

# Synthesis of 3-Methoxyazetidines via an Aziridine to Azetidine Rearrangement and Theoretical Rationalization of the Reaction Mechanism

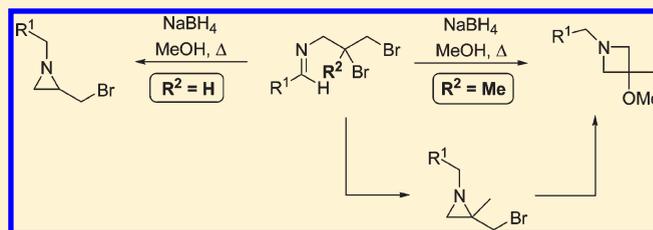
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**S** Supporting Information

**ABSTRACT:** The synthetic utility of *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines and *N*-(2,3-dibromo-2-methylpropylidene)benzylamines was demonstrated by the unexpected synthesis of 3-methoxy-3-methylazetidines upon treatment with sodium borohydride in methanol under reflux through a rare aziridine to azetidine rearrangement. These findings stand in contrast to the known reactivity of the closely related *N*-alkylidene-(2,3-dibromopropyl)amines, which are easily converted into 2-(bromomethyl)aziridines under the same reaction conditions. A thorough insight into the reaction mechanism was provided by both experimental study and theoretical rationalization.

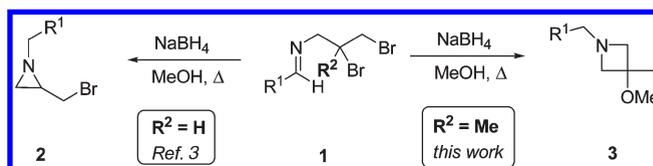


## INTRODUCTION

Imines carrying halogens in their side chain display a high intrinsic reactivity, and the selective introduction of halogens in imino substrates has led to building blocks with high synthetic potential as shown amply for the useful class of  $\alpha$ -haloimines.<sup>1</sup> The halogen can be introduced in the aldehyde (or ketone)-derived part, either before or after imination.<sup>1</sup> On the other hand, examples are known regarding halogenated imines in which the halogen is present in the amine-derived part.<sup>2</sup> The latter type of imines is usually accessed through imination of carbonyl compounds by means of halogenated (and thus reactive) amines, or via electrophilic addition of, e.g., bromine across *N*-alkenylimines. As a subclass, *N*-alkylidene- and *N*-arylmethylidene-(2,3-dibromopropyl)amines **1** comprise useful intermediates for the preparation of azaheterocyclic compounds such as aziridines and azetidines.<sup>3,4</sup>

Within azaheterocyclic chemistry, aziridines and azetidines are extraordinary classes of strained compounds with diverse synthetic and biological applications. Aziridines are versatile synthetic intermediates for the preparation of a variety of ring-opened and ring-expanded amines via regio- and stereoselective ring-opening reactions with nucleophiles.<sup>5</sup> Next to their synthetic relevance,<sup>6</sup> compounds containing an azetidine moiety have been shown to possess a wide range of biological activities.<sup>7</sup> In particular, 3-alkoxy- and 3-aryloxyazetidines have been described as, for example, G-protein-coupled receptor agonists,<sup>8</sup> inhibitors of stearyl-coenzyme d-9 desaturase,<sup>9</sup> and antibacterial agents.<sup>10</sup> The present paper describes a hitherto unexploited, yet remarkable, synthesis of azetidines **3** through formation and

## Scheme 1



subsequent ring expansion of aziridines as intermediates derived from *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **1** (R<sup>2</sup> = Me) upon treatment with NaBH<sub>4</sub> in methanol under reflux. These findings stand in sharp contrast to the known reactivity of the closely related *N*-alkylidene-(2,3-dibromopropyl)amines **1** (R<sup>2</sup> = H), which are easily converted into 2-(bromomethyl)aziridines **2**<sup>3,11</sup> under the same reaction conditions (Scheme 1).

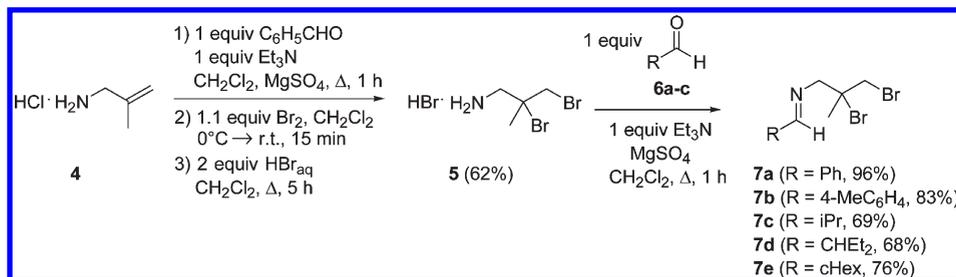
## RESULTS AND DISCUSSION

**Experimental Results.** *N*-Alkylidene- and *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)amines **7a–e** were formed by condensation of 2,3-dibromo-2-methylpropylamine hydrobromide **5**<sup>12</sup> with different aldehydes **6a–c** in the presence of 1 molar equiv of triethylamine and magnesium sulfate in dichloromethane after reflux for 1 h (Scheme 2). The synthesis of 2,3-dibromo-2-methylpropylamine hydrobromide **5** commenced with the imination of benzaldehyde using 2-methylallylamine hydrochloride **4** in

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Scheme 2

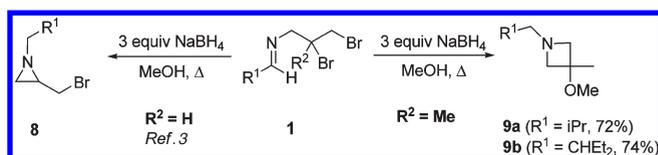


dichloromethane in the presence of triethylamine and magnesium sulfate, followed by bromination of the alkene moiety in the resulting *N*-(2-methyl-2-propenyl)imine in dichloromethane and subsequent treatment with 2 equiv of hydrogen bromide (48% solution in water) in dichloromethane (two-phase system). In this way, the desired 2,3-dibromo-2-methylpropylamine **5** was obtained as the corresponding hydrobromide salt in 62% overall yield in a short and easy approach (Scheme 2) through a large-scale synthesis (up to 50 g).

Despite their reactive nature, imines **7c** and **7d** were purified through distillation (Scheme 2, yields after distillation), whereas the other derivatives were judged to be pure enough to be used in further reactions without prior purification (purity >95% based on  $^1\text{H}$  NMR). It should be noted that *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **7c–e** cannot be obtained via bromination of the corresponding *N*-alkylidene-(2-methyl-2-propenyl)amines due to the presence of an  $\alpha$ -hydrogen atom with regard to the  $\text{C}=\text{N}$  double bond, as in this case  $\alpha$ -bromination (and further reaction) prevails through imine–enamine tautomerism. The condensation of aldehydes **6** bearing an  $\alpha$ -hydrogen atom with 2,3-dibromo-2-methylpropylamine **5** offers a convenient alternative in that respect.

In the literature, *N*-alkylidene- and *N*-arylmethylidene-(2,3-dibromopropyl)amines **1** ( $\text{R}^2 = \text{H}$ , Scheme 3) have been used as intermediates for the straightforward preparation of 2-(bromomethyl)aziridines **8** via reductive 3-*exo-tet*-cyclization using sodium borohydride in methanol under reflux.<sup>3</sup> This convenient synthesis of 2-(bromomethyl)aziridines **8** has formed the onset of a very fruitful research area in organic chemistry, leading to the development of a variety of novel classes of target compounds via further elaboration.<sup>3,11</sup> In analogy, the same methodology was applied to *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **1** ( $\text{R}^2 = \text{Me}$ , Scheme 3) with the intention to prepare 2-bromomethyl-2-methylaziridines as a novel class of substrates. Surprisingly, 3-methoxy-3-methylazetidines **9** were obtained instead, giving rise to a new synthetic methodology toward this type of compounds. Apparently, the presence of an additional methyl group ( $\text{R}^2 = \text{Me}$ ) in imines **1** has a profound influence on the reaction outcome. In a previous study, treatment of *N*-alkylidene-(2,2,3-tribromopropyl)amines with  $\text{NaBH}_4$  in methanol has been reported to furnish 3,3-dimethoxyazetidines via double methanolysis,<sup>4</sup> although in that case the direct formation of azetidines was foreseen as nucleophilic substitution at the dibrominated carbon atom toward aziridines is highly unlikely. The spectral data of 3-methoxyazetidines **9a–b** were identical to those reported in the literature,<sup>13</sup> prepared via a totally different route through  $\text{NaBH}_4$ -mediated cyclization of *N*-alkylidene-(3-bromo-2-methoxy-2-methylpropyl)amines.

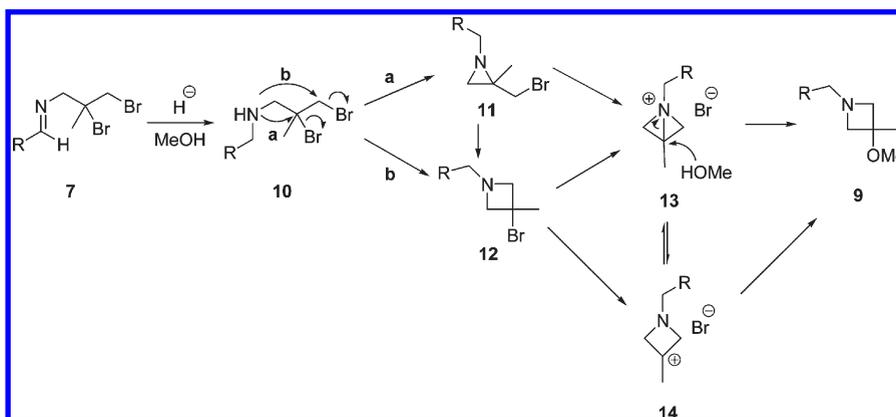
Scheme 3



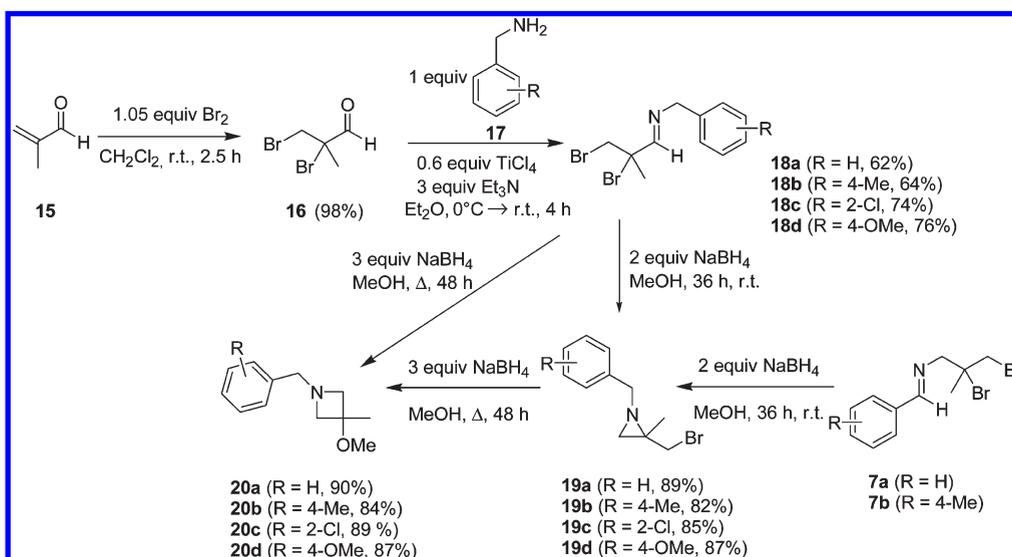
From a mechanistic point of view, different pathways can be considered to explain the observed reactivity (Scheme 4). Reduction of imines **7** in methanol via hydride addition across the imino bond toward amines **10** can either be followed by a 3-*exo-tet*-cyclization affording 2-bromomethyl-2-methylaziridines **11** (pathway **a**) or a 4-*exo-tet*-cyclization toward 3-bromoazetidines **12** (pathway **b**). Subsequently, both types of  $\beta$ -bromoamines (**11** and **12**) can be transformed into bicyclic aziridinium salts **13** through intramolecular displacement of bromide by the nucleophilic nitrogen atom, which stand in equilibrium with the nonbridged carbenium ions **14**. Alternatively, the formation of carbenium species **14** can be the result of spontaneous expulsion of bromide in 3-bromoazetidines **12**. Ring opening of intermediates **13** by methanol at the more hindered position<sup>14</sup> or solvolysis of carbenium species **14** by methanol finally affords 3-methoxyazetidines **9**.

On the basis of previous findings,<sup>15</sup> the 3-*exo-tet*-cyclization of amines **10** toward 2-bromomethyl-2-methylaziridines **11** (pathway **a**) will probably prevail (kinetic effect). The cyclization of 2-bromomethyl-2-methylaziridines **11** to strained intermediates **13** stands in contrast with the well-known chemistry of 2-(bromomethyl)aziridines bearing no additional substituent at the 2-position, as in this case the intramolecular cyclization and further transformation has never been observed.<sup>3,11</sup> The spontaneous cyclization of 2-bromomethyl-2-methylaziridines **11** under thermodynamic conditions can be rationalized considering the Thorpe–Ingold effect due to the *gem*-disubstitution at the aziridine carbon atom, resulting in a more favorable geometric positioning of the nucleophilic nitrogen atom with respect to the halogenated carbon atom. Alternatively, 2-bromomethyl-2-methylaziridines **11** can first be transformed into 3-bromoazetidines **12** via a concerted mechanism, which comprises simultaneous cleavage and formation of a carbon–nitrogen bond along with bromide migration. Furthermore, 3-bromoazetidines **12** can be converted into 3-methoxyazetidines **9** either via bicyclic aziridinium salts **13** or via carbenium ions **14**. The presence and formation of strained intermediates **13** is regarded as reasonable in a view of various reports involving this type of intermediates. For example, the formation of a bicyclic

Scheme 4



Scheme 5

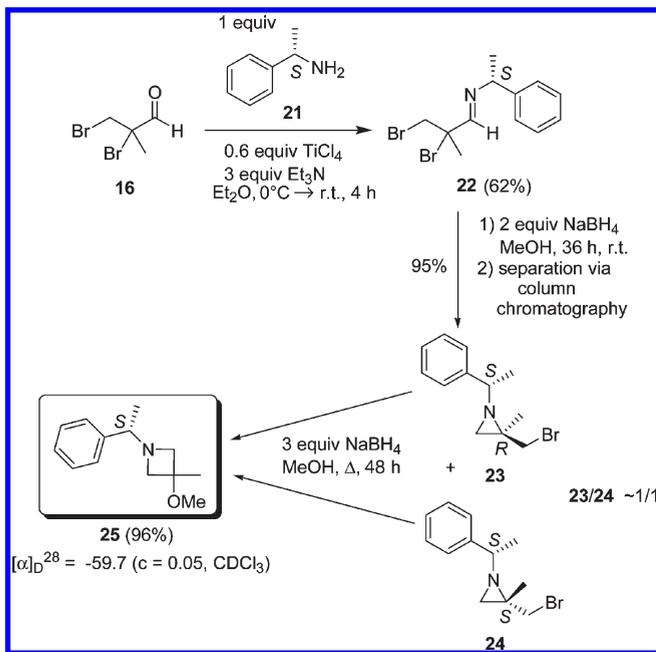


aziridinium intermediate has been suggested in the literature based on the stereospecific transformation of 3-tosyloxy- and 3-haloazetidines after hydrolysis and substitution reactions, and ring contraction to aziridinylmethyl derivatives.<sup>16</sup> Moreover, it has been established that the substitution of 3-chloroazetidines with different nucleophiles occurs via formation of an analogous bicyclic intermediate which is then regioselectively opened at the C3 position.<sup>17</sup> In light of these reports, the ring opening of bicyclic aziridinium salts **13** by methanol is expected to proceed in a regioselective way at the more hindered carbon atom, furnishing 3-methoxyazetidines **9**. However, the formation of intermediate carbenium species **14** and their subsequent solvolysis by methanol should not be completely neglected as an alternative pathway toward azetidines **9**. It is worth mentioning that the isomerization of 2-(halomethyl)aziridines to 3-haloazetidines has been observed in the literature in only two cases,<sup>18</sup> and that isolated examples are known in which ring opening of strained bicyclic intermediates does not occur in a regioselective way.<sup>16c</sup>

In the next part, a stepwise experimental approach was applied in order to shed more light on the underlying reaction

mechanism. At first, a kinetically controlled synthesis of 1-arylmethyl-2-bromomethyl-2-methylaziridines **19** was envisaged starting from  $\alpha,\beta$ -dibromoaldimines **18** (Scheme 5). Bromination of 2-methylpropanal **15** using 1.05 equiv of bromine in dichloromethane afforded the corresponding 2,3-dibromopropanal **16** in nearly quantitative yield, which was subsequently condensed with 1 equiv of different *N*-(arylmethyl)amines **17** by means of 0.6 equiv of titanium(IV) chloride and 3 equiv of triethylamine in diethyl ether,<sup>15</sup> furnishing  $\alpha,\beta$ -dibromoimines **18** in good yields (Scheme 5). The latter imines **18** were reduced by means of 2 molar equiv of sodium borohydride in methanol, resulting in 2-bromomethyl-2-methylaziridines **19** after 36 h at room temperature. Alternatively, imines **18** were reduced toward aziridines **19a–d** utilizing two molar equiv of sodium cyanoborohydride in methanol in the presence of 1 equiv of acetic acid, however, without providing better yields. In addition, 2-bromomethyl-2-methylaziridines **19a,b** were also obtained through reaction of *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)amines **7a** and **7b** with 2 molar equiv of NaBH<sub>4</sub> in methanol after 36 h at room temperature. The formation of 2-bromomethyl-2-

Scheme 6



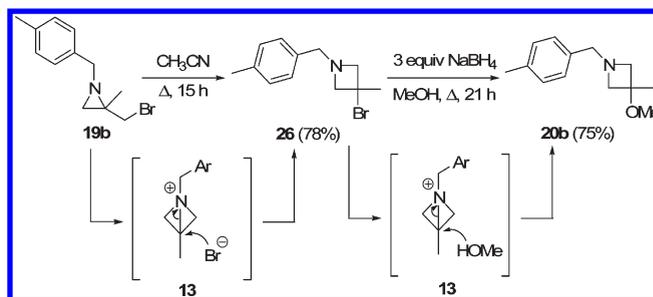
methylaziridines **19** from both *N*-(2,3-dibromo-2-methylpropylidene)amines **18** and *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)amines **7** is rationalized by the intermediacy of the same amines **10** (Scheme 4) obtained upon reduction of imines **7** and **18** with  $NaBH_4$ . From these findings, it is clear that aziridines **11** are the kinetic and azetidines **9** the thermodynamic products obtained through  $NaBH_4$ -mediated reduction of imines **7** and **18** in methanol under reflux (Scheme 4).

Nonactivated 2-bromomethyl-2-methylaziridines **19** represent a novel class of synthons suitable for further elaboration to a variety of nitrogen-containing compounds. Under thermodynamic conditions, i.e., treatment of aziridines **19** with sodium borohydride in methanol under reflux for 48 h, 3-methoxy-3-methylazetidines **20** were formed in high yields as the sole reaction products (Scheme 5). This prolonged reaction time appeared to be necessary in order to drive the reaction to completion. Again, it should be remarked that applying the same reaction conditions to 2-(bromomethyl)aziridines **8** without a 2-methyl substituent is known to result in full recovery of the starting material.

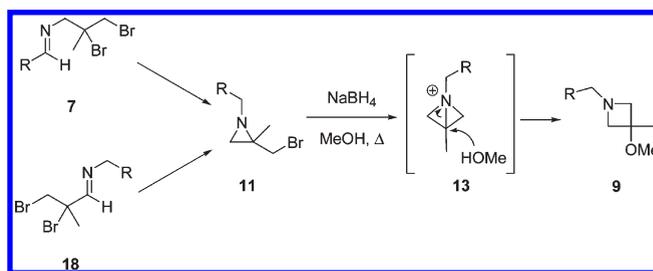
Heating of aziridines **19** in methanol under reflux for 24 h resulted in a complex reaction mixture, pointing to the necessity of a basic environment for this aziridine to azetidine rearrangement process. Furthermore, treatment of aziridines **19** with 1.5 equiv of NaOMe in MeOH (2 M) furnished azetidines **20**, although a prolonged reaction time was required (72 instead of 48 h).

The above-described synthetic route was also applied for a straightforward synthesis of chiral 2-bromomethyl-2-methylaziridines. Thus, *N*-(2,3-dibromo-2-methylpropylidene)-1(*S*)-phenylethylamine **22** was prepared by imination of 2,3-dibromopropanal **16** with 1 equiv of (*S*)- $\alpha$ -methylbenzylamine **21** in the presence of titanium(IV) chloride and triethylamine. Next, imine **22** was reduced utilizing 2 molar equiv of sodium borohydride in methanol, resulting in a mixture of two diastereomeric 2-bromomethyl-2-methylaziridines **23** and **24** (~1/1) after 36 h at room temperature (Scheme 6).

Scheme 7



Scheme 8

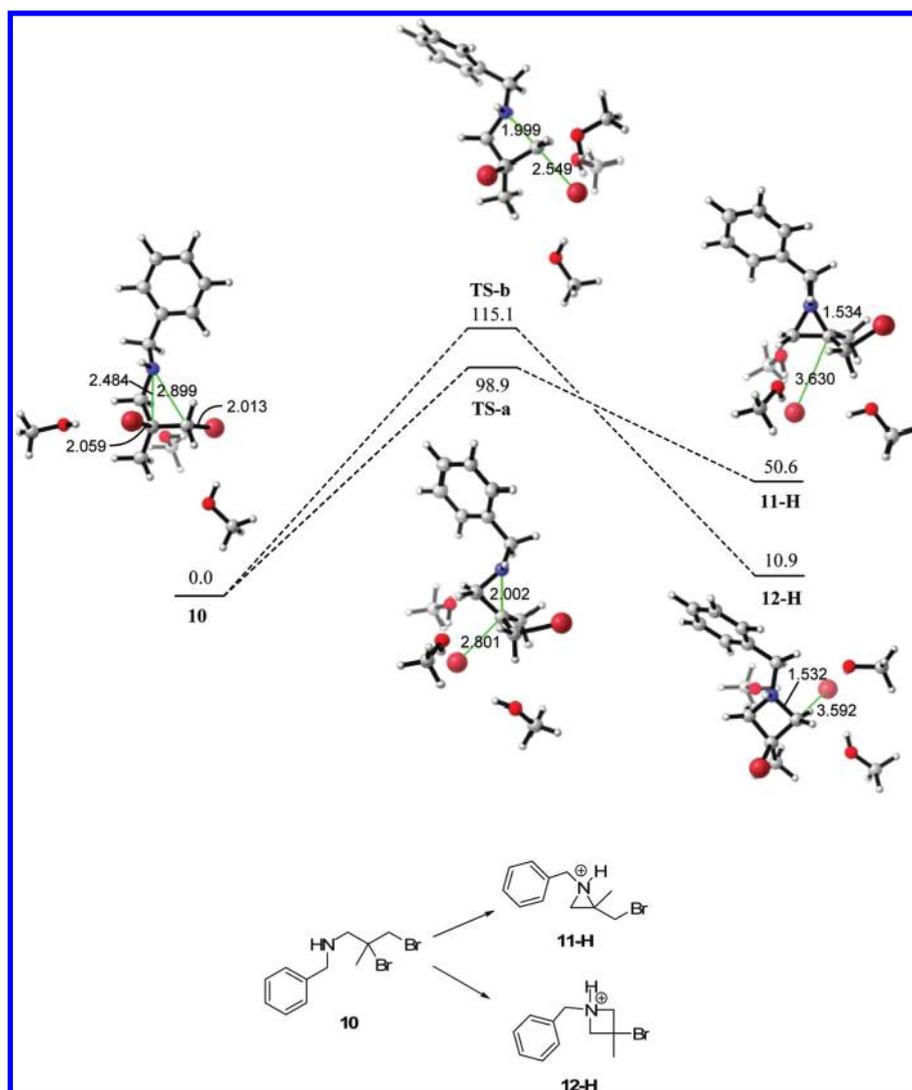


After successful separation by column chromatography on silica gel, chiral aziridines **23** and **24** were separately subjected to 3 molar equiv of  $NaBH_4$  under reflux in methanol for 48 h. As expected, both reactions provided the same chiral azetidine **25**, which can be explained considering the loss of chirality of the azetidine carbon atom due to  $C_2$ -symmetry (Scheme 6).

Once again, it should be stressed that only two reports are available in the literature describing the ring expansion of aziridines toward azetidines,<sup>18</sup> pointing to the peculiar nature of this type of rearrangements.

In order to evaluate the intrinsic reactivity of 2-bromomethyl-2-methylaziridines **19**, aziridine **19b** as a selected example was heated in acetonitrile under reflux for 15 h (Scheme 7), affording 3-bromoazetidine **26** in 78% yield. The unprecedented transformation of aziridine **19b** into azetidine **26** as the thermodynamic product further illustrates the relevance of this aziridine to azetidine ring expansion and can be explained by formation of bicyclic aziridinium salt **13** followed by attack of bromide at the more hindered carbon atom. Moreover, when this 3-bromoazetidine **26** was treated with  $NaBH_4$  in methanol under reflux, 3-methoxy-3-methylazetidine **20b** was formed via solvolysis of the same bicyclic intermediate **13** through ring opening (Scheme 7).<sup>16,17</sup> The replacement of bromide by methanol in azetidine **26** via an  $S_N2$  protocol should be neglected as an alternative reaction pathway due to the steric hindrance at the tertiary carbon center, although  $S_N1$  reaction through solvolysis of a tertiary carbenium ion might involve a plausible alternative.

In summary, a novel aziridine to azetidine rearrangement protocol was established involving the conversion of 2-bromomethyl-2-methylaziridines **11**, obtained via reductive cyclization of halogenated imines **7** or **18**, into 3-methoxy-3-methylazetidines **9** through ring opening of bicyclic intermediates **13** by methanol upon treatment with  $NaBH_4$  in methanol under reflux (Scheme 8).



**Figure 1.** Gibbs free energy profiles for the conversion of *N*-benzyl-*N*-(2,3-dibromo-2-methylpropyl)amine **10** (R = Ph) via pathways **a** and **b** (kJ/mol, MPW1B95/6-31++G\*\*). (B3LYP/6-31++G\*\* geometries. Critical distances in Å.)

In the next part, a careful theoretical rationalization was performed for a complete elucidation of the reaction mechanism. Particular attention was devoted to the nature of the intermediates in this reaction, in particular the occurrence of bicyclic aziridinium ions **13** versus nonbridged carbenium ions **14**.

**Theoretical Rationalization.** A thorough computational analysis was performed on the possible reaction pathways proposed in Scheme 4 (R = Ph), in order to rationalize the experimentally observed rearrangement and identify the reactive intermediates involved. The most plausible pathway will be determined through comparison of reaction barriers.

**Computational Methodology.** Possible pathways were investigated at the B3LYP/6-31++G\*\* level of theory.<sup>19</sup> Conformational analysis was performed on all ground states to determine the most plausible conformers. Stationary points were characterized as minima (ground states) or first-order saddle points (transition states) via frequency calculations. IRC (intrinsic reaction coordinate) calculations<sup>20</sup> followed by full geometry optimizations were used to locate the corresponding reactant and product complexes. Energies were refined at the MPW1B95/

6-31++G\*\* level of theory,<sup>21</sup> as previous studies have shown its efficiency on aziridine species.<sup>11,22</sup> Thermal free-energy corrections were taken from B3LYP/6-31++G\*\* optimizations at 1 atm and 298 K. The effect of a polar environment was introduced by the use of self-consistent reaction field (SCRF) theory.<sup>23</sup> Solvation free energies in methanol ( $\epsilon = 32.6$ ) were obtained via the conductor-like polarizable continuum model (C-PCM).<sup>24</sup> All calculations were carried out with the Gaussian 03 and 09 program packages.<sup>25</sup>

Since nucleophilic substitution reactions are known to be influenced by reaction conditions,<sup>26</sup> pathways under study were modeled with a proper solvent environment. Simulation of reactions in organic solvents can be performed in a continuum model,<sup>24,27</sup> where the solvent is modeled as a continuous medium characterized by a dielectric constant. However, if explicit solvent interactions are present, discrete solvent molecules should be placed around the chemically active species to form a so-called "supermolecule" structure.<sup>22b,22c,28</sup> Nevertheless, since this method only takes into account short-range interactions to account for potential long-range interactions with the solvent environment, the supermolecule can also be placed in a dielectric continuum,

leading to a mixed implicit/explicit model.<sup>29</sup> A comparative study has shown that mixed solvation models should be used with caution as they can give unreliable results with increasing numbers of explicit solvent molecules, and are highly influenced by their orientation/alignment.<sup>30</sup> Furthermore, a previous study on the nucleophilic ring opening of aziridines has shown that embedding the supermolecule in a dielectric continuum does not have an appreciable effect and observed trends are similar to that of the discrete solvent model.<sup>11o</sup> Therefore, in this study a discrete solvent approach, where explicit methanol molecules were used to build a supermolecule, was adapted.

**Cyclization of *N*-Benzyl-*N*-(2,3-dibromo-2-methylpropyl)amine 10 (R = Ph).** There are two competing pathways in the first step of the conversion of the *N*-benzyl-*N*-(2,3-dibromo-2-methylpropyl)amine 10 to azetidine 9. Ring closure can lead to aziridine 11 via pathway a or to azetidine 12 via pathway b. Free energy profiles and relative energies along the reaction coordinate for pathways a and b are illustrated in Figure 1 and Table 1. Three explicit methanol molecules, which help to stabilize the bromide ion through charge-dipole interactions, were used to solvate the bromide ion, which is expelled during the S<sub>N</sub>2 reaction. The choice of three methanol molecules is justified by a former study, which showed that only three acetic acid (also a polar protic solvent) molecules have explicit contacts with the bromide ion of an aziridinium-bromide complex.<sup>22c</sup> Typical Br...HOMe distances are around 2.4 Å. Free energies of activation show that pathway a is the kinetically preferred route ( $\Delta G^\ddagger = 16.2$  kJ/mol MPW1B95/6-31++G\*\*), which is in accordance with experimental findings. Although the azetidinium ion (denoted as 12-H in Figure 1) is the thermodynamically preferred product, thermodynamic equilibration is not feasible as the aziridinium ion (denoted as 11-H in Figure 1) is immediately deprotonated toward the neutral, nonactivated aziridine 11 (which is thus not able to undergo ring opening by bromide at C2). Therefore, aziridine 11 is the preferred product for the cyclization, as observed experimentally.

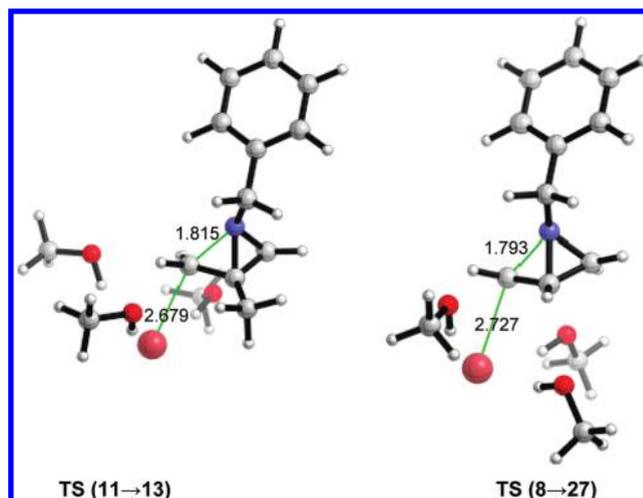
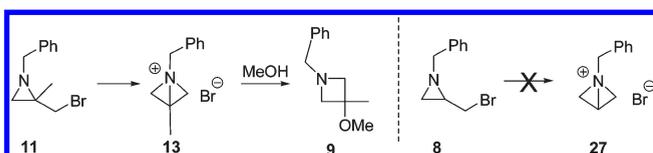
**Bicyclic Aziridinium Intermediates.** As previously described, aziridine 11 is suggested to undergo further cyclization to yield the bicyclic aziridinium ion 13, a bicyclic intermediate that will undergo nucleophilic ring opening to form azetidine 9 (Scheme 9). However, as discussed previously, applying the same reaction conditions to imines 1 (Scheme 3) with R<sup>2</sup> = H and R<sup>2</sup> = Me resulted in 2-(bromomethyl)aziridines and 3-methoxy-3-methylazetidines, respectively (Scheme 3). In other words, the presence of an additional methyl group in imines 1 seems to have a

**Table 1. Relative Gibbs Free Energies (kJ/mol) of Stationary Points along the Reaction Coordinate for the Conversion of 10 via Pathways a and b<sup>a</sup>**

	10	TSa	11	TSb	12
B3LYP/6-31++G**	0.0	93.3	56.8	108.9	20.2
MPW1B95/6-31++G**	0.0	98.9	50.6	115.1	10.9

<sup>a</sup> B3LYP/6-31++G\*\* geometries.

#### Scheme 9



**Figure 2.** Transition-state geometries for the formation of bicyclic aziridinium species. (B3LYP/6-31++G\*\* geometries. Critical distances in Å.)

**Table 2. Relative Gibbs Free Energies (kJ/mol) of Stationary Points along the Reaction Coordinate for the Formation of the Bicyclic Aziridinium Ions<sup>a</sup>**

	11 <sup>b</sup>	TS (11→13)	13	8 <sup>b</sup>	TS (8→27)	27
B3LYP/6-31++G**	0.0	96.0	61.4	0.0	120.9	75.6
MPW1B95/6-31++G**	0.0	103.6	53.4	0.0	119.1	61.1

<sup>a</sup> B3LYP/6-31++G\*\* geometries. <sup>b</sup> Trans invertomers used for 8 and 11.

profound influence on the reaction outcome. Since intramolecular cyclization and further transformation to azetidines was observed for 2-bromomethyl-2-methylaziridines 11 and not for 2-(bromomethyl)aziridines 8 (Scheme 9), which lack an additional substituent at the 2-position, cyclization pathways for both compounds were investigated in detail.

Transition-state geometries and relative energies for the formation of the bicyclic aziridinium ion 13 and 27 are shown in Figure 2 and Table 2. The difference in free energies of activation could explain why 2-bromomethyl-2-methylaziridines 11 undergo cyclization and further transformation as opposed to 2-(bromomethyl)aziridines 8, which lack an additional substituent at the 2-position. As mentioned earlier, this difference can be rationalized considering the Thorpe-Ingold effect due to the *gem*-disubstitution at the aziridine carbon atom, resulting in a more favorable geometry for nucleophilic attack.<sup>31</sup> Replacement of the methyl group at the 2-position of aziridine 11 by a hydrogen atom increases the distance between the nucleophilic nitrogen atom and the halogenated carbon atom in aziridine 8, as shown in Figure 3, which in turn gives rise to a reduced reactivity.

As suggested previously, bicyclic aziridinium ion 13 can be in equilibrium with its nonbridged carbenium ion counterpart 14 (Scheme 10). The free energy profile and relative energies for this equilibrium are shown in Figure 4 and Table 3, along with atomic charges, calculated by means of natural population analysis (NPA).<sup>32</sup> The difference in relative stabilities of bicyclic aziridinium ion 13 and cyclic carbenium ion 14 shows that the former, where all atoms have full octet structure, is far more stable than the latter. These results are consistent with earlier calculations on bicyclic aziridinium intermediates performed at

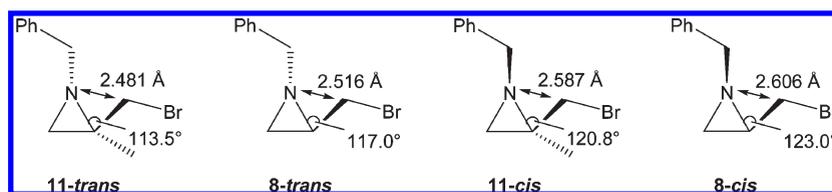
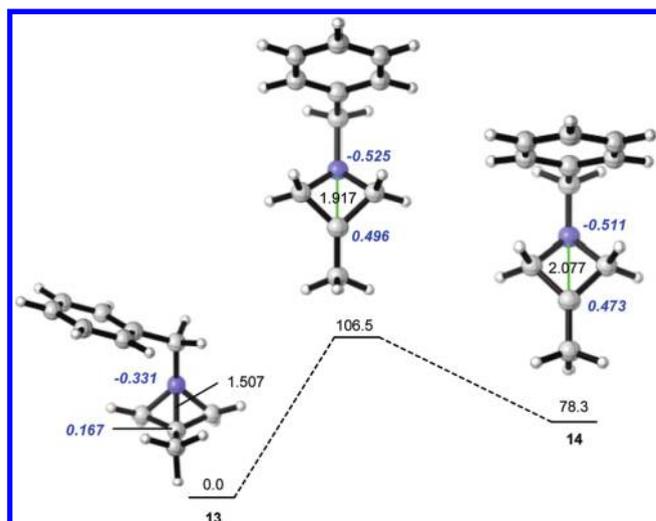
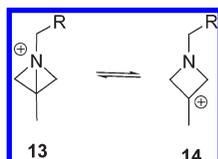


Figure 3. Invertomers of 8 and 11.

Figure 4. Gibbs free energy profile for the 13 to 14 equilibration (kJ/mol, CPCM ( $\epsilon = 32.6$ ) MPW1B9S/6-31++G\*\*). (B3LYP/6-31++G\*\* geometries. Critical distances in Å. Atomic charges in italic.)

## Scheme 10



MP2/6-311G\*\*//HF/6-31G\*\* level of theory, which showed that open-ring structures are considerably less stable than the corresponding bicyclic ions.<sup>14</sup>

Therefore, the reaction is expected to proceed through the bicyclic aziridinium ion 13, and the carbenium species 14 is less likely to be formed or will be short-lived. Next, possible fates of the bicyclic species 13 were investigated.

Although initially proposed as an alternative route, the direct transformation of aziridine 11 to azetidine 12 was not computationally viable. All attempts to locate a concerted transition state for this transformation, where a simultaneous cleavage and formation of a carbon–nitrogen bond is accompanied by bromide migration, failed. It has already been established that an equilibration between 11 and 12 through ring opening/ring closure is unfeasible as the aziridinium ion (11-H, Figure 1) is immediately deprotonated toward the neutral aziridine 11. However, it is possible to obtain 12 via bromide-induced ring opening of the bicyclic aziridinium 13 (pathway a, Scheme 11).

Figure 5 shows transition states for the transformation of 13 to 12 and 9, respectively. Due to its excessive strain, the bicyclic intermediate 13 easily undergoes nucleophilic ring opening to

Table 3. Relative Gibbs Free Energies (kJ/mol) for the 13 to 14 Equilibration<sup>a</sup>

	13	TS (13→14)	14
B3LYP/6-31++G**	0.0	86.2	63.2
MPW1B9S/6-31++G**	0.0	108.7	84.6
<sup>b</sup> MPW1B9S/6-31++G**	0.0	106.5	78.3

<sup>a</sup>B3LYP/6-31++G\*\* geometries. <sup>b</sup>CPCM ( $\epsilon = 32.6$ ).

## Scheme 11

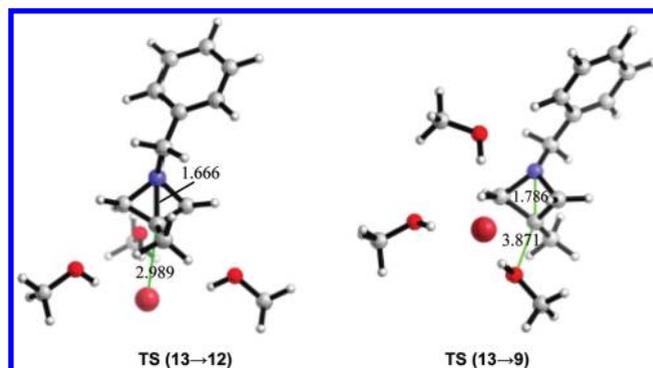
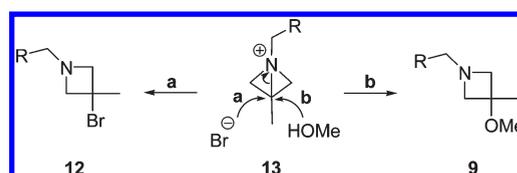


Figure 5. Transition state geometries for the formation of bromide- and methanol-induced ring-opening reactions of bicyclic aziridinium species 13. (B3LYP/6-31++G\*\* geometries. Critical distances in Å.)

form azetidines 12 and 9. The transformation of 13 to 12 is energetically more favorable ( $\Delta\Delta G^\ddagger = 38.9$  kJ/mol MPW1B9S/6-31++G\*\*), since the bromide anion—solvated or not—is a stronger nucleophile than neutral methanol.<sup>33</sup> However, it should be noted that the relative probabilities of these events are dependent on concentration, and reaction conditions highly favor the formation of 9 (pathway b, Scheme 11) since the concentration of methanol is much higher than that of bromide. However, in the absence of methanol, azetidine 12 would be the observed product, as was experimentally shown (Scheme 7).

Nonetheless, if 13 is transformed to 12, its transformation to 9 through an S<sub>N</sub>2 reaction is hindered due to sterics that disable a backside attack. On the other hand, an S<sub>N</sub>1 reaction would require the formation of the highly activated carbenium species 14, which is also not energetically feasible. It is more likely that azetidine 12 will be transformed into azetidine 9 through bicyclic aziridinium 13.

**Table 4. Relative Gibbs Free Energies (kJ/mol) of Stationary Points along the Reaction Coordinate for the Bromide- and Methanol-induced Nucleophilic Ring Opening of the Bicyclic Aziridinium Ion 13.<sup>a</sup>**

	13 <sup>b</sup>	TS (13→12)	12 <sup>c</sup>	TS (13→9)	9 <sup>d</sup>
B3LYP/6-31++G**	0.0	10.8	-78.9	42.1	-49.1
MPW1B95/6-31++G**	0.0	18.8	-67.6	57.7	-38.4

<sup>a</sup> B3LYP/6-31++G\*\* geometries. <sup>b</sup> Reactant-complex of bicyclic aziridinium 13 and bromide ion solvated by three methanol molecules. <sup>c</sup> Product-complex of azetidine 12 and three methanol molecules. <sup>d</sup> Product-complex of azetidine 9 with hydrogen bromide and two methanol molecules.

Computational analysis of the possible reaction pathways proposed in Scheme 4 (R = Ph) has revealed that pathway a is the kinetically preferred route (Figure 1) and aziridine 11 is the subsequent product for the cyclization, as observed experimentally. Unlike aziridines 8, which lack an additional substituent at the 2-position, aziridine 11 then undergoes further cyclization to yield the bicyclic aziridinium ion 13 (Figure 2), a strained intermediate, which can undergo nucleophile-induced ring opening to form azetidines 12 or 9, depending on the relative abundance of the nucleophilic entity (Figure 5).

## CONCLUSIONS

The synthesis of 3-methyl-3-methoxyazetidines starting from *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines and *N*-(2,3-dibromo-2-methylpropylidene)benzylamines through intermediate bicyclic aziridinium species has been reported for the first time. It was shown that treatment of the above-mentioned dibromoimines with NaBH<sub>4</sub> in methanol selectively provides 2-bromomethyl-2-methylaziridines at room temperature and 3-methoxy-3-methylazetidines under reflux, pointing to the conclusion that 3-methoxy-3-methylazetidines are thermodynamic and 2-bromomethyl-2-methylaziridines are kinetic products obtained in the reaction of these imines with NaBH<sub>4</sub> in methanol under reflux through a rare aziridine to azetidine ring expansion. Furthermore, a careful theoretical rationalization of the reaction protocol provided a detailed elucidation of possible mechanistic pathways indicating the initial formation of 2-bromomethyl-2-methylaziridines and subsequent ring expansion toward azetidines via intermediate bicyclic aziridinium salts.

## EXPERIMENTAL SECTION

**General Methods.** <sup>1</sup>H NMR spectra were recorded at 300 MHz with CDCl<sub>3</sub> as solvent and tetramethylsilane as internal standard. <sup>13</sup>C NMR spectra were recorded at 75 MHz with CDCl<sub>3</sub> as solvent. Mass spectra were recorded using either a direct inlet system (electron spray, 4000 V) or LC-MS coupling (UV detector). IR spectra were recorded on a FT-IR spectrometer in neat form with an ATR (Attenuated Total Reflectance) accessory. Dichloromethane was distilled over calcium hydride, while diethyl ether and THF were distilled from sodium and sodium benzophenone ketyl before use.

**Synthesis of 2-Bromomethyl-2-methylaziridines 19.** As a representative example, the synthesis of 2-bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine 19d is described here. *N*-(2,3-Dibromo-2-methylpropylidene)-4-methoxybenzylamine 18d (3.49 g, 10 mmol) was dissolved in methanol (30 mL), after which NaBH<sub>4</sub> (0.76 g, 2 molar

equiv) was added in small portions at 0 °C, and the mixture was stirred for 36 h at room temperature. The reaction mixture was poured into water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic extracts were washed with H<sub>2</sub>O (2 × 15 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), filtration of the drying agent, and evaporation of the solvent afforded 2-bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine 19d (2.36 g, 87%), which was purified by filtration through silica gel (hexane/ethylacetate 7:1) in order to obtain an analytically pure sample.

**2-Bromomethyl-1-(4-methylbenzyl)-2-methylaziridine 19b:** yellow oil; *R*<sub>f</sub> = 0.16 (hexane/ethyl acetate 9:1); yield 82%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.43 (3H, s), 1.50 (1H, s), 1.98 (1H, s), 2.33 (3H, s), 3.28 and 3.36 (2H, 2d, *J* = 9.9 Hz), 3.50 and 3.71 (2H, 2d, *J* = 13.7 Hz), 7.13–7.15 and 7.24–7.26 (4H, 2m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.6 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>), 40.2 (C), 41.7 (CH<sub>2</sub>), 44.1 (CH<sub>2</sub>), 57.1 (CH<sub>2</sub>), 127.7 and 129.1 (4 × CH), 136.5 (2 × C); IR (neat, cm<sup>-1</sup>) *ν*<sub>max</sub> = 3024, 2962, 2922, 2851, 1671, 1515, 1451, 1384, 1348, 1216, 1167, 1046, 798, 647; MS *m/z* 254/6 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>12</sub>H<sub>16</sub>BrN: C, 56.71; H, 6.35; N, 5.51. Found: C, 56.47; H, 6.63; N, 5.44.

**2-Bromomethyl-1-(2-chlorobenzyl)-2-methylaziridine 19c:** yellow oil; *R*<sub>f</sub> = 0.24 (hexane/ethyl acetate 9:1); yield 85%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.44 (3H, s), 1.58 (1H, s), 2.07 (1H, s), 3.35 and 3.40 (2H, 2d, *J* = 10.2 Hz), 3.63 and 3.85 (2H, 2d, *J* = 15.7 Hz), 7.20–7.36 and 7.66–7.69 (4H, 2m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.6 (CH<sub>3</sub>), 40.2 (C), 42.0 (CH<sub>2</sub>), 43.9 (CH<sub>2</sub>), 54.3 (CH<sub>2</sub>), 126.9, 128.0, 129.0, and 129.1 (4 × CH), 132.8 (C), 137.3 (C); IR (neat, cm<sup>-1</sup>) *ν*<sub>max</sub> = 3035, 2964, 1470, 1443, 1386, 1348, 1218, 1171, 1037, 748, 644; MS *m/z* 274/6/8 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>11</sub>H<sub>13</sub>BrClN: C, 48.12; H, 4.77; N, 5.10. Found: C, 48.55; H, 4.92; N, 5.19.

**2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine 19d:** yellow oil; *R*<sub>f</sub> = 0.10 (hexane/ethyl acetate 7:1); yield 87%; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.43 (3H, s), 1.50 (1H, s), 1.97 (1H, s), 3.29 and 3.34 (2H, 2d, *J* = 10.2 Hz), 3.47 and 3.69 (2H, 2d, *J* = 13.8 Hz), 3.80 (3H, s), 6.86–6.89 and 7.27–7.29 (4H, 2m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.6 (CH<sub>3</sub>), 40.2 (C), 41.7 (CH<sub>2</sub>), 44.2 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>), 56.8 (CH<sub>2</sub>), 113.8 and 129.0 (4 × CH), 131.7 (C), 158.6 (C); IR (neat, cm<sup>-1</sup>) *ν*<sub>max</sub> = 3030, 2959, 2933, 2834, 1612, 1511, 1463, 1244, 1172, 1034, 819, 644; MS *m/z* 270/2 (M<sup>+</sup> + 1, 100). Anal. Calcd for C<sub>12</sub>H<sub>16</sub>BrNO: C, 53.35; H, 5.97; N, 5.18. Found: C, 53.55; H, 6.27; N, 5.24.

**Synthesis of Optically Active 2-Bromomethyl-2-methylaziridines 23 and 24.** *N*-(2,3-Dibromo-2-methylpropylidene)-1(*S*)-phenylethylamine 22 (3.33 g, 10 mmol) was dissolved in methanol (30 mL), after which NaBH<sub>4</sub> (0.76 g, 2 molar equiv) was added in small portions at 0 °C, and the mixture was stirred for 36 h at room temperature. The reaction mixture was poured into water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The combined organic extracts were washed with H<sub>2</sub>O (2 × 15 mL) and brine (20 mL). Drying (MgSO<sub>4</sub>), filtration of the drying agent, and evaporation of the solvent afforded a mixture of 2(*R*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine and 2(*S*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine 23 and 24 (2.42 g, 95%), which were separated by silica gel column chromatography (petroleum ether/ethyl acetate 9:1) in order to obtain analytically pure samples.

**2(*R*)-2-Bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine 23 and 2(*S*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine 24.** 23: light yellow oil; *R*<sub>f</sub> = 0.28 (petroleum ether/ethyl acetate 9:1); yield 45%; [α]<sub>D</sub><sup>28</sup> = -48.4 (*c* = 0.05, CDCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 1.38 (1H, s), 1.43 (3H, d, *J* = 6.6 Hz), 1.51 (3H, s), 1.79 (1H, s), 3.10 (1H, q, *J* = 6.6 Hz), 3.25 and 3.46 (2H, 2d, *J* = 9.9 Hz), 7.25–7.40 (5H, m); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.4 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>), 40.6 (CH<sub>2</sub>), 41.1 (C), 44.9 (CH<sub>2</sub>), 61.6 (CH), 127.0 and 128.3 (5 × CH), 145.0 (C); IR (neat, cm<sup>-1</sup>) *ν*<sub>max</sub> = 3027, 2969, 2927, 2866, 1449, 1348, 1222, 1172, 755, 699, 646; MS *m/z* 254/6

( $M^+ + 1$ , 100). Anal. Calcd for  $C_{12}H_{16}BrN$ : C, 56.71; H, 6.35; N, 5.51. Found: C, 56.35; H, 6.63; N, 5.44. **24**: light yellow oil;  $R_f = 0.15$  (petroleum ether/ethyl acetate 9:1); yield 42%;  $[\alpha]_D^{28} = -44.2$  ( $c = 0.06$ ,  $CDCl_3$ );  $^1H$  NMR (300 MHz,  $CDCl_3$ ) 1.21 (3H, s), 1.40 (3H, d,  $J = 6.6$  Hz), 1.48 (1H, s), 2.00 (1H, s), 3.16 (1H, q,  $J = 6.6$  Hz), 3.22 and 3.34 (2H, 2d,  $J = 9.9$  Hz), 7.23–7.39 (5H, m);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  13.6 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 40.3 (CH<sub>2</sub>), 41.0 (C), 43.6 (CH<sub>2</sub>), 62.8 (CH), 126.5, 126.8, and 128.3 (5  $\times$  CH), 145.4 (C); IR (neat,  $cm^{-1}$ )  $\nu_{max} = 3028, 2967, 2926, 2866, 1450, 1349, 1217, 1173, 757, 699, 646$ ; MS  $m/z$  254/6 ( $M^+ + 1$ , 100). Anal. Calcd for  $C_{12}H_{16}BrN$ : C, 56.71; H, 6.35; N, 5.51. Found: C, 56.62; H, 6.55; N, 5.46.

**Synthesis of 3-Methoxy-3-methylazetidines 20 from 2-Bromomethyl-2-methylaziridines 19.** As a representative example, the synthesis of 1-(2-chlorobenzyl)-3-methoxy-3-methylazetidene **20c** is described here. 2-Bromomethyl-1-(2-chlorobenzyl)-2-methylaziridine **19c** (2.76 g, 10 mmol) was dissolved in methanol (30 mL), after which  $NaBH_4$  (1.13 g, 3 molar equiv) was added in small portions at 0 °C, and the mixture was heated for 48 h under reflux. The reaction mixture was poured into water (20 mL) and extracted with  $CH_2Cl_2$  (3  $\times$  20 mL). The combined organic extracts were washed with  $H_2O$  (2  $\times$  15 mL) and brine (20 mL). Drying ( $MgSO_4$ ), filtration of the drying agent, and evaporation of the solvent afforded 1-(2-chlorobenzyl)-3-methoxy-3-methylazetidene **20c** (2.01 g, 89%), which was purified by filtration through silica gel (ether/hexane 10:1) in order to obtain an analytically pure sample.

**1-(2-Chlorobenzyl)-3-methoxy-3-methylazetidene 20c:** yellow oil;  $R_f = 0.15$  (ether/hexane 10:1); yield 89%;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.51 (3H, s), 3.16 and 3.31 (4H, 2d,  $J = 8.3$  Hz), 3.21 (3H, s), 3.79 (2H, s), 7.14–7.42 (4H, m);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  21.8 (CH<sub>3</sub>), 50.6 (CH<sub>3</sub>), 60.2 (CH<sub>2</sub>), 65.0 (2  $\times$  CH<sub>2</sub>), 73.0 (C), 126.8, 127.8, 129.3, and 129.4 (4  $\times$  CH), 133.5 and 136.3 (2  $\times$  C); IR (neat,  $cm^{-1}$ )  $\nu_{max} = 2968, 2930, 2827, 1469, 1443, 1371, 1359, 1232, 1067, 1050, 1038, 748$ ; MS  $m/z$  226/8 ( $M^+ + 1$ , 100). Anal. Calcd for  $C_{12}H_{16}ClNO$ : C, 63.85; H, 7.14; N, 6.21. Found: C, 63.72; H, 7.33; N, 6.44.

**1-(4-Methoxybenzyl)-3-methoxy-3-methylazetidene 20d:** yellow oil;  $R_f = 0.17$  (ether/hexane 10:1); yield 87%;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.47 (3H, s), 3.04 and 3.21 (4H, 2d,  $J = 7.7$  Hz), 3.18 (3H, s), 3.60 (2H, s), 3.79 (3H, s), 6.83–6.86 and 7.19–7.22 (4H, 2m);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  21.6 (CH<sub>3</sub>), 50.4 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 63.1 (CH<sub>2</sub>), 64.5 (2  $\times$  CH<sub>2</sub>), 72.8 (C), 113.7 and 129.6 (4  $\times$  CH), 130.4 and 158.7 (2  $\times$  C); IR (neat,  $cm^{-1}$ )  $\nu_{max} = 2933, 2833, 1611, 1511, 1463, 1241, 1173, 1065, 1034, 820$ ; MS  $m/z$  222 ( $M^+ + 1$ , 100). Anal. Calcd for  $C_{13}H_{19}NO_2$ : C, 70.56; H, 8.65; N, 6.33. Found: C, 70.75; H, 8.83; N, 6.24.

**Synthesis of Optically Pure 3-Methoxy-3-methyl-1-[1(S)-phenylethyl]azetidene 25.** The mixture of 2(R)-2-bromomethyl-1-[1(S)-phenylethyl]-2-methylaziridine and 2(S)-2-bromomethyl-1-[1(S)-phenylethyl]-2-methylaziridine **23** and **24** (2.55 g, 10 mmol) was dissolved in methanol (30 mL), after which  $NaBH_4$  (1.13 g, 3 molar equiv) was added in small portions at 0 °C, and the mixture was heated for 48 h under reflux. The reaction mixture was poured into water (20 mL) and extracted with  $CH_2Cl_2$  (3  $\times$  20 mL). The combined organic extracts were washed with  $H_2O$  (2  $\times$  15 mL) and brine (20 mL). Drying ( $MgSO_4$ ), filtration of the drying agent, and evaporation of the solvent afforded 3-methoxy-3-methyl-1-[1(S)-phenylethyl]azetidene **25** (1.97 g, 96%), which was purified by filtration through silica gel (ether/hexane 10:1) in order to obtain an analytically pure sample.

**3-Methoxy-3-methyl-1-[1(S)-phenylethyl]azetidene 25:** light yellow oil;  $R_f = 0.23$  (ether/hexane 10:1); yield 96%;  $[\alpha]_D^{28} = -51.6$  ( $c = 0.05$ ,  $CDCl_3$ );  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.22 (3H, d,  $J = 6.6$  Hz), 1.46 (3H, s), 2.93 and 2.99 (2H, 2d,  $J = 7.5$  Hz); 3.05 and 3.27 (2H, 2d,  $J = 7.4$  Hz), 3.18 (3H, s), 3.33 (1H, q,  $J = 6.6$  Hz), 7.20–7.33 (5H, m);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  21.6 (CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 50.5 (CH<sub>3</sub>), 63.7 and 63.8 (2  $\times$  CH<sub>2</sub>), 68.9 (CH), 71.9 (C), 127.1,

127.3, and 128.4 (5  $\times$  CH), 143.8 (C); IR (neat,  $cm^{-1}$ )  $\nu_{max} = 2966, 2929, 2825, 1451, 1370, 1235, 1067, 762, 700$ ; MS  $m/z$  206 ( $M^+ + 1$ , 100). Anal. Calcd for  $C_{13}H_{19}NO$ : C, 76.06; H, 9.33; N, 6.82. Found: C, 76.15; H, 9.60; N, 6.69.

**Synthesis of 3-Bromo-1-(4-methylbenzyl)-3-methylazetidene 26.** 2-Bromomethyl-1-(4-methylbenzyl)-2-methylaziridine **19b** (2.54 g, 10 mmol) was dissolved in acetonitrile (30 mL), and the mixture was heated for 15 h under reflux. The reaction mixture was poured into water (20 mL) and extracted with  $CH_2Cl_2$  (3  $\times$  20 mL). The combined organic extracts were washed with  $H_2O$  (2  $\times$  15 mL) and brine (20 mL). Drying ( $MgSO_4$ ), filtration of the drying agent, and evaporation of the solvent afforded 3-bromo-1-(4-methylbenzyl)-3-methylazetidene **26** (1.98 g, 78%), which was purified by filtration through silica gel (hexane/ethyl acetate 7:1) in order to obtain an analytically pure sample.

**3-Bromo-1-(4-methylbenzyl)-3-methylazetidene 26:** light yellow oil;  $R_f = 0.41$  (hexane/ethylacetate 7:1); yield 78%;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.99 (3H, s), 2.33 (3H, s), 3.51 and 3.69 (4H, 2d,  $J = 8.2$  Hz), 3.67 (2H, s), 7.10–7.18 (4H, m);  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  21.2 (CH<sub>3</sub>), 31.6 (CH<sub>3</sub>), 52.0 (C), 63.0 (CH<sub>2</sub>), 70.8 (2  $\times$  CH<sub>2</sub>), 128.5 and 129.2 (4  $\times$  CH), 134.6 and 136.9 (2  $\times$  C); IR (neat,  $cm^{-1}$ )  $\nu_{max} = 2922, 2848, 2807, 1514, 1440, 1360, 1244, 1206, 1178, 806, 734$ ; MS  $m/z$  254/6 ( $M^+ + 1$ , 100). Anal. Calcd for  $C_{12}H_{16}BrN$ : C, 56.71; H, 6.35; N, 5.51. Found: C, 56.55; H, 6.54; N, 5.37.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Spectra ( $^1H$  and  $^{13}C$  NMR) of **19b**, **19c**, **19d**, **20c**, **20d**, **23**, **24**, **25** and **26**. Cartesian coordinates and energies of the optimized geometries (B3LYP/6-31++G\*\*) of ground states; Cartesian coordinates, energies, imaginary and low frequencies of the optimized geometries (B3LYP/6-31++G\*\*) of transition states. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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#### ■ NOTE ADDED AFTER ASAP PUBLICATION

Scheme 3 contained an erroneous compound number and the name of compound **19b** was incomplete in the second to last paragraph in the version published ASAP March 9, 2011. The correct version reposted March 11, 2011.