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Iodocyclization of Chiral CF_3-Allylmorpholinones: A Versatile Strategy for the Synthesis of Enantiopure α-Tfm-Prolines and α-Tfm-Dihydroxyprolines

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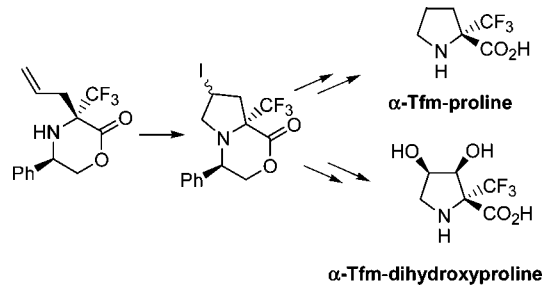
ABSTRACT



An efficient iodocyclization reaction of a chiral Tfm-allylmorpholinone provides a straightforward route to α-Tfm-prolines and α-Tfm-dihydroxyprolines. The methodologies developed are particularly well adapted for gram-scale synthesis of enantiopure compounds.

It is well known that proline and proline derivatives play a unique and important role in the conformation of peptides and proteins. In this context, ring-substituted and quaternary proline analogues are of special interest.[1] Because of the unique effects due to the incorporation of fluorine atoms into molecules, fluorinated amino acids are very attractive target molecules for the design of biologically active compounds, and several methods have been reported for their stereoselective synthesis.[2] Among them, enantiopure β-fluorinated proline derivatives are interesting, but their stereoselective synthesis constitutes a challenge. To our knowledge only (*R*)-β,β-difluoroproline[3] and (*R*)- and (*S*)-α-trifluoromethylprolines[4] have been synthesized in enantiopure form. As part of our research program related to the stereoselective

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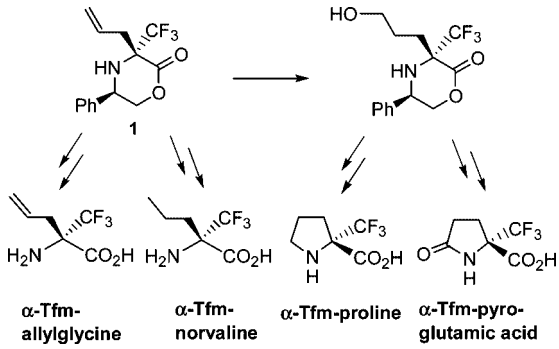
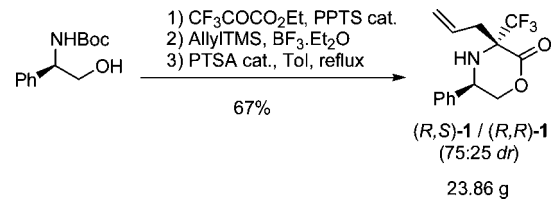
Scheme 1. Synthesis of Enantiopure α-Tfm-Amino Acids from Allylmorpholinone **1**



synthesis of ring-substituted α-Tfm-prolines, we are now interested in the synthesis of enantiopure 3,4-dihydroxy-α-Tfm-prolines. Because of their potential as azasugar analogues and in peptide synthesis, numerous syntheses of 3,4-dihydroxyprolines are reported in the literature[5] but none in the fluorinated series. We report here an efficient stereoselective synthesis of 3,4-dihydroxy-α-Tfm-proline, as well as an improved synthesis of enantiopure α-Tfm-prolines using the same chiral Tfm-allylmorpholinones intermediate.

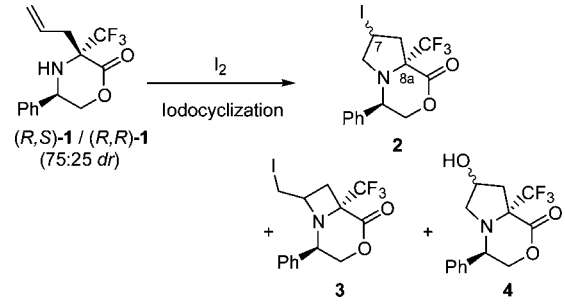
We recently reported that the allylic lactone **1** (Scheme 1) obtained from (*R*)-phenylglycinol and ethyl trifluoropyruvate was a multipotent intermediate for the synthesis of various α-Tfm amino acids such as α-Tfm-allylglycine, α-Tfm-norvaline, α-Tfm-proline,[4] and α-Tfm-pyroglutamic acids.[6] Both enantiomers of the cyclic α-Tfm-proline were obtained from 9-BBN hydroboration reaction of **1** followed by H_2O_2 oxidation and cyclization of the corresponding alcohols. However, this pathway is not suitable for the multigram-scale synthesis of α-Tfm-proline. As we are interested in the development of scalable methods for the synthesis of enantiopure cyclic α-Tfm amino acids, we decided to explore the scope of the iodocyclization[7] reaction of the allylic lactone **1**.

Scheme 2. Multigram-Scale Synthesis of Allylmorpholinone **1**



According to our previously reported three-step procedure,[4,6] an improved efficient multigram-scale synthesis of a 75:25 diastereomeric mixture of (*R*,*S*)-**1** and (*R*,*R*)-**1** was achieved (Scheme 2). The (*R*,*S*) configuration of the major **1** diastereomer was assigned according to our previous communication.[4]

Table 1. Iodocyclization of **1**



entry	conditions	I_2 (equiv)	product (yield %)[a]
1	THF/Et_2O/satd $NaHCO_3$	2.5	low conversion
2	CH_3CN (wet)/ K_2CO_3	3.3	low conversion
3	$CH_2Cl_2/Na_2CO_3{\cdot}5H_2O$	3.3	**2** (40),[b] **3** (22),[c] **4** (38)[d]
4	CH_2Cl_2/K_2CO_3	2.8	**2** (32),[b] **3** (40),[c] **4** (5)[d]
5	CH_2Cl_2	2.6	**2** (87)[b]
6	toluene	1.5	**2** (71)[b]

[a] Isolated yield. [b] Four diastereomers. [c] One diastereomer. [d] Two diastereomers.

The iodocyclization reaction was first attempted in basic conditions following known procedures reported in the literature for similar substrates (Table 1). The reaction in $THF/Et_2O/H_2O$ mixture with $NaHCO_3$ as the base[8] or in wet CH_3CN in the presence of K_2CO_3[9] afforded only very low conversion of the starting allylic compound (entries 1 and 2). The conversion of **1** was complete with $Na_2CO_3{\cdot}5H_2O$ in refluxing CH_2Cl_2,[10] but 5 days reaction time was required and a mixture of five-membered ring compounds **2** (40%), four-membered ring compounds **3** (22%), and five-membered

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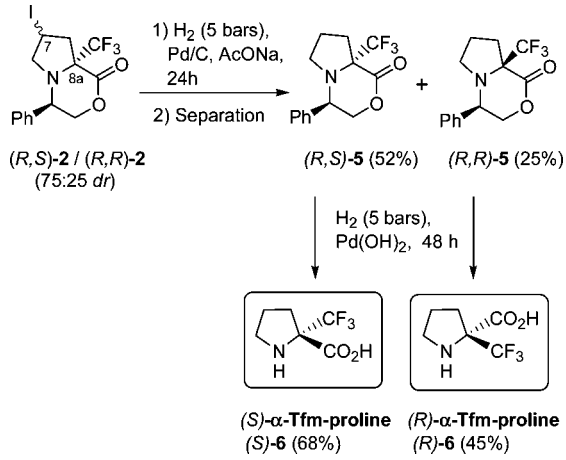
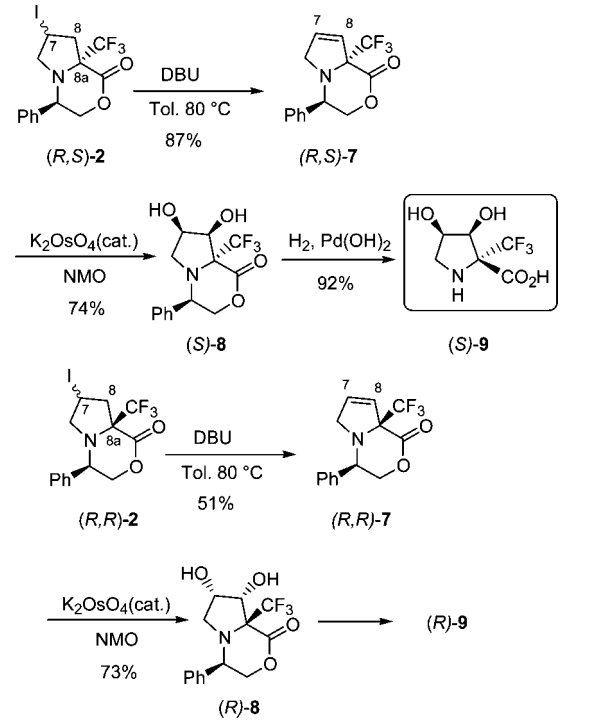
Scheme 3. Synthesis of (*S*)- and (*R*)-α-Tfm-Prolines in Enantiopure Form



Scheme 4. Synthesis of 3,4-Dihydroxy-2-trifluoromethylprolines in Enantiopure Form



hydroxylated compound **4** (38%) was obtained (entry 3). The formation of **4** (5%) was reduced by the use of anhydrous CH_2Cl_2 and K_2CO_3, but a mixture of five- and four-membered ring iodocompounds **2** (32%) and **3** (40%) was still obtained (entry 4). It should be noted that there are very few reports in the literature of the formation of such four-membered rings through electrophilic cyclization of homoallylamine derivatives.[11] We suppose that this uncommon cyclization is due to the cyclic nature of our substrate. Fortunately, when the reaction was performed without neutralization of the medium with a base, the formation of both four-membered ring **3** and hydroxylated compound **4** was avoided. We assume that the use of a base is not necessary in our case because of the strong deactivation of the nitrogen atom in α-position of the trifluoromethyl group. When the reaction was carried out in refluxing CH_2Cl_2 or refluxing toluene, the expected five-membered ring products **2** were highly selectively obtained in 87% and 71% yield (entries 5 and 6). The advantage of the use of toluene as the solvent was that the amount of iodine required to achieve a good yield was reduced to 1.5 equiv. The iodocompounds **2** were obtained as a mixture of diastereomers.[12] At this stage, the separation of the diastereomers was not necessary because this separation was very conveniently achieved at the next step of the synthesis.

The 75:25 diastereomeric mixture of (*R*,*S*)-**2**[13] and (*R*,*R*)-**2**[13] was then submitted to a reductive deiodination reaction to give a diastereomeric mixture of (*R*,*S*)-**5** and (*R*,*R*)-**5** bicyclic compounds (Scheme 3). At this stage, the (*R*,*S*)-**5** and (*R*,*R*)-**5** compounds were very easily separated by silicagel chromatography because of their very large R_f difference.[14] The corresponding enantiopure (*S*)- and (*R*)-α-Tfm-prolines were then very conveniently obtained from each bicyclic compound after removal of the phenylglycinol side chain by hydrogenolysis.[15] As a result, the iodocyclization-hydrogenolysis sequence from lactone **1** constitutes an improved alternative method to the hydroboration-cyclization[4] of **1** for the gram-scale synthesis of α-Tfm-prolines.

We surmised that the bicyclic iodinated compounds **2** would also be very valuable intermediates for the synthesis of highly substituted α-Tfm-prolines. Because of the biological importance of hydroxyproline derivatives, we considered that 3,4-dihydroxylated α-Tfm-prolines would be relevant challenging target molecules. We envisaged their straightforward stereoselective synthesis from **2** through an elimination-dihydroxylation sequence, provided that the elimination was regioselective and that the dihydroxylation was stereoselective. Thus, the isolated iodinated bicyclic compounds (*R*,*S*)-**2** and (*R*,*R*)-**2** were submitted to DBU-mediated dehydroiodination (Scheme 4). In opposition to the unfluorinated series with similar substrates,[5i] the elimination reaction was completely regioselective to give exclusively the C_7-C_8 elimination products (*R*,*S*)-**7** and (*R*,*R*)-**7**. We assume that the enamimes are not formed because of the increased acidity of the protons on C_8 caused by the electron-

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(12) The 75:25 ratio of (*S*) and (*R*) compounds at the C_{8a} carbon was reflecting the initial 75:25 diastereomeric ratio of the allylmorpholinones **1**. Each (*S*) and (*R*) diastereomer at the C_{8a} cabone gave two diastereomers because of the non-stereoselective introduction of the iodine atom at the C_7 carbon. A pure analytical samples of each diastereomers was isolated for the determination of their analytical data.

(13) Two diastereomers because of the iodinated C_7 stereogenic center.

(14) With petroleum ether/ethyl acetate (90:10) system: R_f of (*R*,*R*)-**5** = 0.43 and R_f of (*R*,*S*)-**5** = 0.13.

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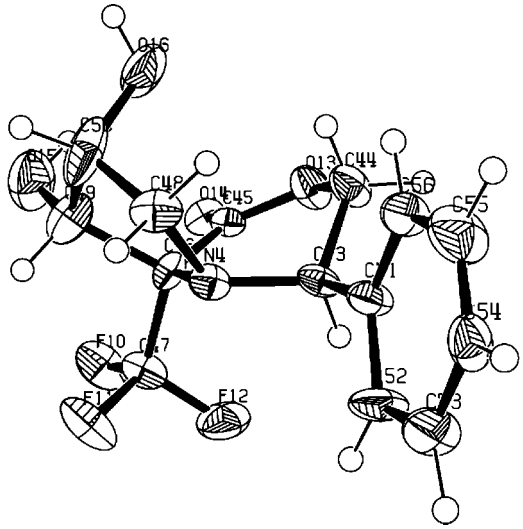

Figure 1. ORTEP diagram of (*S*)-**8**.

withdrawing effect of the trifluoromethyl group in α position. The dihydroxylation reaction of alkenes (*R*,*S*)-**7** and (*R*,*R*)-**7** was then performed with the osmium tetroxide/ NMO system.[5i,16] The dihydroxylation reaction occurred with a complete diastereoselectivity in relative *trans* position of the trifluoromethyl group to give the compounds (*S*)-**8** and (*R*)-**8** in good yields. The trifluoromethyl group is thus the stereodirecting group, and the configuration of the phenylglycinol moiety has no influence on the diastereoselectivity of the dihydroxylation reaction. The absolute configurations of the newly generated centers were assigned by X-ray crystallographic analysis of (*S*)-**8** (Figure 1).[17] The target enantiopure 3,4-dihydroxy-2-trifluoromethylproline (*S*)-**9** was obtained in 92% yield after hydrogenolysis of (*S*)-**8**. In a similar manner, an analytical sample of the bicyclic dihydroxylated compound (*R*)-**8** was submitted to the same hydrogenolysis conditions to give the (*R*)-**9** enantiomer.[18] This result confirms that the dihydroxylation reaction takes place in *trans* position of the trifluoromethyl group.

Thus, in this work, we have demonstrated that the iodocyclization reaction of a chiral CF_3-allylmorpholinone constitutes an efficient scalable pathway for the synthesis of enantiopure α-Tfm-prolines and dihydroxyprolines. Further development in the synthesis and the applications of cyclic enantiopure Tfm-aminoacids is currently in progress.

Acknowledgment. We thank Central Glass Company for their financial support and the gift of ethyl trifluoropyruvate.

Supporting Information Available: General experimental methods, complete experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Crystallographic data for compound (*S*)-**8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 710191. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44 1223 336033 or email: deposit@ccdc.cam.ac.uk.

(18) Spectral data of (*R*)-**9** were identical to those of (*S*)-**9**.