A new entry into *cis*-3-amino-2-methylpyrrolidines *via* ring expansion of 2-(2-hydroxyethyl)-3-methylaziridines†

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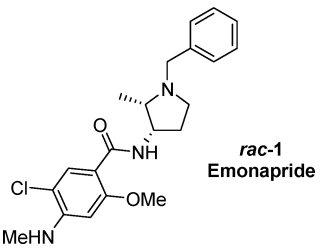
3-Amino-2-methylpyrrolidines were prepared *via* a novel protocol, involving the reductive ring closure and *O*-deprotection of γ-acetoxy-α-chloroketimines towards 2-(2-hydroxyethyl)-3-methylaziridines, followed by ring expansion of the latter into 3-bromopyrrolidines *via* intermediate bicyclic aziridinium salts and consecutive nucleophilic displacement of the bromo atom by azide towards 3-azidopyrrolidines. A final reduction of the azide moiety furnished 3-amino-2-methylpyrrolidines in high yields. Thus, a new formal synthesis of the antipsychotic emonapride was developed through preparation and further aroylation of *cis*-3-amino-1-benzyl-2-methylpyrrolidine.

Introduction

3-Aminopyrrolidines have received considerable interest from a medicinal point of view due to their broad applicability. For example, 7-(3-aminopyrrolidin-1-yl)-substituted naphthyridones and quinolones (such as clinafloxacine and tosufloxacine) have been described as broad-spectrum antibacterial agents,[1] and different types of 3-aminopyrrolidines have been reported in the framework of anti-cancer research.[2] Furthermore, the antipsychotic emonapride **1**, a benzamide derived from the 3-amino-2-methylpyrrolidine scaffold, is of significant pharmacological interest.[3] Consequently, a variety of 3-amino-2-methylpyrrolidine derived benzamides has been prepared and evaluated in terms of potential bioactivity.[4] Despite the pharmaceutical importance of the 3-amino-2-methylpyrrolidine motif, few general and convenient approaches towards this class of compounds are known. 3-Amino-1-benzyl-2-methylpyrrolidine has been prepared from the corresponding pyrrolidin-3-one *via* imination with hydroxylamine and subsequent reduction,[3] and different chiral 3-amino-1-(2-hydroxy-1-phenylethyl)-2-methylpyrrolidines have been synthesized *via* asymmetric conjugate additions to chiral bicyclic lactams followed by reductive cleavage.[5] The first asymmetric synthesis of (2*R*,3*R*)-3-amino-1-benzyl-2-methylpyrrolidine *via* a diastereoselective reductive alkylation has been reported starting from (*S*)-malic acid in 11 steps[6] and, more recently, a one-pot synthesis of 2-substituted 3-nitropyrrolidines has been published based on a multicomponent domino reaction between imines and 3-nitro-1-(methanesulfonyloxy)propane.[7]

In the present paper, a short and straightforward synthetic approach towards *cis*-3-amino-2-methylpyrrolidines *via* ring expansion of 2-(2-hydroxyethyl)-3-methylaziridines is disclosed. Moreover, the high yielding preparation of *cis*-3-amino-1-benzyl-2-methylpyrrolidine implies a new formal synthesis of the antipsychotic emonapride **1**.



***rac*-1**
Emonapride

Results and discussion

As a model substrate for ring expansions of aziridines into pyrrolidines, the synthesis of 2-(2-hydroxyethyl)-2,3-dimethylaziridine **4** was envisaged. Thus, regiospecific alkylation of α-chloroketimine **2**[8] was performed by treatment of the corresponding 3-chloro-1-azaallyl anion, obtained *via* α-deprotonation by means of 1.2 equivalents of lithium diisopropylamide (LDA) in ice-cooled THF for one hour, with 1.05 equivalents of 1-bromo-2-[(trimethylsilyl)oxy]ethane in THF, affording the functionalized ketimine **3** in 70% yield (Scheme 1). Further reaction of the latter imine **3** with 2 molar equivalents of sodium borohydride in methanol under reflux furnished the corresponding 2-(2-hydroxyethyl)aziridine **4** as a 1/1 mixture of *cis*- and *trans*-isomers through hydride addition across the imino bond and subsequent cyclization upon expulsion of chloride (Scheme 1). During the reductive cyclization, hydride-induced deprotection of the silyl ether occurred, resulting in a free hydroxyl terminus. Attempted purification of aziridine **4** by distillation led only to a moderate yield of 44% and a purity of 85%. Treatment of distilled 2-(2-hydroxyethyl)aziridine **4** with 1.2 equivalents of triphenylphosphine and 1.2 equivalents of *N*-bromosuccinimide (NBS) in THF at room temperature for 20 hours furnished 3-bromopyrrolidine **6** as a mixture of *cis*- and *trans*-isomers, which could be separated and isolated by means of column chromatography on silica gel, albeit in low yield due to the small scale experiment. The formation of pyrrolidine **6** can be rationalized considering the initial replacement of the hydroxyl group by a bromo atom, followed by intramolecular nucleophilic substitution by nitrogen upon expulsion of bromide. The thus

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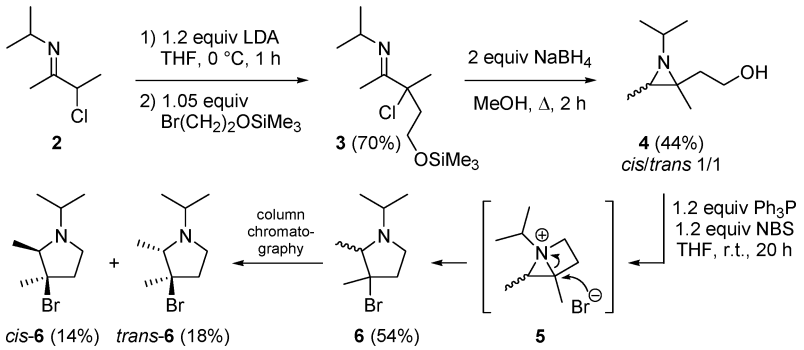
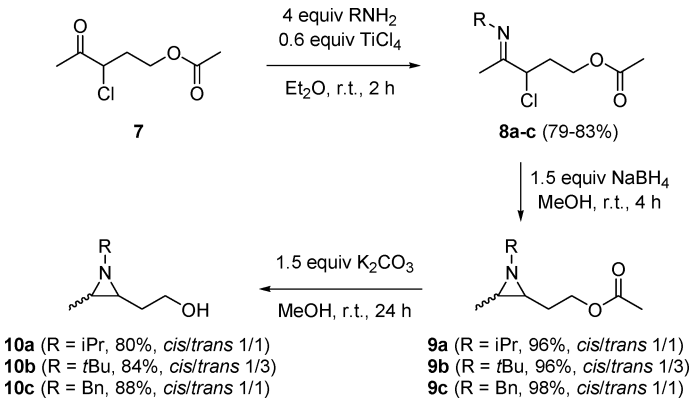


Scheme 1

formed bicyclic aziridinium salt **5** is prone to ring opening by bromide towards pyrrolidine **6** (Scheme 1). Alternatively, the reaction could proceed *via* an oxyphosphorane intermediate instead of *via* the bromide, leading to the same bicyclic intermediate **5**. The ring expansion of 2-(2-hydroxyethyl)aziridines into pyrrolidines *via* intermediate 1-azoniabicyclo[2.1.0]pentanes comprises an unexplored field of research, as only one literature example is known to date.[9] Previously, the alcoholysis of different α-chloro-γ-[(trimethylsily)oxy]ketimines such as **3** has been described, affording a stereospecific entry into *cis*-2-alkoxy-3-aminooxolanes,[10] which underlines the synthetic versatility of this class of imines.

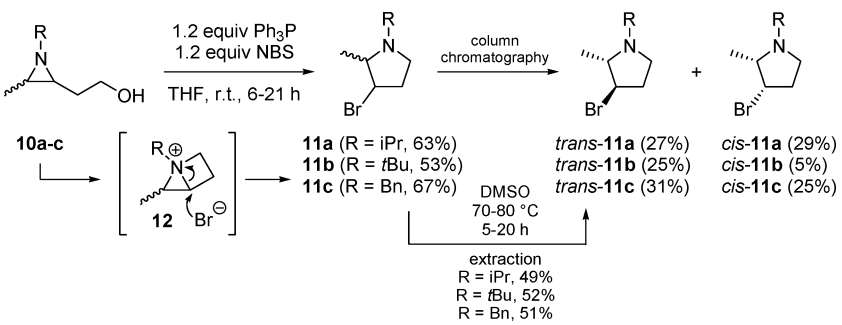
Despite the synthetic relevance of the transformations depicted in Scheme 1, the low yield and purity in which aziridine **4** was isolated called for a different approach. As the hydride-induced *in situ* formation of a free hydroxyl group might be responsible for side reactions in the synthesis of 2-(2-hydroxyethyl)aziridine **4**, a different type of *O*-protecting group was required which is less reactive towards sodium borohydride. Thus, γ-acetoxyketimines **8a–c** were prepared *via* imination of 5-acetoxy-3-chloropentan-2-one **7**[11] utilizing 4 equivalents of a primary amine in diethyl ether in the presence of 0.6 equivalents of titanium(IV) chloride at room temperature (Scheme 2). Subsequent reduction of the imino moiety and ring closure by means of 1.5 equivalents of sodium borohydride in methanol at room temperature furnished 2-(2-acetoxyethyl)aziridines **9a–c** as mixtures of *cis*- and *trans*-isomers (1/1–1/3) in excellent yields (Scheme 2). The *O*-protecting group in the latter aziridines **9** was easily removed upon reaction with a methanolic solution of 1.5 equivalents of potassium carbonate at room temperature for 24 hours, yielding 2-(2-hydroxyethyl)aziridines **10a–c** in high yields and purity (Scheme 2).



Scheme 2

The ratio of *cis*/*trans*-isomers for aziridines **9** and **10** could be assigned by comparison of ^{13}C NMR values for both isomers with literature data of analogous 2,3-dimethylaziridines.[12]

In the next step, 2-(2-hydroxyethyl)-3-methylaziridines **10** were converted into 3-bromo-2-methylpyrrolidines **11a–c** *via* intermediate bicyclic aziridinium salts **12** by the action of 1.2 equivalents of triphenylphosphine and 1.2 equivalents of NBS in THF at room temperature (Scheme 3). Although *cis*- and *trans*-pyrrolidines **11** could be separated by means of column chromatography, a convenient alternative for this laborious method comprised heating of the mixtures of *cis*/*trans*-**11** in DMSO at 70–80 °C for 5–20 hours, followed by aqueous workup and extraction with diethyl ether. In this way, only *trans*-pyrrolidines *trans*-**11** were obtained in high yields (49–52% after purification by column chromatography).



Scheme 3

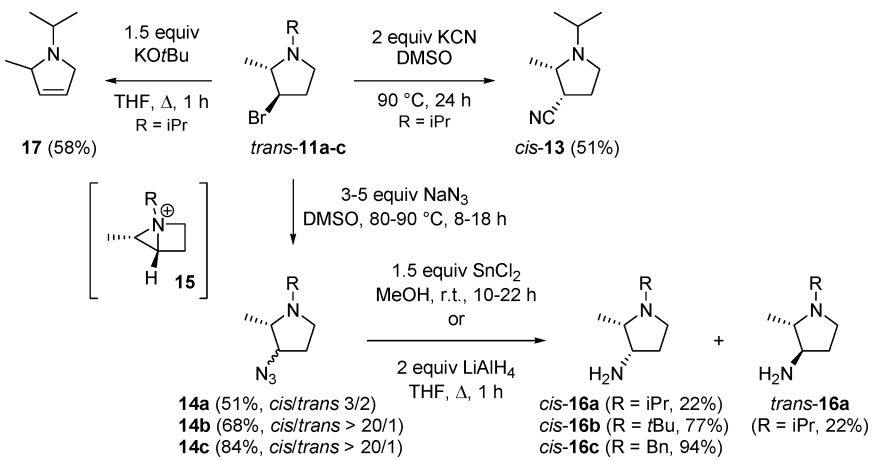
At first instance, an equilibrium shift from the bridged bicyclic ammonium ions **12**–formed by heating of the mixture of *cis*/*trans*-**11** in DMSO–to the corresponding carbenium ions by spontaneous ring opening, followed by neutralization of the latter carbenium ions by bromide was assumed to be responsible for the preferential formation of the more stable *trans*-pyrrolidines *trans*-**11**. However, this assumption could not be supported by experimental observations, as no isomerisation of *cis*-**11** into *trans*-**11** occurred by simply heating pure *cis*-pyrrolidines *cis*-**11** under the same conditions (DMSO, 70 °C, 20 h). At present, no conclusive explanation can be provided for the experimental observation that only *trans*-pyrrolidines *trans*-**11** were obtained upon heating of the mixtures of *cis*/*trans*-**11** in DMSO at 70–80 °C for 5–20 hours, followed by aqueous workup and extraction with diethyl ether. The fact that heating of *cis*/*trans*-pyrrolidines *cis*/*trans*-**11** was performed on the crude reaction mixture, in which presumably some bromine or another weak Lewis acid activator was present, might be of importance in that respect.

3-Bromopyrrolidines **11** constitute suitable substrates for further functionalization upon nucleophilic substitution of the halo atom. Treatment of *trans*-**11a** with 2 equivalents of potassium cyanide in DMSO for 24 hours at 90 °C afforded the corresponding *cis*-3-cyanopyrrolidine *cis*-**13** *via* a clean S_N2 protocol (Scheme 4). Recently, a variety of 2-substituted pyrrolidine-3-carbonitriles has been prepared as potential therapeutics for the treatment of glaucoma.[13] When azide was used instead of cyanide, 3-azidopyrrolidines **14a–c** were formed utilizing 3–5 equivalents of sodium azide in DMSO at 80–90 °C for 8–18 hours (Scheme 4). Remarkably, 3-azido-1-isopropylpyrrolidine **14a** was obtained as a mixture of *cis*/*trans*-isomers (*cis*/*trans* 3/2), whereas 3-azido-substituted 1-*tert*-butyl- and 1-benzylpyrrolidines **14b** and **14c** were formed predominantly as *cis*-isomers (*cis*/*trans* > 20/1). The formation of *trans*-3-azidopyrrolidines **14** can be explained considering the formation of an intermediate bicyclic aziridinium salt **15**, followed by ring opening by azide at the more hindered position. In this case, double Walden inversion – *i.e.* two times S_N2 reaction – results in retention of configuration, affording *trans*-pyrrolidines as the substitution products. Obviously, the competition between direct S_N2 substitution and formation of a constrained bicyclic intermediate in these reactions is dependant on the type of nucleophile (cyanide *vs.* azide) and, to a lesser extent, the *N*-substituent in the substrate (isopropyl *vs. tert*-butyl and benzyl). In the literature, nucleophilic substitutions of 3-halo- or 3-(sulfonyloxy)pyrrolidines usually proceed *via* a direct S_N2 process, although also double substitution reactions *via* intermediate bicyclic aziridinium salts are known.[14] The preference for one of these routes has been described to be dependant on different factors such as the solvent,[15] the type of nucleophile[16] and the relative stereochemistry of the substrate.[17]

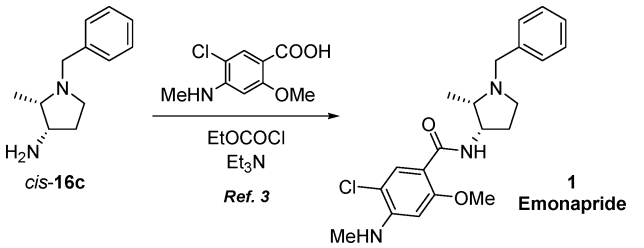
The final goal of this work comprised the synthesis of biologically relevant 3-amino-2-methylpyrrolidines **16**, which were obtained by azide reduction upon treatment of pyrrolidines **14** with 1.5 equivalents of tin(II) chloride in methanol at room temperature (for R = iPr and *t*Bu) or with 2 equivalents of lithium aluminium hydride in THF under reflux (for R = Bn) (Scheme 4). The relative stereochemistry of pyrrolidines **11**, **13**, **14** and **16** could be assigned based on NOE effects between the 2-methyl group and the hydrogen atoms at the 2- and the 3-position (for example, a NOE of 1.8% and 2.5% was observed between 2-H and 3-H for *cis*-1-isopropylpyrrolidines **13** and **14a**, respectively). Besides substitution reactions, dehydrobromination of 3-bromopyrrolidine *trans*-**11a** was evaluated using 1.5 equivalents of potassium *tert*-butoxide in THF under reflux, affording 2-methyl-3-pyrroline **17** in 58% yield (Scheme 4).

The stereochemical assignment of *cis*-/*trans*-pyrrolidines **11a–c**, **14a** and **16a** was further supported by careful analysis of spectroscopical data. In the literature, 2,3-disubstituted pyrrolidines are characterized by a so called "γ-gauche effect" in ^{13}C NMR for the carbon atom present at the 2-position. This effect results in a significant difference in chemical shift $\Delta(\delta_{trans} - \delta_{cis})$ of 3–5 ppm between *cis* and *trans* isomers.[18] Also for pyrrolidines **11a–b**, **14a** and **16a**, a $\Delta(\delta_{trans} - \delta_{cis})$ ranging from 2.2 to 3.8 was observed, which confirmed the postulated stereochemical assignment.

The above-described methodology for the preparation of *cis*-3-amino-1-benzyl-2-methylpyrrolidine *cis*-**16c** allows the formal synthesis of the antipsychotic (±)-emonapride **1** in high overall yield, as the coupling of pyrrolidine *cis*-**16c** with 5-chloro-2-methoxy-4-(methylamino)benzoic acid in the presence of ethyl chloroformiate and triethylamine has been described in the literature to afford emonapride **1** (Scheme 5).[3] In the light of the pharmaceutical importance of emonapride **1** and its derivatives, the present methodology offers a useful and efficient alternative



Scheme 4



Scheme 5

for the limited number of known synthetic methodologies towards this class of compounds.

In conclusion, a novel and efficient approach towards biologically relevant 3-amino-2-methylpyrrolidines has been developed starting from γ-acetoxy-α-chloroketimines. This methodology involves the reductive ring closure and *O*-deprotection of γ-acetoxy-α-chloroketimines towards 2-(2-hydroxyethyl)-3-methylaziridines, followed by ring expansion of the latter into 3-bromopyrrolidines *via* intermediate bicyclic aziridinium salts and consecutive nucleophilic displacement of the bromo atom by azide. A final reduction of the azide moiety afforded the title compounds in good yields. Furthermore, the straightforward preparation of *cis*-3-amino-1-benzyl-2-methylpyrrolidine implies a new formal synthesis of the antipsychotic emonapride.

Experimental section

Synthesis of *N*-[2-chloro-1-methyl-2-(2-trimethylsilyloxyethyl)propylidene] isopropylamine 3

To an ice-cooled solution of diisopropylamine (12 mmol) in dry THF (10 mL) under nitrogen atmosphere was added *n*-BuLi (12 mmol, 2.5 M in hexane) *via* a syringe. After 10 minutes, a solution of α-chloroketimine **2**[8] (10 mmol) in THF (5 mL) was added *via* a syringe, after which the resulting solution was stirred for 1 hour at 0 °C. Subsequently, a solution of 1-bromo-2-[(trimethylsilyl)oxy]ethane (10.5 mmol) in THF (5 mL) was added *via* a syringe at 0 °C, and the resulting solution was stirred for 15 hours at room temperature. Afterwards, the reaction mixture was poured into an aqueous solution of NaOH (15 mL, 0.5 M) and extracted with Et_2O (3 × 15 mL). Drying (K_2CO_3), removal of the drying agent and evaporation of the solvent afforded the crude imine **3**, which was purified by distillation (Bp. 60–62 °C/0.05 mmHg).

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.10 (9H, s); 1.10 (6H, d, J = 6 Hz); 1.70 (3H, s); 1.99 (3H, s); 2.0-2.4 (2H, m); 3.6-3.8 (1H, m); 3.76 (2H, t, J = 7 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ –0.5, 12.9, 23.2, 28.4, 44.5, 50.7, 59.3, 74.9, 164.5. IR (NaCl): $\nu_{C=N}$ = 1651 cm^{-1}. MS (70 eV): *m*/*z* (%): no M$^+$; 248/50 (7); 228 (5); 147/9 (92); 132 (17); 112 (23); 96 (20); 84 (100); 73 (21).

Synthesis of 2-(2-hydroxyethyl)-1-isopropyl-2,3-dimethylaziridine 4

To an ice-cooled solution of imine **3** (5 mmol) in methanol (10 mL) was added $NaBH_4$ (10 mmol) in small portions, and the resulting mixture was heated under reflux for 2 hours. Afterwards, the reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded the crude aziridine **4**, which was purified by distillation (Bp. 50–54 °C/0.3 mmHg).

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.05 (3H, d, J = 6.6 Hz); 1.09 and 1.10 (6H, 2 × d, J = 6.3 Hz); 1.00-1.24 (11H, m); 1.25 and 1.26 (6H, 2 × s); 1.61 (4H, ~t, J = 6.3 Hz); 2.19 (2H, ~septet, J = 6.3 Hz); 3.56–3.92 (4H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.9, 17.2, 20.6, 23.1, 23.2, 23.3, 23.4, 35.9, 36.5, 41.8, 43.2, 43.5, 44.4, 52.8, 52.9, 60.77, 60.81. IR (NaCl): ν_{OH} = 3570–3050 cm^{-1}. MS (70 eV): *m*/*z* (%): 157 (M$^+$, 1); 142 (5); 128 (3); 126 (6); 124 (5); 114 (16); 112 (13); 98 (10); 96 (4); 94 (5); 86 (32); 84 (29); 82 (8); 70 (79); 67 (6); 58 (10); 55 (12); 53 (6).

Synthesis of 3-bromo-1-isopropyl-2,3-dimethylpyrrolidine 6

To a solution of aziridine **4** (5 mmol) in THF (30 mL) was added *N*-bromosuccinimide (6 mmol) and triphenylphosphine (6 mmol) at room temperature, after which the mixture was stirred for 20 hours at room temperature. Afterwards, the reaction mixture was poured into water (30 mL) and extracted with Et_2O (3 × 25 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded a residue, to which Et_2O (25 mL) was added. After a second filtration, Et_2O (25 mL) was added and the suspension was stored at –20 °C for 15 hours. A final filtration and evaporation of the solvent afforded the crude pyrrolidine *cis*/*trans*-**6**, which was purified by column chromatography on silica gel (hexane/EtOAc/MeOH 90/7/3) in order to separate both isomers.

cis-3-Bromo-1-isopropyl-2,3-dimethylpyrrolidine *cis*-6

R_f 0.11 (hexane/EtOAc/MeOH 90/7/3). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 and 1.15 (6H, 2 × d, J = 6.6 Hz); 1.14 (3H, d, J = 5.9 Hz); 1.79 (3H, s); 1.97 (1H, d × d × d, J = 14.1, 9.9, 7.7 Hz); 2.27 (1H, q, J = 5.9 Hz); 2.46 (1H, d × d × d, J = 14.1, 7.9, 3.6 Hz); 2.68 (1H, t × d, J = 9.9, 3.6 Hz); 3.01-3.12 (1H, m); 3.09 (1H, septet, J = 6.6 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.3, 16.8, 22.1, 30.0, 42.3, 43.1, 47.4, 65.8, 75.5. IR (NaCl): ν_{max} = 2958, 1448, 1375, 1358, 1100 cm^{-1}. MS (70 eV): *m*/*z* (%): 219/21 (M$^+$, 11); 204/6 (49); 140 (50); 137 (11); 125 (21); 124 (61); 122 (12); 110 (18); 98 (91); 96 (21); 94 (31); 84 (22); 83 (28); 82 (25); 81 (19); 69 (17); 56 (100); 53 (19); 49 (11). Anal. Calcd for $C_9H_{18}BrN$: C 49.10, H 8.24, N 6.36. Found: C 49.73, H 8.56, N 6.52.

trans-3-Bromo-1-isopropyl-2,3-dimethylpyrrolidine *trans*-6

R_f 0.29 (hexane/EtOAc/MeOH 90/7/3). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 and 1.11 (6H, 2 × d, J = 6.6 Hz); 1.02 (3H, d, J = 6.6 Hz); 1.77 (3H, s); 2.04 (1H, d × d × d, J = 13.6, 9.0, 7.6 Hz); 2.27 (1H, d × d×d, J = 13.6, 7.1, 2.6 Hz); 2.82-3.00 (2H, m); 3.00 (1H, septet, J = 6.6 Hz); 3.36 (1H, q, J = 6.6 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 16.9, 22.3, 17.9, 28.5, 42.2, 45.6, 50.4, 68.0, 72.2. IR (NaCl): ν_{max} = 2960, 1500, 1378, 1210, 1170, 1074 cm^{-1}. MS (70 eV): *m*/*z* (%): 219/21 (M$^+$, 16); 204/6 (77); 140 (58); 137 (16); 125 (45); 124 (87); 122 (14); 110 (33); 98 (99); 96 (22); 94 (36); 83 (30); 82 (35); 81 (20); 70 (16); 56 (100). Anal. Calcd for $C_9H_{18}BrN$: C 49.10, H 8.24, N 6.36. Found: C 49.39, H 8.38, N 6.27.

Synthesis of *N*-(4-acetoxy-2-chloro-1-methylbutylidene)amines 8

General procedure: To a solution of 5-acetoxy-3-chloropentan-2-one **7**[11] (10 mmol) in dry Et_2O (25 mL) was added amine (40 mmol), followed by the gentle addition of a solution of $TiCl_4$ (6 mmol) in pentane (10 mL) at 0 °C, after which the resulting mixture was stirred for 2 hours at room temperature. Afterwards, the reaction mixture was poured into an aqueous solution of NaOH (15 mL, 0.5 M) and extracted with Et_2O (3 × 25 mL). Drying (K_2CO_3), removal of the drying agent and evaporation of the solvent afforded the crude imine **8**, which was purified by distillation. For the synthesis of *N*-benzylimine **8c**, a mixture of 1 equiv of benzylamine and 3 equiv of Et_3N was used instead of 4 equiv of benzylamine.

***N*-(4-Acetoxy-2-chloro-1-methylbutylidene)isopropylamine 8a**

Bp. 53–56 °C/0.03 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.10 and 1.13 (6H, 2 × d, J = 6.3 Hz); 1.94 (3H, s); 2.05-2.35 (2H, m); 3.69 (1H, septet, J = 6.3 Hz); 4.15–4.30 (2H, m); 4.49 (1H, d × d, J = 8.9, 6.0 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.9, 20.9, 23.0, 34.1, 50.8, 61.2, 64.0, 163.2, 170.9. IR (NaCl): $\nu_{C=O}$ = 1740 cm^{-1}, $\nu_{C=N}$ = 1658 cm^{-1}. MS (70 eV): *m*/*z* (%): 218/220 (M^+, 0.4); 184/6 (3); 144/6 (5); 134/6 (3); 133/5 (21); 120 (3); 119 (2); 118 (5); 112 (2); 108 (2); 104 (2); 98 (7); 85 (4); 84 (37); 82 (4); 80 (2); 76 (4); 70 (2); 68 (2); 67 (3); 61 (3); 60 (2); 55 (5); 54 (3); 53 (2); 49 (2); 42 (100).

Synthesis of 2-(2-acetoxyethyl)-3-methylaziridines 9

General procedure: To an ice-cooled solution of imine **8** (5 mmol) in methanol (10 mL) was added $NaBH_4$ (7.5 mmol) in small portions, and the resulting mixture was stirred at room temperature for 4 hours. Afterwards, the reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded aziridine **9**. The isomers *cis*/*trans*-**9a** and *cis*/*trans*-**9b** were separated by preparative gas chromatography.

***cis*-2-(2-Acetoxyethyl)-1-isopropyl-3-methylaziridine *cis*-9a**

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.09 and 1.11 (6H, 2 × d, J = 6.3 Hz); 1.15 (3H, d, J = 5.6 Hz); 1.36-1.58 (3H, m); 1.60-1.88 (2H, m); 2.07 (3H, s); 4.20 (2H, t, J = 6.5 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.7, 21.0, 21.9, 27.5, 37.8, 40.1, 61.1, 63.2, 171.1. IR (NaCl): $\nu_{C=O}$ = 1738 cm^{-1}. MS (70 eV): *m*/*z* (%): 185 (M^+, 4); 170 (5); 142 (14); 126 (24); 125 (6); 112 (45); 110 (16); 100 (9); 85 (7); 84 (16); 83 (13); 82 (100); 72 (5); 71 (5); 70 (64); 69 (8); 68 (12); 67 (6); 58 (5); 57 (6); 56 (23); 55 (25); 54 (13); 42 (100). Anal. Calcd for $C_{10}H_{19}NO_2$: C 64.83, H 10.34, N 7.56. Found: C 64.62, H 10.07, N 7.44.

***trans*-2-(2-Acetoxyethyl)-1-isopropyl-3-methylaziridine *trans*-9a**

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.10 (6H, d, J = 6.1 Hz); 1.28 (3H, d, J = 5.9 Hz); 1.10-1.25 (1H, m); 1.45-1.92 (3H, m); 2.06 (3H, s); 2.21 (1H, septet, J = 6.1 Hz); 4.18 (2H, d × d, J = 7.4, 5.8 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 11.1, 21.0, 22.9, 23.0, 32.5, 38.2, 41.5, 50.8, 63.0, 171.1. IR (NaCl): $\nu_{C=O}$ = 1739 cm^{-1}. MS (70 eV): *m*/*z* (%): 185 (M^+, 4); 170 (5); 142 (14); 126 (24); 125 (6); 112 (45); 110 (16); 100 (9); 85 (7); 84 (16); 83 (13); 82 (100); 72 (5); 71 (5); 70 (64); 69 (8); 68 (12); 67 (6); 58 (5); 57 (6); 56 (23); 55 (25); 54 (13); 42 (100). Anal. Calcd for $C_{10}H_{19}NO_2$: C 64.83, H 10.34, N 7.56. Found: C 64.59, H 10.10, N 7.54.

Synthesis of 2-(2-hydroxyethyl)-3-methylaziridines 10

General procedure: To a solution of aziridine **9** (10 mmol) in dry methanol (20 mL) was added K_2CO_3 (15 mmol), and the resulting mixture was stirred at room temperature for 24 hours. Afterwards, the reaction mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded the crude aziridine **10**, which was purified by distillation.

2-(2-Hydroxyethyl)-1-isopropyl-3-methylaziridine 10a

Bp. 85–92 °C/8 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11, 1.13, 1.15, 1.16 and 1.28 (2 × 9H, 5 × d, J = 6.2 Hz); 1.39-2.25 (2 × 5H, m); 3.57-3.92 (2 × 2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): $\delta_{cis\text{-}\mathbf{10a}}$ 13.6, 21.8, 21.9, 29.9, 37.6, 40.8, 61.1, 61.3. $\delta_{trans\text{-}\mathbf{10a}}$ 10.8, 22.7, 23.0, 32.8, 36.2, 42.6, 50.9, 60.3. IR (NaCl): ν_{OH} = 3540–3020 cm^{-1}. MS (70 eV): m/z$_{cis\text{-}\mathbf{10a}}$ (%): 143 (M^+, 4); 128 (17); 112 (57); 100 (27); 98 (11); 84 (11); 70 (100); 57 (17); 56 (82); 55 (14). m/z$_{trans\text{-}\mathbf{10a}}$ (%): 143 (M^+, 8); 128 (19); 112 (55); 100 (28); 99 (11); 98 (13); 84 (25); 70 (100); 56 (84). Anal. Calcd for $C_8H_{17}NO$: C 67.09, H 11.96, N 9.78. Found: C 67.27, H 12.19, N 7.66.

Synthesis of 3-bromo-2-methylpyrrolidines 11

General procedure: To a solution of aziridine **10** (5 mmol) in THF (30 mL) was added *N*-bromosuccinimide (6 mmol) and triphenylphosphine (6 mmol) at room temperature, after which the mixture was stirred for 6–21 hours at room temperature. Afterwards, the reaction mixture was poured into water (30 mL) and extracted with Et_2O (3 × 25 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded a residue, to which Et_2O (25 mL) was added. After a second filtration, Et_2O (25 mL) was added and the suspension was stored at −20 °C for 15 hours. A final filtration and evaporation of the solvent afforded the crude pyrrolidine *cis*/*trans*-**11**, which was purified by column chromatography on silica gel in order to separate both isomers.

Remark. As an alternative for the separation of *cis*/*trans*-pyrrolidines **11** by column chromatography, the following procedure can be applied. Heating of the crude mixture of *cis*/*trans*-**11** in DMSO at 70–80 °C for 5–20 hours, followed by aqueous workup and extraction with diethyl ether afforded only *trans*-pyrrolidines *trans*-**11**, which were purified by column chromatography on silica gel to furnish pure *trans*-**11** in 49–52% yield.

***cis*-3-Bromo-1-isopropyl-2-methylpyrrolidine *cis*-11a**

R_f 0.15 (hexane/EtOAc/MeOH 90/8/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 and 1.12 (6H, 2 × d, J = 6.4 Hz); 1.14 (3H, d, J = 6.3 Hz); 2.15-2.47 (2H, m); 2.65 (1H, d × t, J = 8.9, 6.5 Hz); 2.84–3.05 (3H, m); 4.40 (1H, d × t, J = 6.6, 5.3 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.6, 16.7, 21.9, 34.5, 44.6, 48.5, 55.5, 58.2. IR (NaCl): ν_{max} = 2960, 1450, 1380, 1188 cm^{-1}. MS (70 eV): *m*/*z* (%): 205/7 (M^+, 24); 190/2 (100); 148/50 (11); 126 (43); 111 (26); 110 (26); 96 (20); 85 (13); 84 (77); 83 (15); 82 (22); 81 (10); 80 (16); 69 (38); 68 (22); 67 (29); 57 (34); 56 (69); 55 (28); 54 (12); 53 (11). Anal. Calcd

for $C_8H_{16}BrN$: C 46.62, H 7.82, N 6.80. Found: C 46.49, H 7.73, N 6.85.

***trans*-3-Bromo-1-isopropyl-2-methylpyrrolidine *trans*-11a**

R_f 0.11 (hexane/EtOAc/MeOH 90/8/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.97 and 1.12 (6H, 2 × d, J = 6.6 Hz); 1.14 (3H, d, J = 6.3 Hz); 1.98-2.11 and 2.32-2.50 (2H, 2 × m); 2.74–3.10 (3H, m); 3.02 (1H, septet, J = 6.6 Hz); 3.89 (1H, d × t, J = 7.6, 5.0 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.5, 18.9, 21.9, 33.8, 45.2, 49.3, 54.5, 65.1. IR (NaCl): ν_{max} = 2960, 1455, 1381, 1363, 1208, 1171 cm^{-1}. MS (70 eV): *m/z* (%): 205/7 (M^+, 20); 190/2 (100); 148/50 (15); 126 (20); 111 (33); 110 (25); 96 (21); 84 (45); 83 (11); 82 (16); 80 (12); 69 (37); 68 (22); 67 (21); 57 (23); 56 (52); 55 (23); 54 (10). Anal. Calcd for $C_8H_{16}BrN$: C 46.62, H 7.82, N 6.80. Found: C 46.81, H 8.06, N 6.93.

Synthesis of *cis*-3-cyano-1-isopropyl-2-methylpyrrolidine *cis*-13

To a solution of pyrrolidine *trans*-**11a** (2 mmol) in DMSO (10 mL) was added KCN (4 mmol), and the resulting mixture was heated at 90 °C for 24 hours. Afterwards, the reaction mixture was poured into water (15 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were then washed with brine (2 × 20 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded 3-cyanopyrrolidine *cis*-**13**, which was purified by column chromatography on silica gel (hexane/EtOAc/MeOH 76/19/5).

R_f 0.20 (hexane/EtOAc/MeOH 76/19/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.93 and 1.13 (6H, 2 × d, J = 6.6 Hz); 1.20 (3H, d, J = 5.9 Hz); 1.97 and 2.18 (2H, 2 × d, J = 12.9 Hz); 2.53 (1H, d × d×d, J = 9.6, 7.9, 6.5 Hz); 2.60-2.72 and 2.85-3.01 (2H, m); 2.81-2.95 (1H, m); 3.07 (1H, septet, J = 6.6 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.8, 22.1, 18.1, 26.9, 35.0, 44.3, 47.4, 59.7, 121.9. IR (NaCl): ν_{CN} = 2213 cm^{-1}. MS (70 eV): *m/z* (%): 152 (M^+, 13); 137 (100); 109 (6); 95 (23); 84 (7); 71 (5); 70 (8); 68 (10); 57 (15); 56 (18). Anal. Calcd for $C_9H_{16}N_2$: C 71.01, H 10.59, N 18.40. Found: C 71.16, H 10.70, N 18.32.

Synthesis of 3-azido-2-methylpyrrolidines 14

General procedure: To a solution of pyrrolidine *trans*-**11** (6 mmol) in DMSO (30 mL) was added NaN_3 (18-30 mmol), and the resulting mixture was heated at 80–90 °C for 8–18 hours. Afterwards, the reaction mixture was poured into water (45 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were then washed with brine (2 × 50 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded 3-azidopyrrolidine **14**, which was purified by column chromatography on silica gel.

***cis*-3-Azido-1-isopropyl-2-methylpyrrolidine *cis*-14a**

R_f 0.18 (hexane/EtOAc/MeOH 76/19/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.90 and 1.12 (6H, 2 × d, J = 6.6 Hz); 1.09 (3H, d, J = 6.3 Hz); 1.89 and 2.10 (2H, d × d×d × d, J = 13.4, 9.0, 7.3, 4.5 Hz); 2.55 (1H, t × d, J = 9.0, 7.3 Hz); 2.81-2.98 (2H, m); 3.00 (1H, septet, J = 6.6 Hz); 3.78 (1H, d × t, J = 7.3, 4.5 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.5, 14.2, 22.0, 28.7, 43.6, 47.5, 58.4, 64.3. IR (NaCl): ν_{N3} = 2100 cm^{-1}. MS (70 eV): *m/z* (%): 168 (M^+, 14); 153 (13); 125 (12); 113 (15); 98 (8); 85 (18); 84 (28); 83 (21); 82 (14); 70 (100); 68 (14); 68 (14); 56 (86); 55 (17). Anal. Calcd for $C_8H_{16}N_4$: C 57.11, H 9.59, N 33.30. Found: C 57.37, H 9.95, N 33.54.

***trans*-3-Azido-1-isopropyl-2-methylpyrrolidine *trans*-14a**

R_f 0.20 (hexane/EtOAc/MeOH 76/19/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96, 1.11 and 1.13 (9H, 3 × d, J = 6.3 Hz); 1.68-1.81 and 2.08-2.21 (2H, m); 2.61-2.73 and 2.82-3.05 (4H, m); 3.51 (1H, t × d, J = 8.1, 4.0 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 15.8, 18.3, 21.9, 28.7, 45.0, 48.8, 61.0, 67.3. IR (NaCl): ν_{N3} = 2085 cm^{-1}. MS (70 eV): *m/z* (%): 168 (M^+, 7); 153 (7); 125 (11); 113 (15); 98 (9); 85 (16); 84 (25); 83 (12); 70 (100); 68 (11); 56 (69); 55 (13). Anal. Calcd for $C_8H_{16}N_4$: C 57.11, H 9.59, N 33.30. Found: C 57.43, H 9.82, N 33.46.

Synthesis of 3-amino-2-methylpyrrolidines 16a,b

General procedure: To a solution of pyrrolidine **14** (1 mmol) in dry methanol (3 mL) under nitrogen atmosphere was added $SnCl_2$ (1.5 mmol), and the resulting mixture was stirred for 10–22 hours at room temperature. Afterwards, the reaction mixture was poured into an aqueous solution of NaOH (30 mL, 0.5 M) and extracted with CH_2Cl_2 (3 × 20 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded the crude pyrrolidine **16**, which was purified by column chromatography on silica gel.

***cis*-3-Amino-1-isopropyl-2-methylpyrrolidine *cis*-16a**

R_f 0.11 (CH_2Cl_2/MeOH/NH_4OH(25%) 43.7/10.9/1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.98 and 1.15 (6H, 2 × d, J = 6.6 Hz); 1.04 (3H, d, J = 6.3 Hz); 1.44-1.55 and 1.96-2.15 (2H, 2 × m); 2.56 (1H, ~q, J = 8.6 Hz); 2.79 (1H, pent, J = 6.3 Hz); 2.92 (1H, t × d, J = 8.6, 4.0 Hz); 2.99 (1H, septet, J = 6.6 Hz); 3.30 (1H, q, J = 6.3 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.6, 15.4, 21.6, 32.5, 44.4, 48.8, 54.3, 58.7. IR (NaCl): ν_{NH2} = 3560–3000 cm^{-1}. MS (70 eV): *m/z* (%): 142 (M^+, 26); 127 (31); 99 (38); 86 (25); 85 (25); 84 (50); 82 (23); 80 (24); 72 (26); 71 (32); 70 (26); 57 (88); 56 (100). Anal. Calcd for $C_8H_{18}N_2$: C 67.55, H 12.75, N 19.69. Found: C 67.72, H 12.91, N 19.51.

***trans*-3-Amino-1-isopropyl-2-methylpyrrolidine *trans*-16a**

R_f 0.14 (CH_2Cl_2/MeOH/NH_4OH(25%) 43.7/10.9/1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96 and 1.14 (6H, 2 × d, J = 6.5 Hz); 1.11 (3H, d, J = 6.2 Hz); 1.33-1.46 (1H, m); 1.45-1.90 (2H, m); 2.15 (1H, d × q, J = 12.7, 7.9 Hz); 2.34 (1H, pent, J = 6.0 Hz); 2.70 (1H, d × t, J = 8.9, 8.2 Hz); 2.88 (1H, t × d, J = 8.9, 4.0 Hz); 2.90–3.02 (1H, m); 3.03 (1H, septet, J = 6.5 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.7, 17.1, 21.8, 32.5, 44.0, 48.4, 58.4, 64.5. IR (NaCl): ν_{NH2} = 3590–3000 cm^{-1}. MS (70 eV): *m/z* (%): 142 (M^+, 40); 127 (47); 99 (54); 86 (39); 85 (42); 84 (64); 80 (36); 72 (41); 71 (46); 70 (41); 58 (40); 57 (97); 56 (100). Anal. Calcd for $C_8H_{18}N_2$: C 67.55, H 12.75, N 19.69. Found: C 67.80, H 12.97, N 19.81.

Synthesis of *cis*-3-amino-1-benzyl-2-methylpyrrolidine *cis*-16c

To an ice-cooled solution of pyrrolidine **14c** (4 mmol) in dry THF (10 mL) was added $LiAlH_4$ (8 mmol) in small portions, and the resulting suspension was heated under reflux for 1 hour. Afterwards, water (3 mL) was added at 0 °C in order to neutralize

the excess of $LiAlH_4$. The mixture was stirred for 10 minutes, after which the grey suspension was filtered over K_2CO_3 and celite. The filter cake was then washed thoroughly with dry ether (3 × 20 mL). Removal of the solvent *in vacuo* afforded pyrrolidine *cis*-**16c** (purity > 97% based on GC).

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.12 (3H, d, J = 6.4 Hz); 1.35-1.51 and 1.96-2.19 (5H, 2 × m); 2.34 (1H, quint, J = 6.4 Hz); 2.89 (1H, t × d, J = 8.7, 2.3 Hz); 3.14 (1H, d, J = 13.1 Hz); 3.21-3.29 (1H, m); 3.97 (1H, d, J = 13.1 Hz); 7.19-7.38 (5H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.6, 33.0, 51.8, 54.6, 57.9, 63.0, 126.8, 128.1, 128.8, 139.5. IR (NaCl): ν_{NH2} = 3380–3200 cm^{-1}. MS (70 eV): *m*/*z* (%): 190 (M^+, 1); 173 (12); 147 (19); 91 (30); 65 (6); 56 (100). Anal. Calcd for $C_{12}H_{18}N_2$: C 75.74, H 9.53, N 14.72. Found: C 75.96, H 9.70, N 14.87.

Synthesis of 1-isopropyl-2-methyl-3-pyrroline 17

To a solution of pyrrolidine **11a** (2.5 mmol) in THF (5 mL) was added KO*t*Bu (3.75 mmol), and the resulting mixture was heated under reflux for 1 hour. Afterwards, the reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent afforded pyrroline **17** (purity > 95% based on GC).

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.03 and 1.12 (6H, 2 × d, J = 6.4 Hz); 1.15 (3H, d, J = 6.3 Hz); 2.92 (1H, septet, J = 6.4 Hz); 3.46 and 3.67 (2H, 2 × d, J = 13.9 Hz); 3.68-3.83 (1H, m); 5.62 and 5.71 (2H, 2 × d, J = 6.1 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.9, 22.0, 21.5, 50.9, 55.8, 62.0, 125.9, 133.4. IR (NaCl): ν_{max} = 2960, 1382, 1365, 1180 cm^{-1}. MS (70 eV): *m*/*z* (%): 125 (M^+, 19); 110 (67); 82 (19); 80 (7); 68 (100); 55 (21). Anal. Calcd for $C_8H_{15}N$: C 76.74, H 12.07, N 11.19. Found: C 76.97, H 12.26, N 11.04.

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