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An Efficient Synthesis of the Precursors of [^{11}C]MDL 100907 Labeled In Two Specific Positions

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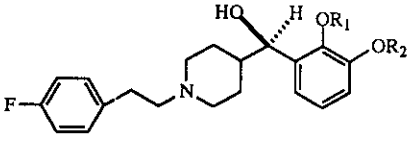
Summary

An efficient, integrated route for the synthesis of two precursors of [^{11}C]MDL 100907 labeled in the 2'- or 3'-methoxy position is reported. The synthesis involved a one-pot, two-step process to transform the intermediate esters to ketones and subsequent resolution of the racemic alcohols to their respective enantiomers. The resolved, enantiomerically pure phenol precursors were reacted with high specific activity [^{11}C]methyl iodide to produce [^{11}C]MDL 100907 labeled in two specific positions.

Key Words: 5-HT$_{2A}$ receptor, carbon-11, radiosynthesis, positron emission tomography

Introduction

The serotonin receptor antagonist, MDL 100907 {**1**, (R)-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol}(Figure 1), has high affinity and selectivity for serotonin 5-HT$_{2A}$ receptors (Ki 0.85 nM for 5-HT$_{2A}$ and Ki's for other receptor subtypes, including 5-HT$_{2C}$, α_1, σ, and dopamine D_1, D_2, D_3, D_4, and D_5 receptors >100-fold higher) (1). Carbon-11 labeled MDL 100907, with the C-11 radiolabel at either the 2'- or 3'-position of the molecule, has been prepared and evaluated as a radioligand for serotonin 5-HT$_{2A}$ receptor mapping (2). Rat and baboon studies have been carried out with the 2'-labeled compound **2**, while the 3'-labeled compound **3** has been evaluated in monkeys and humans (3). Data from both animal and human studies indicated that [^{11}C]MDL 100907 labeled either at the 2'- or 3'-position is a useful radioligand for the in vivo studies of brain serotonin 5-HT$_{2A}$ receptors using positron emission tomography (PET). Despite the demonstrated usefulness of [^{11}C]MDL 100907, neither MDL 100907 nor the two precursors for C-11 labeling is commercially available at present. Compound **4** , the precursor for



1: $R_1 = R_2 = CH_3$, **MDL 100907**
2: $R_1 = [^{11}C]CH_3$, $R_2 = CH_3$
3: $R_1 = CH_3$, $R_2 = [^{11}C]CH_3$
4: $R_1 = H$, $R_2 = CH_3$
5: $R_1 = CH_3$, $R_2 = H$

Figure 1

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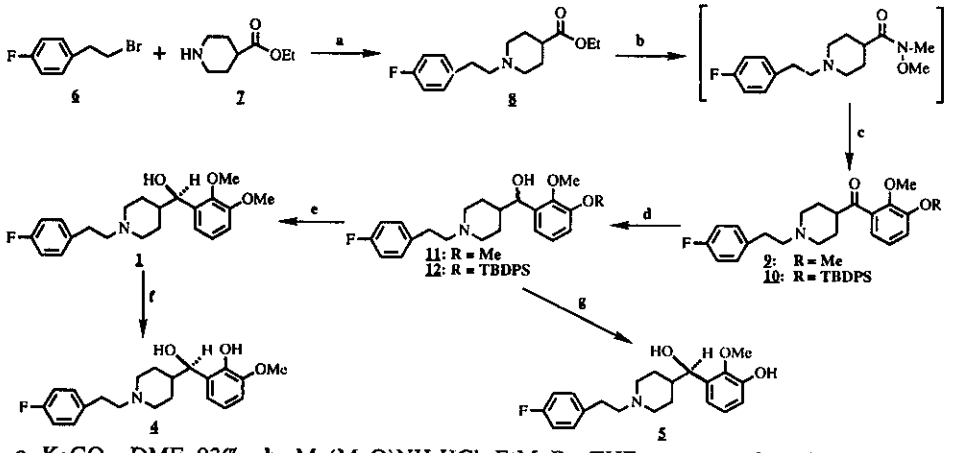
the 2'-labeled radioligand **2**, has been previously prepared via regioselective demethylation of MDL 100907 (2a, 3a). However synthesis of MDL 100907 itself, as disclosed in the patent literature (4), involved protection and deprotection of functional groups and was lengthy and inefficient.

In contrast, compound **5**, the precursor for the 3'-labeled radioligand **3**, could not be synthesized by regioselective demethylation of MDL 100907. Instead, **5** was previously prepared by a separate synthetic route distinct from that for the synthesis of MDL 100907 and the 2'-precursor (2a). Reported herein is an efficient, integrated synthetic route requiring no protection or deprotection of functional groups. This route involves a new methodology for transforming an ester directly to a ketone functionality in a one-pot, two-step process, and both MDL 100907 (**1**) and its two C-11 labeling precursors (**4** and **5**) can be prepared via a single synthetic pathway.

Results and Discussion

The synthetic route for the precursors of [^{11}C]MDL 100907 depended upon a key transformation of ester to ketone via an amide intermediate (Scheme 1). Compound **8**, prepared by the coupling of starting materials 2-(4-fluorophenyl)ethyl bromide **6** and ethyl isonipecotate **7**, was converted to the ketone **9** or **10** by a two-step, one-pot process. First, the N-alkylated isonipecotate **8** was reacted with N,O-dimethylhydroxylamine hydrochloride and ethylmagnesium bromide to produce the amide intermediate (5). Without separation, this intermediate underwent subsequent reaction with the aromatic anion, prepared from either veratrole or *tert*-butyldiphenylsilyl(TBDPS)-guaiacol with *n*-butyl lithium in THF, to provide the ketone **9** or **10**. It should be noted that lithiation of the TBDPS-guaiacol took place exclusively *ortho* to the methoxy group (6), thus positioning the TBDPS-protected phenolic group at the 3'-position of the ketone product **10**. Reduction of the ketones with sodium borohydride afforded the alcohols **11** and **12**. Derivatization of the racemic dimethoxyphenyl alcohol **11** with (S)-(+)-α-methoxyphenylacetic acid furnished two diastereomeric esters.



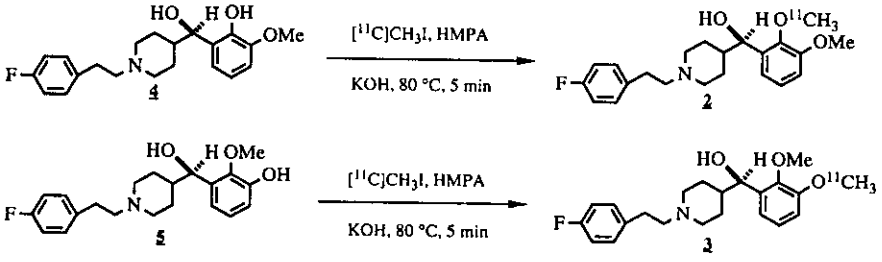
a. K_2CO_3, DMF, 93%. **b.** Me(MeO)NH•HCl, EtMgBr, THF. **c.** veratrole, *n*-BuLi, THF, 70% or TBDPS-guaiacol, *n*-BuLi, THF, 67%. **d.** $NaBH_4$, MeOH, 84%. **e.** 1.(S)-(+)-α-PhCH(OMe)CO_2H, DCC, DMAP, $CHCl_3$. 2.column chromatography (SiO_2). 3.K_2CO_3, MeOH, H_2O, 73%. **f.** *L*-Selectride, THF, 65%. **g.** 1.(S)-(+)-α-PhCH(OMe)CO_2H, DCC, DMAP, $CHCl_3$. 2.column chromatography (SiO_2). 3.K_2CO_3, MeOH, H_2O, 74%.

Scheme 1. Synthesis of MDL 100907 and Two Precursors for C-11 Labeling

Separation of the esters by column chromatography on silica gel and subsequent hydrolysis of the diastereomerically pure (R,S)-(+)-ester provided MDL 100907 **1** in > 98% ee, as determined by chiral HPLC analysis. The resolved, enantiomerically pure MDL 100907 was then regioselectively demethylated at the 2'-position by reaction with *L*-Selectride to produce the (R)-(+)-2'-phenol **4** as the precursor for C-11 radiolabeling at the 2'-position (7). Chiral HPLC analysis indicated that precursor **4** was obtained in > 97% ee.

The preparation of the 3'-phenol precursor **5** followed similar procedures. The racemic alcohol **12** was resolved through the formation of esters by reaction with (S)-(+)-α-methoxyphenylacetic acid and separation of the resulting diastereomeric esters by silica gel column chromatography. Concurrent hydrolysis of the ester group and the TBDPS-protecting group in the (R,S)-(+)-diastereomer then provided the (R)-(+)-enantiomer **5** with over 98% ee, as indicated by chiral HPLC analysis of the final product.

[^{11}C]Methylation of the 2'-phenol **4** and 3'-phenol **5** was performed with [^{11}C]methyl iodide (8) in hexamethylphosphoramide (HMPA)/KOH at 80 °C for 5 min, to produce [^{11}C]MDL 100907 **2** and **3** in 35.3% and 46.1% radiochemical yields, respectively, decay corrected to end of bombardment (EOB) and based upon [^{11}C]CO_2 released from the target (Scheme 2). The total synthesis times were approximately 50 min for compound **2** and 40 min for compound **3**. The longer synthesis time for **2** resulted from the need to remove precursor **4** from the crude reaction mixture with an alumina SepPak cartridge prior to semi-preparative HPLC separation.



Scheme 2. Radiosynthesis of 2'-[^{11}C]MDL 100907 and 3'-[^{11}C]MDL 100907

In summary, an efficient, integrated synthetic route for the preparation of MDL 100907 and the two precursors for C-11 labeling has been successfully implemented. [^{11}C]Methylation of these two precursors produced high specific activity [^{11}C]MDL 100907 labeled at two specific positions (compounds **2** and **3**).

Experimental

General: All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. When reactions were worked up by extraction with dichloromethane (CH_2Cl_2) or ethyl ether (Et_2O), organic solutions were dried with anhydrous $MgSO_4$ and concentrated with a rotary evaporator under reduced pressure. Reactions requiring

anhydrous conditions were carried out in oven-dried glassware under an inert atmosphere of nitrogen. Anhydrous THF was prepared by distillation over Na/benzophenone. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Column chromatography was performed using silica gel 60, 230-400 mesh (EM Reagents). IR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrophotometer. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AF300 spectrometer at 300 MHz and 75 MHz respectively, with $CDCl_3$ as solvent and tetramethylsilane as the internal standard (0 ppm). Mass spectra were taken on a VG 70S spectrometer and are reported in relative intensities. Optical rotations were determined on a Perkin Elmer 241 polarimeter. Elemental analyses were performed at Midwest Microlab, Indianapolis, IN.

1-[2-(4-Fluorophenyl)ethyl]-4-piperidinecarboxylic acid ethyl ester (8): To the solution of ethyl isonipecotate 7 (7.86 g, 50 mmol) and 2-(4-fluorophenyl)ethyl bromide 6 (11.17 g, 55 mmol) in DMF (100 mL) was added potassium carbonate (20.73 g, 150 mmol). The reaction mixture was stirred at 90 °C for 22 h, then cooled to room temperature, and filtered. The solid was rinsed with Et_2O and the filtrate partitioned between water and Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL x 3). The combined Et_2O extracts were washed with H_2O, dried, and concentrated to give a yellowish oil. Kugelrohr distillation (100-120 °C, 1.0 mm Hg) gave compound 8 (13.00 g, 93%) as a colorless oil. A second Kugelrohr distillation (100-105 °C, 1.0 mm Hg) provided an analytical sample. IR (neat): 1730 cm^{-1}. ^{1}H NMR: δ 7.14 (m, 2H), 6.96 (m, 2H), 4.13 (q, 2H, J = 7.1 Hz), 2.94 (td, 2H, J = 3.3, 11.4 Hz), 2.76 (m, 2H), 2.54 (m, 2H), 2.29 (tt, 1H, J = 4.1, 11.0 Hz), 2.08 (dt, 2H, J = 2.5, 11.4 Hz), 1.90 (m, 2H), 1.79 (m, 2H), 1.25 (t, 3H, J = 7.1 Hz). ^{13}C NMR: δ 174.9, 160.6 (d, J = 243 Hz), 135.9 (d, J = 5 Hz), 129.9 (d, J = 8 Hz), 115.0 (d, J = 21 Hz), 60.6, 60.2, 52.9, 41.1, 32.8, 28.2, 14.1. MS: 279 (M^+, 6), 278 (18), 234 (37), 170 (100). Anal. Calcd for $C_{16}H_{22}FNO_2$: C, 68.79; H, 7.94; N, 5.01. Found: C, 68.58; H, 8.15; N, 5.03.

2,3-Dimethoxyphenyl[1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl]methanone (9): Under nitrogen stream N,O-dimethylhydroxylamine hydrochloride (1.46 g, 15 mmol) was added to the solution of ester 8 (2.79 g, 10 mmol) in THF (60 mL). The mixture was cooled to -30 °C, and ethylmagnesium bromide (30 mL, 1.0 M solution in THF, 30 mmol) was injected slowly. The resulting reaction mixture was stirred for 1.5 h, during which the temperature rose to 0 °C.

In a second flask, a cooled (0 °C) solution of veratrole (2.90 g, 21 mmol) in anhydrous THF (40 mL) was prepared, and to this solution was added *n*-butyl lithium (9.3 mL, 2.5 M solution in THF, 23 mmol). The reaction mixture was allowed to warm to 22 °C, stirred for 2 h, cooled to 0 °C again, and then transferred, via a cannula, to the reaction mixture prepared above. After the addition, the resulting reaction mixture was stirred at room temperature for 3 h, quenched with saturated NH_4Cl solution, and extracted with Et_2O (100 mL x 3). The combined Et_2O extracts were washed twice with water, dried, and concentrated to give crude product. Chromatography on silica gel and elution with Et_2O provided pure ketone 9 (2.58 g, 69.5%) as a colorless oil. IR (neat): 1692 cm^{-1}. ^{1}H NMR:

δ 7.15-6.80 (m, 7H), 3.87 (s, 3H), 3.85 (s, 3H), 3.12 (m, 1H), 2.98 (m, 2H), 2.78 (m, 2H), 2.57 (m, 2H), 2.15 (m, 2H), 1.94 (m, 2H), 1.78 (m, 2H). ^{13}C NMR: δ 206.4, 161.2 (d, J = 243 Hz), 152.6, 146.8, 135.9, 134.2, 129.9 (d, J = 7.2 Hz), 124.2, 120.2, 115.0 (d, J = 20.6 Hz), 114.6, 61.6, 60.6, 55.8, 53.2, 48.0, 32.8, 27.9. MS: 370 (25, [M$^+$-1]), 356 (5), 340 (6), 262 (100), 165 (6), 123 (7), 96 (8).

(±)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (11): The solution of **9** as hydrochloride salt (2.00 g, 4.9 mmol) in methanol (70 mL) was treated with $NaBH_4$ (0.56 g, 14.7 mmol) at 0 °C. The reaction mixture was warmed to 22 °C and stirred for 12 h. Methanol was removed, and the residue was partitioned between H_2O (100 mL) and Et_2O (100 mL). The layers were separated, and the H_2O layer was extracted with Et_2O (50 mL x 2). The combined Et_2O layers were washed with water, dried, and concentrated. The residue was chromatographed on silica gel, and elution with acetone gave pure alcohol **11** (1.48 g, 81%) as a solid. An analytical sample was obtained by crystallization from EtOAc/hexane, mp 128-130 °C [lit. 126-127 °C (4)]. IR (neat): 3375 cm^{-1}. ^{1}H NMR: δ 7.13 (m, 2H), 7.05 (t, 1H, J = 7.9 Hz), 7.0-6.83 (m, 4H), 4.63 (d, 1H, J = 8.0 Hz), 3.87 (s, 6H), 3.12-2.85 (m, 2H), 2.75 (m, 2H), 2.51 (m, 2H), 2.15-1.82 (m, 3H), 1.68 (m, 1H), 1.56-1.20 (m, 3H). ^{13}C NMR: δ 161.2 (d, J = 244 Hz), 152.3, 146.4, 136.5, 136.0, 129.9 (d, J = 7.2 Hz), 123.8, 119.6, 115.0 (d, J = 21.2 Hz), 111.2, 73.9, 60.8, 55.6, 53.6, 42.8, 32.8, 28.7, 26.8. Anal Calcd for $C_{22}H_{28}FNO_3$: C, 70.75; H, 7.56; N, 3.75. Found: C, 70.86; H, 7.59; N, 3.81.

(R)-(+)-α-(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (1): To the solution of compound **11** (0.62 g, 1.66 mmol) in $CHCl_3$ (20 mL) were added sequentially (S)-(+)-α-methoxyphenylacetic acid (276 mg, 1.66 mmol), dicyclohexylcarbodiimide (DCC) (343 mg, 1.66 mmol), and 4-dimethylaminopyridine (DMAP) (20 mg, 0.16 mmol). The reaction mixture was heated at 68 °C for 15 h, cooled to room temperature, and filtered. The solid was rinsed with Et_2O. The filtrate was collected and evaporated to dryness. The resulting syrup was chromatographed. Elution with EtOAc/hexane (45:55) separated the two diastereomeric esters. The fractions containing the first-eluting diastereomeric ester were combined and evaporated to give 165 mg of (R,S)-(+)-α-[(2,3-dimethoxyphenyl)[1-[2-(4-fluorophenyl)ethyl]4-piperidinyl]methyl]-α-methoxybenzene acetate.

The ester (96 mg, 1.84 mmol) obtained above was dissolved in MeOH (5 mL). A solution of K_2CO_3 (51 mg, 3.69 mmol) in H_2O (1.5 mL) was added, and the reaction mixture was stirred vigorously at 22 °C for 21 h. Water was added, and the mixture extracted with Et_2O (10 mL x 3). The combined Et_2O layers were washed twice with H_2O, dried, and evaporated. The oily residue was chromatographed to give MDL 100907 **1** (50 mg, 73 % from the ester) as a colorless resin, which solidified on standing. The enantiomeric excess (ee) of alcohol **1** was determined to be > 98% using chiral HPLC analysis [Chiracel OD-H column, 4.6 x 250 mm; hexane/*i*-PrOH/DEA 95:5:0.2,

0.5 ml/min; t_R 20.4 min for compound **1** (for comparison a t_R of 23.2 min was obtained for the S-(-)-enantiomer using the same conditions)]. $[\alpha]_D^{22}$ = + 21.6° (c 2.14, MeOH) [lit. $[\alpha]_D^{20}$ = + 13.9° (4)]. IR, ^{1}H NMR, and MS spectra of the enantiomerically pure compound **1** were the same as the racemic compound **11**.

(R)-(+)-α-(2-Hydroxy-3-methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol (4): A solution of alcohol **1** (40 mg, 0.11 mmol) in THF (12 mL) was treated with *L*-Selectride (0.33 mL, 1.0 M solution in THF, 0.33 mmol). The reaction mixture was heated at 67 °C for 24 h, then cooled to room temperature, and poured into ice water. The mixture was extracted with Et_2O (8 mL x 4). The combined Et_2O layers were washed with water, dried, and concentrated. The crude product was purified by column chromatography ($MeOH/CH_2Cl_2$, 10:90) to provide compound **4** (25 mg, 65 %) as an off-white solid. Recrystallization from CH_2Cl_2/Et_2O afforded an analytical sample, mp 147-149 °C. The enantiomeric excess (ee) of compound **4** was determined to be > 97% using chiral HPLC analysis (Chiracel OD-H column, 4.6 x 250 mm; hexane/*i*-PrOH/DEA 90:10:0.2, 0.5 ml/min; t_R 26.3 min for compound **4**. For comparison, a t_R of 21.1 min was obtained for the S-(-)-enantiomer using the same conditions). $[\alpha]_D^{22}$ = + 22.6 ° (c 1.04, MeOH). IR (KBr): 3484 cm^{-1}. ^{1}H NMR: δ 7.03 (m, 2H), 6.91 (m, 2H), 6.77 (m, 2H), 6.68 (m, 1H), 4.54 (d, 1H, J = 7.7 Hz), 3.83 (s, 3H), 3.13-2.88 (m, 2H), 2.69 (m, 2H), 2.46 (m, 2H), 2.20-1.70 (m, 4H), 1.65-1.30 (m, 3H). ^{1}H NMR (DMSO-d_6): δ 8.46 (s, 1H), 7.23 (m, 2H), 7.07 (m, 2H), 6.85 (d, 1H, J = 7.7 Hz), 6.79 (d, 1H, J = 7.7 Hz), 6.72 (t, 1H, J = 7.7 Hz), 5.02 (m, 1H), 4.68 (m, 1H), 3.77 (s, 3H), 2.90 (m, 2H), 2.68 (m, 2H), 2.43 (m, 2H), 1.80 (m, 2H), 1.65 (m, 1H), 1.55-1.10 (m, 4H). ^{13}C NMR: δ 161.3 (d, J = 244 Hz), 147.4, 144.1, 135.4, 129.9 (d, J = 9 Hz), 128.1, 120.0, 119.1, 115.0 (d, J = 20 Hz), 109.8, 60.5, 55.8, 53.4, 41.7, 32.1, 29.6, 28.2. MS: 359 (M^+, 0.5), 358 (0.5), 340 (1), 264 (4), 250 (100), 232 (69), 137 (6), 123 (7), 116 (11). Anal Calcd for $C_{21}H_{26}FNO_3$: C, 70.17; H, 7.29; N, 3.90. Found: C, 70.02; H, 7.35; N, 3.91.

[2-Methoxy-3-[(1,1-dimethylethyldiphenylsilyl)oxy]phenyl][1-[2-(4-fluorophenyl)-ethyl]-4-piperidinyl]methanone (10): In a manner analogous to the preparation of **9**, the amide intermediate was prepared by the addition of N,O-dimethylhydroxylamine hydrochloride (1.72 g, 17.63 mmol) to a solution of ester **8** (3.29 g, 11.78 mmol) in THF (60 mL) followed by the slow addition of ethylmagnesium bromide (35.3 mL, 1.0 M solution in THF, 35.3 mmol) at -35 °C.

In a second flask a cooled (0 °C) solution of TBDPS-guaiacol (5.90 g, 24.75 mmol) in anhydrous THF (200 mL) was prepared, and to this solution was added *n*-butyl lithium (9.9 mL, 2.5 M solution in THF, 24.75 mmol). This mixture was treated in a manner analogous to that for the preparation of **9**, and chromatography on silica gel and elution with Et_2O provided pure ketone **10** (4.71 g, 67.1%) as a colorless oil. An analytical sample was prepared by Kugelrohr distillation (200-210 °C, 0.3 mm Hg). IR (neat): 1682 cm^{-1}. ^{1}H NMR: δ 7.74 (m, 4H), 7.50-7.30 (m, 6H), 7.17 (m, 2H), 6.98 (m, 2H), 6.87 (dd, 1H, J = 1.7, 7.7 Hz), 6.70 (t, 1H, J = 7.7 Hz), 6.64 (dd, 1H, J = 1.7, 7.7 Hz), 3.94

(s, 3H), 3.15-2.92 (m, 3H), 2.79 (m, 2H), 2.58 (m, 2H), 2.14 (dt, 2H, J = 2.2, 11.2 Hz), 1.98-1.67 (m, 4H), 1.15 (s, 9H). ^{13}C NMR: δ 206.6, 161.3 (d, J = 244 Hz), 148.8, 148.4, 136.1, 135.5, 135.0, 132.3, 130.1 (d, J = 6 Hz), 127.8, 123.9, 123.3, 120.9, 115.0 (d, J = 21 Hz), 61.9, 60.7, 53.3, 47.8, 32.9, 28.0, 26.5, 19.5. MS: 595 (M^+, 32), 594 (64), 580 (50), 564 (13), 538 (92), 486 (100). Anal Calcd for $C_{37}H_{42}FNO_3Si$: C, 74.59; H, 7.10; N, 2.35. Found: C, 74.41: H, 7.19; N, 2.34.

(±)-α-[2-Methoxy-3-[(1,1-dimethylethyldiphenylsilyl)oxy]phenyl]-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (12): A solution of the ketone **10** (1.50 g, 2.52 mmol) in MeOH (100 mL) was treated with sodium borohydride (286 mg, 7.56 mmol) in a manner analogous to that described for the preparation of **11**. The product purified by column chromatography (EtOAc) to afford pure alcohol **12** (1.27 g, 84 %) as a colorless solid, mp 68-70 °C. IR (neat): 3400 (br) cm^{-1}. ^{1}H NMR: δ 7.73 (m, 4H), 7.47-7.30 (m, 6H), 7.15 (m, 2H), 6.96 (m, 2H), 6.80 (dd, 1H, J = 1.4, 7.9 Hz), 6.66 (t, 1H, J = 7.9 Hz), 6.42 (dd, 1H, J = 1.4, 7.9 Hz), 4.62 (d, 1H, J = 8.1 Hz), 3.99 (s, 3H), 3.13-2.88 (m, 2H), 2.78 (m, 2H), 2.54 (m, 2H), 2.15-1.85 (m, 3H), 1.78-1.25 (m, 4H), 1.21 (s, 9H). ^{13}C NMR: δ 161.3 (d, J = 243 Hz), 148.4, 148.2, 136.9, 136.1, 135.5, 132.7, 132.4, 130.0 (d, J = 8 Hz), 127.7, 123.5, 120.1, 119.7, 115.0 (d, J = 20 Hz), 74.2, 61.0, 60.9, 53.7, 42.9, 32.9, 28.8, 26.5, 19.4. MS: 598 (M^+, 3), 597 (12), 540 (47), 522 (6), 488 (100), 216 (10), 135 (9). Anal Calcd for $C_{37}H_{44}FNO_3Si$: C, 74.34; H, 7.42; N, 2.34. Found: C, 73.97; H, 7.54; N, 2.38.

(R)-(+)-α-(3-Hydroxy-2-methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (5): Compound **12** (951 mg, 1.59 mmol) and (S)-(+)-α-methoxyphenylacetic acid (317 mg, 1.91 mmol) were dissolved in anhydrous $CHCl_3$ (40 mL). To the solution were then added DCC (393 mg, 1.90 mmol) and DMAP (20 mg, 0.16 mmol). The reaction mixture was heated at 70 °C for 20 h, cooled to room temperature, and concentrated. The residue was chromatographed on silica gel. Elution with EtOAc/hexane (30:70) separated the two diastereomeric esters. Fractions containing the first-eluting component (R_f 0.40 on TLC; solvent: EtOAc/hexane 35:65) were combined and concentrated to afford 256 mg of the desired (R,S)-(+)-diastereomer.

A solution of the (R,S)-(+)-diastereomeric ester (210 mg, 0.282 mmol) in MeOH (10 mL) was treated with K_2CO_3 (195 mg, 1.41 mmol) in H_2O (3 mL). The reaction mixture was stirred at 22 °C for 42 h. Water was added and the mixture extracted with CH_2Cl_2 (15 mL x 4). The combined CH_2Cl_2 extracts were washed with H_2O, dried, and concentrated. The resulting crude product was chromatographed on silica gel (MeOH/CH_2Cl_2 10:90) to give compound **5** (75 mg, 74 % from the ester) as an off-white solid. An analytical sample was obtained by recrystallization from EtOAc/Et_2O, mp 75-80 °C. $[\alpha]_D^{22}$ = + 22.2° (c 1.58, MeOH). IR (neat): 3400 (br) cm^{-1}. ^{1}H NMR: δ 7.09 (m, 2H), 7.04-6.89 (m, 3H), 6.85 (m, 2H), 4.63 (d, 1H, J = 8.1 Hz), 3.81 (s, 3H), 3.18-2.90 (m, 2H), 2.76 (m, 2H), 2.54 (m, 2H), 2.15-1.87 (m, 3H), 1.70 (m, 1H) 1.58-1.25 (m, 3H). ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H), 7.23 (m, 2H), 7.07 (m, 2H), 6.86 (t, 1H, J = 7.7 Hz), 6.78 (dd, 1H,

J = 1.4, 7.7 Hz), 6.71 (dd, 1H, J = 1.4, 7.7 Hz), 4.89 (d, 1H, J = 4.7 Hz), 4.57 (m, 1H), 3.70 (s, 3H), 3.00-2.80 (m, 2H), 2.69 (m, 2H), 2.48 (m, 2H), 1.90-1.70 (m, 2H), 1.43 (m, 1H), 1.35-1.10 (m, 4H). ^{13}C NMR: δ 161.3 (d, J = 244 Hz), 149.5, 145.6, 136.1, 135.0, 129.9 (d, J = 9 Hz), 124.4, 118.4, 116.2, 115.1 (d, J = 19 Hz), 73.1, 60.8, 60.1, 53.2, 42.1, 31.7, 27.8. MS: 359 (M, 0.1), 358 (0.2), 250 (100), 232 (12), 123 (11), 103 (7). HRMS (EI): calcd for $C_{14}H_{20}FNO_3$ (M^+ - F-Ph-$(CH_2)_2$): 250.1443; found 250.1450.

Radiosynthesis of (R)-(+)-α-(2-[^{11}C]methoxy-3-methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (2). The phenol precursor **4** (2.0 mg) was reacted with [^{11}C]CH_3I (8) and KOH (15 μL, 1.0 N) in HMPA (0.50 mL) at 80 °C for 5 min. The reaction mixture was passed through a neutral alumina SepPak cartridge to remove >90% of the precursor **4**. Compound **2** was eluted from the alumina SepPak with acetone (5 mL), and the acetone eluent was loaded onto a C_{18} SepPak cartridge after dilution with water (45 mL). The C_{18} SepPak was eluted with MeOH (1 mL) and the eluent was loaded onto a semi-preparative Alltech Econosil C_{18} column. High specific activity (54.4 ± 28.9 GBq/μmol: 1470 ± 780 Ci/mmol) product **2** was obtained by eluting the column with MeOH/pH 7.3 buffered water (65:35; capacity factor (k') of **2** = 3.7). The eluent fraction containing the product was collected, diluted with water (100 mL), and **2** was retained by passing the solution through a C_{18} SepPak cartridge. The C_{18} SepPak was then eluted with ethanol (1 mL) to provide **2** in ≥95% chemical and radiochemical purities. The radiochemical yields of **2** (decay corrected to EOB and based upon [^{11}C]CO_2 removed from the target) averaged 35.3% with a synthesis time of 50 min (n = 21).

Radiosynthesis of (R)-(+)-α-(2-methoxy-3-[^{11}C]methoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol (3). The phenol precursor **5** (1.0 mg) was reacted with [^{11}C]CH_3I (8) and KOH (15 μL, 1.0 N) in HMPA (0.40 mL) at 80 °C for 5 min. The crude reaction mixture was loaded onto a semi-preparative Alltech Econosil C_{18} column and subsequent separation and purification of **3** was performed in a manner analogous to that described above for **2** (note that the k' values of **2** and **3** are identical). High specific activity (74.7 ± 53.6 GBq/μmol; 2020 ± 1450 Ci/mmol) product **3** was obtained in ≥95% chemical and radiochemical purities. The radiochemical yields of **3** (decay corrected to EOB and based upon [^{11}C]CO_2 removed from the target) averaged 46.1% with a synthesis time of 40 min (n = 20).

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