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Enantiospecific, Stereoselective Synthesis of Enantiomerically Pure Aziridine-2-carboxylic Acids from Aspartic Acid

Marco A. Montaos, Eduardo Fernández-Megía, Celia Penide and F. Javier Sardina*

Departamento de Química Orgánica. Universidad de Santiago de Compostela, 15706 Santiago de Compostela. SPAIN.
E-mail: qojskd@usc.es

Abstract: Enantiomerically pure aziridine-2-carboxylates containing a CH_2OMs group, and azetidine-3-mesyloxy-2-carboxylates were prepared by cyclization of 2-amino-3,4-dimesyloxybutyrates, stereoselectiveprepared from aspartic acid. The outcome of the cyclization was dictated by the configuration of the C-3 stereogenic center. The mesylate group of the aziridino mesylates could be displaced by nucleophiles without opening of the aziridine ring.

Keywords: Aziridine-2-carboxylic acids, azetidine-2carboxylic acids, aziridine ring formation, azetidine ring formation.

Introduction

Aziridine-2-carboxylic acids can be viewed as conformationally restricted analogues of both a- and b-amino acids, as well as synthetically useful intermediates due to the high reactivity of the aziridine ring [1]. The interest on this class of compounds has been further deepened by the fact that incorporation of aziridine-2-carboxylate residues into peptides affords compounds with interesting biological activities [1d], or which can be used as probes to study fundamental biological processes [2]. These facts have contributed to draw the attention of several research groups towards the development of syntheses of aziridine-2-carboxylic acid derivatives [1, 3], and the exploration of their chemistry [4]. Despite the numerous efforts in this area the need for a divergent synthetic approach to the many structurally varied aziridine-2-carboxylic acid derivatives from a common precursor is still felt. We describe herein an approach that can provide aziridine-2-carboxylate derivatives incorporating different side chains, analogous to the proteinogenic amino acids.

Discussion

Our retrosynthetic approach is shown in figure 1.

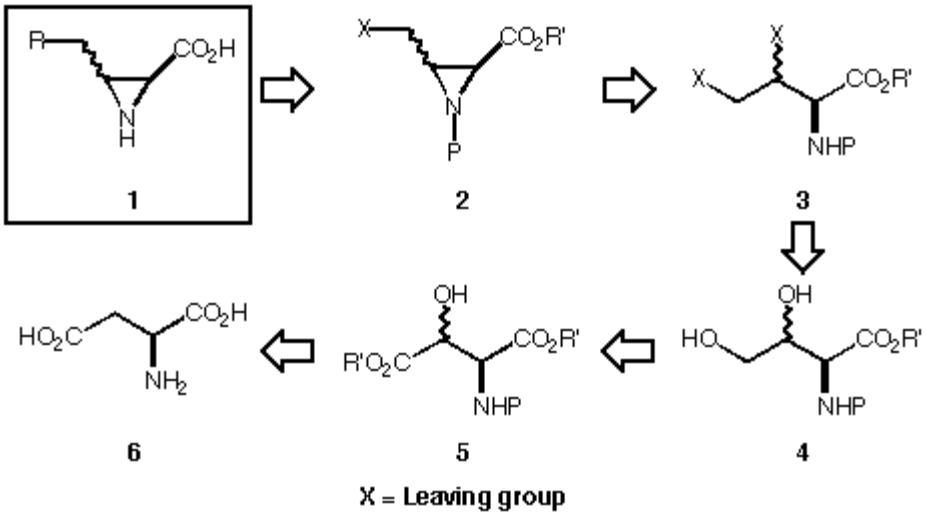


Figure 1

We envisioned the target aziridine-2-carboxylic acids **1** as derived from the reaction of aziridine **2**, armed with a leaving group at the appropriate position, with suitable nucleophiles. In this way a host of different compounds could be prepared from a common precursor. Chemoselective cyclization of a-aminobutyrates **3** should provide the desired key intermediates **2**. In turn, **3** should be available by hydroxylation and selective reduction of a protected derivative of aspartic acid **6**.

We have recently reported the efficient, stereodivergent, stereoselective hydroxylation of *N*-9-phenylfluoren-9-yl (Pf) aspartate diesters, which provides access to both C-3 epimers of 3-hydroxyaspartates **5** [5]. The Pf protecting group on the nitrogen atom had three beneficial effects: it allowed us to steer the enolization reaction towards the C-4 carboxylate as well as to control the stereoselectivity of the hydroxylation step; in addition it ensured the integrity of the asymmetric center of the products.

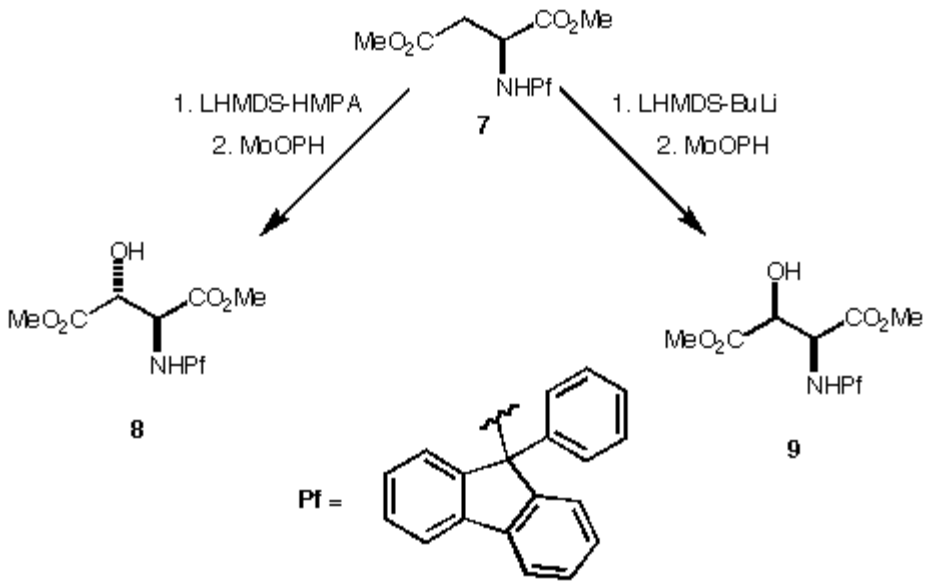


Figure 2

Once a way of introducing the hydroxyl group at C-3, needed for aziridine formation, had been secured, we turned our attention towards the transformation of hydroxyaspartates **8** and **9** into the key intermediates **2**. Chemoselective reduction of the carboxylate group at C-4 was achieved by treatment of **8** or **9** with $BH_2.SMe_2$, and a catalytic amount of $NaBH_4$, at room tempereture [6], affording the dihydroxyamino butyrates **10** and **11** in excellent yield. Attempts to reduce **8** or **9** with other hydride reagents led to overreduction or to the formation of lactones **14** and **15** (figure 3).

Dimesylation of **10** and **11** proceeded uneventfully to provide the substrates for aziridine ring formation, dimesylates **12** and **13**.

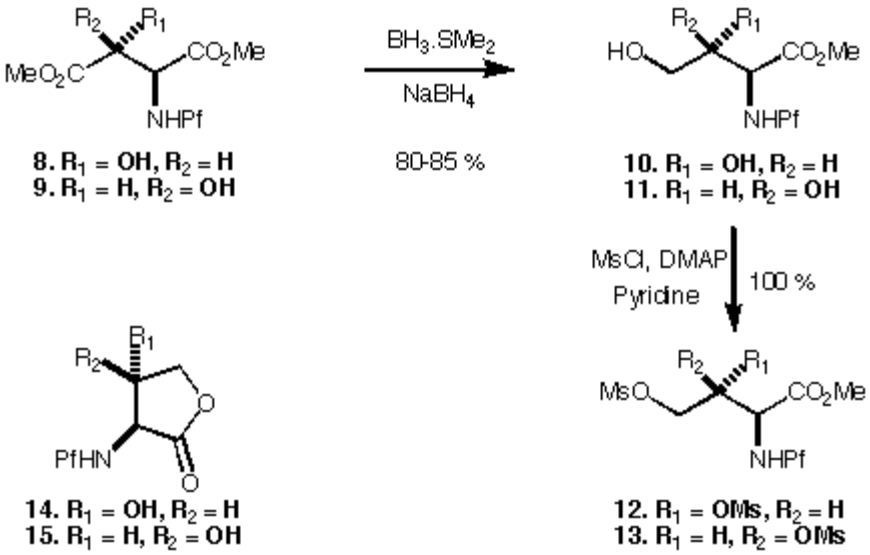
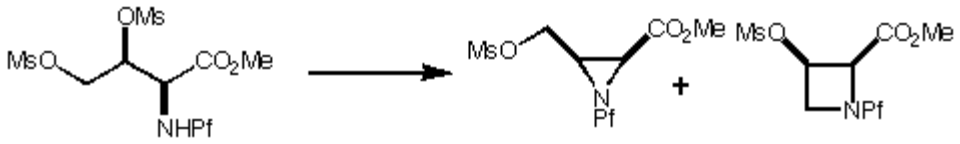


Figure 3

The cyclization of 3-amino-1,2-dimesylates under basic conditions at room temperature has been studied by the group of Pericàs and Riera [7]. These reactions resulted in the *exclusive* formation of aziridino mesylates (in moderate yields for the *cis*- isomers, and good to excellent yields for some of the *trans* isomers), through the displacement of the secondary mesylate; no azetidines, resulting from the displacement of the primary mesyl groups, were detected in the reaction mixtures.

In our case dimesylate **13** was recovered unchanged when treated with Et_3N at 60 °C, but afforded a 4/1 mixture of aziridine **16** and azetidine **17** (80 % yield) when DMF was used as solvent and the temperature was raised to 80 °C.



Solvent/Base	Temperature (°C)	Ratio 16/17
DMF/Et_3N	80	4/1
DMF/Et_3N/$LiClO_4$	92	7/1
THF/Et_3N/$LiClO_4$	Refl.	25/1
Dioxane/s-Collidine/$LiClO_4$	75	100/0

Figure 4

After careful optimization of solvent, base, additives and temperature, the aziridino mesylate **16** could be obtained as the sole reaction product in 91 % yield. In stark contrast with this behavior, the cyclization of dimesylate **12** afforded azetidine **18** as the mayor or exclusive product under all the conditions tested.

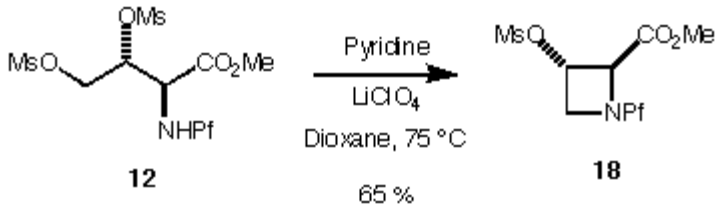
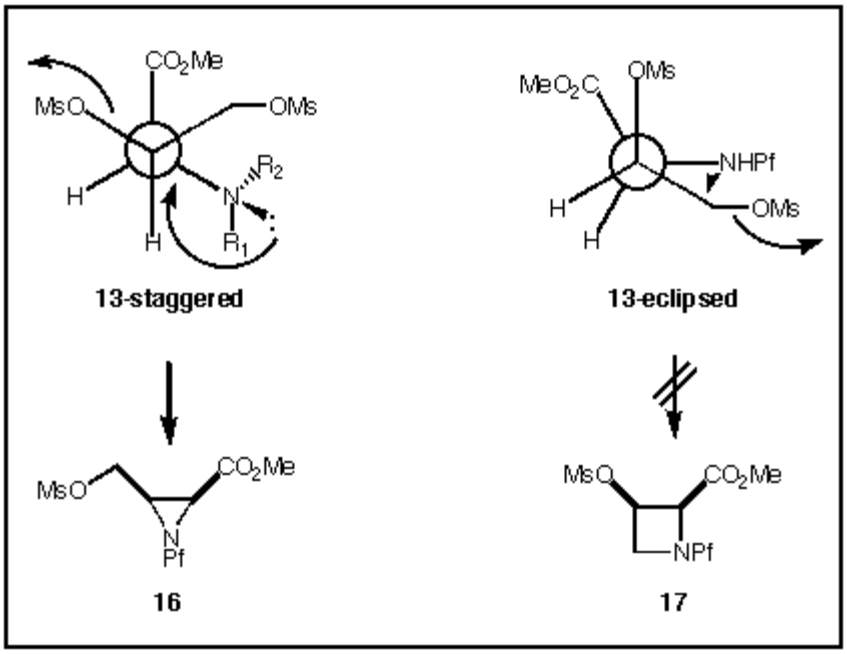


Figure 5

The different outcomes of the cyclizations of **12** and **13** can be rationalized by inspection of the conformations leading to aziridine and azetidine closing for each stereoisomer (figures 6 and 7).

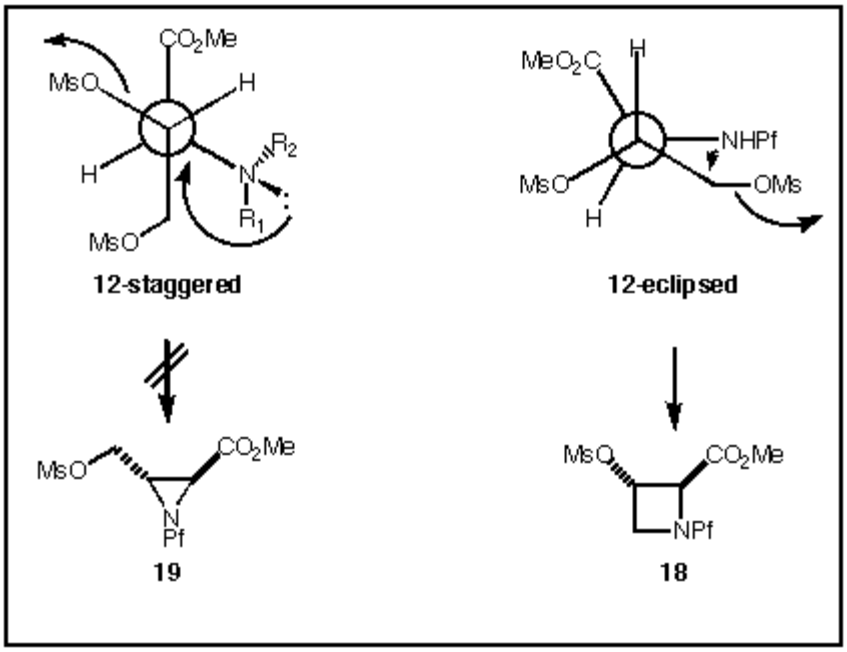
The cyclization of **13** should proceed mainly through the staggered conformation (figure 6) to provide the aziridine **16**, since the eclipsed conformation, that leads to azetidine **17**, has two very unfavorable interactions: CO_2Me-OMs and NHPf-OMs. The addition of $LiClO_4$ favors the formation of the aziridine over the azetidine probably by quelation of the Li cation with both mesyl groups; this should move the mesylate at C-4 away from the trayectory of the nucleophile towards C-3, and increase the selectivity of the cyclization.



R_1, R_2 = Pf, H

Figure 6

In the case of dimesylate **12**, the cyclization to give aziridine **19** should proceed through the staggered conformation, but, in this case as the nucleophile approaches C-3 the bulky Pf group must be disposed in a position in which it should eclipse either the CH_2OMs or the carboxylate group. This unfavorable interactions lead to the cyclization through the eclipsed conformation (to give azetidine **18**) to become competitive (figure 7).



R_1, R_2 = Pf, H

Figure 7

With an efficient synthesis of aziridino mesylate **16** in hand we proceeded to study its reaction with nucleophiles in order to prepare the desired aziridine-2-carboxylates analogues of proteinogenic amino acids. Unfortunately clean displacement of the mesylate group of **16** with a variety of nucleophiles (NaCN, NaN_3, cuprates) did not proceed cleanly. Figure 8 shows a typical result from these reactions

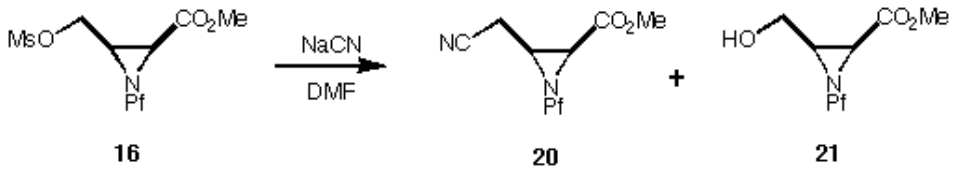


Figure 8

We attributed these failures to the bulkiness of the Pf group, which should hinder the approach towards C-4. Thus we decided to exchange the Pf group for a Boc. Hydrogenolysis of **16** over Pd/C, in the presence of $(Boc)_2O$, afforded the desired Boc-aziridine **22** quantitatively.

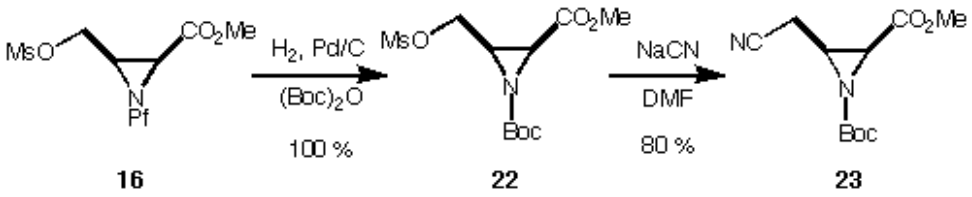


Figure 9

When **22** was treated with NaCN in DMSO at room temperature, the desired cyano aziridine was isolated in good yield, thus opening a route towards the target aziridine-3carboxylates.

We are currently exploring the reaction of **22** with other nucleophiles in order to prepare aziridine analogues of other proteinogenic amino acids.

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