxylate **24b** and 3-aminoazetidine-3-carboxylate **26a** (Scheme 1 and 2).

Table 5 Reactions of alkyl 3-bromoazetidines **15** with different nucleophiles

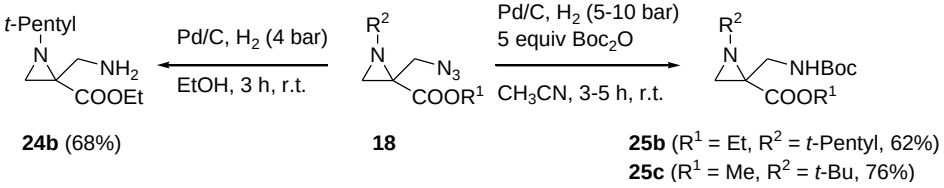


15a (R^1 = Et, R^2 = *t*-Bu)
15b (R^1 = Et, R^2 = *t*-Pentyl)
15c (R^1 = Me, R^2 = *t*-Bu)

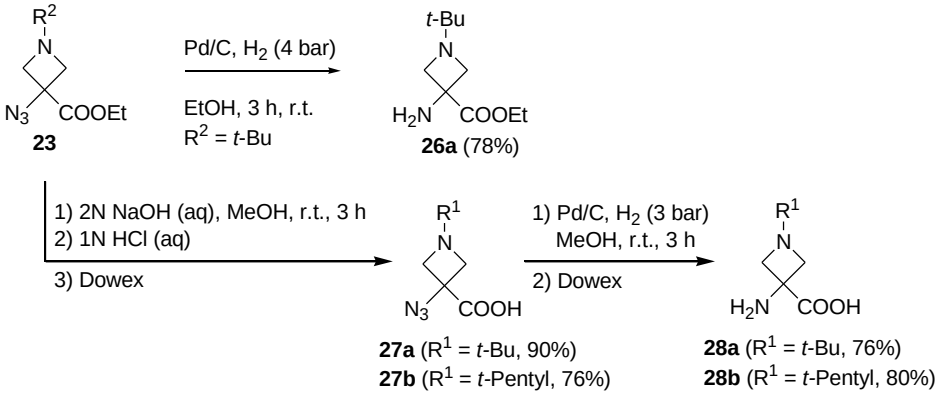
20 (Nu = OPh)
21 (Nu = CN)
22 (Nu = SCN)
23 (Nu = N_3)

Entry	Substrate	Reaction conditions	Result (%)
1	**15a**	2 equiv KCN, DMSO, 60 ºC, 4 h	**21a** (79)
2	**15a**	1.5 equiv KSCN, DMSO, 60 ºC, 3 h	**22a** (59)
3	**15b**	1.5 equiv KSCN, DMSO, 60 ºC, 3 h	**22b** (83)
4	**15a**	2 equiv NaN_3, DMSO, 60 ºC, 3 h	**23a** (86)
5	**15b**	2 equiv NaN_3, DMSO, 60 ºC, 3 h	**23b** (98)
6	**15c**	2 equiv NaN_3, DMSO, 60 ºC, 3 h	**23c** (79)
7	**15a**	3 equiv PhOH, 6 equiv K_2CO_3, DMSO, 60 ºC, 3 h	**20a** (36)
8	**15b**	2.5 equiv PhOH, 5 equiv K_2CO_3, DMSO, 60 ºC, 4 h	**20b** (81)

Noteworthy, the ring opening of 2-(aminomethyl)aziridine templates with thioacid peptides has recently been developed as a method for chemoselective peptidomimetic ligation (Assem et al. 2010). Furthermore, 2-(azidomethyl)aziridines **18** could be directly transformed into the corresponding *N*-Boc-protected 2-(aminomethyl)aziridines **25** by hydrogenation in the presence of di-*tert*-butyl dicarbonate (Scheme 1). All efforts to saponify 2-(azidomethyl)aziridine-2-carboxylic esters via basic hydrolysis (aq. Na_2CO_3 or aq. LiOH) failed, resulting in either no reaction or formation of complex reaction mixtures. However, simple hydrolysis of ethyl 3-azidoazetidine-3-carboxylates **23a**,**b** to the corresponding 3-azidoazetidine-3-carboxylic acids **27** was achieved upon reaction with 2N aqueous NaOH solution in methanol at room temperature for 3 h (Scheme 2). Further hydrogenolysis of 3-azidoazetidine-3-carboxylic acids **27** afforded 3-aminoazetidine-3-carboxylic acids **28**. Besides their potential use as foldameric building blocks, the elaborated 3-aminoazetidine-3-carboxylates **26**-**28** can be important for the synthesis of series of active compounds used in SAR, as exemplified for EGF receptor tyrosine kinase inhibitors (Hennequin et al. 2006), CB_1 receptor antagonists (Brandt et al. 2009), and modulators of the NMDA receptor complex (Kozikowski and Fauq 1991).



Scheme 1



Scheme 2

In conclusion, 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. The aziridines are the kinetically favored cyclization products and could be transformed into 3-bromoazetidine-3-carboxylic acid derivatives via thermal isomerization. The new small ring azaheterocyclic α- and β-amino acid derivatives proved to be excellent building blocks for the synthesis of different substituted aziridines and azetidines through nucleophilic substitution of the bromide by different carbon, sulfur, oxygen and nitrogen nucleophiles in good to high yields. Elaboration of the amino and carboxyl group made new conformationally constrained functionalized α- and β-amino acids synthetically accessible for potential application in foldamer research.

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