Facile Radiosynthesis of Fluorine-18 Labeled β-Blockers. Synthesis, Radiolabeling, and ex Vivo Biodistribution of [^{18}F]-(2*S* and 2*R*)-1-(1-Fluoropropan-2-ylamino)-3-(*m*-tolyloxy)propan-2-ol

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An efficient and general method has been developed for fluorine-18 labeling of β-blockers that possess the propanolamine moiety. A new synthetically versatile intermediate, 3-(1-(benzyloxy)propan-2-yl)-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate (**13**), was prepared and can be conjugated to any phenoxy core. To demonstrate the synthetic methodology, fluorinated derivatives of toliprolol were prepared, namely, [^{18}F]-(2*S* and 2*R*)-1-(1-fluoropropan-2-ylamino)-3-(*m*-tolyloxy)propan-2-ol ((2*S* and 2*R*)-[^{18}F]**1**). The radiosyntheses were accomplished in <1 h, with 20−24% (uncorrected for decay, $n = 7$) radiochemical yields, >96% radiochemical and >99% enantiomeric purities, with specific activities of 0.9−1.1 Ci/μmol (EOS). Ex vivo biodistribution studies with the radiotracers demonstrated excessively rapid washout that may limit their use for cerebral PET imaging.

Introduction

Cerebral β-adrenergic receptors (β-ARs[a]) are primarily localized in the frontal cortex, caudate, and putamen.[1] These receptors are of interest in several disorders including Parkinson's disease, Alzheimer's disease, and major depressive disorder (MDD).[1] Cerebral β-ARs have been of longstanding interest in MDD because they are sometimes elevated in the prefrontal cortex of suicide victims.[2] Moreover, β-AR density is lowered by some antidepressant treatments in animal studies.[3,4] Therefore, measuring the concentration and affinity of β-ARs in the living human brain has important potential for understanding both the pathophysiology of depression and how to improve treatment.

Quantitation of cerebral β-AR levels could be accomplished by medical imaging with positron emission tomography (PET); however, no successful PET radiopharmaceutical with adequate biological properties has been developed to achieve this goal in humans. The most promising PET radiotracers to date have been [^{18}F]fluorocarazolol and [^{18}F]fluoroethylcarazolol.[1,5,6] Both compounds have demonstrated high specific β-AR binding in the human and/or rodent brain. Unfortunately, both of these radiotracers were deemed unsuitable for human use because of safety concerns[1,5,7] and were not further pursued.

A remarkable common structural feature of several β-adrenergic agonists and antagonists is the 1-*tert*-butyl- or 1-isopropylamino-3-phenoxy-2-propanol (propanolamine) moiety (Figure 1). Numerous radioligands have been developed by introduction of positron-emitting isotopes ^{11}C (half-life = 20.4 min) or ^{18}F (half-life = 109.7 min) into the isopropylamine or fluoroisopropylamine side chains, and their applications as PET radiopharmaceuticals for imaging cerebral β-ARs have been extensively reviewed.[1,5] To our knowledge, only two methods for the introduction of the [^{18}F]fluoroisopropyl group into biomolecules have been reported. Both methods are time-consuming and involve multiple steps, as intermediate fluorinating agents are employed. In this previous work, the *N*-[^{18}F]fluoroisopropyl side chain has been introduced into β-blockers by fluorination with [^{18}F]fluoroisopropyl tosylate, resulting in very low radiochemical yields (∼2%).[5,8,9] The inefficiency of this method is primarily attributed to the synthetic route (Figure 2A) that results in the generation of two regioisomers (45% radiochemical yield). This methodology was improved by reductive alkylation of amino alcohol precursors with [^{18}F]fluoroacetone (Figure 2B).[5,10,11] However, this procedure is time-consuming (90 min) and results in moderate radiochemical yields (∼10−25% (decay-corrected)).[10,11] The lack of an efficient radiosynthesis of [^{18}F]-labeled β-blockers has hampered the development of a suitable PET radiotracer for cerebral β-AR imaging in humans.

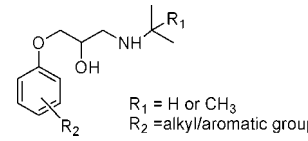

Figure 1. General structure of several β-adrenergic agonists and antagonists.

To overcome the limitations of [^{18}F]-labeling β-blockers at the *N*-isopropyl moiety, we have developed a new general fluorine-18 labeling approach that can be applied to any β-blocker containing the propanolamine group. A versatile synthon was prepared from enantiopure starting materials, namely, 3-(1-(benzyloxy)propan-2-yl)-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate (**13**). The new method employs an oxazolidinone group to simultaneously protect the free amine and hydroxy group and allows for facile deprotection, following nucleophilic displacement of the tosyl leaving group with [^{18}F]fluoride sources. As **13** can be conjugated to any β-blocker's phenoxy core, small libraries of [^{18}F]-labeled β-blockers can be rapidly prepared. In order to validate this new methodology, the present study reports the synthesis, radiolabeling, and biological evaluation of ^{18}F and ^{19}F derivatives of (*S*)-1-(isopropylamino)-3-(*m*-tolyloxy)propan-2-ol ((2*S*)-toliprolol), a potent and selective β-AR antagonist ($\beta_1 = 0.38$ nM and $\beta_2 = 1.2$ nM (K_d values)).[11]

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[a] Abbreviations: EOS, end of synthesis; β-ARs, β-adrenergic receptors; MDD, major depressive disorder; DS1, diastereomer 1; DS2, diastereomer 2.

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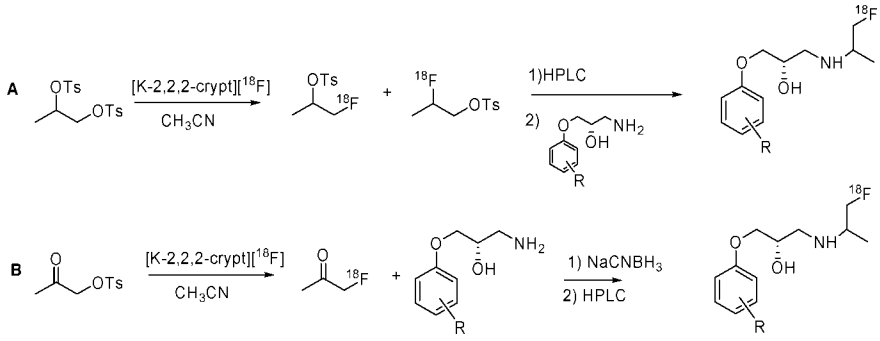
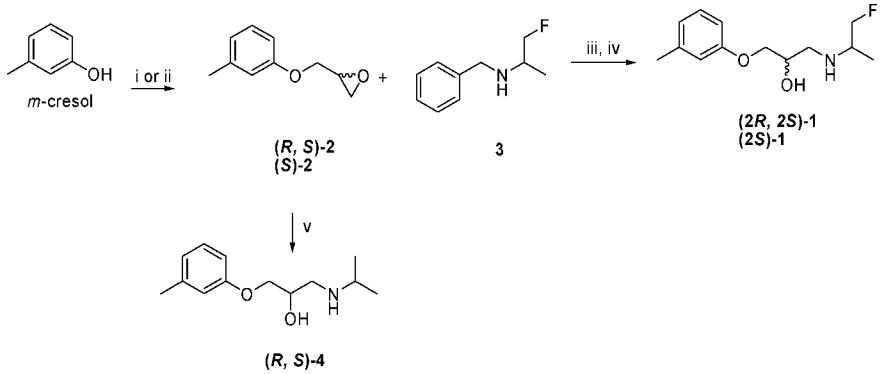


Figure 2. Traditional approaches to prepare ^{18}F-labeled β-blockers.

Scheme 1. Synthesis of Fluorinated Toliprolol Derivatives (2*R*,*S*)-**1**, (2*S*)-**1**, and (*R*,*S*)-**4**[a]



[a] (i) (1) KOH, DMSO, epichlorohydrin (99%); (ii) (1) NaH, DMF, (2) (S)-(+)-glycidyl nosylate (97%); (iii) MeOH (57%); (iv) H_2(g), Pd/C, $Pd(OH)_2$, MeOH (90%); (v) isopropylamine (97%).

Results and Discussion

Although, [^{11}C]-(2*S*)-toliprolol has been prepared and evaluated in rodent models, the radiotracer had poor brain uptake likely because of its low lipophilicity (log *P* (pH 7.4) value of 0.2).[11,12] Fluorination can increase the lipophilicity of β-blockers,[5] for example, the log*P* of carazolol increased from 1.36 to 2.2 when fluorinated at the isopropylamine group,[11] likely because of decreased basicity of the nitrogen.[13,14] Fluorinating toliprolol in the isopropylamine position is expected to increase the lipophilicity and consequently may improve the brain uptake and pharmacological profile.

Traditionally, the 2-hydroxyl group of the general β-blocker structure (Figure 1) is on a stereogenic carbon for which the 2*S*-enantiomer has higher affinity for the receptor than the 2*R*-enantiomer.[10,15] The 2*R*-enantiomer most often has very similar transport properties to the 2*S*-enantiomer but displays lower binding affinity and is consequently used as a benchmark to determine nonspecific binding of novel PET radiopharmaceuticals that target β-ARs.[10,15,16]Therefore, both 2*S* and 2*R*-[^{18}F]-fluorinated toliprolol derivatives, (2*R* and 2*S*)-[^{18}F]**1** were prepared, rigorously characterized (including chiral HPLC to confirm the stereochemistry about carbon-2) and evaluated biologically. Fluorinated standards (2*S*)-**1** and (2*R*,*S*)-**1** were prepared to assign the stereochemistry about carbon-2 of the radiolabeled products. Racemic toliprolol, (*R*,*S*)-*4*, was also prepared via reaction of (*R*,*S*)-**2** and isopropylamine (Scheme 1).

Synthesis of the fluorinated standards (2*S*)-**1** and (2*R*,*S*)-**1** were accomplished in good yields as outlined in Scheme 1. The fluoroisopropyl moiety was previously introduced into a structurally related molecule, fluoropropranolol, via reductive alkylation of a free amine with fluoroacetone.[10] We opted to first prepare *N*-benzyl protected fluoroisopropylamine (**3**) and combine it directly with epoxides (*S*)-**2** and (*R*,*S*)-**2**. This convergent approach was straightforward and, following deprotection, yielded the fluorinated standard compounds (2*S*)-**1** and (2*R*,*S*)-**1**. It is noteworthy that the chiral HPLC conditions enabled the separation of all four diastereomers of compound (2*R*,*S*)-**1** (Figure 3A). The diastereomeric excess (de) of (2*S*)-**1** at carbon-2 was >99%, as determined using chiral HPLC (Figure 3B). The two diastereomers of (2*S*)-**1** were also separated, clearly identifying the stereochemistry at carbon-2 (Figure 3B). Furthermore, synthesis of precursors **10** and **15** (Scheme 2) facilitated the separation of the second stereogenic center at the fluoroisopropyl moiety (defined as carbon-5). This was evident in the chiral HPLC chromatograms (Figure 3C,D) for compound **10**, which after radiolabeling, led to the preparation of (2*S*,5*R*)- and (2*S*,5*S*)-[^{18}F]**1**. When compound **15** was radiolabeled,

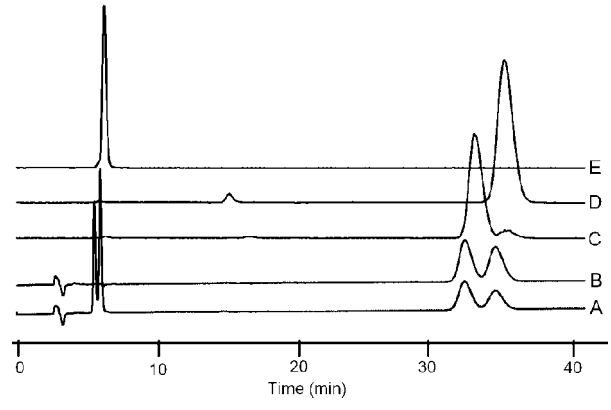
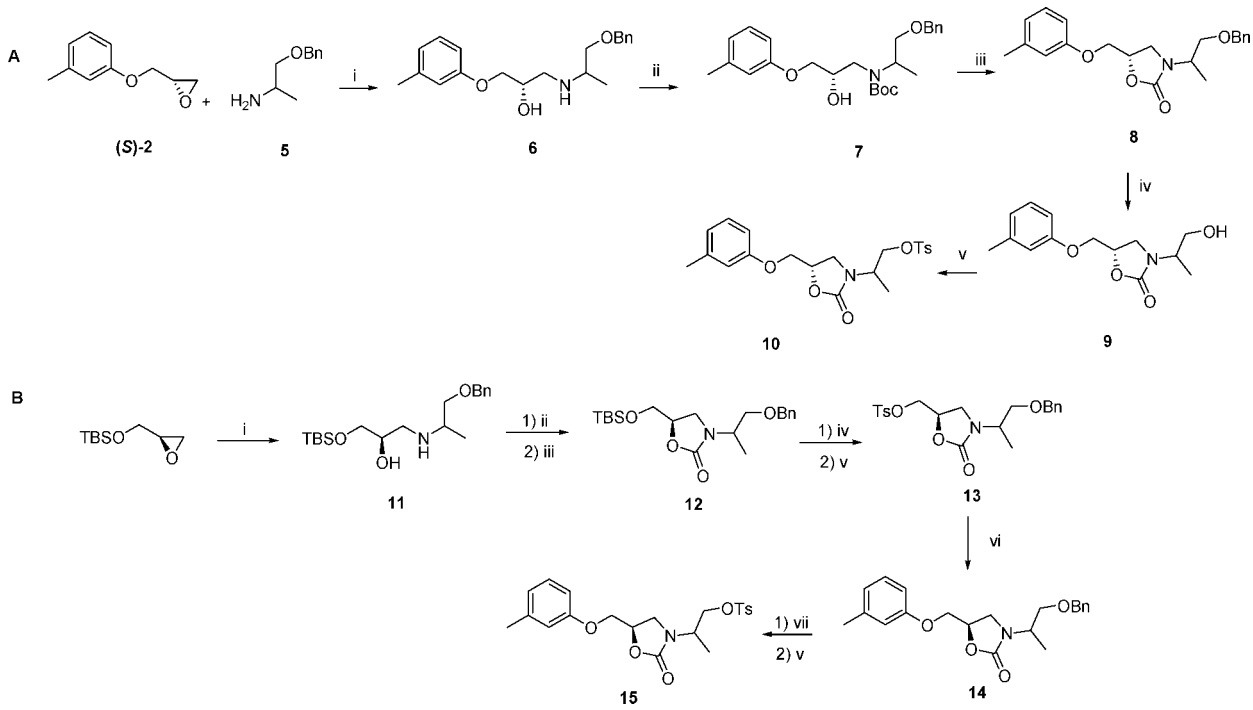


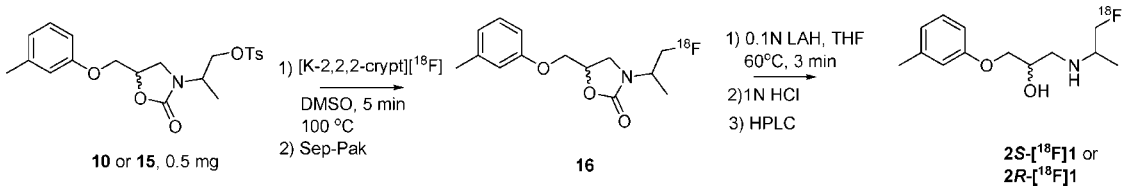
Figure 3. Chiral HPLC (chiracel OD, 20:80:0.1 IPA/hexanes/DEA, 1.0 mL/min, 254 nm) of (A) (2*R*,2*S*)-**1** (UV trace, 254 nm), (B) (2*S*)-**1** (UV trace, 254 nm), (C) (2*S*)-[^{18}F]**1** (γ trace), (D) (2*S*)-[^{18}F]**1** (γ trace), and (E) (2*R*)-[^{18}F]**1** (γ trace).

Scheme 2. Syntheses of Radiolabeling Precursors **10** and **15**[a]



[a] For part A: (i) MeOH cat. H_2O (50%); (ii) Boc_2O, CH_2Cl_2, room temp (71%); (iii) NaH, THF, room temp (83%); (iv) H_2(g) Pd/C, $Pd(OH)_2$, CH_2Cl_2 (94%); (v) TsCl, DMAP, TEA, CH_2Cl_2 (68%). For part B: (i) 5, MeOH, room temp to 50 °C (55%); (ii) Boc_2O, CH_2Cl_2, room temp (used directly in next step); (iii) NaH, toluene, 80 °C (85% from 11); (iv) TBAF, THF, CH_2Cl_2 (90%); (v) TsCl, cat. DMAP, TEA, CH_2Cl_2 (86%); (vi) m-cresol, K_2CO_2, DMF, 80 °C (62%); (vii) H_2(g), Pd/C, $Pd(OH)_2$, MeOH (92%).

Scheme 3. Syntheses of (2*R* and 2*S*)-[^{18}F]**1**



separation of the stereogenic center was not as clear because of the closer retention times of the two enantiomers; however, the purity with respect to carbon-2 was >99% (Figure 3E). No attempt was made to assign the stereochemistry at carbon-5 because it has been shown that β-blockers fluorinated on the *N*-isopropyl chain do not show diastereomeric differences in metabolism or binding in vivo.[17]

Preparation of radiolabeling precursors, **10** and **15**, was accomplished using complementary syntheses. Compound **10** was prepared via a six-step linear synthesis (Scheme 2A). Epoxide (*S*)-**2** was ring-opened with 1-(benzyloxy)propan-2-amine[18] (**5**) and the resulting amine, **6**, was Boc-protected to yield **7**. In the presence of sodium hydride, compound **7** cyclizes, retaining the stereochemistry at carbon-2 to form the oxazolidinone-protected product, **8**. Catalytic hydrogenation of **8** led to quantitative debenzylation generating compound **9**. The free hydroxyl group of **9** was reacted with *p*-toluenesulfonyl chloride to produce the radiolabeling precursor, **10**. The enantiomeric excess with respect to carbon-2 was determined to be the desired *S*-configuration following radiolabeling with fluorine-18 and found to be >98% (Figure 3C,D).

Synthesis of radiolabeling precursor, **15**, followed a similar approach (Scheme 2B) using a more convergent methodology that employs a synthetically versatile intermediate, **13**, and coupling it to *m*-cresol. The free hydroxyl group of (*S*)-glycidol was initially protected with the *tert*-butyldimethylsilyl group following standard methods and then moved through the same steps described for compound **8** to give the TBS-protected intermediate, **12**. The TBS group was removed with TBAF and subsequently reacted with *p*-toluenesulfonyl chloride to yield compound **13**. Compound **13** was then coupled to *m*-cresol to give **14**, which was then deprotected and reacted with *p*-toluenesulfonyl chloride to yield the radiolabeling precursor **15**. The enantiomeric excess of **15**, determined after radiolabeling, was >99% *R*-configuration with respect to carbon-2 (Figure 3E). Compound **13** facilitates the generation of new β-blockers and β-amino alcohols for radiolabeling in three steps, thereby enabling libraries of new radiotracers to be rapidly and efficiently prepared from a single intermediate.

Radiolabeling of **10** or **15** with fluorine-18 was accomplished using the method outlined in Scheme 3. Fluorine-18 was incorporated into the isopropyl group via nucleophilic tosyl displacement in almost quantitative yields with no evidence of unreacted fluoride. Removal of the oxazolidinone group proved to be challenging, and our attempts using standard methods including reagents KOH, LiOH, NaOH, H_2NNH_2, and KOTMS in various solvents (MeOH, EtOH, water) and at various temperatures (80−160 °C), using both microwave and traditional heating, were unsuccessful.[19–27] However, LAH in THF at 60 °C was very effective for deprotection, and at this temperature

Table 1. Ex Vivo Biodistribution of (2*S*)-[^{18}F]**1** in Rodents (% ID/g)

	time			
	5 min	15 min	30 min	60 min
cerebellum	0.75 ± 0.07	0.46 ± 0.02	0.21 ± 0.01	0.08 ± 0.01
hippocampus	0.91 ± 0.10	0.63 ± 0.05	0.31 ± 0.02	0.12 ± 0.02
striatum	0.97 ± 0.04	0.59 ± 0.04	0.27 ± 0.01	0.11 ± 0.01
cortex (front)	1.21 ± 0.07	0.67 ± 0.07	0.30 ± 0.01	0.12 ± 0.01
cortex (rest)	1.12 ± 0.16	0.62 ± 0.04	0.29 ± 0.02	0.11 ± 0.01
thalamus	1.03 ± 0.08	0.65 ± 0.03	0.29 ± 0.01	0.11 ± 0.01
hypothalamus	0.77 ± 0.07	0.50 ± 0.04	0.22 ± 0.02	0.09 ± 0.01
rest of brain	0.84 ± 0.10	0.50 ± 0.02	0.24 ± 0.02	0.10 ± 0.01
heart	0.59 ± 0.26	0.26 ± 0.02	0.15 ± 0.00	0.06 ± 0.00
bone	0.18 ± 0.02	0.21 ± 0.02	0.18 ± 0.03	0.18 ± 0.01
plasma	0.16 ± 0.05	0.13 ± 0.02	0.13 ± 0.01	0.08 ± 0.01

Table 2. Ex Vivo Biodistribution of (2*R*)-[^{18}F]**1** in Rodents (% ID/g)

	time			
	5 min	15 min	30 min	60 min
cerebellum	0.82 ± 0.01	0.43 ± 0.02	0.23 ± 0.03	0.08 ± 0.01
hippocampus	1.01 ± 0.06	0.60 ± 0.04	0.31 ± 0.05	0.12 ± 0.02
striatum	1.04 ± 0.04	0.54 ± 0.04	0.26 ± 0.03	0.11 ± 0.02
cortex (front)	1.30 ± 0.06	0.59 ± 0.06	0.29 ± 0.05	0.12 ± 0.02
cortex (rest)	1.12 ± 0.02	0.55 ± 0.02	0.29 ± 0.05	0.11 ± 0.01
thalamus	1.19 ± 0.02	0.62 ± 0.04	0.30 ± 0.04	0.12 ± 0.01
hypothalamus	0.92 ± 0.07	0.46 ± 0.02	0.23 ± 0.03	0.09 ± 0.01
rest of brain	0.88 ± 0.02	0.47 ± 0.02	0.25 ± 0.03	0.10 ± 0.01
heart	0.51 ± 0.01	0.26 ± 0.03	0.15 ± 0.02	0.07 ± 0.01
bone	0.30 ± 0.02	0.22 ± 0.05	0.30 ± 0.01	0.25 ± 0.03
plasma	0.16 ± 0.01	0.13 ± 0.01	0.13 ± 0.00	0.07 ± 0.01

formation of the *N*-methyl byproduct[28] was minimized. As a result, both (2*R* and 2*S*)-[^{18}F]**1** were prepared in good radiochemical yields (24 ± 3% uncorrected for decay, (n = 7)), in high purity (>96%) and enantiopurity (>99%), and with specific activities of approximately 0.9 to 1.1 Ci/μmol at the end of synthesis in ~1 h. The efficient radiosynthesis of (2*R* and 2*S*)-[^{18}F]**1** improves upon the two previous methods (Figure 2) both in reducing the synthesis time and in improving the radiochemical yields.

Lipophilicity is often a predictor of the ability of a compound to cross the blood−brain barrier and is therefore an important factor in determining the feasibility of new radiopharmaceuticals.[29,30] Specifically for β-AR imaging in the CNS, log *P* values between +2 to +3 are generally considered to be ideal.[1] The log *P* (pH 7.4) values for (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1** were measured to be within the expected range for good brain penetration, with values of 1.68 and 1.79, respectively, and are more promising than that of [^{11}C]toliprolol (log *P* (pH 7.4) of 0.22).[11]

Ex vivo biodistribution studies with both tracers, (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1**, were carried out in conscious male Sprague−Dawley rats, using previously described techniques.[31] At 5 min after injection, both radiotracers had good brain uptake with values between 0.8% and 1.3% injected dose per gram of wet tissue (% ID/g) in all brain regions. Unfortunately, both tracers were rapidly cleared from all examined regions including the frontal cortex, caudate, and putamen, where cerebral β-adrenergic receptors (β-ARs) are primarily localized and no specific binding was observed (Tables 1 and 2 for (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1**, respectively). Preparation of both isomers is useful to assist in determining specific and nonspecific binding. This approach has been used successfully with (*R* and *S*)-[^{11}C]bisoprolol[15], (*R* and *S*)-[^{11}C]bisoprolol[15] as well as with (*R* and (*S*)-[^{18}F]fluoropropranolol.[10] Unfortunately, both radiolabeled enantiomers in the present work showed similar uptake and rapid clearance from the brain. Heart and bone uptake was also examined. Their values were similar and minimal for both tracers (bone uptake was 0.18 and 0.25 % ID/g for (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1**, respectively, at 60 min after injection, and whole heart uptake was 0.59 and 0.51 % ID/g for (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1**, respectively, at 5 min after injection). Metabolism studies in plasma were performed concurrently (Table 3) with the ex vivo biodistribution. Both tracers had similar metabolism, showing no enantiomeric differentiation, and neither (2*S*)-[^{18}F]**1** nor (2*R*)-[^{18}F]**1** displayed lipophilic metabolites. Unfortunately, the rank order of regional uptake did not differ between regions of low β-AR density, such as the thalamus verses regions of high β-AR density such as the striatum or hippocampus. This apparent lack of specific binding in all brain regions precludes the use of (2*S*)-[^{18}F]**1** or (2*R*)-[^{18}F]**1** for cerebral PET studies.

Table 3. Results from Metabolite Analysis of (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1** in Rat Plasma at Various Times after Injection

time (min)	% unmetabolized (2*S*)-[^{18}F]**1**	% unmetabolized (2*R*)-[^{18}F]**1**
control	96	98
5	59.2	61.9
15	28.6	25.5
30	16.4	12.6
60	11.9	7.7

Conclusion

The development of PET radiopharmaceuticals for cerebral β-adrenergic imaging has been hindered by their affinity toward 5-HT$_{1A}$ receptors,[32] safety concerns,[1,7] and inefficient radiosyntheses.[5,11] Since improving on the first two of these limitations will be highly compound specific and on the basis of the need for a suitable PET tracer, we have developed a new general radiofluorination strategy that can be applied to numerous β-blockers in good radiochemical yields, high purity, and shorter radiosynthesis times. The new approach utilizes a tosyl group at the isopropyl side chain for rapid nucleophilic displacement with fluoride and an oxazolidinone group to simultaneously protect both the free amino and hydroxy group of the propanolamine moiety. Synthesis of labeling precursors can be readily accomplished using a convergent approach by linking a new synthetically versatile intermediate, 3-(1-(benzyloxy)propan-2-yl)-2-oxooxazolidin-5-yl)methyl 4-methylbenzenesulfonate (**13**) to a β-blocker core. This new radiolabeling strategy is not only applicable to the stereoselective syntheses of numerous β-amino alcohols but also significantly improves upon previous [^{18}F]-fluorination methods for introduction of a fluoroisopropyl group, thereby enabling the facile preparation of small libraries of [^{18}F]-labeled β-blockers for in vivo evaluation.

Experimental Section

General Methods. (*S*)-(+)-Glycidyl nosylate was purchased from Toronto Research Chemicals. All other chemicals were obtained from Aldrich or Caledon and were used as received without further purification unless indicated. For radiochemistry, THF was freshly distilled under nitrogen from $LiAlH_4$. All water used was distilled and deionized (unless otherwise stated). Flash column chromatography purification was accomplished using silica gel 60 (63−200 μm, Caledon). Preparative thin layer chromatography (PTLC) was accomplished using silica gel GF plates (20 cm × 20 cm, 2000 μm) from Analtech. A Scanditronix MC 17 cyclotron was used for radionuclide production. Purifications and analyses of radioactive mixtures were performed by HPLC with an in-line UV (254 nm) detector in series with a NaI crystal radioactivity detector (radiosynthesis and QC). Isolated radiochemical yields were determined with a dose calibrator (Capintec CRC-712M).

Electrospray ionization mass spectrometry was conducted with MDS Sciex QStar mass spectrometer to obtain the high resolution mass spectra. Electron impact mass spectrometry was conducted on either a VG 70-250S or Waters GCT Premier mass spectrometer. Elemental analysis was performed by the Analytical Laboratory for Environmental Science Research and Training, University of Toronto, using a Perkin-Elmer model 2400II CHN analyzer with Perkin-Elmer AD-6 autobalance. Samples were calibrated against thermal standard acetanilide (C, 71.09; H, 6.71; N, 10.36) before and after analysis.

One-dimensional proton and carbon-13 NMR spectra were recorded at 25 °C on a Varian Mercury 300 or 400 MHz spectrometer with an autoswitchable H/F/C/P 5 mm probe with gradients. The samples were dissolved in $CDCl_3$ (Cambridge Isotope Laboratories, Inc.), unless otherwise indicated. Proton NMR chemical shifts were reported using tetramethylsilane (TMS, 0.00 ppm) as an internal standard or referencing on residual $CHCl_3$ (at 7.26 ppm) and correcting to TMS. For ^{13}C NMR spectra, referencing was relative to $CDCl_3$ (referencing at 77.0 ppm) and to correcting the shifts to TMS. The ^{19}F NMR spectra were referenced relative to $CFCl_3$.

All animal experiments were carried out under humane conditions, with approval from the Animal Care Committee at the Centre for Addiction and Mental Health and in accordance with the guidelines set forth by the Canadian Council on Animal Care.

2-(*m*-Tolyloxymethyl)oxirane ((*R*,*S*)-2). *m*-Cresol (4.62 mmol) was dissolved in 2 mL of DMSO. KOH (23.1 mmol) was then added followed by epichlorohydrin (22 mL). The resultant heterogeneous mixture was vigorously stirred at room temperature for 3 h and then poured into 175 mL of H_2O. The mixture was extracted with EtOAc (3 × 75 mL). Organic fractions were combined, washed with H_2O (3 × 75 mL), brine (1 × 75 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. After the oil was dried under reduced pressure, no further purification was required (99% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.16 (dd, $J = 7.7$ Hz, $J = 7.6$ Hz, 1H), 6.79−6.70 (m, 3H), 4.18 (dd, $J = 11.0$ Hz, $J = 3.2$ Hz, 1H), 3.95 (dd, $J = 11.0$ Hz, $J = 5.5$ Hz, 1H), 3.36−3.31 (m, 1H), 2.89 (dd, $J = 4.8$ Hz, $J = 4.2$ Hz, 1H), 2.74 (dd, $J = 4.9$ Hz, $J = 2.6$ Hz, 1H), 2.32 (s, 3H).

(*S*)-2-(*m*-Tolyloxymethyl)oxirane ((*S*)-2). *m*-Cresol (4.62 mmol) was dissolved in 23 mL of anhydrous DMF and cooled to 0 °C. Sodium hydride (60%, 4.62 mmol) was then added and the mixture stirred at 0 °C for 30 min. (*S*)-(+)-Glycidyl nosylate (5.54 mmol) was then added and the mixture stirred at room temperature for 40 min. The mixture was poured into 150 mL of water and extracted with EtOAc (3 × 75 mL). The combined organic fractions were washed with H_2O (2 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a thick oil. The product was isolated by column chromatography (35:65 v/v, EtOAc/hexanes) as a clear colorless oil in 97% yield (note: chiral purity was assessed after preparation of the fluoroisopropyl derivative (2*S*)-**1**). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.17 (dd, $J = 5.9$ Hz, $J = 5.7$ Hz, 1H), 6.80−6.78 (m, 1H), 6.75−6.71 (m, 2H), 4.19 (dd, $J = 8.2$ Hz, $J = 4.2$ Hz, 1H), 3.96 (dd, $J = 8.2$ Hz, $J = 4.2$ Hz, 1H), 3.37−3.33 (m, 1H), 2.90 (dd, $J = 3.7$ Hz, $J = 3.2$ Hz, 1H), 2.75 (dd, $J = 3.7$ Hz, $J = 2.0$ Hz, 1H), 2.33 (s, 3H).

1-(1-Fluoropropan-2-ylamino)-3-(*m*-tolyloxy)propan-2-ol ((2*R*,2*S*)-1). *N*-Benzyl-1-fluoropropan-2-amine, **3**, was prepared via reductive amination from benzylamine and fluoroacetone.[10,33] Compound **3** (4.23 mmol) was combined with (*R*,*S*)-**2** (3.22 mmol) in 3 mL of MeOH. The resultant homogeneous mixture was heated to 50 °C for 5 h, after which the mixture was cooled to room temperature and 3 mL of CH_2Cl_2 was added. Pd/C (50 mg) and $Pd(OH)_2$ (50 mg) were then added followed by a large balloon of H_2(g). The heterogeneous mixture was stirred vigorously overnight at room temperature. The mixture was then filtered through diatomaceous earth (Celite 545) and concentrated. The unresolved diastereomers were isolated by flash column chromatography (5:95 v/v, MeOH/CH_2Cl_2) as a white solid in 52% yield (from (*R*,*S*)-**2**). Mp: 56−57 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.16 (dd, $J = 7.8$ Hz, $J = 7.8$ Hz, 1H), 6.78−6.71 (m, 3H), 4.44−4.20 (dm, CH_2F, $J_{H-F} = 47.7$ Hz, 2H), 4.04−3.97 (m, 3H), 3.04−2.90 (m, 2H), 2.83−2.75 (m, 1H), 2.32 (s, 3H), 1.10 (dm, $J = 6.5$ Hz, 3H). ^{19}F NMR ($CDCl_3$, 376 MHz) δ: −226.0 (m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.8(7), 158.8(6), 139.7, 129.4, 122.1, 115.6, 111.6, 87.2 (d, $^1J_{C-F} = 170.2$ Hz), 87.0 (d, $^1J_{C-F} = 170.2$ Hz), 70.5(3), 70.4(3), 68.9(9), 68.9(6), 53.2(4) (d, $^2J_{C-F} = 18.7$ Hz), 53.2(1) (d, $^2J_{C-F} = 18.7$ Hz), 49.5(2), 49.4(5), 21.7, 16.6(3) (d, $^3J_{C-F} = 6.9$ Hz), 16.5(6) (d, $^3J_{C-F} = 6.8$ Hz). Anal. ($C_{13}H_{20}FNO_2$) C, H, N.

(2*S*)-1-(1-Fluoropropan-2-ylamino)-3-(*m*-tolyloxy)propan-2-ol ((2*S*)-1). (2*S*)-**1** was prepared according to the method described for synthesis of (2*R*,2*S*)-**1**. The product was isolated as a white solid (49% yield from (*S*)-**2**). HPLC was used to determine the chiral purity (Chiracel OD column, 80:20:0.1 (v/v/v) hexanes/IPA/DEA, 1.0 mL/min, $\lambda = 254$ nm). Retention times of 2*R* isomers were 6.5 and 6.9 min, and those for 2*S* isomers were 36.5 and 39.0 min. (2*S*)-**1** was >99% pure with respect to the stereogenic center at carbon-2 (Figure 3A,B). Mp: 56−57 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.16 (dd, $J = 7.8$ Hz, $J = 7.7$ Hz, 1H), 6.79−6.70 (m, *3*H), 4.47−4.17 (dm, CH_2F, $J_{H-F} = 47.6$ Hz, 2H), 4.05−3.96 (m, 3H), 3.06−2.89 (m, 2H), 2.83−2.75 (m, 1H), 2.32 (s, 3H), 1.10 (dt, $J = 6.6$ Hz, $J = 1.56$ Hz, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −226.0 (m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.6(4), 158.6(3), 139.6, 129.2, 121.9, 115.4, 111.4, 86.9(7) (d, $^1J_{C-F} = 170.2$ Hz), 86.8(5) (d, $^1J_{C-F} = 170.2$ Hz), 70.2(7), 70.1(8), 68.7(7), 68.7(0), 53.0(3) (d, $^2J_{C-F} = 18.7$ Hz), 52.9(9) (d, $^2J_{C-F} = 18.7$ Hz), 49.2(7), 49.2(0), 21.5, 16.4(3) (d, $^3J_{C-F} = 6.6$ Hz), 16.3(4) (d, $^3J_{C-F} = 6.7$ Hz). Anal. ($C_{13}H_{20}FNO_2$) C, H, N.

1-(2-Cyclohexylphenoxy)-3-(isopropylamino)propan-2-ol ((*R*,*S*)-4). Compound (*R*,*S*)-**2** (0.91 mmol) and 2.0 mL of isopropylamine were heated to 50 °C overnight. The mixture was subsequently cooled to room temperature and excess isopropylamine removed under vacuum to yield (*R*,*S*)-**4**) as a white solid (97%). Mp: 74−75 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.16 (dd, $J = 7.8$ Hz, $J = 7.6$ Hz, 1H), 6.78−6.70 (m, 3H), 4.02−3.94 (m, 3H), 2.90−2.69 (m, 3H), 2.32 (s, 3H), 1.08 (d, $J = 6.3$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.9, 139.7, 129.4, 122.1, 115.6, 111.7, 70.6, 68.8, 49.5, 49.1, 23.4, 23.3. Anal. ($C_{13}H_{21}NO_2$) C, H, N.

(2*S*)-1-(1-(Benzyloxy)propan-2-ylamino)-3-(*m*-tolyloxy)propan-2-ol (6). Compound (*S*)-**2** (3.52 mmol) and **5** (prepared as previously described by Hu et al.[18]) (7.04 mmol) were combined in 10 mL of MeOH with a catalytic amount of H_2O (20 μL). The mixture was stirred at room temperature overnight, after which the solvent was removed and the product isolated via flash column chromatography (5:95 (v/v), MeOH/CH_2Cl_2) as a clear colorless oil in 50% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.32−7.26 (m, 5H), 7.14 (dd, $J = 7.7$ Hz, $J = 7.6$ Hz, 1H), 6.77−6.69 (m, 3H), 4.52 (s, 2H), 4.03−3.92 (m, 3H), 3.43 (ddd, $J = 9.2$ Hz, $J = 4.3$ Hz, $J = 1.5$ Hz, 1H), 3.34 (dd, $J = 9.2$ Hz, $J = 7.0$ Hz, 1H), 2.97−2.85 (m, 2H), 2.77−2.70 (m, 3H), 2.31 (s, 3H), 1.06 (d, $J = 6.4$ Hz, 3H).

***tert*-Butyl 1-(benzyloxy)propan-2-yl((*S*)-2-hydroxy-3-(*m*-tolyloxy)propyl)carbamate (7).** Compound **6** (1.52 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL). Di-*tert*-butyl dicarbonate (1.821 mmol) was added and the mixture stirred at room temperature for 1.5 h. The mixture was then diluted with additional CH_2Cl_2 (70 mL), washed with H_2O (3 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The crude product was purified via flash column chromatography (80:20 (v/v), EtOAc/hexanes) and used directly in the next step (71% yield).

(5*S*)-3-(1-(Benzyloxy)propan-2-yl)-5-(*m*-tolyloxymethyl)oxazolidin-2-one (8). Compound **7** (1.04 mmol) was dissolved in anhydrous THF (12 mL) and cooled to 0 °C. Sodium hydride (60%, 2.09 mmol) was added and the resultant mixture stirred at room temperature for 4 h. The mixture was then cooled to 0 °C and quenched with 1 mL of H_2O added dropwise, after which the mixture was concentrated under vacuum. The residue was taken up in CH_2Cl_2 (75 mL), washed with H_2O (3 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The crude product was isolated via PTLC (50:50 (v/v), EtOAc/hexane) to yield clear colorless unresolved diastereomers in 83% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.37−7.23

(m, 5H), 7.15 (ddd, $J = 7.8$ Hz, $J = 7.8$ Hz, $J = 4.6$ Hz, 1H), 6.79 (d, $J = 7.5$ Hz, 1H), 6.70−6.63 (m, 2H), 4.80−4.76 (m, 1H), 4.60−4.43 (m, 2H), 4.23−4.18 (m, 1H), 4.10−3.97 (m, 2H), 3.71−3.65 (m, 1H), 3.57−3.48 (m, 3H), 2.32−2.31 (2 × S, 3H), 1.22 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.4, 157.4(8), 157.4(3), 139.9(4), 139.8(9), 138.2(1), 138.1(4), 129.5(5), 129.5(3), 128.6(9), 128.6(5), 128.0, 127.9(3), 127.9(1), 127.8(8), 122.6(0), 122.5(6), 115.6(5), 115.6(3), 111.6(4), 111.6(0), 73.2(3), 73.2(0), 71.7(1), 71.6(6), 71.3(0), 71.2(8), 68.3(4), 68.3(3), 48.6(7), 48.6(2), 43.8(9), 43.6(6), 21.7, 14.6(9), 14.6(5).

(5*S*)-3-(1-Hydroxypropan-2-yl)-5-(*m*-tolyloxymethyl)oxazolidin-2-one (9). Compound **8** (0.70 mmol) was dissolved in 2 mL of MeOH and 2 mL of CH_2Cl_2. $Pd(OH)_2$ (30 mg) and 10% Pd/C (30 mg) were added followed by a balloon of H_2 gas. The heterogeneous mixture was stirred rapidly at room temperature for 1 h and then filtered over diatomaceous earth (Celite 545) and concentrated. The products, as diastereomers, were inseparable as a clear colorless oil that did not require further purification (94% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16 (dd, $J = 7.7$ Hz, $J = 7.7$ Hz, 1H), 6.80 (d, $J = 7.5$ Hz, 1H), 6.72−6.68 (m, 2H), 4.86−4.83 (m, 1H), 4.12 (dd, $J = 9.2$ Hz, $J = 4.0$ Hz, 2H), 4.05−3.99 (m, 1H), 3.80−3.70 (m, 2H), 3.63−3.52 (m, 2H), 3.48 (s, 1H), 2.32 (s, 3H), 1.21−1.18 (2 × d, $J = 6.7$ Hz, 3H).

2-((*S*)-5-((2-Cyclohexylphenoxy)methyl)-2-oxooxazolidin-3-yl)-propyl 4-Methylbenzenesulfonate (10). Compound **9** (0.105 mmol) was dissolved in 1 mL of CH_2Cl_2. Triethylamine (0.211 mmol), catalytic 4-(dimethylamine)pyridine (spatula tip), and *p*-toluenesulfonyl chloride (0.157 mmol) were added and the resultant mixture stirred at room temperature for 3 h. The mixture was subsequently diluted with CH_2Cl_2 (75 mL), washed with H_2O (3 × 75 mL), brine (1 × 75 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The two diastereomers were separable and isolated via PTLC (50:50 (v/v), EtOAc/hexane) as colorless semisolids in an overall yield of 65%. The diastereomers are either 2*S*,5*R* or 2*S*,5*S* and arbitrarily differentiated as *S*-DS1 and *S*-DS2. The % de was determined with respect to carbon-2 after radiolabeling. No attempts were made to prepare authentic standards to assign the stereogenic center on the isopropyl moiety.

***S*-DS1.** ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.79 (d, $J = 8.3$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.16 (dd, $J = 7.8$ Hz, $J = 7.7$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 6.69−6.67 (m, 2H), 4.81−4.73 (m, 1H), 4.20−4.04 (m, 5H), 3.69 (dd, $J = 8.7$ Hz, $J = 8.6$ Hz, 1H), 3.54 (dd, $J = 8.6$ Hz, $J = 6.2$ Hz, 1H), 2.45 (s, 3H), 2.32 (s, 3H), 1.24 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.3, 157.1, 145.5, 139.9, 132.7, 130.3, 129.6, 128.1, 122.7, 115.6, 111.6, 71.6, 71.0, 68.1, 48.2, 43.7, 21.9, 21.7, 14.1. HRMS (EI) for $C_{21}H_{25}NO_6S$: [M^+] calcd 419.1403, found 419.1412.

***S*-DS2.** ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.74 (d, $J = 8.3$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.17 (dd, $J = 7.8$ Hz, $J = 7.8$ Hz, 1H), 6.82 (d, $J = 7.5$ Hz, 1H), 6.72−6.67 (m, 2H), 4.84−4.76 (m, 1H), 4.18−4.00 (m, 5H), 3.71 (dd, $J = 8.8$ Hz, $J = 8.7$ Hz, 1H), 3.53 (dd, $J = 8.6$ Hz, $J = 5.6$ Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 1.26 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.3, 156.9, 145.4, 139.9, 132.7, 130.2, 129.5, 128.1, 122.7, 115.7, 111.7, 71.5, 70.8, 68.3, 48.3, 44.1, 21.9, 21.7, 14.2. HRMS (EI) for $C_{21}H_{25}NO_6S$: [M^+] calcd 419.1403, found 419.1408.

(2*R*)-1-(1-(Benzyloxy)propan-2-ylamino)-3-(*tert*-butyldimethylsilyloxy)propan-2-ol (11). (*R*)-*tert*-Butyldimethyl(oxiran-2-ylmethoxy)silane (prepared as described by Pospisil et al.,[34] 15.9 mmol) and **5** (15.9 mmol) were combined in 30 mL of MeOH and stirred at room temperature for 3 days and then heated at 50 °C for 4 h. The solvent was removed and the product isolated via flash column chromatography (65:35:0.1 (v/v/v), hexanes/EtOAc/TEA) as a thick oil in 55% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.37−7.26 (m, 5H), 4.52 (s, 2H), 3.73−3.54 (m, 3H), 3.43−3.28 (m, 2H), 2.94−2.58 (m, 3H), 1.05−1.02 (m, 3H), 0.90−0.88 (m, 9H), 0.08−0.05 (m, 6H).

(5*R*)-3-(1-(Benzyloxy)propan-2-yl)-5-((*tert*-butyldimethylsilyloxy)methyl)oxazolidin-2-one (12). Compound **11** (7.92 mmol) was dissolved in 16 mL of CH_2Cl_2. Di-*tert*-butyl dicarbonate (10.3 mmol) was added and stirred at room temperature for 1.5 h. The mixture was subsequently diluted with additional CH_2Cl_2 (75 mL), washed with H_2O (3 × 75 mL), brine (1 × 75 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The Boc-protected intermediate of **11** was then dissolved in 35 mL of anhydrous toluene. Sodium hydride (60%, 17.06 mmol) was added and the heterogeneous mixture heated to 80 °C for 3 h. The mixture was then cooled to room temperature, diluted with 100 mL of EtOAc, washed with H_2O (3 × 75 mL), brine (1 × 75 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The product was isolated in 85% yield (from **11**) as unresolved diastereomers via flash column chromatography (20:80 (v/v), EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.32−7.20 (m, 5H), 4.55−4.38 (m, 3H), 4.17−4.05 (m, 1H), 3.75−3.61 (m, 2H), 3.53−3.38 (m, 4H), 1.22−1.11 (m, 3H), 0.84−0.82 (m, 9H), 0.02−0.01 (m, 6H).

((*R*)-3-(1-(Benzyloxy)propan-2-yl)-2-oxooxazolidin-5-yl)methyl 4-Methylbenzenesulfonate (13). Compound **12** (2.5 mmol) was dissolved in 13 mL of CH_2Cl_2 and cooled to 0 °C. TBAF (1.0 M in THF, 5.08 mmol) was then added dropwise and stirred for 60 min. The mixture was then diluted with an additional 60 mL of CH_2Cl_2, washed with H_2O (3 × 75 mL), brine (1 × 75 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The OTBS deprotected product was isolated in 90% yield via flash column chromatography (80:20 (v/v), EtOAc/hexanes) as an oil and used immediately in the next step.

All of the isolated OTBS deprotected **12** was dissolved in 11 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. Triethylamine (6.5 mmol), catalytic 4-(dimethylamine)pyridine (5 mg), and *p*-toluenesulfonyl chloride (4.5 mmol) were added, and the resultant mixture was stirred at room temperature for 1.5 h. The solution was then diluted with 75 mL of additional CH_2Cl_2, washed with H_2O (3 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The products (as diastereomers) were isolated together via flash column chromatography (50:50 (v/v), EtOAc/hexanes) in 86% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.79−7.73 (m, 2H), 7.37−7.28 (m, 7H), 4.66−4.59 (m, 1H), 4.55 (dd, $J = 12.0$ Hz, $J = 2.9$ Hz, 1H), 4.44 (dd, $J = 12.0$ Hz, $J = 5.0$ Hz, 1H), 4.16−4.07 (m, 3H), 3.62 (dd, $J = 16.0$ Hz, $J = 8.9$ Hz, 1H), 3.54−3.36 (m, 3H), 2.45−2.44 (m, 3H), 1.20−1.14 (m, 3H).

(5*R*)-3-(1-(Benzyloxy)propan-2-yl)-5-(m-tolyloxymethyl)oxazolidin-2-one (14). Unresolved diastereomers of **13** (0.47 mmol), *m*-cresol (0.52 mmol), and K_2CO_3 (1.4 mmol) were combined in 3 mL of anhydrous DMF and heated to 80 °C for 4 h. The mixture was then cooled to room temperature and poured into 100 mL of H_2O. The crude product was then extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were combined, washed with H_2O (3 × 100 mL), brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated to yield a colorless oil. The diastereomers were inseparable and isolated together via PTLC (50:50 (v/v), EtOAc/hexanes) in 62% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.37−7.23 (m, 5H), 7.16 (ddd, $J = 7.7$ Hz, $J = 3.5$ Hz, $J = 3.4$ Hz, 1H), 6.79 (d, $J = 7.5$ Hz, 1H), 6.70−6.63 (m, 2H), 4.81−4.74 (m, 1H), 4.61−4.43 (m, 2H), 4.24−4.17 (m, 1H), 4.11−3.97 (m, 2H), 3.72−3.65 (m, 1H), 3.57−3.47 (m, 3H), 2.32−2.31 (2 × S, 3H), 1.22 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.4, 157.4(9), 157.4(4), 139.9(4), 139.8(9), 138.2(0), 138.1(3), 129.5, 128.6(9), 128.6(5), 128.0(4), 128.0(1), 127.9(4), 127.9(1), 127.8(9), 122.6(0), 122.5(7), 115.6(4), 115.6(3), 111.6(4), 111.6(0), 73.2(3), 73.2(0), 71.7(0), 71.6(5), 71.3(0), 71.2(9), 68.3(3), 68.3(2), 48.6(8), 48.6(3), 43.9(0), 43.6(5), 21.7, 14.6(9), 14.6(7). MS (ES +ve): [M + H] calcd 356.4, found 356.2.

2-((*R*)-2-Oxo-5-(*m*-tolyloxymethyl)oxazolidin-3-yl)propyl 4-Methylbenzenesulfonate (15). Removal of the benzyl group was accomplished using the procedure described for the synthesis of **9** in 99% yield and used directly in the next step which followed the method described for the preparation of **10**. Compound **15** was isolated as two diastereomers (the diastereomers are either 2*R*,5*R* or 2*R*,5*S* and differentiated as *R*-DS1 and *R*-DS2) via PTLC (50:50 (v/v), EtOAc/hexanes) in a combined yield of 92% (note: % de with respect to carbon-2 assayed after radiolabeling (Figure 3)).

***R*-DS1.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79 (d, J = 8.3 Hz, 2H), 7.36 (dm, J = 8.0 Hz, 2H), 7.16 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.71−6.67 (m, 2H), 4.81−4.75 (m, 1H), 4.20−4.16 (m, 1H), 4.13−4.06 (m, 4H), 3.69 (dd, J = 8.7 Hz, J = 8.6 Hz, 1H), 3.54 (dd, J = 8.5 Hz, J = 6.1 Hz, 1H), 2.45 (s, 3H), 2.32 (s, 3H), 1.24 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.3, 157.1, 145.5, 139.9, 132.7, 130.3, 129.6, 128.1, 122.7, 115.6, 111.6, 71.6, 71.1, 68.1, 48.2, 43.7, 21.9, 21.7, 14.1. HRMS (EI) for $C_{21}H_{25}NO_6S$: [M^+] calcd 419.1403, found 419.1408.

***R*-DS2.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.74 (d, J = 8.3 Hz), 7.27 (d, J = 8.5 Hz), 7.17 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.73−6.67 (m, 2H), 4.84−4.77 (m, 1H), 4.18−4.01 (m, 5H), 3.71 (dd, J = 8.8 Hz, J = 8.8 Hz, 1H), 3.54 (dd, J = 8.6 Hz, J = 5.5 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H), 1.25 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.3, 156.9, 145.4, 139.9, 132.7, 130.2, 129.5, 128.1, 122.7, 115.8, 111.7, 71.5, 70.8, 68.3, 48.3, 44.1, 21.9, 21.7, 14.2. HRMS (ES +ve) for $C_{21}H_{25}NO_6S$: [M + H] calcd 420.1475, found 420.1484.

Radiochemistry. Preparation of Reactive [^{18}F]Fluoride. Fluorine-18-labeled fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction, using a 17 MeV proton beam current to irradiate [^{18}O]H_2O (10−97% enriched, Medical Isotopes Inc.), which was subsequently removed from the target and trapped on an anion exchange resin (Sep-Pak Light Accell Plus QMA cartridge 37−55 μm, preactivated with 5 mL of 8.4% sodium bicarbonate, 5 mL of H_2O (TraceSelectUltra Water from Fluka), and 5 mL of anhydrous CH_3CN, followed by N_2 flow to dry). The resin was eluted with 1.2 mL of a 2,2,2-crypt (Kryptofix)/K_2CO_3 solution, which is made up of 22 mg of Kryptofix and 4.6 mg of potassium carbonate in CH_3CN/H_2O (1.77/0.23) in a 5 mL open test tube. The vial was then placed into a 100 °C oil bath and azeotropically dried with 1.5 mL of anhydrous CH_3CN under a continuous nitrogen flow.

Radiosynthesis of (2*R* and *S*)-[^{18}F]1. Precursor **10** (or **15**) (0.5 mg) dissolved in 0.3 mL of DMSO was then added and the vial vortexed and placed back into the 100 °C bath for 5 min. The solution was then removed from the bath, diluted with 5 mL of H_2O, and loaded onto a tC18 Sep-Pak (preactivated with 5 mL of EtOH and 5 mL of H_2O). The Sep-Pak was then washed with 2 mL of H_2O, and the desired intermediate **16** eluted with 1 mL of CH_3CN into a 2−5 mL glass vial (that can be sealed via crimping an aluminum cap containing the septum (Biotage). The CH_3CN was subsequently removed under N_2 flow in a 100 °C oil bath and azeotropically dried with an additional 0.5 mL of anhydrous CH_3CN, after which the vial was promptly crimp-sealed and transferred to a 60 °C oil bath. LAH (1 mL, 20−30 mg in 4 mL of anhydrous THF) was then added and the mixture heated for 3 min. Upon completion, the vial was transferred to a room temperature bath, the seal removed, and 0.1 mL of 1 N HCl added to quench the reaction. The THF was then removed with under N_2 flow at room temperature. An additional 0.6 mL of 1 N HCl was added followed by 1 mL of mobile phase to yield a clear solution that was purified by reverse phase HPLC (Phenomenex Prodigy ODS Prep, 250 mm × 10 mm, 10 μm, λ = 254 nm) with a mobile phase consisting of CH_3CN/H_2O (30:70 v/v) + 0.1 N ammonium formate (AF) at a flow rate of 6 mL min^{-1}. The product, (2*R* or *S*)-[^{18}F]**1**, eluting at 6 min was led into a rotary evaporation flask and heated to dryness at 70 °C, under vacuum. The product was dissolved in 1 mL of ethanol and transferred into a vial containing 9 mL of phosphate buffered saline (pH 7.4, Invitrogen). The pH of the final solution was ∼7. Analytical HPLC was performed using a Phenomenex Luna C18, 250 mm × 4.6 mm, 10 μm, and the sample was eluted with CH_3CN/H_2O (30:70 v/v) + 0.1 N AF using a flow rate of 1.2 mL min^{-1}. Authentic (2*R*,*S*)-**1** coeluted with the ^{18}F-labeled product under these conditions (t_R = 4.2 min) and under several different analytical HPLC conditions (mobile and stationary phases, pHs and wavelengths). The product (2*R* or *S*)-[^{18}F]**1** was isolated in 24 ± 3% (n = 7) radiochemical yield (uncorrected for decay). No significant radiolysis was observed over 6 h (>96% radiochemical purity). The specific activity of the formulated product was 985−1145 mCi/μmol, and the log *P* was 1.68 and 1.79 for (2*S*)-[^{18}F]**1** and (2*R*)-[^{18}F]**1**, respectively, as measured using a previously published method.[30]

Ex Vivo Biodistribution in Rodents. Ex vivo biodistribution studies following administration of (2*S* or 2*R*)-[^{18}F]**1** in unanesthetized male Sprague−Dawley rats (294 ± 9 g) were conducted as previously described by our group.[31,35] All rats received about 70 μCi of (2*S* or 2*R*)-[^{18}F]**1** in 0.3 mL of buffered saline via the tail vein. They were sacrificed by decapitation at 5, 15, 30, and 60 min after injection (n = 3 per time point). The brains were removed, and regions of interest (striatum, thalamus, hypothalamus, hippocampus, frontal cortex, rest of cortex, cerebellum, rest of brain, bone, and heart) were excised, blotted, weighed and then radioactivity measurements taken. Whole blood was collected from the trunk in a heparinized tube and centrifuged, and the plasma was separated for radioactivity measurement and metabolite analysis. Results are summarized in Tables 1 and 2.

Metabolite Analysis. Rat plasma was used directly for HPLC metabolite analysis. The analysis that was performed follows the method of Hilton[36] with minor modifications.[35] Samples from each time point were loaded onto a 5 mL HPLC injector loop and injected onto a capture column (4.6 mm × 20 mm) that was packed in house with OASIS HLB 30 μm (Waters, NJ). The capture column was eluted with 1% aqueous CH_3CN (2 mL/min) for 4 min and then back-flushed (20% CH_3CN/80% water + 0.1 N ammonium formate, 2 mL/min) onto a Phenomenex 10 μm Luna C18 column (250 mm × 4.6 mm). The column effluents from both columns were monitored through a flow detector (Bioscan Flow-Count) operated in coincidence mode. Results are summarized in Table 3.

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Supporting Information Available: Combustion analysis details for compounds **1** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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