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Straightforward Synthesis of Novel Enantiopure α-Trifluoromethylated Azetidine 2-Carboxylic Acid and Homoserines

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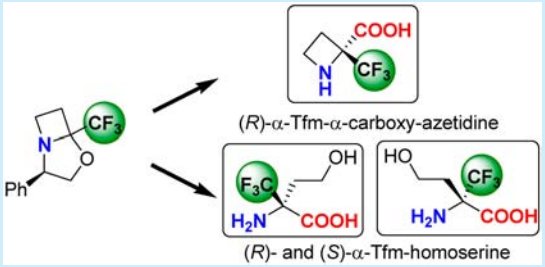
Supporting Information

ABSTRACT: The straightforward syntheses of enantiopure (2*R*)-2-trifluoromethyl-2-carboxyazetidine and (*R*)- and (*S*)-trifluoromethyl-homoserines are reported. The key step is a Strecker-type reaction on a common chiral CF_3-containing bicyclic oxazolidine intermediate obtained by a condensation reaction of (*R*)-phenylglycinol and ethyl-4,4,4-trifluoroacetoacetate (ETFAA).



The synthesis of α-amino acids and their derivatives has been a subject of major interest over the past 50 years. Indeed they constitute one of the most important classes of compound as precursors in peptides syntheses. The introduction of fluorine atoms into bioactive compounds is also marked by exponentially growing interest as demonstrated by the increasing pharmaceutically active molecules containing fluorine (ca. 20%).[1] Due to its high electronegativity, the fluorine atom generally induces significant modifications of the biological behavior of biomolecules such as their acido-basic properties and their lipophilicity.[2] The incorporation of fluorinated amino acids (FAAs) into peptides increases their chemical stability and their resistance to the degradation by proteases and enhances their hydrophobicity.[3] Their incorporation may also induce particular conformations.[4] Moreover, the trifluoromethyl group is useful as a label for solid state ^{19}F NMR studies.[5]

Nonfluorinated azetidines have been extensively studied, and several reviews and articles have been published on this topic.[6] Bioactive compounds containing the azetidine ring have also been reported.[6] Nonfluorinated azetidine amino acid derivatives have already been synthesized and incorporated into peptides in order to compare conformational consequences with proline or α-methyl-proline introduction.[7] It was found that while proline inclines to induced β-turns, the four member ring of azetidine tends to force the peptide to adopt γ-turn conformations. Moreover, if a methyl group is present in the α-position of a proline or an azetidine-2-carboxylate ring the turn inducing ability raises significantly.[8]

For several years we have been involved in the development of scalable synthetic methods for the preparation of α-trifluoromethyl amino acids (α-Tfm-AAs) in enantiomerically pure form.[9] Although this synthetic effort is a prerequisite for the synthesis of trifluoromethylated peptides, it is still a challenge.[10] Because of the great steric hindrance and the low nucleophilicity of the nitrogen atom caused by the trifluoromethyl group, specific reaction conditions are required for the introduction of these amino acids into peptides.[11] In the course of our research on new highly constrained amino acids, we report herein the synthesis of an original azetidine bearing both a trifluoromethyl and a carboxylic acid group in the α position to the nitrogen. This azetidine can be considered as a new quaternary α-Tfm-AA and a new scaffold for the construction of constrained peptides.

To our knowledge only few reports on the preparation of CF_3-azetidines have been published. Jiang et al. described the synthesis of 4-CF_3-2-alkyl azetidines via a Wittig reaction on a 4-CF_3β-lactam followed by alkylation and hydrogenation reactions.[12] Zanda et al. reported the synthesis of a trisubstituted azetidine using a stereoselective Mannich-type reaction between an ozazolidinone-based enolate and the *N*-Cbz-imine of ethyl trifluoropyruvate.[13] The synthesis of 3-aza-4-perfluoroalkyltricyclo[4.2.1.0]nona-3,7-dienes has also been reported using a [2 + 2 + 2] strategy.[14] Two patents display the synthesis of copolymers with a fused four-membered heterocyclic ring containing a CF_3 group.[15] During our investigations, a four-step synthesis of racemic 1-alkyl-2-CF_3-azetidines and their reactivity were reported by De Kimpe et al. starting from ethyl-4,4,4-trifluoroacetoacetate (ETFAA) or from trifluoromethylaziridine.[16]

The chiral fluorinated oxazolidine required as starting material for our strategy was prepared from the commercially available ethyl trifluoroacetoacetate (ETFAA) and 2-(*R*)-phenylglycinol.[17] The condensation reaction of ethyl trifluoroacetoacetate (ETFAA) **1** with (*R*)-phenylglycinol **2** gave the oxazolidine **3** in a good yield as a single diastereomer (Scheme 1). $LiAlH_4$, $NaBH_4$, and $LiBH_4$ were found to be unsuitable for

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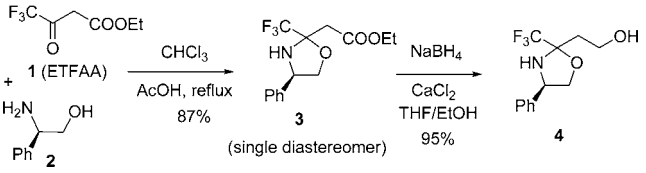
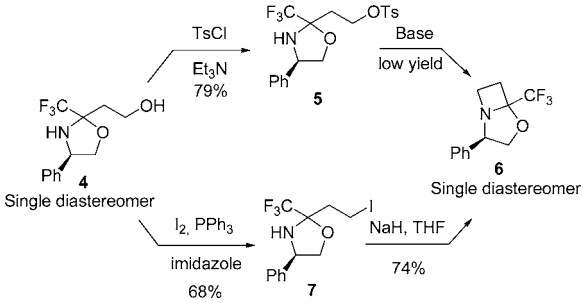
Scheme 1. Synthesis of the Oxazolidine 4



the selective reduction of the ester moiety even when positioned near an activating group such as a trifluoromethyl group. However, the reaction of a $NaBH_4/CaCl_2$[18] mixture in a freshly distilled ethanol/THF (2:1) solution gave the expected alcohol **4** in a very good yield without any degradation of the oxazolidine moiety (Scheme 1).

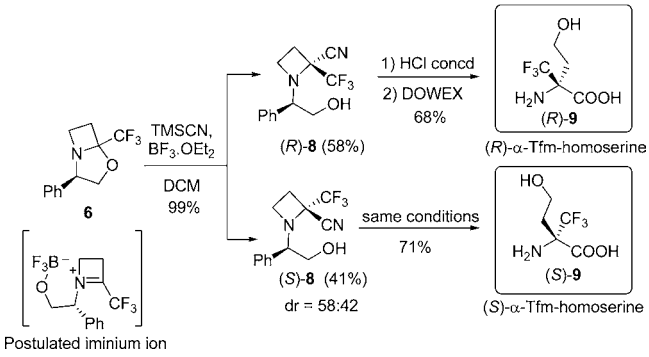
The synthesis of the bicyclic compound **6** was first attempted starting from the tosylated oxazolidine **5**. Several conditions, using different bases (NaH, K_2CO_3) and/or solvent, were tested to promote the cyclization of **5**. However, none of them gave the expected bicyclic compound **6** in more than 23% yield. At this stage we planned to perform the cyclization reaction from the iodo derivative **7** which was conveniently obtained from the alcohol **4** using the I_2, PPh_3, imidazole protocol. The cyclization reaction was performed under various conditions. The best conditions involving NaH in refluxing THF gave the expected bicyclic trifluoromethylated oxazolidine in 74% yield as a single diastereomer. Therefore, the exchange of the tosylate group by an iodide atom dramatically enhances the yield of the cyclization step (Scheme 2).

Scheme 2. Two Alternative Synthetic Pathways to the Key Bicyclic Oxazolidine 6



The nitrile precursor of the carboxylic function was introduced through a Strecker-type reaction according to our previously reported conditions.[19] Although the formation of the highly constrained cyclic azetidine iminium ion was anticipated to be difficult,[20] the expected azetidine-2-carbonitriles **8** were obtained in a very good yield (99%) as a 58:42 mixture of diastereomers. This remarkable reactivity is undoubtedly due to the strong electron withdrawing effect of the trifluoromethyl group. Indeed, in the nonfluorinated series, although very few Strecker-type reactions have been reported via 2-unsubstituted azetidine iminium ions,[21] to our knowledge, no iminium ions mediated carbon−carbon bond formation reactions are found in the literature starting from hindered 2-substituted azetidines. Even though the Strecker-type reaction was performed on a diastereomerically pure oxazolidine **6**, the low diastereoselectivity observed is consistent with the formation of an iminium ion intermediate. Fortunately, due to a large polarity difference, the two diastereomers were very conveniently separated by silica gel chromatography to give (*R*)-**8** and (*S*)-**8** in 58% and 41% isolated yield respectively (Scheme 3). The simultaneous hydrolysis of the nitrile function and the removal of the

Scheme 3. Synthesis of Enantiopure (*R*)- and (*S*)-α-Tfm-homoserines 9



phenylethanol moiety were first envisioned by treatment with concentrated HCl at reflux. Under these harsh acidic reaction conditions the hydrolysis of the nitrile and the deprotection of the amino group were accompanied by the acid-promoted ring opening and hydroxylation reaction of the azetidine ring providing the (*R*)- and (*S*)-α-Tfm-homoserines **9** in 68% and 71% yield (Scheme 3). Thus, this reaction constitutes an efficient and straightforward route to these unreported original side chain functionalized enantiopure α-Tfm-amino acids. It should be noted that the ring-opening reactions of 2-trifluoromethylazetidines under quite similar acidic conditions were reported by De Kimpe et al. to give the corresponding chlorinated compound.[16]

The absolute configuration of the major and less polar intermediate azetidine-2-carbonitriles (*R*)-**8** was assigned by X-ray analysis (Figure 1).

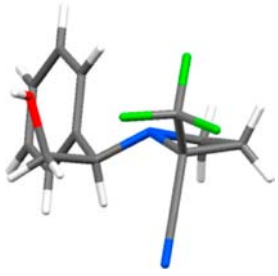


Figure 1. X-ray structure of (*R*)-**8**.

Since the direct hydrolysis of both the phenylglycinol moiety and the nitrile function under acidic conditions did not afford the expected α-Tfm-azetidine, we attempted to proceed through a two-step procedure involving a sequential hydrolysis of the cyano group under basic conditions followed by the hydrogenolysis of the phenylglycinol moiety. The sodium hydroxide treatment of the cyano derivatives (*R*)-**8** and (*S*)-**8** gave the corresponding carboxylic acids (*R*)-**10** and (*S*)-**10** in quantitative yields after neutralization (Scheme 4).

The corresponding azetidino carboxylic acid (*R*)-**10** and (*S*)-**10** were obtained in quantitative yield. Unfortunately the hydrogenolysis reactions of their phenylglycinol moieties failed and gave only degradation products and unreacted starting material. We postulated that protection of the carboxylic acid function as an ester would favor the hydrogenolysis reaction as

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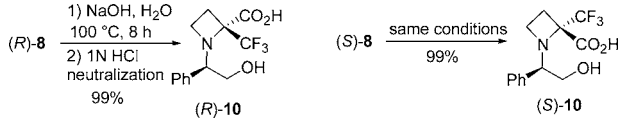
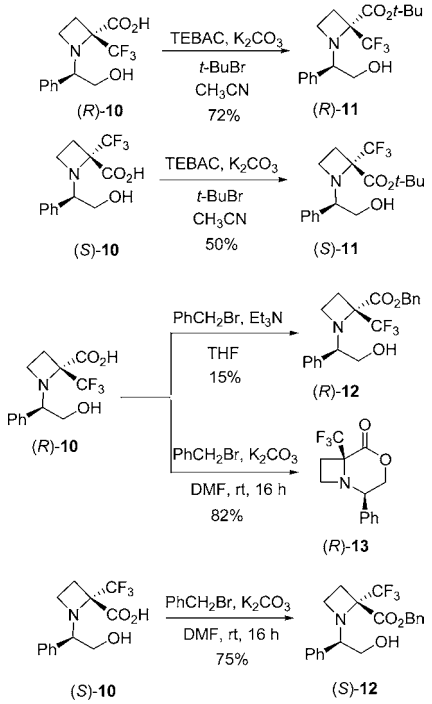
Scheme 4. Basic Hydrolysis of the Amino Nitriles (*R*)- and (*S*)-8



well as the isolation of the amino ester. The *tert*-butylation of (*R*)-**10** and (*S*)-**10** was achieved under phase-transfer catalysis to give (*R*)-**11** and (*S*)-**11** in 72% and 50% yield (Scheme 5).

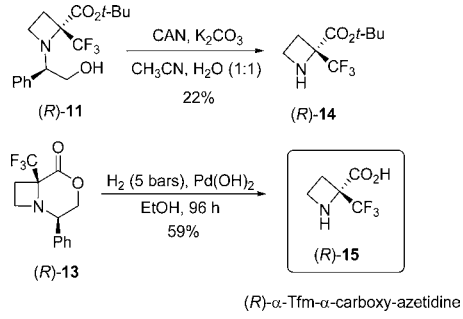
Scheme 5. Esterification Reactions of (*R*)-10 and (*S*)-10



The benzylation reaction of (*R*)-**10** occurred in low yield (15%) in the presence of triethylamine. When the benzylation was performed with K_2CO_3 as the base, the intramolecular cyclization of (*R*)-**10** gave the lactone (*R*)-**13** in 82% yield. However, under the same conditions, the other diastereomer (*S*)-**10** provided the benzyl ester (*S*)-**12** in 75% yield.[23]

All the hydrogenolysis attempts to cleave the phenylglycinol side chain of the *tert*-butyl esters (*R*)-**11**, (*S*)-**11**, and (*S*)-**12** failed, despite changes in the palladium catalyst (Pd/C or $Pd(OH)_2$), its amount (from 0.1equiv to 2.5 equiv), or the reaction solvent (ethyl acetate or methanol). Finally, the reaction of CAN with (*R*)-**11** gave the corresponding amino ester (*R*)-**14**, but in a modest 22% yield (Scheme 6). Unfortunately the reaction of (*S*)-**11** with CAN under similar conditions only afforded degradation products. However, the unprotected target α-Tfm-α-carboxyazetidine (*R*)-**15** was obtained in 59% yield by palladium mediated hydrogenolysis of the lactone (*R*)-**13** (Scheme 6). Because of the observed difference in reactivity of the (*S*)- and (*R*)- diastereomeric precursors, the alternative pathway to obtain the (*S*)-α-Tfm-α-carboxyazetidine should be to follow the same strategy as in the case for (*R*)-**15** but starting from the commercially available (*S*)-phenylglycinol.

Scheme 6. Synthesis of α-Tfm-α-carboxyazetidine (*R*)-15



In conclusion, straightforward syntheses of the new enantiomerically pure nonproteogenic quaternary amino acids (*R*)- or (*S*)-α-Tfm-homoserines and (*R*)-α-Tfm-α-carboxy-azetidinine are reported starting from commercially available ETFAA and (*R*)-phenylglycinol. This azetidine amino acid is a promising tool as a proline surrogate in peptide chemistry. The additive constraints induced by the trifluoromethyl group and the azetidine ring contribute to the originality of this new amino acid. When incorporated into a peptide chain, conformational restrictions, higher resistance toward proteases, and increased hydrophobicity and bioavailability are expected and will be investigated.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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