Synthesis of 3-functionalized 3-methylazetidines

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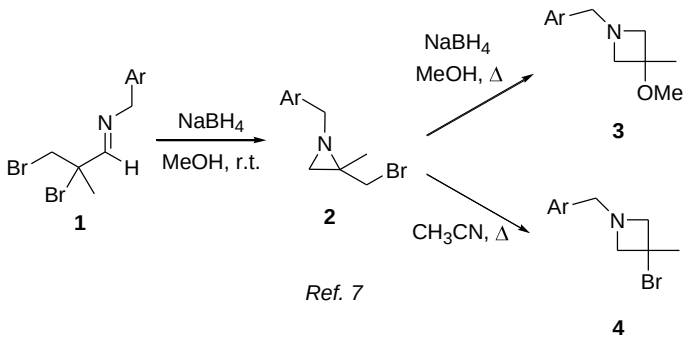
Abstract – 1-*t*-Butyl- and 1-(4-methylbenzyl)-3-bromo-3-methylazetidines were prepared from the corresponding *N*-(2,3-dibromo-2-methylpropylidene)alkylamines and their propensity to undergo nucleophilic substitution at the 3-position by different nucleophiles was assessed, providing a convenient access to novel 3-alkoxy-, 3-aryloxy-, 3-hydroxy-, 3-cyano-, 3-carboxy-, 3-(aminomethyl)- and 3-(hydroxymethyl)azetidines.

Key words: aziridines, azetidines, aziridinium salts, imines, substitution

Within azaheterocyclic chemistry, azetidines represent a valuable class of strained nitrogen-containing compounds from both a biological[1] and a synthetic point of view.[2] In particular, 3-substituted azetidines have attracted considerable interest because of the diverse biological activities associated to this type of compounds. For example, 3-alkoxy- and 3-aryloxyazetidines have been described as G-protein coupled receptor agonists,[3] inhibitors of stearoyl-coenzyme d-9 desaturase,[4] and antibacterial agents.[5] Moreover, 3-haloazetidines (without an additional alkyl group at the 3-position) are generally recognized as good substrates in organic chemistry for the preparation of other 3-functionalized azetidines.[6]

Recently, the convenient synthesis of 3-methoxy-3-methylazetidines **3** through ring rearrangement of 2-bromomethyl-2-methylaziridines **2**, obtained by $NaBH_4$-mediated reduction of the corresponding α,β-dibromo imines **1**, upon treatment with $NaBH_4$ in methanol under reflux has been described by us.[7] The same azetidines **3** have also been prepared via a different route through $NaBH_4$-mediated cyclization of *N*-alkylidene-(3-bromo-2-methoxy-2-methylpropyl)amines.[8] In general, halogenated imines comprise useful intermediates for the preparation of azaheterocyclic compounds such as aziridines and azetidines.[9]

Furthermore, if aziridines **2** were heated in acetonitrile under reflux, 3-bromoazetidines **4** were obtained as the thermodynamic products (Scheme 1).[7] Until then, the peculiar rearrangement of 2-(halomethyl)aziridines to 3-haloazetidines had been observed in the literature in only two specific cases.[10]



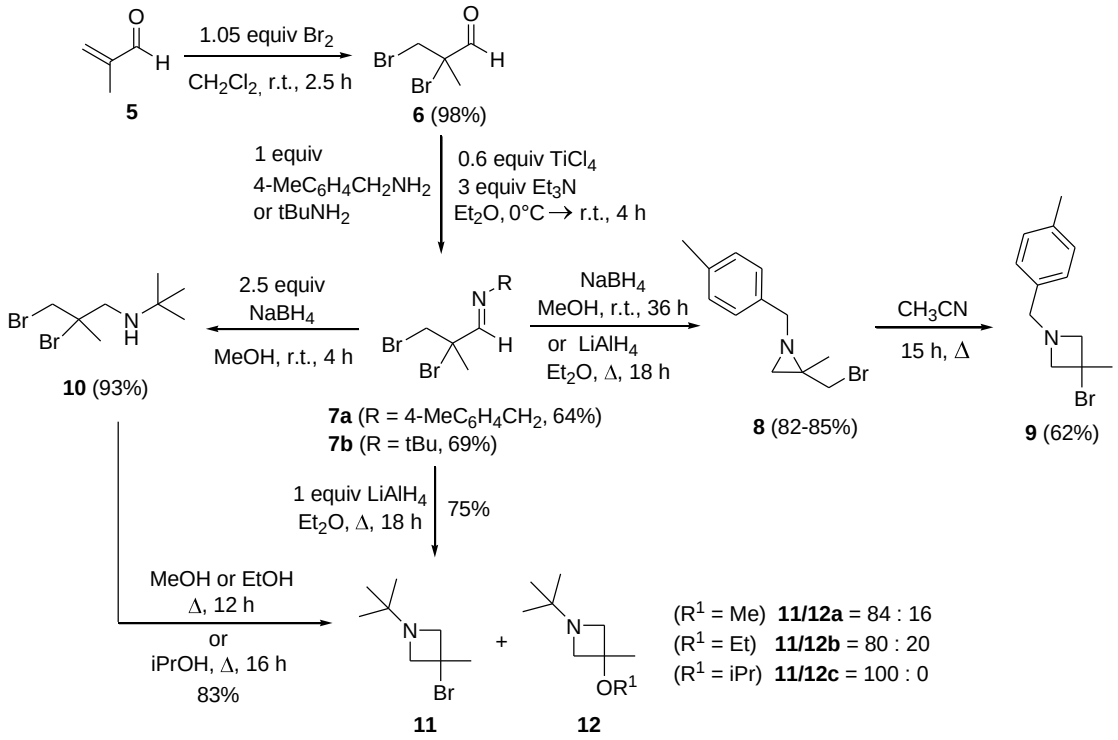
Scheme 1. Reactivity of 2-bromomethyl-2-methylaziridines **2**.

In general, the reactivity profile of 3-bromo-3-methylazetidines as useful synthons in organic chemistry has not been studied so far. In this Letter, the synthesis of 3-bromo-3-methyl-1-(4-methylbenzyl)azetidine and 3-bromo-1-*t*-butyl-3-methylazetidine will be covered, as well as their propensity to undergo nucleophilic substitution at the 3-position to access a window of novel 3-functionalized azetidines.

The synthesis of 3-bromo-3-methyl-1-(4-methylbenzyl)azetidine **9** was performed via thermal ring expansion of 2-bromomethyl-2-methylaziridine **8** upon heating in acetonitrile under reflux according to a literature protocol (Scheme 2).[7] Aziridine **8** was prepared by reductive cyclization of α,β-dibromoaldimine **7a** (R = 4-$MeC_6H_4CH_2$), obtained via bromination of 2-methylpropenal **5** and subsequent condensation with 4-methylbenzylamine in the presence of titanium(IV) chloride and triethylamine.[7] In the same work, it has been shown that 3-methoxy-3-methylazetidines **3** were obtained upon treatment of imines **7** (R = CH_2Ar) with sodium borohydride in methanol under reflux. Considering this smooth imine **7** (R = CH_2Ar) to azetidine **3** transformation, different reaction conditions were evaluated to obtain 3-bromoazetidine **9** directly from imine **7a**. The reaction of imine **7a** with 1 molar equiv of $LiAlH_4$ in diethyl ether for 18 hours under reflux resulted only in aziridine **8**, while the same reaction in tetrahydrofuran for a prolonged reaction time (5 days) gave a mixture of ring-opened amines derived from the hydride-induced ring opening of aziridine **8**.[11] The reduction of imine **7a**, either with 1 molar equiv of $LiAlH_4$ in dioxane for 15 hours under

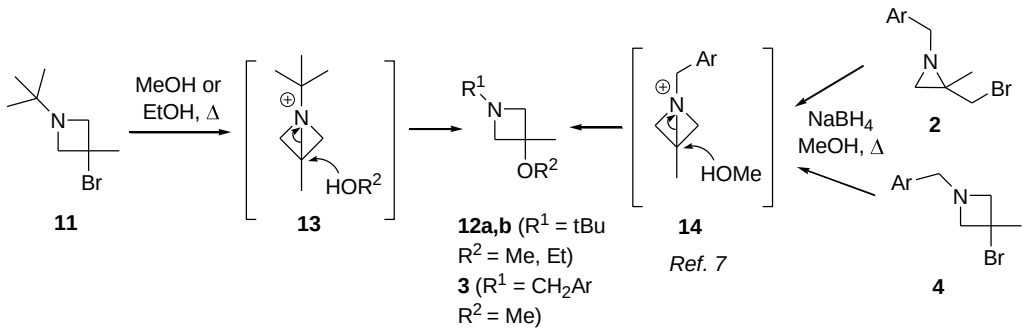
reflux or with 2 molar equiv of $NaBH_4$ in isopropanol for 15-24 hours under reflux, gave complex reaction mixtures, in which no 3-bromoazetidine **9** could be detected. Therefore, the most efficient synthesis of azetidine **9** was shown to occur via thermal rearrangement of aziridine **8**.

Contrary to the reactivity of *N*-(arylmethyl)imine **7a**, treatment of *N*-*t*-butylimine **7b** with 2.5 molar equiv of $NaBH_4$ in methanol for 4 hours at room temperature selectively provided amine **10** instead of 2-bromomethyl-1-*t*-butyl-2-methylaziridine (Scheme 2). These observations are in accordance with the $NaBH_4$-mediated reduction of chlorinated imines towards the synthesis of different 1-alkyl-2-chloromethyl-2-methylaziridines, except in the case of the 1-*t*-butyl derivative where the formation of the corresponding aziridine was also never observed.[12] When amine **10** was further heated in methanol or ethanol for 12 hours under reflux, a mixture of azetidines **11** and **12a,b** (as their hydrobromic salt) was obtained. It should be noted that even if the corresponding 2-bromomethyl-2-methylaziridine was formed in this step, it immediately rearranged into azetidines **11** and **12** as the thermodynamically preferred products. Heating of amine **10** in a less nucleophilic solvent such as isopropanol for 16 hours under reflux provided only 3-bromoazetidine hydrobromide **11**, which was then isolated as a neutral compound upon treatment with a sodium hydroxide solution in 83% yield. In addition, treatment of imine **7b** with 1 molar equiv of $LiAlH_4$ in diethyl ether for 18 hours under reflux gave 3-bromoazetidine **11** as the major product (75%), together with some non-identified side products (Scheme 2). Again, no traces of 2-bromomethyl-1-*t*-butyl-2-methylaziridine were observed.



Scheme 2. Synthesis of 3-bromo-3-methylazetidines **9** and **11**.

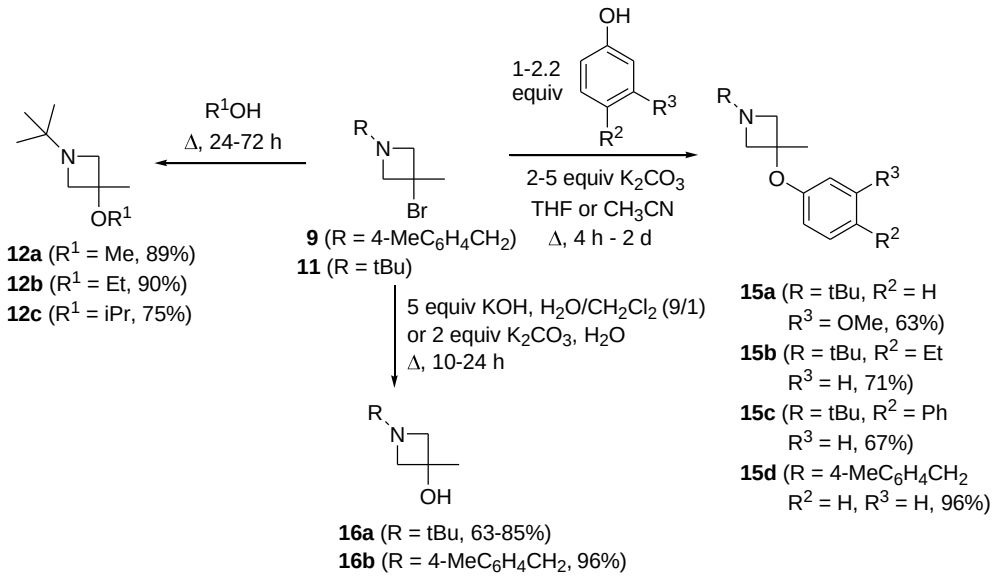
The formation of 3-alkoxyazetidines **12a,b** from amine **10** is proposed to occur via nucleophilic attack of the solvent molecule (methanol or ethanol) at the more-substituted carbon atom of the intermediate bicyclic aziridinium ion **13** (Scheme 3). This strained intermediate **13** is most probably formed via intramolecular nucleophilic displacement of bromide in the initially formed 3-bromoazetidine **11**. The proposed pathway concurs with the previously reported synthesis of 3-methoxy-3-methylazetidines **3** (R^1 = CH_2Ar, R^2 = Me, Scheme 3) comprising the smooth ring expansion of 2-bromomethyl-2-methylaziridines **2** via bicyclic aziridinium intermediates **14** upon heating in methanol in the presence of $NaBH_4$.[7] In the same study, it has been shown that 3-methoxy-3-methylazetidines **3** can also be obtained starting from 3-bromoazetidines **4** applying the same reaction conditions ($NaBH_4$, MeOH, Δ).



Scheme 3. Synthesis of 3-alkoxy-3-methylazetidines **12**.

The latter transformation served as a starting point to thoroughly investigate the synthetic potential of 3-bromo-3-methylazetidines for the preparation of novel 3-substituted azetidines. For this purpose, 3-bromo-3-methyl-1-(4-methylbenzyl)azetidine **9** and 3-bromo-1-*t*-butyl-3-methylazetidine **11** were selected as eligible substrates for reactions with different nucleophiles.

Upon heating of 3-bromo-1-*t*-butylazetidine **11** (R = tBu) in different alcohols (MeOH, EtOH, iPrOH) for 24-72 hours under reflux, the corresponding 3-alkoxyazetidines **12a-c** were formed in pure form after basic work-up (Scheme 4). Furthermore, the reactions of azetidines **9** and **11** with 1-2.2 equiv of different phenols and 2-5 equiv of K_2CO_3 in tetrahydrofuran or acetonitrile for 4-48 hours under reflux provided the corresponding 3-aryloxyazetidines **15a-d** in good yields, which were purified by means of column chromatography on silica gel in order to obtain analytically pure samples.[13] When substrates **9** and **11** were heated in water or water/CH_2Cl_2 (9/1) for 10-24 hours under reflux in the presence of 5 equiv of KOH or 2 equiv of K_2CO_3, 1-*t*-butyl-3-methyl-3-azetidinol **16a** and 3-methyl-1-(4-methylbenzyl)-3-azetidinol **16b** were obtained in high yields (Scheme 4).[14] The above-described findings support the suitability of 3-bromo-3-methylazetidines as substrates for nucleophilic substitutions by different oxygen-centered nucleophiles.



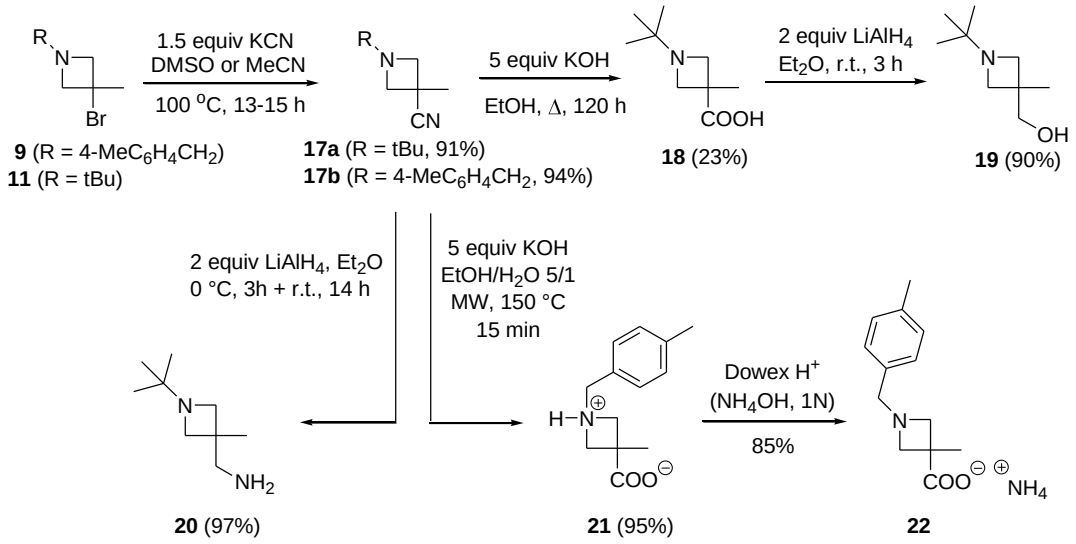
Scheme 4. Reactivity of 3-bromo-3-methylazetidines **9** and **11** towards oxygen nucleophiles.

In the literature, it is known that azetidine-3-carbonitriles can be prepared via nucleophilic substitution of 3-mesyloxy- and 3-tosyloxyazetidines.[15] In that respect, 3-bromo-3-methylazetidines **9** and **11** were also shown to be good substrates for the synthesis of azetidine-3-carbonitriles **17a,b** upon treatment with 1.5 equiv of KCN in dimethylsulfoxide or acetonitrile for 13-22 hours under reflux (Scheme 5). Azetidine **17a** was purified via distillation and azetidine **17b** by means of column chromatography on silica gel, which were then used for further derivatization.

The hydrolysis of the cyano group in azetidines **17** can provide an access towards cyclic amino acids which can be considered as analogues of azetidine-2-carboxylic acid, a natural molecule isolated from *Convallaria majalis* (lily-of-the-valley) and endowed with impressive biological activities such as the inhibition of the proliferation of *Escherichia coli*, alteration of the structure of collagen, keratin and haemoglobin in human proteins, and teratogenic effects and various malformations in animals.[1e] Thus, the reaction of azetidine **17a** with 5 equiv of KOH in ethanol under reflux resulted in the corresponding new amino acid 1-*t*-butyl-3-methylazetidine-3-carboxylic acid **18** (23% after purification on a Dowex column) after a prolonged reaction time (120 hours) and without traces of the corresponding amide. The carboxy group in azetidine **18** was then successfully reduced using 2 molar equiv of $LiAlH_4$ in diethyl ether for 3 hours at room temperature to form 3-(hydroxymethyl)azetidine **19** in 90% yield. Furthermore, 3-(aminomethyl)azetidine **20** was obtained after reduction of

the cyano group with 2 molar equiv of $LiAlH_4$ in diethyl ether for 14 hours at room temperature.[16]

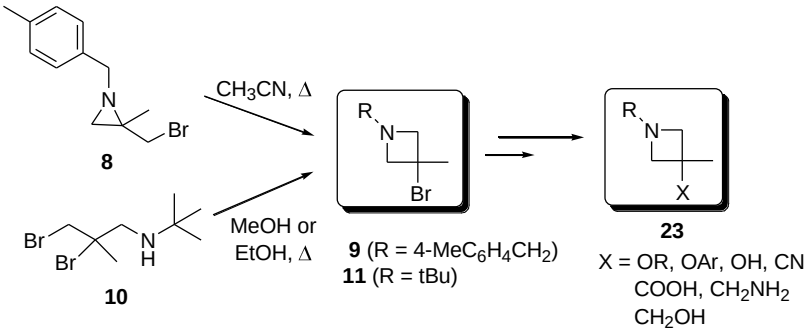
A number of experiments were also performed concerning the hydrolysis of the cyano group in 1-(4-methylbenzyl)azetidine-3-carbonitrile **17b**. The treatment of azetidine **17b** with 5 equiv of KOH in $EtOH/H_2O$ (5/1) under microwave irradiation (150 °C, 15 min, 150 W) and subsequent neutralization with a solution of hydrochloric acid (1M) gave the corresponding new amino acid **21**. Interestingly, two isomeric structures (ratio 3/2) of azetidine **21** were observed upon NMR analysis (CD_3OD), which can be attributed to the zwitterionic nature of this compound providing two diastereomeric counterparts. The purification of amino acid **21** on Dowex H^+ (NH_4OH) afforded ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate **22** as a single isomer in pure form.[17] These observations further support the synthetic utility of 3-bromo-3-methylazetidines as substrates for nucleophilic displacements, e.g. towards the synthesis of versatile 3-methylazetidine-3-carbonitriles.



Scheme 5. Synthesis and reactivity of 3-methylazetidine-3-carbonitriles **17a,b**.

In conclusion, efficient syntheses of 3-bromo-3-methylazetidines **9** and **11** were disclosed starting from 2-bromomethyl-2-methylaziridine **8** and β,γ-dibrominated amine **10**, respectively. Through a number of examples, the azetidines **9** and **11** were shown to easily undergo nucleophilic substitution with different nucleophiles, providing a convenient method for the preparation of new synthetically and biologically attractive 3-substituted azetidines **23**

such as 3-alkoxy-, 3-aryloxy-, 3-hydroxy-, 3-cyano-, 3-carboxy-, 3-(aminomethyl)- and 3-(hydroxymethyl)azetidines (Scheme 6).



Scheme 6. 3-Bromo-3-methylazetidines **9** and **11** as building blocks for the preparation of 3-substituted 3-methylazetidines **23**.

Acknowledgments

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References and notes

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[13] As a representative example, the synthesis of 1-*t*-butyl-3-(4-ethylphenoxy)-3-methylazetidine **15b** is described here. 3-Bromo-1-*t*-butyl-3-methylazetidine **11** (1.03 g, 5 mmol) was dissolved in THF (10 mL), after which 4-ethylphenol (0.61 g, 1 equiv) and K_2CO_3 (1.38 g, 2 equiv) were added, and the mixture was stirred for 48 hours under reflux. The reaction mixture was poured into an aqueous sodium hydroxide solution (1M, 15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-*t*-butyl-3-(4-ethylphenoxy)-3-methylazetidine **15b** (0.88 g, 71%), which was purified by column chromatography (CH_2Cl_2/MeOH 96/4, R_f = 0.15) in order to obtain an analytically pure sample. 1-*t*-Butyl-3-(4-ethylphenoxy)-3-methylazetidine **15b**: Yield 71%; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (9H, s), 1.21 (3H, t, *J* = 7.6 Hz), 1.68 (3H, s), 2.58 (2H, q, *J* = 7.6 Hz), 3.32 (2H, d x d, *J* = 6.9, 1.6 Hz), 3.45 (2H, d, *J* = 6.9), 6.64-7.07 (4H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.8, 22.0, 24.2, 27.9, 52.0, 58.8, 72.1, 116.7, 128.6, 136.5, 153.2. IR (NaCl, cm^{-1}) ν_{max} = 2958, 1602, 1503, 1356, 1310, 1228, 828. MS (70 eV) m/z (%) 247 (M^+, 5), 232 (16), 163 (15), 162 (100), 147 (12), 133 (36), 122 (21), 120 (14), 119 (57), 107 (44), 86 (28), 70 (30), 57 (18), 55 (14).

[14] As a representative example, the synthesis of 3-methyl-1-(4-methylbenzyl)-3-azetidinol **16b** is described here. 3-Bromo-3-methyl-1-(4-methylbenzyl)azetidine **9** (1.27 g, 5 mmol) was added to a two-phase solvent system (H_2O/CH_2Cl_2 9/1, 15 mL), after which KOH (1.40 g, 5 equiv) was added, and the mixture was stirred for 10 hours under reflux. The reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-methyl-1-(4-methylbenzyl)-3-azetidinol **16b** as white crystals (0.92 g, purity > 95% based on NMR analysis). 3-Methyl-1-(4-methylbenzyl)-3-azetidinol **16b**: White crystals; Mp = 85.3 °C. Yield 96%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s), 2.25 (3H, s), 2.99 and 3.20 (4H, 2 x d, *J* = 6.9 Hz), 3.53 (3H, s), 7.02-7.10 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2, 26.1, 63.2, 68.0, 68.9, 128.6, 128.8, 134.9, 136.8. IR (neat, cm^{-1}) ν_{OH} = 3359. MS (70 eV) m/z (%) 192 (M^+ + 1, 100).

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[16] Synthesis of 3-aminomethyl-1-*t*-butyl-3-methylazetidine **20**. To an ice-cooled solution of 1-*t*-butyl-3-methylazetidine-3-carbonitrile **17a** (0.76 g, 5 mmol) in dry diethyl ether (10 mL), $LiAlH_4$ (0.38 g, 2 equiv) was slowly added, and the reaction mixture was stirred first for 3 hours at 0 °C, and then for 14 hours at room temperature. The resulting mixture was poured cautiously into water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-aminomethyl-1-*t*-butyl-3-methylazetidine **20** (0.76 g, 97%) in high purity (purity > 95% based on NMR analysis). 3-Aminomethyl-1-*t*-butyl-3-methylazetidine **20**: Yield 97%; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (9H, s), 1.18 (3H, s), 1.63 (2H, broad s), 2.78 (2H, s), 2.91 and 3.03 (4H, 2 x d, *J* = 7.3 Hz). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 22.7, 24.1, 33.4, 50.9, 51.6, 55.2. IR (NaCl, cm^{-1}) ν_{NH2} = 3680-3000. MS (70eV) m/z (%) no M^+, 141 (M^+-Me, 58), 84 (36), 72 (72), 70 (100), 57 (69), 55 (47), 49 (35).

[17] Synthesis of ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate **22**. 1-(4-Methylbenzyl)azetidine-3-carbonitrile **17b** (0.20 g, 1 mmol) was dissolved in EtOH/H_2O (5/1, 5 mL), after which KOH (0.28 g, 5 equiv) was added. The mixture was placed in an 6-mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (150 °C, 15 min, 150 W). The reaction mixture was neutralized with a solution of hydrochloric acid (1M) to pH = 7 and water was evaporated under high vacuum. Purification of amino acid **21** (two isomeric forms confirmed by NMR analysis) by means of ion-exchange chromatography on Dowex H^+ (50 x 8-100) afforded ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate **22** (0.20 g, 85%). White crystals; Mp > 350 °C. Yield 85%; ^{1}H NMR (300 MHz, CD_3OD) δ 1.41 (3H, s), 2.24 (3H, s), 3.73 and 4.20 (4H, 2 x d, *J* = 10.7 Hz), 4.20 (2H, s), 7.16-7.27 (4H, m). ^{13}C NMR (75 MHz, CD_3OD) δ 21.3, 23.3, 42.3, 59.4, 63.7, 128.6, 131.0, 131.1, 141.2, 180.5. IR (neat, cm^{-1}) ν_{CO} = 1603. MS (70eV) m/z (%) 218 (M^+ + 1, 100).