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Asymmetric Synthesis of *cis*-(*S*,*R*)-3-Amino-4-fluoro-1-methylpyrrolidine

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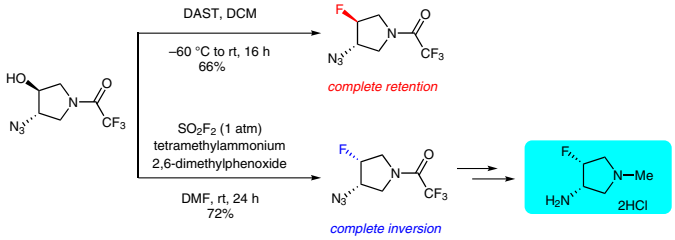

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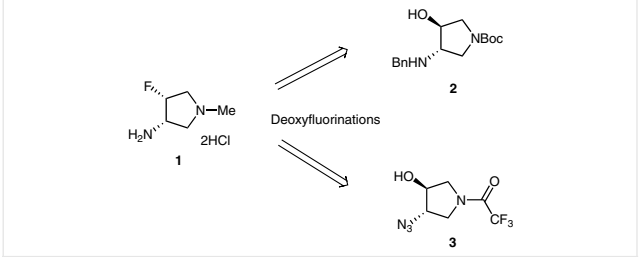
Abstract The development of the stereoselective synthesis of *cis*-(*S*,*R*)-3-amino-4-fluoro-1-methylpyrrolidine is described starting from chiral, non-racemic 1-[(3*S*,4*S*)-3-azido-4-hydroxypyrrolidin-1-yl]-2,2,2-trifluoroethan-1-one. Two sets of deoxyfluorination conditions are developed for achieving inversion of the chiral center with high or complete stereoselectivity.

Key words stereoselective, azides, deoxyfluorination, sulfuryl fluoride, pyrrolidines

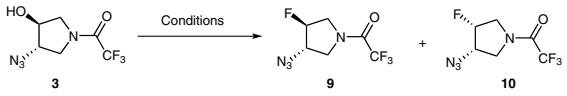
cis-(*S*,*R*)-3-Amino-4-fluoropyrrolidines are common structural moieties often found in biologically important compounds.[1] However, there are limited reports of asymmetric syntheses of these compounds.[2] In support of our drug development programs, we were interested in producing *cis*-(*S*,*R*)-3-amino-4-fluoro-1-methylpyrrolidine (**1**) in an efficient manner. Herein, we report an asymmetric synthesis of compound **1**, which was developed as part of these efforts. Our strategy for the asymmetric synthesis of **1** was to utilize an appropriate chiral and easily accessible substrate reported in the literature for stereospecific deoxyfluorination. After carefully reviewing literature reports, we directed our efforts to examine deoxyfluorination on substrates of type **2** and **3**, as shown in Scheme 1. Substrate **2**, in its chiral non-racemic form, was reported by Tsuzuki et al. and generated via chemical resolution.[3] Substrate **3** has been reported by Jacobsen et al. and prepared via desymmetrization of the corresponding epoxide.[4] It was expected that the nucleophilic amino group on **2** would participate in substitution to form the aziridine in the course of deoxyfluorination. We envisioned that this neighboring group participation could be prevented by installing an electron-withdrawing group on the amino group prior to deoxyfluorination, or by employing substrate **3** possessing the azido group as an amino surrogate for the deoxyfluorination, given that azides have been proven to be non-participating neighboring groups in sugar chemistry.[5]



Scheme 1 Synthetic plan

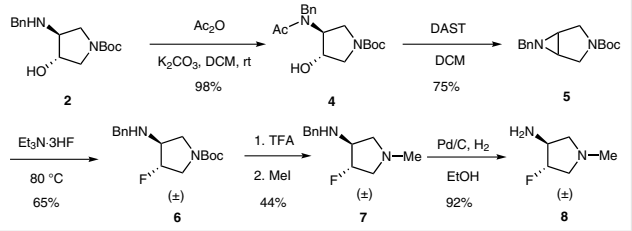
We prepared substrate **2** according to Tsuzuki's procedure,[3] and then converted it into the acetylated substrate **4** in 98% yield (Scheme 2). When subjecting **4** to deoxyfluorination using DAST (diethylaminosulfur trifluoride), we obtained aziridine **5** in 75% yield. This suggested that either the electron-withdrawing acetyl group did not prevent the electron pair of the amino group from participating in the substitution, or that anchimeric assistance via the amide oxygen occurred. In theory, there would be an opportunity to screen other electron-withdrawing groups, but this would be less attractive in comparison to using substrate **3** for the deoxyfluorination. Nevertheless, aziridine **5** could serve as a reliable intermediate to access the *trans*-3-amino-4-fluoropyrrolidine, a reference sample for confirming the relative configuration of the desired *cis* product. We therefore proceeded with the synthesis by ring-opening of

Table 1 Deoxyfluorination of **3**



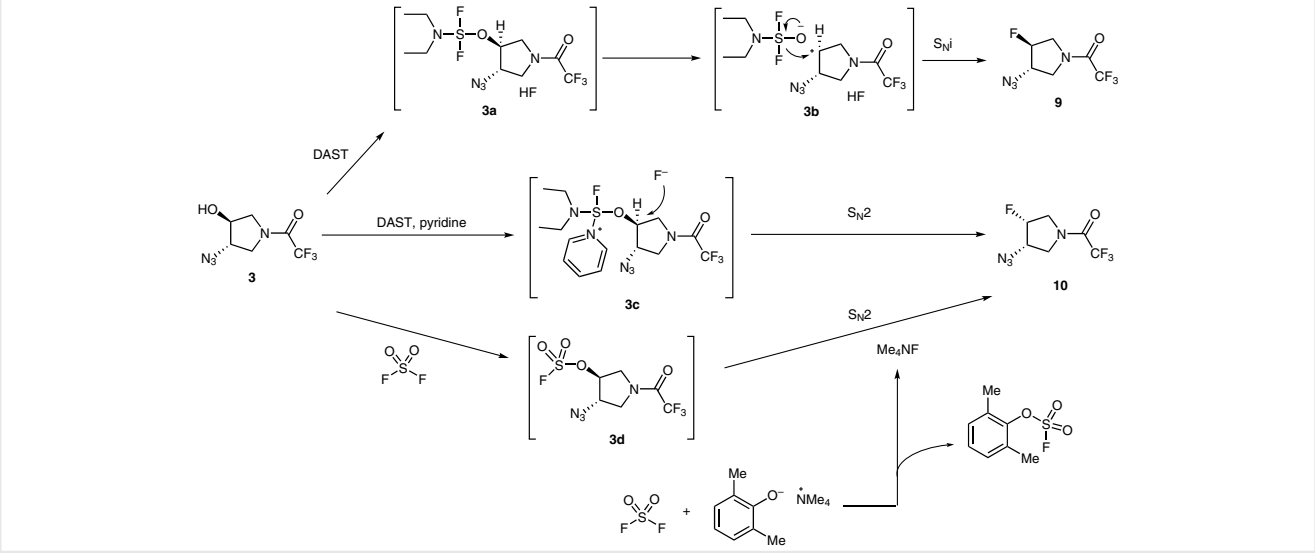
Entry	Conditions	Results
1	DAST, DCM	only *trans* **9**, 66% yield
2	DAST, pyridine, DCM	*trans* **9**/*cis* **10** = 1:11, 70% yield
3	SO_2F_2, tetramethylammonium 2,6-dimethylphenoxide, DMF	only *cis* **10**, 72% yield

aziridine **5** with gentle warming in $Et_3N{\cdot}3HF$ at 80 °C to give *trans*-substituted **6** in 65% yield. Using pyridine·HF instead led to a messy reaction. Removal of the Boc protecting group followed by methylation provided **7**. Debenzylation of **7** under hydrogenation conditions afforded the *trans*-3-amino-4-fluoropyrrolidine **8** in racemic form.



Scheme 2 Synthesis of *trans*-3-amino-4-fluoropyrrolidne **8**

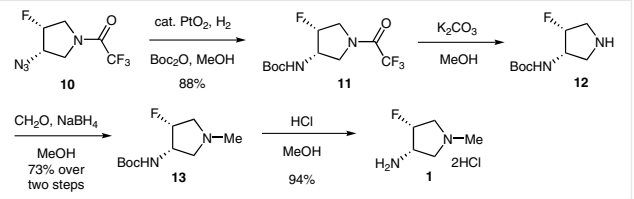
Our efforts were then focused on the deoxyfluorination of **3**. Enantiomerically enriched **3** (93% *ee*) was smoothly prepared by following the reported protocols.[4] However, deoxyfluorination of **3** using DAST still provided the *trans* product **9** (Table 1, entry 1), as observed for analogous substrates.[2] As Paulsen et al. had shown that azides serve as non-participating neighboring groups for the synthesis of 1,2-*cis* glycosides,[5] we suspected that this reaction proceeded through an S_Ni pathway, and not an S_N2 process.[6] In this S_Ni pathway, the substrate **3** was activated to form **3a**, but the desired rear-face attack of fluoride was hindered by the neighboring azido group, which allowed the formation of intimate ion pair **3b**. The concerted release of the sulfuramidous fluoride and fluoride-bonding to the carbon from the same face (the front face) gave *trans* product **9** (Scheme 3). The S_Ni pathway is reported to be inhibited by using pyridine as an additive.[7] Indeed, by adding one equivalent of pyridine to this deoxyfluorination, the desired *cis* product **10** was favored over *trans* product **9** with an 11:1 ratio (entry 2). With pyridine present, the transient intermediate was assumed to be **3c**, the productive pathway of which for *trans* product **9** was inhibited due to preferential release of pyridine instead of fluoride from the sulfite if the intimate ion pair of **3c** had indeed formed (Scheme 3). Alternatively, we sought to perform the deoxyfluorination with cheap and readily available sulfuryl fluoride, as the reported observation of direct deoxyfluorination of α-hydroxy acetates



Scheme 3 Plausible pathways for the deoxyfluorination of **3**

drew our attention.[8] Simple exposure of the substrate, as a solution in DMF, to gaseous sulfuryl fluoride as reported did not provide any conversion, but subsequent addition of tetramethylammonium 2,6-dimethylphenoxide to this solution led to formation of the desired *cis* product **10** in 72% yield (entry 3). Sanford's group reported the in situ generation of anhydrous tetramethylammonium fluoride from the combination of sulfuryl fluoride with tetramethylammonium 2,6-dimethylphenoxide.[9] We therefore proposed that the formed intermediate **3d** underwent S_N2 reaction with in situ generated anhydrous tetramethylammonium fluoride to give the product (Scheme 3). To the best of our knowledge, this is a new application of Sanford's conditions for the deoxyfluorination of an aliphatic alcohol.

From **10**, we completed the synthesis of target **1** as shown in Scheme 4. Reduction of the azido group under hydrogenation in the presence of Boc_2O directly converted **10** into **11** in 88% yield. Methanolysis of the latter provided **12**, and subsequent reductive methylation afforded **13**. Finally, acid treatment of **13** to remove the Boc protecting group and purification by recrystallization provided **1** as a single diastereomer in 94% yield and with 99.9% *ee*.[10]



Scheme 4 Completion of the synthesis of **1**

In summary, we have developed a stereoselective synthesis of *cis*-(*S*,*R*)-3-amino-4-fluoro-1-methylpyrrolidine (**1**) starting from known chiral non-racemic **3**, which is easily accessible by applying Jacobsen's desymmetrization of an epoxide. The deoxyfluorination of **3** was studied toward the *cis* selectivity. While DAST alone led to the *trans* isomer exclusively, the conditions were tuned by adding pyridine to improve the *cis* selectivity. Eventually, complete *cis* selectivity was achieved by applying the combination of SO_2F_2 with tetramethylammonium 2,6-dimethylphenoxide (Sanford conditions). Due to its unique properties, we believe that the synthesis of this highly valuable chiral building block will be of significant interest to chemists and pharmacologists.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611553.

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(10) Characterization of **1**. Yield: 99 mg (94%); white solid; mp 264–266 °C. ^{1}H NMR (400 MHz, D_2O): δ = 5.55 (dt, *J* = 51.7, 3.5 Hz, 1 H), 4.36 (dtd, *J* = 23.4, 8.9, 3.5 Hz, 1 H), 4.01 (m, 1 H), 3.88 (m, 1 H), 3.82–3.52 (m, 2 H), 3.00 (s, 3 H). ^{13}C NMR (101 MHz, D_2O): δ = 90.4 (d, *J* = 183.82 Hz), 59.6 (d, *J* = 21.21 Hz), 54.4, 50.3 (d, *J* = 17.17 Hz), 42.6. ^{19}F NMR (376 MHz, D_2O): δ = –196.7. ^{19}F NMR (376 MHz, CD_3OD): δ = –198.1. HRMS (ESI): *m*/*z* [M + H – 2 HCl]$^+$ calcd for $C_5H_{12}FN_2$: 119.0979; found: 119.0978.