Aziridine Carboxylates, Carboxamides and Lactones: New Methods for Their Preparation and Their Transformation into α- and β-Amino Acid Derivatives

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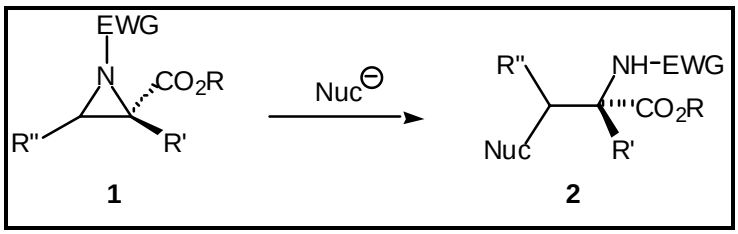
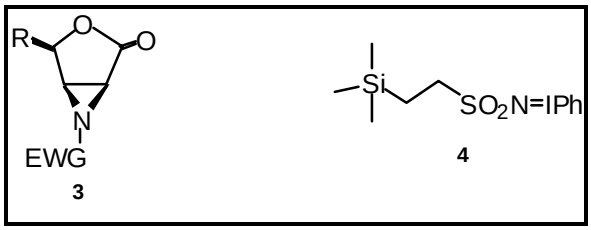
Abstract: The preparation of a variety of novel aziridine-γ-lactones (**3**) from carbohydrates is described. In contrast to aziridine-2-carboxylates, the lactones react regiospecifically at C-2 with soft nucleophiles to provide optically pure substituted β-amino acid precursors. Hard nucleophiles react exclusively at the C-3 position to provide α-amino acid precursors. The utility of this methodology was demonstrated by the preparation of (3S,4S)-dihydroxy-L-glutamic acid (DHGA) from the appropriate aziridine-γ-lactone. DHGA was subsequently shown to be a selective partial agonist of mGluR1 receptors. A more concise preparation of aziridine-γ-lactones was achieved by 1,4-Michael addition of benzylamine to 2-O-triflylbutenolides. Use of a 2-O-mesylbutenolide led, under the same conditions, to the corresponding aziridine-2-carboxamides or 2-carboxylates. Finally, a new Evans-type aziridinating agent, Ses-iminoiodinane, was developed and shown to react efficiently with unsaturated substrates to give the corresponding aziridines, whose N-Ses protecting groups can be removed under mild conditions.

Introduction

α- and β-Amino acids, both natural and unnatural, are important synthetic targets in organic chemistry. While synthetic methodologies for the common amino acids encountered in nature have been well developed, those for less commonly occurring amino acids or for completely non-natural amino acids are areas of continuing effort. Many non-natural amino acids have been shown to display biological activity by virtue of their capacity to bind to receptors or to inhibit enzymes. Such molecules can also be used to impart biological and conformational stability to the peptides they are incorporated in. The use of chiral, substituted aziridine-2-carboxylates for the preparation of a variety of non-natural α-amino acids (e.g. **1**) has been amply demonstrated. Thus, attack of **1** by a nucleophile generally leads to opening of the aziridine ring at the C-3 position by an SN_2 process to give β-substituted (R=H) or α,β-substituted ($R^1 \neq H$) α-amino acids.



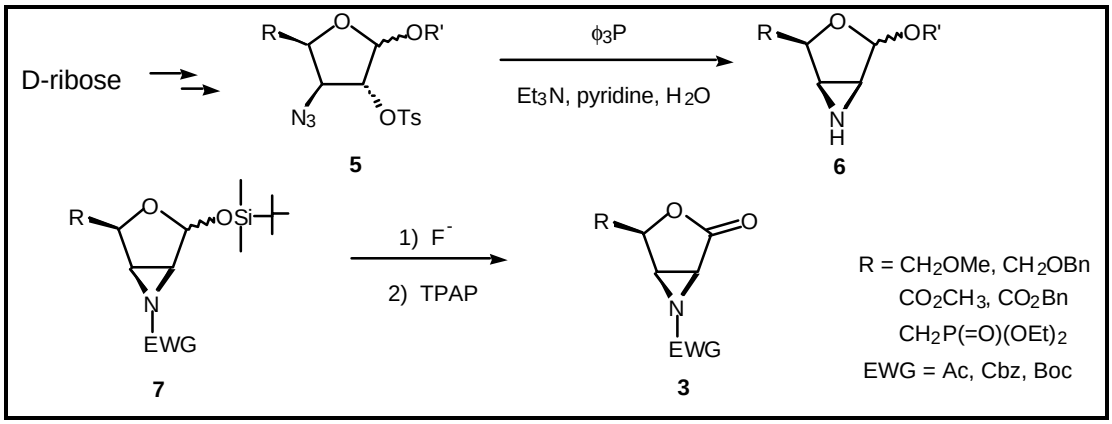
However, the preparation of chiral **1** can pose problems, complete stereoselectivity of the ring opening reaction is not always achieved and β-amino acid derivatives are generally not accessible by this process, at best mixtures of α- and β-amino acids being obtained. To bypass some of these problems, we describe the use of aziridine-γ-lactones **3** for the enantiospecific synthesis of α- or β-amino acid derivatives.



The development of a new Evans-type aziridinating agent, the Ses-iminophenyliodinane **4**, is also described.

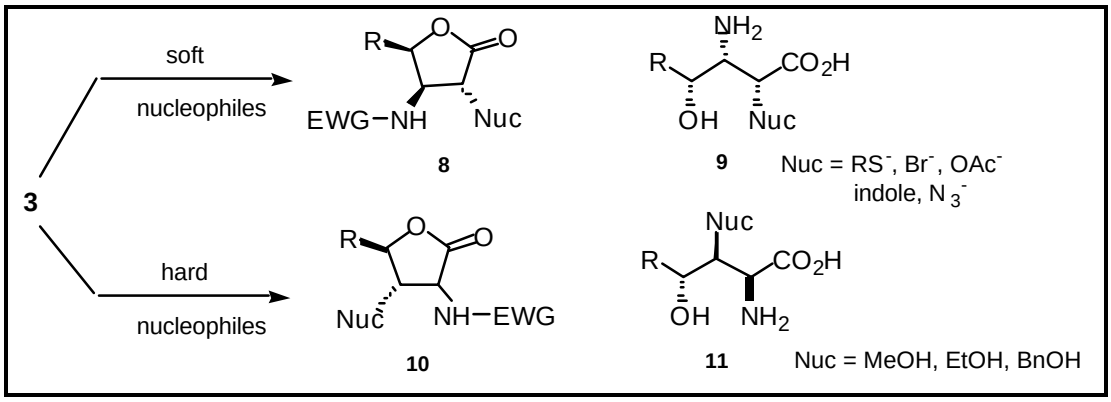
Synthesis and Reactivity of Aziridino-γ-lactones

Optically pure 4-substituted 2,3-aziridino-γ-lactones can be prepared in 10 to 12 steps (depending on the substituent at the C-4 position) from carbohydrate precursors, notably D-ribose or D-lyxose. Key steps include the transformation of a 2-O-tosyl-3-azido furanoside (e.g., **5**) into an aziridine (e.g., **6**) via a modified Staudinger reaction and conversion of the trialkylsilylfuranoside **7** into the desired aziridine-γ-lactone by sequential treatment with fluoride anion and TPAP [1-4].



The reaction of aziridine-γ-lactones with a variety of nucleophiles led to different regioselectivities of aziridine ring opening depending on the nature of the nucleophiles [5,6]. Thus, soft nucleophiles

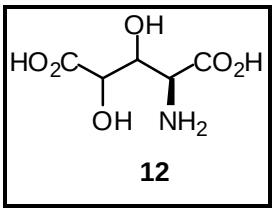
gave exclusively the product of C-2 attack, in contrast to reaction of these nucleophiles with aziridine-2-carboxylates (**1**), which attack only at the C-3 position (to give α-amino acids **2**). This unexpected regioselectivity in the case of aziridine-γ-lactones thus gives access to substituted β-amino acids (e.g., **9**) in an enantiospecific fashion.

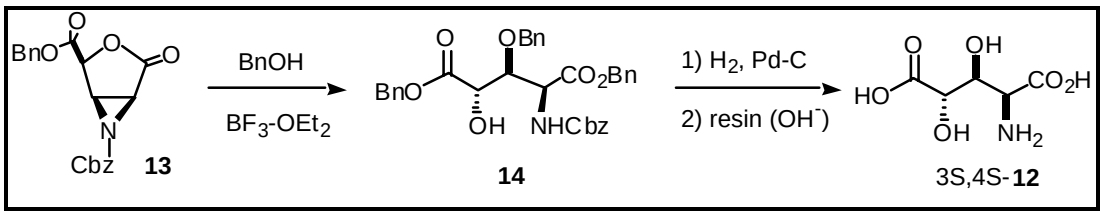


On the other hand, reaction of aziridino-γ-lactones with hard nucleophiles (i.e. alcohols) leads uniquely to the product of C-3 attack (e.g. **10**), a precursor of optically active α-amino acids (e.g. **11**). The use of the equivalent aziridine γ-lactone prepared from D-lyxose produces amino acids having the D-configuration.

Use of Aziridine-γ-lactone Methodology for the Preparation of Biologically Active Amino Acids

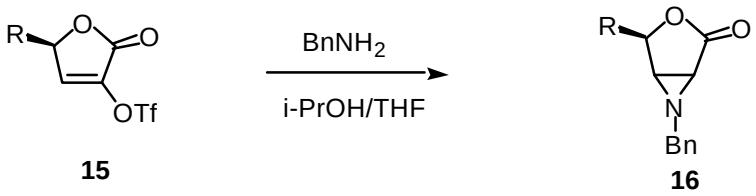
3,4-Dihydroxy-L-glutamic acid (**12**) is a natural product of unknown configuration isolated from a variety of plants and mushrooms. As part of a program aimed at the discovery of novel, selective ligands of the glutamic acid receptors of the central nervous system, we undertook the synthesis of one of the stereoisomers of 3,4-dihydroxyglutamic acid (DHGA) in order to study its activity. This was done by first preparing the appropriate aziridine-γ- lactone **13** and reacting it with benzyl alcohol to give the protected glutamic acid derivative **14**. Hydrogenolysis of the latter led to isolation of the (3S,4S)-isomer of dihydroxy-L-glutamic acid [7]. Pharmacological study of this compound showed that it is a partial but selective agonist of metabotropic glutamic acid receptors of type 1 (mGluR1) [8].



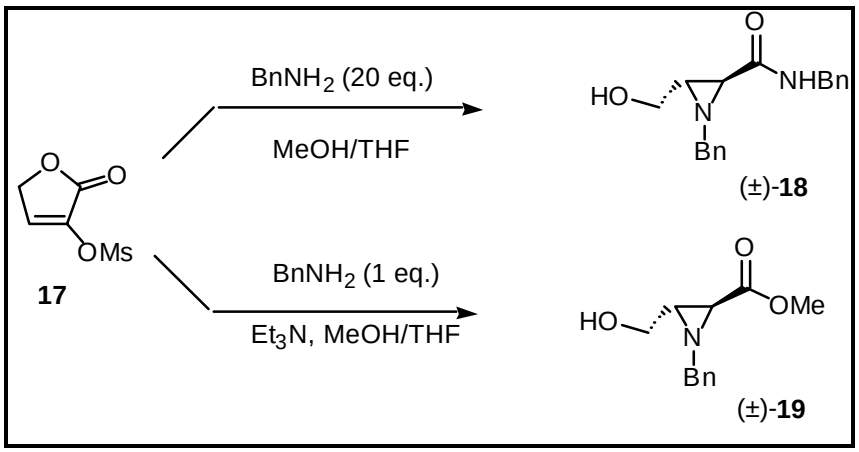


Development of a More Concise Procedure for the Preparation of Aziridine-γ-lactones

Having demonstrated the utility of aziridine-γ-lactones for the enantiospecific synthesis of multi-substituted α- and β-amino acids, we next turned our attention to the development of a more efficient route to these synthons. A very simple procedure was found to consist of 1,4-Michael addition of benzylamine to the 2-O-triflylbutenolides of type **15** to give in one step, the N-benzyl aziridino-γ-lactones **16**. In the case of R=H, a mixture of enantiomers was obtained. When R was a bulky substituent such as a benzyloxymethyl group, only a single isomer of **16** was obtained (aziridine ring *trans* to the R group), though in modest yield.

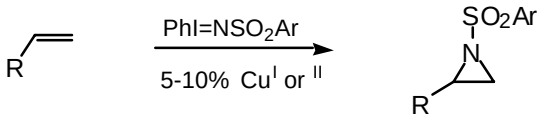


Interestingly, use of the mesylate analogue of **15** (i.e. **17**) gave entirely different results. The reaction of **17** with excess benzylamine in methanol-THF gave as major product the *trans* aziridine-2-carboxamide (±)-**18** while use of only one equivalent of benzylamine in methanol-THF led to formation of the analogous aziridine-2-carboxylate (±)-**19**. This represents a novel procedure for the formation of aziridine carboxylates and carboxamides.

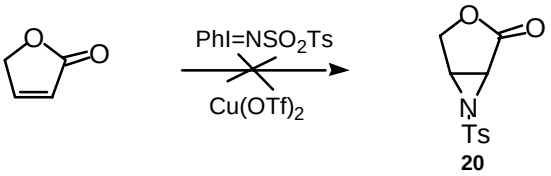


Development of a New Aziridination Reagent, Ses-iminophenyliodinane

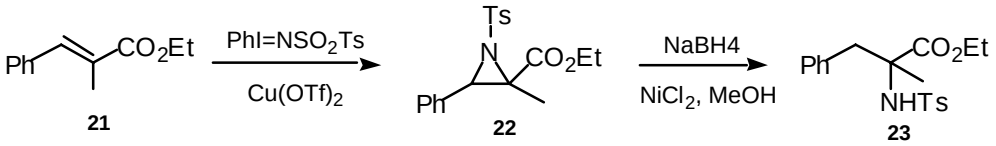
The copper-catalyzed aziridination of olefins developed by Evans involves the formation of a nitrene generated from an (arenesulfonyl)iminophenyliodinane.



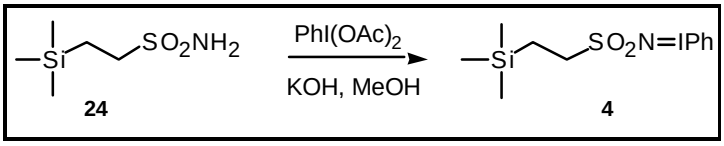
Enantioselectivity can be controlled by the addition of chiral ligands to the reaction mixture. While an attempt to prepare aziridine-γ-lactones (e.g. **20**) by Evans

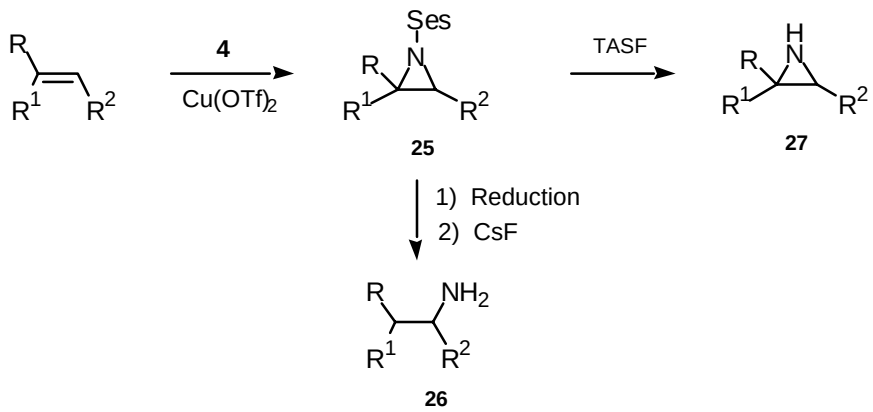


aziridination of a butenolide was unsuccessful, we have been able to prepare α–methyl α-amino acids by reaction of substituted acrylates and cinnamates with an iminoiodinane [9]. For example, treatment of cinnamate **21** with N-tosyliminoiodinane gave aziridine **22** which could be reductively opened to afford the α-methyl phenylalanine derivative **23**.



Because N-arenesulfonyl blocking groups are sometimes difficult to remove, we decided to prepare an iminophenyliodinane-type reagent incorporating an easily removable (trimethylsilyl)ethanesulfonyl (Ses) functionality (e.g. **4**). This was achieved by reacting (trimethylsilyl)ethanesulfonamide **24** with iodosobenzene diacetate [10]. Reagent **4** reacts well with unsaturated substrates to give the corresponding N-Ses aziridines (**25**). The aziridine can be opened and the Ses group removed using fluoride anion (e.g. **26**). Alternatively, reaction of **25** with TASF yields the N-deprotected aziridine **27**.





Conclusion

Aziridine-γ-lactones can now be considered important synthons for the enantiospecific synthesis of a wide variety of substituted α- and β-amino acids. Moreover, their new method of preparation from butenolides makes these molecules easily accessible. While the new aziridinating agent developed, Ses-iminoiodinane, cannot be used to form aziridine-γ-lactones from butenolides, this reagent has been shown to be extremely efficient in forming N-Ses aziridines in general from unsaturated substrates, with the added advantage that the N-Ses blocking group can be easily removed either before or after nucleophilic opening of the aziridine ring.

References and Notes

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