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Synthesis of 1-alkyl-2-methylazetidin-3-ones and 1-alkyl-2-methylazetidin-3-ols

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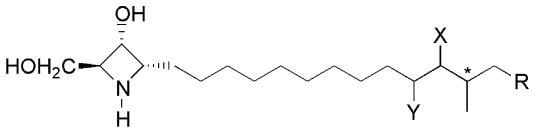
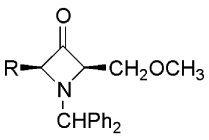
Abstract—Several 1-alkyl-2-methylazetidin-3-ones were prepared in good yield by the hydride-induced cyclization of the corresponding β-bromo-α,α-dimethoxyketimines, the resulting 3,3-dimethoxyazetidines being hydrolyzed by acid. Imination of these 1,2-disubstituted azetidin-3-ones, followed by alkylation under kinetic control conditions resulted in regioisomeric mixtures of 2,4- and 2,2-dialkylated compounds. Analytical samples of the major 2,4-disubstituted derivatives were obtained after extensive chromatographic separation. The *cis* stereochemistry of the major 2,4-dialkylated isomer was demonstrated on the basis of NMR data.

1. Introduction

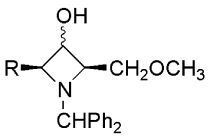
In our research group, we have been engaged in the development of versatile synthetic methods for the preparation of small-size heterocyclic compounds, such as some azetidine derivatives.[1,2] In a previous research, we described a general method to prepare 2,4-disubstituted azetidin-3-ones **1** and azetidin-3-ols **2**,[3] as related structural motifs of the alkaloids penaresidine A, penaresidine B and penazetidine A (Fig. 1).[4] The synthetic protocol that was developed consisted of the regio- and stereoselective alkylation of 1-benzhydryl-2-(methoxymethyl)azetidin-3-one **3**, followed by the hydride reduction of the carbonyl group. In order to gain insight into the mechanism that rules the stereoselectivity of the alkylation protocol, and to fully exploit the synthetic possibilities of this method, it was decided to prepare 2-substituted azetidin-3-one derivatives, and to study their alkylation. Of prime importance was the



Penaresidin A	X = OH, Y = H, R = Me
Penaresidin B	X = H, Y = OH, R = Me
Penazetidin A	X = Y = H, R = C_5H_{11}



1a R = Et
1b R = n-Pr



2a R = Et
2b R = n-Pr

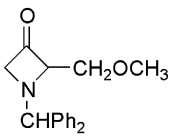


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Figure 1.

Keywords: azetidin-3-ones; azetidin-3-ols; azetidines; bromoimines.

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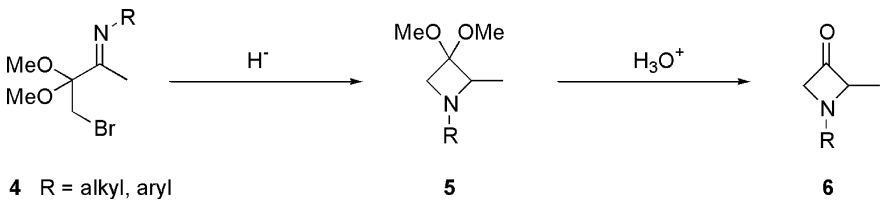


4 R = alkyl, aryl **5** **6**

Scheme 1.

development of an efficient and straightforward synthesis of more azetidin-3-ones because such procedures are lacking until now.[5]

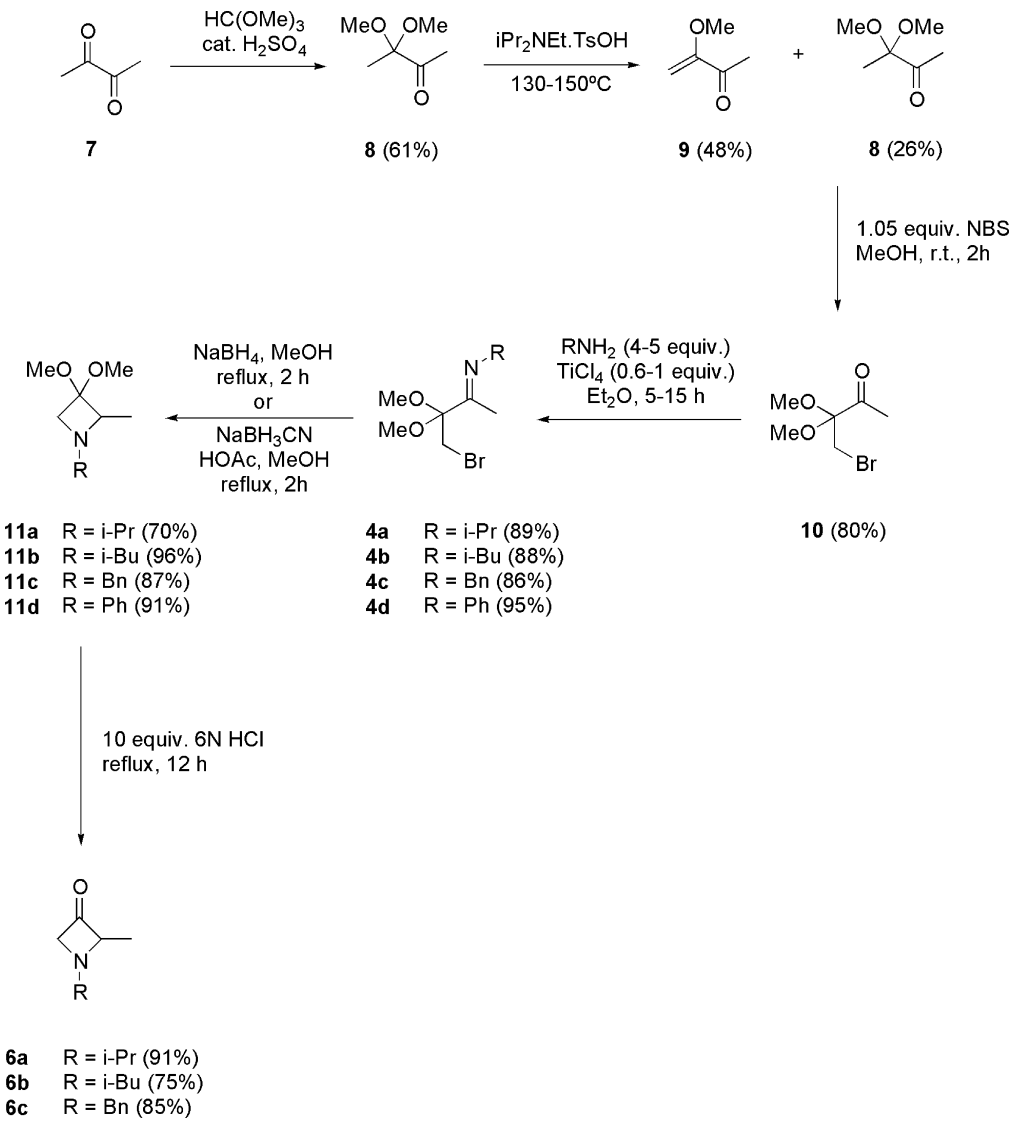
The key step for this synthesis would be the cyclization induced by the addition of hydride to an α,α-dimethoxy-β-bromoketimine **4**. One of the most relevant features of the azetidine synthesis from β-haloimines is that different functionalities could be introduced via appropriate substituents in the haloimine precursor.[2b] Consequently, if an acetal moiety was conveniently placed like in the haloimine precursor **4**, it could be converted into a carbonyl group by conventional acid hydrolysis after the cyclization step (Scheme 1).

2. Results and discussion

2.1. Preparation of 1-alkyl-2-methylazetidin-3-ones 6

The synthetic route which was followed to prepare 1-alkyl-2-methylazetidin-3-ones **6** is described below (Scheme 2).

Butane-2,3-dione **7** was converted into 3,3-dimethoxy



7 **8** (61%) **9** (48%) **8** (26%)

10 (80%)

11a R = i-Pr (70%)
11b R = i-Bu (96%)
11c R = Bn (87%)
11d R = Ph (91%)

4a R = i-Pr (89%)
4b R = i-Bu (88%)
4c R = Bn (86%)
4d R = Ph (95%)

6a R = i-Pr (91%)
6b R = i-Bu (75%)
6c R = Bn (85%)

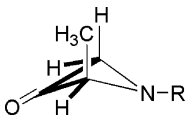
Scheme 2.

2-butanone **8** by selective protection of one of the two carbonyl groups with methyl orthoformate in the presence of a catalytic amount of sulfuric acid.[6] Pyrolysis of the ketoacetal **8** with diisopropylethylammonium tosylate as cracking catalyst[7] gave 3-methoxy-3-buten-2-one **9**,[8] which could only be partially purified by distillation. This resulted in a mixture of 3-methoxy-3-buten-2-one **9** and unreacted **8** in a 2.6:1 ratio (^{1}H NMR). This mixture was reacted with *N*-bromosuccinimide in methanol at room temperature[9] to afford 4-bromo-3,3-dimethoxy-2-butanone **10** in 80% yield after distillation in vacuo.

The β-bromoketone **10** was reacted with different aliphatic and aromatic amines in the presence of titanium(IV) chloride at room temperature.[10] The *E* isomers of the corresponding imines **4a–d** were in each case exclusively obtained with good yield (88–95%) and pure enough (>96%) to be used as such in the following step. Only when the less reactive aniline was used, harsher reaction conditions were required to bring the reaction to completion. For the less sterically hindered imines **4a–c**, reaction with 2 equiv. of sodium borohydride in methanol at reflux afforded the desired 1-alkyl-2-methyl-3,3-dimethoxyazetidines **11a–c** in good yield (70–96%). The phenyl derivative **11d**, however, could only be obtained after attempted activation (protonation) of the Schiff base **4d** to the corresponding iminium ion.[11] Reflux of **4d** with sodium cyanoborohydride in methanol in the presence of 1 equiv. of acetic acid gave 3,3-dimethoxy-2-methyl-1-phenylazetidine **11d** in excellent yield (91%).

The following step concerned the acidic hydrolysis of the protecting ketal functionality of the dimethoxyazetidines **11a–d**. Stirring the azetidines **11a–c** in 6N hydrochloric acid and under reflux resulted in the complete hydrolysis to the desired azetidin-3-ones **6a–c**, which were obtained in high purity after alkaline workup. However, these conditions proved unsuccessful with the *N*-phenylazetidine **11d**, as no hydrolysis was observed to occur and only unreacted **11d** was recovered. This apparent lack of reactivity of **11d** could not be improved by the use of stronger acidic conditions, such as 10 equiv. of sulfuric acid, which also led at room temperature to unreacted **11d**. When this reaction mixture was heated at reflux, complete decomposition was observed and no azetidin-3-one could be isolated.

The structure of the 2-methylazetidin-3-ones **6a–c** was determined on the basis of their spectroscopic data. The presence of the carbonyl group was in each case demonstrated by the ^{13}C NMR spectra (204.74 ppm, $CDCl_3$, 67.5 MHz, **6a**) and by the strong absorptions in the IR spectra (1809 cm^{-1}, NaCl, **6a**). The ^{1}H NMR spectra of compounds **6a–c** with the remarkably comparatively large coupling constants between the protons at positions C-2 and C-4 ($J_{2,4}$=4.3 Hz, **6a**) are consistent with a four-membered cyclic structure. The magnitude of these coupling constants has been associated to a planar W geometry of the molecule, in which the hydrogen atoms at positions C-2 and C-4 were on the same side of the molecule, as shown in Figure 2.[12] These findings were in agreement with some reported data of other 2-substituted azetidin-3-one derivatives.[5b]



6a $J_{2,4}$ = 4.3 Hz (*cis*); $J_{2,4}$ = 0.7 Hz (*trans*)
6b $J_{2,4}$ = 4.5 Hz (*cis*); $J_{2,4}$ = 0.5 Hz (*trans*)
6c $J_{2,4}$ = 4.3 Hz (*cis*); $J_{2,4}$ = 0.8 Hz (*trans*)

Figure 2.

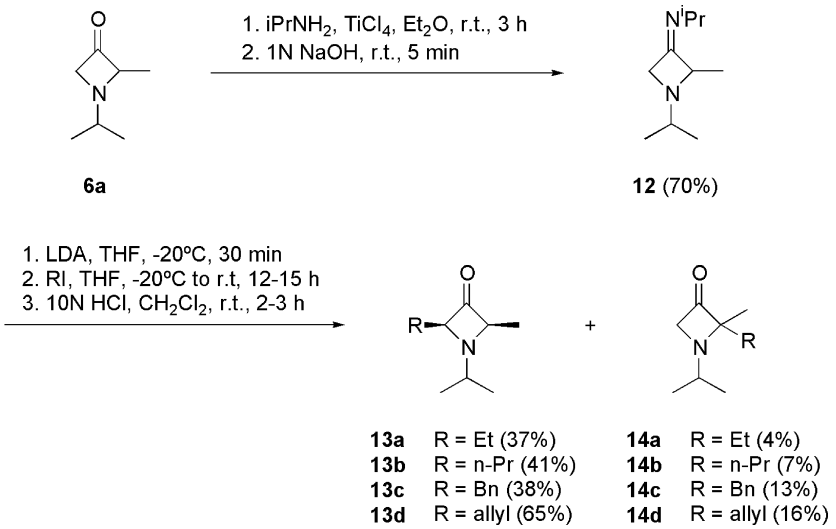
The rigid conformation associated to the planar W-arrangement of the hydrogen atoms H-2 and H-4 would necessarily imply that these two hydrogen atoms adopted a pseudo-equatorial disposition, the methyl group at position C-2 being pseudoaxial. It must be quoted that, for four-membered cyclic compounds like **6a–c**, long distance coupling between equatorial H-2 and axial H-4, where a planar W disposition would not be observed, would give rise to smaller values of the coupling constant ($J_{2,4}$=0.7 Hz, **6a**), also this being in accordance to the literature.[12] These results strongly support the conformation of **6a–c** shown in Figure 2.

2.2. Alkylation of 1-isopropyl-2-methylazetidin-3-one 6a

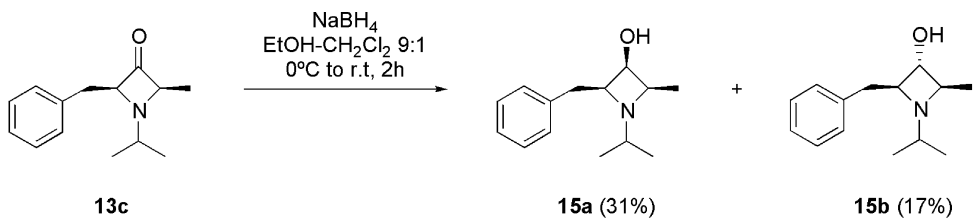
In a previous work, it was found that 1-benzhydryl-2-(methoxymethyl)azetidin-3-one **3** could be regio- and stereoselectively alkylated via the corresponding *N*-isopropylimine.[3] Therefore, and as part of our research on the synthesis of penaresidin-like alkaloids, it was decided to study the possibilities of 1-alkyl-2-methylazetidin-3-ones **4a–c** as substrates for the synthesis of 2,4-disubstituted azetidin-3-ols **11**.

As a model reaction, only the alkylation of 1-isopropyl-2-methylazetidin-3-one **6a** was attempted (Scheme 3). Compound **6a** was reacted with isopropylamine in the presence of titanium(IV) chloride in diethyl ether, which afforded *E*-*N*-isopropyl-3-[(*N*-isopropyl)-imino]-2-methylazetidin-3-one **12** in 70% yield. This compound was converted to its 1-azaenolate anion under kinetic control conditions, i.e. by addition of lithium diisopropylamide in anhydrous THF at −20°C. This was followed by the addition of the alkylating agent, also at −20°C, and finally by acidic hydrolysis of the imino group at room temperature.

Under these conditions, the alkylation of *N*-isopropyl-3-[(*N*-isopropyl)imino]-2-methylazetidin-3-one **12** with alkyl iodides always afforded mixtures of the desired 2,4-dialkylated azetidinones **13a–d** and their regioisomeric 2,2-dialkylated analogues **14a–d**. In every case, the ratio between both regioisomers **13** and **14** was determined by comparing the relative intensity of the signals in the ^{1}H NMR spectrum of the crude reaction mixture. In the case of the 2,4-dialkylated compounds **13a–d**, only one stereoisomer was obtained in each case, as evidenced by analytical GC and by the fact that the signals in the ^{1}H and ^{13}C NMR spectra were not doubled. The structure of the minor isomers **14a–d** was demonstrated by the DEPT NMR spectrum of the reaction crudes. These NMR experiments proved that, for compounds **14a–d**, C-2 were quaternary carbons and C-4 were methylenic. In addition to this lack of regioselectivity, the two different regioisomers proved very difficult to separate, and extensive chromatographic treatment was required, in every case, to obtain analytical samples of each 2,4-dialkylated compound **13a–d**. In our



Scheme 3.



Scheme 4.

Table 1. Selected ^{1}H NMR data of 2-methyl azetidin-3-ols **15a** and **15b** ($CDCl_3$, 270 MHz)

Compound	Configuration	δ H-2 (ppm)	δ H-3 (ppm)	δ OH (ppm)	δ H-4 (ppm)	$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)	$J_{3,OH}$ (Hz)
15a (*cis*, *cis*)	2*RS*,3*RS*,4*SR*	3.25	4.23	1.91	3.17	Not observed	Not observed	7.9
15b (*trans*, *trans*)	2*RS*,3*SR*,4*SR*	2.95	3.48	2.10	2.77	5.4	5.4	Not observed

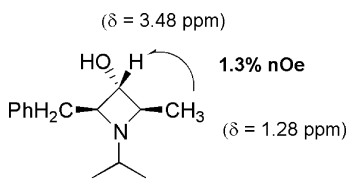
hands, only the benzyl derivative **13c** could be completely purified by flash chromatography.

2.3. Reduction of 2-benzyl-1-isopropyl-4-methylazetidin-3-one 13c

In order to elucidate the relative stereochemistry of the 2,4-disusbtituted azetidin-3-ones **13a–c**, the corresponding azetidin-3-ol derivatives **15** were prepared. Accurate measuring of the coupling constants in the ^{1}H NMR spectrum of **15** and direct comparison with published data[3] would thus provide information on the stereochemistry of the precursor azetidin-3-ones **13a–c**. Due to the above mentioned difficulty with the isolation of reasonably large amounts of the pure 2,4-disubstituted azetidin-3-ones **13a–c**, only the reduction of the benzyl derivative **13c** was attempted (Scheme 4).

The reduction of azetidinone **13c** with sodium borohydride in a 9:1 mixture of ethanol and dichloromethane afforded two epimeric azetidinols **15a** and **15b** which were separated by flash chromatography. The most relevant NMR data of these two azetidin-3-ols are summarised below (Table 1).

The first eluting isomer was identified as the *trans* epimer (2*RS*,3*SR*,4*SR*) 2-benzyl-1-isopropyl-4-methyl azetidin-3-ol **15b** by comparison of its NMR data with those of **2a** and **2b**.[3] The measured value of the coupling constant ($J_{2,3}$=$J_{3,4}$=5.4 Hz) proved the *trans* relationship of the hydroxy group with the substituents at C-2 and C-4. Likewise, the second eluting isomer was identified as the all *cis* (2*RS*,3*RS*,4*SR*) 2-benzyl-1-isopropyl-4-methylazetidin-3-ol **15a** on the basis of the $J_{3,OH}$ constant (7.9 Hz). These findings were supported by a nOe experiment of the minor isomer **15b** ($CDCl_3$, 270 MHz, rt). Irradiation of the signal due to the methyl group at C-4 lead to a 1.3% nOe interaction with the hydrogen at C-3 (Fig. 3). This implied that these two groups lie on the same side of the molecule, which can only be explained by the *trans* relationship



15b

Figure 3.

between H-3 and H-4 of **15b**, as discussed before. No long range W-coupling for **15a** and **15b** was observed.

All these facts concluded that the alkylation of *N*-isopropylimine **12**, although not completely regioselective, occurred with some degree of stereoselectivity, and only one of the two possible diastereoisomers of the 2,4-dialkylated azetidin-3-ones **13a–d** were obtained in each case. Further research to improve the encountered regioselectivity in the alkylation step and the asymmetric reduction of the imine functionality[13] in order to prepare enantiomerically pure azetidinols is currently being done.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 NMR spectrometer, operating at 270 and 67.5 MHz, respectively. GC analytical and preparative separations were done with a DELSI Intersmat IGC 120 ML gas chromatograph. FT-IR spectra were recorded on a Perkin–Elmer model 1310 spectrophotometer. The Electron Impact (EI) mode mass spectra were obtained with a Varian MAT 112 mass spectrometer, operating at 70 eV. Boiling points are uncorrected. Tetrahydrofuran was distilled over sodium benzophenone ketyl prior to use. Dichloromethane was distilled over calcium hydride prior to use. Diethyl ether was dried and distilled over sodium wire. Chromatographic separations were done using Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254} precoated tlc plates (0.25 mm thickness). All other solvents and chemicals were used as supplied.

3.1.1. Preparation of 3,3-dimethoxy-2-butanone 8.[6] In a 500 ml round-bottomed flask, provided with a magnetic stirrer and reflux condenser, 2,3-butadione (**7**, 86.0 g, 1.0 mol) and methyl orthoformate (106.0 g, 1.0 mol) were placed. Concentrated sulfuric acid (ca. 0.2 ml) was added and the mixture was refluxed for 5 h, cooled down to room temperature and neutralised by slow and careful addition of 10% sodium bicarbonate (100 ml). The reaction mixture was extracted with chloroform (3×100 ml), the combined organic phases were dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was distilled to give 3,3-dimethoxy-2-butanone (**8**, 80.44 g, 0.609 mol, 60.9%) as a pale yellow liquid. Bp 56°C/24 mm Hg; (lit.[6] 58°C/28 mm Hg). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 3.26 (s, 6H, OCH_3); 2.24 (s, 3H, H-1); 1.38 (s, 3H, H-4).

3.1.2. Preparation of 3-methoxy-3-buten-2-one 9.[8] In a 250 ml round-bottomed flask, provided with a magnetic stirrer and a fractional distillation set, 3,3-dimethoxy-2-butanone (**8**, 54.37 g, 0.446 mol) and diisopropylethylammoniun tosylate[7] (1.56 g, 5.18 mmol) were heated at ca. 165°C (oil bath temperature), when a yellowish liquid distilled (110°C). A main fraction (38.4 g) was collected, which contained 3-methoxy-3-buten-2-one, (**9**, 19.26 g, 0.214 mol, 48%), unreacted 3,3-dimethoxy-2-butanone (**8**, 14.26 g, 0.117 mol, 26%) and methanol, according to the relative integration in the ^{1}H NMR spectrum. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 5.22 and 4.53 (each s, 1H, H-4); 3.66 (s, 3H, OCH_3); 2.34 (s, 3H, H-1).

3.1.3. Preparation of 4-bromo-3,3-dimethoxy-2-butanone 10. In a 250 ml round-bottomed flask, provided with a magnetic stirrer and an air condenser, a solution of 3-methoxy-3-buten-2-one (**9**, 8.78 g, 87.8 mmol) and 3,3-dimethoxy-2-butanone (**8**, 4.91 g, 3.7 mmol) in methanol (60 ml) was prepared. *N*-Bromosuccinimide (18.75 g, 105.4 mmol) was added and the mixture was stirred for 3 h at room temperature under subdued light. The solvent was evaporated, the residue was diluted in carbon tetrachloride (150 ml) and succinimide was filtered off. 4-Bromo-3,3-dimethoxy-2-butanone (**10**, 14.90 g, 70.6 mmol, 80.2%) was obtained as a pale yellow liquid after evaporation of the solvent and distillation in vacuo. Bp 95–97°C/19–20 mm Hg. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 3.51 (s, 2H, H-4); 3.29 (s, 6H, OCH_3); 2.34 (s, 3H, H-1). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 206.23 (C-2); 101.42 (C-3); 50.01 (OCH_3); 29.49 (C-4); 28.37 (C-1). IR (NaCl, cm^{-1}): 1732 (C═O). Elemental analysis $C_6H_{11}BrO_3$; calculated 34.14% C, 5.25% H; found 34.05% C, 5.14% H.

3.1.4. General preparation of the *N*-(4-bromo-3,3-dimethoxy-2-butylidene)amines 4a–d. The preparation of *N*-(4-bromo-3,3-dimethoxy-2-butylidene)isopropylamine **4a** is representative. In a 250 ml three-necked round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, 4-bromo-3,3-dimethoxy butanone (**10**, 6.86 g, 32.5 mmol) and isopropylamine (11.15 ml, 130.0 mmol) were dissolved in dry diethyl ether (100 ml). The mixture was cooled to 0°C and titanium(IV) chloride (2.14 ml, 19.5 mmol) dissolved in 5 ml of pentane was added dropwise over 5 min at 0°C. After stirring at room temperature for 6 h the reaction mixture was poured onto 0.5N sodium hydroxide (150 ml) and stirred for 5 min. Then it was filtered through celite and the filtrate was extracted with diethyl ether (3×40 ml), the combined organic phases were dried over potassium carbonate, filtered and the solvent was evaporated. *N*-(4-Bromo-3,3-dimethoxy-2-butylidene)isopropylamine (**4a**, 7.29 g, 28.9 mmol, 89%) was obtained as a yellow liquid. Bp 47.5–50.0°C/0.15–0.20 mm Hg. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 3.78 (heptaplet, J=6.2 Hz, 1H, C*H*$(CH_3)_2$); 3.66 (s, 2H, H-4); 3.25 (s, 6H, OCH_3); 1.93 (s, 3H, H-1); 1.16 (d, J=6.2 Hz, 6H, CH(C*H*$_3)_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 164.72 (C-2); 101.29 (C-3); 51.05 (*C*H$(CH_3)_2$); 49.33 (OCH_3); 32.96 (C-4); 23.09 (CH(*C*H$_3)_2$); 14.93 (C-1). IR (NaCl, cm^{-1}): 1669 (C═N). Elemental analysis $C_9H_{18}BrNO_2$; calculated 42.87% C, 7.20% H, 5.55% N; found 42.70% C, 7.31% H, 5.45% N.

3.1.5. *N*-(4-Bromo-3,3-dimethoxy-2-butylidene)isobutylamine 4b. Yellow liquid (yield 88%). Bp 49–51°C/0.07 mm Hg. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 3.67 (s, 2H, H-4); 3.25 (s, 6H, OCH_3); 3.23 (m, 2H, C*H*$_2$CH$(CH_3)_2$); 2.05 (m, 1H, CH_2C*H*$(CH_3)_2$); 1.92 (s, 3H, H-1); 0.95 (d, J=6.5 Hz, 6H, CH_2CH(C*H*$_3)_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 166.23 (C-2); 104.05 (C-3); 56.10 (*C*H$_2$CH$(CH_3)_2$); 48.46 (OCH_3); 31.66 (C-4); 28.57 (CH_2*C*H$(CH_3)_2$); 19.86 (CH_2CH(*C*H$_3)_2$); 14.25 (C-1). IR (NaCl, cm^{-1}): 1655 (C═N). MS (EI, *m/z*, %): no M^+; 234 (5); 186 (2); 99 (7); 98 (77); 89 (5); 88 (12); 73 (6); 58 (9); 57 (100); 43 (10);

42 (71); 41 (21). Elemental analysis $C_{10}H_{20}BrNO_2$; calculated 45.12% C, 7.57% H, 5.26% N; found 45.02% C, 7.71% H, 5.08% N.

3.1.6. *N*-(4-Bromo-3,3-dimethoxy-2-butylidene)benzylamine 4c. Yellow liquid (yield 86%). Bp decomp. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 7.30 (m, 5H, Ph); 4.69 (s, 2H, H-4); 3.27 (s, 6H, OCH_3); 2.15 (s, 3H, H-1); 2.03 (s, 2H, CH_2Ph). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 168.77 (C-2); 139.19 (Ph -ipso-); 127.24, 127.89 (Ph-2, Ph-3); 126.18 (Ph-4); 101.15 (C-3); 54.81 (CH_2Ph); 49.15 (OCH_3); 32.15 (C-4); 15.24 (C-1). IR (NaCl, cm^{-1}): 1665 (C=N). MS (EI, *m/z*, %): no M^+; 271 (1); 270 (1); 269 (1); 268 (1); 220 (1); 169 (10); 167 (10); 132 (31); 92 (9); 91 (100); 88 (21); 73 (14); 65 (9); 58 (5); 43 (19). Elemental analysis $C_{13}H_{18}BrNO_2$; calculated 52.01% C, 6.04% H, 4.67% N; found 52.15% C, 5.95% H, 4.59% N.

3.1.7. *N*-(4-Bromo-3,3-dimethoxy-2-butylidene)phenylamine 4d. Yellow liquid (yield 95%). Bp 95–98°C/0.4 mm Hg. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 6.70–7.30 (m, 5H, Ph); 3.74 (s, 2H, H-4); 3.36 (s, 6H, OCH_3); 1.92 (s, 3H, H-1). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 166.58 (C-2); 146.74 (Ph -ipso-); 125.25 (Ph-2); 119.91 (Ph-4); 115.08 (Ph-3); 97.58 (C-3); 45.91 (OCH_3); 28.63 (C-4); 14.41 (C-1). IR (NaCl, cm^{-1}): 1670 (C=N). MS (EI, *m/z*, %): 285/287 (M^+, 2); 257 (1); 256 (1); 255 (1); 254 (1); 206 (1); 192 (2); 119 (10); 118 (100); 88 (19); 77 (32); 51 (8). Elemental analysis $C_{12}H_{16}BrNO_2$; calculated 50.37% C, 5.64% H, 4.89% N; found 50.53% C, 5.71% H, 4.82% N.

3.1.8. General preparation of 1-substituted 3,3-dimethoxy-2-methylazetidines 11a–d. The preparation of 3,3-dimethoxy-1-isopropyl-2-methylazetidine **11a** is representative. In a 100 ml round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, *N*-(4-bromo-3,3-dimethoxy-2-butylidene)isopropylamine (**4a**, 3.77 g, 14.96 mmol) was dissolved in methanol (40 ml). After cooling to 0°C, sodium borohydride (1.13 g, 29.92 mmol) was added portionwise over 5 min at 0°C. A reflux condenser was then fitted and the mixture was refluxed for 2 h and cooled down to room temperature. The reaction mixture was poured into ice-water (ca. 100 g) and was then extracted with dichloromethane (3×70 ml). The combined organic phases were dried over potassium carbonate, filtered and the solvent was evaporated. 3,3-Dimethoxy-1-isopropyl-2-methylazetidine (**11a**, 1.80 g, 10.41 mmol, 70%) was obtained as a yellow liquid after distillation. Bp 68–74°C/8–9 mm Hg. R_f: 0.32 (silica gel, hexane–AcOEt 60:40). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 3.63 (d, J_{gem}=8.2 Hz, 1H, H-4); 3.26 (s, 3H, OCH_3); 3.19 (q, J=6.6 Hz, 1H, H-2); 3.17 (s, 3H, OCH_3); 2.70 (d, J_{gem}=8.2 Hz, 1H, H-4); 2.42 (heptet, J=6.3 Hz, 1H, $CH(CH_3)_2$); 1.25 (d, J=6.6 Hz, 3H, CH_3); 0.95, 1.02 (each d, J=6.3 Hz, 3H, $CH(CH_3)_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 97.79 (C-3); 68.41 (C-2); 59.00 (C-4); 58.56 ($CH(CH_3)_2$); 48.61 and 49.15 (OCH_3); 20.56 and 21.33 ($CH(CH_3)_2$); 17.23 ($CHCH_3$). MS (EI, *m/z*, %): $C_9H_{19}NO_2$ requires 173.1416, found 173.1419 (M^+, 3).

3.1.9. 3,3-Dimethoxy-1-isobutyl-2-methylazetidine 11b. Yellow liquid (yield 96%). Bp 90–94°C/17 mm Hg. R_f: 0.20 (silica gel, hexane–AcOEt 80:20). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 3.64 (dd, J_{gem}=8.2 Hz, J_{vic}=1 Hz, 1H, H-4); 3.16, 3.26 (each s, 3H, OCH_3); 3.09 (q, J=6.6 Hz, 1H, H-2); 2.69 (d, J_{gem}=8.2 Hz, 1H, H-4); 2.43 (dd, J_{gem}=11.5 Hz, J_{vic}=6.6 Hz, 1H, $CH_2CH(CH_3)_2$); 2.16 (dd, J_{gem}=11.5 Hz, J_{vic}=7.6 Hz, 1H, $CH_2CH(CH_3)_2$); 1.64 (m, 1H, $CH_2CH(CH_3)_2$); 1.18 (d, J=6.3 Hz, 3H, CH_3); 0.87, 0.89 (each d, J=6.5 Hz, 3H, $CH_2CH(CH_3)_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 99.06 (C-3); 70.28 (C-2); 67.53 ($CH_2CH(CH_3)_2$); 61.33 (C-4); 48.48 and 49.15 (OCH_3); 27.74 ($CH_2CH(CH_3)_2$); 21.02 and 21.17 ($CH_2CH(CH_3)_2$); 15.54 ($CHCH_3$). MS (EI, *m/z*, %): 187 (M^+, 2); 172 (7); 156 (7); 144 (9); 102 (45); 101 (5); 100 (6); 89 (26); 88 (100); 72 (17); 58 (43); 57 (30); 56 (40); 55 (8); 45 (5); 43 (33); 42 (17); 41 (13). Elemental analysis $C_{10}H_{21}NO_2$; calculated 64.13% C, 11.30% H, 7.48% N; found 64.04% C, 11.49% H, 7.35% N.

3.1.10. 1-Benzyl-3,3-dimethoxy-2-methylazetidine 11c. Yellow liquid (yield 82%). Bp decomp. R_f: 0.39 (silica gel, hexane–AcOEt 60:40). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 7.3 (m, 5H, Ph); 3.60, 3.75 (each d, J_{gem}=12.5 Hz, 1H, AB system, CH_2Ph); 3.57 (dd, J_{gem}=8.4 Hz, J_{vic}=1 Hz, 1H, H-4); 3.26 (q, J=6.6 Hz, 1H, H-2); 3.17, 3.24 (each s, 3H, OCH_3); 2.80 (d, J_{gem}=8.6 Hz, 1H, H-4); 1.05 (d, J=6.3 Hz, 3H, CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 138.13 (Ph -ipso-); 128.19 and 129.00 (Ph-2 and Ph-3); 127.35 (Ph-4); 99.06 (C-3); 69.77 (C-2); 62.39 (CH_2Ph); 60.16 (C-4); 48.75 and 49.29 (OCH_3); 15.34 ($CHCH_3$). MS (EI, *m/z*, %): no M^+; 206 (6); 191 (1); 190 (4); 130 (1); 102 (47); 92 (5); 91 (51); 89 (42); 88 (100); 72 (14); 59 (6); 58 (39); 57 (21); 56 (10); 43 (31). Elemental analysis $C_{13}H_{19}NO_2$; calculated 70.56% C, 8.65% H, 6.33% N; found 70.44% C, 8.60% H, 6.24% N.

3.1.11. 3,3-Dimethoxy-2-methyl-1-phenylazetidine 11d. Yellow liquid (yield 95%). Bp 69–71°C/0.01 mm Hg. R_f: 0.19 (silica gel, hexane–AcOEt 97:3). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 6.5–7.3 (m, 5H, Ph); 4.10 (q, J=6.2 Hz, 1H, H-2); 3.54, 4.07 (each d, J_{gem}=8.2 Hz, 1H, H-4); 3.21, 3.32 (each s, 3H, OCH_3); 1.44 (d, J=6.3 Hz, 3H, CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 151.07 (Ph -ipso-); 128.82 (Ph-2); 117.80 (Ph-4); 112.09 (Ph-3); 98.87 (C-3); 68.18 (C-2); 59.62 (C-4); 48.66 and 49.38 (OCH_3); 16.12 ($CHCH_3$). MS (EI, *m/z*, %): 207 (M+, 21); 192 (3); 176 (13); 169 (3); 159 (1); 132 (6); 119 (100); 102 (76); 88 (40); 77 (35); 57 (24); 43 (19). Elemental analysis $C_{12}H_{17}NO_2$; calculated 69.54% C, 8.27% H, 6.76% N; found 69.42% C, 8.39% H, 6.65% N.

3.1.12. General preparation of 1-alkyl-2-methylazetidin-3-ones 6a–c. The preparation of 1-isopropyl-2-methylazetidin-3-one **6a** is representative. In a 50 ml round-bottomed flask, provided with a magnetic stirrer, reflux condenser and nitrogen inlet, 3,3-dimethoxy-1-isopropyl-2-methylazetidine (**11a**, 1.80 g, 10.41 mmol) was cooled to 0°C and to this 6N hydrochloric acid (17.3 ml, 104 mmol, precooled to 0°C) was added in one portion. The mixture was refluxed for 12 h, cooled down to room temperature and then it was carefully poured into ice-cooled 2N sodium hydroxide (150 ml). After stirring for 5 min, it was transferred to a 250 ml separatory funnel and extracted with diethyl ether (3×40 ml). The combined organic phases were dried over potassium carbonate, filtered and the solvent was evaporated. 1-Isopropyl-2-methylazetidin-3-one (**6a**, 1.20 g, 9.47 mmol, 91%) was obtained as a pale

yellow liquid. R_f: 0.22 (silica gel, Et_2O). ^1H NMR (270 MHz, $CDCl_3$, δ): 4.19 (dd, J_{gem}=15.8 Hz, J_{2-4}=4.3 Hz, 1H, H-4); 3.92 (dq, J=6.9 Hz, J_{2-4}=4.3 Hz, 1H, H-2); 3.74 (dd, J_{gem}=15.8 Hz, J_{2-4}=0.7 Hz, 1H, H-4); 2.62 (heptet, J=6.3 Hz, 1H, C*H*(CH_3)$_2$); 1.33 (d, J=6.9 Hz, 3H, CH_3); 1.08, 1.12 (each d, J=6.3 Hz, 3H, CH(C*H*$_3$)$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 204.74 (C-3); 80.38 (C-2); 71.46 (C-4); 58.99 (*C*H(CH_3)$_2$); 21.65 and 21.71 (CH(*C*H$_3$)$_2$); 16.82 (CH*C*H$_3$). IR (NaCl, cm^{-1}): 1809 (C=O). MS (EI, *m*/*z*, %): $C_7H_{13}NO$ requires 127.0997, found 127.1011 (M^+, 2).

3.1.13. 1-Isobutyl-2-methylazetidin-3-one 6b. Yellow liquid (75% yield). Bp 65–67°C/25 mm Hg. R_f: 0.22 (silica gel, Et_2O). ^1H NMR (270 MHz, $CDCl_3$, δ): 4.19 (dd, J_{gem}=15.7 Hz, J_{2-4}=4.5 Hz, 1H, H-4); 3.85 (m, 1H, H-2); 3.70 (dd, J_{gem}=15.7 Hz, J_{2-4}=0.5 Hz, 1H, H-4); 2.59 (dd, J_{gem}=11.3 Hz, J_{vic}=6.9 Hz, 1H, C*H*$_2$CHMe$_2$); 2.43 (dd, J_{gem}=11.3 Hz, J_{vic}=7.3 Hz, 1H, C*H*$_2$CHMe$_2$); 1.65 (m, 1H, CH$_2$C*H*Me$_2$); 1.27 (d, J=6.9 Hz, 3H, CH_3); 0.94, 0.96 (each d, J=6.3 Hz, 3H, CH$_2$CH(C*H*$_3$)$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 204.85 (C-3); 82.05 (C-2); 73.03 (C-4); 67.82 (N*C*H$_2$CHMe$_2$); 28.30 (*C*HMe$_2$); 20.56 and 20.69 (CH(*C*H$_3$)$_2$); 15.10 (CH*C*H$_3$). IR (NaCl, cm^{-1}): 1810 (C=O). MS (EI, *m*/*z*, %): 141 (M^+, 2); 126 (3); 113 (13); 99 (9); 98 (100); 84 (3); 71 (29); 70 (31); 69 (10); 68 (8); 58 (13); 57 (37); 56 (49); 55 (10); 42 (60); 41 (34); 39 (9). Elemental analysis $C_8H_{15}NO$; calculated 68.04% C, 10.71% H, 9.92% N; found 67.89% C, 10.85% H, 9.87% N.

3.1.14. 1-Benzyl-2-methylazetidin-3-one 6c. Yellow liquid (yield 85%). R_f: 0.38 (silica, hexane–AcOEt 60:40). ^1H NMR (270 MHz, $CDCl_3$, δ): 7.30 (m, 5H, Ph); 4.18 (dd, J_{gem}=15.8 Hz, J_{2-4}=4.3 Hz, 1H, H-4); 4.02 (m, 1H, H-2); 3.88, 3.92 (each d, J_{gem}=12.7 Hz, 1H, AB system, C*H*$_2$Ph); 3.82 (dd, J_{gem}=15.8 Hz, J_{2-4}=0.8 Hz, 1H, H-4); 1.15 (d, J=6.6 Hz, 3H, CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 204.37 (C-3); 137.77 (Ph -ipso-); 128.28 and 128.63 (Ph-2 and Ph-3); 127.33 (Ph-4); 81.47 (C-2); 72.26 (*C*H$_2$Ph); 62.54 (C-4); 14.95 (CH*C*H$_3$). IR (NaCl, cm^{-1}): 1805 (C=O). MS (EI, *m*/*z*, %): $C_{11}H_{13}NO$ requires 175.0997, found 175.1003 (M^+, 3).

3.1.15. Preparation of (*E*)-1-isopropyl-3-[(*N*-isopropyl)-imino]-2-methylazetidine 12. In a 50 ml round-bottomed flask, provided with magnetic stirrer and nitrogen inlet, *N*-isopropyl-2-methylazetidin-3-one (**6a**, 747 mg, 5.88 mmol) and isopropylamine (3.0 ml, 35.3 mmol) were dissolved in dry diethyl ether (15 ml). To this titanium(IV) chloride (0.38 ml, 3.53 mmol) was added at room temperature under nitrogen. The mixture was stirred at room temperature for 3 h, then it was poured into 1N sodium hydroxide (50 ml), stirred for five more minutes and extracted with diethyl ether (3×20 ml). The combined organic phases were dried over potassium carbonate, filtered and the solvent was evaporated. (*E*)-1-Isopropyl-3-[(*N*-isopropyl)imino]-2-methylazetidine (**12**, 693 mg, 4.12 mmol, 70%) was obtained as a caramel coloured liquid. ^1H NMR (270 MHz, $CDCl_3$, δ): 4.24 (dd, J_{gem}=13.8 Hz, J_{2-4}=3.6 Hz, 1H, H-4); 3.86 (ddq, J=6.6 Hz, J_{2-4}=3.6 Hz, J_{2-4}=2.0 Hz, 1H, C*H*CH$_3$); 3.56 (dd, J_{gem}=13.8 Hz, J_{2-4}=2.0 Hz, 1H, H-4); 3.35 (heptaplet, J=6.3 Hz, 1H, C=NC*H*(CH_3)$_2$); 2.54 (heptet, J=6.3 Hz, 1H, NC*H*(CH_3)$_2$); 1.37 (d, J=6.6 Hz, 3H, CH_3); 1.12, 1.13 (each d, J=6.3 Hz, 3H, C=NCH(C*H*$_3$)$_2$); 1.02, 1.08 (each d, J=6.3 Hz, 3H, NCH(C*H*$_3$)$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 165.03 (C-3); 72.74 (C-2); 61.06 (C-4); 58.33 (N*C*H(CH_3)$_2$); 52.60 (C=N*C*H(CH_3)$_2$); 23.58 (C=NCH(*C*H$_3$)$_2$); 21.19 and 21.38 (NCH(*C*H$_3$)$_2$); 18.81 (CH*C*H$_3$). IR (NaCl, cm^{-1}): 1740 (C=N). MS (EI, *m*/*z*, %): $C_{10}H_{20}N_2$ requires 168.1626, found 168.1631 (M^+, 2).

3.1.16. General preparation of (2*RS*,4*SR*) 2-alkyl-1-isopropyl-4-methylazetidin-3-ones 13a–d. The preparation of (2*RS*,4*SR*) 2-ethyl-1-isopropyl-4-methylazetidin-3-one **13a** is representative. In a 25 ml round-bottomed flask, provided with magnetic stirrer and nitrogen inlet, 1-isopropyl-3-[(*N*-isopropyl)imino]-2-methylazetidine (**12**, 223 mg, 1.33 mmol), dissolved in 6 ml of tetrahydrofuran, was added dropwise at −20°C over 5 min to a solution of diisopropyl amine (161 mg, 1.59 mmol, 1.2 equiv.) and *n*-butyllithium (0.58 ml of a 2.5 M solution in hexane, 1.46 mmol, 1.1 equiv.) in 2 ml of tetrahydrofuran. After stirring at −20°C for 3 h, ethyl iodide (414 mg, 2.65 mmol, dissolved in 2.0 ml of tetrahydrofuran, was added dropwise at −20°C. The mixture was left stirring to warm up to room temperature for 16 h, poured into 1N sodium hydroxide (25 ml) and extracted with diethyl ether (2×25 ml). The combined organic phases were dried over potassium carbonate, filtered and the solvent was evaporated. The obtained residue was dissolved in dichloromethane (20 ml) and to this solution was added 2N hydrochloric acid (6.5 ml). The two-phase system was vigorously stirred for 2.5 h at room temperature and then was carefully neutralised with ice-cooled 1N sodium hydroxide (ca. 25 ml). Then, the aqueous phase was extracted with fresh dichloromethane (2×20 ml). The combined organic phases were dried over potassium carbonate, filtered and the solvent was evaporated. The residue was chromatographed (silica gel, column dimensions 13.0 cm×2.5 cm, hexane–AcOEt 10:1). Appropriate fractions were pooled and evaporated. A yellow residue (84 mg, 0.54 mmol, 41%) containing (2*RS*,4*SR*) 2-ethyl-1-isopropyl-4-methylazetidin-3-one **13a** and 2-ethyl-1-isopropyl-2-methylazetidin-3-one **14a** in a *ca*. 9:1 ratio, respectively, was obtained. An analytical sample of (2*RS*,4*SR*) 2-ethyl-1-isopropyl-4-methyl azetidin-3-one **13a** was obtained after preparative GC. R_f: 0.25 (silica, hexane–AcOEt 5:1). ^1H NMR (270 MHz, $CDCl_3$, δ): 3.75–3.83 (m, 2H, H-2 and H-4); 2.68 (heptaplet, J=6.3 Hz, 1H, C*H*(CH_3)$_2$); 1.65–1.76 (m, 2H, C*H*$_2$CH$_3$); 1.28 (d, J=6.9 Hz, 3H, CH_3); 1.08, 1.10 (each d, J=6.3 Hz, 3H, CH(C*H*$_3$)$_2$); 0.99 (t, J=7.6 Hz, 3H, CH$_2$C*H*$_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 209.34 (C-3); 84.15 (C-2); 78.18 (C-4); 58.94 (*C*H(CH_3)$_2$); 25.39 (*C*H$_2$CH$_3$); 21.92 and 22.03 (CH(*C*H$_3$)$_2$); 16.80 (CH*C*H$_3$); 9.97 (CH$_2$*C*H$_3$). IR (NaCl, cm^{-1}): 1809 (C=O). MS (EI, *m*/*z*, %): 155 (M^+, 2); 141 (1); 140 (7); 127 (26), 112 (14); 98 (7); 85 (14); 84 (100); 70 (29); 56 (20); 43 (15); 42 (10); 41 (33). Elemental analysis $C_9H_{17}NO$; calculated 69.63% C, 11.04% H, 9.02% N; found 69.70% C, 11.21% H, 8.90% N.

3.1.17. (2*RS*,4*SR*) 1-Isopropyl-4-methyl-2-propylazetidin-3-one 13b. Yellow liquid (yield 48%, 85:15 mixture of **13b** and **14b**, analytical sample of **13b** obtained after preparative GC). R_f: 0.43 (silica gel, hexane–AcOEt 5:1). ^1H NMR (270 MHz, $CDCl_3$, δ): 3.74–3.82 (m, 2H, H-2 and

H-4); 2.67 (heptaplet, J=6.3 Hz, 1H, CH(CH_3)$_2$); 1.50–1.70 (m, 4H, CH_2CH_2CH_3); 1.29 (d, J=6.9 Hz, 3H, CH_3); 1.08, 1.11 (each d, J=6.3 Hz, 3H, CH(CH_3)$_2$); 0.92 (t, J=7.6 Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 209.37 (C-3); 82.96 (C-2); 78.11 (C-4); 59.08 (*C*H(CH_3)$_2$); 34.66 (*C*$H_2CH_2CH_3$); 21.89 and 22.07 (CH(*C*H_3)$_2$); 18.98 (CH_2*C*H_2CH_3); 16.99 (CH*C*H_3); 14.12 (CH_2CH_2*C*H_3). IR (NaCl, cm^{-1}): 1803 (C=O). MS (EI, *m*/*z*, %): 169 (M$^+$, 4); 154 (10); 141 (37); 136 (5); 126 (43); 112 (45); 98 (100); 85 (16); 84 (37); 71 (20); 70 (64); 69 (11); 44 (36); 43 (41); 42 (34); 41 (44). Elemental analysis $C_{10}H_{19}NO$; calculated 70.96% C, 11.31% H, 8.28% N; found 70.78% C, 11.19% H, 8.22% N.

3.1.18. (2*RS*,4*SR*) 2-Benzyl-1-isopropyl-4-methylazetidin-3-one 13c. Yellow liquid (yield 51.1%, 3:1 mixture of **13c** and **14c**, considerable amount of pure **13c** was obtained after flash chromatography, silica, hexane–AcOEt 9:1). R_f: 0.20 (silica gel, hexane–AcOEt 9:1). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 4.02 (dd, J=7.6, 4.6 Hz, 1H, H-2); 3.80 (q, J=6.9 Hz, 1H, H-4); 3.04 (dd, J_{gem}=14.3 Hz, J_{vic}=7.6 Hz, 1H, CH_2Ph); 2.90 (dd, J_{gem}=14.3 Hz, J_{vic}=4.6 Hz, 1H, CH_2Ph); 2.69 (heptaplet, J=6.3 Hz, 1H, CH(CH_3)$_2$); 1.14 (d, J=6.9 Hz, 3H, CH_3); 1.06, 1.08 (each d, J=6.3 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 207.96 (C-3); 137.72 (Ph -ipso-); 127.30, 128.40 and 129.50 (Ph); 83.52 (C-2); 77.95 (C-4); 58.56 (*C*H(CH_3)$_2$); 38.74 (*C*H_2Ph); 21.74 and 22.16 (CH(*C*H_3)$_2$); 16.82 (CH*C*H_3). IR (NaCl, cm^{-1}): 1802 (C=O). MS (EI, *m*/*z*, %): no M$^+$; 202 (3); 190 (4); 189 (22); 174 (4); 160 (1); 146 (14); 126 (100); 105 (6); 91 (12); 84 (39); 70 (10); 65 (4); 56 (19); 43 (16). Elemental analysis $C_{14}H_{19}NO$; calculated 77.38% C, 8.81% H, 6.45% N; found 77.32% C, 8.69% H, 6.58% N.

3.1.19. (2*RS*,4*SR*) 2-Allyl-1-isopropyl-4-methylazetidin-3-one 13d. Yellow residue (yield %, 4:1 mixture of **13d** and **14d**, analytical sample of **13d** was obtained after preparative GC). R_f: 0.42 (silica gel, hexane–AcOEt 5:1). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 5.82–5.94 (m, 1H, CH_2=CH); 5.06–5.14 (m, 2H, CH_2=CH); 3.78–3.89 (m, 2H, H-2 and H-4); 2.70 (heptet, J=6.3 Hz, 1H, CH(CH_3)$_2$); 2.41–2.49 (m, 2H, CH_2=CHCH_2); 1.29 (d, J=6.9 Hz, 3H, CH_3); 1.09, 1.11 (each d, J=6.3 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 208.15 (C-3); 133.87 (CH_2=*C*H); 117.39 (*C*H_2=CH); 83.52 (C-2); 78.24 (C-4); 58.78 (*C*H(CH_3)$_2$); 36.75 (CH_2=CH*C*H_2); 21.85 and 22.17 (CH(*C*H_3)$_2$); 16.89 (CH*C*H_3). IR (NaCl, cm^{-1}): 1804 (C=O). MS (EI, *m*/*z*, %): $C_{10}H_{17}NO$ requires 167.1310, found 167.1316 (M$^+$, 3).

3.1.20. Reduction of (2*RS*,4*SR*) 2-benzyl-1-isopropyl-4-methylazetidin-3-one 13c. In a 50 ml round-bottomed flask, provided with a magnetic stirrer and nitrogen inlet, sodium borohydride (223 mg, 5.88 mmol) was added dropwise to an ice-cooled solution of (2*RS*,4*SR*) 2-benzyl-1-isopropyl-4-methyl azetidin-3-one (**13c**, 510 mg, 2.35 mmol) in dichloromethane (2 ml) and absolute ethanol (18 ml). This mixture was stirred while warmed up to ambient temperature for 2 h, water (4 ml) was then added, and the stirring was continued for another hour. Ethyl acetate (10 ml) was added, and the aqueous phase was extracted with ethyl acetate (2×5 ml). The combined organic phases were dried over magnesium sulfate, filtered and the solvent was evaporated in vacuo. The residue was chromatographed (silica, column dimensions 13×2.5 cm, hexane–AcOEt 4:1). Two compounds were isolated after pooling and evaporation of the appropriate fractions.

First eluting compound. (2*RS*,3*SR*,4*SR*) 2-Benzyl-1-isopropyl-4-methylazetidin-3-ol (**15b**, 87.5 mg, 0.40 mmol, 17%). R_f: 0.31 (silica, AcOEt–hexane–MeOH 83:12:5). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 7.15–7.31 (m, 5H, phenyl); 3.48 (t, J_{2-3}=$J_{3,4}$=5.4 Hz, 1H, H-3); 3.07 (dd, J_{gem}=12.8 Hz, J_{vic}=4.0 Hz, 1H, CH_2Ph); 2.95 (m, 1H, H-2); 2.80 (m, 1H, CH_2Ph); 2.77 (m, 1H, H-4); 2.55 (heptet, J=6.3 Hz, 1H, CHMe$_2$); 2.10 (s, 1H, OH); 1.28 (d, J=6.3 Hz, 3H, CH_3–C-4); 1.01, 1.06 (each d, J=6.3 Hz, 3H, CH*Me*$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 138.29 (Ph -ipso-); 128.89, 128.50 (Ph-2 and Ph-3); 126.27 (Ph-4); 74.37 (C-3); 72.28 (C-2); 66.76 (C-4); 58.87 (*C*HMe$_2$); 42.73 (*C*H_2Ph); 21.01 and 21.46 (CH*Me*$_2$); 14.20 (*Me*–C-2). MS (EI, *m*/*z*, %): $C_{14}H_{21}NO$ requires 219.1623, found 219.1631 (M$^+$, 3).

Second eluting compound. (2*RS*,3*RS*,4*SR*) 2-Benzyl-1-isopropyl-4-methyl azetidin-3-ol (**15a**, 159 mg, 0.73 mmol, 31%). R_f: 0.18 (silica gel, AcOEt–hexane–MeOH 83:12:5). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 7.00–7.20 (m, 5H, phenyl); 4.22 (m, 1H, H-3); 3.25 (m, 2H, H-2 and CH_2Ph); 3.17 (m, 1H, H-4); 2.72–2.79 (m, 1H, CH_2Ph); 2.51 (heptet, J=6.3 Hz, 1H, CHMe$_2$); 1.91 (d, J=7.9 Hz, 1H, OH); 1.20 (d, J=6.3 Hz, 3H, CH_3–C-4); 1.01, 1.07 (each d, J=6.3 Hz, 3H, CH*Me*$_2$). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 139.32 (Ph-ipso-); 128.46 and 128.96 (Ph-2 and Ph-3); 126.07 (Ph-4); 68.52 (C-2); 66.36 (C-3); 62.12 (C-4); 58.45 (*C*HMe$_2$); 36.39 (*C*H_2Ph); 21.53 and 21.92 (CH*Me*$_2$); 15.83 (*Me*–C-2). MS (EI, *m*/*z*, %): $C_{14}H_{21}NO$ requires 219.1623, found 219.1637 (M$^+$, 4).

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