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Stereoselective synthesis of *cis*- and *trans*-3-fluoro-1-phenylcyclobutyl amine

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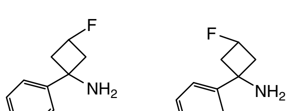
Abstract

A stereoselective approach to the synthesis of *cis*- and *trans*-3-fluoro-1-phenylcyclobutylamine has been developed. Excellent stereoselectivity was obtained by the reduction of the appropriately substituted cyclobutanone to give either cis- or trans-isomers of 3-hydroxyl-1-phenylcyclobutylamine, which was stereoselectively converted to the 3-fluoro derivative.

Introducing fluorine to organic molecules is a common practice in medicinal chemistry due to the unique steric and electronic properties of this substituent.[1] Fluorine is a close steric replacement for hydrogen. As the most electronegative element, fluorine produces significant electronic changes in a molecule without creating substantial steric perturbation. Additionally, fluorine forms strong covalent bonds with carbon (116 kcal/mol for C–F bond versus 100 kcal/mol for C–H bond),[2] which makes fluorine substitution a preferred method to block C–H activated metabolic transformations.

1-Phenylcyclobutylamine is a common structural motif in biologically active molecules, and it is widely used in drug discovery and agriculture chemical projects.[3] In order to decrease the possible metabolic liability of the cyclobutyl ring, we were interested in the synthesis of fluorinated 1-phenylcyclobutylamines such as **1a** and **1b** for use in a recent drug discovery project.



1a **1b**

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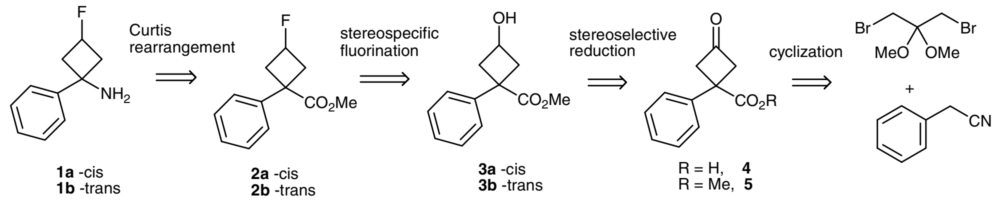
Our retrosynthetic analysis of **1a** and **1b** is outlined in Scheme 1. We envisioned that **1a** and **1b** could be conveniently synthesized from the corresponding carboxylic acid precursors via a Curtius rearrangement. Since the polarity difference between cis- and trans-fluoro compounds is expected to be small, we anticipated that purification of cis- and trans-isomers should be carried out at the hydroxy ester stage (**3a**,**3b**), and that a stereospecific conversion of the hydroxy group to fluorine would be required. The synthesis of 3-hydroxy-1-phenylcyclobutanecarbonitrile was previously reported, but the stereoselectivity had not been determined.[4] Cyclization of 4-chloro-phenylacetonitrile and epibromohydrin was reported to give modest selectivity in favor of the cis-isomer (cis:trans = 3.3:1).[5,6] It was our interest to develop a synthesis in which both isomers could be selectively synthesized from a common precursor. We hoped to access both isomers selectively by screening of different ketone reduction conditions. However, the stereoselectivity of cyclobutanone (**4**,**5**) reduction is hard to predict due to the small energy difference between planar and the puckered conformation of cyclobutane.[7] Finally, **4** and **5** may be prepared from commercially available 1,3-dibromo-2,2-dimethoxypropane and phenylacetonitrile.[8]

Our synthesis that involved the treatment of phenylacetonitrile and 1,3-dibromo-2,2-dimethoxypropane with 2.2 equiv of NaH in dry DMSO at 60 °C for 6 h afforded ketal **6** in 73% yield following the silica gel chromatography



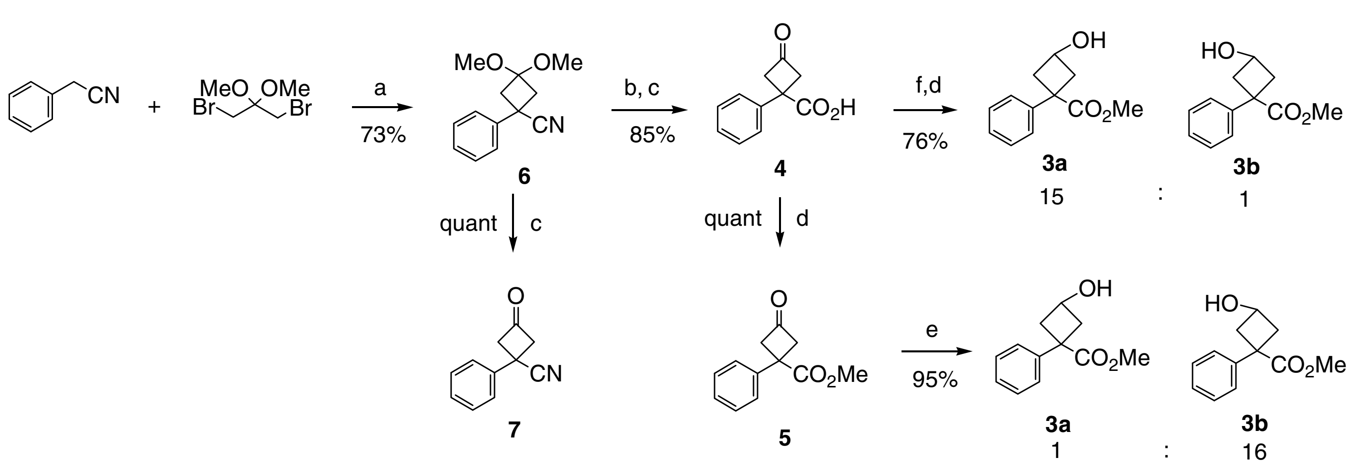
Scheme 1. Retrosynthetic analysis.

(Scheme 2). The deprotection of dimethylketal gave ketonitrile **7** in quantitative yield. The hydrolysis of the sterically hindered nitrile from the ketal intermediate **6** afforded low yield under acidic conditions. However, the nitrile was cleanly hydrolyzed under basic conditions after refluxing in a mixture of 1-BuOH and 50% KOH aqueous solution for 12 h.[9] The subsequent deprotection of this dimethylketal intermediate gave ketoacid product **4** as a colorless solid. Ketoacid **4** was then converted to ketoester **5** conveniently by treatment with $TMSCHN_2$.

We next investigated the stereoselective ketone reduction, and the results are summarized in Table 1. The reduction of ketonitrile **7** with $NaBH_4$ gave low selectivity for the trans-isomer, while selectivity was reversed with L-Selectride favoring the cis-isomer.[10] However, the selectivity using either reagent was modest (cis:trans $\leqslant$ 4:1), and the apparent effect of temperature on selectivity was quite small. We then turned our attention to ketoester **5**. The trans-isomer **3b** was the favored product with both $NaBH_4$ and L-Selectride reduction of **5**; however, selectivity was much higher with $NaBH_4$. A more significant effect of temperature on stereoselectivity was also observed with $NaBH_4$ reduction of **5**, as lower temperatures gave higher trans-selectivity. The ester substituent afforded a moderate influence on stereoselectivity in $NaBH_4$ reductions as demonstrated by slightly better selectivity with benzylester **8** than methylester **5**. The $NaBH_4$ mediated reduction of ketoacid **4** was completely non-selective over a wide range of temperatures. However, to our surprise, excellent cis-selectivity was observed with L-Selectride reduction of **4**. Higher temperatures afforded higher selectivity, and selectivity was severely eroded when the reduction was carried out at −78 °C. Thus, with proper starting materials and reduction conditions, excellent selectivity can be achieved for both cis- and trans-isomers.

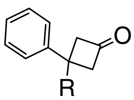
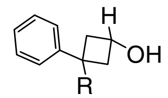
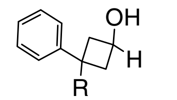
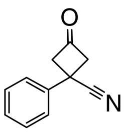
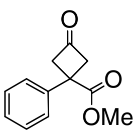
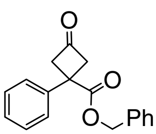
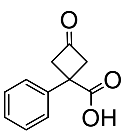
The factors influencing stereoselectivity in these cases are not apparent. However, it is likely that the conformation of cyclobutanone, the steric bulkiness and electronic nature of the substituents, the size and reactivity of the reducing agent all contribute to the stereoselectivity outcome. The conformation difference of cyclobutanone of nitrile **7** and ester **5** is likely one of the main contributors causing drastic difference in stereoselectivity between these two compounds. NOE data indicated that nitrile **7** prefers puckered conformation IV positioning the larger phenyl group at equatorial position with smaller NOE effect between H^1 and H^2 (Fig. 1), while ester **5** adopts the conformation closer to planar V.[11] In the case of ketoacid reduction, carboxylic acid may react with the reducing agent (VI and VII) before the ketone gets reduced, likely affecting the selectivity.

Once a selective synthesis for both isomers **3a** and **3b** was established, we turned to investigate the stereospecific conversion of the hydroxy group to fluorine (Scheme 3). The conversion of the hydroxyl to fluorine with (diethylamino)sulfur trifluoride (DAST) afforded scrambling of the carbinol stereocenter.[12] We were pleased to find a two step, one-pot procedure by first converting alcohol to triflate following the displacement of triflate with tetrabutylammonium fluoride (TBAF), which gave excellent yield



Scheme 2. Reagents and conditions: (a) NaH, DMSO, 60 °C, 6 h; (b) ^{n}BuOH, KOH 50%, 125 °C, 12 h; (c) 50% H_2SO_4 (cat), acetone, 75 °C, 2 h; (d) $TMSCHN_2$, MeOH, CH_2Cl_2, 21 °C; (e) $NaBH_4$, MeOH, −78 °C, 15 min; (f) L-Selectride, THF, 50 °C, 15 min.

Table 1
Cis- and trans-selectivity from cyclobutanone reduction

 Ketones	Reducing agent	Temperature (°C)	 cis- isomer*	 trans- isomer*
 **7**	$NaBH_4$	21	3	4
		0	2	3
		−78	1	2
	L-Selectride	21	4	1
		−78	7	2
 **5**	$NaBH_4$	0	1	8
		−35	1	11
		−78	1	16
	L-Selectride	21	1	1
		−78	1	2
 **8**	$NaBH_4$	21	1	8
		−78	1	20
	L-Selectride	21	1	1
		−78	2	3
 **4**	$NaBH_4$	21	1	1
		−78	1	1
	L-Selectride	50	15	1
		21	11	1
		−78	2	1

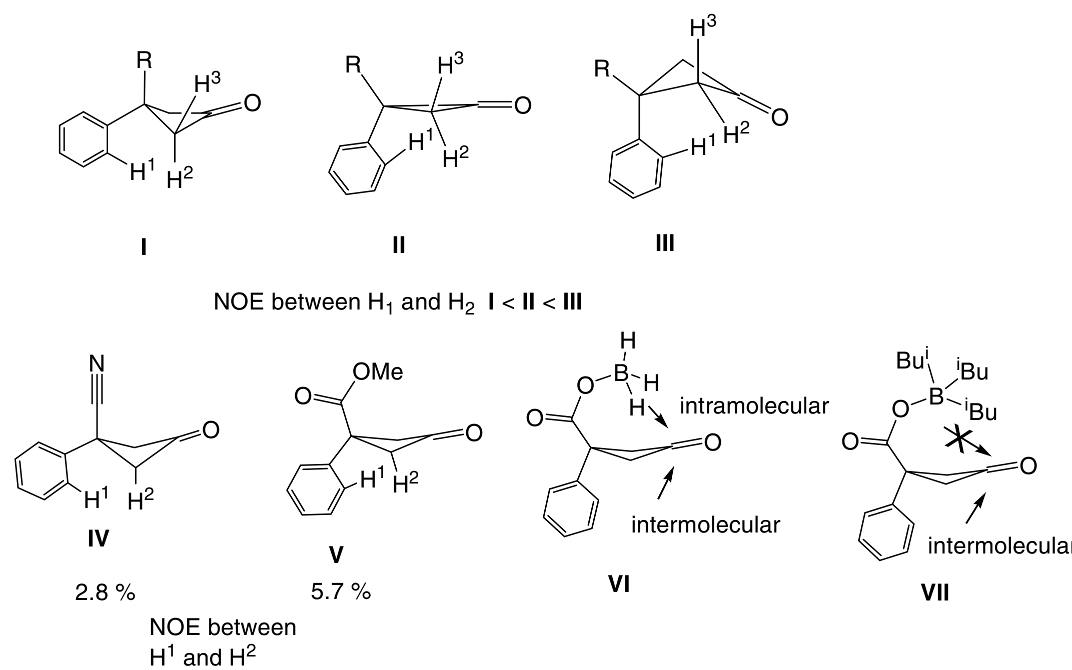
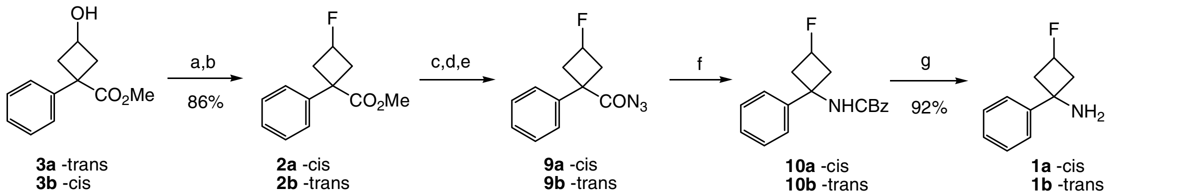


Fig. 1.



Scheme 3. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, −78 °C to 21 °C over 15 min; (b) TBAF 2 equiv, 21 °C, 15 min; (c) LiOH, MeOH, H_2O, 50 °C, 2 h; (d) DIEA, Ethylchloroformate, acetone, 0 °C, 30 min; (e) NaN_3, 21 °C, 30 min; (f) BnOH, toluene, 110 °C, 16 h; (g) Pd/C, H_2 50 psi, EtOH, 4 h.

of the fluorinated product with complete inversion of stereochemistry.

With pure **2a** and **2b** in hand, the final conversion of the ester to the corresponding amine was accomplished. The hydrolysis of esters **2a** and **2b**, and the subsequent addition of sodium azide to the activated carboxylates afforded the corresponding acyl azides **9a** and **9b**. These were converted to the benzyl carbamate-protected amines **10a** and **10b** by Curtius rearrangement of the acyl azides followed by trapping of the isocyanate intermediates with benzyl alcohol (40% yield over 4 steps). Finally, removal of the CBz group by hydrogenolysis was straightforward, affording **1a** and **1b** in 24% and 19% overall yield, respectively, from common starting materials.[13]

In summary, we report the first stereoselective synthesis of *cis*- and *trans*-3-fluoro-1-phenylcyclobutyl amines **1a** and **1b**. Excellent selectivity for both cis- and trans-isomers has been achieved from the reduction of ketoacid **4** with L-Selectride or from ketoester **5** with $NaBH_4$, respectively.

Acknowledgments

We thank Professor Robert Boeckman for useful discussions on the mechanism of stereoselectivity in cyclobutanone reduction, Dr. Jinjun Yin for sharing unpublished results, and Dr. Daniel McMasters for performing the molecular mechanics and ab initio calculations. We also thank Ms. Deborah Pan and Dr. Joseph L. Duffy for proof-reading the manuscript.

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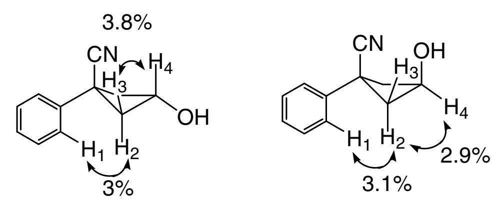
10. Cis- and trans-isomers were assigned based on NOE effects, and the ratio was determined by ^1H NMR integration of H_1 and H_2 of the cis- and trans-isomers.



11. The preferred conformations of 3-Ph-3-R-substituted cyclobutanones (**4**, **7**, **5**, and **8**) were calculated using two molecular mechanics methods, MMFFs and OPLS-2005, in simulated high-dielectric solvent. However, the two methods yielded conflicting results. MMFFs calculation showed conformation *I* is the preferred conformation (pucker angle θ for **4**, **7**, **5**, and **8**: 29.2°, 22.6°, 29°, and 29.4°) while OPLS calculation indicated conformation III being preferred (pucker angle θ for **4**, **7**, **5**, and **8**:23°, 21.4°, 23.2°, and 22.8°). Density functional theory (DFT) calculations (B3LYP/6-31G*) indicated that the cyclobutanone is nearly planar (conformation II with pucker angle θ for **4**, **7**, **5**, and **8**: 8.4°, 8.8°, 8.6°, and 9.4°).
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13. Compound **1a**: ^1H NMR (500 MHz, CDCl3): δ (ppm) 7.46 (d, $^3J_{H–H'}$ = 7.4 Hz, 2H), 7.40 (t, $^3J_{H–H'}$ = 7.6 Hz, 2H), 7.30 (t, $^3J_{H–H'}$ = 7.4 Hz, 1H), 4.88 (dm, $^2J_{H–F}$ = 62.7 Hz, 1H), 3.1 (m, 2H), 2.5 (m, 2H); ^{13}C NMR ($CDCl_3$): δ (ppm) 146.5, 128.9, 127.3, 125.8, 82.3 (d, $^1J_{C–F}$ = 205.4 Hz), 52.1 (d, $^3J_{C–F}$ = 17.3 Hz), 46.8 (d, $^2J_{C–F}$ = 19.2 Hz); ^{19}F NMR ($CDCl_3$): δ (ppm) −65.8. Compound **1b**: ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.40 (t, $^3J_{H–H'}$ = 7.6 Hz, 2H), 7.32 (d, $^3J_{H–H'}$ = 7.6 Hz, 2H), 7.28 (t, $^3J_{H–H'}$ = 7.4 Hz, 1H), 5.43 (dm, $^2J_{H–F}$ = 56.3 Hz, 1H), 2.7 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 150.1, 129.0, 126.9, 124.3, 85.0 (d, $^1J_{C–F}$ = 208.3 Hz), 51.7 (d, $^3J_{C–F}$ = 19.2 Hz), 44.1 (d, $^2J_{C–F}$ = 20.2 Hz); ^{19}F NMR ($CDCl_3$): δ (ppm) −65.8.