SYNTHESIS OF AZETIDINE-BASED β-AMINO ALCOHOLS

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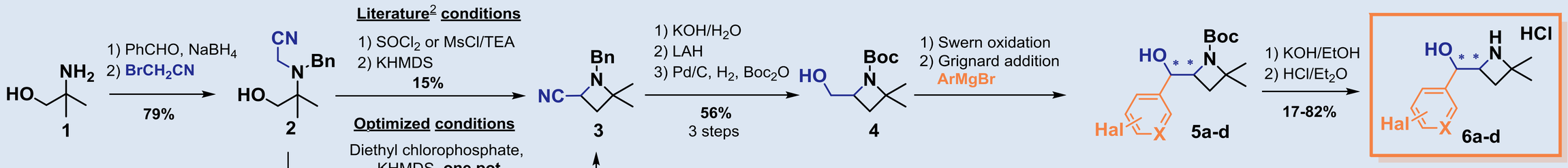
Abstract

(Azetidine-2-yl)aryl alcohols promote glucose uptake in skeletal muscle cells and are promising for use in treatment of hyperglycaemia.[1] Our objective was development of synthetic pathway towards all possible isomers of 4,4-dimethylazetidin-2-yl (hetero)aryl alcohols **6** starting from commercially available 2-amino-2-methylpropan-1-ol **1**.

Synthetic route to enantiopure 4,4-dimethylazetidin-2-yl (hetero)aryl alcohols 6a-d

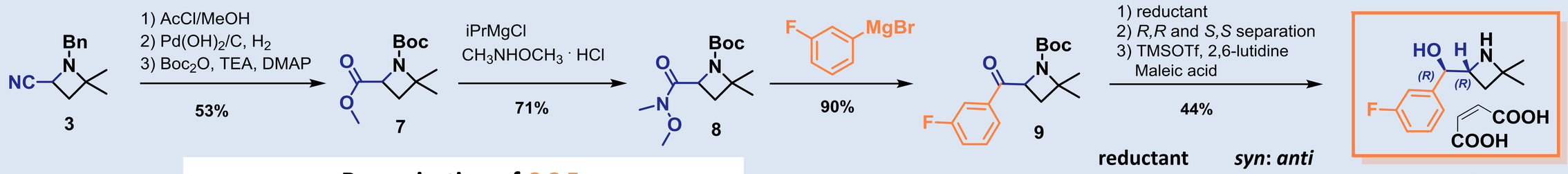


5	Hal	X	Yield, %	*syn: anti*, %
a	3-F	C	47	66:34
b	2-F	C	20	70:30
c	3-Cl	C	43	69:31
d	3-F	N	36	61:39

- ***Syn* and *anti* diastereomers were separated by column chromatography**
- **Enantiomers were separated by chiral HPLC**

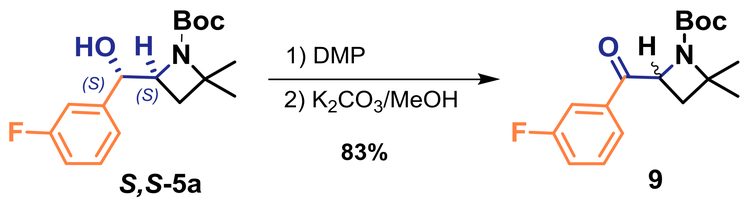
- **Introduction of Cl or OMs (good leaving groups) leads to poor yields**
- **Phosphate is not active enough to form aziridine**

Focused synthesis of *R,R*-6a



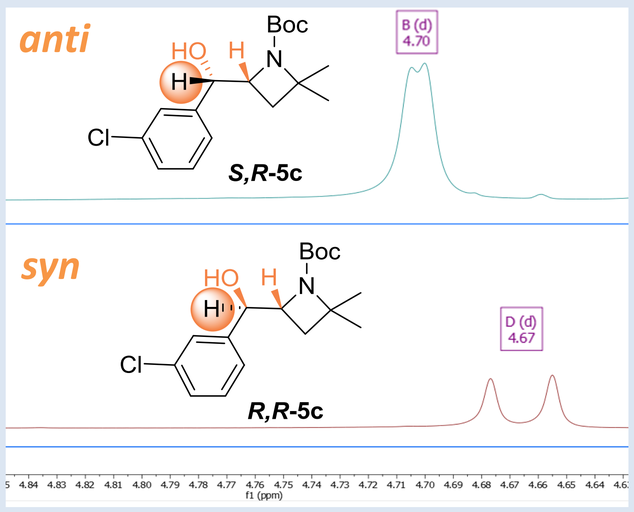
reductant	*syn*: *anti*
$NaBH_4$	85:15
$LiEt_3BH$	**95:5**

Racemization of *S,S*-5a



- **Reaction scale: 100 mg – 10 g**
- **Recycling of unwanted diastereomers by oxydation/racemization**
- **Allover yield: 14%**

Syn and *anti* distinction

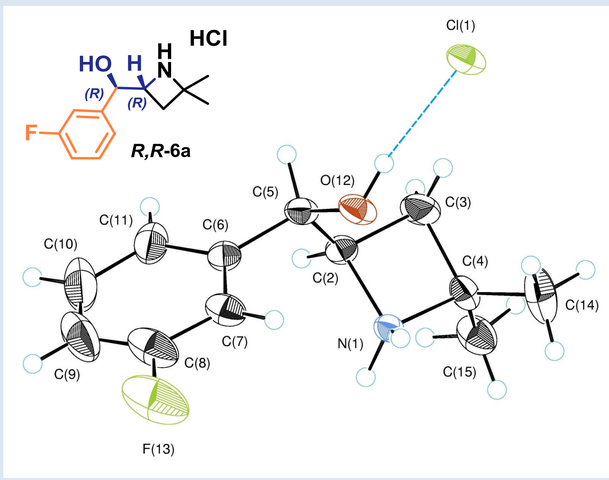


Summary

Synthetic pathway to obtain all 4 isomers of 4,4-dimethylazetidin-2-yl (hetero)aryl alcohols **6a-d** was developed sucessfully. Asymmetric scaleable synthesis towards ***syn*** alcohols with yield improvement was developed.

Synthesized compounds showed good activity towards target receptors and further biological evaluation is currently under progress.

Absolute configuration



References

1. Pelcman, B.; Bengtsson, T. WO2020188299 A1, September 24, **2020**.
2. Agami, C., Couty, F., Evano, G. *Tetrahedron Asymmetry* **2002**, *13*, 297.

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