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Chemistry of vinyl sulfones. Approach to novel conformationally restricted analogues of glutamic acid

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Abstract—A totally different approach to conformationally restricted glutamic acid analogues is described, in which one of the acid functions is replaced by a cyclopropanol. The reactivity of cyclopropanol vinyl sulfones toward addition of lithiated Schöllkopf bislactim ether provides a facile synthesis of α-amino acid diastereoisomers. Conformational analysis of these analogues, incorporating solvation effects, and docking to a glutamate receptor model, are used to show the relevance of the conformational restrictions employed.

1. Introduction

S-Glutamic acid (Glu) is the major excitatory neurotransmitter in the central nervous system of vertebrates.[1] Many strategies have been devised to reduce or eliminate the conformational flexibility of the natural ligand. Among these, the most widely used technique is ring insertion. There has been a vast body of work in this area, with the synthesis of three to six-membered carbocyclic analogues, bicyclo[1.1.1]pentane,[2] spiro[2.2]pentane,[3] bicyclo[2.1.1]-hexane,[4] and compounds built upon the bicyclo[2.2.1]heptane,[5] 7-azanorbornane[6] and 2-azanorbornane[7] skeletons. Among all these analogues, the carboxycyclopropylglycines (CCGs) represent the most important source of active analogues for the Glu receptors.[8] The vast majority of analogues described up to the present time have two carboxylic acids, so in order to obtain a totally new approach, we decided to replace one of the carboxylic acids with a cyclopropanol group. This change may also be justified on the basis that the delta carboxylate of glutamate is known to interact with at least some of its ionotropic receptors via a hydrogen bond to an uncharged alcohol sidechain of serine, in contrast to the alpha carboxylate which interacts via a salt bridge with an arginine residue and would probably be more difficult to replace with an uncharged group. We also planned to provide greater conformational rigidity via inclusion of a methyl group, suggesting that amino acids such as **1** or **2** could be of interest (Fig. 1).

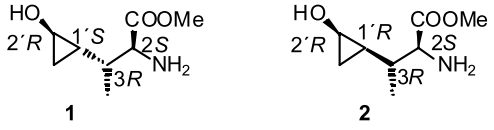

Figure 1. Novel conformationally restricted analogues of glutamic acid.

2. Results and discussion

Recently, we have described a new methodology for the synthesis of cyclopropanols[9] that leads, by choice of the appropriate protecting group and double bond stereochemistry of the allyl sulfone, to *trans* or *cis* 2-substituted cyclopropanols (Scheme 1).[10,11]

The synthesis of amino acid **1** has been described recently[10] following Schöllkopf's methodology,[12] starting from the vinyl sulfone **5**, which in turn is obtained stereoselectively from allyl sulfones **3** or **4**. In this paper we communicate the study of the addition of the lithiated bislactim ether to the vinyl sulfone **6** which presents the *cis* stereochemistry in the cyclopropane ring, and describe how following the same methodology leads to various potential analogues of glutamate.

Keywords: Cyclopropanes; Allyl and vinyl sulfones; Aminoacids.
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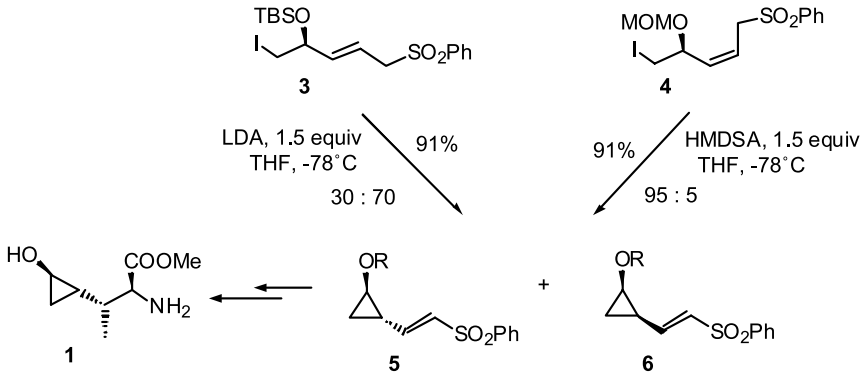


Scheme 1.

The initial coupling of lithiated Schöllkopf's bislactim ether with the vinyl sulfone **6** proceeds in the same way as for the corresponding *trans* diastereoisomer **5**, to give (in this case with complete diastereoselectivity) only one diastereoisomer **8**. This stereoselectivity can be understood by reference to transition states similar to those proposed by Schöllkopf for the addition of the lithiated bislactim ether to α-β unsaturated ester or nitro compounds.[12] The stereochemistry of the addition product **8** was established by examination of the NMR spectra and by means of NOE experiments (Scheme 2).

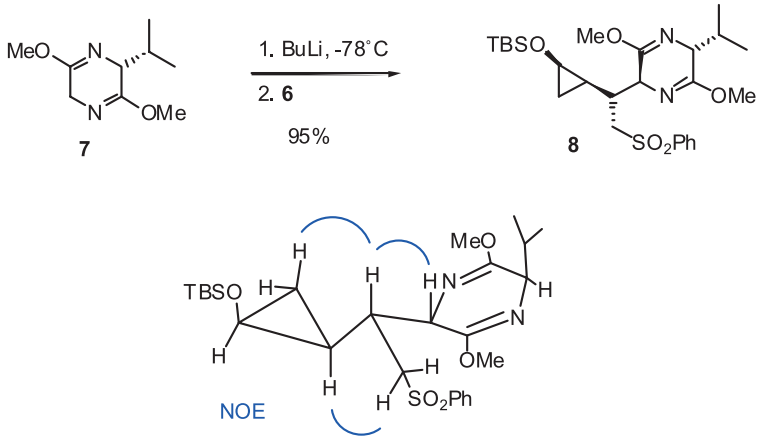
Deprotection of the auxiliary was more problematic than expected. Hydrolysis of compound **8** under the usual conditions gives the required compound **9** in low yield. When compound **8** was treated with TBAF in THF the unstable cyclopropanol **10** was obtained. If, after deprotection of the TBS group, the resulting crude mixture is treated in situ under hydrolytic conditions, compound **11** was obtained as the major component in 84% yield. When shorter reaction times were used, **11** was obtained in 30% yield along with **12** (60% yield). In order to purify **11**, it was submitted to acetylation. Acetate **13** was isolated (Scheme 3). The structures of both compounds (**12** and **13**) were determined by extensive NMR studies.

Due to the problems encountered in the hydrolysis of compound **8** we decided to desulfonylate first. Desulfonylation of **8** under the usual conditions gave **14** (Scheme 4).

The hydrolysis of the auxiliary was again found to be difficult. Problems with the deprotection of this auxiliary have already been reported by Undheim et al.[13] When compound **14** was deprotected with TBAF the cyclopropanol **15** was obtained, although in low yield, but if the crude mixture was treated with MOM chloride the yield of protected material **16** rose to 88%. Deprotection of the auxiliary in this case takes place smoothly to give the amino ester **17**, but this could not be deprotected under any conditions.

In order to circumvent this problem, the strategy for deprotection was changed. We decided to replace the TBS group by something that could be hydrolyzed in the organism but which would be stable to deprotection under mild acidic conditions, and selected the acetoxy group as an appropriate example. Compound **14** was deprotected and acetylated to give acetate **18** in one step. This compound was submitted to the usual hydrolysis conditions giving the corresponding amino ester **19** in excellent yield. Transformation to compound **20** is observed in the NMR tube where the acetoxy group migrates to the neighbouring amino group. Column chromatography of the mixture gives a small amount of urethane **21** (Scheme 4).

We have already described our work[10] on a comparative conformational analysis of *trans*-**1** with the conformation of glutamic acid proposed to be required for activity at group II metabotropic glutamate receptors (based upon the activities



Scheme 2.