Fluoroamines via Chiral Cyclic Sulfamidates

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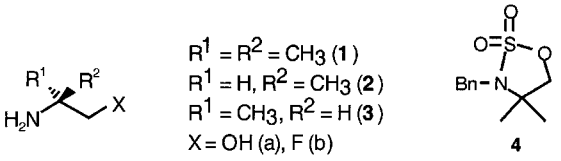
Received 20 April 2001; revised 6 March 2002

Abstract: *N*-benzyl [1,2,3]-oxathiazolidine 2,2-dioxides (cyclic sulfamidates) were synthesized from their corresponding β-amino alcohols and used as substrates in fluorination reactions with tetrabutylammonium fluoride (TBAF). After desulfonation of the intermediates, the *N*-benzyl fluoroamines were debenzylated by transfer hydrogenolysis with Pd/C to yield (*S*) and (*R*)-2-amino-1-fluoropropanes (**2b** and **3b**, respectively, both with 95% ee). The reactions were carried out on multi-gram scale without the need for chromatographic purification of the intermediates. In the presence of carbonate, the (*S*)- and (*R*)-*N*-benzylfluoroamines underwent intramolecular cyclizations in which fluoride was displaced to yield cyclic carbamates **13** and **14**.

Key words: fluoroamines, nucleophilic addition, cyclizations, cyclic sulfamidates, beta-adrenergic ligands

As part of an ongoing effort to develop non-invasive, in vivo imaging of heart receptor populations using positron emission tomography (PET),[1–6] we required a convenient syntheses of fluoro-*tert*-butylamine (**1b**) and enantiomerically pure (*S*)-and (*R*)-1-fluoro-2-propylamine (**2b** and **3b**, respectively) in order to synthesize selected β-adrenoceptor ligands. The β-adrenergic receptors are present in the receptor rich tissues in concentrations of nanomoles per gram of tissue. In order to achieve specific labeling of the receptors, the labeled ligands must be delivered to the receptors at concentrations substantially lower than those of the receptor but still with sufficient radioactivity to perform PET imaging. As such, a specific activity of >1Ci/micromole of the final ligand is required, which limits the fluorination reagent to the fluoride anion. Thus, we chose to develop the synthetic route utilizing a hydroxide to fluoride conversion starting from the readily available amino alcohols (**1a**–**3a**; Figure).



Figure

Initial investigations focused on the synthesis of **1b** as this likely represents the most challenging transformation since it requires substitution adjacent to a quaternary carbon, similar to that of a neopentyl position, at which substitutions occur with difficulty. Our attempts to fluorinate *N*-protected (FMOC or BOC) **1a** using conventional nucleophilic fluorination strategies were unsuccessful. For example, treatment of *N*-(carbamate)-**1a** with DAST resulted in complex mixtures of products, which were likely the result of intramolecular cyclization reactions involving the protecting group and intermolecular reactions of the required intermediate.[7,8] In addition, no fluorination product was observed when the hydroxyl of the *N*-protected **1a** was converted to its triflate (OTf) and then treated with TBAF. We then turned to the cyclic sulfamidates, [1,2,3]-oxathiazolidine-2,2-dioxides, which are readily prepared from *N*-protected amino alcohols. They are versatile substrates that undergo nucleophilic displacement with carbon (cyanide, and organometallic reagents), [^{18} and ^{19}]F^-, nitrogen (e.g. azide, thiocyanate, amines, and pyrazole), oxygen (e.g. MeO^-, AcO^-, and ArO^-) and RS^- nucleophiles.[9–14]

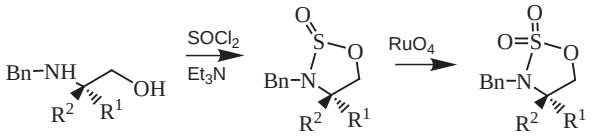
We previously reported the fluorination reaction of *N*-benzyl sulfamidate (**4**),[6] the precursor to **1b·HCl**. At nearly the same time, Ok, et al. described the synthesis of **1b·HCl** via **10,**[15] and as such, the production of **1b** and its precursors will not be further elaborated here. However, the independently developed conditions described here are applicable for the synthesis of **1b** as well as **2b**, **3b** and have been applied on a scale of tens of grams without time consuming chromatographic purification of the intermediates. We report the preparation of highly enantiopure fluoroamines **2b** and **3b**, which were previously described as an unresolved enantiomeric mixture.[16] Also described is an unusual intramolecular cyclization reaction in which fluoride is displaced from the chiral *N*-benzyl amines **11** and **12**. The corresponding chemistry with radiolabeled fluoride has been developed and will be reported elsewhere; subsequent references to fluorine in this paper refer to ^{19}F.

Preparation of the *N*-benzyl sulfamidates **9** and **10** was based on White and Garst's method[17] which involves synthesis of the sulfamidite intermediates **7**, **8** from thionyl chloride and the amino alcohols **5**, **6**, followed by RuO_4-oxidation (Scheme 1). After RuO_4-oxidation, **9** and **10** were isolated as stable, crystalline products in fair overall

Synthesis 2002, No. 6, 29 04 2002. Article Identifier:
1437-210X,E;2002,0,06,0766,0770,ftx,en;M02401SS.pdf.

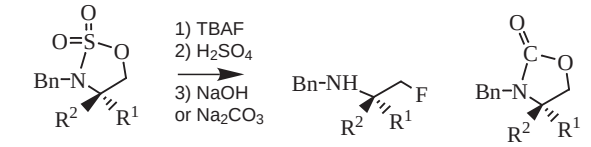
ISSN 0039-7881

yields (~35%) each with >99.5% ee. The yields of **9** and **10** were somewhat lower than the overall yield of **4** reported by Ok, et al. (64%),[15] which was similar to our own results. In our experience, sterically uncongested sulfamidates such as **9** and **10** are notably more reactive than their hindered counterparts and the same may be true for their sulfamidite precursors, although they generally require more vigorous conditions to react.[14] This may explain, in part, the moderate overall yields obtained for **9** and **10**. Attempts to synthesize sulfamidates directly via thionyl chloride and triethylamine[18] or sodium hydride and sulfonyl diimidazole[12,19] yielded, at most, traces of the desired products and we had no success using unprotected amino alcohols. In contrast to the procedure described by Ok, et al.,[15] our procedure does not employ column chromatography and is thus more amenable to multigram-scale syntheses. Indeed we have applied our conditions to ~25 g of **5** with good results.



Scheme 1

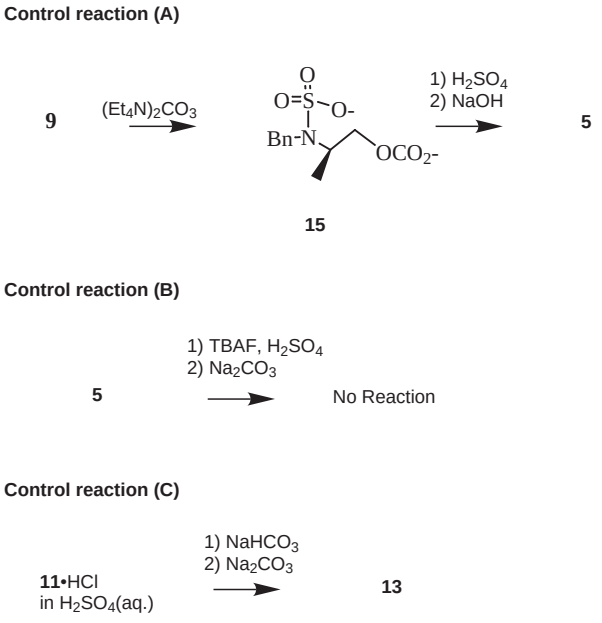
Using conditions described in the literature,[17] **9**–**10** reacted with TBAF at room temperature and the intermediate products were subsequently hydrolyzed to yield **11**–**12** (Scheme 2).



Scheme 2

In some experiments with **11** and **12**, sodium carbonate was used to neutralize the aqueous acid in the hydrolysis step and significant amounts (up to 45% yield) of the cyclic carbamates **13** and **14** were isolated. We investigated the origin of **13** and **14** by analyzing control reactions by HPLC, described here for the *S*-isomer series. Three possible origins were considered. In pathway (A), carbonate, present in the TBAF reagent solutions, would react with **9** to afford **13** upon workup. In pathway (B), TBAF would promote the formation of **13** from carbonate and **5** (**5** being formed via a possible side reaction involving adventitious H_2O in the TBAF solutions and **9**). In pathway (C), **11** would react with carbonate, which was used to neutralize the acidic hydrolysis solution.

In control reaction (A), the test for pathway (A) (Scheme 3), carbonate reacted with **9** to form a new product, putatively **15**, (~90% by HPLC, Table); however, this yielded **5** (92% isolated yield) after the sulfuric acid hydrolysis. In control reaction (B), no reaction occurred. In control reaction (C), when the aqueous, acidic (sulfuric acid) solution of **11** was neutralized with sodium bicarbonate, **13** began to form (10% yield after 40 min) and its yield increased when sodium carbonate was added (up to 80% yield HPLC, 60% isolated yield). Thus, it is highly likely that **13** and **14** originated from **11** and **12** and carbonate from sodium carbonate, in an unusual cyclization step that involves displacement of fluoride. The phase transfer catalyst properties of the tetrabutylammonium cation, present in the synthesis of **11** and **12**, would likely facilitate the formation of **13** and **14** under these conditions. Thus sodium hydroxide is recommended for neutralization of the hydrolysis solution in the synthesis of **11** and **12**. No such cyclization was observed during the fluorination of hindered sulfamidate **4** when sodium carbonate was used to neutralize the hydrolysis solution.

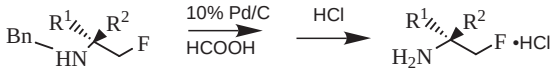


Scheme 3

Table Reverse Phase HPLC Retention Times

Compound	Retention Time (min)
5	5.3
9	14.0
15 (putative)	8.6
11	10.4
13	13.6

The hydrogen-transfer debenzylation (Scheme 4) using formic acid and 10% Pd/C[20] cleanly debenzylated **11** and **12** to afford **2b** and **3b** in high yield (81% and 94%). The transfer hydrogenolysis described here is much milder than the H_2/Pd/C debenzylations described by Ok, et al. and may be suitable for the preparation of other compounds with reduction-labile components. The isolated fluoroamines were then derivatized with (*S*)-MTPA (quantitative yield) to yield the Mosher amides. By ^{1}H NMR, the methoxy and fluoromethyl signals were resolved and the integrations demonstrated 95% ee for both **2b** and **3b**. By, ^{19}F NMR, integrations of the trifluoromethane signals indicated 95 % ee and 98% ee for both **2b** and **3b**.



R^1 = H, R^2 = CH_3 (**11**)
R^1 = CH_3, R^2 = H (**12**)

(**2b**) 81%
(**3b**) 94%

Scheme 4

In summary, a useful method for the synthesis of multigram quantities of fluoroamines **2b**–**3b** in high enantiomeric purity from the corresponding *N*-benzyl amino alcohols (**5** and **6**) via the cyclic sulfamidates (**9** and **10**) has been developed. Fluorination of **9** and **10** was facile, proceeding to completion within a few minutes at room temperature with ca. 1:1 ratio of sulfamidate–TBAF. The yields are good to moderate and this methodology is amenable to large-scale preparations of **1b**–**3b**. Furthermore, the fluorination reaction lends itself to the use of short-lived [^{18}F]-fluoride. *N*-benzyl fluoroamines **11** and **12** reacted with carbonate to afford the corresponding cyclic carbamates (**13** and **14**) in a cyclization reaction in which fluoride is displaced.

Melting points were determined using an Electrothermal® melting point apparatus and are uncorrected. Low resolution mass spectrometry was performed on a Micromass Quattro II Tandem Quadrupole Mass Spectrometer (electrospray ionization). High resolution mass spectrometry was performed using a Micromass 70SEQ Tandem Hybrid Mass Spectrometer (FAB) or a PE Biosystems Mariner electrospray (TOF) instrument. ^{1}H- and ^{19}F NMR spectra were obtained with a GE Omega 300 MHz spectrometer. ^{1}H-chemical shifts are reported in ppm (δ) and ^{19}F-chemical shifts are referenced to $CFCl_3$. Coupling constants are rounded to the nearest 0.5 Hz. Elemental analyses were performed by Galbraith Laboratories, Knoxville TN. Prior to elemental analysis, samples were dried under vacuum at 40–50 °C. Optical rotation measurements were made using a Jasco DIP-370 digital polarimeter. Flash column chromatography was performed using silica gel (Merck, grade 9385, 230–400 mesh). Analytical TLC and R_f values were determined using Analtech GF silica gel plates (0.25 mm); preparative TLC was performed using Analtech GF silica gel plates (1 mm). Unless otherwise noted, reagents were purchased from Aldrich Chemical Co. Solvents were ACS reagent grade or better. Unless otherwise noted, anhyd solvents (Aldrich) were used as received except for CH_2Cl_2, which was dried by storing over activated, crushed 4 Å molecular sieves. Solid TBAF or a 1.0 M solution (in THF with 5% H_2O) was dried by azeotropic H_2O removal (CH_3CN) prior to use. Stable·HCl salts were obtained by dissolving the product in Et_2O or Et_2O/MeOH and bubbling $HCl_{(g)}$ through the solutions; the resulting precipitate was collected and washed thoroughly with Et_2O. The HPLC analyses were performed using Waters 515 HPLC Pumps controlled by Millenium-32® software and the detection was performed by monitoring the eluate at 256 nm using a Waters 2487 dual wavelength absorbance detector. The organic solvents were HPLC grade and the aq solutions were filtered through a 0.45 μm nylon membrane (Phenomenex) prior to use. Chiral HPLC was used to determine the enantiomeric purity of compounds **9** and **10** using a Chiracel® OD column (Chiral Technologies Incorporated) and isocratic elution (heptane with 0.25% TFA– *i*-PrOH, 4:1) at 1 mL/min. Reverse phase HPLC was used to investigate the formation of **13** and **14**. The Prodigy ODS (2) column (5μ, 150 × 4.60 mm, Phenomenex) was eluted using a gradient elution protocol at 1 mL/min as follows: solvent A (0.1 M NH_4OAc) and solvent B (MeOH); 0–3 min (4:1, A:B); 3–13 min (4:1, A:B changing to 0:1) and 13–17 min (0:1, A:B).

N-Benzyl-(*S*)-2-methyl-aminopropan-1-ol (5) and *N*-Benzyl-(*R*)-2-methyl-aminopropan-1-ol (6)

A mixture of benzaldehyde (0.262 mol) and the chiral amino alcohol (*S*, or *R* -isomer, 0.262 mol) in benzene (100 mL) was refluxed with the azeotropic removal of H_2O (4 h). The solvent was reduced to 50 mL, and the mixture refrigerated. The intermediate, crude imine crystallized and was subsequently dissolved in MeOH (300 mL). The soln was cooled to 0 °C under Ar, and then $NaBH_4$ (9.6 g, 0.254 mol) was added in gram-portions. After stirring for 2 h at 0 °C, 6 N NaOH (60 mL) was added and the solvent was evaporated. The residue was extracted with H_2O (250 mL) and Et_2O (4 × 100 mL). Compounds **5** and **6** were obtained.

The characterization data for **5** (mp 42.5–45.5 °C) match those reported previously.[21]

6

Mp 41.5–43.5 (lit. 46.5).[22]

^{1}H NMR ($CDCl_3$): δ = 1.07 (d, 3 H, *J* = 6 Hz, CH_3), 2.2 (br s, 2 H, NH and OH), [2.92 (m, 1 H), 3.27 (dd, 1 H) and 3.57 (dd, 1 H); AMX system J_{AM} = 10.5 Hz, J_{AX} = 7 Hz, J_{MX} = 4 Hz, $CHCH_2$], 3.70 and 3.85 (dd, 2 H, AB system, *J* = 13 Hz, benzyl H), 7.24–7.35 (m, 5 H, phenyl H).

Cyclic Sulfamidite Formation; General Procedure

We modified the method by White and Garst[17] for the synthesis of compounds **7** and **8**. Briefly, a soln of the *N*-benzyl amino alcohol (~0.33 M) and Et_3N (2.1 equiv) in anhyd CH_2Cl_2 under Ar was cooled to –78 °C with stirring. $SOCl_2$ (1.05 equiv, ~1.5 M in anhyd CH_2Cl_2) was added dropwise over 45 min. The soln was allowed to warm to r.t., filtered (Et_3N·HCl removal), and was washed with H_2O and brine. The organic phase was dried (Na_2SO_4) and the solvent was removed to afford an oil. This material was dissolved in a minimum of Et_2O and filtered through a short plug of silica followed by continued elution with Et_2O until no more sulfamidite eluted. The crude sulfamidite was used directly in the RuO_4-oxidation procedure described below.

RuO_4 Oxidation; General Procedure

We adapted White and Garst's procedure[17] for the synthesis of **9** and **10**. The conditions described below were based on 0.15 mol of sulfamidite. Briefly, the sulfamidite was dissolved in CH_3CN (300 mL) and the soln cooled to 0 °C. $RuCl_3·3H_2O$ (10 mg) and then $NaIO_4$ (1 equiv) were added, followed by distilled H_2O (300 mL). After 10 min, the ice bath was removed and the soln was stirred for 2 h. H_2O (250 mL) was added and the mixture was extracted with Et_2O (3 × 200 mL). The volume of the organic phase was reduced

(100 mL) and the crude mixture was filtered through a plug of silica, which was eluted with additional Et_2O. The solvent was removed and the product was crystallized from CH_2Cl_2–heptane.

3-Benzyl-(*S*)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide (7)
Compound **5** (27.0 g, 0.167 mol) afforded 28.3 g of crude **7**. A sample of the crude product (0.50 g) was purified by column chromatography (CH_2Cl_2–acetone, 20:1, R_f 0.75) to yield 0.27 g of an oil (1.3 mmol, 44%). Although NMR spectral data can be used to identify **7**, a satisfactory elemental analysis was not obtained.

^{1}H NMR ($CDCl_3$): δ = 1.21 (d), 1.32 (d), 3.50 (m), 3.78 (m), 3.99 (dd), 4.10 (d), 4.17 (d), 4.26 (d), 4.40 (d), 4.53 (d), 4.85 (dd), 7.28–7.43 (m).

MS: *m*/*z* = 211.9 (100, M + H), 166.0 (50) 148, 147, 146 cluster (30).

3-Benzyl-(*R*)-4-methyl-[1,2,3]-oxathiazolidine-2-oxide (8)
Compound **6** (18.5 g, 0.112 mol) afforded 19.2 g of crude **8**. A sample of the crude product (0.50 g) was purified by column chromatography (CH_2Cl_2–acetone, 20:1, R_f 0.75) to yield 0.42 g of an oil (69%).

^{1}H NMR ($CDCl_3$): δ = 1.21 (d), 1.32 (d), 3.50 (m), 3.78 (m), 3.99 (dd), 4.10 (d), 4.17 (d), 4.26 (d), 4.40 (d), 4.53 (d), 4.85 (dd), 7.28–7.43 (m). The NMR spectrum showed very few impurities, but a satisfactory elemental analysis was not obtained.

MS: *m*/*z* = 211.9 (10, M + H), 166.0 (100) 148, 147, 146 cluster (10).

3-Benzyl-(*S*)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (9)
Crude **7** (27.8 g) afforded 12.2 g of crystalline **9** (33.5% from **5**, 77% this step). After removal of the ice bath, the mixture turned brown/red.

$[\alpha]_D^{23}$ +25 (*c* 0.86, MeOH); mp 64.5–66 °C.

Chiral chromatography of **9** on a Chiracel® OD column (R_t 8.60 min) demonstrated >99.5% ee.

^{1}H NMR ($CDCl_3$): δ =1.21 (d, 3 H, *J* = 6 Hz, CH_3), [3.74 (m, 1 H), 4.13 (dd, 1 H) and 4.57 (dd, 1 H); AMX system J_{AM} = 8 Hz, J_{AX} = 7 Hz, J_{MX} = 6.5 Hz, $CHCH_2$], 4.22 and 4.41 (dd, 2 × 1 H each, AB system, *J* = 15 Hz, benzyl H), 7.3–7.45 (m, 5 H, phenyl H).

MS: *m*/*z* = 249.9 (100, M + Na), 227.9 (20, M + H).

Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.77; N, 6.16. Found: C, 52.82; H, 6.01; N, 6.13.

3-Benzyl-(*R*)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (10)
Crude **8** (18.7 g) afforded 9.05 g of **10** (36.5% from **6**, 52% this step).

$[\alpha]_D^{23}$ –29.3 (*c* 1.07, MeOH); mp 65–66 °C.

Chiral chromatography of **10** on a Chiracel® OD column (R_t 10.73 min) demonstrated >99.5% ee.

^{1}H NMR ($CDCl_3$): spectrum was identical to **9**.

MS: *m*/*z* = 249.9 (10, M + Na).

Anal. Calcd for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.77; N, 6.16. Found: C, 52.91; H, 6.00; N, 6.14.

(*S*)-*N*-Benzyl-2-amino-1-fluoropropane (11)
TBAF (1.2 mL of a 1.0 M soln in THF) was dried and the residue was dissolved in anhyd CH_3CN (5 mL). Compound **9** (0.25 g, 1.1 mmol) was added and the mixture was stirred for 30 min at r.t. TLC indicated complete conversion of **9** to non-mobile material. After solvent removal, the formed NSO_3 intermediate was hydrolyzed by treating with 20% $H_2SO_{4(aq)}$–Et_2O (1:1, 20 mL/g of sulfamidate). The mixture was stirred for 2 h at r.t. and then the organic phase containing unreacted starting material was separated from the aq phase. The aq phase was adjusted to pH 10–12 using aq NaOH. The product was extracted into Et_2O and subsequently purified by column chromatography (CH_2Cl_2–acetone, 20:1, R_f 0.36) to yield 0.16 g of crude **11**. The reaction was scaled up to 50 mmol of **9** without a decrease in yield.

^{1}H NMR ($CDCl_3$): δ = 1.10 (dd, 3 H, J_1 = 7 Hz, J_2 = 1.5 Hz, CH_3), 1.93 (s, 1 H, NH), 3.79 and 3.88 (2 × d, 2 × 1 H, AB system, *J* = 13 Hz, benzyl H), {3.02 (m, 1 H), [4.29 (dd) and 4.36 (dd), 2 H total, each split by J_{HF} = 48 Hz]; ABX pattern J_{AB} = 9 Hz, J_{AX} = 6.5 Hz, J_{BX} = 6 Hz, $CHCH_2F$}, 7.22–7.36 (m, 5 H, phenyl H).

^{19}F NMR ($CDCl_3$): δ = –225.37 (td, J_1 = 48 Hz, J_2 = 17 Hz, additional splitting *J* = 1.5 Hz due to coupling to CH_3 group is observed).

MS: *m*/*z* = 168 (100, M + H).

The product was converted to its HCl salt and recrystallized from MeOH–EtOAc–Et_2O to yield 0.17 g (76%) of **11**·HCl.

Mp 159.5–160.5 °C; $[\alpha]_D^{23}$ +4.8 (*c* 0.92, MeOH).

Anal. Calcd for $C_{10}H_{15}ClFN$: C, 58.97; H, 7.42; N, 6.87. Found: C, 58.77; H, 7.71; N, 6.81.

3-Benzyl-(*S*)-4-methyl-oxazolidin-2-one (13)
R_f 0.69 (CH_2Cl_2–acetone, 20:1); $[\alpha]_D^{23}$ –23 (*c* 0.93, MeOH).

^{1}H NMR: δ = 1.22 (d, 3 H, *J* = 6 Hz, CH_3), [3.7 (m, 1 H), 3.85 (dd, 1 H) and 4.37 (dd, 1 H); AMX system J_{AM} = 8.5 Hz, J_{AX} = 7 Hz, J_{MX} = 8.5 Hz, $CHCH_2$], 4.11 and 4.79 (2 × d, 2 × 1 H, AB system, *J* = 15 Hz, benzyl H), 7.25–7.3 (m, 5 H, phenyl H).

MS: *m*/*z* = 192 (100, M + H).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.25; H, 6.95; N, 7.35.

(*R*)-*N*-Benzyl-2-amino-1-fluoropropane (12)
Procedure was identical to that used to synthesize **11**.

^{1}H NMR ($CDCl_3$): identical to **11**.

^{19}F NMR ($CDCl_3$): –225.22 (td, J_1 = 48 Hz, J_2 = 17 Hz, additional splitting *J* = 1.5 Hz due to coupling to CH_3 group is observed).

MS: *m*/*z* = 168 (40, M + H), 90.9 (100).

12·HCl

$[\alpha]_D^{23}$ –6.9 (*c* 0.58, MeOH); mp 160.5–162 °C.

Anal. Calcd for $C_{10}H_{15}ClFN$: C, 58.97; H, 7.42; N, 6.87. Found: C, 58.88; H, 7.55; N, 6.70.

3-Benzyl-(*R*)-4-methyl-oxazolidin-2-one (14)
R_f 0.69 (CH_2Cl_2–acetone, 20:1); $[\alpha]_D^{23}$ +19.9 (*c* 1.23, MeOH).

^{1}H NMR ($CDCl_3$): spectrum identical to **13**.

MS: *m*/*z* = 214.0 (100, M + Na), 192.0 (70, M + H).

HRMS: *m*/*z* calcd for $C_{11}H_{14}NO_2$, 192.10245; found, 192.1023.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.09; H, 6.99; N, 7.20.

Formation of (13) and (14)
Control reactions A, B, and C were monitored by reverse phase HPLC. In control reaction (A), **9** (0.1 g, 0.44 mmol) and bis(tetraethylammonium)carbonate (0.16 g,.48 mmol) were dissolved in CH_3CN. After hydrolysis and neutralization (Na_2CO_3), **5** was isolated (73 mg, 92%). In control reaction (B), standard hydrolysis conditions were applied to amino alcohol **5** in the presence of 1 equiv TBAF. In control reaction (C), **11**·HCl (45 mg, 0.22 mmol) was treated with the standard hydrolysis conditions. The acid was neutralized using $NaHCO_3$, Na_2CO_3 was added (to pH 10–12) after 40

min and the mixture stirred for 3 h. The product was extracted into Et_2O (2 × 10 mL), the solvent was dried (Na_2SO_4) and the mixture was chromatographed using CH_2Cl_2–acetone, 20:1 to afford **13** (25 mg, 60%).

(*S*)-1-Methyl-2-fluoroethylamine·HCl salt (2b·HCl)

Adapting the conditions described by ElAmin et al.,[20] **11** (3.5 g, 21 mmol) was treated with 10% Pd/C (0.5 g) and HCOOH (4 mL, 0.11 mol) in MeOH (250 mL). After stirring for 3.5 h at r.t., the reaction was complete (TLC). The mixture was filtered over celite followed by a MeOH rinse (50 mL). The solvent was removed under reduced pressure to yield 2.97 g of crude **2b**·HCOOH. The crude product was dissolved in MeOH (10 mL) and then was treated with $HCl_{(g)}$. MeOH was repeatedly added and then removed under reduced pressure (5 × 20 mL); the residual solid was then dissolved in a minimum amount of MeOH and was precipitated by adding EtOAc, yielding 1.93 g (81%) of **2b·HCl**. An analytical sample was recrystallized again from MeOH–EtOAc.

$[\alpha]_D^{23}$ = +12.7 (c 1.01, MeOH); mp 127–127.5 °C.

^{1}H NMR (CD_3OD): 1.32 (dd, 3 H, J_1 = 7 Hz, J_2 = 1.5 Hz, CH_3), [3.55–3.70 (m, 1 H), (4.44 (dd) and 4.63 (dd), 2 H total, each split by J_{HF} = 47 Hz); ABX pattern J_{AB} = 10.5 Hz, J_{AX} = 6.5 Hz, J_{BX} = 3 Hz, $CHCH_2F$].

^{19}F NMR (CD_3OD): −230.94 (td, J_1 = 47 Hz, J_2 = 19 Hz); additional splitting was observed in each of the peaks, J = 1.5 Hz.

MS: *m*/*z* = 78 (100, M + H).

Anal. Calcd for C_3H_9ClFN: C, 31.73; H, 7.99; N, 12.33. Found: C, 31.88; H, 8.04; N, 12.24.

The Mosher amide of **2** was prepared by adding **2**·HCl (46 mg, 0.40 mmol) to a soln of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.23 g, 0.925 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.438 g, 0.99 mmol), and diisopropyethylamine (0.28 mL, 1.6 mmol) in DMF (2 mL) at 0 °C in a 5 mL round bottom flask to minimize loss of the potentially volatile fluoroamine. The soln was stirred for 24 h allowing the soln to gradually warm to r.t., the solvent was removed and the product isolated by chromatography (EtOAc-hexanes, 1:1, R_f 0.57) to yield 0.116 mg (quantitative yield).

^{1}H NMR ($CDCl_3$): δ = 1.26 (dd, 3 H, J_1 = 7 Hz, J_2 = 1 Hz, CH_3), 3.44 (q, J = 1.5 Hz, OCH_3), 4.2–4.6 (m, 3 H, $CHCH_2F$), 6.95 (br s, 1 H, NH), 7.4 and 7.55 (m, 5 H, phenyl H).

^{19}F NMR ($CDCl_3$): δ = −69.10 (s), −232.3 (td, J_1 = 47 Hz, J_2 = 27 Hz).

MS: *m*/*z* = 294 (25, M + H), 316 (100, M + Na).

(*R*)-1-Methyl-2-fluoroethylamine·HCl salt (3b·HCl)

N-Benzylfluoroamine **12** (2.7 g, 16 mmol) was debenzylated via transfer hydrogenation as for **2b**, to afford 1.69 g (94%) of **3b·HCl**. An analytical sample was obtained by recrystallization from MeOH–EtOAc.

$[\alpha]_D^{23}$ −14.9 (*c* 1.10, MeOH); mp 127–128 °C.

^{1}H NMR (CD_3OD): spectrum identical to **2b**·HCl.

^{19}F NMR (CD_3OD): δ = −231.4 (td; identical coupling constants as observed for **2b**·HCl).

Anal. Calcd for C_3H_9ClFN: C, 31.73; H, 7.99; N, 12.33. Found: C, 31.97; H, 8.14; N, 12.26.

The Mosher amide was prepared in the same manner as for **2b**.

^{1}H NMR ($CDCl_3$): δ = 1.30 (dd, 3 H, J_1 = 7 Hz, J_2 = 1 Hz, CH_3), 3.37 (q, J = 1.5 Hz, OCH_3), 4.2–4.6 (m, 3 H, $CHCH_2F$), 6.9 (br s, 1 H, NH), 7.4 and 7.55 (m, 5 H, phenyl H).

^{19}F NMR ($CDCl_3$): δ = −69.19 (s), −231.9 (td, J_1 = 47 Hz, J_2 = 27 Hz).

MS: *m*/*z* = 294 (25, M + H), 316 (100, M + Na).

Acknowledgement

We would like to thank Dr. John Grierson for many useful discussions and the National Institutes of Health for funding: Grants HL60221 and HL36728.

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