# Synthesis and structural characterization of trifluoromethylated tetrahydroisoquinolines as new constrained aromatic amino acid surrogates

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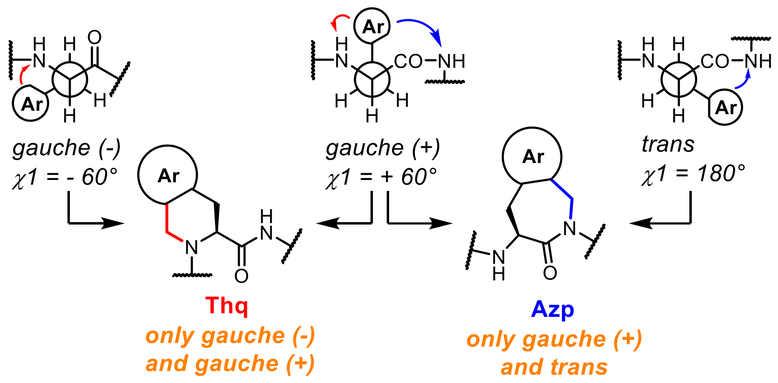
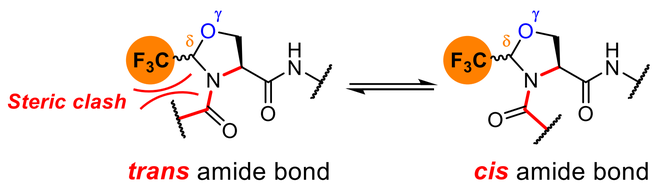
## Introduction

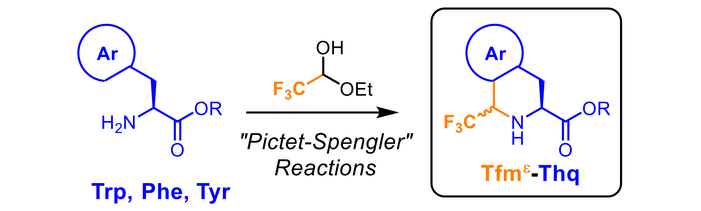
It is often necessary to apply **conformational restrictions** to peptides in order to fine tune their activity in vivo.
Local constrains, such as **cyclization**, applied to (aromatic) amino acids can restrain **dihedral angles** and the so-called **χ-space**, and improve peptides' **activity, selectivity, or stability**.[1]

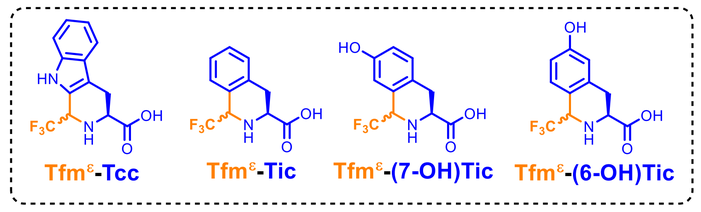


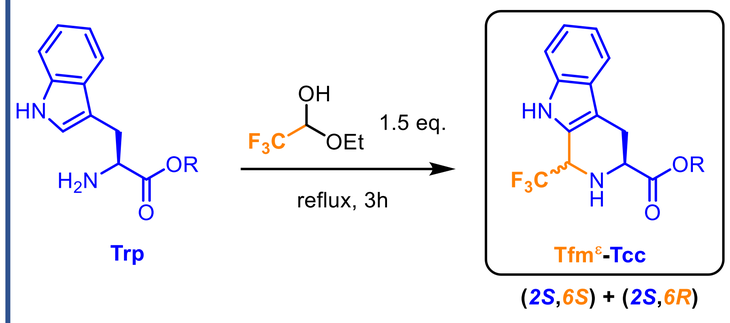

In addition to enhancement of peptide's **stability**,[2] and membrane permeation due to **increased hydrophobicity**,[3] introduction of **fluorine** in peptides and amino acids can have remarkable effects on their **structure**. Notably, we demonstrated that a **trifluoromethyl** (**Tfm**) group, introduced in δ position of proline derivatives, exerts a stereoelectronic effect lowering the *cis*/*trans* isomerization barrier and **favors the *cis* amide bond** conformer.[4]

We herein invistigate the combination of **cyclic constrains** and the **stereoelectronic effect of Tfm** on aromatic amino acids. Cyclization on the $N^{\alpha}$ *via* **Pictet-Spengler type reactions** should provide the desired trifluoromethylated **tetrahydro-β-carboline** or **tetrahydroisoquinolines** (**Thq**).



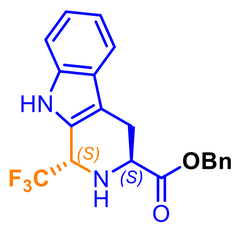




## Synthesis



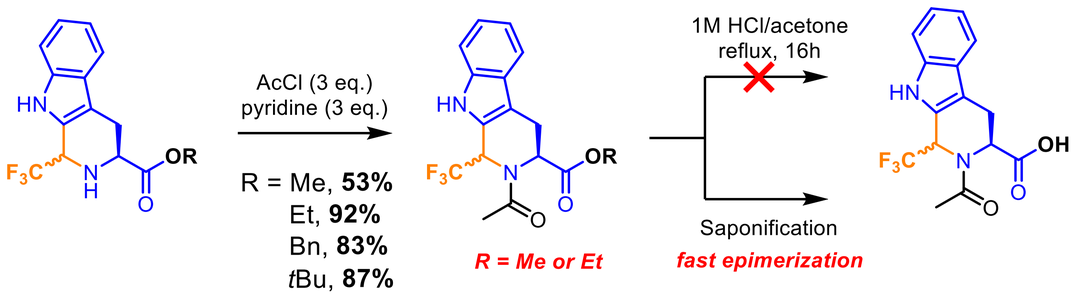

| R | Yield | dr |
|---|---|---|
| Me | 62% | 52/48 |
| Et | 75% | 54/46 |
| Bn | 62% | **71/29** |
| *t*Bu | 81% | 51/49 |

- First on Trp **without solvent** as published by Nishida.[5]
- Different protecting groups are **well tolerated**.
- **No significant diastereoselectivity**, except for the **(*2S*,*6S*)** isomer with Bn as protecting group.
- Two diastereomers **separable on silica gel**.

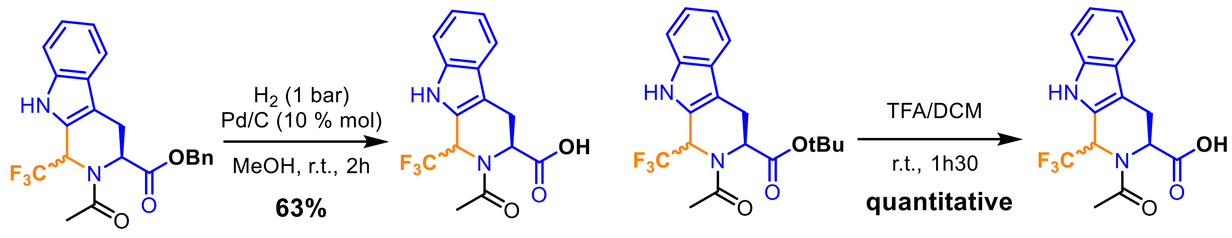


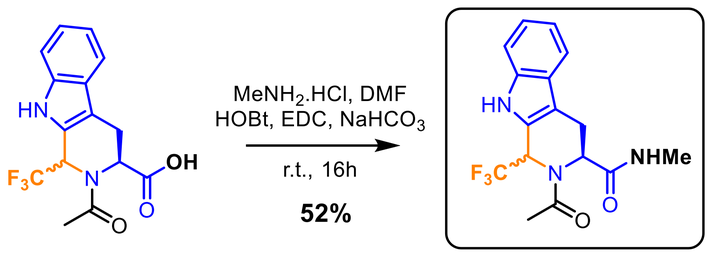
H-(*2S*,*6S*)-Tfmᵋ-Tcc-OBn

### *Derivatization and acetylated models synthesis*




Acidic hydrolysis of esters failed while saponification **led to fast epimerization** (with NaOH or LiOH) or no conversion (NaOH + $CaCl_2$).

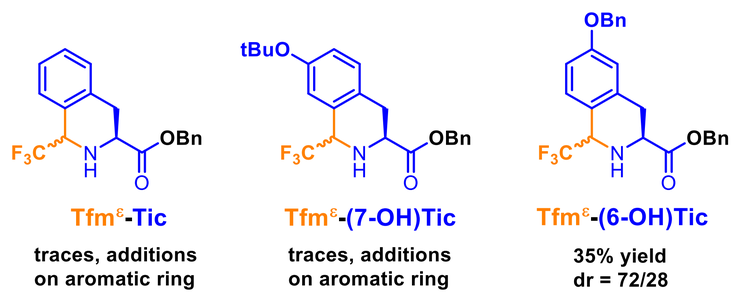



- Bn or *t*Bu ester deprotection **proceeded smoothly**.
- Coupling with methyl amine afforded the expected models for both diastereomers.

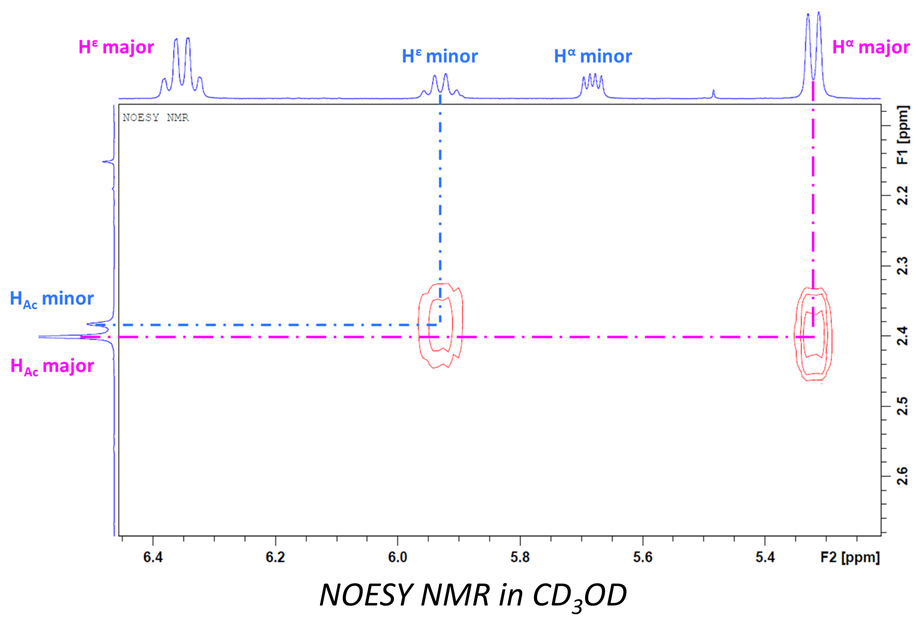
### *Other amino acids*

- Only **traces obtained with Phe or Tyr**. Complex mixture of side products.
- **Decent result with *m*Tyr** but also side reactions.

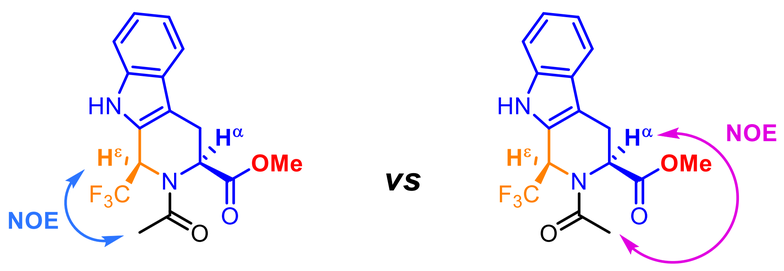



**Require milder conditions**

## Structural characterization




*NOESY NMR in $CD_3OD$*




Ac-(*2S*,*6R*)-Tfmᵋ-Tcc-OMe with ***trans*** amide bond conformation

Ac-(*2S*,*6R*)-Tfmᵋ-Tcc-OMe with ***cis*** amide bond conformation

| Amino acid | Cis/trans ratio |
|---|---|
| Ac-(*2S*,*6R*)-Tfmᵋ-Tcc-OMe | 58/42 |
| Ac-(*2S*,*6S*)-Tfmᵋ-Tcc-OMe | **70/30** |
| Ac-Tcc-OMe | 45/55 |
| Ac-(*2S*,*6R*)-Tfmᵋ-Tcc-NHMe | 61/39 |
| Ac-(*2S*,*6S*)-Tfmᵋ-Tcc-NHMe | **69/31** |

- Both diastereomers show a **preference for the *cis* conformation**, especially the **(*2S*,*6S*)** analog.
- **Remarkable effect of the $CF_3$** compared to the non fluorinated Tcc (*trans* as major conformer).
- No clear influence of the *C*-terminus.

## Conclusion

- Cyclization was **performed efficiently on Trp** with various tolerated protecting groups, but **no clear diastereoselectivity** except with Bn esters.
- Derivatization more difficult than expected since the product quickly **undergo complete epimerization in basic conditions**.
- Cyclization worked with the **activated *m*Tyr** but not with Tyr or Phe, probably due to side reactions on the aromatic ring. **Milder conditions** should be attempted.
- Effect of Tfm on the *cis*/*trans* ratio with an **increased *cis* population** compared to the non fluorinated analog.

**Incorporation into peptides and structural implications**

## References

**[1]** ***(a)*** De Neve, J. *et al. J. Med. Chem.* **2024**, *67* (9), 7603-7619, ***(b)*** Lozada, C. *et al. Bioorg. Chem.* **2023**, *139*, 106731, ***(c)*** Gonzalez, S. *et al., J. Med. Chem.* **2020**, *63* (21), 12929-12941. **[2]** Huhmann, S. *et al. Eur. J. Org. Chem.* **2018**, *2018* (27-28), 3667-3679. **[3]** Oliver, M. *et al. RSC Adv.* **2018**, *8*, 14597-14602. **[4]** Chaume, G. *et al. J. Org. Chem.* **2017,** *82* (24), 13602-13608. **[5]** Maki, Y. *et al. J. Fluor. Chem.* **1989,** *43* (2), 189-205.

## Aknowledgements

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