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Small Ring Constrained Peptidomimetics. Synthesis of Aziridine Parallel β-Sheet Mimetics

Silvia N. Filigheddu and Maurizio Taddei*

Dipartimento di Chimica, Università di Sassari, Via Vienna 2, I-07100 Sassari, Italy (E-mail: mtad@ssmain.uniss.it)

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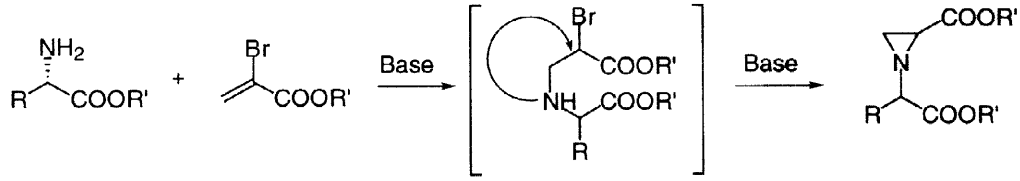
Abstract: The synthesis of a series of novel amino acids and peptides containing an aziridine ring is described. Their preparation is based on the Gabriel-Cromwell reaction of amino acids or peptides with different 2-bromo acrylates and acrylamides. These products are constituted by a turned scaffold (the aziridine) where two parallel peptidic strands can be grown to produce a β-sheet mimetic.

The introduction of a rigid or semirigid core inside an oligopeptidic frame is an efficient way to produce low molecular weight molecules that could efficiently mimic the folding arrangement of an active protein.[1] Although the β-sheet arrangement is one of the most common elements of protein structure domains[2] relatively little progress has been made on parallel or antiparallel β-sheet peptidomimetics.[3]

Following our interest in the synthesis of new peptidomimetics,[4] we report here the preparation of a new peptide-like structure containing an aziridine ring where two parallel peptidic strands can be installed to obtain a mimic of a β-sheet. A common strategy for the synthesis of aziridine carboxylates is the so called Gabriel-Cromwell reaction of primary amines with 2-bromo acrylates.[5] This reaction has the potential to produce peptidic analogues containing aziridines where the aziridine ring is a simple "turned scaffold" containing two terminal carboxylic groups that could be elongated with two parallel peptidic strands. Thus we tried the 1,4 addition of several amino acids and peptides to 2-bromo acrylates and found that the Gabriel-Cromwell reaction is a really simple method for the preparation of this type of small ring containing peptidomimetic (scheme 1).



Scheme 1

At first, model reactions were attempted using simple α-amino acid methyl or *tert*-butyl esters and methyl or *tert*-butyl 2-bromo acrylates, previously prepared[6] or generated *in situ* from the corresponding 2,3 dibromopropionates (Table 1). In a typical experimental procedure the salt of the amino acid ester (generally an hydrochloride, 1 eq) was dissolved in $CHCl_3$ at 0°C in the presence of 3 eq of triethylamine and 2-bromoacrylate (generated from 2,3-dibromopropionate, 1 eq).

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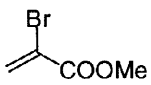
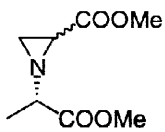
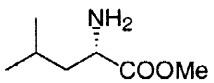
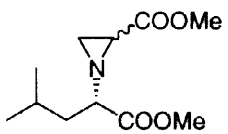
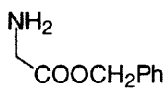
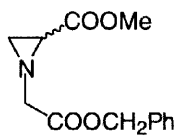
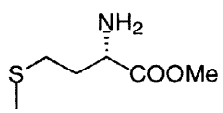
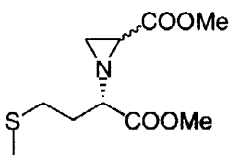
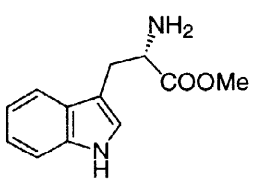
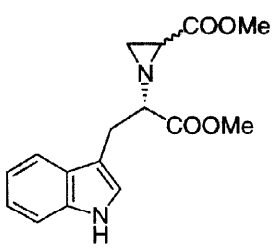
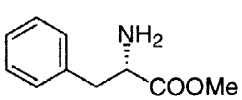
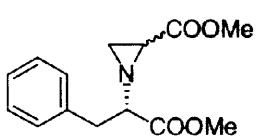
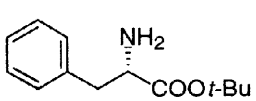
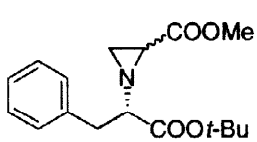
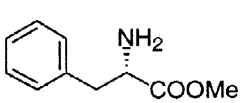
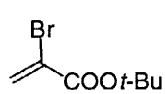
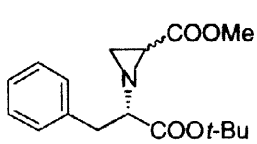
Table 1 . Products of the reaction of **1** or **2** with different amino acids.

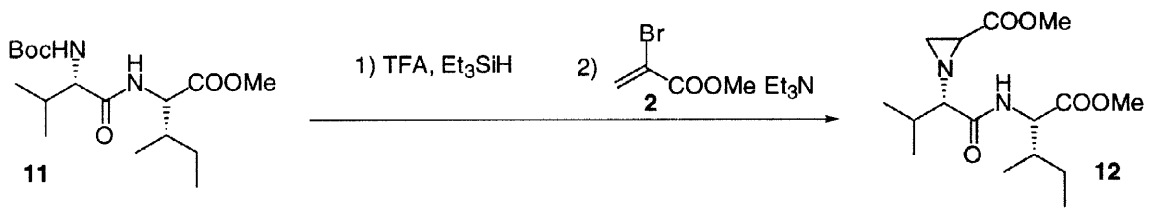
Amino acid ester	Bromo acrylates	Products (diasteroisomeric ratio)[a]	Yields (as mixture of the two diastereoisomers)[b]	
	 **1**		**3** (1.5 : 1)	53%
	**1**		**4** (1.5 : 1)	48%
	**1**		**5**	67%
	**1**		**6** (1 : 1)	60%
	**1**		**7** (1.3 : 1)	60%
	**1**		**8** (1.5 : 1)[c]	72%
	**1**		**9** (1.3 : 1)[c]	30%
	 **2**		**10** (2 : 1)	73%

a) Ratio determined by inspection of the ^{1}H NMR spectra before chromatographic separation. b) Yields of isolated and fully characterized products. c) The same ratio was obtained starting from **1** previously prepared and purified by distillation

The mixture was stirred for 24 h at room temperature and, after aqueous work up, column chromatography on silica gel gave the desired products with the yields reported in Table 1.

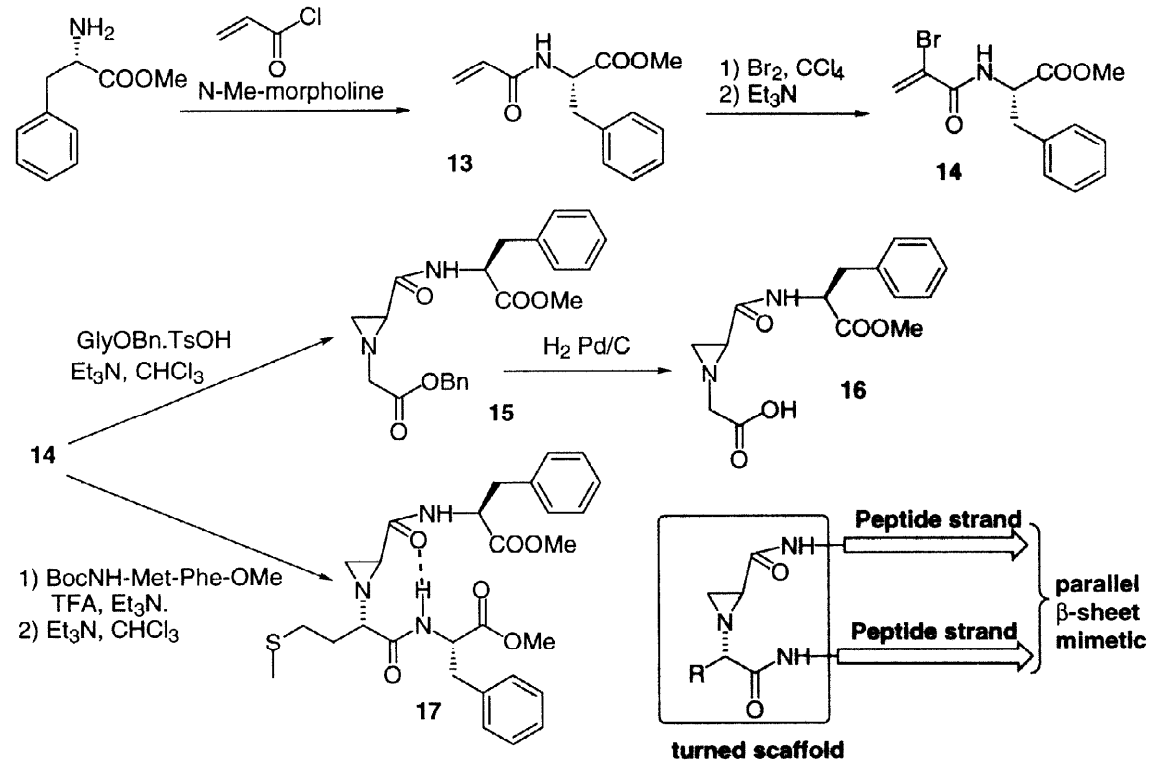
We always obtained a mixture of diastereoisomers that could be separated during flash chromatography. We attempted the reaction with the *tert*-butyl acrylate **2** or with the *tert*-butyl ester of phenyl alanine to verify if the increase of the hindrance at the ester substituent would improve the stereoselectivity[7] but we did not get any appreciable result. Also the use of 2-bromoacrylate **1**, previously prepared and distilled, did not give any improvement in the product composition and yields.

As sometimes medicinal chemists prefer to have access to all the possible diastereoisomers of a certain product to study the influence of the stereochemistry on its pharmacological action, we decided to proceed with the investigations using oligopeptides. Thus dipeptide **11** was prepared using a simple protocol for liquid phase synthesis and, after deprotection at the nitrogen with TFA and Et_3SiH, reacted with **2**, following the standard conditions, to give the aziridine peptide **12** in 50% isolated yield as the sum of the two separated diastereoisomers (scheme 2).



Scheme 2

Analogously the 2-bromo acrylamide of phenylalanine (**14**) was obtained by reaction of freshly distilled acryloyl chloride with phenyl alanine, in the presence of N-methyl morpholine, followed by addition of bromine to the double bond (solvent: CCl_4) and further elimination of HBr mediated by Et_3N (scheme 3).



Scheme 3

This product (**14**) reacted with glycine benzyl ester *p*-tosylate in the presence of Et_3N to give product **15** (65%) that was selectively deprotected at one of the two carboxylic groups (H_2, 1 atm, Pd/C, MeOH) to yield compound **16** in 74% yield. The carboxylic group of **17** could be used to introduce a polypeptide followed, after saponification of the other carboxylate, by introduction of a different peptidic strand.

In a different strategy, the assembly of the two strands was realised during the aziridine ring formation, as exemplified by the preparation of **16**. The N-Boc protected dipeptide methyl ester Boc-Met-Phe-OMe was deprotected at the nitrogen (TFA, Et_3SiH) and the crude trifluoroacetate treated with a solution of **14** and Et_3N in $CHCl_3$ to give **17** in 57% yield as the sum of the two separated diastereoisomers. ^1H NMR studies on one of the isomers of **17** established that at least one of the NH groups was intramolecularly bonded as we observed a downfield shift from δ 7.30, recording the spectrum in 0.1M solution, to δ 7.69 recording the spectrum in 1mM $CDCl_3$ solution.[8]

As this strategy could be applied to solid phase synthesis, we are currently investigating the preparation of libraries of aziridine for enzyme inhibition or other molecular recognition processes and the results will be reported in due course.

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5. Nagel, D.L.; Woller, P.B.; Cromwell, N.H. *J. Org. Chem.* **1971**, *36*, 3911. For more recent references see: Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.* **1994**, *35*, 1653. Cardillo, G.; Gentilucci, L. Tomassini, C.; Visa Castejon-Bordas, M.P. *Tetrahedron Asymmetry* **1996**, *7*, 755. For recent reviews on the synthesis of aziridines see: Osborn, H.M.I.; Sweeney, J. *Tetrahedron Asymmetry* **1997**, *8*, 1693. Zwanenburg, B.; Thijs, L. *Pure Appl. Chem.* **1996**, *68*, 735.
6. Marvel, C.S.; Cowan, J.C. *J. Am. Chem. Soc.* **1939,** *61*, 3156.
7. It is known that the stereoselection occurs during the protonation of the bromo enolate obtained after the Michael-type reaction of the amine that subsequently closes the ring through a S_{N2} mechanism. See Garner in ref. 5.
8. A downfield shift on dilution may be reflective of an intramolecular hydrogen bond as, at this concentration, we assume that the values would be relative to unassociated molecules. Saunders, J.K.M.; Hunter, B.K. *Modern NMR Spectroscopy, a Guide for Chemists*. Oxford University Press, 1989, 208. The same approach was taken in ref. 3.