Fluoroamines via Chiral Cyclic Sulfamidates

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Abstract: N-benzyl [1,2,3]-oxathiazidine 2,2-dioxides (cyclic sulfamidates) were synthesized from their corresponding β-amino alcohols and used as substrates in fluorination reactions with tert-butyllammonium fluoride (TBAF). After desulfonation of the intermediates, the N-benzyl fluorescence were debenzylated by transfer hydrogenolysis with Pd/C to yield intermediates, the tetrabutylammonium fluoride (TBAF). After desulfonation of the alcohols and used as substrates in fluorination reactions with tetrafluoropropanes (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 sulfamidates 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 synthesis 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 1.1 Ci/g 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 19F.

Preparation of the N-benzyl sulfamidates 9 and 10 was based on White and Garst’s method7,8 which involves synthesis of the sulfamidite intermediates 7, 8 from thionyl chloride and the amino alcohols 5, 6, followed by RuO4 oxidation (Scheme 1). After RuO4 oxidation, 9 and 10 were isolated as stable, crystalline products in fair overall

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 intramolecular 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]-oxathiazidine-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),15 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),8 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 19F.

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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 triethylamine18 or sodium hydride and sulfonyl diimidazole12,19 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.

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).

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 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 1

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Scheme 2

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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.

Table Reverse Phase HPLC Retention Times

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min)</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>5.3</td>
</tr>
<tr>
<td>9</td>
<td>14.0</td>
</tr>
<tr>
<td>15 (putative)</td>
<td>8.6</td>
</tr>
<tr>
<td>11</td>
<td>10.4</td>
</tr>
<tr>
<td>13</td>
<td>13.6</td>
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</table>
The hydrogen-transfer debenzylation (Scheme 4) using formic acid and 10% Pd/C 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 H2/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 1H NMR, the methoxy and fluoromethyl signals were resolved and the integrations determined 95% ee for both 2b and 3b. By 19F NMR, integrations of the trifluoromethane signals indicated 95% ee and 98% ee for both 2b and 3b.

![Scheme 4](image)

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 [19F]-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. 1H- and 19F-NMR spectra were obtained with a GE Omega 300 MHz spectrometer. 1H-chemical shifts are reported in ppm (δ) and 19F-chemical shifts are referenced to CFCl3. 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 °C/45°C. Unless otherwise noted, reagents were purchased from Aldrich grade 9385, 230–400 mesh. Analytical TLC and Rf 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, unhydronated solvents (Aldrich) were used as received except for CH2Cl2, which was dried by storing over activated, crushed 4 Å molecular sieves. Solid TBAF or a 1.0 M solution (in THF with 5% H2O) was dried by azetrope H2O removal (CH3CN) prior to use. Stable-HCl salts were obtained by dissolving the product in Et2O or Et2O/MeOH and bubbling HCl(g) through the solutions; the resulting precipitate was collected and washed thoroughly with Et2O. 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 NH4OAc 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-amino propan-1-ol (5) and N-Benzyl-(R)-2-methyl-amino propan-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 azetrope removal of H2O (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 NaBH4 (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 H2O (250 mL) and EtO2 (4 × 100 mL). Compounds 5 and 6 were obtained.

The characterization data for 5 (mp 42.5–45.5 °C) match those reported previously.1

6  
Mp 41.5–43.5 (lit. 46.5).2
1H NMR (CDCl3): δ = 1.07 (d, 3 H, J = 6 Hz, CH3), 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 JAM = 10.5 Hz, JAX = 7 Hz, JMX = 4 Hz, CH3C), 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 Sulfamidate Formation; General Procedure**

We modified the method by White and Garst2 for the synthesis of compounds 7 and 8. Briefly, a soln of the N-benzyl amino alcohol (0.33 M) and Et2N (2.1 equiv) in anhyd CH2Cl2 under Ar was cooled to –78 °C with stirring. SOCl2 (1.05 equiv, ~1.5 M in anhyd CH2Cl2) was added dropwise over 45 min. The soln was allowed to warm to r.t., filtered (Et3N/HCl removal), and was washed with H2O and brine. The organic phase was dried (Na2SO4) and the solvent was removed to afford an oil. This material was dissolved in a minimum of Et2O and filtered through a short plug of silica followed by continued elution with Et2O until no more sulfamidate eluted. The crude sulfamidate was used directly in the RuO2-oxidation procedure described below.

**RuO2 Oxidation; General Procedure**

We adapted White and Garst’s procedure17 for the synthesis of 9 and 10. The conditions described below were based on 0.15 mol of sulfamidate. Briefly, the sulfamidate was dissolved in CH2CN (300 mL) and the soln cooled to 0 °C. RuCl3·3H2O (10 mg) and then NaNO2 (1 equiv) were added, followed by distilled H2O (300 mL). After 10 min, the ice bath was removed and the soln was stirred for 2 h. H2O (250 mL) was added and the mixture was extracted with Et2O (3 × 200 mL). The volume of the organic phase was reduced.
was dissolved in anhyd CH$_3$CN (5 mL). Compound TBAF (1.2 mL of a 1.0 M soln in THF) was dried and the residue indicated complete conversion of 7 to 8. A sample of the crude product (0.50 g) was purified by column chromatography (CH$_2$Cl$_2$–aceton, 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, 3 H, J = 6 Hz, CH$_3$), [3.74 (m, 1 H), 4.13 (dd, 1 H) and 4.57 (dd, 1 H); AX = 8 Hz, J$_{AX}$ = 7 Hz, J$_{AX}$ = 6.5 Hz, CH$_2$CH$_3$], 4.42 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$_{11}$H$_{13}$NO$_2$: C, 58.77; H, 7.71; N, 7.32. Found: C, 58.77; H, 7.71; N, 6.81.

3-Benzyl-4-(1,2,3)-oxathiazolidine-2,2-dioxide (8)

Crude 7 (27.8 g) afforded 12.2 g of crude 8. A sample of the crude product (0.50 g) was purified by column chromatography (CH$_2$Cl$_2$–aceton, 20:1, R$_f$ 0.75) to yield 0.42 g of an oil (69%).

$^1$H NMR (CDCl$_3$); δ = 1.21 (d, 3 H, J = 6 Hz, CH$_3$), 3.78 (m, 1 H), 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) 147, 146 cluster (30).

3-Benzyl-(R)-4-methyl-[1,2,3]-oxathiazolidine-2,2-dioxide (9)

Compound 6 (18.5 g, 0.112 mol) afforded 19.2 g of crude 9. A sample of the crude product (0.50 g) was purified by column chromatography (CH$_2$Cl$_2$–aceton, 20:1, R$_f$ 0.75) to yield 0.42 g of an oil (69%).

$^1$H NMR (CDCl$_3$); δ = 1.22 (d, 3 H, J = 6 Hz, CH$_3$), [3.73 (m, 1 H), 4.13 (dd, 1 H) and 4.57 (dd, 1 H); AX = 8 Hz, J$_{AX}$ = 7 Hz, J$_{AX}$ = 6.5 Hz, CH$_2$CH$_3$], 4.42 and 4.41 (dd, 2 × 1 H each, 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.

$^1$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$_2$O to yield 0.17 g (76%) of HCl H$_2$.

Anal. Calcd for C$_{11}$H$_{13}$FNN: C, 58.97; H, 7.42; N, 6.87. Found: C, 58.77; H, 7.71; N, 6.81.

3-BenzyI-(S)-4-methyl-oxazolidin-2-one (11)

R$_f$ 0.69 (CH$_2$Cl$_2$–aceton, 20:1); $|\delta^1_0|$ = 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); AX = 8.5 Hz, J$_{AX}$ = 7 Hz, J$_{AX}$ = 8.5 Hz, CH$_2$CH$_3$], 4.11 and 4.79 (2 × 1 H each, 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.

3-Benzyl-(R)-4-methyl-oxazolidin-2-one (14)

R$_f$ 0.69 (CH$_2$Cl$_2$–aceton, 20:1); $|\delta^1_0|$ = 23 (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$_{13}$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), 0.1 g, 0.44 mmol) and bis(tetraethylammonium)carbonate (0.16 g, 48 mmol) were dissolved in CH$_3$CN. After hydrolysis and neutralization (Na$_2$CO$_3$), 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$_2$CO$_3$ was added (to pH 10–12) after 40
min and the mixture stirred for 3 h. The product was extracted into Et₂O (2 × 10 mL), the solvent was dried (Na₂SO₄) and the mixture was chromatographed using CH₂Cl₂–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., 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 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 was precipitated by adding EtOAc, yielding 1.93 g (81%) of 2b-HCl. An analytical sample was recrystallized again from MeOH–EtOAc.

\[ \alpha^\circ_{D}^2 = +12.7 \text{ (c 1.01, MeOH); mp 127-127.5 °C.} \]

1H NMR (CDCl₃): 1.32 (dd, 3 H, J₁ = 7 Hz, J₂ = 1.5 Hz, CH₃), 3.55–3.70 (m, 1 H), 4.44 (dd) and 4.63 (dd), 2 H total, each split by \( J_{ab} = 47 \text{ Hz} \); ABX pattern \( J_{ab} = 10.5 \text{ Hz, } J_{AX} = 6.5 \text{ Hz, } J_{BX} = 3 \text{ Hz, CHClF} \).

19F NMR (CDCl₃): \( \delta = -230.94 \text{ (td, } J_{1} = 47 \text{ Hz, } J_{2} = 19 \text{ Hz); additional splitting was observed in each of the peaks, } J = 1.5 \text{ Hz.} \)

MS: \( m/z = 78 \text{ (100, M + H).} \)


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

1H NMR (CDCl₃): \( \delta = 1.30 \text{ (dd, } 3 \text{ H, } J_{1} = 7 \text{ Hz, } J_{2} = 1 \text{ Hz, CH₃}, J = 1.7 \text{ Hz, CHClF}, J = 1.5 \text{ Hz, MeO} \text{H).} \)

19F NMR (CDCl₃): \( \delta = -69.19 \text{ (s), } -231.9 \text{ (td, } J_{1} = 47 \text{ Hz, } J_{2} = 27 \text{ Hz.} \)

MS: \( m/z = 294 \text{ (25, M + H), 316 (100, M + Na).} \)

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References


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