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Synthesis of Nα, Nβ-alkylated Diaminopropionic Acid Analogs

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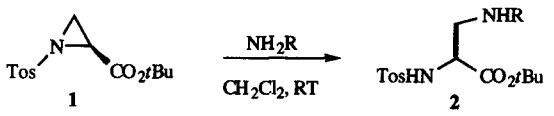
Abstract: A general route for the preparation of Nα-alkylated and Nβ-alkylated derivatives of diaminopropionic acids is described. Nucleophilic ring opening of N-tosyl aziridine-2-*t*-butyl carboxylate with primary amines leads to the corresponding Nβ–alkyl derivative. Reaction of the Nα–tosyl diaminopropionic derivative with Cs_2CO_3 and alkyl iodide selectively produces the Nα-alkylated compound.

L-2,3-Diaminopropionic acid, a non-proteinogenic amino acid found in a variety of natural products, has attracted synthetic attention, and numerous syntheses of 2,3-diaminopropionic acid and closely related analogs[1] have been developed. In order to synthesize novel side-chain functionalized cyclosporin analogs, we needed an efficient route to regioselectively N-alkylated derivatives of α, β-diaminopropionic acid. Herein, we report a general method for preparing this class of compounds by reaction of N-tosyl aziridine-2-*t*-butyl carboxylate at the β-carbon with primary amines, followed by selective sulfonamide alkylation at the α-nitrogen by alkyl iodides.

Activation of aziridine-2-carboxylates with electron-withdrawing groups (e.g. tosyl), or by Lewis acids, is known to lead to nucleophilic attack at the α or β carbon with a variety of nucleophiles.[2] In the case of amines, ammonia attacks the β–carbon of aziridine-2-amides,[3] while primary amines preferentially undergo transacylation with acyl-aziridine peptides.[4] Our initial experiments with N-tosyl aziridine-2-carboxylic acid and methylamine showed that the aziridine was opened at the α- and β-carbons equally well. These results prompted us to direct nucleophilic attack at the β-carbon using sterically demanding esters. Reaction of aziridine-2-*t*-butyl carboxylate[5] **1** with various amines gave excellent yields of the desired β-amino derivatives, resulting in good regioselectivity at the β-carbon (Table 1). Variation of solvent or temperature had little effect on the reaction outcome, except for increased reaction time. However, reactions carried out in a pressure vessel gave slightly improved β:α selectivities and proceeded more rapidly (see general procedure).[10] The absence of racemization was confirmed by comparing the optical rotation of **5** with a sample synthesized by an alternate route.[6]

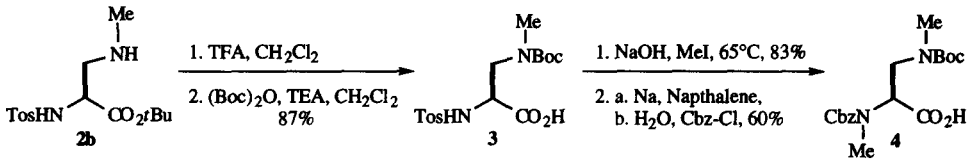
Table 1. Reaction of Aziridine-2-*t*-butyl Carboxylate with Amines



	R	β:α	Yield
a	H	8.5:1	88%
b	Me	6.3:1	90%
c	Et	6.2:1	86%
d	Pr	6.3:1	95%

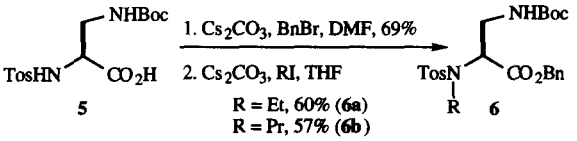
Sulfonamide intermediate **2** can be alkylated at the α-nitrogen[7] under mild conditions. First, the *t*-butyl ester of compound **2** was cleaved, and the β-nitrogen was protected as the carbamate to yield diaminopropionic acid **3** (Scheme 1).

Scheme 1



Compound **3** was alkylated by reaction with NaOH and MeI.[7a] The sulfonamide was cleaved with Na/Naphthalene, and the α-nitrogen reprotected as the benzyl carbamate in a one pot procedure, to give 60% of Nα, Nβ-dimethylated-diaminopropionic acid **4**. However, alkylations with other halides are problematic,[7e-g,i,j] and when ethyl iodide was used in place of methyl iodide, no N-ethyl derivative was obtained. After some experimentation,[8] Cs_2CO_3/THF was found to be an effective method for alkylating sulfonamides with higher order alkyl iodides (Scheme 2).

Scheme 2



Saponification of carbamate-protected N-methyl amino esters can cause racemization,[9] and saponification of (S)-Tos-MeVal-OMe leads to considerable racemization.[7j] Racemization also occurred

when N^{α}-ethyl diaminopropionic ethyl ester, formed in good yield by treating diaminopropionic acid **5** with excess ethyl iodide and Cs_2CO_3, was saponified. To avoid the basic conditions, acid **5** was converted instead to the benzyl ester, which was then alkylated to yield **6a** and **6b** in good yields. Cleavage of the benzyl ester by hydrogenation, which does not to cause racemization,[9] gave the desired acid in quantitative yield.

Together, these procedures provide a general and convenient route to both singly and doubly N^{β}-alkylated and N^{α}-alkylated diaminopropionic derivatives in good yields.

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(10) General Procedure for gaseous amines: The aziridine was dissolved in CH_2Cl_2 (0.1 M) in a pressure flask. After cooling the solution to -15°C, the amine was bubbled in for 15 min. The flask was then closed and the reaction was allowed to warm to RT over 4h. The reaction was cooled to 0°C and the flask was opened allowing the excess amine to slowly evaporate. Concentration of the reaction mixture and silica gel chromatography provided the desired diaminopropionic ester. For liquid amines: The amine (10eq) was added to a solution of the aziridine in CH_2Cl_2 (0.1M) at RT. The solution was stirred for 12h, concentrated in vacuo, and applied to a column of silica gel to afford the desired diaminopropionic ester.

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