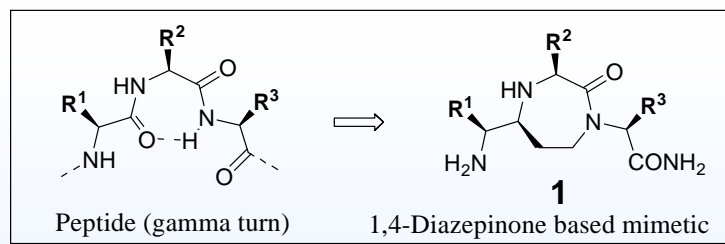


## Chemistry

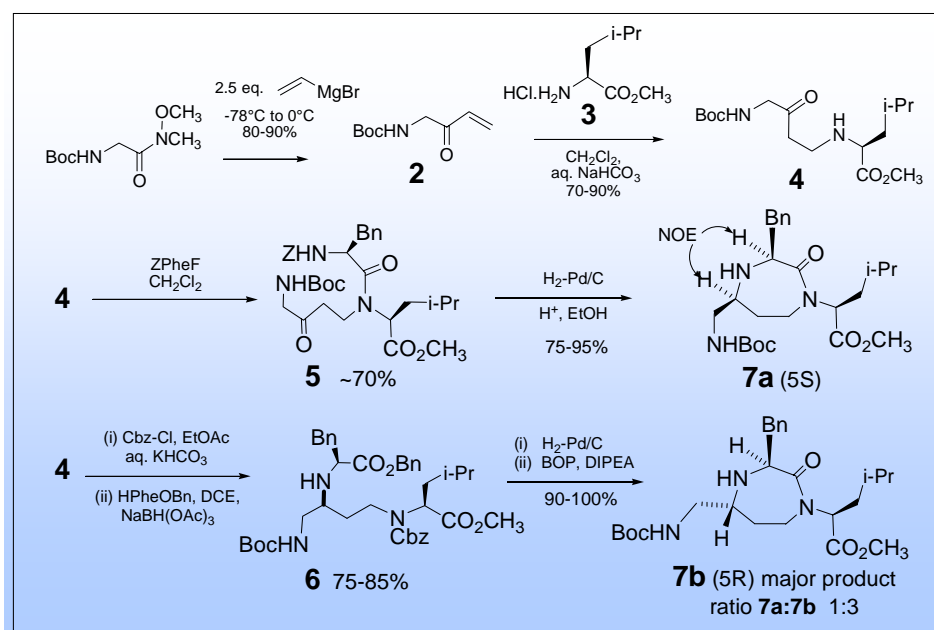
The core chemistry technology provides synthesis of mimetics in a relatively short number of steps and bearing any side-chain groups (except proline in some positions).

The tripeptide mimetic **1** forms the basis of the turn mimetics. The important feature of Mimetica's technology is the ability to selectively produce every one of the sixteen possible diastereomers of **1** having any sidechain combination with only minor changes to the procedure or different starting materials. To the best of our knowledge there is currently no equivalent technology.



## Fast Synthesis of Mimetics

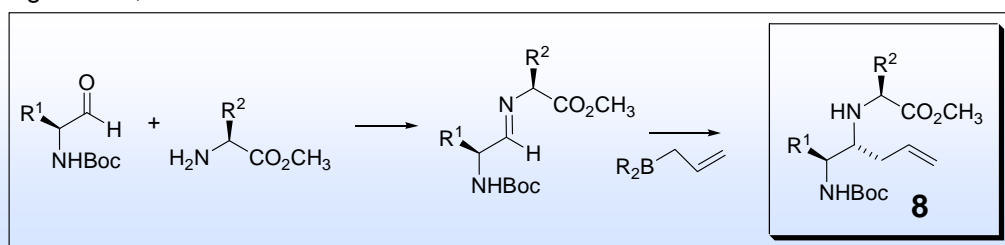
The synthesis of mimetics lacking the R1 group (in **1**) is illustrated in Scheme 1 below. The procedures are 4 or 6 steps – literature methods for similarly complex mimetics are typically much longer. A process synthesis of a drug based on this method would be 6-7 steps from simple starting materials.



Scheme 1

## Allyl Dipeptides – Key Intermediates

The ability to produce all the diastereomers of **1** for the full range of peptide sidechains relies on the discovery by Mimetica that allylated dipeptides **8** can be formed using B-allyl boranes. This selective reaction allows C-C bond formation in the presence of typical peptide protection groups including amides, carbamates and esters.

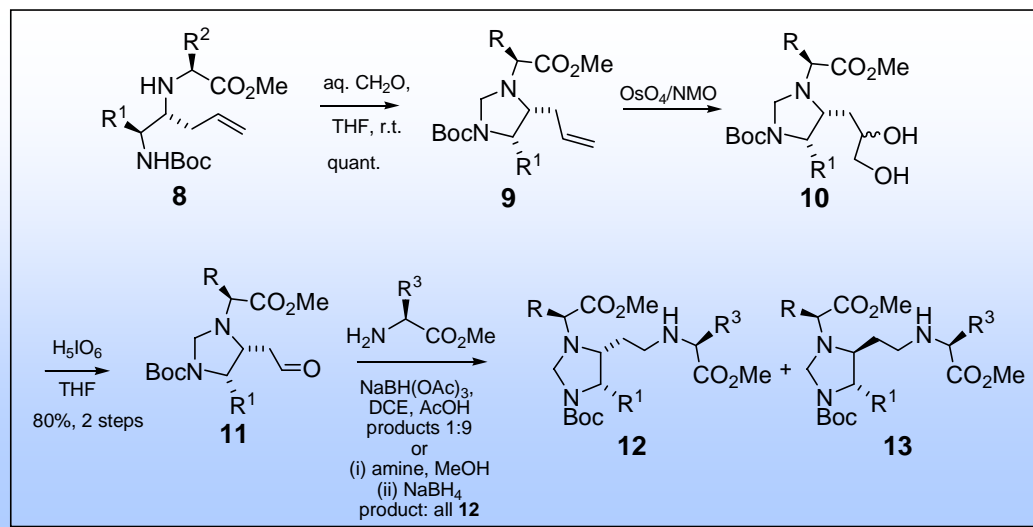


**Scheme 2**

Compound **8** can be formed as a single diastereomer with appropriate chiral ligands on boron. With B-allyl 9BBN the product diastereomers are formed in an 8:2 ratio, the major diastereomer being as indicated in **8**.

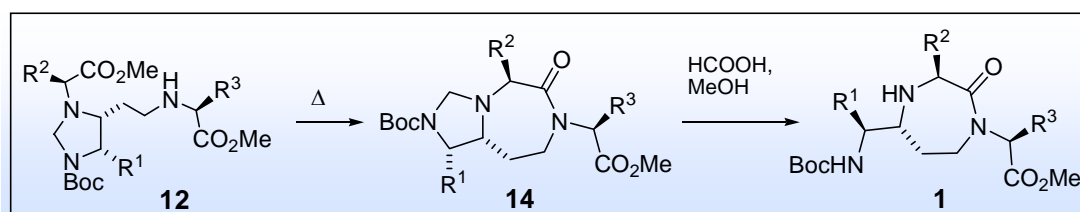
## Synthesis of Mimetics from Allyl Dipeptides

The allyl dipeptides **8** are converted to tripeptide mimetics as described in Schemes 3 and 4. The key feature of this chemistry is the reductive amination of aldehydes **11**. Under normal conditions (presence of acid) the reaction proceeds with inversion of configuration to give 90% of **13**. However, when the reaction is conducted in the absence of acid this isomerization is prevented and the configuration is retained to yield **12**.



**Scheme 3**

Thus, compounds **12** and **13** are selectively accessible depending on reaction conditions. The other three chiral centres in the mimetics are derived from the (amino acid) starting materials and are not racemised during the synthesis. Therefore all four chiral centres can be individually and separately controlled giving access to all sixteen possible diastereomers of **1**.



**Scheme 4**

The cyclisation reaction of **12** or **13** to **14** can be effected by heating or deprotection / coupling (depending on the specific protecting chemistry used).

A process chemistry approach to the production of compounds of type **1** would take 9-11 steps from typical industrial starting materials.