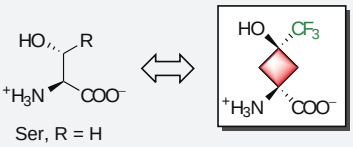
Cyclobutane ring as a conformational restriction tool

D. Radchenko, O. Grygorenko, I. Komarov, I. Kondratov, D. Volochnyuk

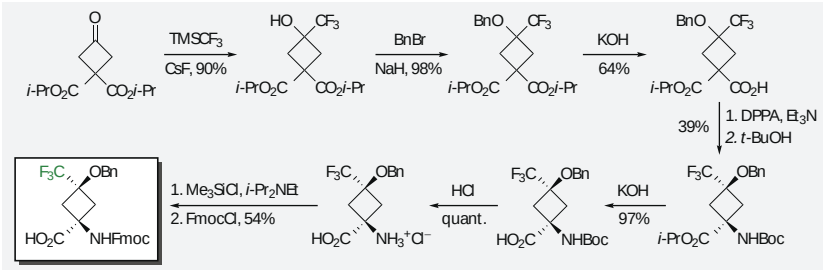
Introduction and Aim

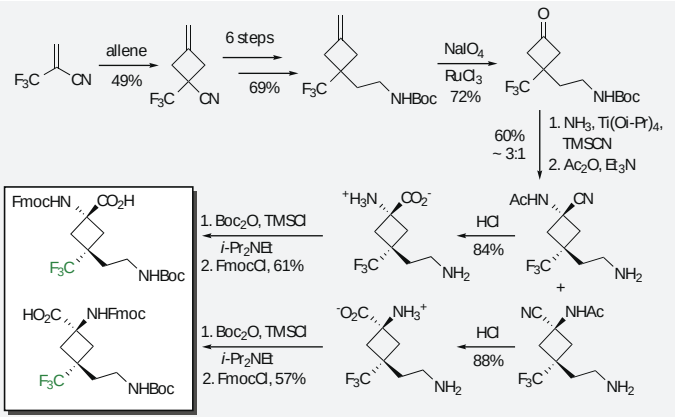
Conformational restriction is a renowned approach to design of analogues in bioorganic and medicinal chemistry. A desirable feature of this methodology is possibility of molecular structure modification without significant perturbation of the compound properties. *Small rings* can provide such possibility; in particular, cyclopropane-containing conformationally restricted analogues ("methanologues") have been widely used to date. However, the cyclopropane moiety can significantly affect electronic properties and chemical reactivity of the molecule due to its partially unsaturated nature. *Cyclobutane* ring does not have such drawbacks; on the other hand, it is small enough to satisfy the above-mentioned criteria as a conformational restriction tool.

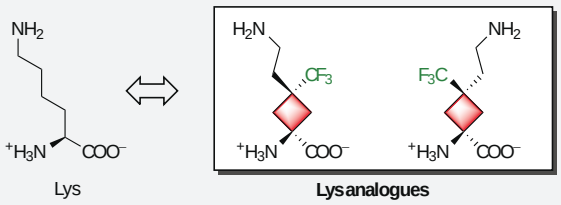
Cyclobutane-derived polar amino acids – ^{19}F NMR labels



First polar CF_3 label for solid-state ^{19}F NMR studies
$pK_a(OH)$ = ***11.7*** (close to that of Ser/Thr)
Validated by incorporation into Temporin A*



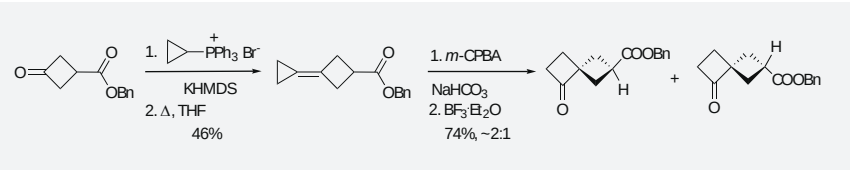


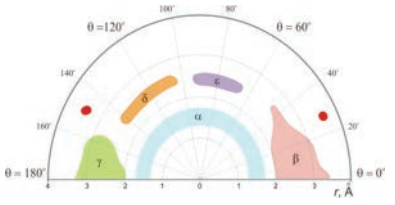


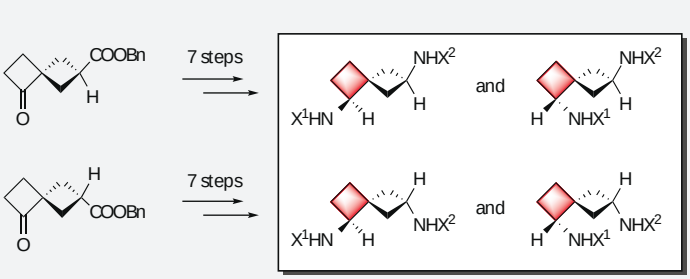
- ***First cationic*** CF_3 label for solid-state ^{19}F NMR studies
- $pK_a(\varepsilon\text{-}NH_2)$ = **9.3** and **9.7** (close to that of Lys)
- ***Validated*** by incorporation into PGLa(Nle)*
- Allowed to considerably increase the ***precision*** of the peptide orientational analysis in model membranes

*Peptide studies were performed in collaboration with the group of Prof. Dr. Anne S. Ulrich (Karlsruhe Institute of Technologies) and Dr. Sci. Pavel K. Mykhailiuk (Enamine Ltd.)

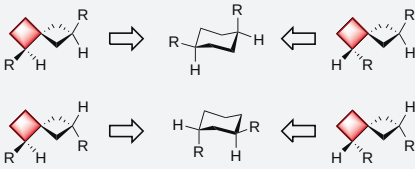
Spiro[3.3]heptane derivatives – advanced building blocks for drug discovery







X^1 = Boc, X^2 = H
or
X^1 = H, X^2 = Cbz



According to exit vector plot analysis, stereoisomers of 1,6-disubstituted spiro[3.3]heptanes can be used as isosteres of either *cis*-1,4- or *trans*-1,3-disubstituted cyclohexanes

Contact

Dmitriy M. Volochnyuk, Dr. Sci., PhD
d.volochnyuk@enamine.net, d.volochyuk@gmail.com
Enamine Ltd, www.enamine.net
78 Chervonotkatska Str, 02660 Kyiv, Ukraine

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