# Regiospecific ring-opening reactions of aziridines bearing an α,β-unsaturated ester group with trifluoroacetic acid or methanesulfonic acid: application to the stereoselective synthesis of (*E*)-alkene dipeptide isosteres

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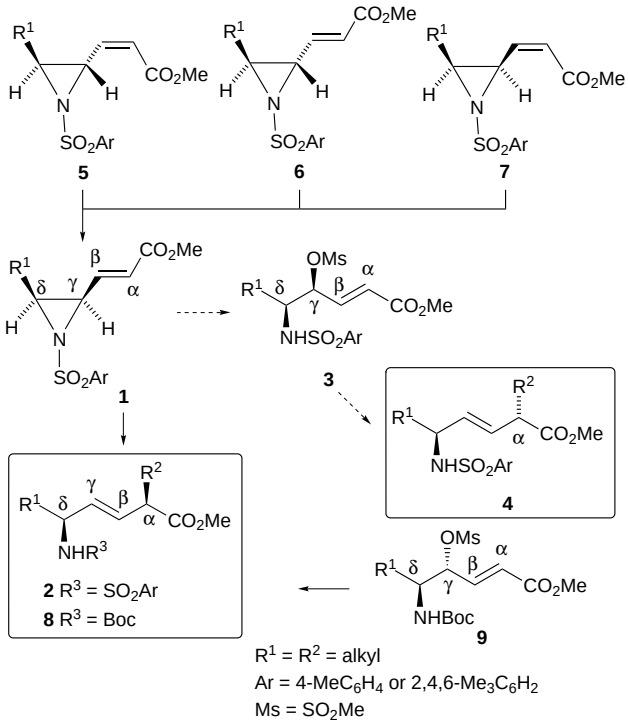
**Reaction of *N*-(2,4,6-trimethylphenylsulfonyl)-γ,δ-*cis*- or -*trans*-γ,δ-epimino (*E*)-α,β-enoates with acids such as TFA or methanesulfonic acid (MSA) affords the stereo- and regioselective ring-opened products in high yields, and subsequent treatment of resulting δ-aminated γ-mesyloxy α,β-enoates with organocopper reagents yields diastereoisomerically pure (*E*)-alkene dipeptide isosteres.**

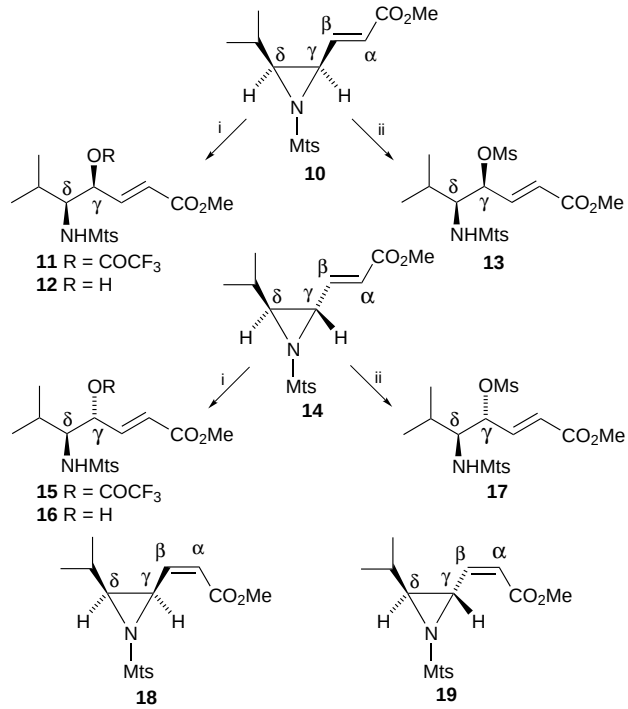
Among various dipeptide isosteres, use of (*E*)-alkene isosteres as backbone replacements of amide bonds in peptides has been well documented.[1] Recently we[2] and others[3] have reported that (*E*)-alkene isostere-containing peptides can exhibit potent biological activity. Because it has been reported that both the (*E*)-configuration and the stereochemistry at the α-position are important factors for biological activity, the stereocontrolled synthesis of both stereoisomers of types **2** and **4** from a single substrate of type **1** would be extremely valuable (Scheme 1). One advantage of such a strategy is that three other stereoisomeric enoates **5**, **6**, and **7** can be converted into the enoate **1** in synthetically acceptable yields merely by exposure to a palladium(0) catalyst (Scheme 1).[4] Previously we and others have developed two synthetic methods for the preparation of diastereomerically pure (*E*)-alkene dipeptide isosteres **2** and **8** by organocopper-mediated *anti*-$S_N2'$ reaction of β-aziridinyl α,β-enoate **1**[5] and δ-aminated γ-mesyloxy α,β-enoate **9**,[6] respectively.

Whereas ample precedent exists that various nucleophilic reagents,[7] including Lewis acids such as acetic acid,[8] TFA[9] and toluene-*p*-sulfonic acid in aqueous acetone,[10] attack simple *N*-unactivated or activated aziridines[11] at either of the two carbon atoms, yielding ring-opened products, the synthetically useful reactions involving γ,δ-epimino α,β-enoates of type **1** with TFA or methanesulfonic acid (MSA) have not previously been reported. Here we report the regio- and stereo-selective ring-opening reactions of aziridines and stereoselective synthesis of (*E*)-alkene dipeptide isosteres by treatment of the ring-opened products with organocopper reagents.

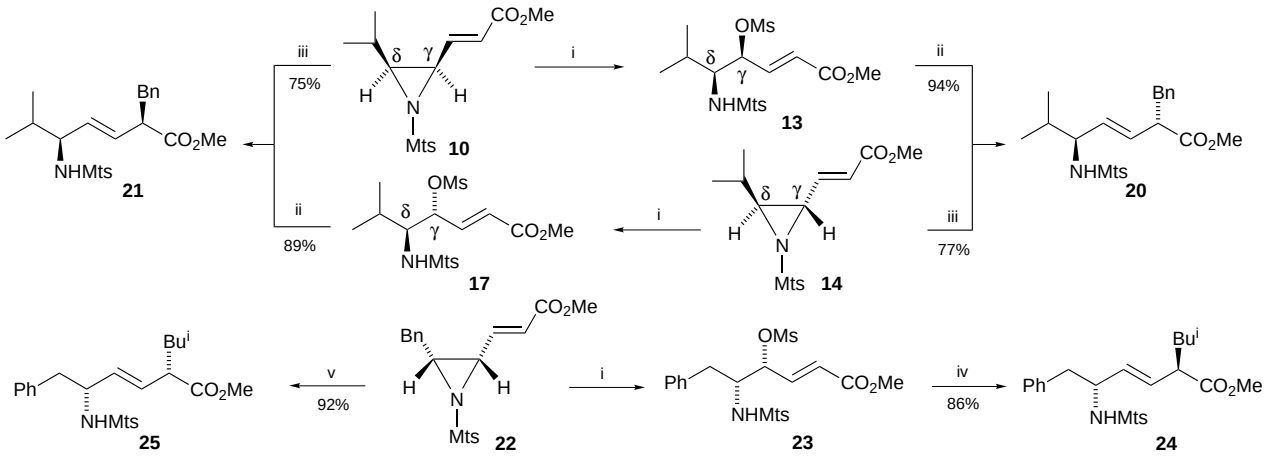
We initially examined ring-opening reactions using TFA. The required diastereoisomerically pure *N*-(2,4,6-trimethylphenylsulfonyl) (Mts)-protected aziridines bearing α,β-unsaturated esters were readily prepared according to reported methods.[4,5] Exposure of enoate **10** derived from L-valine to TFA at room temp. for 15 h afforded γ-trifluoroacetoxy α,β-enoate **11**, presumably *via* regioselective $S_N2$ ring-opening reaction at the γ-carbon position. Hydrolysis of **11** and silica gel flash chromatographic purification yielded the γ-hydroxy α,β-enoate **12** in 93% yield based on **10** (Scheme 2). In a similar manner, treatment of aziridine **10** with MSA (10 equiv.) in $CHCl_3$ at room temp. for 20 min gave exclusively γ-mesyloxy




**Scheme 1**




**Scheme 2** *Reagents*: i, TFA; ii, MSA




**Scheme 3** *Reagents*: i, MSA; ii, BnCu(CN)MgCl·$BF_3$; iii, BnCu(CN)MgCl·2LiCl; iv, $Bu^i$Cu(CN)MgCl·$BF_3$; v, $Bu^i$Cu(CN)MgCl·2LiCl

α,β-enoate **13** in essentially quantitative yield. It was found that the MSA-mediated ring-opening reaction proceeded much more faster than the reaction involving TFA. It is also noteworthy that, in both cases, ring-opened products generated by nucleophilic attack at the α- or δ-carbon positions could not be detected.

Regiochemical assignments for the trifluoroacetate **11** and the mesylate **13** were readily made by $^1$H NMR spectroscopy ($^1$H-$^1$H COSY). The γ,δ-*syn* stereochemistry of the *N*-protected amino alcohol **12** derived from **11** was confirmed by transformation of **12** into the original substrate **10** using the Mitsunobu conditions.[12] Since the mesylate **13** was prone to regenerate the original substrate **10** during silica gel flash chromatographic purification, the mesylate **13** could not be isolated.

Regioselective ring-opening of three other stereoisomeric enoates **14**, **18** and **19** with TFA or MSA was examined. Regioselective ring-opening was successfully carried out on the *trans*-(*E*)-isomer of the aziridine enoate **14** in a similar manner (the yield of **16** based on **14**: 78%). However, treatment of the *cis*-(*Z*)-enoate **18** and the *trans*-(*Z*)-enoate **19** with TFA or MSA gave complex product mixtures. This clearly demonstrates that a slight change in the structure of the substituents can significantly alter the reaction course. Since enoates **18** and **19** can be converted into the enoate **10** *via* $Pd^0$-catalysed reactions,[4] this ring-opening reaction has no significant problems associated with its practical use for the synthesis of (*E*)-alkene isosteres.

Next, treatment of the mesylate **13** with 4 equiv. of BnCu(CN)MgCl·$BF_3$ in THF at −78 °C for 30 min afforded the protected L,D-type (2*S*, 5*S*) dipeptide isostere Mts-L-Val-ψ[(*E*)-CH=CH]-D-Phe-OMe **20** in 94% yield based on **10** (diastereoselection > 99 : 1). This reaction occurred by an *anti*-$S_N2'$ reaction as shown in Scheme 3. In sharp contrast, an *anti*-$S_N2'$ reaction of the *cis*-(*E*)-enoate **10** with 4 equiv. of BnCu(CN)MgCl·2LiCl in THF at −78 °C for 30 min yielded the L,L-type (2*R*, 5*S*) isostere Mts-L-Val-ψ[(*E*)-CH=CH]-L-Phe-OMe **21** in 75% yield, as shown in Scheme 3. One important aspect of MSA-mediated ring-opening reactions is the inversion of configuration at the C-γ carbon *via* an $S_N2$ mechanism. Thus *cis*-(*E*)-enoates produce *syn*-(*E*)-mesylates, which are converted into L,D-type isosteres by organocopper reagents. On the other hand, *cis*-(*E*)-enoates themselves afford L,L-type isosteres with organocopper reagents. In a comparable study, the *trans*-(*E*)-enoate **14** was treated with MSA to yield the *anti*-(*E*)-mesylate **17**, which was converted with the organocopper reagent into the L,L-type isostere **21** in 89% yield based on **14**. In contrast, the organocopper-mediated reaction of the *trans*-(*E*)-enoate **14** afforded the L,D-type isostere **20** in 77% yield. As a result, two types of isosteres were stereoselectively synthesized from either *cis*- or *trans*-(*E*)-enoates. Likewise, the aziridine enoate **22** derived from D-phenylalanine produced the corresponding D,L-type isostere **24** and the D,D-type isostere **25** with the MSA–organocopper and the organocopper treatment, respectively.

In conclusion, regio- and stereo-selective ring-opening reactions of *N*-Mts-protected aziridines bearing an α,β-unsaturated ester by TFA or MSA have been found. These ring-opening reactions provide useful approaches for the stereoselective synthesis of both L,L-type (or D,D-type) and L,D-type (or D,L-type) (*E*)-alkene dipeptide isosteres from either γ,δ-*cis*- or -*trans*-γ,δ-epimino (*E*)-α,β-unsaturated esters. The authors are grateful to Dr Terrence R. Burke, Jr., NCI, NIH, for valuable discussions during the preparation of this manuscript.

## Footnote and References

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