ORGANIC LETTERS

2007
Vol. 9, No. 21
4399−4402

Convenient Synthesis of *trans*-β-Amino Carboxylic Esters with an Azetidine Skeleton via Rearrangement of β,γ-Aziridino α-amino Esters

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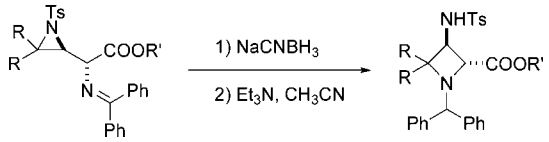
Received August 20, 2007

ABSTRACT



A short and facile approach to biologically interesting N-protected alkyl 3-aminoazetidine-2-carboxylic esters, a new class of conformationally restricted β-amino esters, was developed. Reduction of *anti*-β,γ-aziridino-α-(*N*-diphenylmethylidene)amino esters and subsequent regioselective intramolecular ring opening of the β,γ-aziridine ring via nucleophilic attack of the α-amino function afforded the *trans*-azetidines.

Azetidines are a very important class of compounds because of their wide range of known biological activities.[1] In the literature, 3-aminoazetidines have received considerable attention,[2] especially because of their antibacterial activities.[3] Many natural products such as mugineic acid,[4] 2′-deoxymugineic acid,[5] nicotianamine,[6] medicanine,[7] antifungal and antibiotic polyoxins,[8] substituted azetidine-2,4-dicarboxylic acids,[9] or pharmacologically important molecules such as trombin inhibitor melagatran[10] incorporate L-azetidine-2-carboxylic acid in their structure. As a constrained amino

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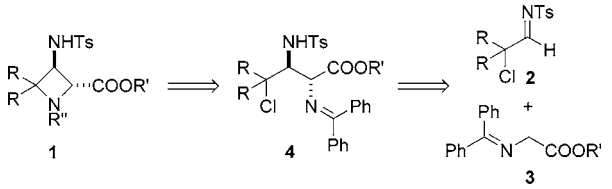
10.1021/ol7020466 CCC: $37.00
Published on Web 09/19/2007

acid, L-azetidine-2-carboxylic acid has found many applications in the modification of peptide conformations.[11] The introduction of conformationally constrained α-amino acids in peptide sequences has been the subject of intensive research in biomedical chemistry.[12,13] These cyclic constrained amino acids in which the nitrogen atom of the amino moiety is part of a ring are of particular interest since these amino acids, when incorporated in peptides, can profoundly influence the spatial conformation of the peptide.[12] In recent years, conformationally constrained cyclic *β*-amino acids also received significant attention as a result of their biological potential.[14] In addition to their pharmacological activities, the alicyclic *β*-amino acids have been used as building blocks for the preparation of biologically active peptides.[15] In the present paper, results are described on the synthesis of alkyl 3-aminoazetidine-2-carboxylates **1**, a new class of cyclic, conformationally restricted α,*β*-diamino ester derivatives,[16] the structure of which incorporates the biologically interesting 3-aminoazetidine moiety as well as the azetidine-2-carboxylic acid moiety. Furthermore, azetidines **1** are the first aza-analogues of oxetin, an antibiotic oxetane *β*-amino acid.[17]

Recently, the Mannich-type reaction of benzophenone imine glycinates **3** with *N*-(*p*-toluenesulfonyl) α-chloroaldimines **2** has been developed for the stereoselective synthesis of *anti*-*γ*-chloro-α,*β*-diamino ester derivatives **4** as intermediates for further cyclization to the corresponding *β*,*γ*-aziridino α-amino ester derivatives **6**.[18] According to the retrosynthetic analysis (Scheme 1), the azetidines **1** should be easily synthesized from the *γ*-chloro-α,*β*-diamino ester derivatives **4** via elaboration of the protected amino function in α-position and subsequent cyclization by intramolecular 1,4-displacement of the chloride at the *γ*-position.

Therefore, the *anti*-*γ*-chloro-α,*β*-diamino ester derivatives **4a**−**e** were synthesized as previously described.[18] To achieve

Scheme 1. Retrosynthetic Analysis of the *trans*-*β*-Amino Ester Derivatives **1** with an Azetidine Skeleton



the cyclization to the azetidine **1a** (R = Me, R′ = Et), the imino functionality in the *anti*-α,*β*-diamino ester **4a** was first reduced with $NaCNBH_3$ in the presence of 1 equiv of AcOH in methanol giving the corresponding amine **5a** in good yield (Scheme 2, path a). The latter amine **5a** was then submitted to the ring closure reaction by treatment with triethylamine in acetonitrile. After being stirred for 20 h at 70 °C, the azetidine **1a** was isolated in 44% yield. However, upon shortening the reaction time of this intramolecular cyclization step of diamino ester **5a** to only 6 h, the aziridine **7a** could be also isolated from the reaction mixture. This observation makes it plausible that the formation of the azetidine **1a** from the α,*β*-diamino ester **5a** occurs via aziridine **7a** as intermediate which undergoes regioselective intramolecular aziridine ring opening by the α-amino group. The latter ring transformation bears similarity to the ring transformation of aziridines derived from α-allylglycines to 4-aminoprolines[19] and the synthesis of azetidin-3-ols from 2,3-epoxypropylamines.[20] For this reason, the synthesis of the azetidine **1a** was performed following another route (Scheme 2, path b). The first step of this path b involved the formation of the *anti*-aziridino amino ester **6a**,[18] which was then reduced in the second step with $NaCNBH_3$ to aziridine **7a**, the same compound which could be isolated in path a, in good yield (86%). Rearrangement of the aziridine **7a** via ring opening by the α-amino group upon treatment with Et_3N in acetonitrile resulted in the same azetidine **1a** as in path a in 80% yield. The synthesis of other azetidine derivatives **1b**−**e** was smoothly accomplished according to the more efficient path b (Table 1).

Table 1. Formation of 3-Aminoazetidine-2-carboxylic Esters **1a**−**e** Starting from α,*β*-Diamino Esters **4**

azetidines **1**	yield[a] (%) path a	yield[a] (%) path b	$J_{H\alpha,H\beta}$[b] (Hz)
1a	36	57	7.43
1b		40	7.43
1c		33	7.15
1d		41	6.88
1e		33	7.43

[a] Isolated overall yield determined starting from α,*β*-diamino esters **4**. [b] Coupling constant between H_α and H_β of azetidines **1** in the ^1H NMR spectra (300 MHz, $CDCl_3$).

The structure and stereochemistry of the aziridine derivatives **6** was proven by X-ray diffraction analysis which

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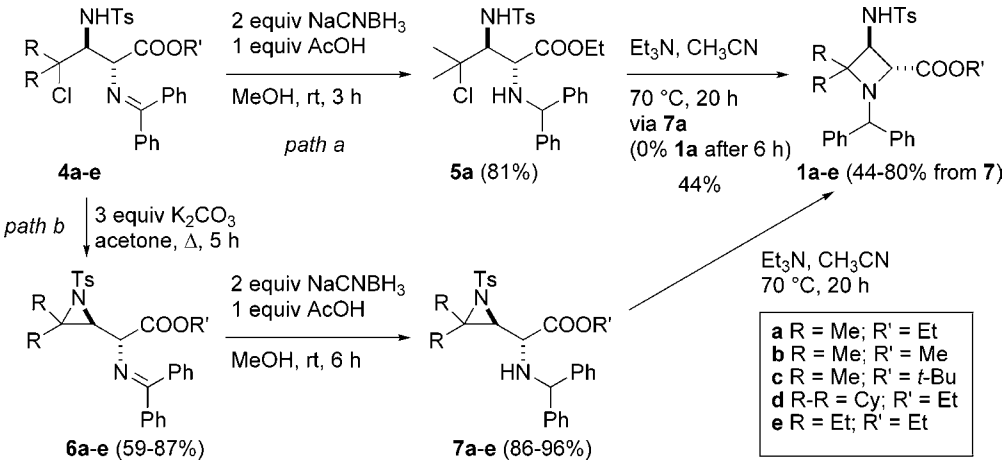
Scheme 2



showed an anti arrangement of the α-amino group and the aziridine moiety.[18] Having performed the ring transformation of different *anti*-aziridino esters **6a**−**e** (R′ = Me, Et, *t*-Bu) bearing several substituents (R = Me, Et or R−R = Cy) (Scheme 2), it can be summarized that the intramolecular aziridine ring transformation reaction in all cases furnishes the azetidines **1a**−**e** with the same relative stereochemistry of the carboxylic ester and exocyclic amino group, based on the small variation of the coupling constant $J_{H\alpha,H\beta}$ (6.88−7.43 Hz). Starting from the relative anti stereochemistry in the starting aziridines **6** and assuming that no base-induced isomerization occurs during the ring transformation to azetidines **1**, the trans stereochemistry in compounds **1a**−**e** can be concluded. According to NOESY experiments of compounds **1a**−**d**, the correlation between the NH and Hα, and the absence of a NOE effect between Hα and H*β* proved the trans arrangement of the tosylamino and the alkoxycarbonyl groups (Figure 1).

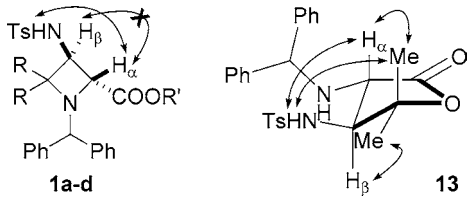
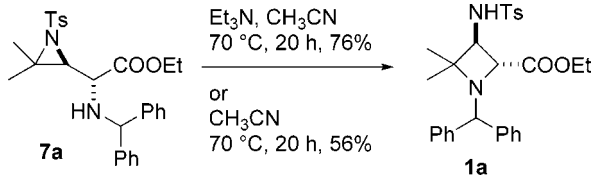


Figure 1. Determination of the trans stereochemistry of azetidines **1** and lactone **13** via NOESY experiments.

The aziridine **7a** underwent cyclization to the same azetidine-2-carboxylate **1a** in refluxing CH_3CN without Et_3N, although with a lower yield as previously in the presence of the base (Scheme 3). This experiment supports the assumption that no base-catalyzed isomerization occurs at the

Scheme 3



α-position in compound **7a** when transformed to azetidine **1a**. To extend the scope of this ring transformation of *β*,*γ*-aziridino α-amino esters to 3-aminoazetidines, also the reactivity of the syn adduct **8**[18] was investigated (Scheme 4). Reduction of the syn adduct **8** with $NaCNBH_3$ afforded diamino ester **9** (89% yield), which was further cyclized to aziridine **11** (59% yield) via treatment with Et_3N in ethanol at 70 °C. The same aziridine **11** was more efficiently synthesized by first cyclization of adduct **8** under basic conditions to aziridine **10**[18] and subsequent reduction (74% yield over two steps). Unfortunately, all attempts to cyclize α,*β*-diamino ester **9** or to induce ring transformation of aziridine **11** to *cis*-ethyl 3-aminoazetidine-2-carboxylate **12** via prolonged heating in acetonitrile or ethanol in the presence of Et_3N were unsuccessful and resulted only in the (re)isolation of aziridine **11** together with untractable decomposition products.

However, in an attempt to activate aziridine **11** toward ring transformation by addition of a Lewis acid, i.e., $LiClO_4$, and heating in acetonitrile, an efficient transformation of the aziridine **11** into α,*β*-diamino-*γ*-butyrolactone **13** (52% yield) was observed. The assignment of trans stereochemistry of 3,4-diamino-5,5-dimethyl-*γ*-butyrolactone **13** is supported by a NOESY experiment (Figure 1) and the observed large coupling constant between H_α and H_β (J_{trans} = 11.3 Hz), which is comparable with experimental (J_{trans} = 11.6 − 12.3 Hz, J_{cis} = 7.3 − 7.8 Hz) and calculated (J_{trans} = 9.9 − 11.0

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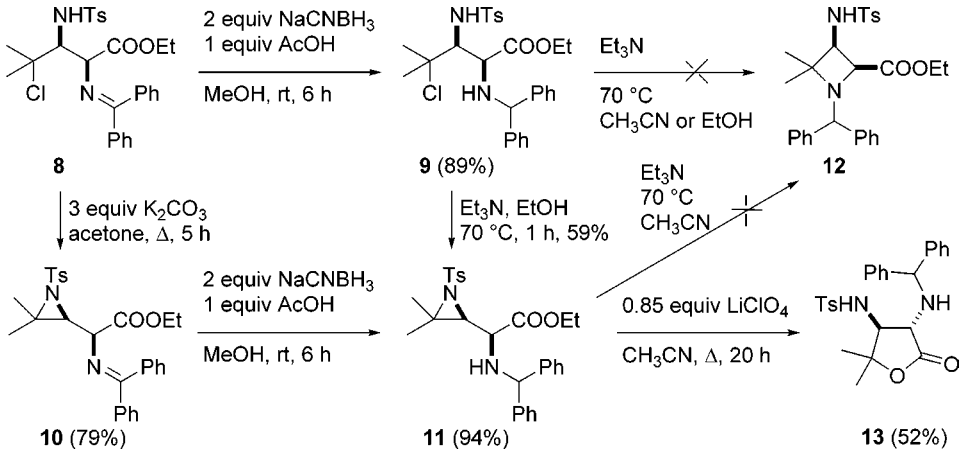
Scheme 4



Hz, J_{cis} = 7.8 − 8.6 Hz) coupling constants between the corresponding protons of similar trans-3,4-disubstituted 5,5-dimethyl-γ-lactones.[21] α,β-Diamino-γ-butyrolactones are important building blocks for the preparation of their corresponding α,β-diamino-γ-hydroxycarboxylic acids,[22] which are constituents of pharmaceutically important β-lactam antibiotics, i.e., isooxacephems.[23] The difference in chemoselectivity of the *anti*-aziridine **7a** and the *syn*-aziridine **11** is ascribed to the occurrence of different conformationally favored rotamers of aziridines **7a** and **11**. Therefore, the nucleophilic attack at the C-3 carbon, which initiates the observed ring transformations to azetidine **1a** and lactone **13**, occurs via the α-amino group of aziridine **7a** and the carbonyl oxygen of aziridine **11**, respectively.

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In conclusion, an efficient short synthesis of a new class of azaheterocyclic β-amino esters, i.e., *trans*-alkyl β-amino-azetidinecarboxylates, from simple aliphatic α-chloro-aldimines and benzophenone imine glycinates as starting materials is described. The key step involved the ring transformation of β,γ-aziridino α-amino ester derivatives to 3-aminoazetidine-2-carboxylic esters.

Acknowledgment. We are indebted to Ghent University (BOF, Bilateral Scientific Cooperation Programme Flanders-Hungary) and the "Fund for Scientific Research-Flanders (Belgium)" (FWO-Vlaanderen) for financial support of this research.

Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7020466