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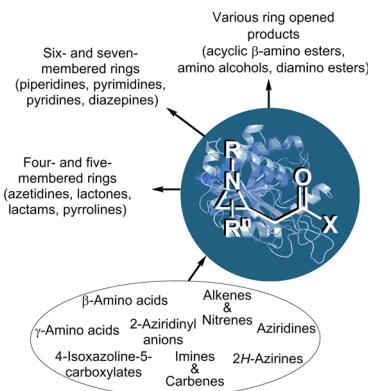
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Synthesis and Reactivity of 2-(Carboxymethyl)aziridine Derivatives

Gert Callebaut,[†] Tamara Meiresonne, Norbert De Kimpe,* and Sven Mangelinckx*

Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium



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1. INTRODUCTION

More than a decade ago, the question was raised by Sweeney if aziridines are epoxides' ugly cousins.¹ The overview on the biological properties, synthetic accessibility, and useful reactivity of aziridines presented therein, and in numerous earlier and later reviews,^{2–11} clearly indicated that this question is purely rhetorical. 2-(Aziridinyl)acetic acid **1**, alternatively named 3,4-iminobutanoic acid or 2-(carboxymethyl)aziridine, is a simple β,γ -aziridino carboxylic acid, which, to the best of our knowledge and somewhat surprisingly, has never been reported (Figure 1). Nevertheless, this aziridine **1** can be considered as the higher homologue of aziridine-2-carboxylic acid **2**,^{12–14}

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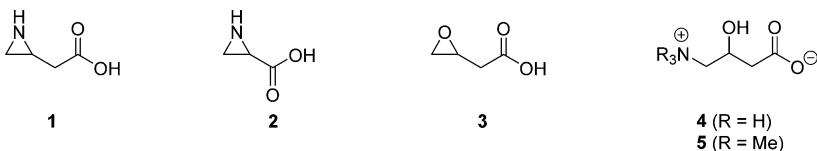


Figure 1. 2-(Aziridinyl)acetic acid **1**, aziridine-2-carboxylic acid **2**, β,γ -epoxy carboxylic acid **3**, γ -amino- β -hydroxybutyric acid **4**, and carnitine **5**.

which represents a very interesting electrophilic scaffold for the design of cysteine protease inhibitors.^{15–17} Furthermore, aziridine **1** is the aza analog of β,γ -epoxy carboxylic acid **3**, which is a valuable building block for ring opening to γ -amino- β -hydroxybutyric acid (GABOB) **4**,¹⁸ and carnitine **5**.¹⁹

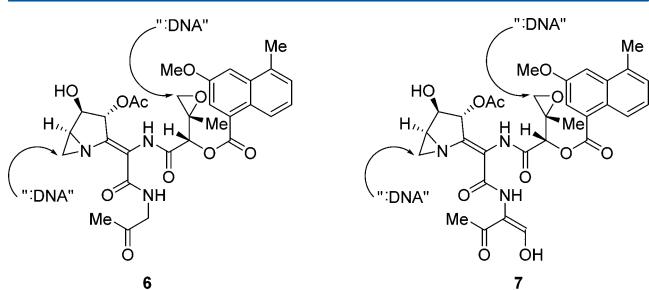


Figure 2. Azinomycin A **6** and azinomycin B **7**.

This β,γ -epoxy carboxylic acid moiety is also present in azinomycin A, **6**, and azinomycin B, **7**, in which the epoxide moiety acts as an electrophile which can easily react with biological nucleophiles (Figure 2). Hereby, azinomycin A and B are behaving as very efficient DNA interstrand cross-linkers as it contains, next to the epoxide moiety, also an electrophilic bicyclic aziridine unit which can react with DNA.²⁰ As azaheterocyclic β -amino acid derivatives,^{21–24} the group of 2-(carboxymethyl)aziridine derivatives **8** covers a specific part of the chemical space which is of interest for development of bioactive products and for further synthetic application toward

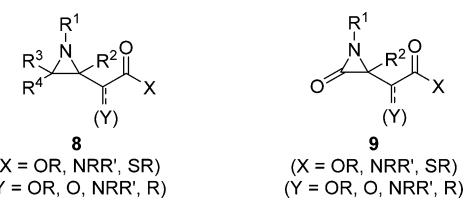


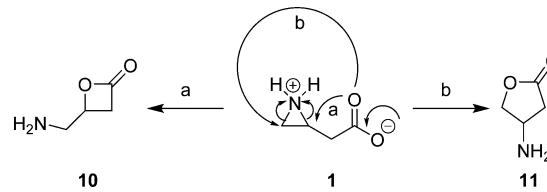
Figure 3. 2-(Carboxymethyl)aziridine derivatives **8** and 3-(carboxymethyl)- α -lactam derivatives **9**.

a wide range of nitrogen-containing compounds such as β - and γ -amino acids,²⁵ amino alcohols, and heterocycles.

The scope of the current review is not limited in time, as it is the first dedicated report concerning the chemistry of 2-(carboxymethyl)aziridine derivatives **8** (Figure 3). Herein, the synthesis and reactivity of 2-(aziridinyl)acetic esters ($X = OR$), 2-(aziridinyl)acetamides ($X = NRR'$), and 2-(aziridinyl)acetic thioesters ($X = SR$) is discussed, without covering 2-(aziridinyl)acetaldehydes ($X = H$) and the corresponding ketones ($X = \text{alkyl, aryl}$), as these compounds have a significant distinct reactivity and applications. Also, synthesis of the 3-(carboxymethyl)- α -lactam derivatives **9** ($X = OR, NRR', SR$) will not be discussed for the same reason.

Although the “poly(carboxymethylethylene imine)” polymer^{26–28} and 2-aziridineacetic acid containing polypeptides²⁹ have been mentioned a few times in the literature, the synthesis of the unprotected 2-(aziridinyl)acetic acid **1** monomer has

Scheme 1



never been reported so far. This could be due to the fact that this 2-(aziridinyl)acetic acid, **1**, is likely to be unstable because it might be prone to rearrange to constitutional isomers such as 3-aminomethyl- β -propiolactone, **10** or, more likely, 3-amino- γ -butyrolactone, **11** (Scheme 1).

Moreover, the challenging (stereoselective) synthesis of 2-(carboxymethyl)aziridines **12** ($Y \neq H$) is hampered by the presence of an acidic proton in the α -position, which can easily

Scheme 2



be deprotonated, leading to ring opening with formation of the corresponding γ -amino- α,β -unsaturated carboxylic acid derivatives **13** (Scheme 2). Also, possible deprotonation and reprotonation at the acidic α -center must be considered as this would lead to epimerization of the chiral center.

Although 2-(carboxymethyl)aziridine derivatives **8** have not yet received a lot of attention as biologically relevant compounds, some of them are exhibiting interesting biological activities. For example, 2-aziridinyl-2-hydroxy- β -lactam **14a** showed promising ACAT inhibitor activity (using Lovastatin as a reference standard) in an *in vitro* assay (Figure 4).³⁰ Furthermore, the four enantiomers of **15a** (“2-benzyl-3,4-iminobutanoic acid”) were evaluated as a novel class of inhibitors of CPA. All four stereoisomers of **15a** were found to have competitive inhibitory activity against CPA, although their inhibitory potencies differ widely, (*2R,3R*)-**15a** being the most potent.³¹ (*1R,6R*)- and (*1S,6S*)-3,4,5-Trihydroxy-7-azabicyclo[4.1.0]heptane-2-carboxylic acids **16** were evaluated as glycosidase inhibitors because they were expected to be chemotherapeutic agents and biological tools for clarifying catalytic mechanisms of glycosidases. The glycosidase inhibitor assay showed that both isomers of **16** are potent inhibitors of β -glucuronidase as they had excellent IC₅₀ values in this assay.³² The 2-(carboxymethyl)aziridine unit is also present in peptide-

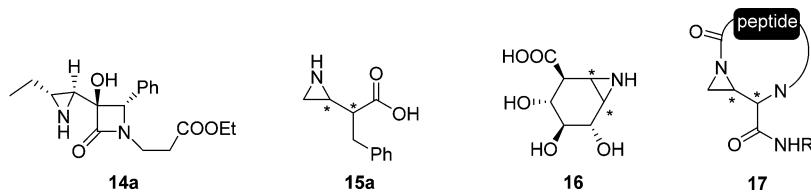


Figure 4. 2-Aziridinyl-2-hydroxy- β -lactam **14a**, 2-(2-aziridinyl)-3-phenylpropanoic acid **15a**, 3,4,5-trihydroxy-7-azabicyclo[4.1.0]heptane-2-carboxylic acid **16**, and peptide-based macrocycles **17**.

based macrocycles **17**, which are of considerable biological interest as their topology allows them to resist digestion by exopeptidases while retaining high affinities for their biochemical targets.^{33–43}

Moreover, the 2-(carboxymethyl)aziridine radical **18** is proposed as one of three stabilized radical intermediates

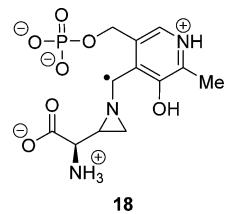
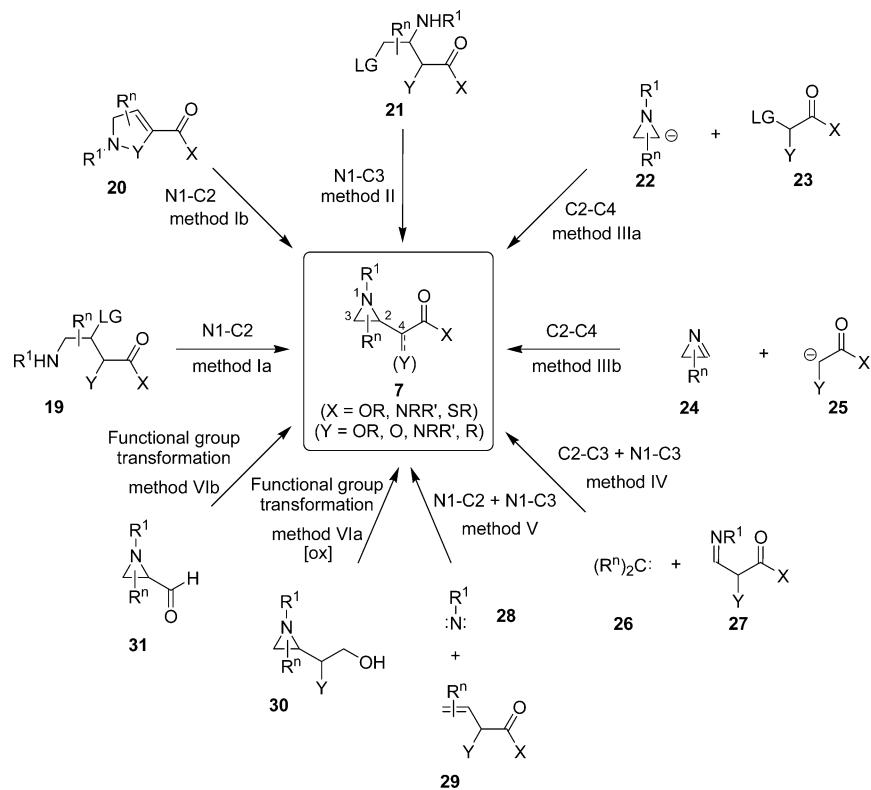


Figure 5. Stabilized 2-(carboxymethyl)aziridine radical **18**.

which inhibits the enzyme activity of ornithine 4,5-amino-mutase (OAM) (Figure 5). Biosynthesis of this radical **18** occurs via reaction of 2,4-diaminobutyric acid (DAB) with holo-OAM.⁴⁴

Scheme 3

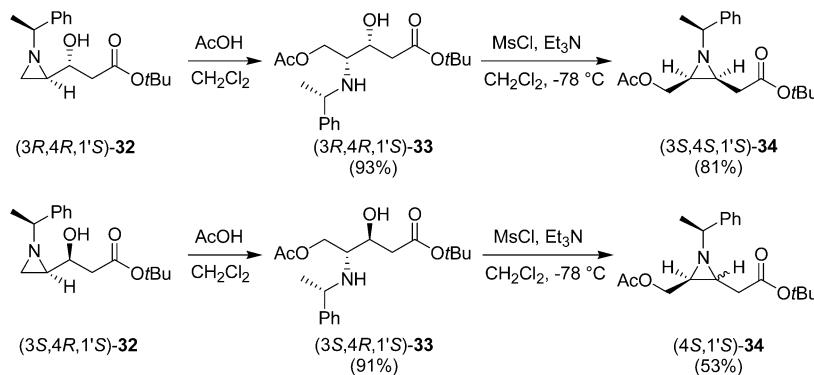


2. SYNTHESIS OF 2-(CARBOXYMETHYL)AZIRIDINE DERIVATIVES

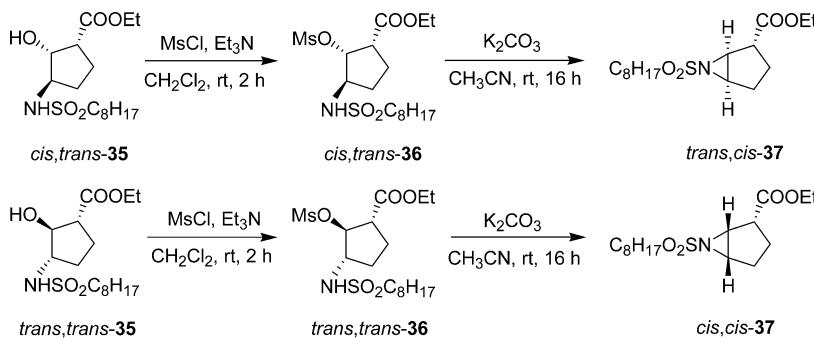
In the following section, synthesis of 2-(carboxymethyl)-aziridine derivatives will be dealt with. Several synthetic approaches toward 2-(carboxymethyl)aziridines based on the different bond connections or transformations are schematically illustrated in Scheme 3. A distinction has been made between three types of intramolecular reactions (methods Ia, Ib, and II), four types of intermolecular reactions (methods IIIa, IIIb, IV, and V), and a functional group transformation (method VI). In addition, a group of miscellaneous reactions toward the synthesis of 2-(carboxymethyl)aziridines will be described.

Furthermore, intramolecular reactions and addition reactions are subdivided with respect to the mechanism of these reactions. The intramolecular nucleophilic substitution reactions (methods Ia and II) involve attack of a nucleophilic amino group of compounds **19** and **21** on an adjacent carbon atom bearing a leaving group (LG) to afford 2-(carboxymethyl)-aziridines. To allow aziridine synthesis in an asymmetric way, use of starting materials derived from the chiral pool was also described (method II). Besides, an intramolecular (thermal) rearrangement of 4-isoxazoline-5-carboxylates **20** ($Y = O$) has

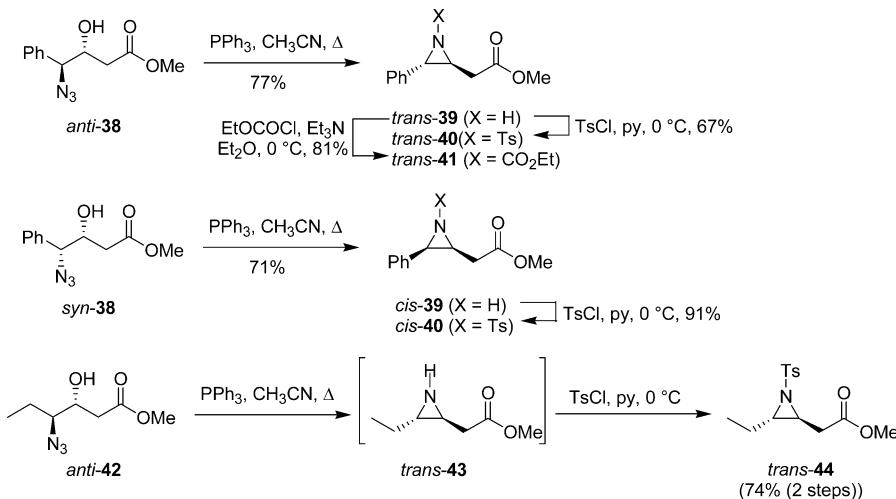
Scheme 4



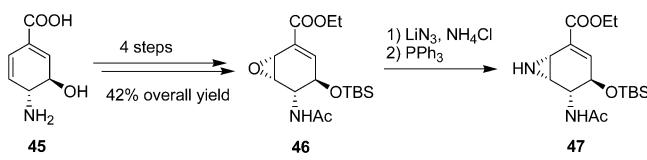
Scheme 5



Scheme 6



Scheme 7



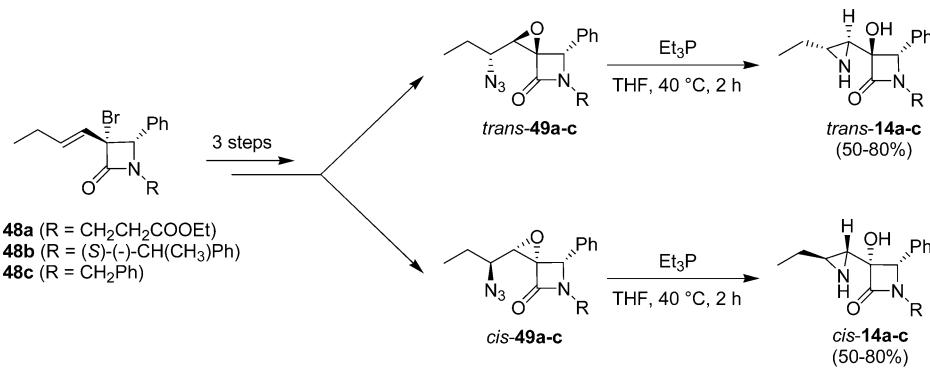
been used as an approach toward synthesis of this type of aziridine (method Ib).

2-(Carboxymethyl)aziridines are also accessible via addition reactions with carbanions (methods IIIa and IIIb). Substitution reactions of stabilized aziridinyl anions **22** with acetates **23**, bearing a leaving group in the α -position, present an efficient

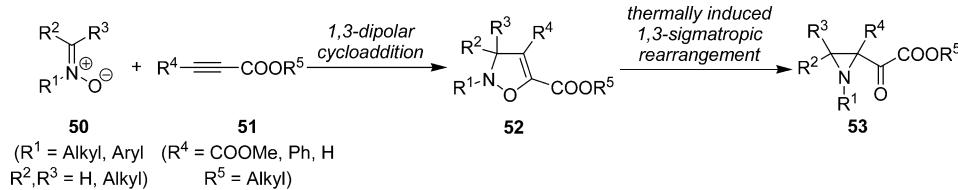
synthetic pathway toward the corresponding 2-(carboxymethyl)aziridines (method IIIa). Furthermore, addition reactions of α -deprotonated acetate derivatives **25** across 2*H*-azirines **24** have been performed as well via Reformatsky, Ivanov, and cycloaddition reactions (method IIIb). Moreover, addition reactions via addition of electron-deficient carbenes or nitrenes to double bonds are discussed (methods IV and V). This part also includes additions of sulfur ylides to imines (method IV) and addition of substituted azides across olefins (method V).

Furthermore, synthesis of 2-(carboxymethyl)aziridines is effectuated via functional group transformations of compounds derived from the chiral pool (method VIa) or starting from 2-formylaziridines **31** (method VIb).

Scheme 8



Scheme 9



2.1. Synthesis Through N1–C2 Bond Formation

2.1.1. Synthesis via Intramolecular Nucleophilic Substitution (Method 1a). γ -Amino carboxylic acid derivatives, which bear a leaving group in the β -position, are suitable building blocks for synthesis of 2-(carboxymethyl)-aziridines.^{30,45–48} For example, γ,δ -aziridino- β -hydroxy esters (*3R,4R,1'S*)-32 and (*3S,4R,1'S*)-32 were transformed into 2-(carboxymethyl)aziridines 34 (Scheme 4).⁴⁵ The enantiopure amino alcohols (*3R,4R,1'S*)-33 and (*3S,4R,1'S*)-33 were obtained in excellent yield by a regioselective ring opening of the chiral aziridines (*3R,4R,1'S*)-32 and (*3S,4R,1'S*)-32 at the less substituted carbon atom with AcOH in CH_2Cl_2 . Intramolecular ring closure of amino alcohols (*3R,4R,1'S*)-33 and (*3S,4R,1'S*)-33 with MsCl and Et_3N provided the corresponding chiral nonactivated 2-(carboxymethyl)aziridines 34. It is well known that *cis*-2,3-disubstituted aziridines with a sizable group on nitrogen are thermodynamically more stable than the corresponding *trans*-2,3-disubstituted aziridines.^{49–53} The *syn*- γ,δ -aziridino- β -hydroxy ester (*3R,4R,1'S*)-32 was readily transformed into the corresponding chiral *cis*-aziridine (*3S,4S,1'S*)-34, but the anti derivative (*3S,4R,1'S*)-32 provided the diastereomeric mixture of chiral *trans*- and *cis*-aziridines 34. Mesylation of the amino alcohols (*3S,4R,1'S*)-33 seemed to be followed by elimination of methanesulfonic acid in the presence of Et_3N to provide the corresponding α,β -unsaturated ester to which the amino group adds conjugatively to result in a mixture of *trans*- and *cis*-aziridines 34 in an unspecified ratio.

In a further study, diastereomerically pure vicinal amino alcohols 35 were treated with MsCl and Et_3N in CH_2Cl_2 (Scheme 5).⁴⁶ The resulting O-mesylated amino alcohols 36 subsequently underwent a ring-closure reaction to the corresponding activated 2-(carboxymethyl)aziridines 37 by treatment with K_2CO_3 , but the yields were unreported.

Azido alcohols 38 and 42 were also used as precursors for stereoselective synthesis of 2-(carboxymethyl)aziridines 39 and 43 via a Staudinger reduction (Scheme 6).⁴⁷ The vicinal azido alcohols (\pm)-*anti*-38, (\pm)-*syn*-38, and (\pm)-*anti*-42 were treated with PPh_3 in anhydrous CH_3CN to afford their corresponding

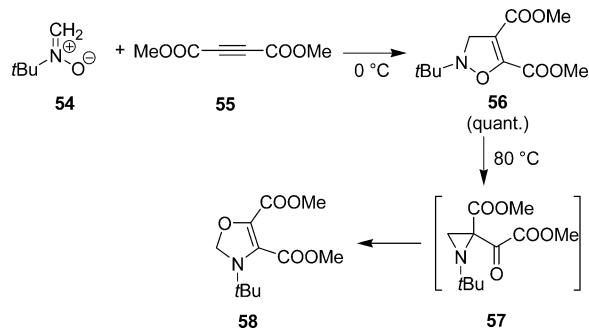
N-H-aziridines (\pm)-*trans*-39, (\pm)-*cis*-39, and (\pm)-*trans*-43, respectively, as the sole products. Purification of *N*-H-aziridine (\pm)-*trans*-43 was problematic due to the low molecular weight of this compound. In order to isolate this aziridine, an in-situ *N*-tosylation was performed, which resulted in formation of *N*-tosyl-2-(carboxymethyl)aziridine (\pm)-*trans*-44 in a good overall yield. Tosylation of the diastereomerically pure aziridines (\pm)-*trans*-39 and (\pm)-*cis*-39 afforded *N*-tosyl-2-(carboxymethyl)aziridines (\pm)-*trans*-40 and (\pm)-*cis*-40 in moderate to good yields. Additionally, aziridine (\pm)-*trans*-39 was reacted with ethyl chloroformate in basic medium to provide carbamate (\pm)-*trans*-41 ($X = \text{COOEt}$).

By analogy, transformation of *trans*-amino alcohol 45, a compound from the shikimate pathway with chorismate as the branching point, has been studied in order to synthesize bicyclic 2-(carboxymethyl)aziridine 47.⁴⁸ Initially, amino alcohol 45 was transformed into the corresponding epoxide 46 in four steps in an overall yield of 42% (Scheme 7).⁴⁸ Ring opening of this epoxide 46 with lithium azide and subsequent treatment with PPh_3 furnished the corresponding bicyclic 2-(carboxymethyl)aziridine 47, but the yields were not presented.

In accordance with these results, Staudinger reduction has also been employed in the synthesis of 3-hydroxy- β -lactams 14, containing an aziridine moiety, starting from vinyl- β -lactams 48.³⁰ The diastereomeric spiro- β -lactams *trans*-49 and *cis*-49 were efficiently synthesized via a three-step synthesis starting from the same vinyl- β -lactam precursor 48 (Scheme 8). In the next step, both diastereomeric azides *trans*-49 and *cis*-49 were reduced with triethylphosphine in dry THF to afford the corresponding β -lactams *trans*-14 and *cis*-14 in good yield via an aza-Payne-like ring opening⁵⁴ of the epoxides 49.

2.1.2. Synthesis via Rearrangement of 4-Isoxazoline-5-carboxylate Derivatives (Method 1b). **2.1.2.1. Synthesis of *N*-Alkyl- and *N*-Aryl-aziridines.** Reaction of nitrones 50 with alkyl acetylenecarboxylates 51 via 1,3-dipolar cycloaddition resulted in selective and efficient synthesis of 4-isoxazoline-5-carboxylates 52, which proved to be excellent precursors for synthesis of the corresponding *N*-alkyl- and *N*-aryl-2-oxazolylazir-

Scheme 10

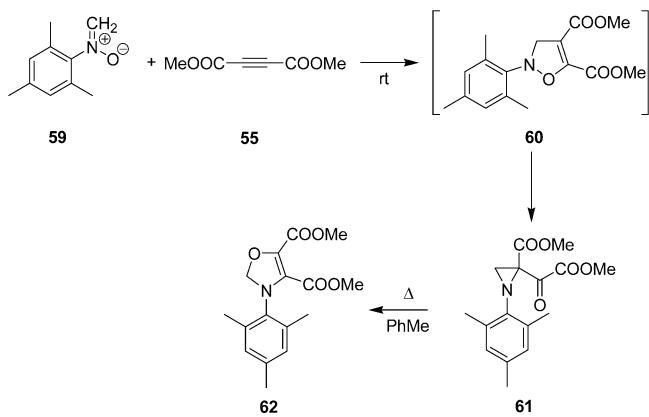


isoxazoles 53 via a thermally induced 1,3-sigmatropic rearrangement (Scheme 9).^{55–64}

A 1,3-dipolar cycloaddition of *tert*-butylmethylenenitron 54 with dimethyl acetylenedicarboxylate 55 proceeded rapidly at 0 °C and resulted in quantitative formation of isoxazoline 56 (Scheme 10).^{55,56} It was shown that the latter compound 56 easily underwent thermal rearrangement upon heating at 80 °C in the dark under an atmosphere of N₂. Isomerization to oxazoline 58 occurred most probably via formation of the aziridine intermediate 57.

Furthermore, it was shown that a suitable choice of substituents could result in formation of the corresponding 4-

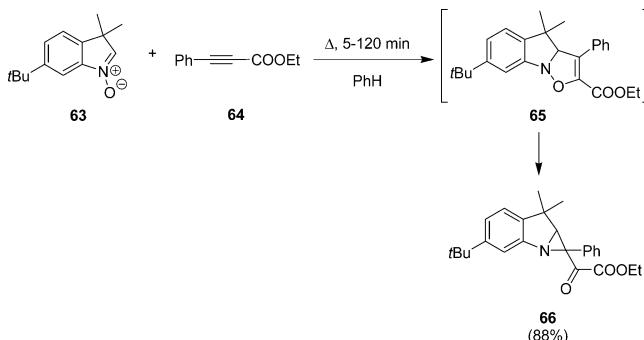
Scheme 11



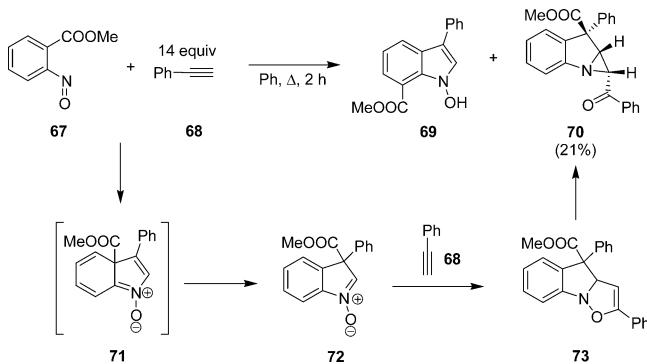
isoxazoline-4,5-dicarboxylate with a weakened N–O bond.⁵⁵ In this way, isolation of aziridine 53 as a potential precursor for this thermal rearrangement would become possible. Thus, reaction of *N*-(2,4,6-trimethylphenyl)methylenenitron 59 with dimethyl acetylenedicarboxylate 55 resulted in synthesis of the more thermally labile 4-isoxazoline 60, which immediately rearranged to the corresponding aziridine 61 at room temperature (Scheme 11).⁵⁶ Treatment of this aziridine 61 in toluene under reflux gave again the thermally more stable 4-oxazoline 62, but no further details about the reaction conditions or yields were mentioned.

In accordance with the previous results, which led to isolation of aziridine 61, synthesis of tricyclic aziridine 66 starting from 3*H*-indole-*N*-oxide 63 has also been described.⁵⁷ Cycloaddition of 3*H*-indole-*N*-oxide 63 to ethyl phenylacetylenecarboxylate 64 afforded the tricyclic aziridine 66 in a highly regio- and stereoselective manner without isolation of the intermediate 4-isoxazoline-5-carboxylate 65 (Scheme 12).⁵⁷ The tricyclic aziridine 66 was obtained in high yield (88%).

Scheme 12



Scheme 13

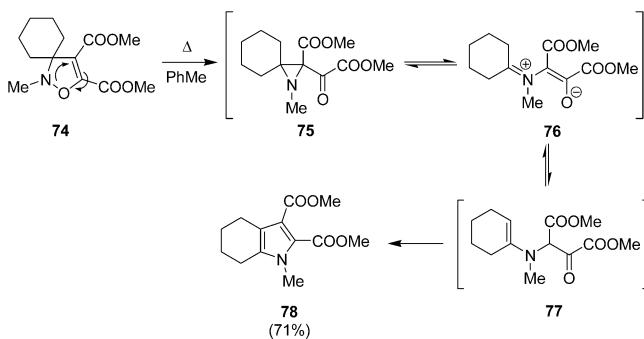


However, spectroscopic data were inadequate to determine if the 2-phenyl group was in the endo or exo position.

Similarly, reaction of methyl 2-nitrosobenzoate 67 with phenylacetylene 68 also afforded, as well as the expected indole 69, the tricyclic aziridine 70 in 21% yield (Scheme 13).⁵⁸ Formation of aziridine 70 was explained by a dipolar cycloaddition of indoline nitron 72, obtained by methoxy-carbonyl-unit migration of intermediate 71 to restore aromaticity, with phenylacetylene 68 followed by electrocyclic rearrangement of the intermediate isoxazoline 73. Recently, this methodology has been further elaborated for synthesis of various tricyclic aziridines 70 using different nitrosobenzene and acetylene derivatives.⁵⁹

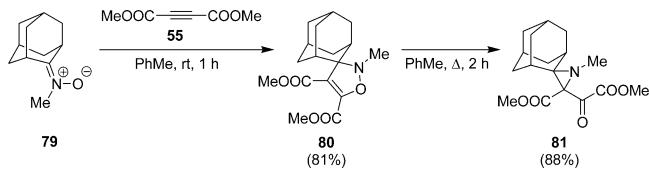
Thermal rearrangement of 4-isoxazoline-5-carboxylates 56 and 60 to the corresponding 4-oxazolines 58 and 62 proceeded via 2-acylaziridine intermediates 57 and 61 in the absence of substituents at the C-3 position of the 4-isoxazoline-5-carboxylates 56 and 60 (Schemes 10 and 11). Each step of this conversion was thermally induced, and the rates and

Scheme 14



products of the rearrangement were not influenced by the presence of either oxygen, radical inhibitors, or small amounts of acids or bases.⁵⁵ However, for the spirocyclic 4-isoxazoline-5-carboxylate **74**, dialkylated at the C-3 position, rearrangement via 2-acylaziridine intermediate **75** provided pyrrole **78** through an iminium to enamine isomerization via an assisted enolate interaction (Scheme 14).^{60–62}

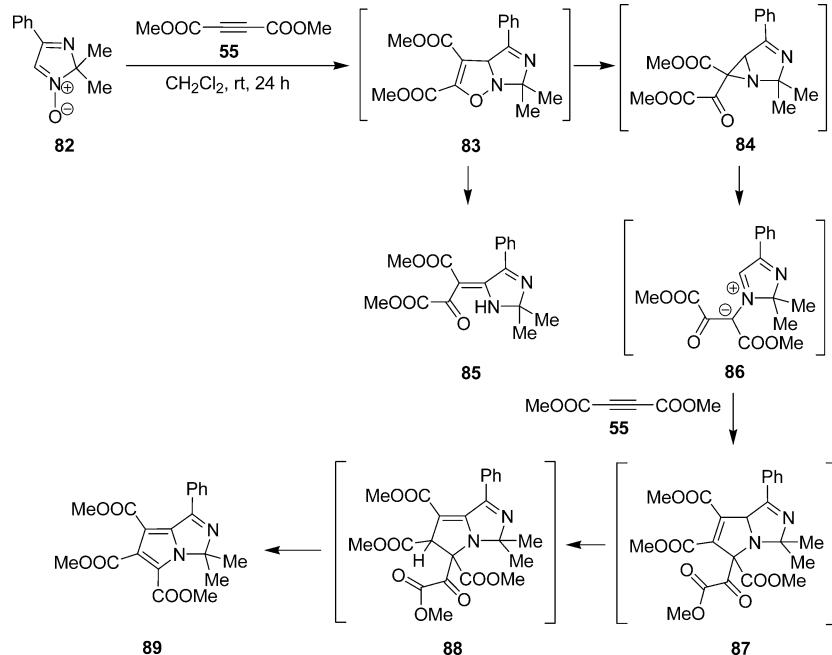
Scheme 15



As the isolation of the intermediate polysubstituted aziridine **75** was not possible due to fast conversion into the corresponding pyrrole **78** upon heating, it was postulated that introducing a bridgehead ring system instead of the cyclohexyl moiety would prevent an iminium to enamine isomerization, thus making the aziridine intermediate stable and possible to isolate.⁶¹ Synthesis of the spiro[adamantane-4-isoxazoline] **80** was performed in high yield (81%) via cycloaddition of nitrone **79** to dimethyl acetylenedicarboxylate **55** in toluene at room temperature (Scheme 15).⁶² In the next step, spiro[adamantane-4-isoxazoline] **80** was heated in toluene at reflux temperature, which resulted in isolation of spiro[adamantane-aziridine] **81** in 88% yield. Formation of spirocyclic aziridine **81** provided the first conclusive evidence that analogously to the isoxazoline–oxazoline rearrangement the isoxazoline–pyrrole thermal rearrangement also proceeded through an initial ring contraction leading to an aziridine ring.

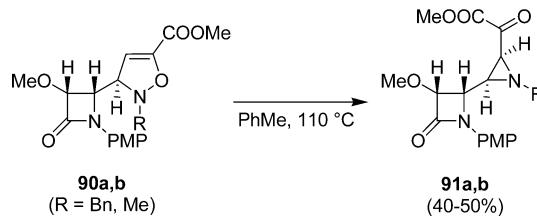
Cycloaddition of aldonitron **82** to dimethyl acetylenedicarboxylate **55** also gave, apart from the expected enamino ketone **85**, the pyrrolo[1,2-*c*]imidazole **89** (Scheme 16).⁶³

Scheme 16



Since treatment of the isolated enamino ketone **85** with dimethyl acetylenedicarboxylate **55** did not result in formation of **89**, while reaction of aldonitron **82** with acetylenedicarboxylate **55** gave both products **85** and **89** in approximately equal amounts, the following mechanism was suggested (Scheme 16). Pyrrole derivative **89** was formed by contraction of the 4-isoxazoline ring **83** to result in formation of a bicyclic aziridine **84**.⁶⁴ The reaction proceeded via ring opening of the reactive aziridine **84** to give 1,3-dipole **86**, which underwent cycloaddition with a second equivalent of dimethyl acetylenedicarboxylate **55** to form cycloadduct **87**. Finally, pyrrolo[1,2-*c*]imidazole **89** was formed by a 1,3-sigmatropic shift and

Scheme 17

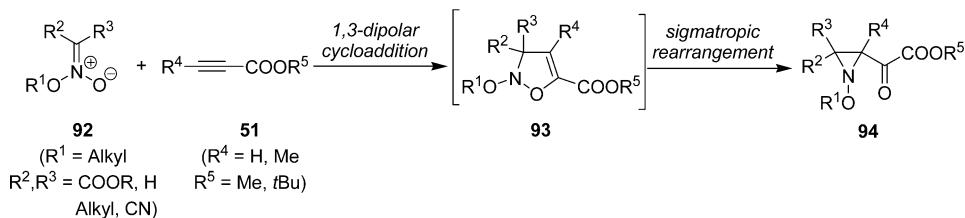


subsequent aromatization of compound **88**. Unfortunately, no further details about the isolated yields were reported.

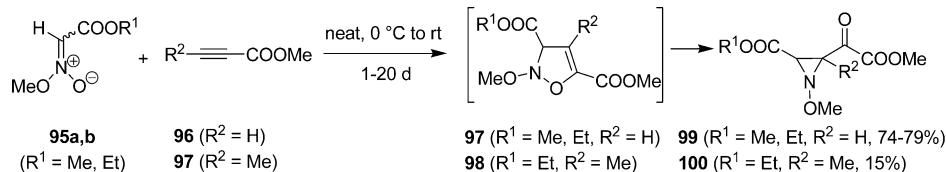
In another report, the reactivity of polyfunctionalized 4-isoxazoline-5-carboxylates **90a,b** has been evaluated by thermal treatment.⁶⁵ Interestingly, by heating these compounds **90a,b** in toluene the aziridinyl-β-lactams **91** were obtained as single isomers (Scheme 17). This result was again rationalized by a thermally induced sigmatropic rearrangement, where the stereochemical outcome of the reaction was controlled by steric interactions.

2.1.2.2. Synthesis of *N*-Alkoxyaziridines. In contrast to the 1,3-dipolar cycloaddition of nitrones **50** (Scheme 9), reaction of nitronium esters **92** with alkyl acetylenecarboxylates **51** resulted in regioselective formation of *N*-alkoxyaziridines **94**

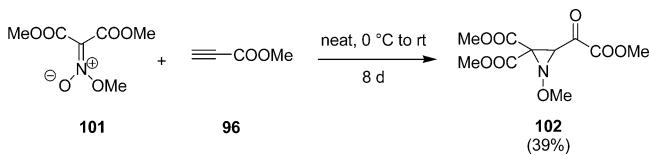
Scheme 18



Scheme 19



Scheme 20



(Scheme 18). This reaction proceeded via a 1,3-dipolar cycloaddition through the intermediacy of 4-isoxazoline-5-carboxylates **93**. These 4-isoxazolines **93** isomerized easily and selectively to deliver the corresponding aziridines **94** via a sigmatropic rearrangement.^{66–71}

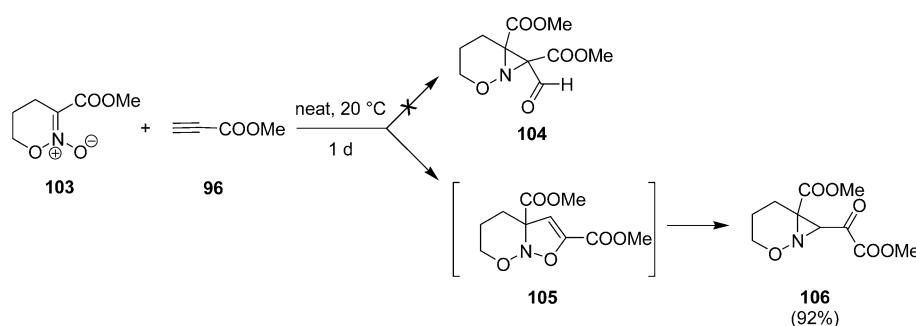
Synthesis of the disubstituted *N*-methoxy-aziridines **99** was accomplished in good yield (74–79%) by reaction of nitronium esters **95a,b** with methyl acetylenecarboxylate **96** for 1–5 days (Scheme 19).^{66,67} Cycloaddition reaction of nitronium ester **95b** across tetrolic acid methyl ester **97** proceeded more slowly and afforded the trisubstituted *N*-methoxy-aziridine **100** in only 15% yield after 20 days.^{66,67}

In a similar manner to the cycloaddition of monosubstituted nitronium esters **95** across methyl acetylenecarboxylate **96**, disubstituted nitronium ester **101** was also used for synthesis *N*-methoxy-aziridine **102** (Scheme 20).⁶⁷

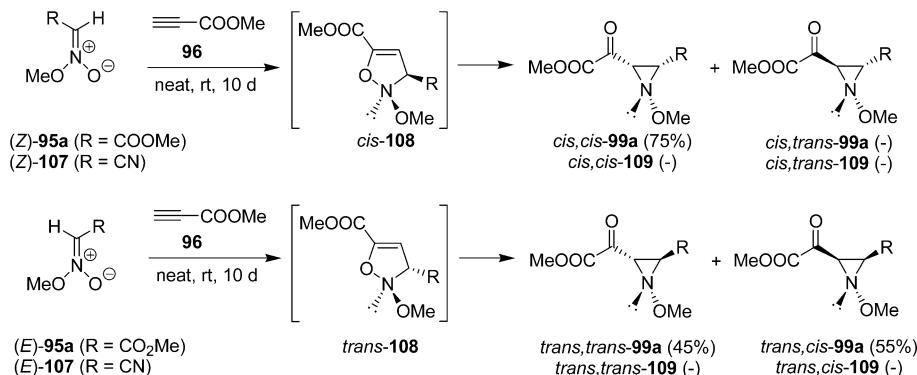
Furthermore, 1,3-dipolar cycloaddition of cyclic nitronium ester **103** across methyl acetylenecarboxylate **96** afforded aziridine **106** as one single isomer in 92% yield without any trace of the corresponding 2-formylaziridine **104** (Scheme 21).⁶⁸ Accordingly, intermediate **105** has the methoxycarbonyl attached at the α -carbon of the enol ether moiety.

In a later report, Grée et al.⁶⁹ studied the stereoselectivity of the 1,3-dipolar cycloaddition of nitronium esters **95a** and **107** across methyl acetylenecarboxylate **96**. The major complication was that the intermediate 4-isoxazoline-5-carboxylates **108** generally exhibited only one conformationally stable asymmetric center due to the fast nitrogen inversion under the conditions of the rearrangement. However, a previous study has shown that the 1,3-dipolar cycloaddition of (*Z*)- and (*E*)-nitronium esters across alkenes took place under kinetic control to afford *N*-alkoxy-isoxazolidines as stable invertomers.^{72,73} The configuration of the (*Z*)- and (*E*)-nitronium esters **95a** and **107** was established previously, and it was shown that these compounds did not isomerize under the conditions of the cycloaddition with alkenes.^{72,74} It was observed that the cycloaddition reaction is completely stereospecific, where each isomeric nitronium ester **95a** and **107** led to different invertomers of the aziridine (Scheme 22).⁶⁹ Cycloaddition of (*Z*)-nitronium ester (*Z*)-**95a** across methyl acetylenecarboxylate **96** delivered quantitatively the two diastereomeric *cis*-2-acylaziridines *cis,cis*-**99a** and *cis,trans*-**99a** (*R* and *OCH*₃ in *cis* relationship), while (*E*)-nitronium ester (*E*)-**95a** gave only the two diastereomeric *trans*-2-acylaziridines *trans,trans*-**99a** and *trans,cis*-**99a** (*R* and *OCH*₃ in *trans* relationship). When the cycloaddition was performed with the isomeric nitronium cyanide **107**, the reaction was very slow and not quantitative. In this case, the presence of decomposition products of the nitronium cyanide **107** (*R* = CN) was observed. By all means tried it was never possible to isolate or even obtain spectroscopic evidence for the 4-isoxazolines **108**, but their presumed existence as intermediates allowed a logical

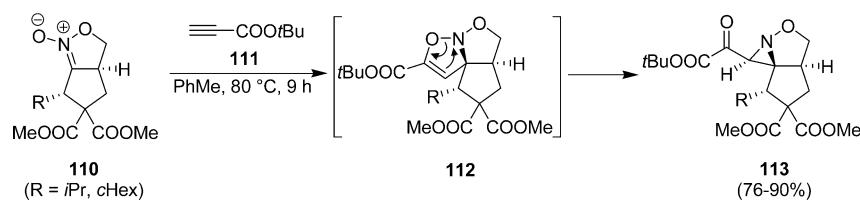
Scheme 21



Scheme 22



Scheme 23



interpretation of the reaction course via a 1,3-sigmatropic rearrangement.

Finally, a 1,3-dipolar cycloaddition of bicyclic nitronium esters **110** across *tert*-butyl acetylenecarboxylate **111** has been performed to afford the corresponding polycyclic aziridines **113** in good yields (Scheme 23).⁷⁰ Thus, the cycloaddition reaction proceeded with excellent regio- and stereoselectivity as only one single isomer of compounds **113** was formed, which was confirmed by X-ray crystallographic analysis. Formation of aziridino-isoxazoles **113** was again attributed to a 1,3-sigmatropic rearrangement of the cycloadduct intermediates **112**, which were previously reported by Seebach.⁷¹

In conclusion, formation of 2-(carboxymethyl)aziridines via a N1–C2 bond formation was subdivided based on two different reaction mechanisms. In a first approach, 2-(carboxymethyl)aziridines were synthesized via intramolecular nucleophilic substitution reactions, which involved an attack of a nucleophilic amino group on an adjacent carbon atom bearing a leaving group (method Ia). These transformations occurred in a stereoselective way, and the formed 2-(carboxymethyl)aziridines were isolated in moderate to high yields. Besides, 2-(carboxymethyl)aziridines were also synthesized via an intramolecular (thermal) rearrangement of 4-isoxazoline-5-carboxylates (method Ib). This approach resulted in formation of different N-substituted 2-(carboxymethyl)aziridines bearing an oxo group in the α -position. However, it was not always possible to isolate these products, since these aziridines could rearrange into more stable compounds under these (harsh) reaction conditions.

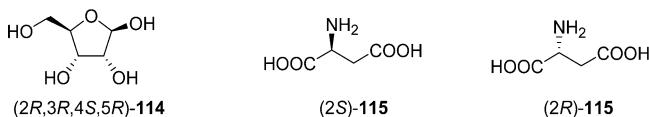


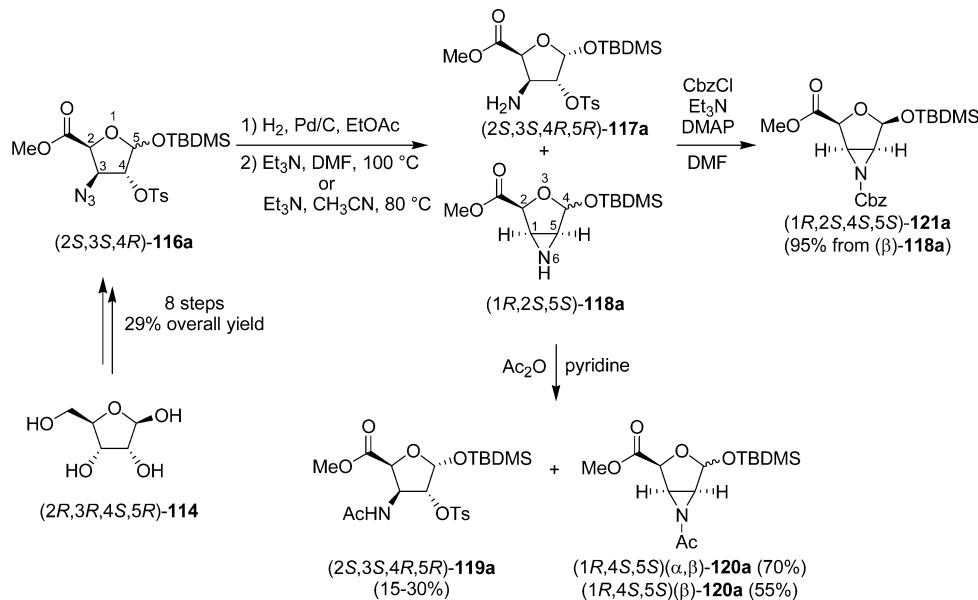
Figure 6. D-ribose D-114 and L- and D-aspartic acid L-115 and D-115.

2.2. Synthesis through N1–C3 Bond Formation (Method II)

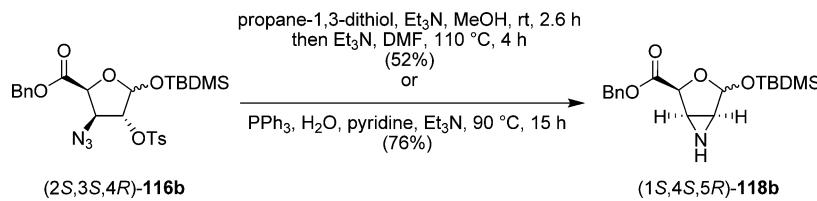
2.2.1. Enantioselective Synthesis Starting from the Chiral Pool. In recent decades, the strategy of using the chiral pool for enantioselective synthesis has received a lot of attention among (bio)organic and medicinal chemists. Chiral pool synthesis is especially helpful if the desired compounds have a great resemblance to cheap and readily available enantiopure natural products. To date, enantiopure synthesis of 2-(carboxymethyl)aziridines starting from the chiral pool has used only three natural products, i.e., D-ribose (D-114) and L- and D-aspartic acid (L-115 and D-115, Figure 6).

2.2.1.1. Synthesis through Modifications of D-Ribose. D-Ribose **114** was transformed into the functionalized azido analog of D-ribose **116a** by means of eight steps in an efficient way in 29% overall yield (Scheme 24).^{75–78} The anomeric mixture of the enantiopure azido-D-ribose derivatives **116a** then underwent a catalytic hydrogenolysis in the presence of palladium on carbon followed by a base-promoted cyclization by treatment with Et₃N in DMF at 100 °C. After completion of this reaction, compound **118a** was characterized as its *N*-acetyl derivative **120a** (70% yield) after treatment of the crude reaction product with acetic anhydride in pyridine. Besides aziridine **120a**, a second minor compound was also isolated after the acylation step in 15% yield, which was shown to be the noncyclized acetamide **119a**. Interestingly, even though the starting material **116a** and the major product **118a** were both α/β anomeric mixtures, ¹H NMR analysis of acetamide **119a** showed that this compound was exclusively the α -anomer. This suggested that the α -anomer of intermediate **117a** cyclized less readily than its β -anomer. This was demonstrated by performing the cyclization in acetonitrile under reflux whereby only the β -anomer of the intermediate amine was cyclized to deliver the pure β -anomer of aziridine **120a** in 55% yield after acylation. In this reaction, the α -anomer led exclusively to the acetamide **119a** in 30% yield.⁷⁵ Since N-Cbz and N-Ac aziridine derivatives were shown to have different reactivity patterns toward nucleophiles,⁷⁹ the N-Cbz analog of 2-(carboxymethyl)aziridine **118a** has also been prepared. Thus, treatment of the

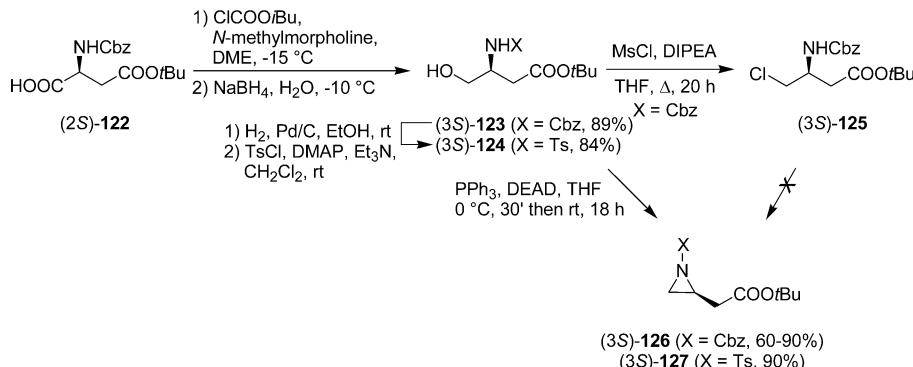
Scheme 24



Scheme 25



Scheme 26



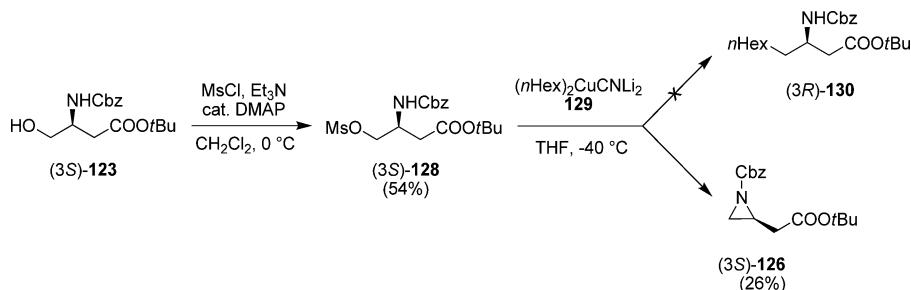
mixture containing azidine (β)-118a and compound 117a with benzyl chloroformate, DMAP, and triethylamine in DMF resulted in formation *N*-Cbz derivative 121a in excellent yield.⁷⁵

Although catalytic hydrogenolysis with palladium on carbon of enantiopure azido-D-ribose derivatives 116a was very useful and efficient, this procedure was not applicable for the corresponding enantiopure benzyl esters 116b as hydrogenolysis of the benzyl ester took place, even if Lindlar's catalyst was used.⁷⁷ An alternative approach to aziridines 118b comprised the use of 1,3-propanedithiol, as this reagent was reported to promote reduction of azides to amines in the presence of reduction-sensitive functionalities.⁸⁰ Thus, treatment of benzyl esters 116b with an excess of 1,3-propanedithiol and triethylamine and subsequent cyclization of the crude

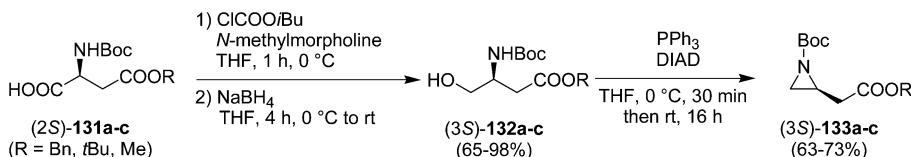
amine with triethylamine in boiling DMF provided the desired 2-(carboxymethyl)aziridines 118b in an overall yield of 52% (Scheme 25).⁷⁷

In an effort to further improve the yield and ease of purification of 2-(carboxymethyl)aziridines 118b, a modified Staudinger reduction was employed (Scheme 25).⁷⁷ A previous study showed that azides could easily be converted into amines by treatment with triphenylphosphine in THF in the presence of a slight excess of water, which served to hydrolyze the intermediate phosphinimine.⁸¹ Unfortunately, application of this procedure delivered only 10% of the desired aziridines 118b. However, performing the modified Staudinger reaction in pyridine in the presence of a slight excess of triphenylphosphine, water, and triethylamine delivered the aziridines 118b in 76% yield.⁷⁷

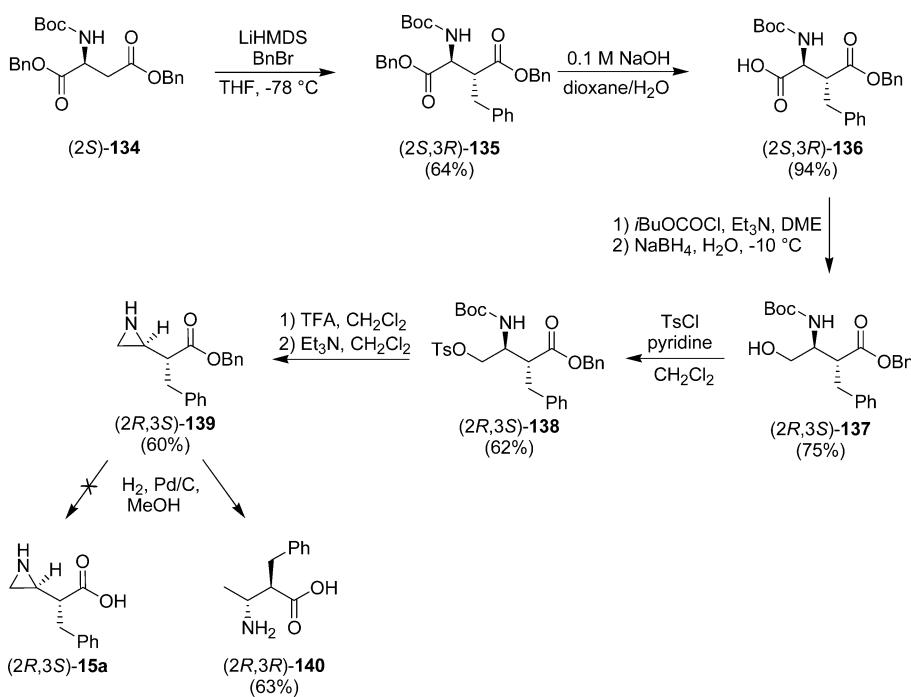
Scheme 27



Scheme 28



Scheme 29

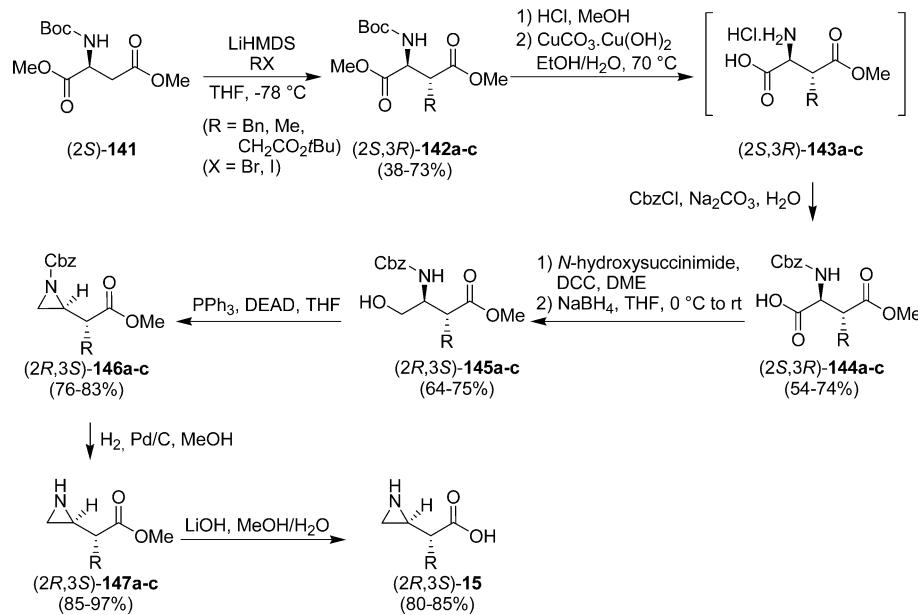


2.2.1.2. Synthesis through Modifications of L-Aspartic Acid. N-Protected L-aspartic acid derivatives have been used for enantioselective synthesis of *N*-Cbz-, *N*-Ts-, and *N*-Boc-protected 2-(carboxymethyl)aziridines.^{82–86} The first step in the synthesis of *N*-Cbz-protected L-aspartic acid derivative 122 was activation of *N*-Cbz-protected L-aspartic acid derivative 122 with isobutyl chloroformate in DME in the presence of *N*-methylmorpholine (Scheme 26).^{82,83,85,87} The activated aspartic acid derivative was subsequently reduced with aqueous sodium borohydride to give the corresponding alcohol 123 in very good yield. In the next step, amino alcohol 123 was treated either under Mitsunobu conditions (*PPh*₃, DEAD, THF) or with methanesulfonyl chloride in the presence of DIPEA (Scheme 26).^{82,83,85} However, only the Mitsunobu reaction yielded *N*-Cbz 2-(carboxymethyl)aziridine 126. Mesylation of amino alcohol 123 followed by heating under reflux in THF

with DIPEA gave the chloride 125 as the sole product.⁸³ This chloride resisted further treatment with various bases (*K*₂*CO*₃, KHCO₃, NaHSO₃, AgO, KF, or NaH), which gave either no reaction or decomposition. Although chloride 125 was unsuitable as a precursor for 2-(carboxymethyl)aziridine 126, similar β -aminobutanoates have already been used as precursors in the synthesis of another class of β -amino acids with a three-membered ring as a core structure, more specifically 2-amino cyclopropanecarboxylic acids,^{88a} which are also accessible from the corresponding related 2-(cyanomethyl)aziridines.^{88b,c}

Remarkably, the procedure for synthesis of *N*-Cbz-protected 2-(carboxymethyl)aziridine 126 starting from *N*-Cbz-protected L-aspartic acid derivative 122 did not work for synthesis of analogous *N*-Ts-protected 2-(carboxymethyl)aziridine 127 as the reduction step did not work at all, even when other reduction methods were applied.⁸⁵ For that reason, an

Scheme 30



alternative attempt to access amino alcohol **124** was made by a deprotection and re-protection sequence starting from amino alcohol **123** (Scheme 26).⁸⁵ Catalytic hydrogenolysis over Pd/C and subsequent *N*-tosylation gave amino alcohol **124** in 84% overall yield. Treatment of this amino alcohol **124**, under the previously mentioned Mitsunobu conditions, delivered the *N*-Ts-protected 2-(carboxymethyl)aziridine **127** in 90% yield.

In contrast with the mesylation procedure of amino alcohol **123** by heating under reflux in THF with DIPEA, which afforded the chloride **125** as the sole product,⁸³ the mesyloxy compound **128** was obtained when amino alcohol **123** was treated with mesyl chloride in the presence of triethylamine and a catalytic amount of DMAP in CH₂Cl₂ at 0 °C (Scheme 27).⁸⁴ In the next step, treatment of mesylate **128** with cyanocuprate **129** in THF gave *N*-Cbz protected 2-(carboxymethyl)aziridine **126** in 26% yield, instead of the expected β -amino ester **130**.

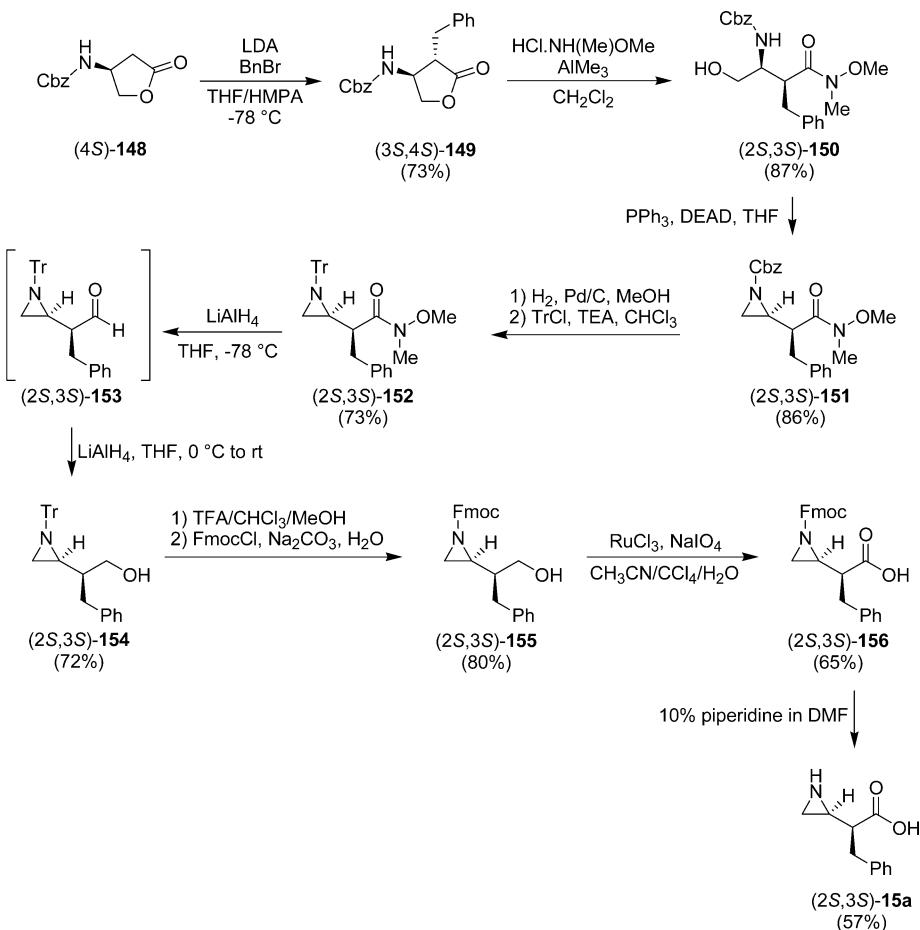
N-Boc 2-(carboxymethyl)aziridines **133a–c** were synthesized via a similar reaction sequence as *N*-Cbz 2-(carboxymethyl)aziridine **126**. The *N*-Boc-protected L-aspartic acid derivatives **131a–c** were also activated with isobutyl chloroformate in the presence of *N*-methylmorpholine, and subsequent reduction with sodium borohydride afforded *N*-Boc amino alcohols **132a–c** in good to high yields (Scheme 28).⁸⁶ Subsequently, a Mitsunobu reaction with DIAD took place which gave the corresponding *N*-Boc 2-(carboxymethyl)aziridines **133a–c** in good yields (63–73%). It is noteworthy that treatment of compound **132a** with a saturated hydrochloric acid solution in diethyl ether resulted in formation of the (*S*)-3-amino- γ -butyrolactone **11**, which is a constitutional isomer of the 2-(aziridinyl)acetic acid **1** (vide supra).⁸⁹

In addition, besides the synthesis of enantiopure unsubstituted 2-(carboxymethyl)aziridines **126**, **127**, and **133**, synthesis of branched 2-(carboxymethyl)aziridines **15** was also performed starting from *N*-protected L-aspartic acid derivatives **134** and **141**.^{31,90} A first attempt at the synthesis of the unprotected (2*R*,3*S*)-2-benzyl-substituted 2-(carboxymethyl)aziridines (2*R*,3*S*)-**15** was made starting from *N*-protected dibenzyl L-aspartate **134** (Scheme 29).⁹⁰ The first step involved introduction of a benzyl group at the β -position

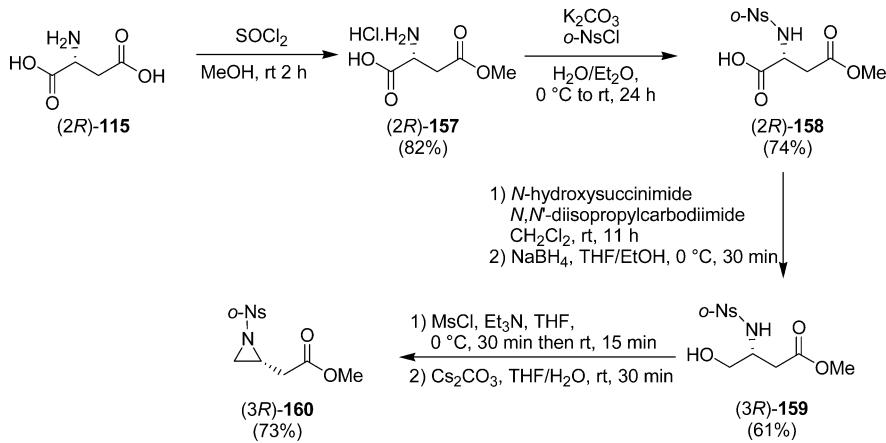
of fully protected aspartate **134**,^{91,92} followed by selective hydrolysis of the α -amino ester moiety in **135** to afford **136**,⁹³ and reduction of the carboxylate moiety via the already known mixed anhydride approach (*i*BuOCOCl and Et₃N, then NaBH₄).⁸⁷ The hydroxyl group formed in this way was tosylated and subjected to cyclization conditions after deprotection of the *N*-Boc-amino group to give **139**. Attempted debenzylation of compound **139** via a catalytic hydrogenolysis with Pd/C failed and resulted in cleavage of the aziridine ring with formation of (2*R*,3*S*)-3-amino-2-benzylbutanoic acid (2*R*,3*S*)-**140**. This result was explained by the initial debenzylation of compound **139**, providing the corresponding acid which then facilitated subsequent aziridine ring opening.⁹⁰

In order to obtain the unprotected branched (2*R*,3*S*)-2-(carboxymethyl)aziridines (2*R*,3*S*)-**15**, another synthetic route was developed starting from *N*-protected dimethyl L-aspartate **141** (Scheme 30).⁹⁰ As debenzylation of 2-(carboxymethyl)aziridine **139** via catalytic hydrogenolysis with Pd/C was not possible without ring opening of the aziridine ring, a final saponification of the methyl ester function has been performed to overcome this problem. Treatment of *N*-protected dimethyl L-aspartate **141**⁹⁰ with 2 equiv of LiHMDS delivered the enolate dianion which reacted with an alkyl halide to give **142a–c**. In the case of methylation, two diastereomeric products in approximately equal amounts were formed and separation by means of column chromatography proceeded readily. Application of bulkier alkylating reagents such as benzyl bromide and *tert*-butyl bromoacetate provided diastereomeric ratios of 4:1 and 7:1, respectively, in favor of the anti alkylation with respect to the BocNH group. Treatment of compounds **142** with a methanolic hydrochloride solution provided the *N*-deprotected products, which were then regioselectively hydrolyzed using CuCO₃·Cu(OH)₂ in aqueous ethanol⁹⁴ to afford the hydrochloride salts **143**. In the case of compound **142c** (R = CH₂CO₂tBu), the *tert*-butyl ester moiety was converted into the corresponding methyl ester under the latter reaction conditions (HCl in MeOH). Subsequently, the amino group of the L-aspartic esters **143a–c** was protected with CbzCl. Conversion of the α -carboxylate group into a hydroxymethyl

Scheme 31



Scheme 32

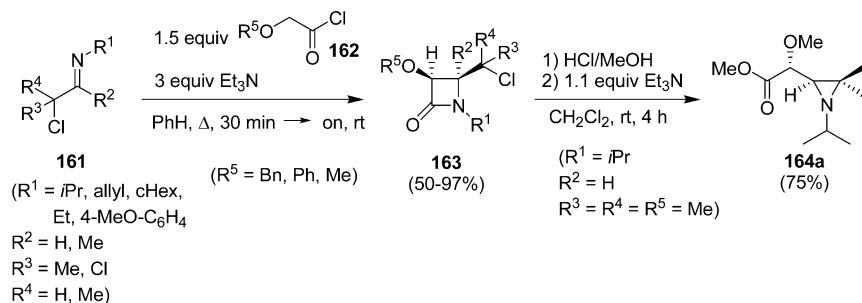


group was accomplished in good yield by sodium borohydride reduction of the activated ester that was formed by treating compound **144** with *N*-hydroxysuccinimide in the presence of DCC.⁹⁵ In the next step, the aziridine ring formation was effected under Mitsunobu conditions with DEAD in 82% yield for **146** ($\text{R} = \text{Bn}$).⁹⁶ The remaining steps to the target compound **(2R,3S)-15a** comprised removal of the Cbz group from the aziridine nitrogen and hydrolysis of the methyl ester moiety by catalytic hydrogenolysis in the presence of Pd/C and subsequent treatment with methanolic lithium hydroxide solution. Synthesis of the **(2S,3R)**-enantiomer of compound

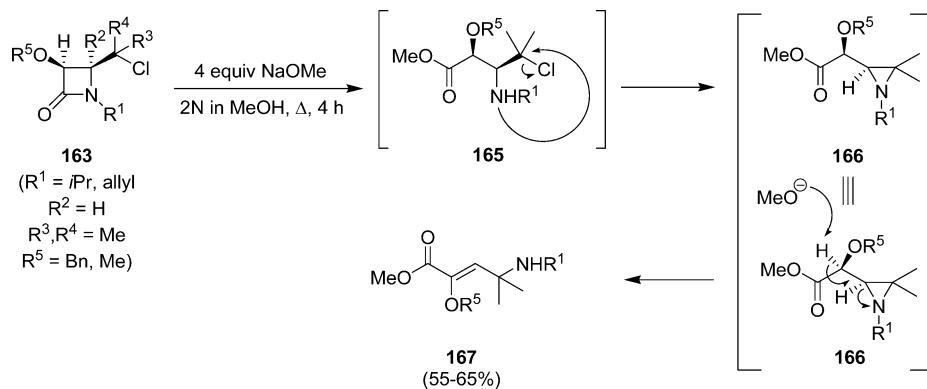
15a ($\text{R} = \text{Bn}$) was also performed in an overall yield of 13%, starting from *D*-aspartic acid **115** by an analogous synthetic pathway used for preparation of **(2S,3S)-15a**.⁹⁰

An alternative route had to be sought for synthesis of the **(2S,3S)**- and **(2R,3R)**-enantiomers, **(2S,3S)-15a** and **(2R,3R)-15a**, because the precursor to the key intermediate, namely, the γ -hydroxy ester that corresponds to **145** in the synthesis of **(2R,3S)-15a**, had a strong tendency to cyclize to the corresponding γ -lactone.^{31,90} Thus, instead of a methyl ester, the corresponding Weinreb amide, which resisted lactonization but still could be readily converted into the carboxylate via an

Scheme 33



Scheme 34



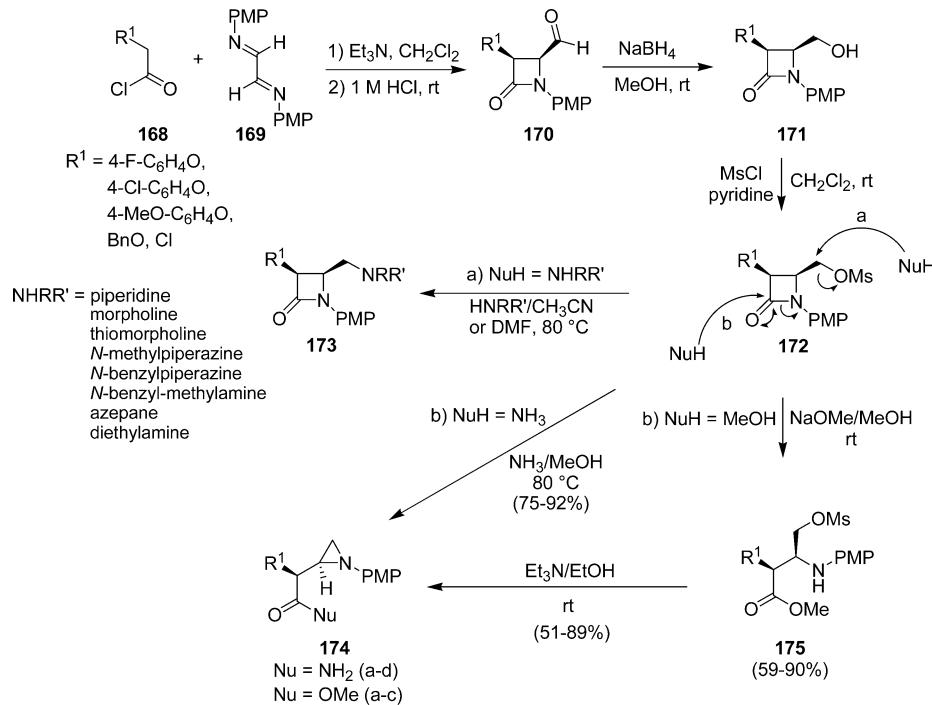
aldehyde moiety, was used (Scheme 31).^{90,97} Lactone **148**, which was prepared from L-aspartic acid,⁹⁸ was subjected to α -benzylation in THF and HMPA using 2 equiv of LDA to give a diastereomeric mixture, from which (2S,3S)-**149** was isolated in 73% yield. Alkylation of γ -lactones such as **148** via a dianion intermediate is known to afford a mixture of diastereoisomers, in which the *trans*-alkylated products predominate, especially when the alkylating reagent bears a bulky group.^{99,100} The lactone **149** was then readily converted into **150** by treatment with *N,O*-dimethylhydroxylamine in the presence of trimethylaluminum.¹⁰¹ The aziridine ring formation was then effected by the intramolecular Mitsunobu-type reaction to yield **151**.⁹⁶ While attempts toward selective reduction of the Weinreb amide moiety in **151** to the aldehyde were unsuccessful, conversion of the Cbz protecting group into a bulkier trityl group allowed selective reduction of the Weinreb amide by lithium aluminum hydride at -78°C to deliver aldehyde **153**.⁹⁷ Since this aldehyde **153** was shown to be unstable upon exposure to air, it was not isolated, and further reduction of the crude reaction mixture with lithium aluminum hydride at elevated temperature gave the stable alcohol **154**. Moreover, there was a potential risk of the aldehyde **153** undergoing racemization during workup and purification. Nonetheless, direct conversion of the Weinreb amide into a hydroxymethyl group with lithium aluminum hydride failed, as the hydride adduct to the carbonyl of the carboxylic amide formed an intramolecular complex with the lithium ion, which resisted further reduction.¹⁰² At this stage, the trityl moiety on the aziridine nitrogen atom was replaced by a Fmoc moiety, which showed excellent acid stability, demonstrated under the oxidation conditions for converting the primary alcohol group to a carboxylic acid.¹⁰³ Ruthenium(VIII) oxide-catalyzed periodate oxidation¹⁰⁴ of compound **155** followed by deprotection of the Fmoc group with piperidine produced

finally (2*S*,3*S*)-**15a**. Compound (2*R*,3*R*)-**15a** was similarly synthesized in an overall yield of 4% starting with D-aspartic acid.

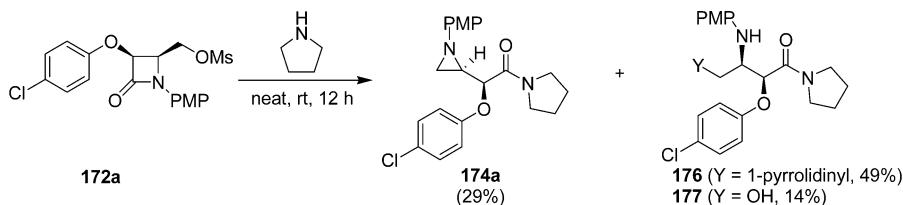
2.2.1.3. Synthesis through Modifications of D-Aspartic Acid. A last example of enantioselective synthesis starting from the chiral pool is the synthesis of 2-(carboxymethyl)aziridine **160** starting from D-aspartic acid **115** (Scheme 32).¹⁰⁵ First, selective esterification of the β -carboxylic group occurred in high yield (82%) by reaction with thionyl chloride in methanol followed by subsequent *o*-nosylation of the amine delivered the monocarboxylic acid **158** in 74% yield. Chemoselective reduction of the carboxylic group by activation with *N,N'*-diisopropylcarbodiimide and *N*-hydroxysuccinimide and subsequent treatment with sodium borohydride in THF/EtOH successfully gave the alcohol **159** in 61% yield. Subsequent mesylation and cyclization using Cs₂CO₃ provided the chiral 2-(carboxymethyl)aziridine **160** in 73% yield.

2.2.2. Stereoselective Synthesis Starting from Addition Reactions Across Imines. **2.2.2.1. Synthesis via Staudinger Reactions.** The utility of β -lactams as synthons for a wide range of heterocyclic compounds has been known for a long time and was demonstrated in the following example where β -lactam **163a**, synthesized via a Staudinger synthesis, was transformed into the corresponding 2-(carboxymethyl)aziridine **164a** (Scheme 33).^{106,107} 4-(1-Chloroalkyl)-substituted 2-azetidinones **163** were prepared in a diastereoselective way by condensation of α -chloroimines **161** with in-situ-generated ketenes in a Staudinger reaction. α -Chloroimines **161** were reacted with different types of acid chlorides **162** in benzene in the presence of triethylamine to generate in situ the intermediate ketenes, which underwent [2 + 2]-cycloaddition to afford the corresponding β -lactams **163** in moderate to excellent yields. In the next step, compound **163a** ($R^1 = i\text{Pr}$, $R^2 = \text{H}$, $R^3 = R^4 = R^5 = \text{Me}$) underwent ring opening via acidic

Scheme 35



Scheme 36



methanolysis (Scheme 33).^{106,107} The intermediate salt was not characterized but was immediately reacted with triethylamine to afford the corresponding 2-(carboxymethyl)aziridine 164a in 75% yield.

It is noteworthy that base-promoted ring opening of β -lactams 163 by treatment with sodium methoxide did not afford the corresponding 2-(carboxymethyl)aziridines 164 but the ring-opened products (*Z*)-167 (Scheme 34).^{106,107} The proposed reaction mechanism involves nucleophilic attack of sodium methoxide across the amide functionality of β -lactam 163, resulting in ring opening. The secondary amine obtained in this way attacked the halogenated carbon leading to ring closure by intramolecular nucleophilic substitution. The ring-closed products 166 were the originally expected aziridine derivatives. However, in the presence of excess sodium methoxide, deprotonation at the α -position of the ester 166 occurred and anti elimination led unexpectedly to stereospecific formation of alkenoates (*Z*)-167.

Another study toward the synthesis of 2-(carboxymethyl)aziridines 174 started from a Staudinger synthesis between diimine 169 and in-situ-generated ketenes from acid chlorides 168, leading to formation of imino- β -lactams, which were directly hydrolyzed to the corresponding aldehydes 170 (Scheme 35).^{108–114} Next, 4-formyl- β -lactams 170 were reduced with sodium borohydride, affording alcohols 171,^{113–115} which were subsequently mesylated to give the corresponding mesyloxy- β -lactams 172.^{114–116} Previously, the

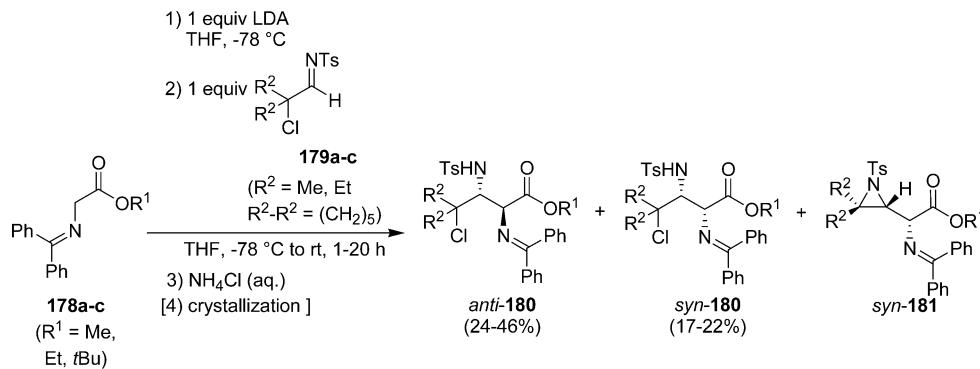
reactivity of these compounds 172 was studied in order to obtain the corresponding aminomethyl- β -lactams 173 by reaction with secondary amines (Scheme 35).¹¹⁷ In an extension of this research, preparation of the unsubstituted aminomethyl analogs was envisioned by changing the nucleophile from a secondary amine to ammonia; however, this resulted in the unexpected formation of 2-(carboxymethyl)aziridines 174.^{108,109}

Furthermore, the same type of aziridines 174 were obtained by reaction of the mesyloxy- β -lactams 172 with sodium methoxide to afford the corresponding ring-opened products 175.^{108,109} Subsequent treatment of 175 with triethylamine furnished 2-(carboxymethyl)aziridines 174 in good yields (51–89%).

Surprisingly, reaction of mesyloxy- β -lactam 172a with pyrrolidine as nucleophile afforded the 2-aziridinylacetamide 174a together with compounds 176 and 177 (Scheme 36).¹⁰⁸ This pyrrolidine-promoted azetidinone to aziridine transformation was in contrast with all other secondary amines used.

A possible explanation of these results was found in the difference in nucleophilicity of these reagents, based on their basicity and steric requirements. Thus, the nucleophilic methoxide anions reacted in all cases selectively with the electrophilic lactam carbonyl function, while nucleophilic attack of piperidine, a quite strong base but more sterically hindered, only occurred at the less hindered side chain electrophilic center. In terms of reactivity, pyrrolidine is intermediate (strong

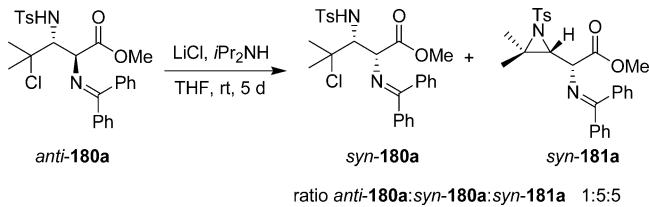
Scheme 37



base with lower steric requirements) between piperidine and ammonia and could react with both electrophilic centers. Therefore, the regioselectivity was here determined by the activation energy requirements being lower in the reaction with the carbonyl in comparison with the side chain center. Bearing in mind the low steric requirements of ammonia, it could react with both centers, as a result of its weak basicity. Since the reaction was carried out at room temperature, the reaction, however, took place exclusively at the carbonyl center, which comprises a lower energy barrier pathway.

2.2.2. Synthesis via Mannich-Type Reactions. In recent years, the diastereo- and enantioselective synthesis of 2-(carboxymethyl)aziridines via Mannich-type addition reactions has gained a lot of attention.^{118–121} This Mannich-type reaction proceeded via addition of enolates, prepared from esters **178**, to *N*-Ts α -haloimines **179** and resulted in formation of γ -chloro- β -amino acid derivatives **180**, which were further transformed into the corresponding 2-(carboxymethyl)aziridines **181** by a base-promoted ring-closure reaction (Scheme 37). In the first reaction, deprotonation of benzophenone imine glycine esters **178a–c** with lithium diisopropylamide (LDA) followed by addition of *N*-Ts α -haloimines **179a–c** resulted in a mixture of anti and syn diastereomers **anti-180** and **syn-180** in good yield with moderate diastereoselectivity (dr 3.5:1 to 1:1) (Scheme

Scheme 38

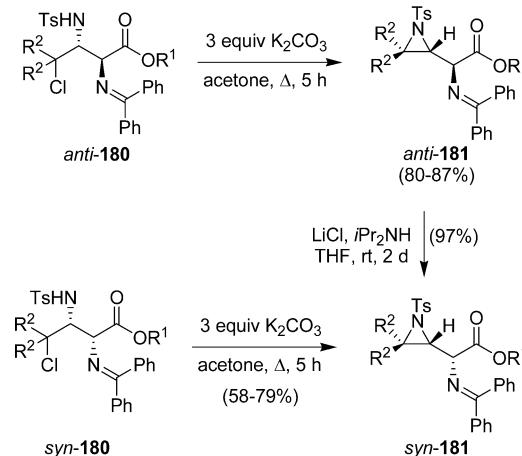


37).¹¹⁸ Performing this reaction under thermodynamic control, i.e., prolonged reaction times (20 h), afforded only *syn*- γ -chloro- β -amino esters **syn-180** and *syn*-2-(carboxymethyl)-aziridines **syn-181** in a 1:1 ratio, while kinetic conditions (THF, -78 °C, 1 h) increased the anti/syn ratio dramatically to 9:1.¹¹⁸

Furthermore, isomerization of the isolated **anti-180a** to the thermodynamically more stable **syn-180a** and **syn-181a** was observed upon stirring under mild basic conditions for an extended time (*iPr*₂NH, LiCl, rt) (Scheme 38).¹¹⁸

It was also possible to access diastereomerically pure β,γ -aziridino carboxylic acid esters **anti-181** and **syn-181** via 1,3-displacement of the chlorine atom under basic conditions.^{118,119}

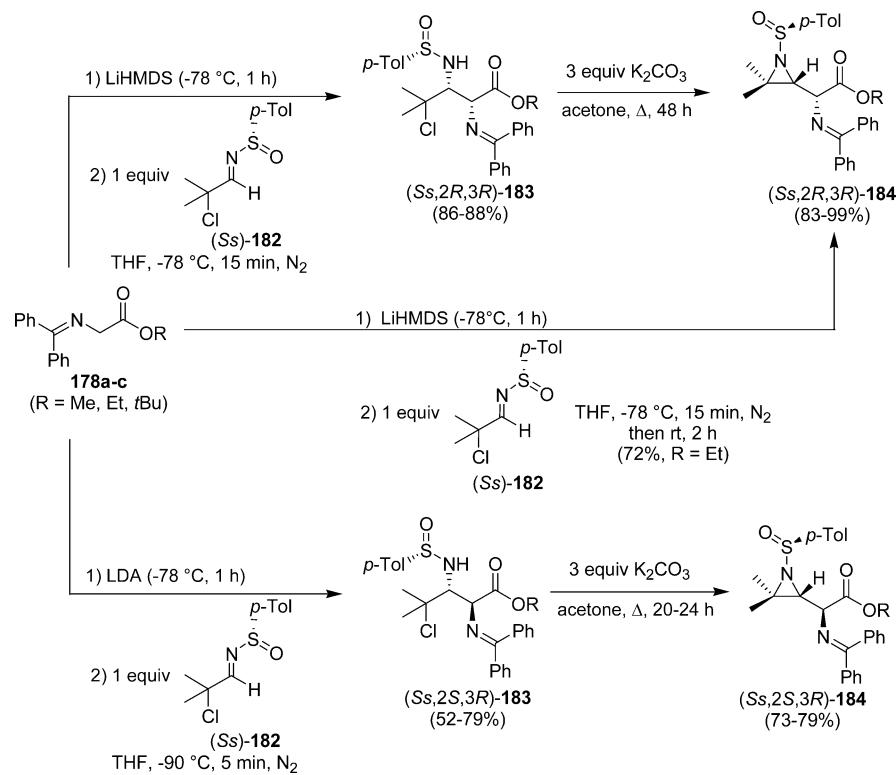
Scheme 39



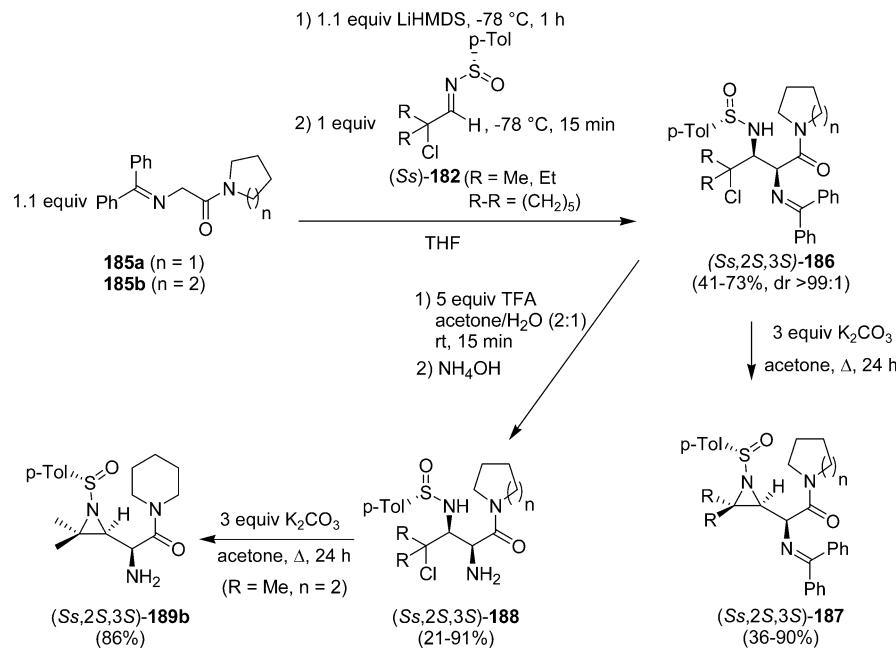
Base-promoted cyclization of the pure diastereomers **anti-180** and **syn-180** was performed easily with K_2CO_3 giving β,γ -aziridino esters **anti-181** and **syn-181** in 58–87% yield (Scheme 39). Interestingly, when the cyclization reaction from **anti-180** was continued for a longer time (16 h), the mixture of aziridines **anti-181** and **syn-181** was obtained in a 5:1 ratio. In analogy with the isomerization of **anti-180** to **syn-180**, compound **anti-181** could be isomerized under mild basic conditions (*iPr*₂NH, LiCl, THF, rt) to the thermodynamically favored **syn-181** in 97% yield (Scheme 39).¹¹⁸

In a recent report, stereoselective synthesis of chiral azaheterocyclic α,β -diamino acid derivatives via Mannich-type addition of *N*-protected glycine esters **178** across chiral imine **182** has been studied.¹²⁰ For the synthesis of *anti*- and *syn*- γ -chloro- β -amino esters (*S,S*,*2S,3R*)-**183** and (*S,S*,*2R,3R*)-**183**, it was found that the choice of base, LDA or LiHMDS, used for deprotonation of compound **178** had a dramatic influence on the *syn* or *anti* selectivity of the reaction (Scheme 40). Performing the Mannich-type addition of *N*-protected glycinate **178** across chiral imine **182** with LiHMDS at -78 °C afforded compound (*S,S*,*2R,3R*)-**183** with excellent *syn* selectivity (dr = 99:1) and high yields (86–88%), while use of LDA resulted in formation of compound (*S,S*,*2S,3R*)-**183** with good *anti* selectivity (dr = 90:10 to 72:28), yet isolation of the single *anti* diastereomers (*S,S*,*2S,3R*)-**183** failed. Both the *syn*- and the *anti*-addition products, (*S,S*,*2R,3R*)-**183** and (*S,S*,*2S,3R*)-**183**, were subsequently cyclized to the corresponding *N*-sulfinyl 2-(carboxymethyl)aziridines (*S,S*,*2R,3R*)-**184** and (*S,S*,*2S,3R*)-**184** in good to excellent yields (73–99%) (Scheme 40). Aziridine (*S,S*,*2R,3R*)-**184** could also be prepared directly in

Scheme 40



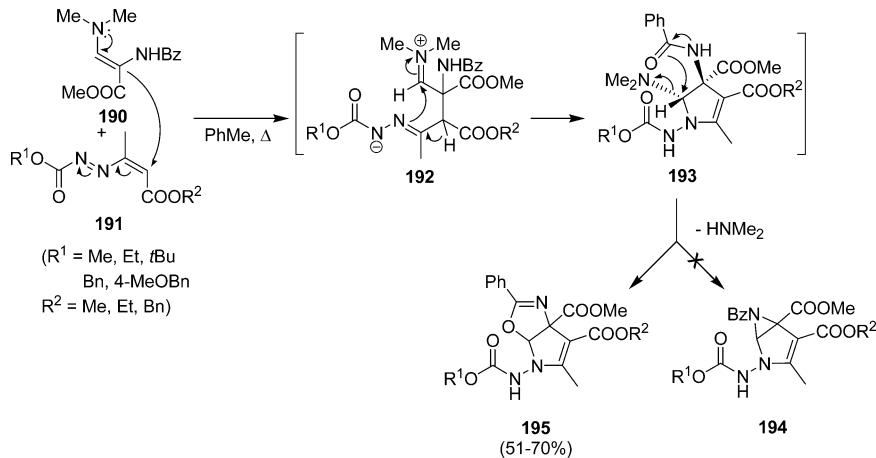
Scheme 41



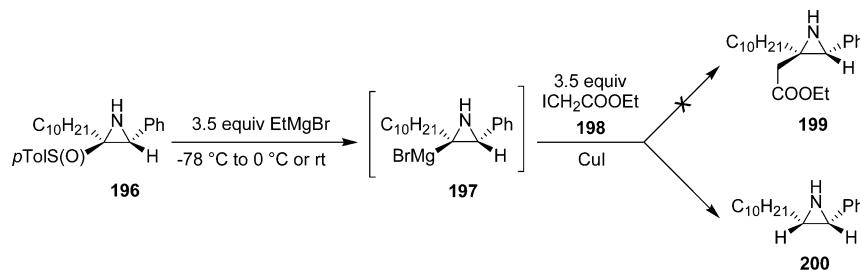
72% yield via a single-step reaction starting from ethyl glycinate **178b**, when the reaction mixture from the Mannich-type addition across imine **182** obtained after 15 min at -78°C was subsequently stirred for 2 h at room temperature (Scheme 40). This procedure was not applicable to the synthesis of aziridines **(S_s,2S,3R)-184** as the anti adducts are the kinetically favored diastereomers, which isomerize to the thermodynamically more stable syn isomers.

Analogously, asymmetric synthesis of chiral aziridines **(S_s,2S,3S)-187**, starting from highly diastereoselective Mannich-type reactions of amides **185** across chiral imines **182**, has been developed (Scheme 41).^{121a} The Mannich-type addition resulted in formation of compounds **(S_s,2S,3S)-186**, which had the opposite enantiotopic face selectivity as compared to compounds **(S_s,2R,3R)-183** obtained via Mannich-type addition of analogous esters **178** across chiral imine **182**.¹²⁰ Base-induced ring closure of compounds **(S_s,2S,3S)-186** resulted

Scheme 42



Scheme 43



again in formation of the corresponding aziridines (S,S , $2S,3S$)-187 in good yields (36–90%). Selective deprotection of the α -amino group by treatment with TFA has also been performed, and the resulting N^{α} -deprotected compound (S,S , $2S,3S$)-188 was subsequently cyclized to the aziridine (S,S , $2S,3S$)-189b. Very recently, this methodology was expanded to asymmetric synthesis of *syn*- β,γ -aziridino- α -hydroxy esters using the Mannich-type reaction of *O*-Boc glycolic esters across chiral *N*-sulfinyl- α -chloroaldimines as a key step in the reaction sequence.^{121b}

2.2.3. Synthesis from 1,2-Diaminoalkenes. It has been reported that 2-(carboxymethyl)aziridines **194** could also be synthesized via a regioselective attack of compound **190** on the terminal carbon atom of the conjugated aza-ene system of 1,2-diaza-1,3-butadienes **191** (Scheme 42).¹²² This reaction led to formation of the intermediate hydrazone 1,4-adducts **192** which were converted into bicyclic compounds in moderate to good yields (51–70%). First, it was reported that these bicyclic compounds were the 2-(carboxymethyl)aziridines **194**.¹²² However, further investigation showed that the resulting compounds were the corresponding oxazoline-fused 1-amino-pyrrolines **195**, the structure being confirmed by X-ray analysis.¹²³

In the proposed mechanism of this cyclization reaction it was suggested that the hydrazone nitrogen of the zwitterionic hydrazone intermediate **192** added to the iminium moiety, leading to a five-membered pyrroline derivative **193**. In this way, the *trans*-pyrroline *trans*-**195** must be formed by an internal nucleophilic substitution with loss of dimethylamine and simultaneous oxazoline formation.

In conclusion, analysis of a large number of reports revealed that β -amino acid derivatives bearing a leaving group in the γ -position were very suitable precursors for synthesis of 2-

(carboxymethyl)aziridines via an N1–C3 bond formation. Moreover, application of this strategy resulted in different stereo- and enantioselective routes toward 2-(carboxymethyl)aziridines. In a first methodology, 2-(carboxymethyl)aziridines were synthesized in an asymmetric way by use of starting materials derived from the chiral pool. This approach resulted in formation of a broad variety of enantiopure 2-(carboxymethyl)aziridines in very good overall yields. Stereo-selective synthesis of 2-(carboxymethyl)aziridines was also performed via addition reactions (Staudinger and Mannich reactions) across functionalized imines, followed by a base-promoted cyclization.

2.3. Synthesis through C2–C4 Bond Formation

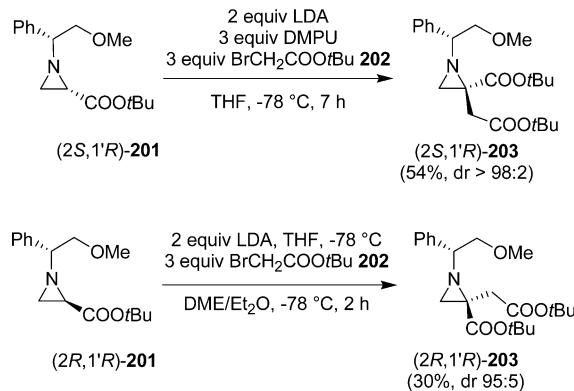
2.3.1. Synthesis through Reaction of a 2-Aziridinyl

Anion (Method IIIa). Several studies have been performed in order to synthesize 2-(carboxymethyl)aziridines via reactions of aziridinyl anions with α -haloacetates.¹²⁴⁻¹²⁶

A first attempt to synthesize β,γ -aziridino carboxylic ester **199** was made by treatment of 2-sulfinylaziridine **196** with EtMgBr resulting in formation of the aziridinylmagnesium species **197** in quantitative yield (Scheme 43).¹²⁴ Compound **197** reacted easily with alkyl halides in the presence of catalytic CuI to form trisubstituted aziridines.¹²⁴ However, reaction with ethyl iodoacetate **198** failed to give 2-(carboxymethyl)aziridine **199** and resulted in desulfinylated aziridine **200**.

In the next study, functionalization of configurationally and chemically stable aziridine carboxylate anions has been performed by reaction with electrophiles with good to excellent retention of configuration.^{125,126} Aziridine ester (2*S*)-**201**¹²⁷ was deprotonated with LDA and subsequently reacted with compound **202** to afford 2-(carboxymethyl)aziridines **203** as single diastereomers after column chromatography (Scheme 44). It was found that use of the less hindered methyl and ethyl

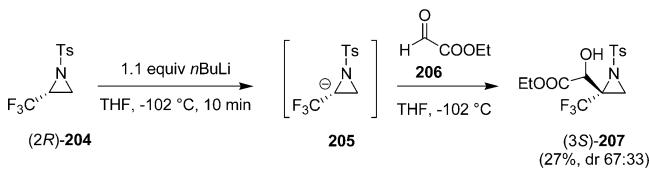
Scheme 44



aziridine esters only led to self-condensation. Use of DMPU as cosolvent resulted in improved chemical yields but was not essential in contrast to previous observations on aziridine carbothioate anions.^{128,129}

When aziridine ester (2*R*)-201 was treated under analogous reaction conditions (LDA, THF, -78 °C), only self-condensation was observed.^{125,126} Since intramolecular stabilization appeared to be negligible in this compound, the highly reactive lithiated intermediate was stabilized by intermolecular

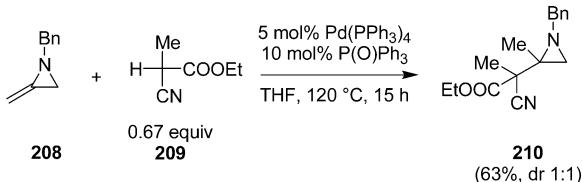
Scheme 45



chelation in a more suitable solvent system. When a 5:1 mixture of DME:Et₂O was used, a more stabilized aziridine carboxylate anion was formed, which reacted with compound 202 to give aziridine (2*R*,1'*R*)-203 in a low yield (30%) but with excellent retention of configuration (Scheme 44).^{125,126}

Besides the synthesis of 2-(carboxymethyl)aziridines 203 via reactions of aziridinyl anions with compound 202, application of ethyl glyoxylate 206 as an electrophile has also been evaluated.^{130–132} In the first step, *N*-tosyl-aziridine 204 was regioselectively deprotonated with *n*-BuLi (Scheme 45). It was stated that generation of the anion was markedly influenced by the nature of the *N*-substituent. *N*-(*o*-Anisyl)- and *N*-(*p*-anisyl)-aziridinyl anions could only be partially generated upon deprotonation with the stronger base *sec*-BuLi, whereas generation of the *N*-benzyl-aziridinyl anion with *sec*-BuLi was unsuccessful. Subsequent reaction of the *N*-tosyl-aziridinyl anion 205 with ethyl glyoxylate 206 afforded the corresponding aziridine 207 in 27% yield as a mixture of two diastereomers (dr = 67:33).

Scheme 46



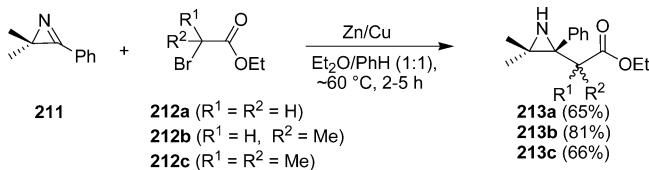
Even though the following example falls outside the scope of nucleophilic addition of aziridinyl anions it is interesting to report here the synthesis of 2-(carboxymethyl)aziridine 210 via palladium-catalyzed hydrocarbonation of methyleneaziridine 208.^{133,134} Reaction of methyleneaziridines 208 with carbon pronucleophile 209 proceeded smoothly in the presence of Pd(PPh₃)₄ and triphenylphosphine oxide to give the non-ring-opened product 210 in 63% yield as a 1:1 mixture of both diastereomers (Scheme 46).

2.3.2. Synthesis Starting from 2*H*-Azirines (Method IIIb).

2.3.2.1. Synthesis via Reformatsky Reactions.

The utility of the Reformatsky reaction for synthesis of 2-(carboxymethyl)-

Scheme 47



aziridines starting from 2*H*-azirines and ethyl α -bromoacetates was demonstrated by several examples.^{135–139}

In the first example, compounds 212 were reacted with a zinc–copper couple¹⁴⁰ in Et₂O/benzene to afford the corresponding Reformatsky reagents, which were immediately reacted with 2*H*-azirine 211 resulting in formation of β,γ -aziridino esters 213 in good yields (65–81%) (Scheme 47).¹³⁵ Changing the solvent to toluene resulted in lower yields of the desired products 213 and formation of 3-pyrrolidinones as side products.¹³⁶

Reaction of the previously described Reformatsky reagents with 2*H*-azirine 214 under the same reaction conditions (Et₂O/benzene, Zn/Cu) afforded a mixture of β,γ -aziridino esters 215 as the major product (37–59%) and diazepinones 216 as minor byproducts (2–22%) (Scheme 48).¹³⁵

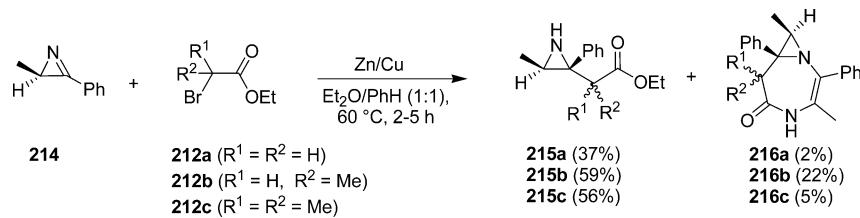
Formation of diazepinones 216 was explained by nucleophilic addition of the organozinc intermediate 217 to 2*H*-azirine 214, Scheme 49.¹³⁵ This reaction was not observed when 2*H*-azirine 211 was used, most probably due to the steric hindrance of the geminal dimethyl groups.

The diastereoselectivity of the Reformatsky reaction of compound 212 with 2*H*-azirines 211, 214, and 219 has been studied (Scheme 50).¹³⁷ As no isomerization of the formed diastereomers, *syn*-220 and *anti*-220, was possible, the major isomer obtained by this reaction was the product of kinetic control.¹³⁷ The structures of *syn*-220 and *anti*-220 have been deduced from those of the corresponding 4-aminolactones, obtained by treatment of both diastereomers separately with Olah's reagent (pyridine–HF) or with aqueous hydrochloric acid (vide infra).¹³⁷

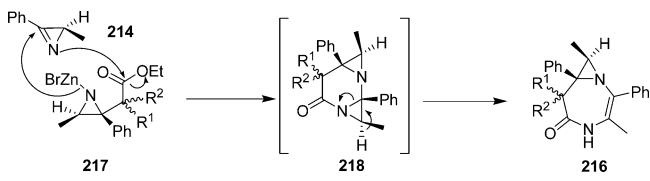
In addition, the Reformatsky reaction of compounds 221 and 2*H*-azirine 211, in the presence of zinc in dimethoxymethane, afforded the 2-(carboxymethyl)aziridines 222 as a single diastereomer in 37–42% yield (Scheme 51).^{138,139} In this case, the yield of pyrrolinone 223 was less than 5%, whereas the same reaction in toluene or THF resulted in pyrrolinone 223, exclusively.¹³⁸

Similar to the Reformatsky reaction, the Ivanov reaction¹⁴¹ was also evaluated for synthesis of 2-(carboxymethyl)aziridines 222 (Scheme 52).¹³⁹ In the first step, arylacetic acids 224 were

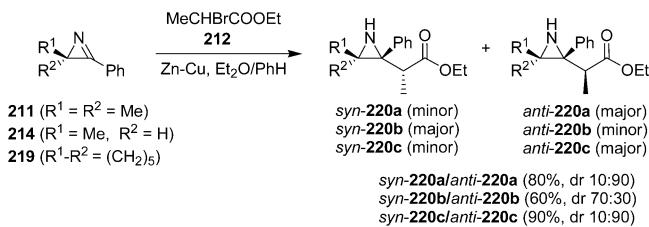
Scheme 48



Scheme 49



Scheme 50



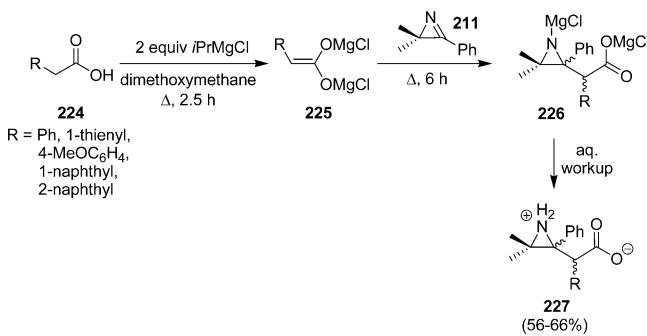
treated with isopropylmagnesium chloride in dimethoxymethane, affording the corresponding organomagnesium compounds **225**. Subsequent addition of *2H*-azirine **211** furnished β,γ -aziridino carboxylic acid salts **226**, which were isolated as the corresponding zwitterions **227**, as single diastereomers in good yields. It is noteworthy that all attempts to synthesize 2-(carboxymethyl)aziridines **227** via deprotonation of arylacetic acids **224** with sodium naphthalenide followed by reaction with *2H*-azirines were shown to be unsuccessful.¹³⁹

Nucleophilic addition of enolates, derived from the corresponding esters **228** upon treatment with sodium hydride in DMSO, across *2H*-azirine **211**, in order to synthesize the corresponding 2-(carboxymethyl)aziridines **213a,b,d** has also been investigated (Scheme 53).¹⁴² This reaction resulted in multicomponent reaction mixtures from which the desired 2-(carboxymethyl)aziridine **213d** was isolated in only 4% yield when ethyl phenylacetate **228c** ($R = \text{Ph}$) was used.

3.3.2.2. Synthesis via Cycloaddition Reactions. Cycloaddition reactions with *2H*-azirines as dipolarophiles have been shown to be very useful in the synthesis of a wide range of 2-(carboxymethyl)aziridines.^{143–156}

The first approach in this methodology concerns the regioselective 1,3-dipolar cycloaddition reaction of 2-phenylazirine **233** and azomethine ylide **232** (Scheme 54).^{143–145} Treatment of compound **231** with K_2CO_3 and subsequent addition of 2-phenylazirine **233** resulted in formation of an

Scheme 52

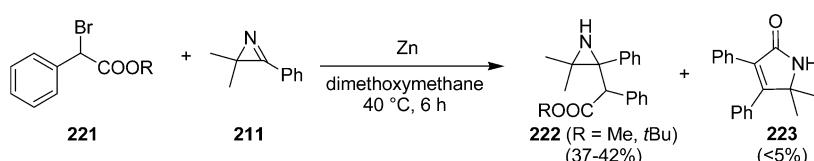


inseparable mixture of both polycyclic 2-(carboxymethyl)aziridines *exo*-**234** and *endo*-**234** in 41% yield.

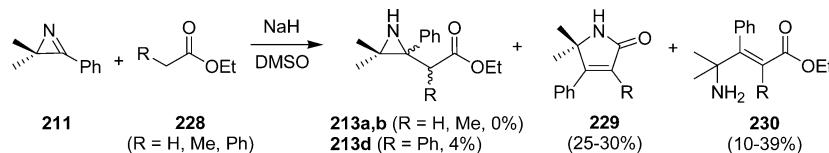
Another study reported the synthesis of bicyclic and tricyclic aziridines **238** and **240** via a photocatalyzed cycloaddition reaction of *2H*-azirines **236** in the absence of external dipolarophiles.^{146–148} Performing a photolysis reaction in quartz or Pyrex with α -azidocinnamates **235** in petroleum ether or acetone resulted in stereoselective formation of tricyclic aziridine **240** (Scheme 55).^{146,147} The mechanism of this reaction has been rationalized by the loss of nitrogen from the azides **235** with formation of *2H*-azirines **236**, which are known to undergo photochemical ring opening to the corresponding nitrile ylides **237**. In the absence of an external dipolarophile the latter formed ylides **237** adds to the imino bond of *2H*-azirine to afford the diastereomeric dimers **238** with a 1,3-diazabicyclo[3.1.0]hex-3-ene structure.^{146,147} Next, photolysis of the bicyclic aziridines **238** resulted in formation of azomethine ylides **239**, which could add across the imino bond of *2H*-azirine **236** to give trimeric aziridines **240** as a single diastereomer.^{146–148}

The reactivity of *2H*-azirines **243** as 1,3-dipolarophiles toward β -lactam-based azomethine ylides **242**, derived from oxazolidinones **241**, has also been evaluated.¹⁴⁹ The azomethine ylide strategy for aziridine synthesis was based on the thermolysis of β -lactam-based oxazolidinones **241**, which led, via a stepwise mechanism, to azomethine ylides **242**.^{157,158} This intermediate **242** reacted with *2H*-azirines **243** to give tricyclic β -lactams **244** after a decarboxylation step, which followed the cycloaddition event. The resulting tricyclic β -

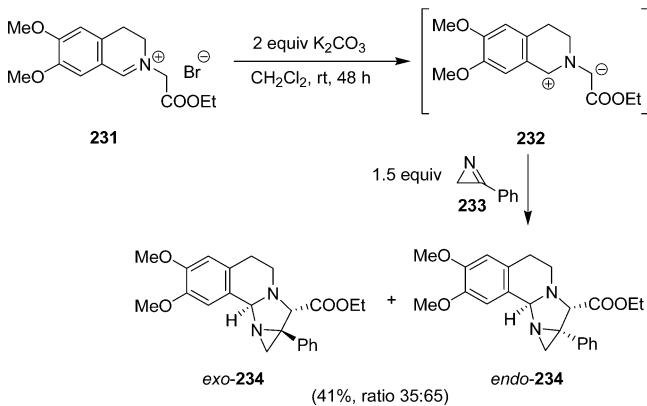
Scheme 51



Scheme 53



Scheme 54



lactams **244** were isolated in 20–66% yield as a mixture of two diastereomers (Scheme 56).¹⁴⁹

Additionally, synthesis of thiolactones **248** and **249** of aziridines via [3 + 2]-cycloaddition reactions of 1,3-dithioles **246** with 2*H*-azirines **214** and **247** has also been investigated.^{150,151}

In a first step, 1,3-dithioles **246** were synthesized in good yields by treatment of acids **245** with acetic anhydride and triethylamine (Scheme 57).¹⁵⁹ The 1,3-dithiole ring system **246a** ($R^1 = H$) contained a masked 1,3-dipole of a thiocarbonyl ylide type, which failed to yield an isolable compound after cycloaddition with 2*H*-azirine **214** ($R^2 = Me$) due to decomposition. However, its 2,5-diphenyl derivative **246b** ($R^1 = Ph$) was considerably more stable thermally and also toward traces of moisture.¹⁶⁰ Therefore, mesoionic compound **246b** ($R^1 = Ph$) reacted with 2*H*-azirine **247** ($R^2 = Ph$), resulting in a two-component reaction mixture where the major compound was the *exo*-polycyclic aziridine **248a**.¹⁵⁰ Aziridine **248a** was subsequently converted into the corresponding sulfoxide **249a** by oxidation with *m*-chloroperbenzoic acid.

The [3 + 2]-cycloaddition with 1,3-dithiole **246b** ($R^1 = Ph$) and 2*H*-azirine **214** ($R^2 = Me$) furnished an inseparable mixture of two isomers *exo*-**248b** and *endo*-**248b** in 57% yield in a ratio of 2.25:1 (Scheme 57).¹⁵⁰ Oxidation of this mixture resulted in isolation of only one sulfoxide **249b** with a syn relationship of the S–O group to the aziridine proton.

Furthermore, a highly regio- and stereospecific [3 + 2]-cycloaddition of 1,3-dithiole **246b** with 2*H*-azirine **250** was performed in toluene at 100 °C for 2 days (Scheme 58).¹⁵¹ This cycloaddition reaction provided selectively bicyclic aziridine **251** in 92% yield, even with prolonged reaction times. Performing this [3 + 2]-cycloaddition reaction at 140 °C resulted also in the bicyclic aziridine **251** but in lower yield (45–57%).

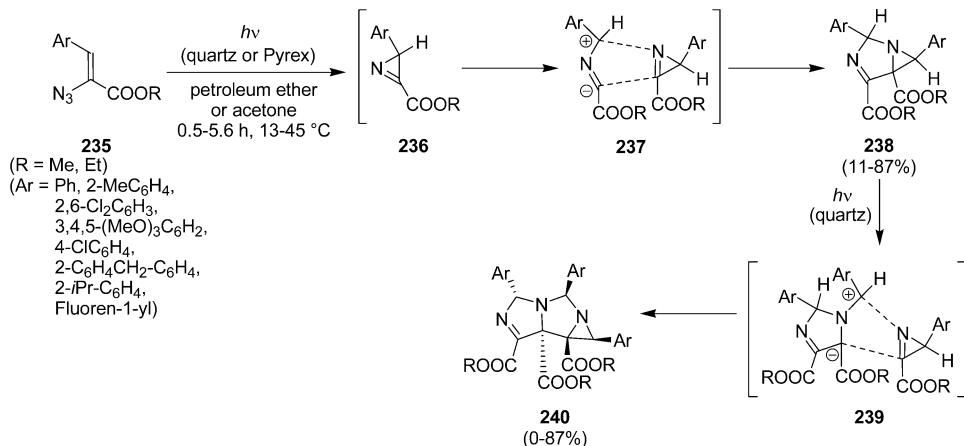
Besides the application of 2*H*-azirines in [3 + 2] cycloaddition reactions, [4 + 2] cycloadditions with 1,3-oxazinones **252** have also been investigated.^{152,153} Cycloaddition reactions of electrophilic 1,3-oxazinones **252** with 2*H*-azirines **247** and **253** furnish fused aziridines **254**, yet the yields of these reactions were not reported (Scheme 59).¹⁵² Furthermore, a crystallographic study was performed to determine the stereochemistry of cycloaddition products **254**.¹⁵³

Use of [4 + 2]-cycloaddition reactions of electron-rich 2-azadienes with 2*H*-azirines for synthesis of 2-(carbamoylmethyl)aziridine derivatives has also been described.^{154–156}

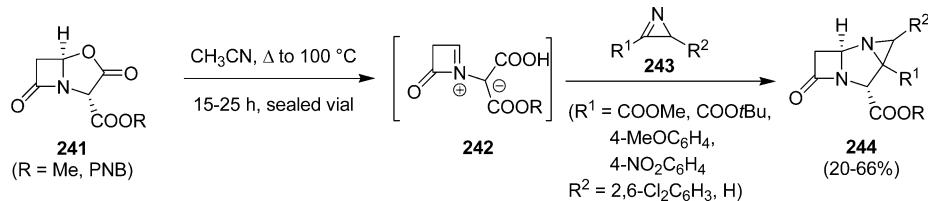
The first step comprised the Diels–Alder reaction of 2-azabutadienes **255** with 2*H*-azirine **236a** (Scheme 60).^{154,155} The resulting Diels–Alder intermediates *cis*-**256** and *trans*-**256** were immediately desilylated to afford the bicyclic compounds *cis*-**257** and *trans*-**257** as a mixture of two diastereomers, which then gave rise to the corresponding 2-(carbamoylmethyl)aziridine derivative **258** as one single diastereomer after treatment with aqueous hydrochloric acid.

Similarly, the Diels–Alder reaction of 2-azabutadienes **259** with 2*H*-azirine **236a** has also been performed.^{155,156} In

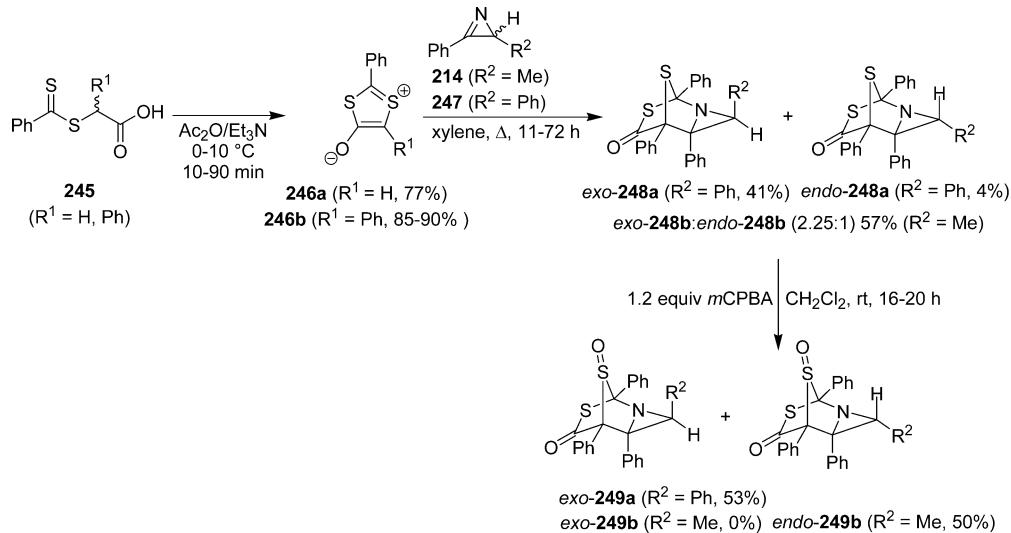
Scheme 55



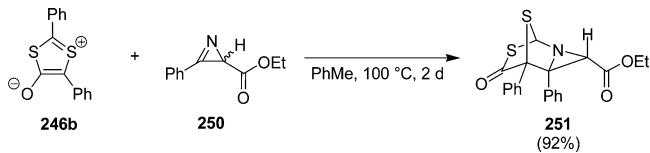
Scheme 56



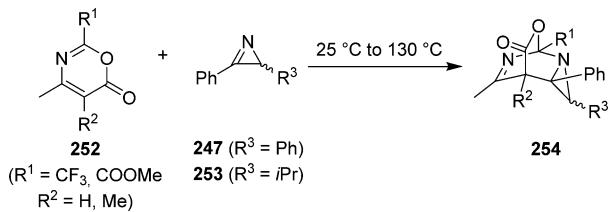
Scheme 57



Scheme 58



Scheme 59



contrast to the Diels–Alder cycloaddition with imidates 255, the reaction with compounds 259 afforded bicyclic aziridines 260 as single diastereomers, which gave rise to formation of β,γ -aziridino carboxylic amide 262 ($\text{R}^1 = \text{R}^2 = \text{Ph}$, Ar = 2,6-dichlorophenyl) in 67% yield after a similar acid hydrolysis (Scheme 61).

By analogy with the previous examples,^{154,155} the Diels–Alder reaction of 2-aza-1,3-dienes 259 and chiral 2H-azirine 263 has also been evaluated.¹⁵⁶ This [4 + 2]-cycloaddition resulted in formation of aziridines (2S,1'R)-264 and (2R,1'R)-264 as a mixture of two diastereomers (Scheme 62). Both diastereomers 264 were formed via an endo approach of the reagents with good selectivity for the major isomer (2S,1'R)-264, which was isolated in 16–65% yield.

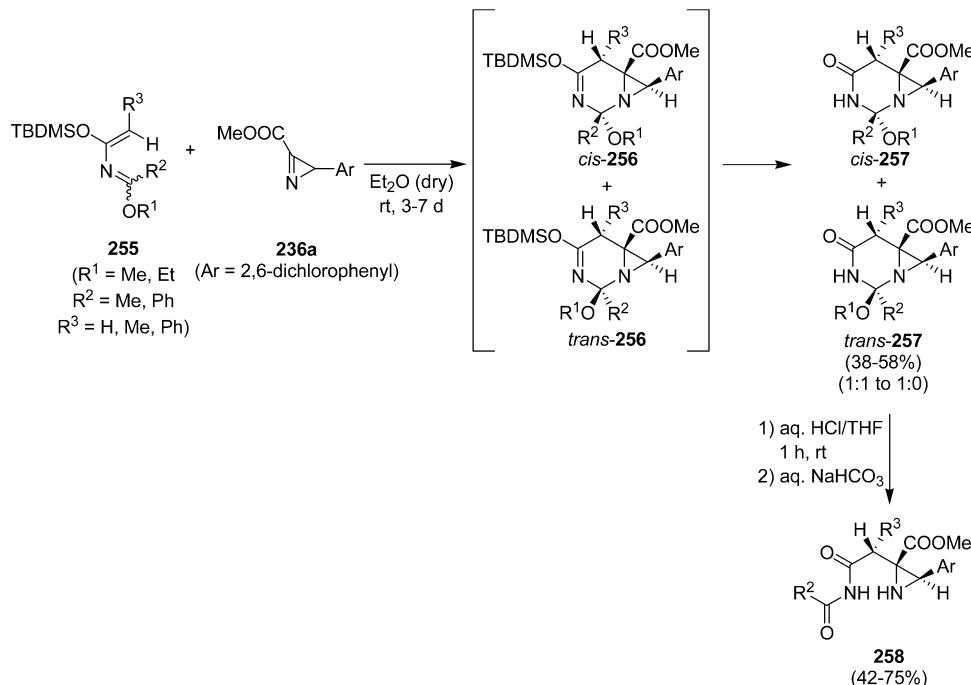
Besides cycloaddition reactions with 2H-azirines as 1,3-dipolarophiles, 1,3-dipolar cycloadditions with ylides derived from 3-arylazirines have also been investigated.^{161,162} Reaction of 2H-azirines 265 with difluorocarbene involved formation of azirinium difluoromethanides 266 which underwent a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate 55 (Scheme 63). The cycloaddition reaction of these strained azomethine ylides 266 furnished the corresponding fluorinated fused aziridinopyrrole derivatives 267 in 27–40% yield.^{161,162}

2.3.2.3. Synthesis via Miscellaneous Reactions. In addition to the synthesis of 2-(carboxymethyl)aziridine derivatives based on Reformatsky reactions or cycloadditions with 2H-azirines, less common reactions with 2H-azirines have also been reported in the literature.^{163–165}

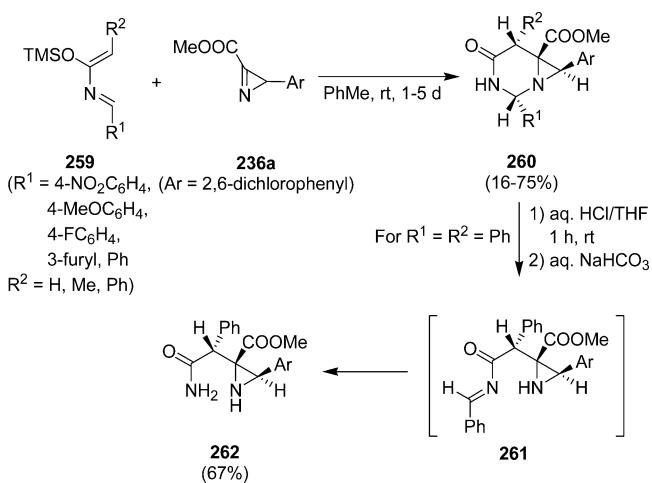
In a first example, the synthesis of aziridines 272 via reaction of phosphonium ylides 269 with nitrile oxide 268 was investigated.¹⁶³ Reaction of phosphonium ylide 269 and nitrile oxide 268 led to a 2H-azirine intermediate 270, which could not be isolated because a second molecule of the phosphonium ylide 269 reacted immediately with the 2H-azirine 270 (Scheme 64). Furthermore, the resulting aziridinium ylide 271 was treated with zinc in glacial acetic acid to afford the substituted 2-(carboxymethyl)aziridine 272 after cleavage of the triphenylphosphonium group.

Synthesis of 2-(carboxymethyl)aziridine derivatives 274 has also been performed via an Alder–ene reaction of 2H-azirines 247, 233, and 211 and compound 273 affording the corresponding aziridines 274a,b in good to excellent yields (62–92%) as a single diastereomer (Scheme 65).¹⁶⁴ Unfortunately, the Alder–ene reaction with 2H-azirines 211 ($\text{R}^1 = \text{R}^2 = \text{Me}$) under the same reaction conditions did not result in formation of aziridine 274c, as both starting compounds were recovered quantitatively.

Scheme 60

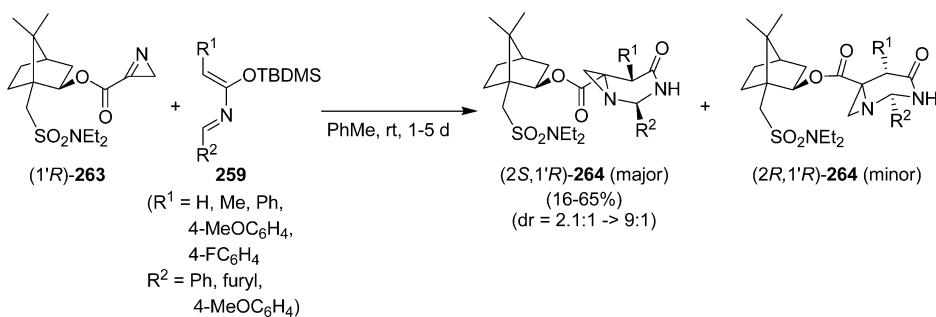


Scheme 61

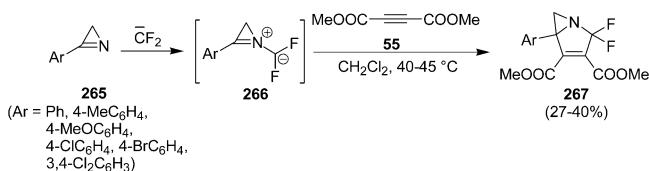


Furthermore, it has been reported that indium-catalyzed carbometalation reactions with 2*H*-azirines 275, 214, and 247 also resulted in formation of β,γ -aziridino carboxylic esters 277.¹⁶⁵ Carbometalation reactions with 2-(hydroxymethyl)-

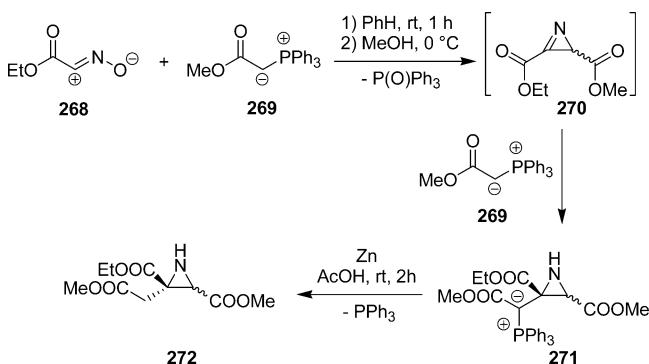
Scheme 62



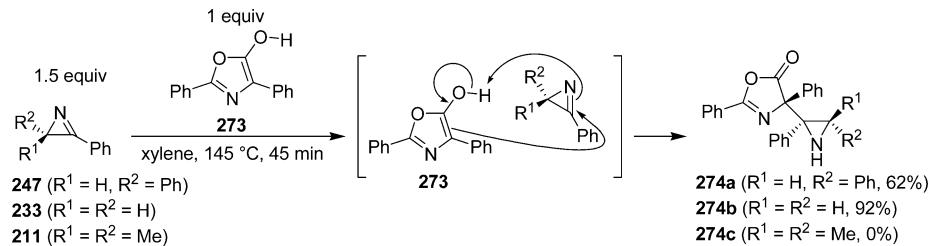
Scheme 63



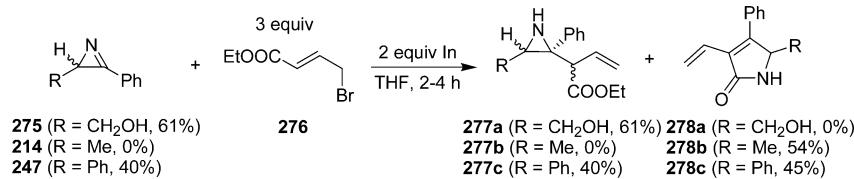
Scheme 64



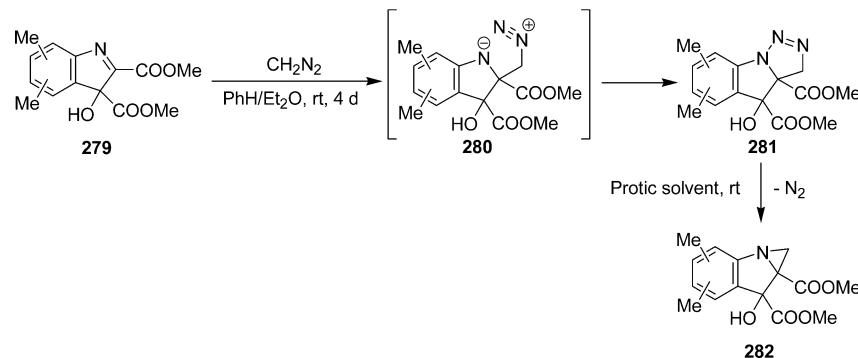
Scheme 65



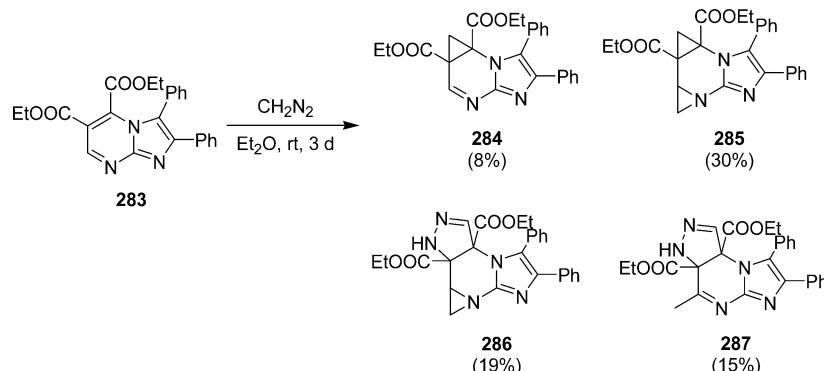
Scheme 66



Scheme 67



Scheme 68



azirine **275** and 2*H*-azirine **247** afforded the corresponding 2-(carboxymethyl)aziridines **277a,c** as a diastereomeric mixture in 40–61% yield, although the α,β -unsaturated lactam **278c** has also been isolated in 45% yield in the case of 2*H*-azirine **247** (Scheme 66). Unexpected formation of the α,β -unsaturated lactam **278** has also been observed when 2*H*-azirine **214** was used in the carbometalation reaction, where the lactam **278b** was the only isolated product (54% yield) (vide infra).

In conclusion, in this part a few examples described stereoselective substitution reactions of stabilized aziridinyll anions with acetates, bearing a leaving group in the α -position, which afforded the corresponding 2-(carboxymethyl)aziridines in acceptable yields (method IIIa). Furthermore, synthesis of 2-

(carboxymethyl)aziridines via addition reactions of α -deprotonated acetate derivatives across 2*H*-azirines via Reformatsky, Ivanov, and cycloaddition reactions has been the topic of a considerable number of literature reports (method IIIb). In general, this methodology resulted in a wide variety of 2-(carboxymethyl)aziridines, which were formed in lower yields due to the presence of side products. This was explained by the very reactive nature of the reagents used in these reactions. In addition, some less common reactions with 2*H*-azirines were also discussed.

2.4. Synthesis via Addition Reactions to Imines (Method IV)

2.4.1. Synthesis through Reaction with Carbenes.

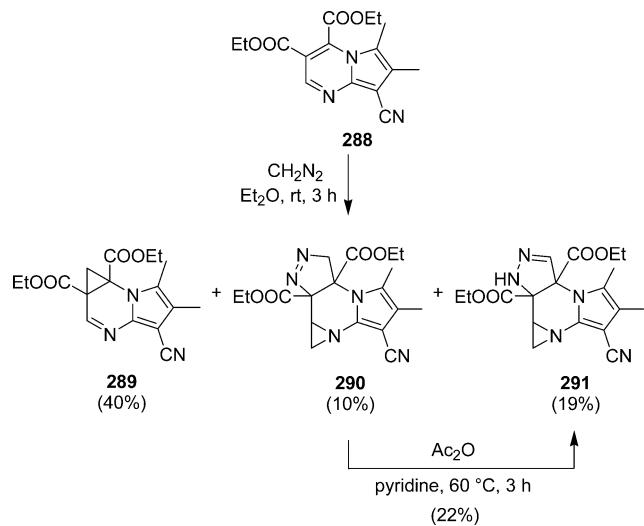
Synthesis of aziridines via addition reactions of carbenes to

imines has been well explored.¹⁶⁶ In a first synthetic strategy, diazomethane was used as a carbenoid compound in addition reactions with imines to afford 2-(carboxymethyl)-aziridines.^{167–170}

Reaction of compounds **279** with diazomethane afforded 1,2,3-triazolines **281**, but the yields were not reported (Scheme 67).¹⁶⁷ Stirring this compound **281** in protic solvents (alcohols, mineral acids, organic acids, water, methyl acetoacetate, dimethyl malonate) resulted in loss of a nitrogen molecule and formation of the 2-(carboxymethyl)aziridines **282**.

Pyrimidine **283** has been used in aziridination reactions upon treatment with diazomethane resulting in formation of the aziridine derivatives **285** and **286** (Scheme 68).¹⁶⁸ Next to formation of the major compounds **285** and **286** in 30% and

Scheme 69



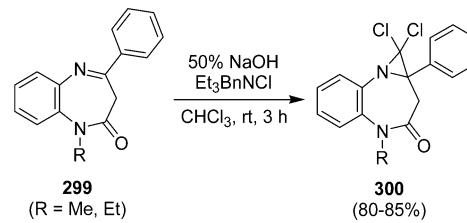
19%, respectively, minor compounds **284** and **287** were also isolated in low yields.

In addition to the previous study,¹⁶⁸ Kurihara et al. investigated the reactivity of pyrimidine **288** in aziridination

reactions with diazomethane.¹⁶⁹ Reaction of compound **288** with diazomethane resulted in cyclopropane **289** (40%) and aziridine derivatives **290** and **291** in 10% and 19% yield, respectively (Scheme 69). In addition, pyrazole **290** has been transformed into the polycyclic aziridine **291** in low yield (22%) by treatment with acetic anhydride in pyridine.

The tetracyclic aziridine derivative **298** was also prepared as a minor product from reaction of compound **292** in ethereal diazomethane.¹⁷⁰ Treatment of compound **292** with an excess of diazomethane resulted in complete consumption of the starting material with initial formation of intermediate **293** (Scheme 70). After tautomerization, intermediate **295** was formed, which easily gave rise to elimination of nitrous acid. The resulting unstable compound **296** was subsequently trapped with excess diazomethane to form **297** (27% yield) through a regio- and diastereoselective cycloaddition of the exocyclic C=N double bond. Further reaction of diazo-

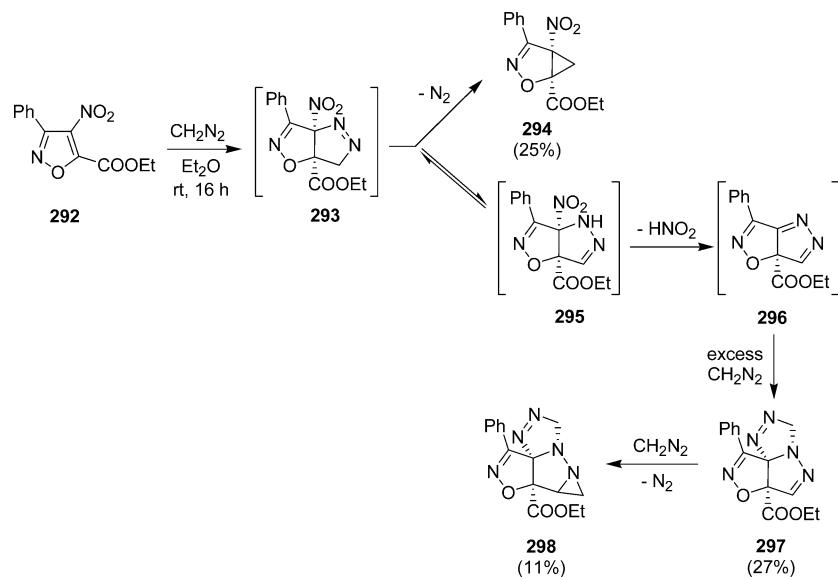
Scheme 71



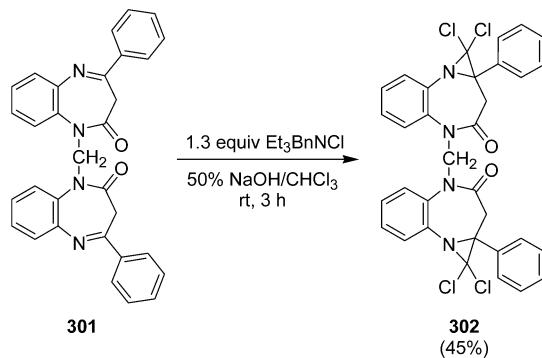
methane with the 2-pyrazoline moiety of **297** finally afforded aziridine **298** in 11% yield with concomitant loss of nitrogen.

As well as the use of diazomethane in the synthesis of 2-(carboxymethyl)aziridines via addition of carbenes to imines, additions of dichlorocarbene have also been described.¹⁷¹ Treatment of benzodiazepines **299** with sodium hydroxide in chloroform, in the presence of Et₃BnNCl as a catalyst, resulted in the in-situ formation of dichlorocarbene, which reacted with the imino moiety of benzodiazepines **299**. This reaction led to selective formation of the corresponding tricyclic dichloroaziridines **300** in 80–85% yield (Scheme 71).

Scheme 70



Scheme 72



The addition reaction with dichlorocarbene was also performed with compound 301 under similar reaction conditions and afforded the corresponding polycyclic dichloroaziridine 302 in 45% yield (Scheme 72).¹⁷¹

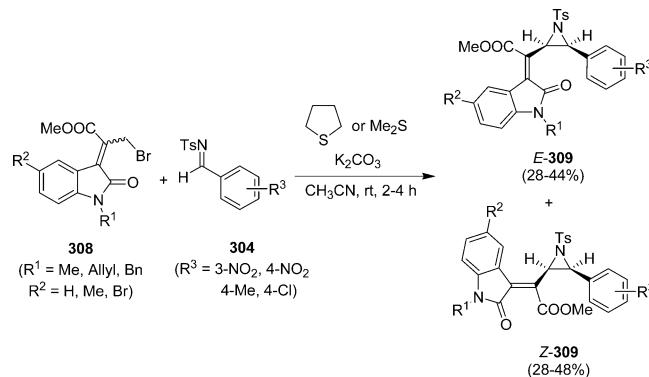
2.4.2. Synthesis through Reaction with Sulfur Ylides.

In the next part, synthesis of 2-(carboxymethyl)aziridines via addition of sulfur ylides to imines is described.^{172–174} Application of the well-known ylide chemistry in aziridination reactions^{175–179} resulted in synthesis of *N*-tosyl-2-(carboxymethyl)aziridines 307 via reaction of *N*-tosylimines 304 and functionalized allyl bromides 303.^{172,173} Hereby, *N*-tosylimines 304 and compounds 303 reacted in the presence of dimethyl sulfide and K₂CO₃ to afford the corresponding *N*-tosyl-2-(carboxymethyl)aziridines 307 in 60–70% yield as an inseparable mixture of *cis* and *trans* diastereomers (Scheme 73).

In a similar manner, treatment of an *E/Z* mixture of bromo compounds 308 with dimethyl sulfide or tetrahydrothiophene as sulfur source, K₂CO₃, and *N*-tosylimines 304 furnished a 1:1 mixture of *E/Z* isomers of alkenylaziridines *E*-309 and *Z*-309 in very good combined yields, which were separated by means of silica gel column chromatography (Scheme 74).¹⁷⁴

In conclusion, some examples were presented on the synthesis of 2-(carboxymethyl)aziridines via addition reaction of electron-deficient carbenes to imines. Both diazomethane and dichlorocarbene have been used for this purpose; however, due to the high reactivity of these carbenes, the desired 2-(carboxymethyl)aziridines were mostly isolated in lower yields from complex reaction mixtures. Besides, two examples were

Scheme 74



described on the synthesis of 2-(carboxymethyl)aziridines via addition reactions of sulfur ylides to imines. These reactions resulted in formation of α -functionalized 2-(carboxymethyl)aziridines in good yields and moderate diastereoselectivities.

2.5. Synthesis through Reactions of Nitrene Equivalents with Olefins (Method V)

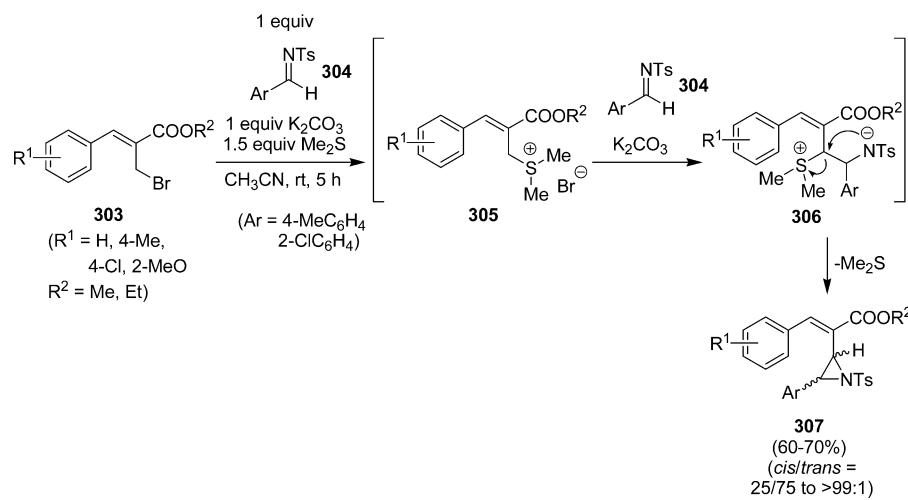
2.5.1. Synthesis through Addition of Azides Across Alkenes. Synthesis of aziridines via addition reactions of azides to olefins has gained a lot of interest in the past decades.^{180–182} Several reports have described the synthesis of 2-(carboxymethyl)aziridines via reactions of azides with α,β -unsaturated esters.^{183–194}

A first attempt to synthesize β,γ -aziridino carboxylic esters 314 involved addition of azide 311 across alkene 310, resulting in a separable mixture of regioisomers 312 and 313, but the isolated yields were not reported (Scheme 75).¹⁸³ Heating of both dihydrotriazoles 312 and 313 afforded the corresponding β,γ -aziridino carboxylic ester 314.

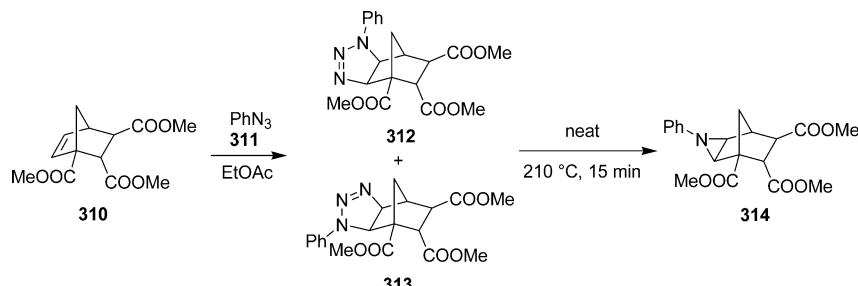
Similarly, synthesis of polycyclic *N*-benzenesulfonyl-2-(carboxymethyl)aziridines 317 via reaction of sulfonyl azide 316 with cyclic alkenes 315 resulted in formation of 2-(carboxymethyl)aziridines 317 in high yields (70–92%) (Scheme 76).^{184–187}

Efforts have also been made to synthesize the bicyclic aziridine carboxylate 320, which was formed by a photochemical reaction between compound 318 and ethyl azidoformate 319 in 20% yield (Scheme 77).¹⁸⁸

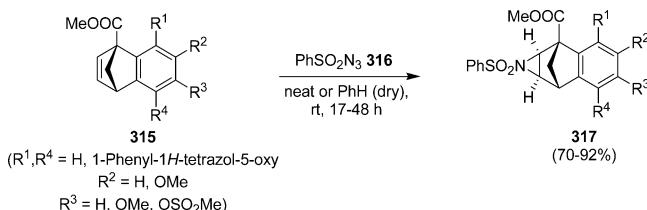
Scheme 73



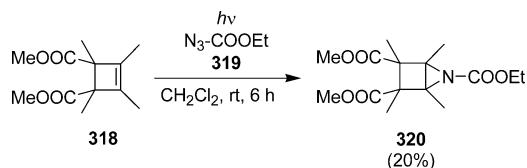
Scheme 75



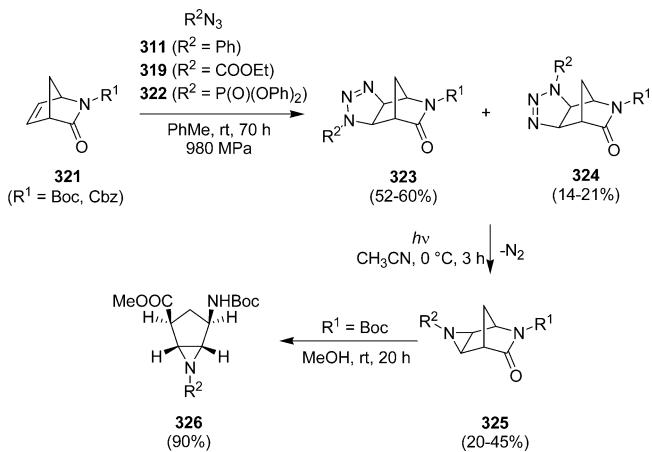
Scheme 76



Scheme 77



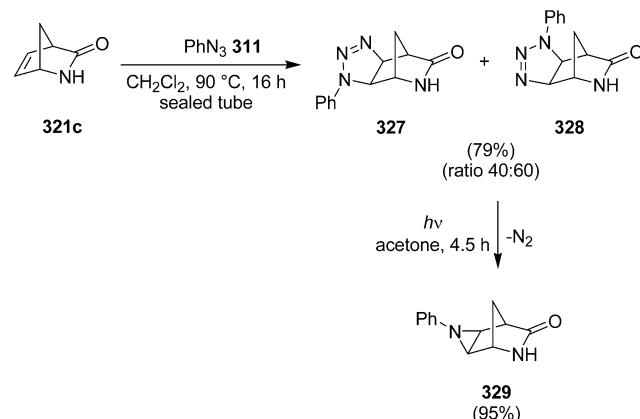
Scheme 78



Synthesis of β,γ -aziridino carboxylic esters via additions of azides to compounds 321 has also been investigated.^{190–194} Initially, bicyclic olefins 321 reacted with different azides 311, 319, and 322 via intermolecular [2 + 3] cycloaddition reactions to afford a mixture of two regioisomeric triazolines 323 and 324, which could be separated via column chromatography in good yields (Scheme 78).¹⁹⁰ However, irradiation of a mixture of both triazolines 323 and 324 afforded polycyclic 2-(carbamoylmethyl)aziridines 325 after loss of nitrogen. Subsequent ring opening of the lactam function of aziridines 325 with methanol furnished the corresponding β,γ -aziridino carboxylic esters 326 in excellent yield.

Similarly, reaction of phenyl azide 311 with the *N*-unsubstituted lactam 321c resulted in the exo-selective synthesis of two regioisomeric triazolines 327 and 328 (ratio

Scheme 79



40:60) in 79% yield (Scheme 79).¹⁹¹ Subsequent photolysis of the regioisomeric mixture gave the corresponding tricyclic 2-(carbamoylmethyl)aziridine 329 as a single stereoisomer in excellent yield (95%).

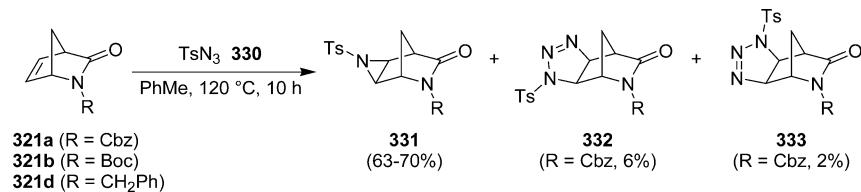
In addition, synthesis of 2-(carbamoylmethyl)aziridines 331 was performed with tosyl azide 330, as a prominent nitrene precursor, and bicyclic olefins 321 under thermal conditions.^{192,193} This thermal approach was a good alternative to the previously described cycloaddition–photolysis reaction sequence.^{190,191} Reaction of *N*-protected lactams 321 with tosyl azide 330 resulted in formation of aziridines 331 as single isomers via exocyclic addition of nitrene to the double bond of 321 (Scheme 80). It is noteworthy that reaction of the *N*-Cbz lactam 321a with azide 330 also gave rise to formation of triazolines 332 (6%) and 333 (2%) as minor products.¹⁹³

Synthesis of β,γ -aziridino carboxylic amides via reaction of bicyclic olefins with different azides was also effected under microwave conditions, with significantly reduced reaction times.¹⁹⁴ After optimization of reaction conditions, microwave irradiation of a mixture of *N*-protected lactams 321 and electron-poor azides 330 and 322 afforded the corresponding tricyclic 2-(carbamoylmethyl)aziridines 334 through nitrene–addition (Scheme 81).

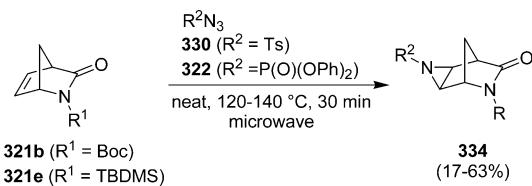
In contrast, when this optimized microwave-assisted reaction was performed with *N*-protected lactams 321 and more electron-rich azides 311 and 335 ($R^2 = Ph, Bn$), the outcome was a separable mixture of two regioisomeric triazolines 336 and 337 via a 1,3-dipolar cycloaddition reaction (Scheme 82).¹⁹⁴

A final example of this synthetic approach comprised the aziridination reaction via an intramolecular 1,3-dipolar cycloaddition of azidodienone 338.¹⁸⁹ Heating of compound 338 resulted in formation of the tricyclic aziridine 339 in 80% yield with complete regio- and stereocontrol (Scheme 83). Isolation

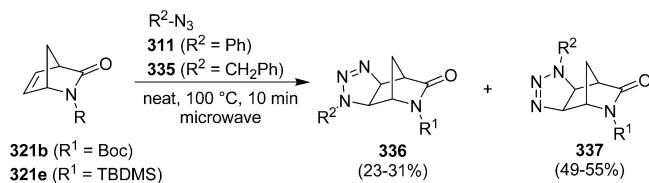
Scheme 80



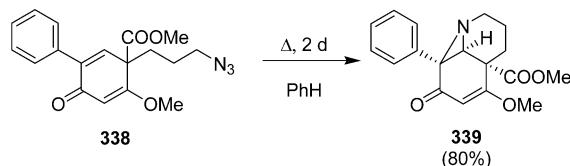
Scheme 81



Scheme 82



Scheme 83



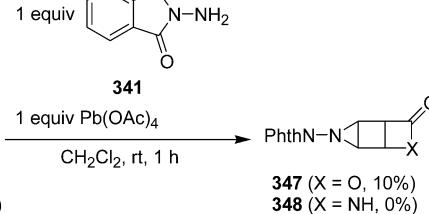
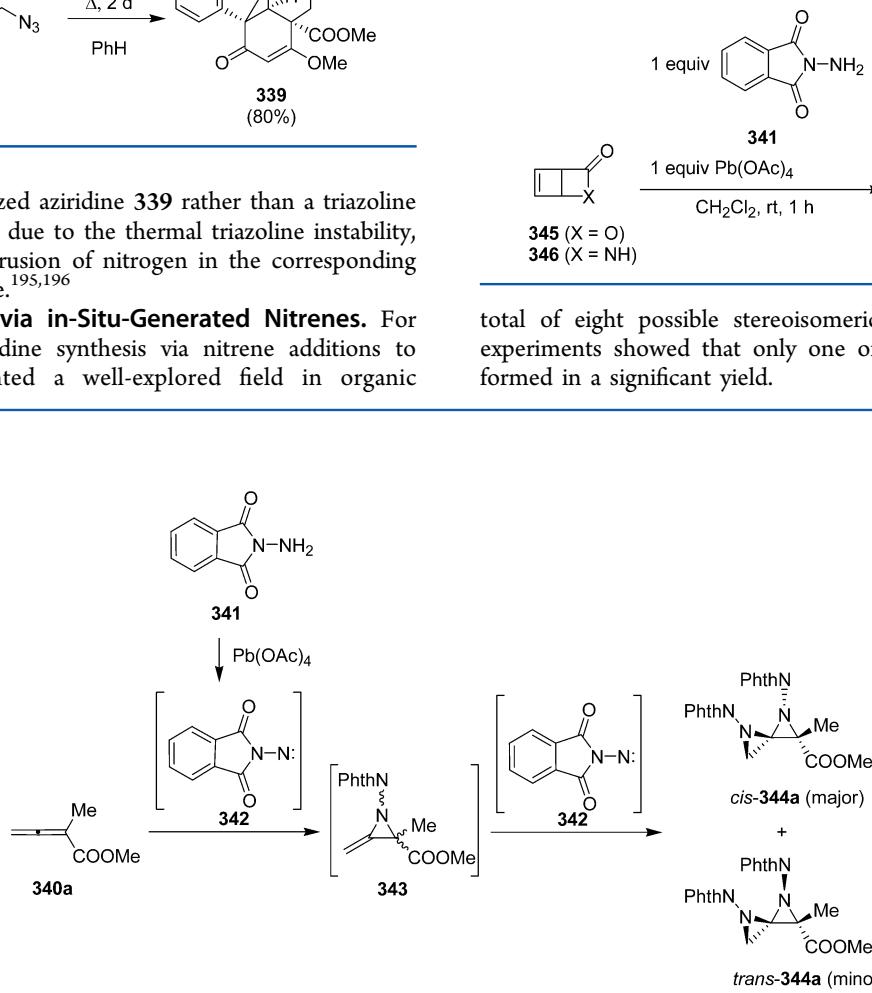
of the fully characterized aziridine 339 rather than a triazoline product was probably due to the thermal triazoline instability, which accelerated extrusion of nitrogen in the corresponding triazoline intermediate.^{195,196}

2.5.2. Synthesis via In-Situ-Generated Nitrenes. For several decades, aziridine synthesis via nitrene additions to olefins has represented a well-explored field in organic

synthesis.^{180,197–199} In order to synthesize *N*-phthalimido-2-(carboxymethyl)aziridines, generation of singlet aminonitrenes for application in cycloaddition reactions with olefins has been frequently reported.^{200–207}

A first approach of this methodology started with the generation of phthalimidonitrene 342 via oxidation of *N*-aminophthalimide 341 with $\text{Pb}(\text{OAc})_4$.^{200,208} This nitrene 342 underwent an addition reaction across the 2,3-double bond of the allenic ester 340a to afford the intermediate methylene-aziridine 343. Subsequently, addition of a second equivalent of nitrene 342 across intermediate 343 led to formation of diazaspiro[2.2]pentane 344a in 14% yield as a mixture of two invertomers *cis*-344a and *trans*-344a in a ratio of 70:30, respectively (Scheme 84).²⁰⁰ No further details about the reaction conditions or the obtained yields were presented. It is noteworthy that compound 344a exists as two diastereomers, and the capability for slow inversion at the two aziridine nitrogen centers in these two diastereomers could lead to a

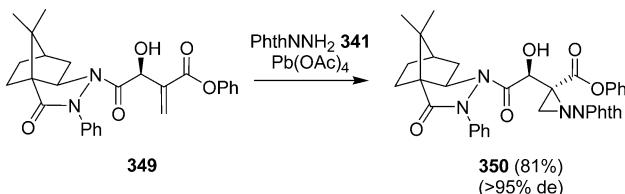
Scheme 84



total of eight possible stereoisomeric forms. In fact, NMR experiments showed that only one of the diastereomers was formed in a significant yield.

Scheme 84

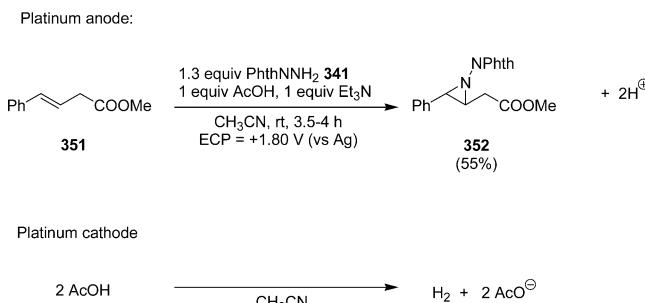
Scheme 86



Addition of a similarly generated nucleophilic phthalimidonitrene across bicyclic lactone **345** ($X = O$) and lactam **346** ($X = NH$) has also been investigated.²⁰¹ Reaction of bicyclic lactone **345** with *N*-aminophthalimide **341** and $Pb(OAc)_4$ furnished the corresponding tricyclic compound **347** in 10% yield (Scheme 85). However, performing the reaction with bicyclic lactam **346** failed to deliver the desired tricyclic aziridino lactam **348** ($X = NH$). Furthermore, reaction of the bicyclic compounds **345** and **346** with the less nucleophilic ethoxycarbonylnitrene also did not result in aziridine formation. While phthalimidonitrene has a distinct nucleophilic character, the strong electron-withdrawing group in ethoxycarbonylnitrene renders it as an electrophilic species whose reactivity is diminished to the point that it only adds to electron-rich double bonds.²⁰¹

More recently, the diastereoselective synthesis of *N*-phthalimidoaziridine **350** via addition of in-situ-generated phthalimidonitrene across α,β -unsaturated ester **349** has been reported.²⁰² Reaction of alkene **349** with *N*-aminophthalimide **341** in the presence of $Pb(OAc)_4$ provided the corresponding *N*-phthalimidoaziridine **350** in 81% yield and excellent diastereoselectivity (Scheme 86).

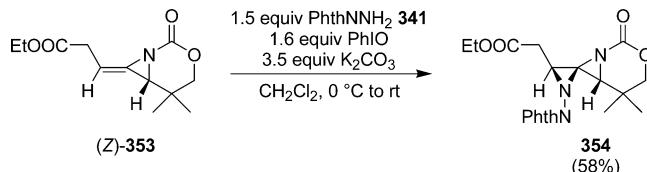
Scheme 87



In addition, electrochemical aziridination of β,γ -unsaturated ester **351** with phthalimidonitrene **342** has been explored.^{203,204} This study illustrated the possibility of a rational approach that bypasses the requirement for stoichiometric amounts of toxic oxidants and metal additives in organic redox reactions.²⁰³ The reaction was performed in an electrochemical cell, where the anodic compartment was charged with olefin **351**, *N*-aminophthalimide **341**, acetic acid, and triethylamine in acetonitrile (Scheme 87). Meanwhile, the cathodic compartment contained a solution of acetic acid in acetonitrile. Implementation of electrolysis at +1.80 V at ambient temperature delivered the *N*-phthalimido-2-(carboxymethyl)-aziridine **352** in good yield (55%) after the reaction was stopped when the cell current dropped to less than 5% of its original value.²⁰⁴

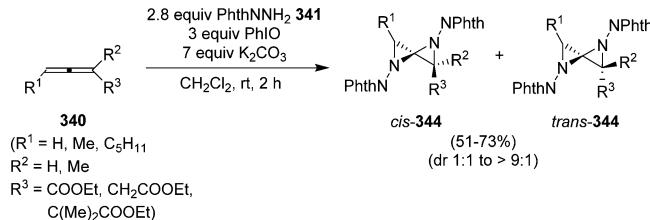
Furthermore, in-situ generation of nitrenes has been performed using hypervalent iodine reagents such as iodosylbenzene and PIDA.^{205–207,209,210}

Scheme 88



In the first study, aziridination of *Z*-alkylideneaziridine (*Z*)-**353** via reaction with *N*-aminophthalimide **341** in the presence

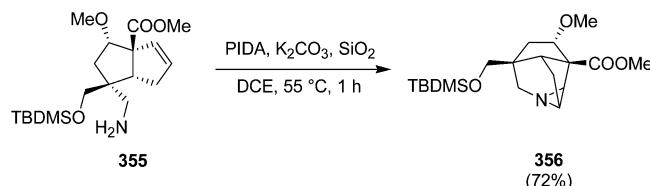
Scheme 89



of iodosylbenzene and potassium carbonate resulted in formation of bisaziridino carboxylic ester **354** in 58% yield as one single diastereomer (Scheme 88).^{205–207}

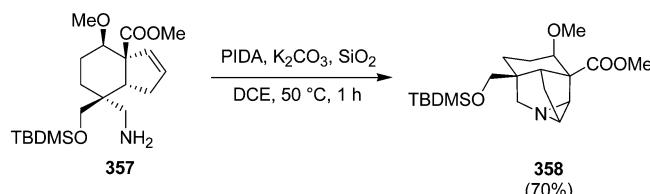
Moreover, synthesis of bisaziridino carboxylic esters **344** was also possible via reaction of allenes **340** with phthalimidonitrene **342** prepared under similar reaction conditions,

Scheme 90



affording bisaziridino carboxylic esters **344** in 51–73% as a mixture of diastereomers and invertomers (Scheme 89).²⁰⁷

Scheme 91

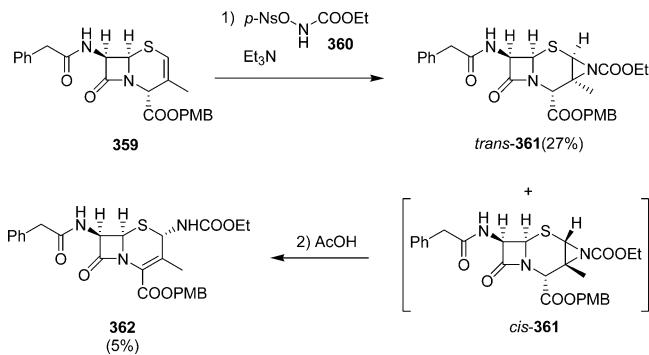


Likewise, synthesis of the bridged aziridine **356** starting from primary amine **355** via a modified Nagata intramolecular aziridination reaction has been investigated.²⁰⁹ Reaction of amine **355** in the presence of PIDA, potassium carbonate, and silica gel gave the bridged aziridine **356** selectively in 72% yield (Scheme 90).²⁰⁹

Similarly, application of the modified Nagata intramolecular aziridination method²⁰⁹ also resulted in formation of aziridine **358** in 70% yield (Scheme 91).²¹⁰

Besides the singlet nitrene-induced aziridination reactions of olefins with phthalimidonitrene **342**, synthesis of 2-

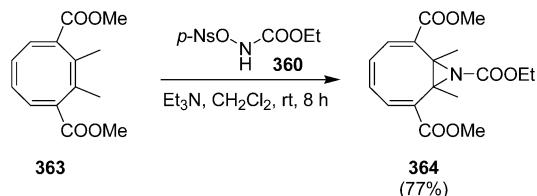
Scheme 92



(carboxymethyl)aziridines has been performed with the less nucleophilic ethoxycarbonylnitrene.^{188,211–213} Ethoxycarbonylnitrene was prepared by base-induced α -elimination of ethyl *p*-nitrophenylsulfonyloxycarbamate (Lwowski's reagent) 360 under homogeneous conditions.²¹⁴

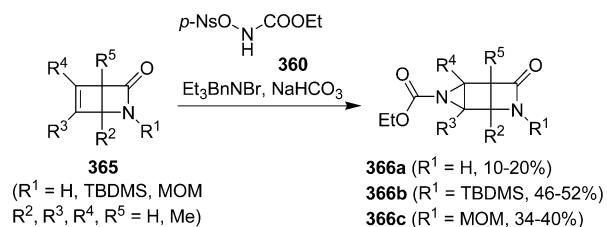
Reaction of 2-cephem 359 with compound 360 in the presence of triethylamine afforded two diastereomers *trans*-361 and *cis*-361 of the tricyclic 2-(carboxymethyl)aziridine (Scheme 92).²¹¹ Subsequent treatment of the diastereomeric mixture of tricyclic compound 361 with acetic acid resulted in a ring

Scheme 93



opening of compound *cis*-361 via an antiperiplanar elimination reaction. Finally, tricyclic 2-(carboxymethyl)aziridine *trans*-361 was obtained in 27% yield after purification.

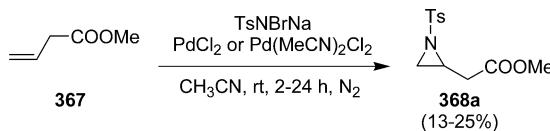
Scheme 94



In a similar manner, aziridination of compound 363 by use of Lwowski's reagent 360 has been reported under comparable reaction conditions.¹⁸⁸ Reaction of compound 363 with *p*-nitrophenylsulfonyloxycarbamate 360 in the presence of triethylamine afforded bicyclic aziridine 364 in 77% yield (Scheme 93).

In a further study, reaction of compounds 365 with ethoxycarbonylnitrene, generated from Lwowski's reagent 360 by treatment with benzyltriethylammonium bromide and sodium bicarbonate, was described (Scheme 94).^{212,213} In the absence of an *N*-protecting group, the corresponding tricyclic aziridine 366a could only be isolated in low yields (10–20%), while use of *N*-TBDMS and *N*-MOM-protecting groups

Scheme 95



afforded tricyclic compounds 366b,c in significantly improved yields (34–52%).

Along with aziridination reactions via in-situ-generated phthalimidonitrene and ethoxycarbonylnitrene across olefins, palladium(II)-mediated aziridination of olefins with bromamine-T has been employed.²¹⁵ Reaction of olefin 367 with bromamine-T in the presence of PdCl₂ or Pd(MeCN)₂Cl₂ afforded the corresponding *N*-tosyl-2-(carboxymethyl)aziridine 368a in low yield (13–25%) (Scheme 95).

2.5.3. Miscellaneous Synthesis. Synthesis of aziridines via a three-component one-step methodology has been accomplished using a *N*-heterocyclic carbene (NHC) catalyst.^{216,217} It was found that benzaldehyde 369a, nitrosobenzene 370, and dimethyl itaconate 371 as Michael acceptor reacted in the presence of an NHC catalyst, generated from the triazolium salt 372 and sodium hydride, with formation of the corresponding *N*-phenyl-2-(carboxymethyl)aziridine 373 in 69% yield (Scheme 96).

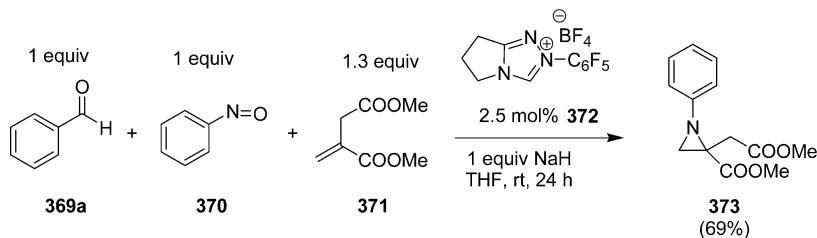
In addition, a multiple electrophilic addition reaction of *Z*-alkenes 374 and *N,N*-dibromo-*p*-toluenesulfonamide (TsNBr₂) has been reported, providing a facile and highly stereoselective synthesis of *N*-tosylaziridines 375.²¹⁸ For several decades, the utility of TsNBr₂ as an electrophilic reagent has been demonstrated as it is a simple and an efficient source of a bromonium ion. In addition, this reagent could also provide a sulfonamide as the nucleophilic component to construct C–N bonds, which made TsNBr₂ a good aminobromination reagent.^{219–225}

Treatment of *Z*-alkenyoates 374 with TsNBr₂ in the presence of potassium carbonate furnished aziridines 375 in moderate to good yields and very high diastereomeric ratios (Scheme 97). In addition to formation of aziridines 375, small amounts of *N*-tosyl-2-(carboxymethyl)aziridine 376a (R¹ = Ph) were also detected, resulting most probably from the presence of a small amount of water. Therefore, the reaction was performed in the presence of 10 equiv of water, resulting in 58% yield of 375 and a somewhat larger amount of 376 (7%). Furthermore, it was found that the presence of K₂CO₃ was crucial, as the use of other bases (Li₂CO₃, Na₂CO₃, or no base) failed to provide aziridines 375 or 376, as this reaction delivered tribromo compound 377 as the final product.

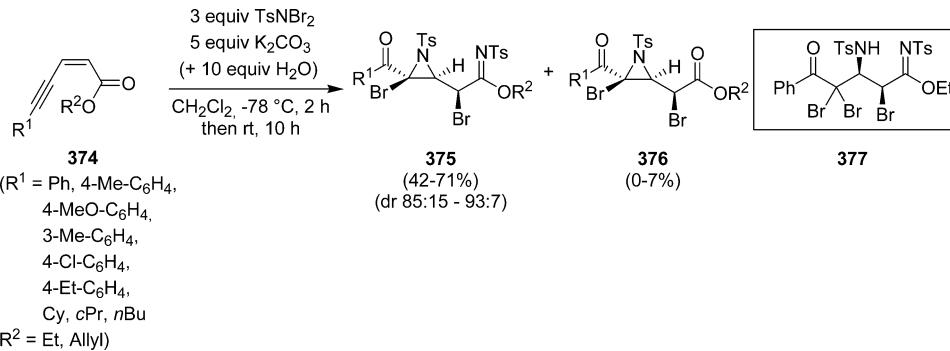
Furthermore, synthesis of 2-(carboxymethyl)aziridine 380 has been performed via a copper(II) triflate-catalyzed aziridination of 1,3-dicarbonyl compound 378 with PhI=NTs 379.²²⁶ This approach included reaction of β -ketoester 378 with iodinane 379 in the presence of catalytic amounts of Cu(OTf)₂, 1,10-phenanthroline, and 4 Å molecular sieves (Scheme 98). The resulting aziridine 380 was obtained in 85% yield as one single diastereomer.

In conclusion, a large number of literature examples of the synthesis of 2-(carboxymethyl)aziridines via addition reactions of nitrenes or nitrene equivalents across olefins was described in this part. In a first approach, 2-(carboxymethyl)aziridines were synthesized via photolytic or thermal reactions of functionalized azides with unsaturated esters or amides in acceptable to high yields. Additionally, it could be observed that

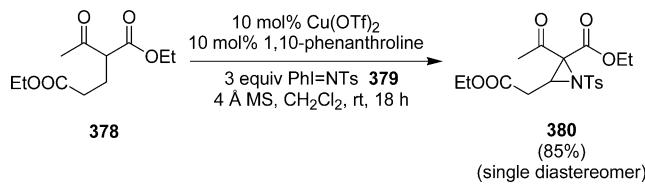
Scheme 96



Scheme 97



Scheme 98



addition reactions of nucleophilic as well as electrophilic nitrenes across olefins provided a variety of substituted 2-(carboxymethyl)aziridines in moderate to good yields.

2.6. Functional Group Transformations

2.6.1. Enantioselective Synthesis Starting from the Chiral Pool (Method VIa). In this part, synthesis of 2-(carboxymethyl)aziridines via functional group transformation starting from products from the chiral pool is described.^{32,227}

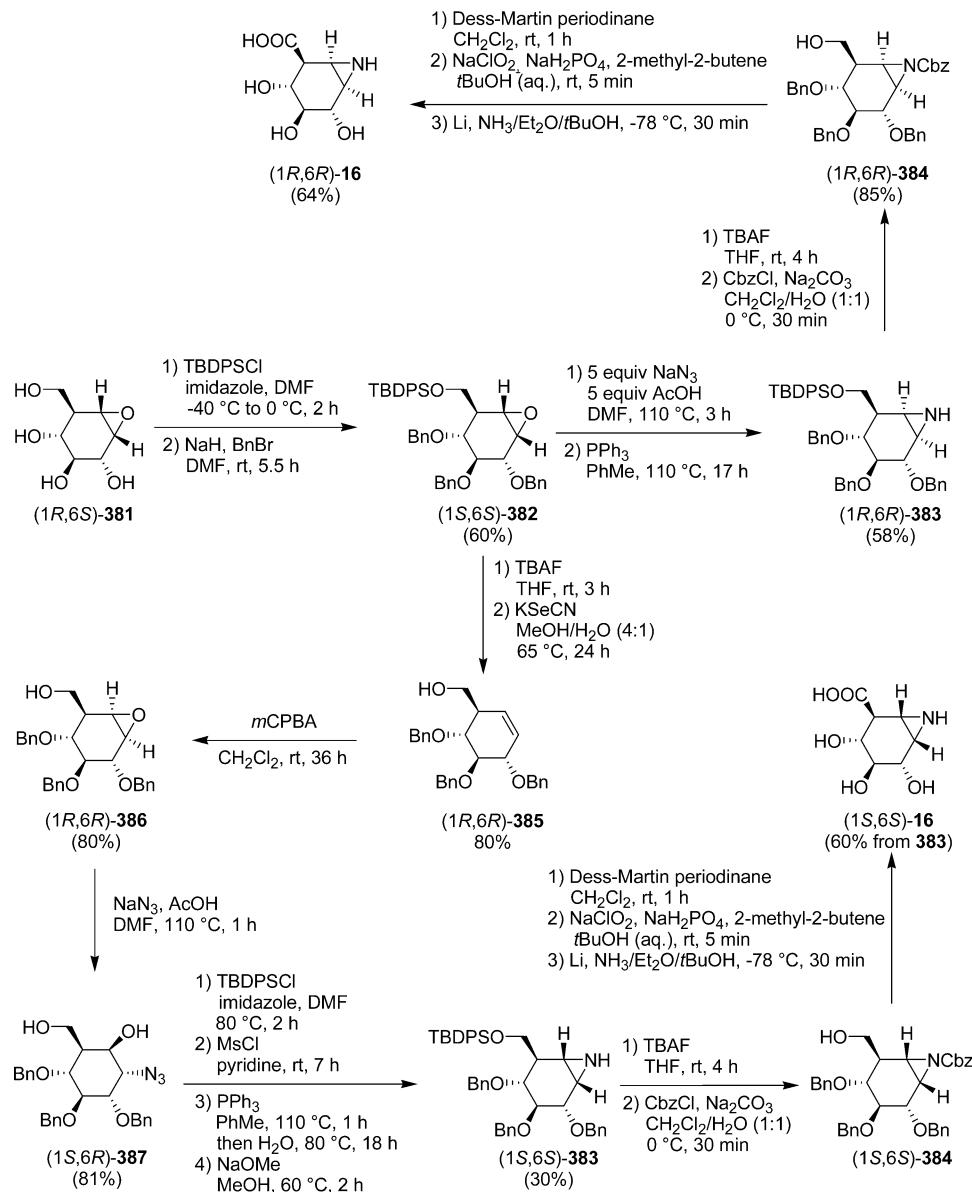
In a first study, the use of (*1R,6S*)-cyclophellitol 381 in the synthesis of two enantiopure aziridines (*1R,6R*)-16 and (*1S,6S*)-16 has been demonstrated.³² Synthesis of the aziridino cyclophellitol carboxylic acid analog (*1R,6R*)-16 started with a two-step protection of the four hydroxyl groups of (*1R,6S*)-381 with TBDPSCl and benzyl bromide, respectively (Scheme 99). The epoxide functionality of the resulting protected compound (*1S,6S*)-382 underwent subsequent ring-opening reaction with sodium azide in the presence of acetic acid and gave the corresponding azide as the sole product, which was directly subjected to reductive aziridination with triphenylphosphine to afford a single aziridine (*1R,6R*)-383 in moderate yield. Desilylation with TBAF followed by Cbz protection of the amino group resulted in compound (*1R,6R*)-384 in 85% yield. As direct oxidation of this compound 384 with $\text{RuCl}_3-\text{NaIO}_4$ failed, a stepwise oxidation with Dess–Martin periodinane and NaClO_2 was necessary to obtain the corresponding carboxylic acid. Subsequently, the resulting carboxylic acid was *O*-debenzylated to afford bicyclic 2-(carboxymethyl)aziridine (*1S,6S*)-16 in good yield.

Next, the enantiomeric aziridine (*1S,6S*)-16 was prepared from the *O*-protected epoxide (*1S,6S*)-382 (Scheme 99). Desilylation of compound (*1S,6S*)-382 with TBAF followed by deoxygenation with KSeCN provided olefin 385 in 80% overall yield. Stereoselective epoxidation of 385 with *m*CPBA gave epoxide (*1R,6R*)-386 in 80% yield, after which ring opening with sodium azide and acetic acid afforded the diaxially opened azide (*1S,6R*)-387 in 81% yield as the sole product. Since direct aziridine formation after silylation of (*1S,6R*)-387 with TBDPSCl was not successful, a stepwise procedure was required. Thus, mesylation with MsCl , reduction with triphenylphosphine, and base-induced cyclization with sodium methoxide afforded the desired aziridine (*1S,6S*)-383 in 30% overall yield. By the same procedure used in the transformation of (*1R,6R*)-383 to (*1R,6R*)-16, (*1S,6S*)-383 was converted to bicyclic 2-(carboxymethyl)aziridine (*1S,6S*)-16 via (*1S,6S*)-384 in 60% overall yield.

cis-Aziridino-L-proline 394, a bicyclic 2-(carboxymethyl)-aziridine, has also been synthesized via functional group transformations starting from *S*-pyroglutamic acid 388.²²⁷ Azidoprolinol derivative 389, derived from *S*-pyroglutamic acid 388, has been shown to be an ideal precursor for the synthesis of aziridinoproline 394 (Scheme 100). Initially, the primary alcohol function was selectively protected as the TBDPS ether, which gave compound 390 upon hydrogenation in the presence of Boc_2O . Subsequent reaction of alcohol 390 with mesyl chloride resulted in formation of the corresponding mesylate 391 in excellent yield. Cyclization to the fully protected *cis*-aziridinoprolinol derivative 392 was achieved with potassium carbonate in 87% yield. After *O*-desilylation of 392 and oxidation of the primary alcohol function with $\text{RuCl}_3-\text{NaIO}_4$, aziridinoproline 394 was obtained in low yield (35%).

2.6.2. Multicomponent Reactions (Method VIb). Recently, synthesis of 2-(carboxymethyl)aziridines incorporated in a cyclic peptide structure, via a multicomponent reaction strategy, has been extensively investigated.^{33–42} This synthetic pathway was achieved by means of the Ugi condensation, which is known to proceed through a series of reversible trans-

Scheme 99



formations that are driven by formation of the thermodynamically more stable amide bond.^{33–36} Performing this multicomponent reaction with α -amino acids 397, unprotected 2-formylaziridines 395, and isocyanide 398 resulted in formation of bicyclic piperazinones 399 in high yields and excellent diastereoselectivity (Scheme 101). It should be mentioned that the 2-formylaziridines 395 exist as homochiral dimers 396, which were in equilibrium with the corresponding monomers 395 when dissolved in a variety of solvents.³⁵ This synchronized Ugi reaction was also successfully accomplished via application of digital microfluid technology.³⁶

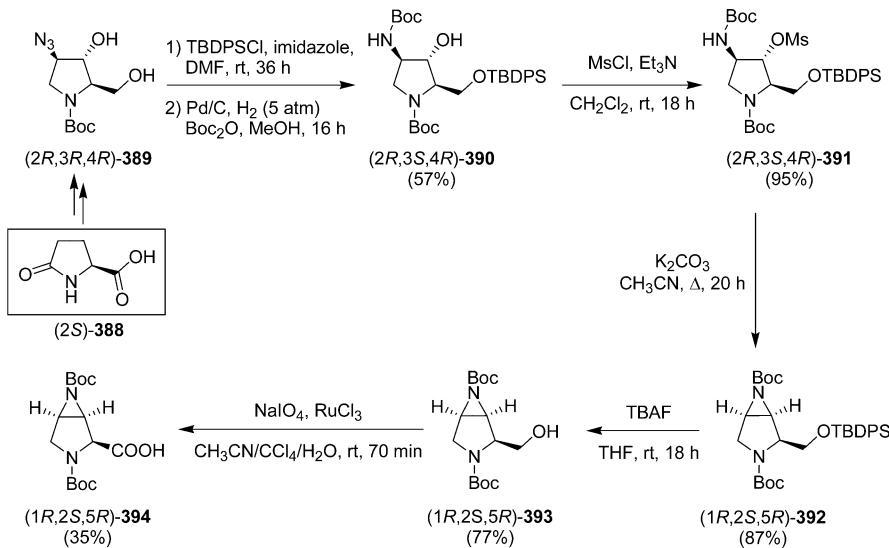
In addition, the influence of the peptide chain length on the selectivity of the Ugi condensation has been evaluated.^{33–38} Performing this reaction with small linear peptides 400 afforded the corresponding medium-sized rings 401, again in high yields and diastereoselectivities (Scheme 102). Furthermore, no racemization has been detected throughout the course of the reaction or during product isolation. The lack of epimerization was further evidenced by the high stereoselectivity of the reaction, as (2S)-2-formylaziridines 395 underwent macro-

cyclization with the peptides that contained an L-amino acid residue at the N-terminus. The “mismatched” reaction with the D-amino acid terminated peptide is unproductive and led only to formation of stable aminals.^{33,34}

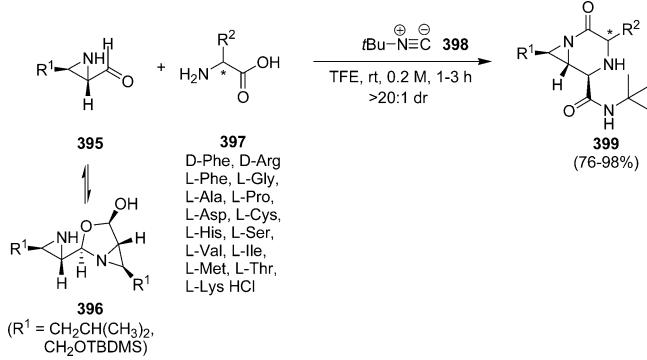
The Ugi reaction has also been performed using more functionalized isocyanides.^{39,40} In the first report, the Ugi condensation was performed with an isocyanide incorporating a solvatochromic group.³⁹ The use of the 4-DMN-labeled isocyanide 402 in this multicomponent reaction resulted in selective formation of a series of fluorescent cyclic peptides 404 in moderate to high yields and diastereoselectivities via reaction with the 2-formylaziridine dimers 396 and peptides 403 (Scheme 103). It is noteworthy that the use of non-proteinogenic β - and γ -amino acids in the Ugi reaction under the latter conditions afforded the corresponding 7- and 8-membered rings, respectively, also in good to high yields (67–93%).³⁹

In a similar manner, Ugi condensation with small linear peptides 403, 2-formylaziridine dimer 396a, and thioester-functionalized isocyanides 405 and 406 has also been reported

Scheme 100



Scheme 101



(Scheme 104).⁴⁰ Attempted optimization of the reaction conditions showed that temperature variations or addition of inorganic salts did not improve the yields. However, the use of HFIP as solvent resulted in better yields for both isocyanides 405 and 406.

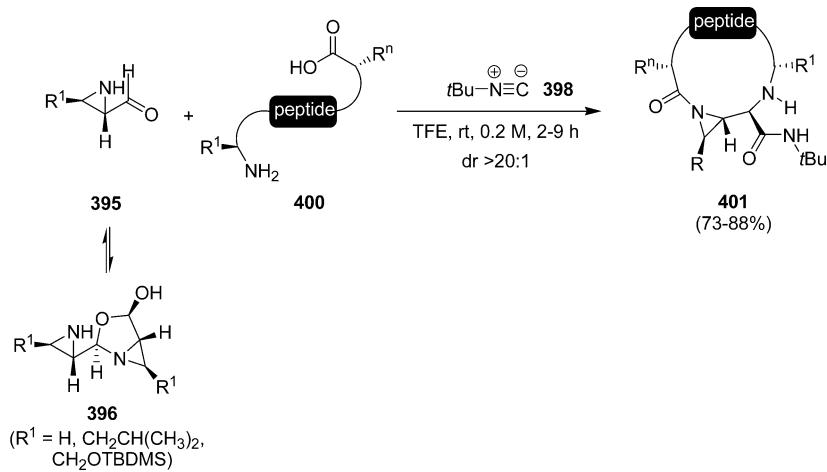
Moreover, it has been reported that the use of catalytic amounts of aryl boronic acids as an additive in the Ugi reaction

significantly decreased the reaction times.⁴¹ For example, it has been shown that the use of 10 mol % of phenylboronic acid, as catalyst, resulted in short reaction times in the highly diastereoselective formation of the corresponding macrocyclic 2-(carboxymethyl)aziridine derivatives 409 with good to high yields (Scheme 105).

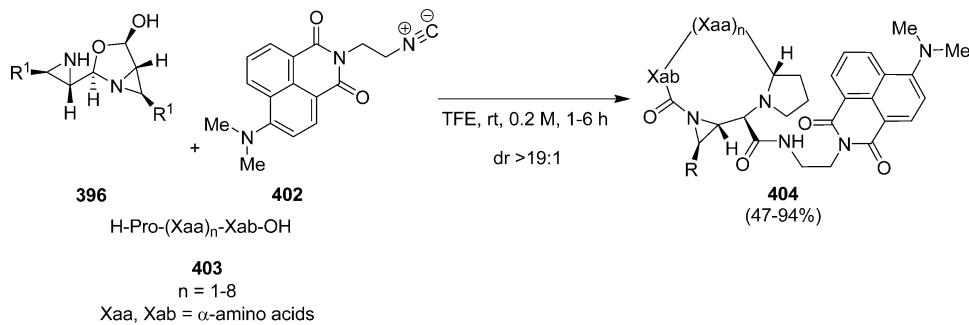
Finally, 2-formylaziridine dimers 396 were also subjected to a homo-Ugi 4-component-5-center reaction.⁴² Unlike the previously described Ugi-type 3-component-5-center reactions, the α-amino acids 397 were replaced by untethered amines 410 and carboxylic acids 411. Performing this multicomponent reaction with carboxylic acids 411, unprotected 2-formylaziridines 396, secondary amines 410, and isocyanides 398, 402, 405, and 406 afforded the “intercepted Ugi” products 413 in good to high yields (Scheme 106, path a). Surprisingly, use of primary amines in the homo-Ugi 4-component-5-center reaction did not afford the β,γ-(acylaziridino)-α-aminoamides 413 but the corresponding “unintercepted Ugi” products 414 via an intramolecular rearrangement (Scheme 106, path b).

In addition, when these multicomponent reactions were performed in the absence of an amine, a Passerini reaction was observed, which led to rapid formation of compounds 415,

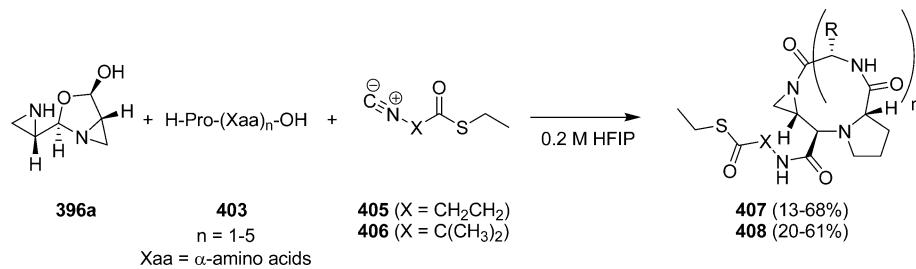
Scheme 102



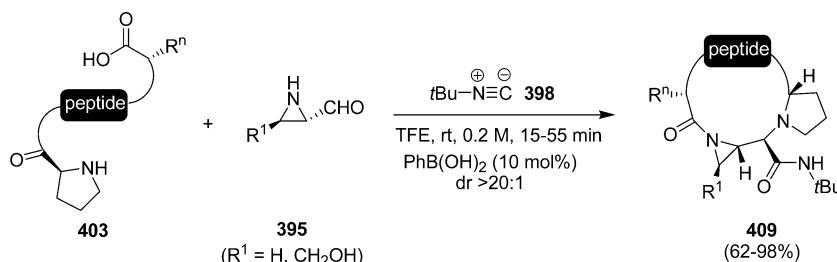
Scheme 103



Scheme 104



Scheme 105



nearly at a comparable rate as for synthesis of the intercepted Ugi products (Scheme 107).⁴²

In conclusion, synthesis of 2-(carboxymethyl)aziridines was effectuated via functional group transformations of compounds derived from the chiral pool or starting from 2-formylaziridines. Two examples were presented on the efficient and enantioselective synthesis of 2-(carboxymethyl)aziridines via modifications of the chiral starting materials cyclophellitol and S-pyroglutamic acid (method VIa). Stereoselective synthesis of 2-(carboxymethyl)aziridines was also disclosed involving multi-component reactions (Ugi and Passerini reaction), affording a variety of new enantiopure functionalized 2-(carboxymethyl)aziridines in moderate to high yields (method VIIb).

2.7. Miscellaneous

Synthesis of polycyclic 2-(carboxymethyl)aziridine derivatives via photochemical rearrangements has been extensively reported in the literature.²²⁸⁻²³³

In a first report, irradiation of benzazocine derivative 416 through a Corex filter gave a mixture of tricyclic aziridine 418 (43%), formamide 421 (14%), and naphthalene 420 (23%) (Scheme 108).^{228,229} Herein, formation of tricyclic aziridine 418 was considered to proceed via a [1,2]-shift of the acyl group. The mechanistic rationalization for formation of competing compounds 420 and 421 involved a photoinduced ring opening to ketene 422 followed by recyclization and subsequent hydrolysis during aqueous workup.^{228,229}

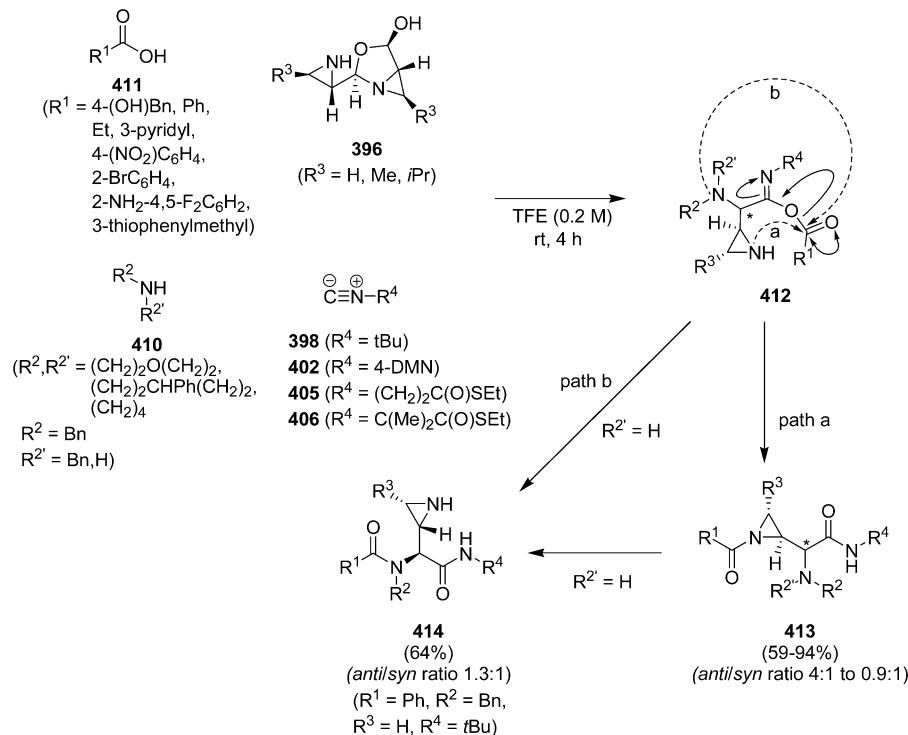
Similarly, photolysis of benzazocine derivative 417 through a Corex filter afforded tricyclic aziridine 419 as the major photoproduct in 61% yield (Scheme 108).²²⁹ The proposed reaction mechanism also proceeded via a [1,2]-acyl shift.

Irradiation of compounds 424 in the presence of alkenes 425 through a Vycor filter resulted in formation of tricyclic aziridines 427 as the only isolated products in 24–45% yield (Scheme 109).^{230,231} This outcome was in contrast with the results obtained by cycloaddition of these compounds 424 and 425 via irradiation through a Pyrex filter, which afforded only the expected [2 + 2]-cycloaddition products 426 in good to high yields (76–91%). Moreover, irradiation of these bicyclic cyclobutanes 426 through a Vycor filter also gave tricyclic aziridines 427 by photoisomerization. Interestingly, irradiation of compound 424b in the presence of alkenes 425 gave only the [2 + 2]-cycloaddition products 426, regardless of the type of filter used.²³¹

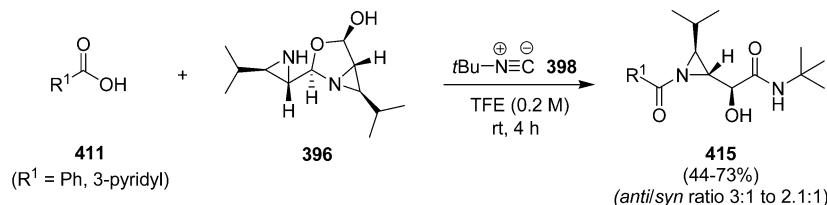
In another study, the ring transformation of 1-Dewar-pyridines 428 upon irradiation has been investigated.^{232,233} Irradiation ($\lambda = 280-370$ nm) of 1-Dewar-pyridine 428 resulted in formation of azaprismanes 429 via a highly selective, intramolecular [2 + 2]-cycloaddition reaction in 35–92% yield (Scheme 110).

A similar outcome has been reported for reaction of spirocyclic diazirine 431 and the kinetically stabilized cyclobutadiene 430.²³⁴ The [4 + 2]-cycloaddition of azo compound

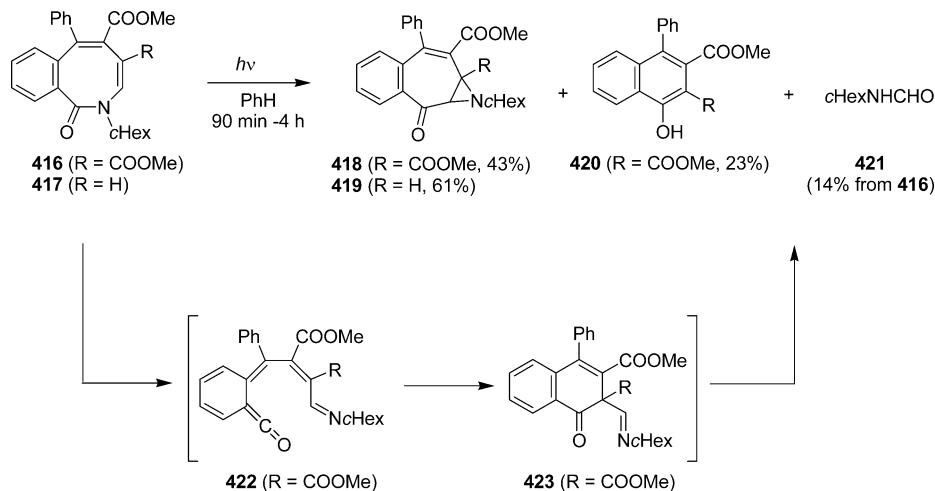
Scheme 106



Scheme 107



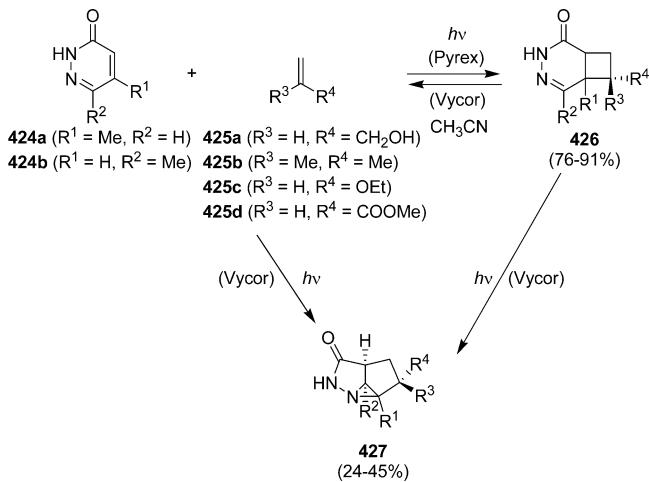
Scheme 108



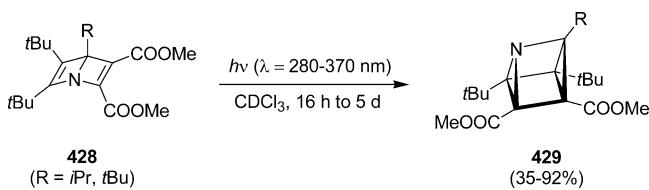
431 and diene 430 resulted, via intermediate 432, in formation of a mixture of 2*H*-1,3-diazepine 433 and 1,4-diazaquadricyclane 434, which were isolated in 39% and 15% yield, respectively (Scheme 111). On the basis of steric implications, a plausible reaction mechanism for formation of aziridine 434 has been proposed.²³⁴

Synthesis of a spirocyclic aziridine 436 has been shown to be possible via thermal decomposition of compound 435.²³⁵ Heating of compound 435 above 70 °C in various solvents such as DMF, toluene, acetonitrile, and isobutanol furnished spirocyclic aziridine 436 by thermal decomposition (Scheme 112). This aziridine, which was a result of a dimerization

Scheme 109



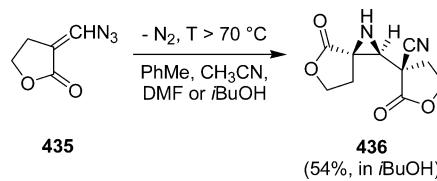
Scheme 110



reaction, was obtained in a moderate yield and with excellent stereoselectivity.

Surprisingly, synthesis of tricyclic aziridines **439** has also been performed via an α -arylation/dehydrogenation/Diels–Alder sequence with *N*-arylamino esters **437**.²³⁶ The reaction sequence started with a palladium-catalyzed synthesis of 1-isoindolecarboxylic acid esters, which were, due to their instability, directly treated with dimethyl acetylenedicarboxylate **55** (Scheme 113). Along with formation of the expected Diels–Alder adducts **438**, tricyclic aziridines **439** were also isolated in low yields (23–35%). The reaction mechanism for formation of **439** was explained by the participation of nitrenium intermediates **440**, originating from Diels–Alder adducts **438**.

Scheme 112



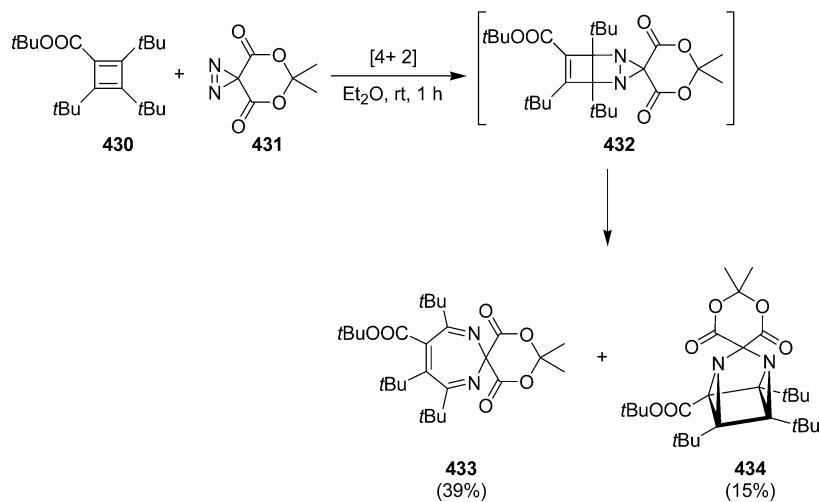
In addition, the dirhodium(II)-catalyzed [3 + 2]-cycloaddition of enol diazoacetates **441** and benzonitrile *N*-oxides **442** affording bicyclic aziridines **443** has also been investigated.²³⁷ The cycloaddition reaction of compounds **441** with nitrile oxides **442** bearing electron-withdrawing substituents in the presence of a dirhodium(II) catalyst resulted in formation of isoxazoline intermediates, which underwent directly a Neber rearrangement to afford the corresponding bicyclic aziridines **443** in good to excellent yields (57–92%) (Scheme 114). Interestingly, application of nitrile oxides **442** with electron-donating substituents resulted in a Lossen rearrangement of the isoxazoline intermediates which afforded compounds **444** in good yields.²³⁷

3. REACTIVITY OF 2-(CARBOXYMETHYL)AZIRIDINES

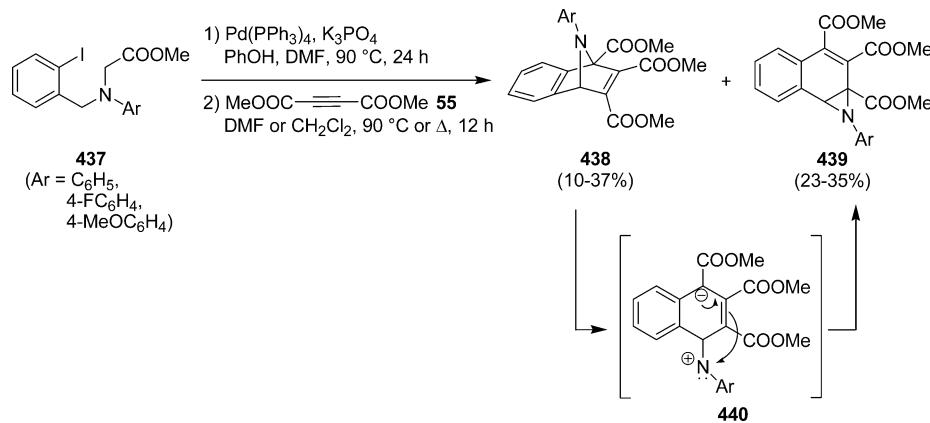
As a first part of this reactivity overview, some representative examples will be given regarding the stability of the 2-(carboxymethyl)aziridine moiety, present in more complex molecules, under certain reaction conditions.

With the aim of synthesizing azacephams (1,5-diazabicyclo[4.2.0]octan-8-ones) **445** starting from tricyclic β -lactams **244**, a controlled C(4)–N(2) cleavage of the aziridine ring was attempted (Scheme 115). To this end, aziridines **244** were subjected to various reaction conditions, but they appeared to be stable under both acidic and basic conditions with or without *N*-activation. Also, reaction of aziridines **244** with several reducing agents did not lead to formation of azacephams **445**, although β -lactam **244** was consumed. Furthermore, methanolysis of the β -lactam ring of compound **244** ($R^1 = \text{H}$, $R^2 = \text{COOtBu}$, $R^3 = \text{Me}$) in the presence of SmI_2 led to formation of the corresponding β -amino ester without affecting the carboxymethylaziridine moiety.¹⁴⁹

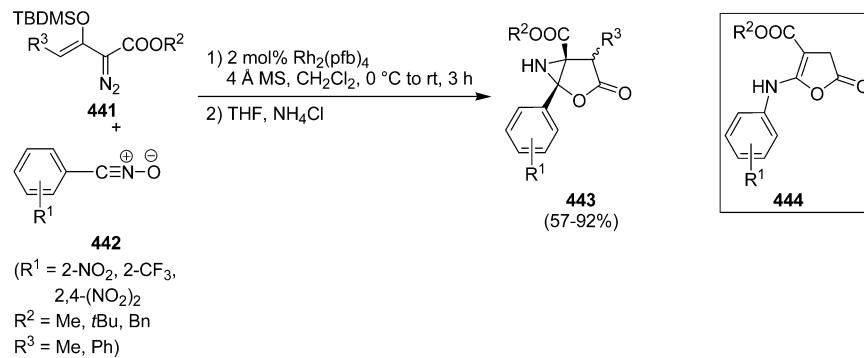
Scheme 111



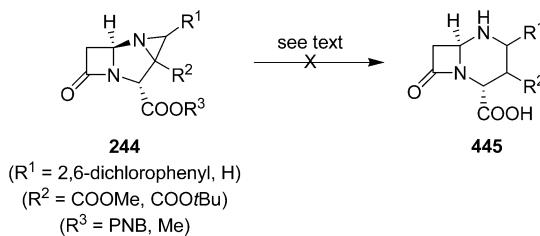
Scheme 113



Scheme 114



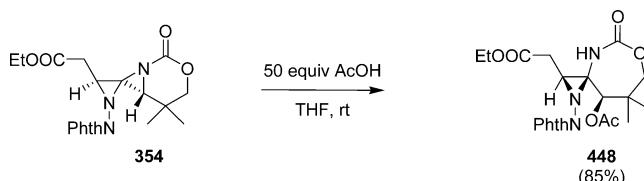
Scheme 115



A few other illustrative examples in which the aziridine ring was preserved upon treatment with a nucleophile have been reported. When bicyclic aziridine **267a** was treated with nitrogen nucleophiles, the aziridine ring remained intact while the two fluorine substituents were substituted via a tele substitution and subsequent ipso substitution affording aziridine-fused pyrroline **447**. The yield of this transformation was not mentioned.¹⁶¹

Another example concerns the preservation of the ethyl β,γ-aziridinocarboxylate moiety in compound **354** upon treatment with an oxygen nucleophile. Due to the presence of the second (activated) aziridine ring in 1,4-diazaspiro[2.2]pentane **354**, treatment of this compound with acetic acid at room

Scheme 117

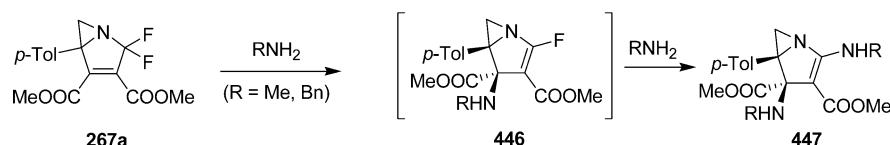


temperature furnished spiro compound **448** in 85% yield (Scheme 117). Although an excess of acetic acid was used, the carboxymethylaziridine moiety remained intact under these reaction conditions.²⁰⁵

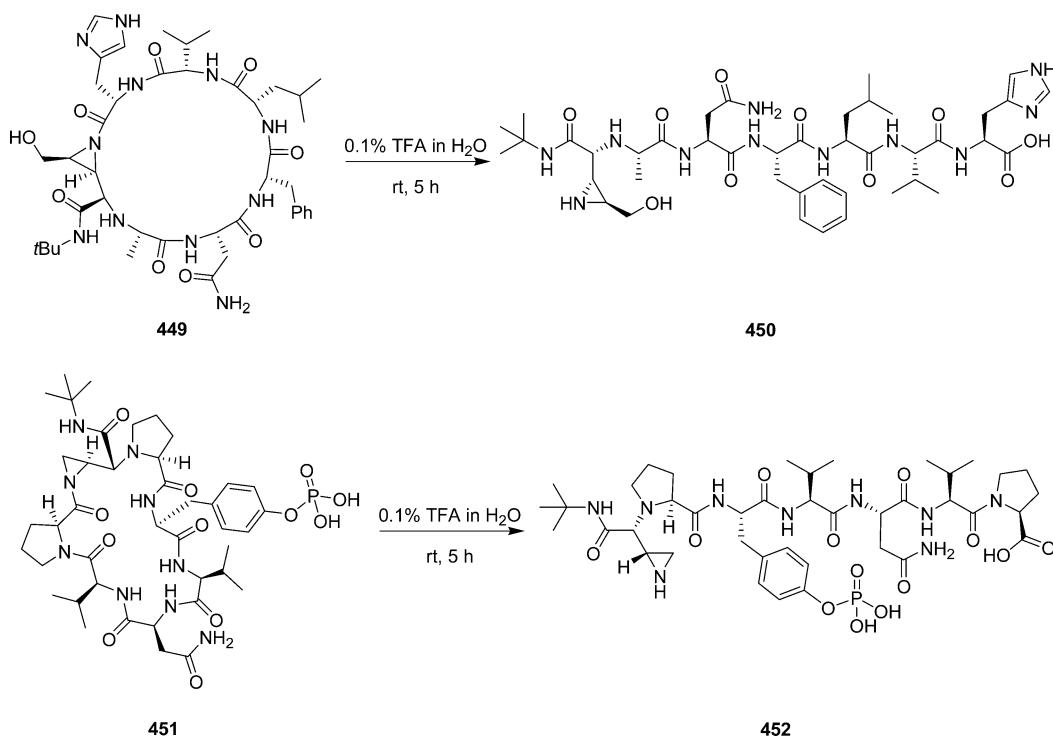
Selective hydrolysis of the aziridine amide bond of macrocyclic peptides **449** and **451** to give the linear peptides **450** and **452**, containing the unaffected 2-(carboxymethyl)-aziridine moiety at the end of the chain, is depicted in Scheme 118. The yields of these selective hydrolysis reactions were not given.⁴¹

In a study concerning the synthesis of cycle-tail peptides, ligation of macrocyclic peptide **453** with a model tetrapeptide **454** was achieved using thiophenol or 4-mercaptophenylacetic

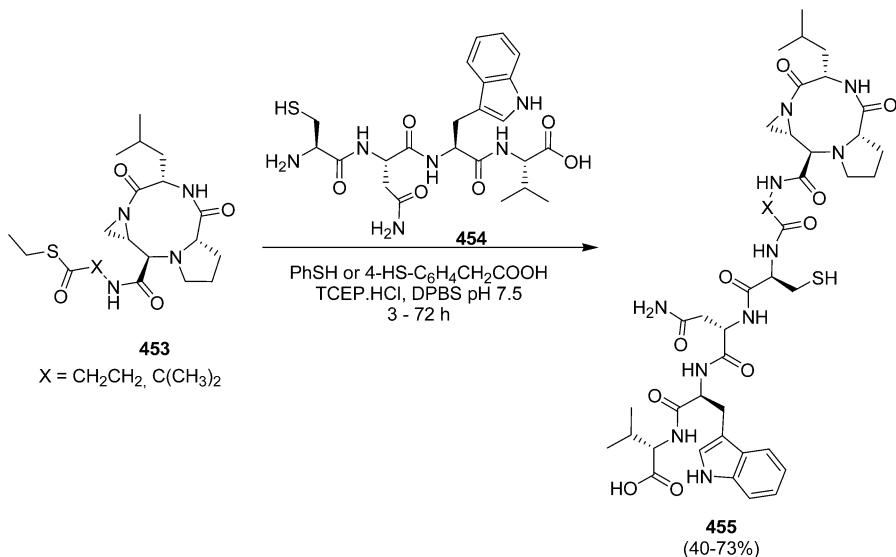
Scheme 116



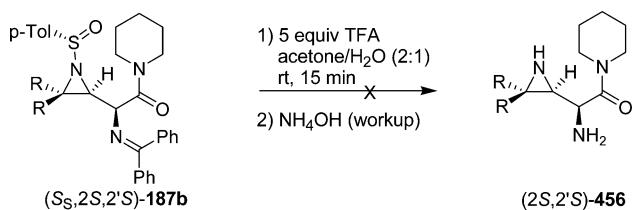
Scheme 118



Scheme 119



Scheme 120



acid as a catalyst. Remarkably, no aziridine ring opening by the thiol nucleophile was observed (Scheme 119).⁴⁰

In the previous examples, the stability of the aziridine ring under the given reaction conditions is due to the presence of a

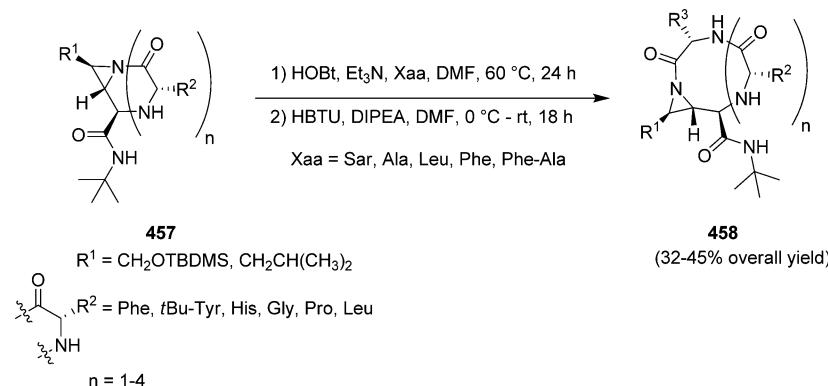
more reactive site in the molecule, for example, the presence of a leaving group or a thioester, or to the complexity of the molecule which renders the aziridine ring less reactive.

3.1. Functional Group Transformations

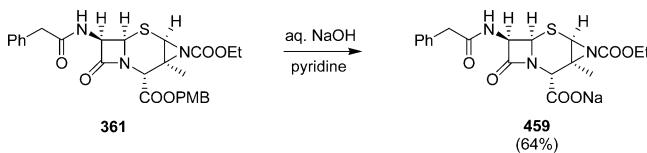
Some research has been done concerning deprotection of the aziridine nitrogen or transformation of the ester function of β,γ -aziridinocarboxylates without opening of the aziridine ring.

As described previously, synthesis of (2*R*,3*S*)- α -substituted β,γ -aziridinocarboxylic acid **15a** has been achieved starting from aspartic acid (Scheme 30). The final steps of this synthesis comprised removal of the Cbz group at nitrogen and saponification of the methyl ester. Both steps were performed without affecting the 2-(carboxymethyl)aziridine moiety.⁹⁰

Scheme 121



Scheme 122



Synthesis of the similar aziridines (*2S,3S*)-**15a** and (*2R,3R*)-**15a** was also achieved and included a Fmoc deprotection using piperidine as the final step (Scheme 31).¹⁰⁴

Deprotection of the *N*-sulfinyl aziridine **187b** with simultaneous removal of the diphenylmethylidene group in preparing enantiopure aziridine **456** has been achieved, but all attempts to purify this compound failed (Scheme 120).^{121a}

Insertion of an amino acid or a peptide fragment into the cyclic peptides **457** could also be achieved with preservation of the carbamoylaziridine moiety (Scheme 121). In a first step, the reaction between the insertion fragment and the aziridine amide moiety was carried out under HOBr catalysis, furnishing a linear fragment containing the unprotected aziridine. Recyclization of the linear peptide using HBTU yielded macrocycle **458**. These two steps, both conducted under basic conditions, could be carried out in a one-pot reaction.²³⁸

Selective saponification of *p*-methoxybenzyl ester **361** to give the corresponding sodium salt **459** has also been achieved without affecting the carbamate function and without opening of the aziridine ring (Scheme 122).²¹¹

In a synthetic route toward the synthesis of epimino-carbocyclic nucleosides **461** the transformation of tricyclic lactams **331** to amino alcohols **460** has been effectuated by treatment with sodium borohydride in methanol (Scheme 123). Under these reaction conditions, the aziridine ring remained intact. Acylation of the hydroxyl group of compounds

460 prior to coupling with 5-amino-4,6-dichloropyrimidine was necessary to avoid complex mixtures, possibly due to an intramolecular nucleophilic attack of the hydroxyl group at the aziridine ring.^{192,193}

A second example of the transformation of a 2-(carboxymethyl)aziridine to the corresponding 2-(hydroxyethyl)aziridine is depicted in Scheme 124. Treatment of aziridines **213** and **215** with an excess of MeMgBr in an attempt to achieve a ring expansion toward γ -lactams **462**, **463**, and **464** led to formation of aziridines **465**, **466**, and **467** as the major reaction products.¹³⁵

Analogously, treatment of aziridine **215c** with an excess of MeMgBr afforded a mixture of lactams **468** and **469** and ketone **470** as the major product, resulting from addition of the Grignard reagent to the ester group (Scheme 125). It is noteworthy that addition of a second equivalent of Grignard reagent to the ketone group was not observed.¹³⁵

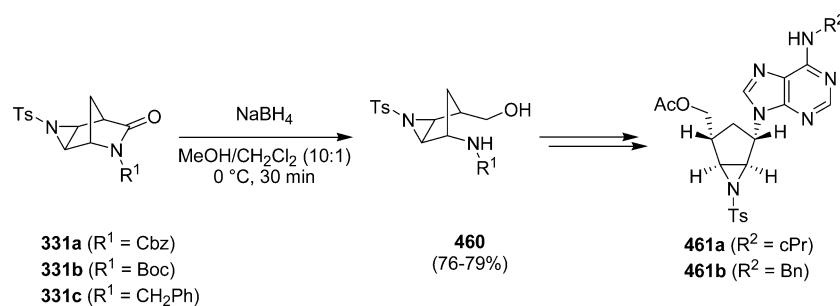
In the above-mentioned examples, the aziridine ring was preserved under certain reaction conditions. In the next sections, conversion of 2-(carboxymethyl)aziridines to five- and six-membered rings will be discussed as well as their reactivity toward oxygen, nitrogen, sulfur, and carbon nucleophiles.

3.2. Ring Expansion to Five-Membered Rings

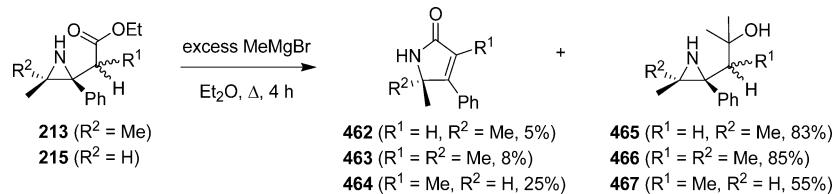
3.2.1. Lactones. As mentioned before, 3-amino-4-hydroxybutanoate **132** could be converted into 3-amino- γ -butyrolactone **11** upon treatment with hydrochloric acid (Scheme 28). 2-(Carboxymethyl)aziridines have also been converted into the corresponding γ -lactones under various reaction conditions.

Conversion of 2-(carboxymethyl)aziridines into β -amino- γ -lactones was first described in 1979. When aziridines **227** were stored in EtOH at room temperature, a ring expansion to γ -

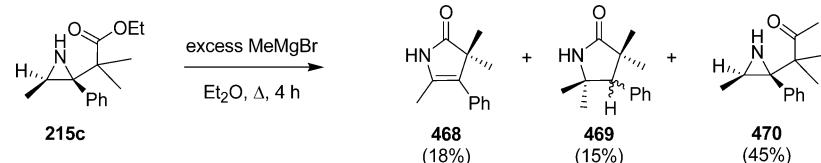
Scheme 123



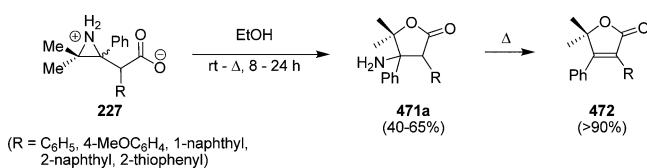
Scheme 124



Scheme 125



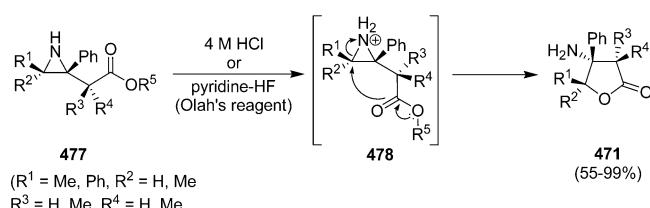
Scheme 126



lactones **467** was observed. Like most amino acids, β,γ -aziridinocarboxylic acids **227** exist in the zwitterionic form in which the aziridine nitrogen is protonated by the acid moiety. This protonation renders the aziridine ring more electrophilic and therefore more prone toward nucleophilic attack by the carboxylate anion. This intramolecular reaction leads to formation of the corresponding γ -lactones **471a** in moderate yields (Scheme 126). Heating of the solution of lactones **471a** led easily to a deamination reaction to give the α,β -unsaturated lactones **472**.^{138,139}

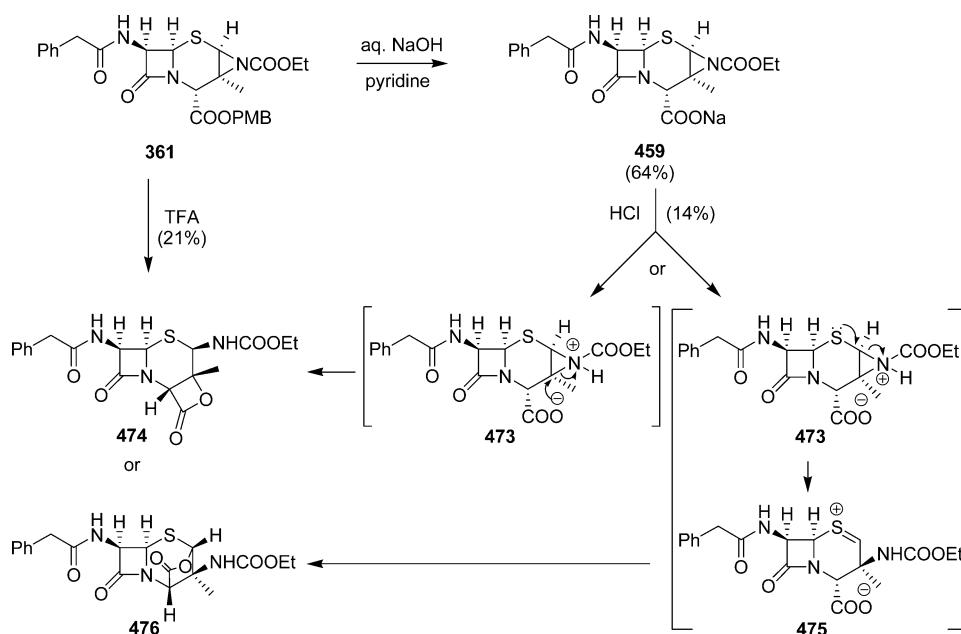
Lactonization of 2-(carboxymethyl)aziridines also occurred upon treatment of ester **361** with trifluoroacetic acid and treatment of sodium carboxylate **459** with HCl. It was unclear

Scheme 128

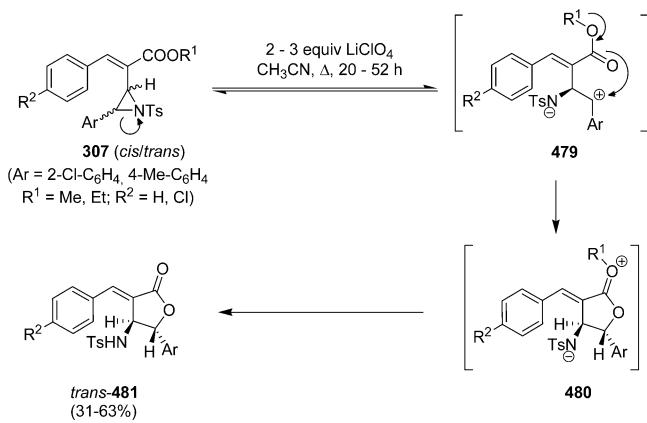


which lactone was formed during this reaction, and a possible route toward each lactone is depicted in Scheme 127. As mentioned previously, sodium carboxylate **459** was stable and could be isolated. On the other hand, acid **473** was not stable since it led to a salt with an activated aziridine ring and a carboxylate anion which can act as a nucleophile. Formation of propiolactone **474** can be rationalized via a direct ring opening of the aziridine ring at the C2 position by the carboxylate anion. In order to form butyrolactone **476**, nucleophilic attack of the carboxylate anion had to occur at the C3 position of the

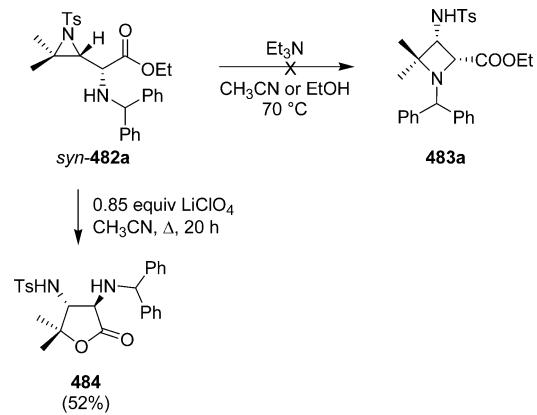
Scheme 127



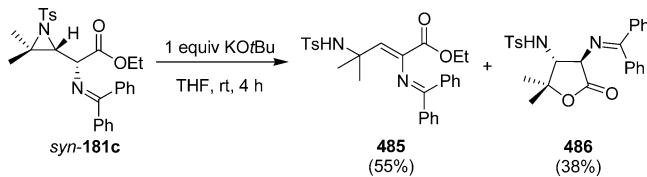
Scheme 129



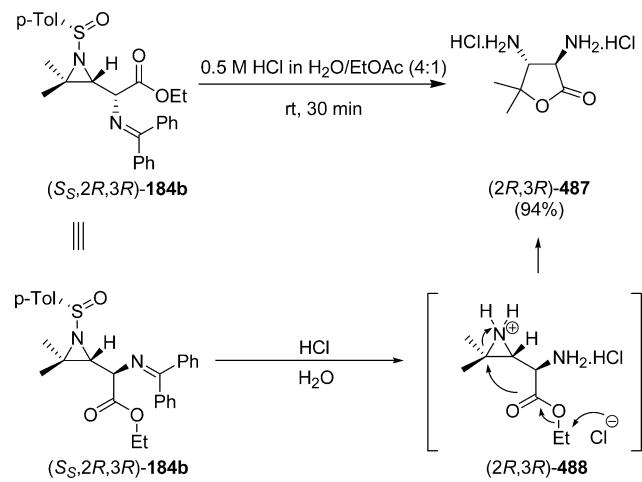
Scheme 130



Scheme 131

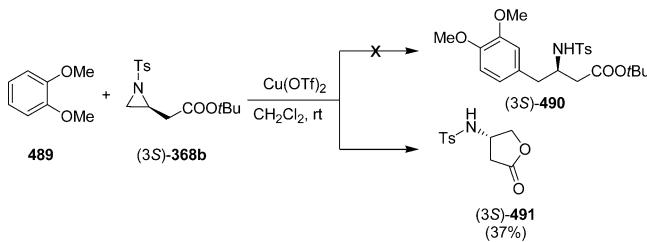


Scheme 132



aziridine. This step was assisted by the neighboring group effect of the sulfur atom, since delocalization of the lone pair on sulfur

Scheme 133



toward nitrogen leads to ring opening of the aziridine. In the next step, the electrophilic carbon atom in 475 was attacked by the carboxylate anion, leading to formation of butyrolactone 476.²¹¹

In the case of β,γ -aziridinocarboxylates, no internal acid function is present to activate the aziridine ring and a Brønsted or Lewis acid has to be added to effectuate a ring expansion toward γ -lactones.

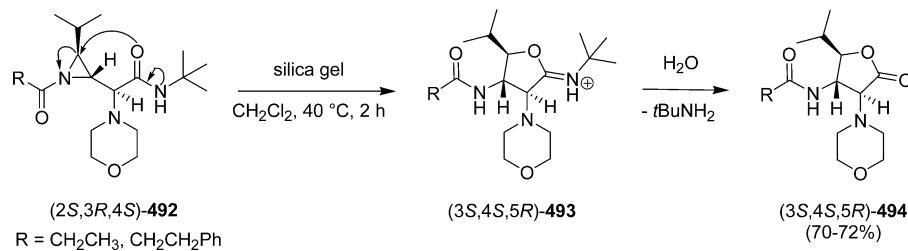
Conversion of alkyl β,γ -aziridinocarboxylates to β -amino- γ -lactones 471 has been observed by treatment of the aziridines 477 with HCl or Olah's reagent (pyridine-HF). Under these acidic conditions an activated aziridinium intermediate 478 is formed followed by lactonization in a stereoselective way with inversion of the configuration (Scheme 128).¹³⁷

Ring expansion of 2-(carboxymethyl)aziridines to lactones was applied in the synthesis of 3-arylidene lactones 481, a moiety which is present in a variety of natural products with interesting bioactivities. Ring transformation of *N*-tosyl aziridines 307 to lactones 481 was achieved upon treatment with lithium perchlorate in acetonitrile, Scheme 129. In the first step, the lithium perchlorate-catalyzed regioselective ring opening of *N*-tosyl aziridine 307 leads to formation of a stabilized benzylic carbenium ion 479, which suffers intramolecular attack of the ester moiety at the less hindered side, leading to *trans*- γ -butyrolactones 480. Due to the presence of moisture in the reaction medium, an alternative reaction pathway involving the initial opening of the aziridine ring by water in an early stage could not be ruled out completely.¹⁷³

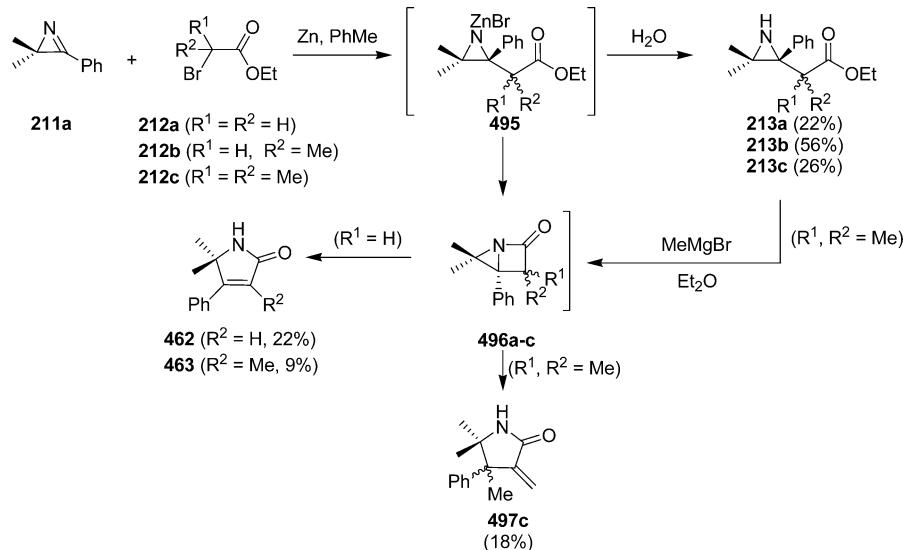
In an attempt to achieve a ring transformation of racemic *syn*-carboxymethylaziridine 482a to racemic *cis*-3-aminoazetidine 483a, the aziridine 482a was treated with Et₃N. Unfortunately, this conversion failed. Activation of aziridine 482a by treatment with lithium perchlorate did not promote the envisaged ring transformation but led to formation of butyrolactone 484 in moderate yield (Scheme 130).¹¹⁹ In contrast, conversion of the corresponding racemic *anti*-aziridines to β -amino esters with an azetidine skeleton did proceed (vide infra).¹¹⁹ The difference in reactivity between the *anti*- and the *syn*-aziridine can be rationalized by the differently favored conformational rotamers of the two aziridines.

A similar 2,3-diaminobutyrolactone 486 was obtained as a side product after treatment of *syn*-*N*-tosylaziridine 181c with KOtBu (Scheme 131). The main product of this reaction appeared to be the α,β -unsaturated ester 485 formed via a base-induced ring-opening reaction of aziridine 181c. Again, a difference in reactivity between the *syn*- and the *anti*-aziridine was observed since treatment of the corresponding *anti*-aziridine with KOtBu did not lead to lactone formation.¹¹⁸ Remarkably, while treatment of 2-(carboxymethyl)aziridines with a base has been described as a way to synthesize functionalized lactams (vide infra), in this case no lactam

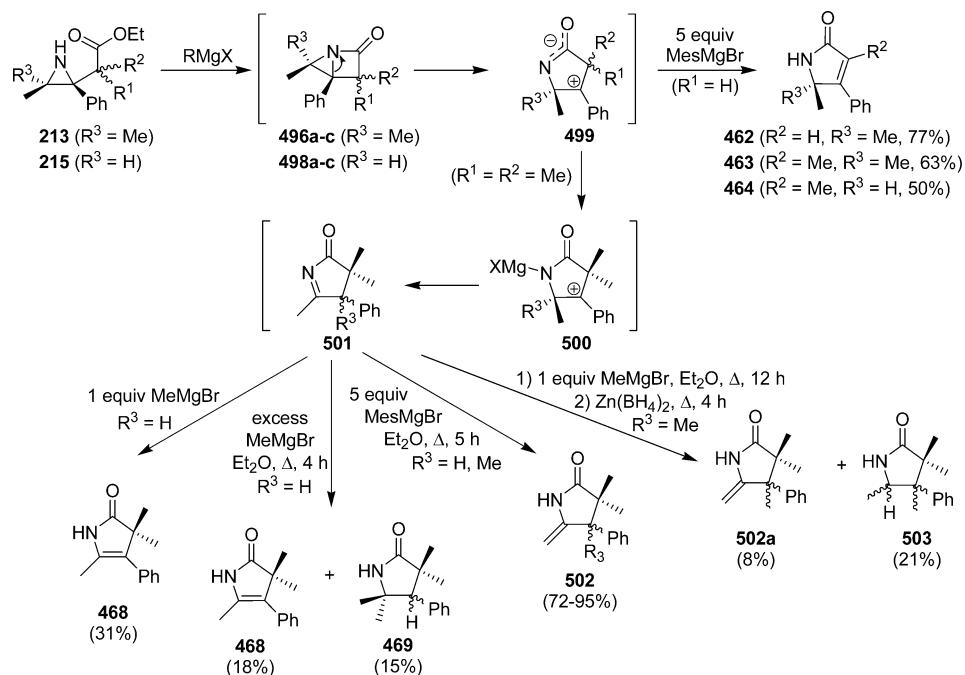
Scheme 134



Scheme 135



Scheme 136

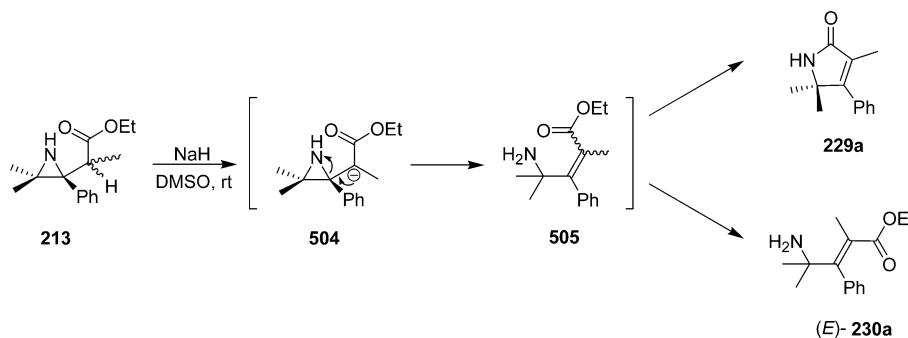


formation was observed. This could be due to the decreased nucleophilicity of the tosylated nitrogen atom.

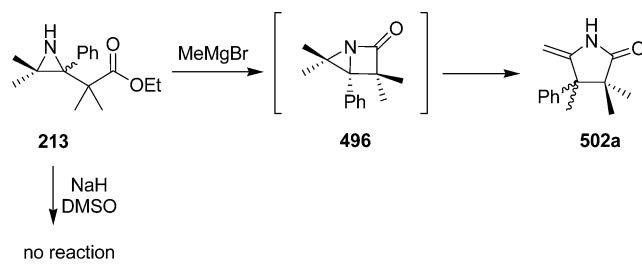
In analogy with the above-mentioned ring expansion of racemic *syn*-*N*-tosylaziridine **181c** to lactone **486** (Scheme 131), asymmetric synthesis to prepare a similar enantiopure

lactone **487** was also developed. Using a chiral sulfinyl group as a protecting group on nitrogen, chiral *syn*-aziridine **184b** was prepared and transformed into chiral lactone **487** by treatment with HCl (Scheme 132). Under these acidic conditions, removal of the sulfinyl and diphenylmethylidene protecting

Scheme 137



Scheme 138



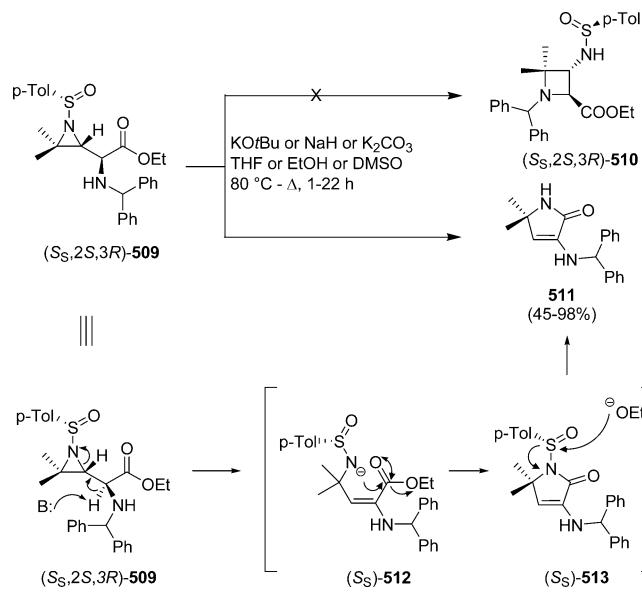
groups was achieved and the HCl salt of *trans*-(2*R*,3*R*)-2,3-diaminobutyrolactone **487** was isolated in excellent yield.¹²⁰

Lactonization of 2-(carboxymethyl)aziridines has also been observed as a side reaction. An example is given in Scheme 133, in which the ring opening of aziridine **368b** by dimethoxybenzene **489** was envisaged but only lactone **491** could be isolated from the reaction mixture containing several unidentified side products.⁸⁵

Also, upon purification of aziridine **492** by column chromatography using silica gel as the stationary phase, a minor fraction of this aziridine **492** was converted into lactone **494** (Scheme 134). Attempts to induce lactone formation by adding different Lewis acids failed, but heating of aziridines **492** in CH₂Cl₂ in the presence of silica gel furnished lactones **494** in good yield.⁴²

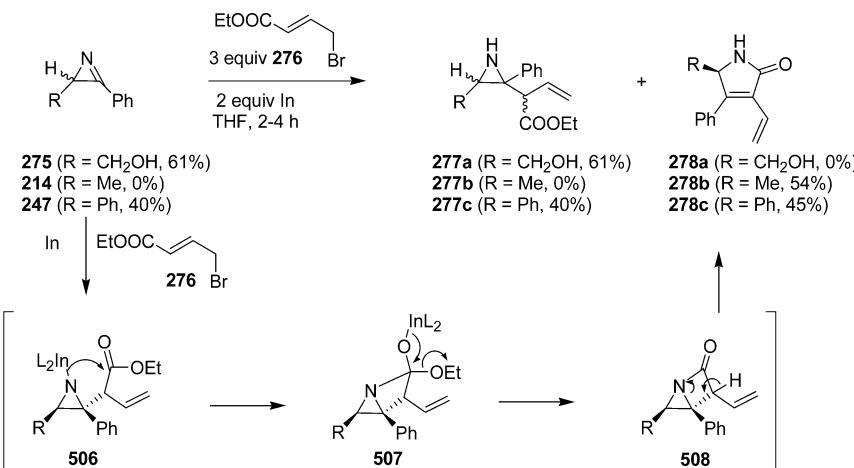
3.2.2. Lactams. A second class of five-membered rings that can be formed starting from 2-(carboxymethyl)aziridines comprises γ -lactams.

Scheme 140

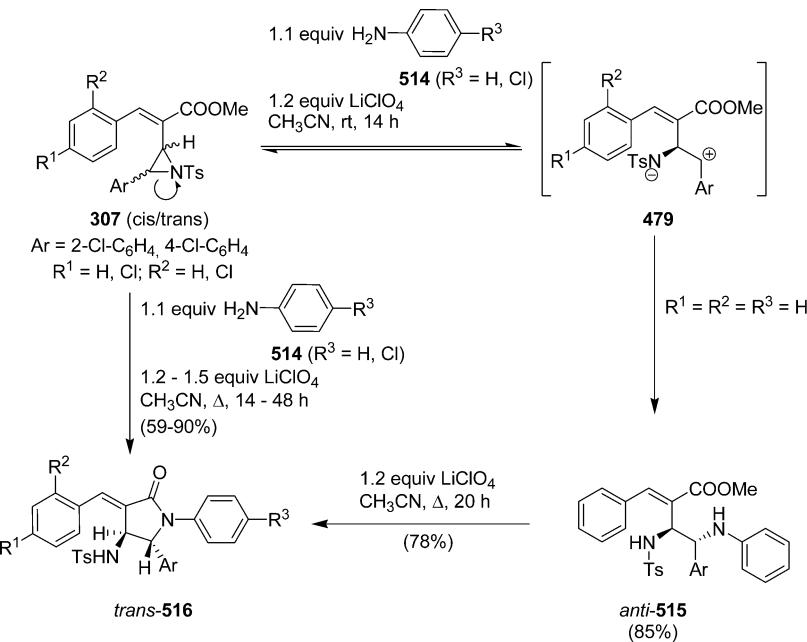


On the basis of the synthesis of the β -lactam core via addition of a Reformatsky reagent across an imine double bond and subsequent ring closure it was attempted to synthesize the β -lactam-fused aziridines **496** using the azirine **211a** as the electrophile. However, when this reaction was conducted, a mixture of 2-(carboxymethyl)aziridines **213** (22–56%) and lactams **462**, **463**, and **497c** was obtained. It was assumed that

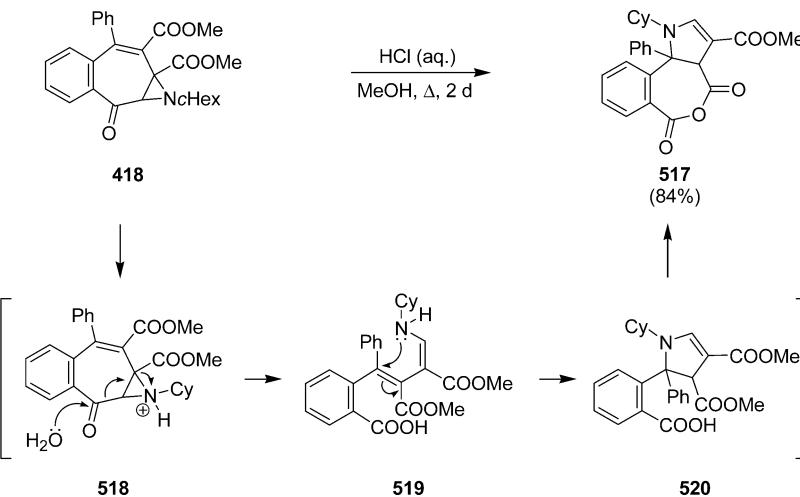
Scheme 139



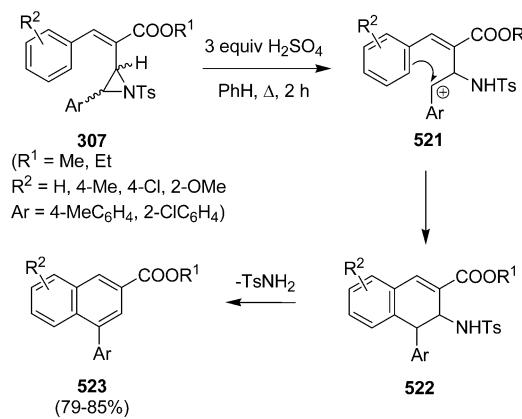
Scheme 141



Scheme 142



Scheme 143

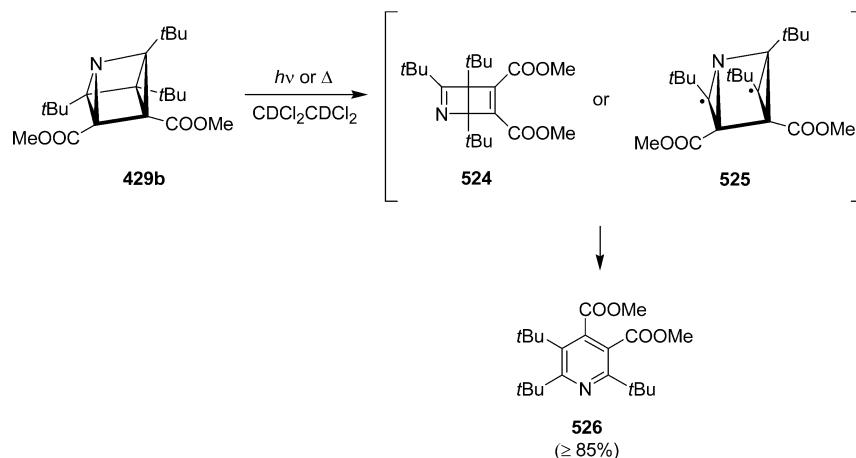


formation of γ -lactams 462, 463, and 497c proceeded via intermediate bicyclic β -lactams 496a–c. Treatment of ethyl β,γ -

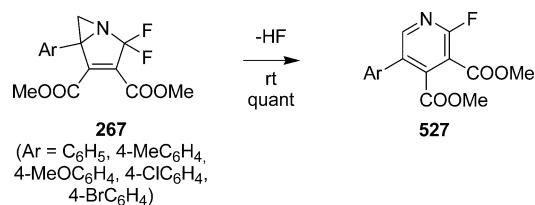
aziridinocarboxylate 213c with the Grignard reagent MeMgBr also led to formation of pyrrolidone 497c in low yield (Scheme 135).¹³⁶

In order to elucidate the reaction mechanism, 2-(carboxymethyl)aziridines 213 and 215 were treated with different Grignard reagents. The results are depicted in Scheme 136. When 2-(carboxymethyl)aziridines 213 and 215 were treated with a Grignard reagent, it was assumed that β -lactam-fused aziridines 496 and 498 were formed in a first step, which were then converted into different lactams, depending on the substituents and the reaction conditions. Heterolytic cleavage of the C–N bond in β -lactams 496 and 498 led to formation of a relatively stable benzylic carbonium ion in intermediate 499. When $\text{R}^1 = \text{H}$, treatment with MesMgBr led to unsaturated lactams 462, 463, and 464 via a proton shift. Use of the sterically hindered Grignard reagent MesMgBr was necessary to avoid Grignard addition to the ester function (Scheme 124). When no proton at the α -position of the carbonyl was present ($\text{R}^1 = \text{R}^2 = \text{Me}$), migration of the R^3 substituent occurred and

Scheme 144



Scheme 145



pyrrolidones **501** were formed. These five-membered rings were unstable in the presence of Grignard reagents, and depending on the substitution pattern and the reaction conditions, they were transformed into a variety of lactams **468**, **469**, **502**, and **503** (Scheme 136).¹³⁵

In contrast to the reaction of 2-(carboxymethyl)aziridines **213** and **215** with Grignard reagents (Scheme 136), NaH-induced ring expansion of these aziridines likely proceeds via an intermediate carbanion **504** which is then converted into lactam **229a** or unsaturated ester (*E*)-**230a** (Scheme 137). The yields of these conversions were not mentioned.¹⁴²

This hypothesis was supported by the fact that dimethyl-substituted aziridine **213** could not be converted into lactam **496** in the presence of NaH. In contrast, treatment of the same aziridine **213** with the Grignard reagent MeMgBr led to its conversion to lactam **502a** (Scheme 138). Again, no yields were reported.¹⁴²

Apparently, ring expansion of 2-(carboxymethyl)aziridines to give γ -lactams can proceed via two different pathways. A first way comprises formation of a bicyclic intermediate followed by opening of the aziridine ring, while in a second route the ring opening, triggered by addition of a base, is followed by ring closure toward the γ -lactam. For each route, another example can be found in the literature.

In the synthesis of 2-allylaziridines **277** by treatment of azirines **275**, **214**, and **247** with an alkylindium reagent, 3-

vinyllactams **278** were obtained as side products. Formation of lactams **278** seemed to be dependent on the nature of the substituent on the azirine ring. A plausible mechanism for formation of lactams **278** is depicted in Scheme 139.¹⁶⁵

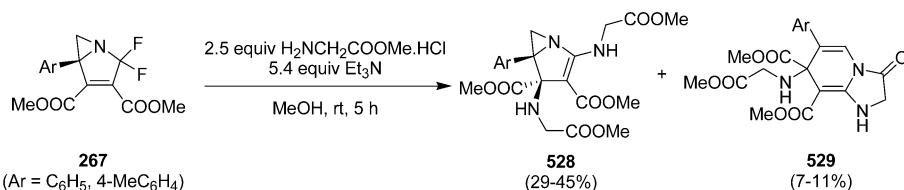
Conversion of 2-(carboxymethyl)aziridines to lactams has also been reported as an undesired reaction in an attempt to achieve ring expansion of the optically pure *N*-sulfinyl aziridine **509** to azetidine **510**. Depending on the reaction conditions, 3-aminobutyrolactam **511** was isolated in 45–98% yield (Scheme 140). Since a similar ring expansion of racemic *N*-tosylaziridines to azetidines could be achieved, it was concluded that the sulfinyl group at nitrogen was not sufficient to activate the aziridine ring toward a ring expansion.¹²⁰

Another route toward the synthesis of functionalized lactams starting from 2-(carboxymethyl)aziridines is depicted in Scheme 141. As mentioned before, heating of 2-(carboxymethyl)aziridines **307** in acetonitrile in the presence of LiClO_4 led to formation of lactones **481** (Scheme 129). By adding an external nucleophile such as an amine, reflux in CH_3CN led to formation of lactams **516**. Lowering of the reaction temperature to room temperature furnished β,γ -diamino ester **515**, which could be converted into lactam **516** by reflux in acetonitrile in the presence of LiClO_4 . In contrast to the previous examples, the nitrogen atom in the lactam ring does not originate from the aziridine ring but from the external nitrogen nucleophile (Scheme 141).¹⁷³

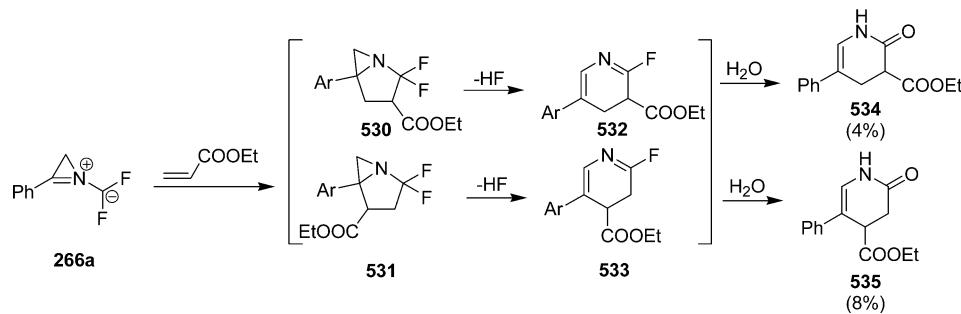
3.2.3. Pyrrolines. Besides their conversion into lactones and lactams, rearrangement of 2-(carboxymethyl)aziridines into pyrrolines has also been observed.

Treatment of tricyclic aziridine **418** with hydrochloric acid in methanol afforded anhydride **517** in 84% yield. Initial activation of the aziridine ring by protonation followed by attack of H_2O across the carbonyl group led to ring opening of the aziridine. Subsequently, an intramolecular aza-Michael-type addition

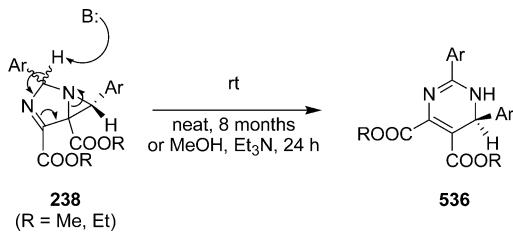
Scheme 146



Scheme 147



Scheme 148



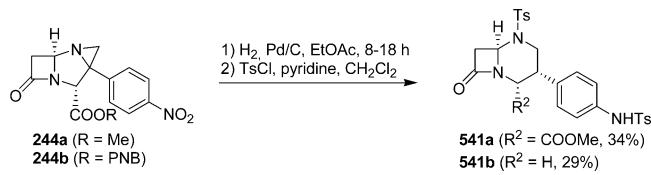
across the double bond furnished pyrroline 520, which cyclized to anhydride 517 (Scheme 142).²²⁹

3.3. Ring Expansions to Six- and Seven-Membered Rings

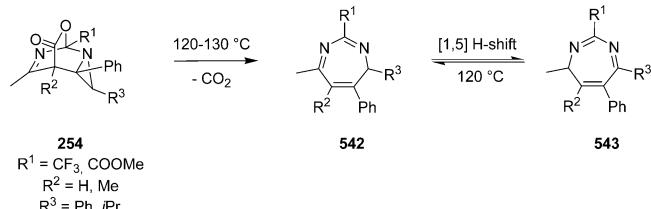
3.3.1. Naphthalenes. As mentioned earlier, α -benzylidene- β,γ -aziridinocarboxylates can be used as precursors in the synthesis of lactones and lactams (Scheme 129, Scheme 141). Under appropriate reaction conditions, similar aziridines 307 could be converted into functionalized naphthalenes 523. Treatment of aziridines 307 with 3 equiv of sulfuric acid in benzene under reflux led to formation of a stabilized carbenium ion 521, followed by an intramolecular Friedel–Crafts alkylation. A final dehydroamination step furnished naphthalenes 523 in good yield (Scheme 143).¹⁷²

3.3.2. Pyridines and Piperidines. Azaprismane 429b was converted to pyridine 526 in good yield upon irradiation or

Scheme 150



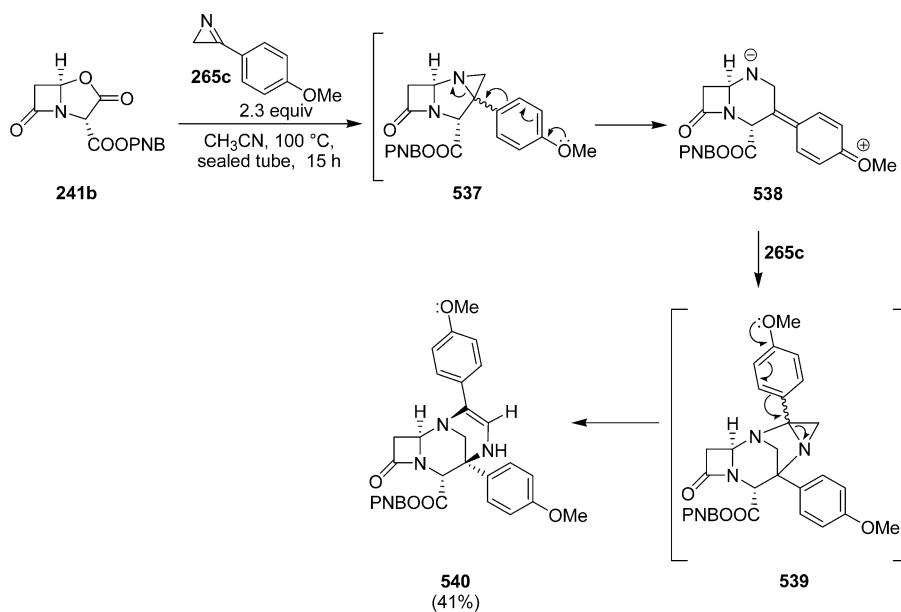
Scheme 151



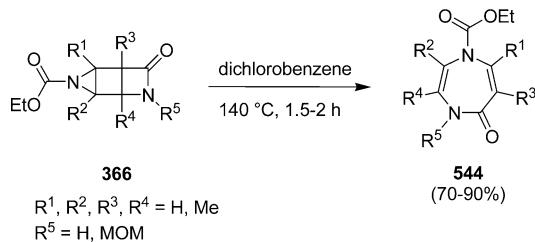
heating in deuterated tetrachloroethane (Scheme 144). The intermediate of this rearrangement could be either Dewar-pyridine 524 or diradical 525.²³²

Besides this particular case, three other examples concerning ring expansion of 1-azabicyclo[3.1.0]hexanes to give pyridines or piperidines can be mentioned.

Scheme 149



Scheme 152



Crystalline azabicyclohexanes **267** could be stored indefinitely at -20°C , but upon storage at room temperature, a quantitative dehydrofluorination and ring expansion to give pyridines **527** was observed, with release of the aziridine ring strain (Scheme 145).^{161,162}

Treatment of azabicyclohexanes **267** with nitrogen nucleophiles did not lead to degradation of the aziridine moiety (vide supra), but when methyl glycinate hydrochloride was used as nucleophile, 1,4-dihydropyridine **529** was isolated as a minor reaction product as well as the bicyclic aziridine **528**. All attempts to convert aziridine **528** into dihydropyridine **529** failed. Therefore, it was concluded that aziridine **528** is not a precursor for the six-membered ring compound **529** (Scheme 146).¹⁶² An explanation for the difference in reactivity between the nitrogen nucleophiles was not given.

In an attempt to synthesize pyrrolidines **530** and **531** via a 1,3-dipolar cycloaddition, azirinium difluoromethanide **266a** was treated with ethyl acrylate. However, this reaction showed low regioselectivity and two isomers **530** and **531** were formed, which proved to be unstable. Dehydrofluorination and ring expansion afforded dihydropyridines **532** and **533**, which were hydrolyzed to piperidinones **534** and **535** in the presence of water albeit in low yield (4–8%) (Scheme 147).¹⁶²

3.3.3. Pyrimidines and Hexahydropyrimidines. Analogously, ring expansion of 1,3-diazabicyclo[3.1.0]hexanes furnishes pyrimidines or hexahydropyrimidines.

Imidazo-fused aziridines **238**, bicyclic dimers of an azirinecarboxylate (vide supra, Scheme 56), rearrange to the dihydropyrimidines **536** upon storage in the dark. The methyl esters proved to be more reactive than the ethyl esters, and the rate of this reaction could be increased by addition of base. The mechanism of the rearrangement with release of the three-membered ring strain is depicted in Scheme 148, but the yield was not given.¹⁴⁸

As mentioned earlier, ring opening of tricyclic aziridine-2-carboxylates to give β -lactam-fused hexahydropyrimidines under various reaction conditions failed (Scheme 115). In order to achieve the envisioned aziridine opening, an electron-donating aryl substituent was introduced at C2 of the aziridine ring. To this end, bicyclic β -lactam **241b** was treated with 2-(4-methoxyphenyl)azirine **265c**, affording the 2:1 adduct **540**. Apparently, the primary adduct **537** was unstable under the reaction conditions due to the presence of the electron-

donating 4-methoxyphenyl substituent. After ring opening of the aziridine, addition to a second equivalent of 2-arylazirine **265c**, and subsequent aziridine opening, tricyclic β -lactam **540** was obtained in 41% yield (Scheme 149).¹⁴⁹

Using an electron-withdrawing aryl substituent, more specifically 4-nitrophenyl, synthesis of the tricyclic aziridines **244** was achieved without further ring opening and second aziridine addition. After conversion of the nitro group to the amine, ring opening of the aziridine ring afforded the envisaged 1-azacephams **541** (Scheme 150).¹⁴⁹

3.3.4. Diazepines. Ring expansion of highly functionalized tricyclic 2-(carboxymethyl)aziridines to give diazepines has also been described in the literature.

When aziridines **254** were heated at $120\text{--}130^\circ\text{C}$, extrusion of CO_2 occurred and 4*H*-1,3-diazepines **542** were formed in high yields which were not specifically reported (Scheme 151). Under these reaction conditions, a thermodynamic equilibrium was formed between the two isomers **542** and **543** via a sigmatropic [1,5] *H*-shift.¹⁵²

Heating of tricyclic compounds **366** in dichlorobenzene also led to a ring opening to give seven-membered rings, more specifically 1*H*-1,4-diazepin-5-ones **544**, which were isolated in 70–90% yield (Scheme 152). These diazepinones **544** were then further converted into fully unsaturated diazepines.^{212,213}

In conclusion, ring expansion of 2-(carboxymethyl)aziridines to a variety of five-, six-, and seven-membered rings has been described. The nature of the ring expansion is highly dependent on the functionalization of the aziridine ring and the reaction conditions. Treatment of 2-(carboxymethyl)aziridines with acids will generally lead to formation of lactones via aziridine activation, while lactams are formed upon treatment with Grignard reagents or base.

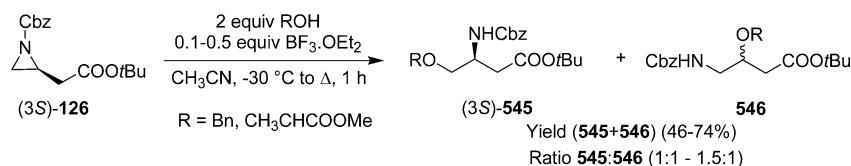
3.4. Ring Opening of 2-(Carboxymethyl)aziridines

Due to the inherent ring strain of aziridines, these small-membered rings can be used as valuable synthons in organic chemistry. In the next section, the various ring-opening reactions leading to a range of organic compounds, including functionalized acyclic β -amino esters, amino alcohols, diamino esters, and 4-aminobut-2-enoates, will be discussed.

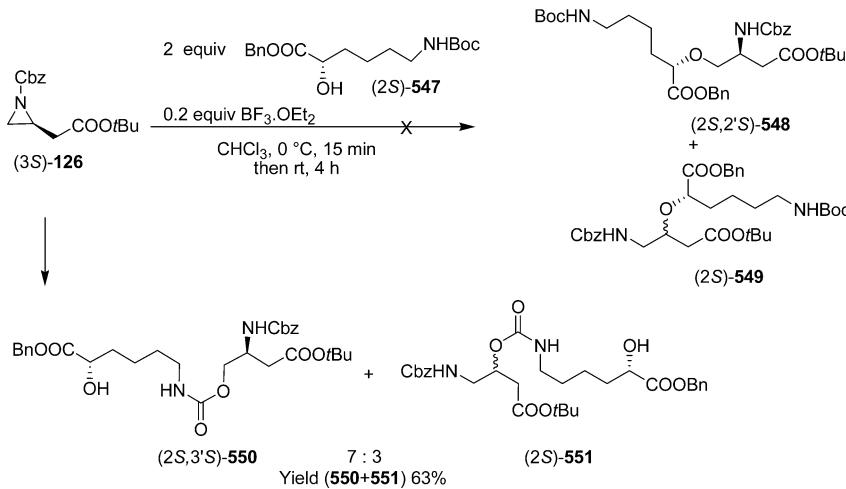
3.4.1. Oxygen Nucleophiles. With the aim of using 1-benzyloxycarbonyl-2-(carboxymethyl)aziridine **126** as a building block for synthesis of novel methyleneoxypseudopeptides, the reactivity of aziridine **126** toward different nucleophiles was investigated. First, ring opening of aziridine **126** using simple oxygen nucleophiles was examined. Treatment of aziridine **126** with benzyl alcohol or methyl lactate resulted in formation of two isomers **545** and **546** in a ratio varying between 1:1 and 1.5, which was independent of the reaction conditions (Scheme 153). Apparently, regioselective opening of the three-membered ring by means of an oxygen nucleophile could not be achieved.

Subsequently, in order to accomplish formation of methyleneoxypseudopeptides **548** and **549**, (2*S*)-benzyl 6-(*tert*-

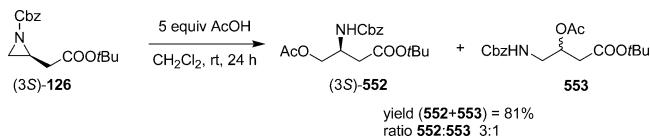
Scheme 153



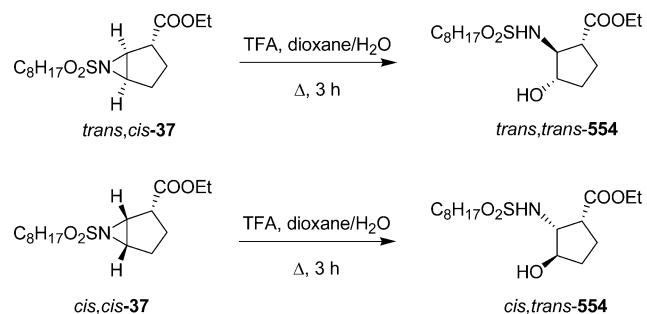
Scheme 154



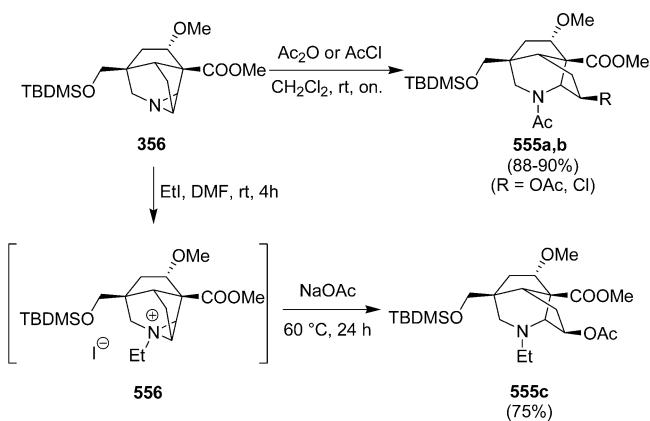
Scheme 155



Scheme 156



Scheme 157



butoxycarbonylamino)-2-hydroxyhexanoate 547 was used in the reaction with *N*-Cbz aziridine 126. In this case, however, the envisioned ring-opened products 548 and 549 were not obtained. After detailed analysis of the reaction mixture, two regioisomers 550 and 551 could be identified as the reaction products. In this case, not the hydroxyl group but the oxygen of the *tert*-butoxycarbonyl group at nitrogen reacted as the

nucleophile to open the aziridine ring, leading to formation of carbamates 550 and 551 in a ratio of 7:3 (Scheme 154).⁸³

Furthermore, aziridine 126 was reacted with acetic acid in order to achieve ring opening, but again, this reaction proved to be poorly regioselective and the two isomers 552 and 553 were formed in a 3:1 ratio (Scheme 155).⁸³

In the examples below, a regioselective ring opening of 2-(carboxymethyl)aziridines with oxygen nucleophiles could be achieved. In all these cases however the aziridine moiety is incorporated in a more complex structure, influencing the regioselectivity of the reaction.

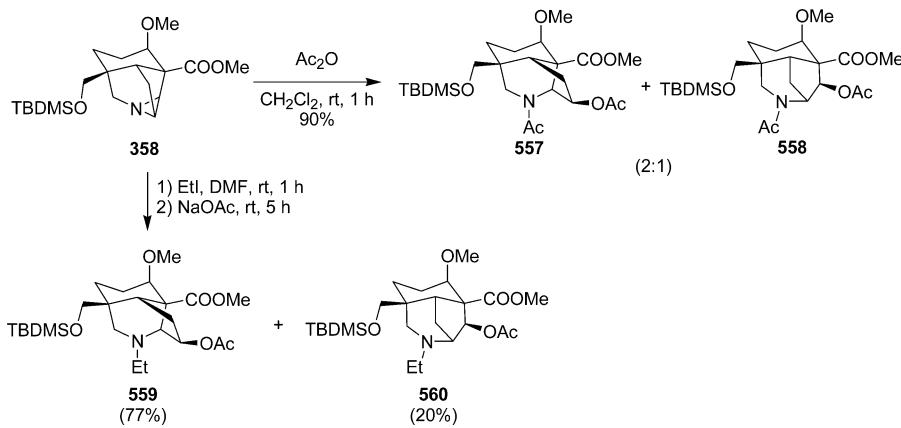
In a synthetic route toward stereochemically defined glycerol 3-phosphate analogs as GPAT inhibitors, cyclopentane-fused aziridines 37 were used as intermediates. In a subsequent step, ring opening of the activated aziridine was achieved with water in the presence of trifluoroacetic acid. In this case, ring opening proceeded selectively and furnished cyclopentanecarboxylates 554 (Scheme 156). The yields of these reactions were not reported.⁴⁶

In a procedure toward synthesis of the 10-azatricyclo-[3.3.2.0^{4,8}]decane core of racemullosine, a C_{20} -diterpene alkaloid, ring opening of tetracyclic aziridine 356 was one of the key steps (Scheme 157). Treatment of carboxylate 356 with acetic anhydride or acetyl chloride in dichloromethane yielded the azatricyclic skeleton 555 via a regio- and stereoselective ring opening of the aziridine in excellent yield. The high regioselectivity was attributed to the steric hindrance of the quaternary carbon atom at the α -position of the ester. Also, the *N*-ethyl derivative 555c was synthesized by treatment of aziridine 356 with EtI, yielding the quaternary ammonium iodide 556, which was then ring opened in a regio- and stereoselective way with NaOAc.²⁰⁹

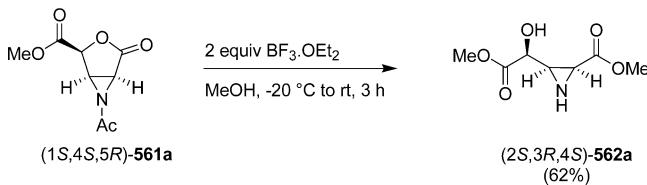
Remarkably, when the same reaction conditions for aziridine ring opening (Ac_2O , CH_2Cl_2) were applied to the homologous tetracyclic aziridine 358, no regioselectivity was observed and an inseparable mixture of isomers 557 and 558 was obtained in 90% yield (Scheme 158). On the other hand, initial activation of the aziridine ring with EtI and ring opening by NaOAc in DMF provided a mixture with regioisomer 559 as the major isomer isolated in 77% yield.²¹⁰

In order to explore building blocks for synthesis of 2,3-disubstituted glutamic acid derivatives, the reactivity profile of a class of lactone-fused 2-(carboxymethyl)aziridines, more specifically 2,3-aziridino- γ -lactones 561, toward oxygen nucleo-

Scheme 158



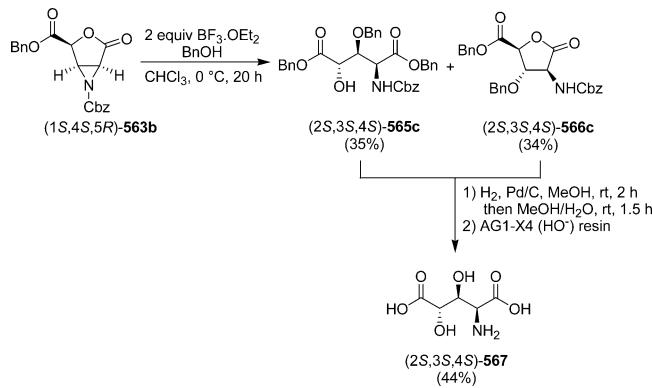
Scheme 159



philes was investigated. When *N*-acetylaziridine **561** was reacted with MeOH in the presence of 2 equiv of BF₃·OEt₂, opening of the lactone ring was observed in combination with removal of the acetyl group on the aziridine nitrogen. This deacetylation deactivated the aziridine ring, preventing further ring opening by MeOH (Scheme 159).⁷⁵

Subsequently, the *N*-Cbz-protected derivative **563a** was treated with MeOH under similar reaction conditions (2 equiv of BF₃·OEt₂, MeOH, rt). Due to the presence of the Cbz-protecting group, which is stable under the applied reaction conditions, it was expected that in addition to lactone ring opening opening of the aziridine ring would also occur, with formation of substituted glutamate analogs **565**. Surprisingly, in this case, no opening of the aziridine ring by MeOH occurred and aziridine **564a** was recovered. Increasing the reaction temperature to 50 °C led to full conversion to the acyclic ester **565a** by regioselective ring opening of the aziridine by MeOH. The acyclic ester **565a** partially cyclized to the corresponding lactone **566a** upon purification on silica gel. Furthermore, the

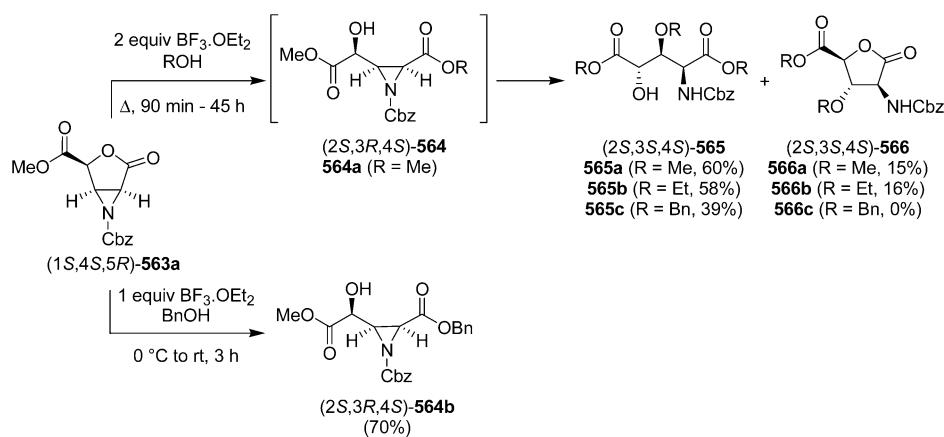
Scheme 161



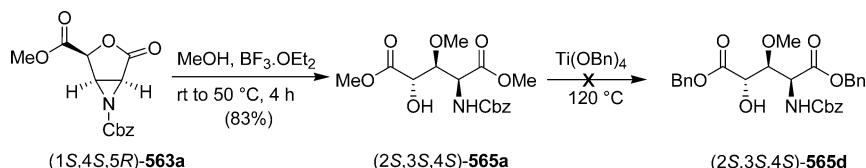
reactivity of bicyclic compound **563a** toward EtOH and BnOH was also investigated. Using EtOH as the nucleophile, partial transesterification of the methyl esters could not be avoided. To achieve full conversion to diethyl dicarboxylate **565b**, the reaction time was extended to 45 h. It is noteworthy that treatment of aziridine **563a** with BnOH at room temperature allowed selective lactone opening without transesterification (Scheme 160).⁷⁵

The above-mentioned methodology was used to synthesize one of the four enantiomers of 3,4-dihydroxyglutamic acid, more specifically (2S,3S,4S)-3,4-dihydroxyglutamic acid **567** (Scheme 161). Synthesis started from benzyl ester **563b**, which

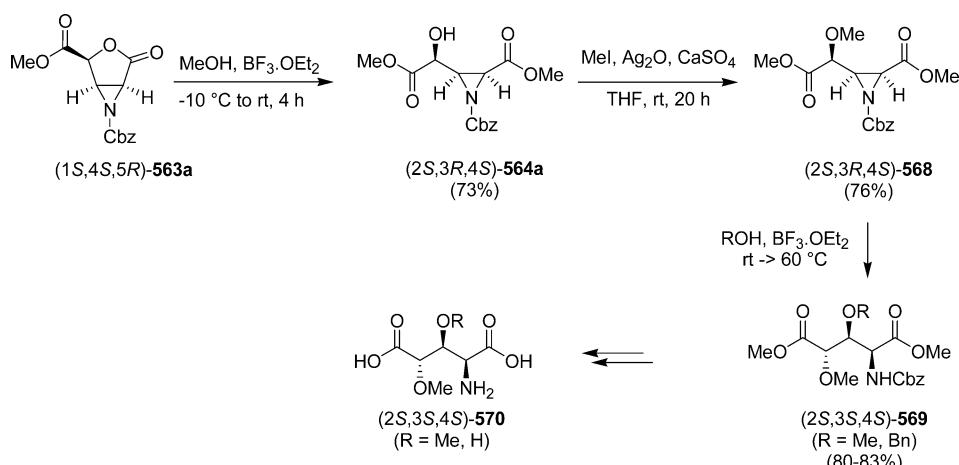
Scheme 160



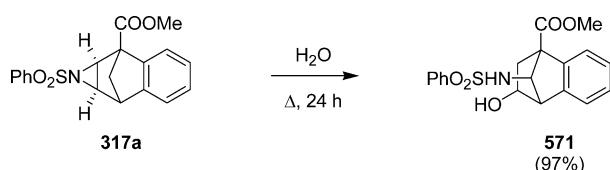
Scheme 162



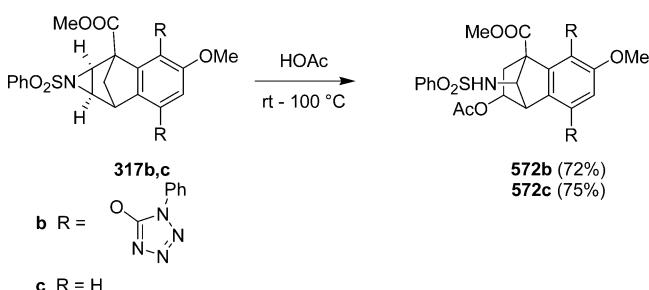
Scheme 163



Scheme 164



Scheme 165



was transformed into the acyclic derivative **565c** upon treatment with benzyl alcohol in the presence of $\text{BF}_3\cdot\text{OEt}_2$. Remarkably, partial lactonization of this compound to give lactone **566c** was observed during the reaction (Scheme 161).^{76,77}

In the next part of this research, the same procedure was used in an attempt to prepare the methoxy and dimethoxy analogs of the glutamic acid derivative **567**. The first step in this synthetic route was again a $\text{BF}_3\text{-OEt}_2$ -promoted ring opening of the bicyclic core with methanol. Further attempts to convert this acyclic scaffold **565a** into the 3-methoxyglutamic acid derivative **565d** failed (Scheme 162).⁷⁸

Preparation of the corresponding 4-methoxyglutamic acid derivatives **570** could be achieved via sequential lactone and aziridine ring openings (Scheme 163). Selective lactone ring opening could be achieved by treatment of (*2S,5S,7R*)-

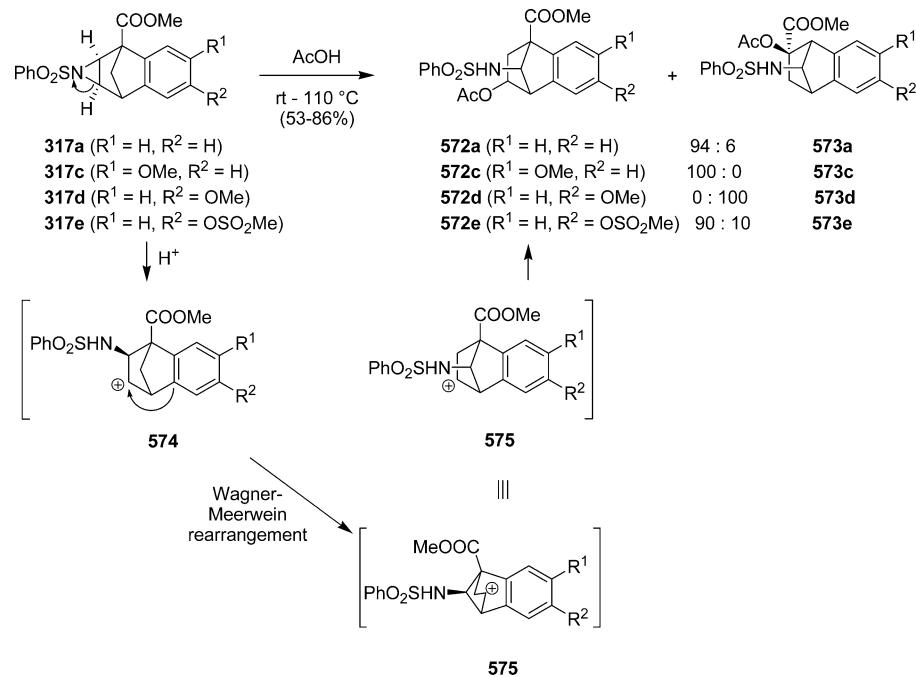
bicycloaziridine **563a** with MeOH at room temperature, affording 2-(carboxymethyl)aziridine **564a** in 73% yield. Methylation of the hydroxyl group at the γ -position of the ester was necessary in order to prevent ring opening of the aziridine by this hydroxyl group at a later stage of the synthesis. Subsequently, opening of the aziridine ring by methanol or benzyl alcohol was achieved regioselectively at the 3 position of the aziridine, furnishing dimethyl dicarboxylate **569**, which could then be converted into 4-methoxyglutamic acid analogs **570** (Scheme 163).⁷⁸

In a synthetic route toward diterpene alkaloids, the synthesis and acetylation of *N*-benzenesulfonyl aziridines was investigated. Heating of aziridine **317a** in H₂O effectuated a rearrangement to give benzonorbornane derivative **571** in excellent yield (Scheme 164).¹⁸⁴

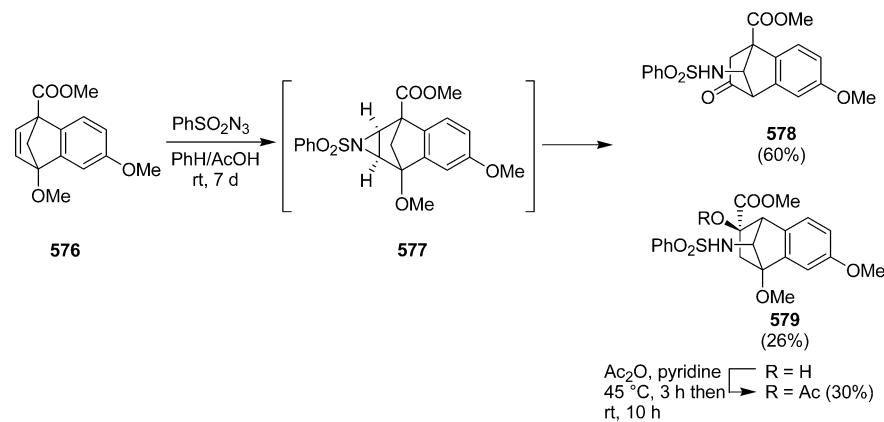
The same rearrangement was achieved by heating compound 317b in glacial acetic acid or even upon storage of aziridine 317c in acetic acid at room temperature (Scheme 165).^{185,186}

The substitution pattern of the aromatic ring proved to be critical for the regioselectivity of the rearrangement (Scheme 166). The mechanism of the reaction is described as initial ring opening of the aziridine followed by a Wagner–Meerwein rearrangement and reaction of the resulting carbenium ion with acetic acid. In the case of an unsubstituted aromatic ring, the regioselectivity of this reaction was high with a ratio of the two isomers of 94:6. Minor isomer **573a** was only obtained upon rearrangement to a carbenium ion next to a carbonyl group, which is energetically unfavorable. In this way, the presence of the ester function was determinative for the regioselectivity of the reaction. Aziridine **317c**, with a methoxy substituent at the para position of the migrating carbon–carbon bond, proved to be unstable and rearrangement toward benzonorbornane **572c** proceeded with complete regioselectivity. By placing the methoxy substituent at the meta position, a complete reversal in regioselectivity was observed and norbornane **573d** was obtained as a single isomer. Apparently, the effect of the

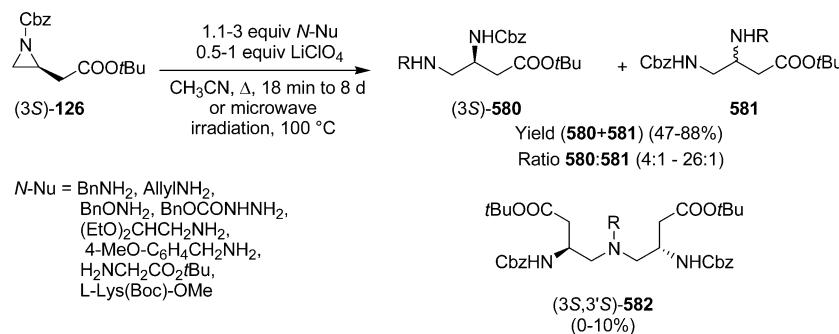
Scheme 166



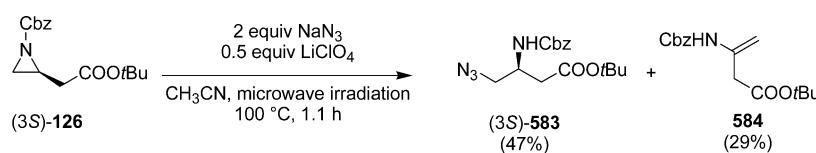
Scheme 167



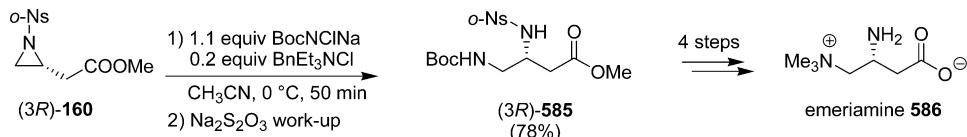
Scheme 168



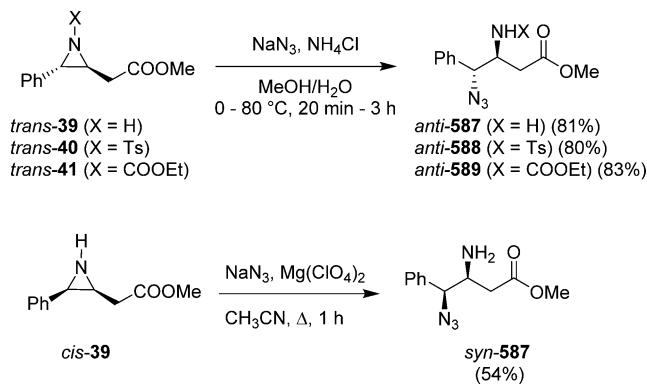
Scheme 169



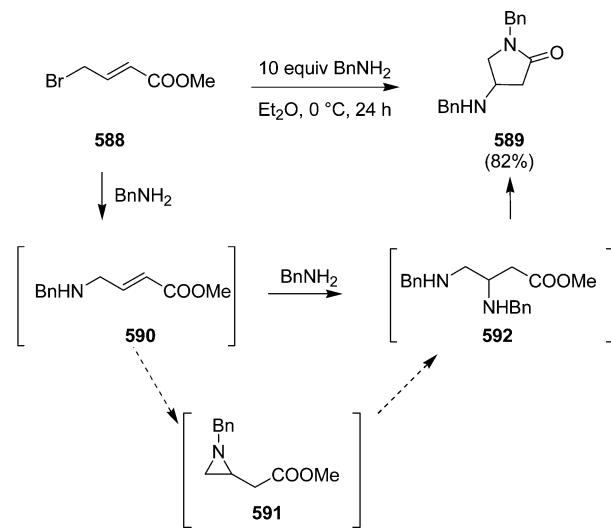
Scheme 170



Scheme 171



Scheme 172



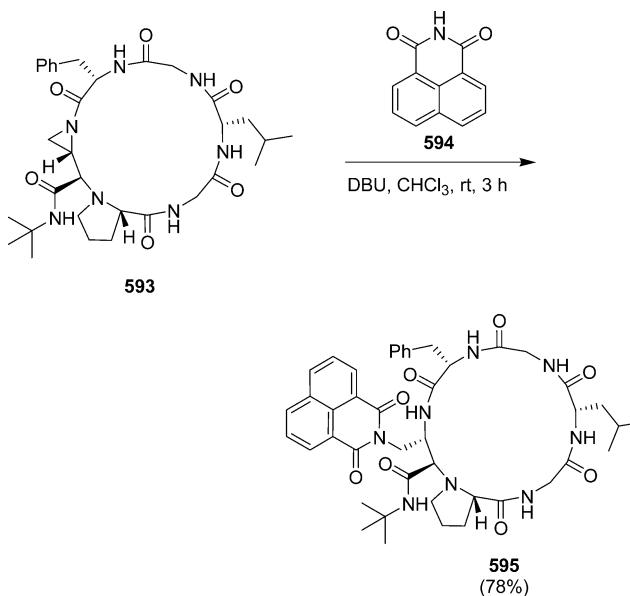
methoxy substituent dominated over the effect of the ester function. By replacing the methoxy substituent by the less electron-donating *O*-mesyl substituent, the regioselectivity was reversed and compound 572e was obtained as the major isomer.¹⁸⁷

The influence of the presence of a methoxy substituent at the bridgehead was more important than the effect of the methoxy group of the aromatic ring and directed the rearrangement toward ketone 578 as major product (Scheme 167).¹⁸⁷

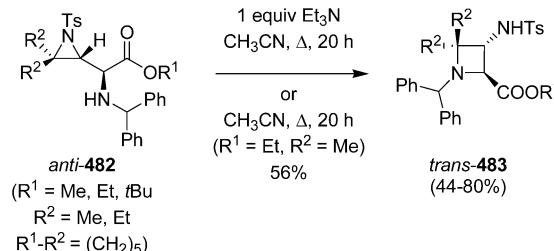
In conclusion, ring opening of simple 2-(carboxymethyl)-aziridines with oxygen nucleophiles proved to be poorly regioselective. Better regioselectivity was obtained using more complex aziridines. In all cases, activation of the aziridine ring prior to ring opening either by the presence of an electron-withdrawing substituent at nitrogen or by addition of a Brønsted or Lewis acid was required.

3.4.2. Nitrogen Nucleophiles. In a study concerning the synthesis of methyleneaminodipeptides, a class of pseudopeptides, ring opening of *tert*-butyl β,γ -aziridinocarboxylate 126

Scheme 173



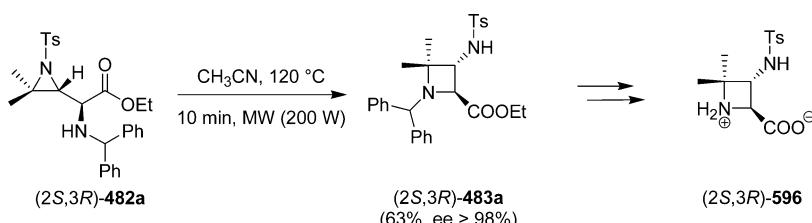
Scheme 174



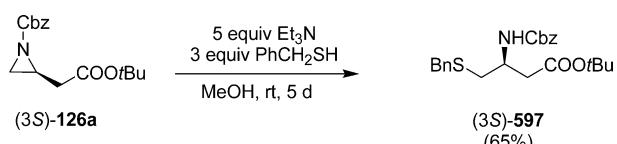
using a variety of nitrogen nucleophiles was investigated (Scheme 168). In contrast to the ring opening of 2-(carboxymethyl)aziridines by oxygen nucleophiles (Scheme 153), nucleophilic attack of the nitrogen nucleophiles showed a better regioselectivity and took place at the less substituted carbon atom, yielding regioisomers 580 and 581 in a ratio varying between 4:1 and 26:1. Formation of tertiary amine 582, resulting from the attack of secondary amine 580 on aziridine 126, could be avoided using 3 equiv of the nitrogen nucleophile. The ring-opening reaction was also performed under microwave irradiation, shortening the reaction time and increasing the yield. When NaN₃ was used as the nucleophile, vinylcarbamate 584 was formed as a side product, resulting from an elimination step (Scheme 169).^{82,83}

Total synthesis of emeriamine 586, an inhibitor of fatty acid oxidation, was developed starting from D-aspartic acid. One of the key steps in this synthesis is regioselective ring opening of *o*-nosyl-protected aziridine 160. Treatment of aziridine 160 with *N*-chloro-*N*-sodio-*tert*-butylcarbamate gave clean conversion to methyl 3,4-diaminobutanoate 585 via a regiospecific ring opening at the less substituted carbon with retention of the

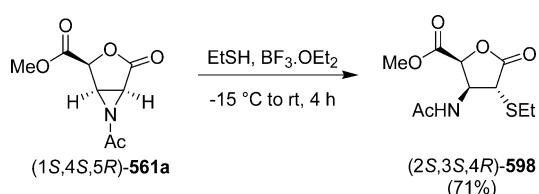
Scheme 175



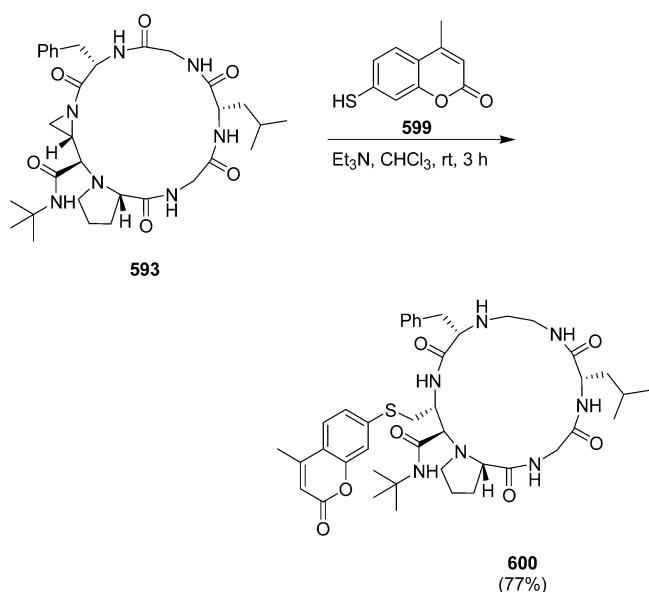
Scheme 176



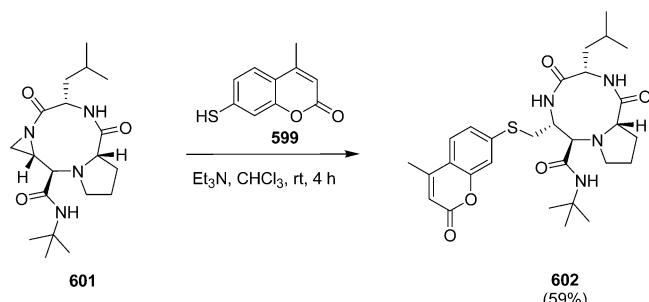
Scheme 177



Scheme 178



Scheme 179



absolute configuration of the chiral center. Diamine **585** could then be converted into emeriamine **586** in four steps (Scheme 170).¹⁰⁵

Azide-induced ring opening of phenyl-substituted aziridines **39**, **40**, and **41** was investigated in the context of the synthesis of functionalized γ -lactams. Regardless of the substituent at nitrogen, treatment of *trans*-aziridines **39**, **40**, and **41** with Na₃NH₄Cl afforded selectively *anti*-methyl γ -azidocarboxylates **587**, **588**, and **589** in good yield (Scheme 171).⁴⁷ In contrast, the similar reaction of the corresponding *N*-tosyl *cis*-aziridine with Na₃N in aqueous MeOH led to an unidentified mixture of products. The nonactivated aziridine *cis*-**39** could be converted into methyl γ -azidocarboxylate *syn*-**587** upon treatment with Na₃N in the presence of Mg(ClO₄)₂, which increased the reaction rate.

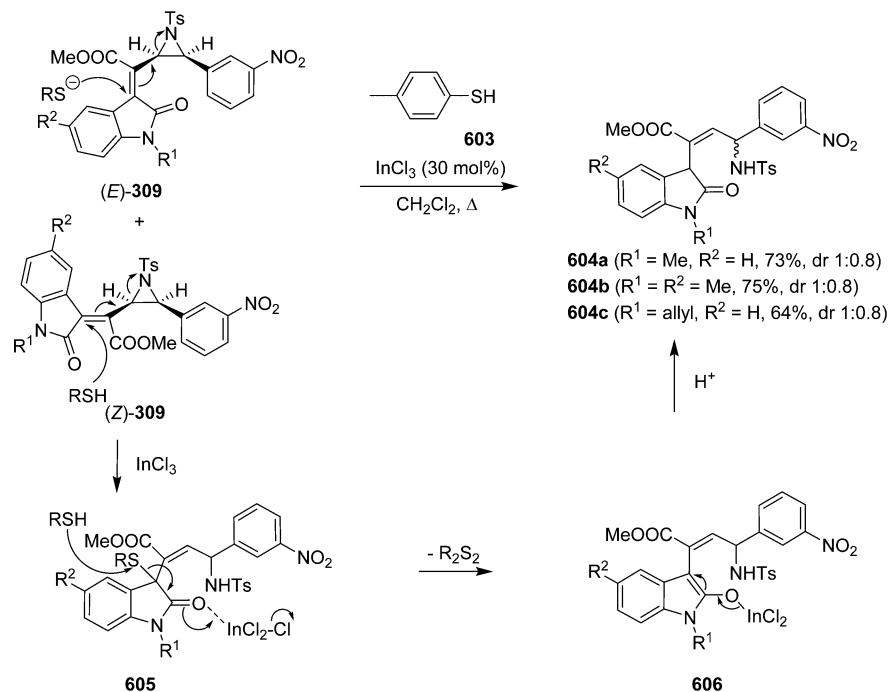
In the synthesis of methyl γ -aminocrotonate **590** starting from methyl γ -bromocrotonate **588**, use of an excess of benzylamine (10 equiv) led to formation of lactam **589** (Scheme 172), which could have proceeded via two different pathways. A first possibility is the aza-Michael addition of benzylamine across α,β -unsaturated methyl ester to give diamino ester **592**, which undergoes ring closure to γ -lactam **589**. In the alternative route, possible intermediate 2-(carboxymethyl)aziridine **591** is formed via an intramolecular aza-Michael addition and is subsequently opened by benzylamine to give methyl 3,4-diaminobutanoate **592**.²³⁹

Cyclic peptide **593** contains an aziridine ring, which can be seen as an electrophilic site enabling introduction of a side chain at a late stage of the peptide synthesis via ring opening of the aziridine by a nucleophile. In this way, treatment of cyclopeptide **593** with imide **594** in chloroform afforded the adduct **595** in good yield via a regioselective ring opening of the aziridine moiety at the least hindered carbon atom (Scheme 173). Other nitrogen nucleophiles, more specifically imides, secondary amines like morpholine and azide, could also be used to achieve the desired aziridine ring opening.^{33,43}

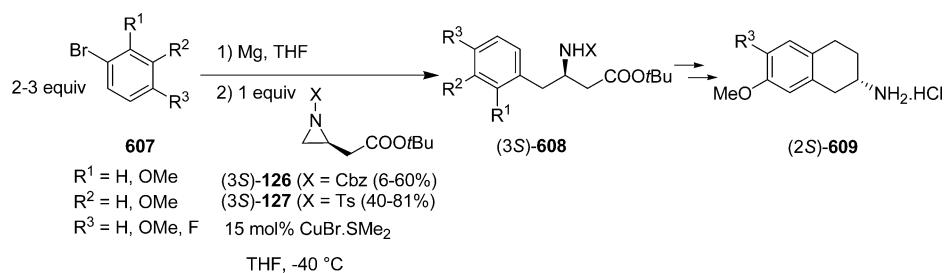
In the above-mentioned examples (Schemes 168–173), 2-(carboxymethyl)aziridines were used as precursors for a variety of 3,4-diaminobutanoates via a nitrogen nucleophile-induced ring opening of the aziridine moiety or as an electrophilic moiety to introduce an extra side chain. In β,γ -azirido- α -(*N*-diphenylmethyl)amino esters **482** the presence of an internal nitrogen nucleophile at the α -position of the ester moiety offered the possibility to effectuate an intramolecular ring opening of the aziridine leading to a rearrangement to give azetidines **483** (Scheme 174). This ring transformation could be achieved by treatment of *N*-tosyl-activated aziridines **482** with triethylamine in acetonitrile under reflux.¹¹⁹

The chiral version of the above-mentioned ring expansion toward azetidines is depicted in Scheme 175 and could be achieved by heating *N*-tosylaziridine **482a** in acetonitrile under microwave irradiation for 10 min. As mentioned before, the presence of the tosyl group at nitrogen was essential in this ring

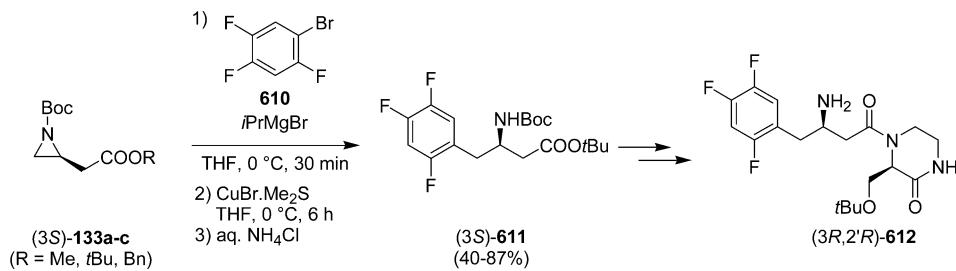
Scheme 180



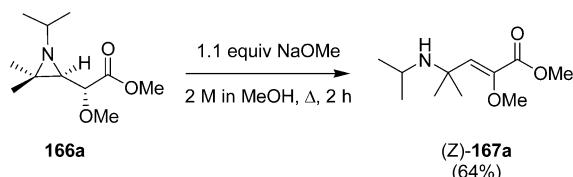
Scheme 181



Scheme 182



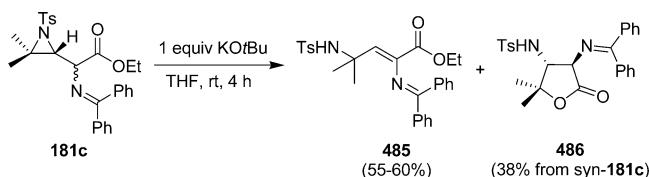
Scheme 183



expansion, since a *p*-toluene sulfinyl group proved to be insufficient for aziridine activation.¹²⁰

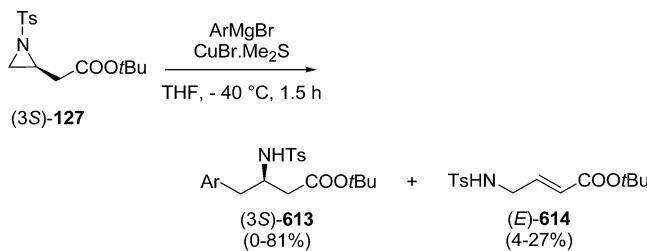
3.4.3. Sulfur Nucleophiles. A third class of nucleophiles that have been used to effectuate aziridine ring opening comprises sulfur nucleophiles.

Scheme 184



Treatment of *N*-benzyloxycarbonyl-protected aziridine 126 with 3 equiv of benzylmercaptan in the presence of Et₃N gave clean conversion to *tert*-butyl butanoate 597 in a regioselective manner with nucleophilic attack at the less hindered carbon atom (Scheme 176).⁸³

Scheme 185



Lactone-fused aziridine **561a** underwent ring opening by treatment with ethanethiol without degradation of the lactone moiety. Attack of the sulfur nucleophile occurred regiospecifically at C2 of the aziridine ring (Scheme 177).⁷⁵

As mentioned previously (*vide supra*), introduction of an aziridine moiety in a cyclic peptide provides an electrophilic site which can be used for conjugation to various side chains. Treatment of cyclic peptide **593** with the fluorescent tag 7-mercaptop-4-methylcoumarin **599** afforded the conjugated peptide **600** in 77% yield via regioselective ring opening of the aziridine (Scheme 178).^{33,34}

A second example of the labeling of a cyclic peptide with 7-mercaptop-4-methylcoumarin **599** is depicted in Scheme 179. Again, a regioselective ring opening of the aziridine was observed, yielding cyclic peptide **602**.³⁵

Besides aromatic thiols, aliphatic thiols (cysteamine) and thioacids (thiobenzoic acid) have also been used as nucleophiles to achieve regioselective ring opening of peptide-fused aziridines.^{36,37}

In a study exploring the synthetic potential of 3-methyleneaziridine-2-oxindoles **309**, these heterocycles reacted with *p*-thiocresol in the presence of indium(III) chloride as catalyst (Scheme 180). Regardless of the configuration of the starting alkene **309** (*E* or *Z*), this reaction afforded amines **604** after reflux in CH_2Cl_2 , pointing to the presence of a common intermediate. In the proposed reaction mechanism, the sulfur nucleophile initiates an S_{N}^2' reaction, accompanied by ring opening of the aziridine, followed by attack of a second

equivalent of sulfur nucleophile with formation of the corresponding disulfide. After protonation and tautomerization, allylamines **604** were obtained as the final products.¹⁷⁴

3.4.4. Carbon Nucleophiles. Ring opening of β,γ -aziridinocarboxylates with carbon nucleophiles, and more specifically Grignard reagents, has been used in synthetic routes toward tetralines, a class of compounds used for treatment of Parkinson's disease and novel potential dipeptidylpeptidase inhibitors.^{85,86}

Treatment of *N*-tosyl- and *N*-benzyloxycarbonyl-protected aziridines **126** and **127** with 2–3 equiv of a Grignard reagent (ArMgBr) in the presence of $\text{CuBr}\cdot\text{SMe}_2$ yielded 3-amino-butanoates **608** selectively via attack of the carbon nucleophile at the less substituted carbon atom of the aziridine ring. Further transformations of one of these functionalized esters yielded enantiopure 2-aminotetraline **609** (Scheme 181).⁸⁵

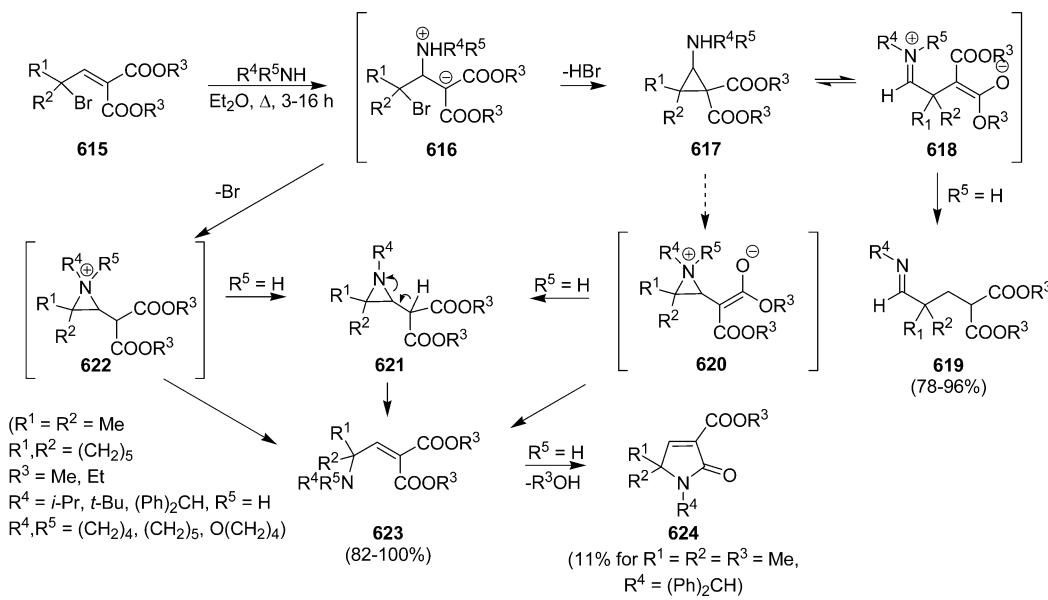
Elaboration of a synthetic route toward a novel potential dipeptidylpeptidase inhibitor used a similar reaction step to build the carbon skeleton of amide **612**. *N*-Boc-protected functionalized aziridines **133** underwent ring opening in a regioselective manner by the Grignard reagent derived from 1-bromo-2,4,5-trifluorobenzene **610**. 3-Aminobutanoate **611** was then further converted into amide **612** (Scheme 182).⁸⁶

In conclusion, it can be stated that nucleophilic ring opening of 2-(carboxymethyl)aziridines proceeds regioselectively, except in some cases where oxygen nucleophiles were tested. Furthermore, activation of the aziridine ring prior to ring opening seems to be required.

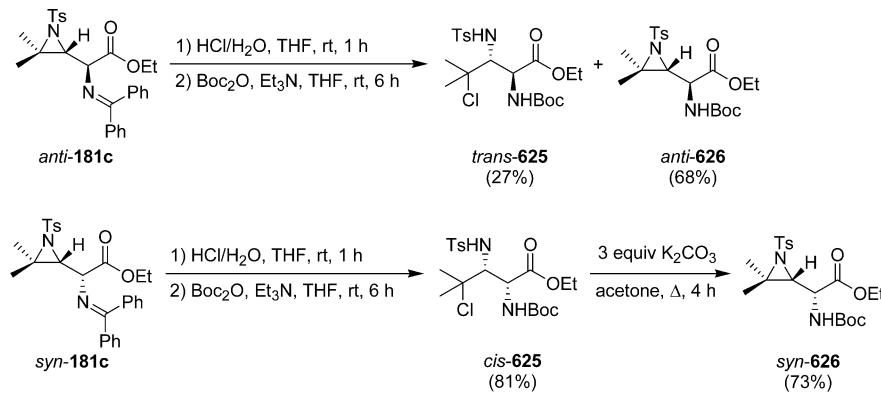
3.4.5. Other. Opening of the aziridine ring has also been accomplished under basic, acidic, reductive, and oxidative reaction conditions.

As mentioned before (Scheme 34), treatment of α -methoxy- β,γ -aziridinocarboxylate **166a** with NaOMe in MeOH under reflux furnished α,β -unsaturated ester **167a** via a NaOMe -induced ring opening of aziridine **166a**. Due to the presence of the acidic proton at the α -position of the ester, deprotonation followed by ring opening of the aziridine yielded methyl 4-aminocarboxylate **167a** (Scheme 183).^{106,107}

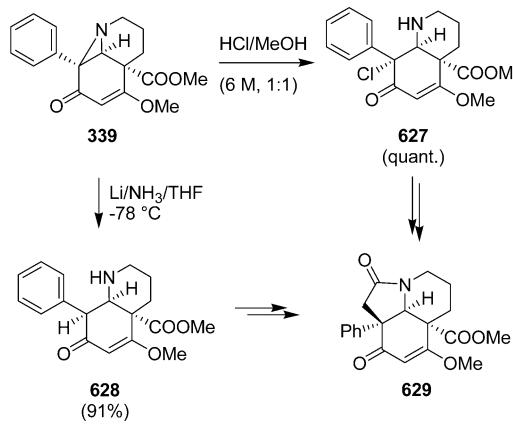
Scheme 186



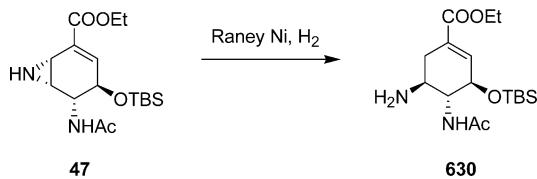
Scheme 187



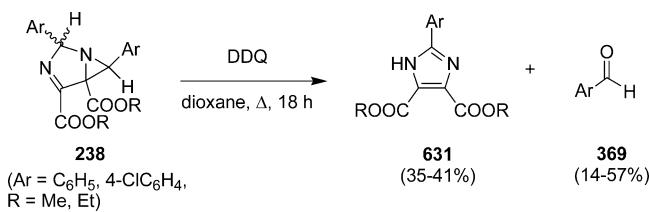
Scheme 188



Scheme 189



Scheme 190



A similar base-induced ring opening was observed upon treatment of *N*-tosyl aziridine 181c with KOtBu in THF at room temperature (Scheme 184). Both the *anti* and *syn* adducts 181c were transformed into the same Z-pentenoate 485. Apparently, isomerization of the *anti*-aziridine to the *syn*-aziridine preceded base-induced ring opening.¹¹⁸

Treatment of *N*-tosyl aziridine 127 with aromatic Grignard reagents in a synthetic route toward 4-aminotetralines (vide supra) yielded unsaturated *tert*-butyl 4-aminocarboxylate 614 as a side product in 4–27% yield (Scheme 185).⁸⁵ Remarkably, this side reaction was not observed upon treatment of the

corresponding *N*-benzyloxycarbonyl protected aziridines with Grignard reagents.

In the reaction of electrophilic allyl halides 615 with primary and secondary amines, 2-(carboxymethyl)aziridines 621 were suggested as intermediates, which rearranged to give the more stable allylamines 623 (Scheme 186). This hypothesis was supported by tentative identification of aziridine 621a ($R^1 = R^2 = R^3 = \text{Me}$, $R^4 = (\text{Ph})_2\text{CH}$, $R^5 = \text{H}$) in the crude reaction mixture after treatment of allyl bromide 615 with benzhydrylamine.²⁴⁰ γ -Lactam 624a was formed from aziridine 621a due to acid-catalyzed ring opening and lactamization during purification via silica gel chromatography.

Besides the base-induced ring opening of 2-(carboxymethyl)-aziridines, ring cleavage under acidic conditions has also been observed. In an attempt to deprotect the diphenylmethylidene-neamino function in the α -position of the ester of aziridines 181c followed by a reprotection using Boc₂O, chlorides 625 were formed as side products. In case of the *syn*-aziridine 181c, chloride 625 was the main reaction product and could be converted into the desired aziridine 626 by treatment with K₂CO₃ (Scheme 187).¹¹⁸

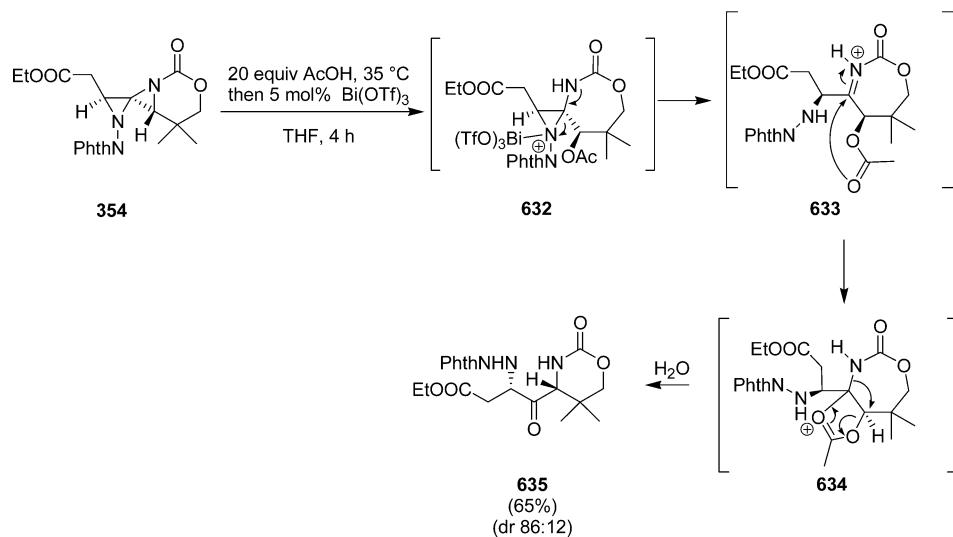
Acid-induced ring opening of tricyclic aziridine 339 could be achieved by treatment with HCl in MeOH. Bicyclic compound 627 was obtained as a single diastereomer, which indicates that a S_N2-type attack of the chloride anion occurred at the protonated aziridine. Chloride 627 was then further converted into the tricyclic core 629 (Scheme 188). Opening of the aziridine ring in tricyclic compound 339 under reductive reaction conditions occurred by treatment with Li in NH₃. Again, this bicyclic compound was further converted into the envisaged end product 629 (Scheme 188).¹⁸⁹

Another example of the reductive ring opening of a 2-(carboxymethyl)aziridine is depicted in Scheme 189. Cyclohexene-fused aziridine 47 was converted into ethyl 5-amino-cyclohexenecarboxylate 630, a precursor of oseltamivir, by treatment with Raney nickel under a H₂ atmosphere in an overall yield of 27% starting from epoxide 46 (Scheme 7).⁴⁸

As mentioned before (Scheme 29), deprotection of benzyl β,γ -aziridinocarboxylate 139 using Pd/C under H₂ atmosphere was accompanied with opening of the aziridine ring. Apparently, the corresponding aziridinocarboxylic acid was not stable under the reductive reaction conditions.

Oxidative ring cleavage has been observed upon treatment of bicyclic dimers 238 (vide supra) with DDQ and furnished imidazoles 631 and aromatic aldehydes 369 (Scheme 190).¹⁴⁸

Scheme 191



3.5. Neighboring Group Effects

A ring-opening reaction that could not be classified in the previous sections is depicted in Scheme 191. Treatment of 1,4-diazaspiro[2.2]pentane **354** with glacial acetic acid in the presence of Bi(OTf)₃ led to formation of 1,3-oxazinan-2-one **635**. Since simple acid-catalyzed hydrolysis of spirocompound **354** did not lead to formation of oxazinan-2-one **635**, careful optimization of the reaction conditions was performed and the mechanism depicted in Scheme 191 was premised. After initial ring opening of the oxazinanone-fused aziridine ring by acetic acid, intermediate **632** was formed. Activation of the second aziridine ring by Bi(OTf)₃ in combination with the neighboring group participation of the nitrogen substituent at C2 led to ring opening and formation of intermediate **633**. Further rearrangement furnished 1,3-oxazinan-2-one **635** in 65% yield.²⁰⁶

4. CONCLUSIONS AND PERSPECTIVES

Recently, aziridines have gained a lot of interest among organic and medicinal chemists as these strained azaheterocycles comprise versatile building blocks for synthesis of a wide range of biologically active nitrogen-containing compounds. Their broad utility has made these aziridines, more specifically the 2-(carboxymethyl)aziridines, a class of useful and attractive substrates in contemporary organic synthesis. Therefore, new synthetic approaches for construction of 2-(carboxymethyl)-aziridines are required, as the current available methodologies often have a limited scope or low yields or limited chemoselectivity. Moreover, application of more appropriate protecting groups at the nitrogen (and carbon) atom would be desirable to allow access to the corresponding unprotected amino acid derivatives. Further elaboration of asymmetric synthetic methods are also required, with special attention to the syntheses of all possible diastereo- and enantiomers. From this point of view, further application of these 2-(carboxymethyl)aziridines as chemical probes, bioactive compounds, and enzyme inhibitors is still largely uninvestigated.

Regarding their chemical reactivity, it is clear that 2-(carboxymethyl)aziridines are already used as synthons for synthesis of a wide range of compounds. As such, 2-(carboxymethyl)aziridines can be considered as densely functionalized building blocks. Nevertheless, additional efforts in the field of intramolecular ring opening and ring-trans-

formation reactions are needed to further explore the chemical space centered around the chemistry of 2-(carboxymethyl)-aziridine derivatives.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: Norbert.DeKimpe@UGent.be.

*E-mail: Sven.Mangelinckx@UGent.be.

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Notes

The authors declare no competing financial interest.

Biographies



Gert Callebaut was born in Zottegem, Belgium, in 1986. He studied at Ghent University, Belgium, where he received his Master of Science degree in Bioscience Engineering: Chemistry and Bioprocess Technology in 2009. During these studies he carried out research under the guidance of Professor N. De Kimpe, studying the use of *N*-sulfinyl- α -chloroimines in the asymmetric synthesis of new β -amino acid derivatives. After receiving a scholarship from the agency for Innovation by Science and Technology, he enrolled in the Ph.D. program at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Belgium, with Professor N. De Kimpe and Professor S. Mangelinckx as

promoters. He obtained his Ph.D. degree in December 2013, and his main interests include the synthesis and applications of chiral *N*-sulfinylimines and -aziridines.



Tamara Meiresonne (1986, Eeklo, Belgium) obtained her Master of Science degree in Bioscience Engineering: Chemistry and Bioprocess Technology from Ghent University, Belgium, in 2009. She performed her Master thesis at the Department of Sustainable Organic Chemistry and Technology. Since October 2009 she has been performing Ph.D. research concerning the synthesis of fluorinated and nonfluorinated amino acid analogs at this department under the guidance of Professor N. De Kimpe and Professor S. Mangelinckx. As an assistant at the department, she is currently in the fourth year of the program.



Sven Mangelinckx obtained his Master degree in Bioscience Engineering-Chemistry in 2001 and Ph.D. degree in 2006, both from Ghent University (Belgium). Subsequently, he was appointed as Postdoctoral Fellow of the Research Foundation-Flanders (FWO) in the group of Professor N. De Kimpe (2006–2012) and postdoctoral researcher in the SynBioC research group of Professor C. Stevens (2012–2013). In 2010 he performed a short postdoctoral stay at the Institute of Organic Chemistry, RWTH Aachen (Germany), with Professor D. Enders. In 2013, he was promoted to Associate Professor at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University. His main research interests include the chemistry of nonproteinogenic amino acids, small-membered azaheterocycles, and isolation and synthesis of bioactive natural products. He is the author of 63 publications in international peer-reviewed journals.



Norbert De Kimpe obtained his diploma of chemical agricultural engineer (1971), Ph.D. degree (1975), and habilitation degree (1985) from Ghent University (Belgium). He performed postdoctoral research work at the University of Massachusetts at Boston (1979) and at the CNRS in Paris (1983). He is now Full Professor at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering at Ghent University. He was a guest professor at the Universities of Perpignan, Helsinki, Siena, Barcelona, Sofia, Buenos Aires, and Pretoria. He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia, 1998) and from the University of Szeged (Hungary, 2007). He is the author of 620 articles in international peer-reviewed journals, and his research interests include (1) the synthesis of bioactive heterocyclic compounds and natural products, (2) isolation of bioactive natural products from medicinal plants, and (3) flavor chemistry.

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ABBREVIATIONS

Ac	acetyl
ACAT	CoA-cholesterol acyltransferase
Ala	alanine
Ar	aryl
Arg	arginine
Asp	asparagine
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
CoA	Coenzyme A
CPA	carboxypeptidase A
Cys	cysteine
DAB	2,4-diaminobutyric acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMN	<i>N,N</i> -dimethylamino-1,8-naphthalimide

DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1 <i>H</i>)-pyrimidinone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPBS	Dulbecco's phosphate-buffered saline
ECP	electrochemical potential
Fmoc	9-fluorenylmethyloxycarbonyl
GABOB	γ -amino- β -hydroxybutyric acid
Gly	glycine
GPAT	glycerol 3-phosphate acyltransferase
HBTU	<i>o</i> -(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
Hex	hexyl
HFIP	hexafluoroisopropanol
His	histidine
HMPA	hexamethylphosphoramide
HOEt	1-hydroxybenzotriazole
IC ₅₀	half-maximal inhibitory concentration
Ile	isoleucine
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LG	leaving group
Lys	lysine
<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid
Mes	2,4,6-trimethylphenyl
Met	methionine
MOM	methoxymethyl
MPa	megapascal
Ms	methanesulfonyl
MW	microwave
Nu	nucleophile
OAM	ornithine 4,5-aminomutase
Ns	nitrobenzenesulfonyl
PIDA	phenyliodine(III) diacetate
Phe	phenylalanine
PhthN	phthalimido
PMP	<i>p</i> -methoxyphenyl
PNB	<i>p</i> -nitrobenzyl
Pro	proline
pTol	<i>p</i> -tolyl
py	pyridine
rt	room temperature
Sar	sarcosine
Ser	serine
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TCEP	tris(2-carboxyethyl)phosphine
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
Thr	threonine
TMS	trimethylsilyl
Tr	triphenylmethyl
Ts	4-toluenesulfonyl
Val	valine

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