Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XLI, No. 1

Stereoconservative Synthesis of the Enantiomerically Pure Precursors of [^{11}C](+)-McN 5652 and [^{11}C](-)-McN 5652

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Summary

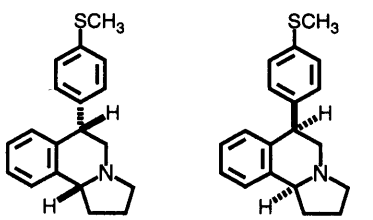
A stereoconservative synthetic route for the preparation of the precursors of [^{11}C](+)-McN 5652 and [^{11}C](-)-McN 5652, also known as [^{11}C]McN-5652-X and [^{11}C]McN-5652-W, is reported. The key steps involved the transformation of the (+)-*trans*-4-bromophenyl or (-)-*trans*-4-bromophenyl analogues of (+)-McN 5652 or (-)-McN 5652 to triisopropylsilyl-protected thioethers and conversion of the thioethers to benzoyl thioesters via a one-pot deprotection and esterification sequence. Subsequent formation of a tartrate salt of the benzoyl thioesters provided stable, convenient precursors for the routine radiosynthesis of [^{11}C](+)-McN 5652 and [^{11}C](-)-McN 5652. The radiosyntheses were accomplished by *S*-methylation with high specific activity [^{11}C]methyl iodide of the phenylsulfides, which were generated in situ from the tartrate salt of the benzoyl thioesters. HPLC analyses of the final products demonstrated that all of the reactions were stereoconservative, with no detectable isomerization or racemization taking place in any of the reaction sequences. [^{11}C](+)-McN 5652 and [^{11}C](-)-McN 5652 were obtained with end of synthesis (EOS) yields of ~120 mCi and EOS specific activities of ~4000 Ci/mmol following radiosynthesis and purification procedures that required approximately 25 min. The chemical and radiochemical purities of the final products were greater than 95%.

Key Words: serotonin transporter, carbon-11, radiosynthesis, positron emission tomography

Introduction

The potent serotonin transporter ligand, (+)-McN 5652 {(+)-1,2,3,5,6β,10bβ-hexahydro-6α-[(4-methylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline, (+)-**1**, or McN-5652-X}, has been radiolabeled with carbon-11 at the thiomethyl group and utilized as a marker of regional serotonin reuptake

Structures of (+)-McN 5652 [(+)-**1**] and (-)-McN 5652 [(-)-**1**]



(+)-McN 5652 (-)-McN 5652

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CCC 0362–4803/98/010009–09$17.50

Received 6 June 1997
Revised 18 August 1997

complex densities in positron emission tomography (PET) brain imaging studies (1). The inactive enantiomer, (-)-McN 5652 [(-)-**1** or McN-5652-W], also was radiolabeled with carbon-11 and used as a regional measure of non-specific binding in the brain.

Radiolabeling has been performed previously using [^{11}C]methyl iodide to methylate a labile thiophenol precursor, which was produced prior to radiolabeling by demethylation of (+)-**1** or (-)-**1** with sodium methylthiolate at high temperature, followed by HPLC separation of the desired *trans*-thiophenols and the undesired *cis*-thiophenols (2). Most of the pure starting materials were lost as a result of isomerization under the stringent demethylation reaction conditions, which produced a 60/40 *cis/trans* diastereomeric mixture. In addition, the thiophenols exhibited a short shelf-life and required preparation immediately prior to radiolabeling.

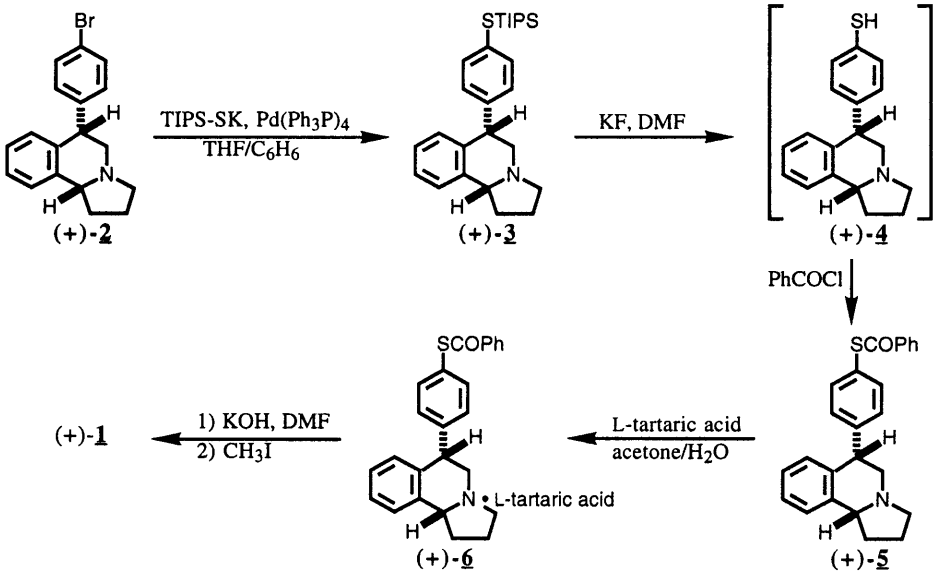
Suehiro and coworkers (3) recently reported a procedure that increased the shelf-life of radiolabeling precursors for [^{11}C](+)-**1** and [^{11}C](-)-**1** by utilizing thioester protecting groups which were removed in situ prior to radiolabeling. However, preparation of the thioesters involved the same stringent demethylation conditions to generate the thiophenols from pure (+)-**1** or (-)-**1**, and material loss associated with isomerization persisted. Furthermore, the starting materials for the preparation of these thioester-protected precursors were obtained from R. W. Johnson Pharmaceutical Research Institute (2) and are no longer available. Methods are reported here to synthesize stable thioester precursors for the preparation of (+)-**1** and (-)-**1** from commercially available starting materials using a stereoconservative route in which *cis/trans* isomerization was eliminated, resulting in the formation of the radiolabeling precursors with high diastereomeric and enantiomeric purities. The precursors synthesized via these new routes are stable, crystalline salts with long shelf-lives (no detectable degradation was observed when the salts were stored at -10 °C for periods greater than 9 months). Immediately prior to radiolabeling, these salts were converted to the reactive phenylsulfides in situ and provided convenient starting materials for the routine production of [^{11}C](+)-McN 5652 and [^{11}C](-)-McN 5652.

Results and Discussion

The stereoconservative synthetic route for the preparation of the precursors is summarized in Scheme 1. The key steps were the transformation of the bromide **2** to the triisopropylsilyl (TIPS) thioether **3**, and the subsequent conversion of **3** to the benzoyl thioester **5** via a one-pot deprotection and esterification sequence (4). The synthetic methods were first evaluated using racemic materials. Starting material (±)-**2**, prepared from 4-bromomandelic acid and 2-phenylpyrrolidine in a process similar to that for the synthesis of the racemate (±)-McN 5652 (also known as McN-5652-Z) (5), was converted to (±)-**3** in 69% yield using a modified literature procedure (4). Desilylation of (±)-**3** resulted in the formation of thiophenol (±)-**4** (not isolated), which was reacted with benzoyl chloride to produce the thioester (±)-**5** in 77% yield. Conversion of (±)-**5** to the salt (±)-**6** was achieved by mixing the free amine in acetone with D-tartaric acid in water. The tartrate salt was crystallized from acetone/water as a white solid. The identities of compounds (±)-**3** and (±)-**5** were confirmed by ^{1}H NMR and mass spectroscopy.

The purified enantiomer, (+)-**2** or (-)-**2**, was then obtained as starting material for the synthesis of precursor (+)-**6** or (-)-**6**. The preparation of enantiopure (+)-**1** and (-)-**1** has been reported in the literature (6) by the repeated crystallization of (±)-**1** with D- or L-tartaric acid. However, satisfactory results were not achieved in our laboratory using this methodology to resolve

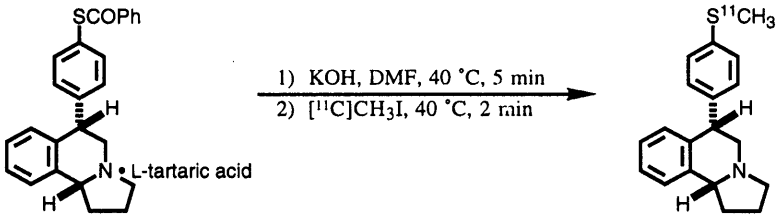
either (±)-McN 5652 or the racemic 4-bromophenyl analogue (±)-**2**. Instead, sequential use of di-*p*-toluoyl-D-tartaric acid and di-*p*-toluoyl-L-tartaric acid (7) resulted in the successful resolution of (+)-**2** and (-)-**2** following three consecutive enrichment cycles for each of the enantiomers. Enantiomeric excess (ee) was determined using chiral HPLC techniques and was >98% for both compounds (+)-**2** and (-)-**2**.



Scheme 1. Stereoconservative synthetic route for the preparation of the radiolabeling precursor (+)-**6** for [^{11}C](+)-McN 5652. Cold (non-radioactive) methyl iodide was utilized to convert either (+)-**6** or (-)-**6** to (+)-**1** or (-)-**1** for chromatographic analyses and comparison to authentic samples of (+)-McN 5652 and (-)-McN 5652.

Following the sequence outlined in Scheme 1 for the synthesis of (+)-**1**, the individual enantiomers (+)-**2** and (-)-**2** were taken to (+)-**6** and (-)-**6**, separately. Compounds (+)-**6** and (-)-**6** were converted to (+)-**1** and (-)-**1**, respectively, in a one-pot process by unmasking the phenylsulfide with potassium hydroxide in DMF followed by *S*-methylation with methyl iodide. Reverse phase and chiral HPLC analyses of the resulting products demonstrated that they were identical to authentic samples of (+)-McN 5652 and (-)-McN 5652. Reverse phase HPLC analyses also demonstrated the absence of detectable amounts of the *cis* isomers under these reaction conditions. Furthermore, chiral HPLC analyses demonstrated that when (+)-**2** or (-)-**2** (each with >98% ee) was utilized in the synthetic course depicted in Scheme 1, the resulting final product [(+)-**1** or (-)-**1**] retained an enantiomeric excess of greater than 98%. Retention of both diastereomeric and enantiomeric purities by (+)-**1** and (-)-**1** demonstrated that the entire synthetic sequence was stereoconservative, with no detectable isomerization or racemization occurring in any of the reactions.

The radiosynthesis of [^{11}C](+)-**1** or [^{11}C](-)-**1** was performed using (+)-**6** or (-)-**6** as the radiolabeling precursor together with high specific activity [^{11}C]CH_3I (Scheme 2). The end of synthesis (EOS) final product yields averaged ca. 120 mCi for both compounds with EOS specific activities of ~4000 Ci/mmol. The isolated radiochemical yields achieved at EOB were ~29%, and these yields are comparable to those reported by Suehiro and coworkers using butyryl thioester precursors (3). Increased reaction times or temperatures for both the thioester hydrolysis and [^{11}C]methylation reactions shown in Scheme 2 resulted in unimproved or lower radiolabeling yields. The advantages associated with the use of the crystalline salts (+)-**6** and (-)-**6** as radiolabeling precursors include both their stability and their ease of handling, thereby providing convenient precursors for the routine production of [^{11}C](+)-**1** and [^{11}C](-)-**1**.



(+)-**6** [^{11}C](+)-**1**

Scheme 2. Radiosynthesis of [^{11}C](+)-McN 5652. The radiosynthesis of [^{11}C](-)-McN 5652 was performed in a similar manner using (-)-**6**.

Experimental

Authentic samples of (+)-McN 5652 [(+)-**1**], (-)-McN 5652 [(-)-**1**], and (±)-McN 5655 were provided by R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, U.S.A. Potassium triisopropylsilanethiolate was prepared according to the literature procedure (8). All the other reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. 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. Anhydrous benzene and DMF were purchased from Aldrich Chemical Co. 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). Analytical reverse phase HPLC was performed at flow rates of 2 mL/min using either a Waters Symmetry C18 column (5 μm, 4.6 x 250 mm) or a Phenomenex Prodigy ODS(3) column (5 μm, 4.6 x 250 mm). Semi-preparative reverse phase HPLC was conducted at flow rates of 15 mL/min using a Phenomenex Prodigy ODS-Prep column (10 μm, 10 x 250 mm). Enantiomeric excess (ee) was determined by chiral HPLC using a Daicel Chiralcel OD-H column (4.6 x 250 mm) at flow rates of 0.5 mL/min. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrophotometer. Proton (^{1}H) NMR spectra were recorded on a Bruker AF300 spectrometer at 300 MHz with $CDCl_3$ as solvent and tetramethylsilane as the internal standard (0 ppm), unless stated otherwise. Mass spectra were obtained using a VG 70S spectrometer and are reported in relative intensities. Optical rotations were determined on a Perkin Elmer 241 polarimeter.

***trans*-(±)-1,2,3,5,6,10b-Hexahydro-6-(4-bromophenyl)pyrrolo[2,1-*a*]isoquinoline [(±)-2]**

Compound (±)-**2** was prepared by a route similar to that reported for the synthesis of (±)-McN 5652 (5) and was obtained as a dark oil. ^{1}H NMR: δ 7.38 (d, 2H, J = 8.3 Hz), 7.22-7.00 (m, 5H), 6.88 (d, 1H, J = 7.6 Hz), 4.14 (t, 1H, J = 4.6 Hz), 3.45 (m, 1H), 3.00 (td, 1H, J = 11.0, 4.4 Hz), 2.96 (m, 1H), 2.87 (dd, 1H, J = 11.0, 5.0 Hz), 2.55 (m, 1H), 2.37 (m, 1H), 2.08-1.65 (m, 3H). MS (EI): 328 (M^+, 96), 326 [$(M-2)^+$, 100], 301 (32), 299 (34), 172 (89).

***trans*-(+)-1,2,3,5,6,10b-Hexahydro-6-(4-bromophenyl)pyrrolo[2,1-*a*]isoquinoline [(+)-2] and *trans*-(-)-1,2,3,5,6,10b-Hexahydro-6-(4-bromophenyl)pyrrolo[2,1-*a*]isoquinoline [(-)-2]**

The racemic amine (±)-**2** (7.0 g, 21 mmol) was dissolved in 200 mL of acetone. Di-*p*-toluoyl-D-tartaric acid (6.1 g, 16 mmol) (7) was dissolved in 150 mL of acetone. The two solutions were filtered, combined, and left to stand at room temperature for two days. The resulting precipitates were filtered and dried to afford 4.0 g of white solids. This material was partitioned between aqueous NaOH/CH_2Cl_2, and the organic phase was separated, dried and evaporated to give the free amine (1.8 g, 5.5 mmol), which was dissolved in 40 mL of acetone and mixed with the solution of di-*p*-toluoyl-D-tartaric acid (2.1 g, 5.5 mmol) in 40 mL of acetone. The combined solution was left to stand at room temperature for one day. The precipitates (2.0 g) were collected and taken through another cycle of partitioning between aqueous NaOH/CH_2Cl_2 followed by crystallization with di-*p*-toluoyl-D-tartaric acid to give 1.4 g of salt. A small amount of the salt was partitioned between CH_2Cl_2 and NaOH solution to obtain a sample of the free amine (+)-**2** as a thick oil which solidified on standing, mp 73-76 °C, $[\alpha]_D$ +131.5° (c 0.84, $CHCl_3$). The enantiomeric excess (ee) of compound (+)-**2** was determined to be >98% by chiral HPLC analysis (k′ 0.53 on Chiralcel OD-H eluted with hexane/*i*-PrOH/DEA 99.3/0.5/0.2). The ^{1}H NMR and MS spectra of (+)-**2** were identical to those of compound (±)-**2**.

The combined mother liquors from the previous crystallizations of (+)-**2** were concentrated and the residue partitioned between aqueous NaOH/CH_2Cl_2. The organic layer was separated, dried, and concentrated to give the free amine (4.0 g). Following the procedures described above, this material was enriched by two additional cycles of crystallization with di-*p*-toluoyl-L-tartaric acid to provide 2.0 g of salt. A sample of the free amine was obtained by partitioning the salt between CH_2Cl_2 and NaOH solution. A thick oil was afforded which solidified on standing to give (-)-**2**, mp 74-75 °C, $[\alpha]_D$ -132.3° (c 0.86, $CHCl_3$). Compound (-)-**2** was obtained in > 98% ee as determined by chiral HPLC analysis (k′ 1.2 on Chiralcel OD-H with the same conditions as given for (+)-**2**). The ^{1}H NMR and MS spectra of (-)-**2** were identical to those of compound (±)-**2**.

***trans*-(±)-1,2,3,5,6,10b-Hexahydro-6-[(4-triisopropylsilylthio)phenyl]pyrrolo[2,1-*a*]-isoquinoline [(±)-3]**

To a solution of compound (±)-**2** (454 mg, 1.38 mmol) in anhydrous THF (15 mL) and benzene (20 mL) was added palladium tetrakis(triphenylphosphine) (344 mg, 0.30 mmol) and potassium triisopropylsilanethiolate (400 mg, 1.75 mmol). The reaction mixture was heated at 70 °C for 8 h, cooled to room temperature, and a second portion of $Pd(PPh_3)_4$ (160 mg, 0.14 mmol) was added. The reaction mixture was heated at 70 °C for an additional 12 h, cooled to room

temperature, and diluted with Et_2O (75 mL). The mixture was washed three times with water, dried ($MgSO_4$), and concentrated. The residue was taken up in CH_2Cl_2, and the solution was filtered through silica gel contained in a Buchner funnel. The contents of the funnel were rinsed successively with CH_2Cl_2 (150 mL) and Et_2O (150 mL). The ether filtrate was collected and concentrated to afford the crude reaction products. Column chromatography was performed on silica gel eluted with EtOAc/hexane (15:85) and provided the pure product (±)-**3** (418 mg, 69%) as a colorless oil. ^{1}H NMR: δ 7.38 (d, 2H, J = 8.2 Hz), 7.20-7.00 (m, 5H), 6.82 (d, 1H, J = 7.6 Hz), 4.13 (t, 1H, J = 5.4 Hz), 3.58 (m, 1H), 2.98 (m, 2H), 2.86 (dd, 1H, J = 11.0, 5.2 Hz), 2.65 (m, 1H), 2.34 (m, 1H), 2.10-1.70 (m, 3H), 1.25 (m, 3H), 1.05 (dd, 18H, J = 7.2, 1.9 Hz). MS (EI): 437 (M^+, 38), 436 [$(M-1)^+$, 59], 394 (15), 280 (97), 171 (100). HRMS (EI): m/z calcd. for $C_{27}H_{38}NSSi$, 436.2494 (M-1); found 436.2479 $(M-1)^+$.

trans-(+)-1,2,3,5,6,10b-Hexahydro-6-[(4-triisopropylsilylthio)phenyl]pyrrolo[2,1-_a_]-isoquinoline [(+)-3]

Compound (+)-**3** was prepared in 78% yield from (+)-**2** according to the procedures described above for (±)-**3**. A colorless oil was obtained, $[\alpha]_D$ +102.0° (c 0.94, $CHCl_3$). The ^{1}H NMR and MS spectra of (+)-**3** were identical to those of compound (±)-**3**.

trans-(-)-1,2,3,5,6,10b-Hexahydro-6-[(4-triisopropylsilylthio)phenyl]pyrrolo[2,1-_a_]-isoquinoline [(-)-3]

Compound (-)-**3** was prepared in 71% yield from (-)-**2** according to the procedures described above for (±)-**3**. A colorless oil was obtained, $[\alpha]_D$ -102.4° (c 0.92, $CHCl_3$). The ^{1}H NMR and MS spectra of (-)-**3** were identical to those of compound (±)-**3**.

trans-(±)-1,2,3,5,6,10b-Hexahydro-6-[(4-benzoylthio)phenyl]pyrrolo[2,1-_a_]isoquinoline [(±)-5]

Potassium fluoride (143 mg, 2.46 mmol) was added to the solution of compound (±)-**3** (330 mg, 0.75 mmol) in DMF (8 mL). The reaction mixture was stirred vigorously at room temperature for 15 min, benzoyl chloride (437 mg, 3.11 mmol) was added, and stirring was continued for another 15 min. The mixture was diluted with water, adjusted to pH 8 with aqueous $NaHCO_3$ solution and extracted with Et_2O (15 mL x 4). The combined Et_2O extracts were washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel. Elution with Et_2O furnished the pure product (±)-**5** (220 mg, 77%) as a colorless oil. IR (neat): 1677 cm^{-1}. ^{1}H NMR: δ 8.04 (d, 2H, J = 7.4 Hz), 7.61 (t, 1H, J = 7.4 Hz), 7.49 (t, 2H, J = 7.4 Hz), 7.40 (d, 2H, J = 8.2 Hz), 7.34 (d, 2H, J = 8.2 Hz), 7.23-7.05 (m, 3H), 6.94 (d, 1H, J =7.6 Hz), 4.23 (t, 1H, J = 4.7 Hz), 3.49 (m, 1H), 3.10 (dd, 1H, J = 11.1, 4.5 Hz), 3.00 (m, 1H), 2.91(dd, 1H, J = 11.1, 5.1 Hz), 2.58 (m, 1H), 2.36 (m, 1H), 2.10-1.75 (m 3H). MS (EI): 385 (M^+, 82), 384 [$(M-1)^+$, 100)], 357 (24), 280 (13), 172 (52), 105 (73). HRMS (EI): m/z calcd. for $C_{25}H_{22}NOS$, 384.1422 (M-1); found 384.1412 $(M-1)^+$.

trans-(±)-1,2,3,5,6,10b-Hexahydro-6-[(4-benzoylthio)phenyl]pyrrolo[2,1-_a_]isoquinoline·D-tartrate salt [(±)-6]

A solution of the free base (±)-**5** (125 mg, 0.32 mmol) in acetone (2 mL) was mixed with D-tartaric acid (73 mg, 0.49 mmol) in water (1 mL). The combined solution was agitated and then

kept at room temperature for several days. The resulting precipitates were collected, washed successively with water, acetone and ether, and dried *in vacuo* to give 163 mg of (±)-**6** as a white solid, mp 173-175 °C (dec.). ^{1}H NMR (DMSO-d_6/$CDCl_3$): δ 7.97 (d, 2H, J = 8.0 Hz), 7.72 (t, 1H, J = 7.4 Hz), 7.59 (t, 2H, J = 7.4 Hz), 7.50-7.32 (m, 4H), 7.28-7.08 (m, 3H), 6.85 (d, 1H, J = 7.6 Hz), 4.34 (t, 1H, J = 4.7 Hz), 4.22 (s, 2H), 3.68 (m, 1H), 3.20 (dd, 1H, J = 11.4, 5.2 Hz), 3.07 (m, 1H), 2.75 (m, 1H), 2.48 (m, 1H), 2.10-1.75 (m, 3H).

trans-(+)-1,2,3,5,6,10b-Hexahydro-6-[(4-benzoylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline [(+)-5] and the L-tartrate salt [(+)-6]

Following the procedure for the synthesis of (±)-**5**, compound (+)-**5** was prepared in 80% yield as a colorless thick oil, $[\alpha]_D$ +108.6° (c 0.86, $CHCl_3$), which was converted to the L-tartrate salt (+)-**6** and crystallized from acetone/water as white solid, mp 104-106 °C. Compound (+)-**5** was obtained in >98% ee, as determined by chiral HPLC analysis (k′ 1.8 for (+)-**5** using a Chiralcel OD-H column eluted with hexane/CH_3CN/EtOH/DEA 97.8/1.0/1.0/0.2).

trans-(-)-1,2,3,5,6,10b-Hexahydro-6-[(4-benzoylthio)phenyl]pyrrolo[2,1-*a*]isoquinoline [(-)-5] and the D-tartrate salt [(-)-6]

Compound (-)-**5** was prepared in 79% yield as a colorless thick oil, $[\alpha]_D$ -110.7° (c 1.04, $CHCl_3$), which was converted to the D-tartrate salt (-)-**6** and crystallized from acetone/water as a white solid, mp 104-105 °C. Compound (-)-**5** was obtained in > 98% ee, as determined by chiral HPLC analysis (k′ 2.3 using a Chiralcel OD-H column eluted with conditions as given for (+)-**5**).

Stability of the tartrate salt precursors (+)-6 and (-)-6

The tartrate salts, (+)-**6** and (-)-**6**, were stored at -10 °C and stability determinations were performed using chiral and reverse phase HPLC and NMR analyses. Chiral HPLC conditions utilized for the stability measurements were identical to those given above for (+)-**5** and (-)-**5** and reverse phase separations were performed using a Prodigy ODS(3) analytical HPLC column (k′ = 15.4) eluted with 70/30 acetonitrile/aqueous buffer (v/v, 0.2% TEA/phosphoric acid, pH 7.3). No detectable degradation of the precursors (<2%) was observed for storage times >9 months.

Synthesis of (+)-McN 5652 [(+)-1]

A solution of the tartrate (+)-**6** (3.0 mg, 5.6 μmol, ee >98%) in DMF (900 μL) was treated with potassium hydroxide (12 μL, 5 M, 60 μmol) with stirring at 40 °C for 5 min. The mixture was cooled to -10 °C and methyl iodide (7.0 μl, 1 M in DMF, 7.0 μmol) was added. The cooling bath was removed and reaction mixture was heated at 40 °C for 15 min, and the reaction was quenched by the addition of aqueous buffer (pH 7.3). Reverse phase HPLC indicated a product with chromatographic properties identical to those of authentic (+)-McN 5652 [k′ 4.7 on Symmetry C18 eluted with acetonitrile/aqueous buffer 70/30 (v/v, 0.2% TEA/phosphoric acid, pH 7.3); k′ 6.4 on Prodigy ODS(3) eluted with acetonitrile/aqueous buffer 70/30 (v/v, 0.2% TEA/phosphoric acid, pH 7.3); UV 254 nm]. Absence of detectable amounts of the *cis* isomer [termed McN 5655 (9)] in the reaction mixture indicated >98% diastereomeric excess (de) for (+)-**1** [k′ 5.3 for (±)-McN 5655 using Prodigy ODS(3) eluted with acetonitrile/aqueous buffer 70/30 (v/v, 0.2% TEA/phosphoric

acid, pH 7.3)]. Compound (+)-**1** was also obtained in >98% ee and demonstrated properties identical to those of authentic (+)-McN 5652 upon chiral HPLC analysis (k′ 1.3 using Chiralcel OD-H eluted with hexane/*i*-PrOH/DEA 99.3/0.5/0.2). Compound (+)-**1** was obtained in 23% chemical yield at 15 min, as determined by reverse phase HPLC analysis of the reaction products.

Synthesis of (-)-McN 5652 [(-)-1]

Following the procedures described above for the synthesis of (+)-**1**, compound (-)-**1** was prepared from (-)-**6** (3.0 mg, 5.6 μmol, ee >98%) in >98% de and ee, as determined by reverse phase and chiral HPLC analyses using the conditions described above for (+)-**1**. Compound (-)-**1** displayed chromatographic properties identical to those of authentic (-)-McN 5652 (k′ 4.7 on Symmetry C18; k′ 6.4 on Prodigy ODS(3); and k′ 2.0 on Chiralcel OD-H). The chemical yield of (-)-**1** was 24% at 15 min, as determined by reverse phase HPLC analysis of the reaction products.

Radiosynthesis of [^{11}C](+)-McN 5652 ([^{11}C](+)-1) and [^{11}C](-)-McN 5652 ([^{11}C](-)-1)

Approximately 1 mg of (+)-**6** or (-)-**6** was added to DMF (300 μL) and KOH (4 μL, 5 M) in a 1 mL V-vial fitted with a teflon-lined septum, and the mixture was heated at 40 °C for 5 min and then cooled to -10 °C. High specific activity [^{11}C]CH_3I was produced on-line (10) and condensed from a carrier nitrogen gas stream in the reaction V-vial. The V-vial was heated at 40 °C for 2 min, and the crude mixture was separated using semi-preparative HPLC [k ' 6.6 on Prodigy ODS-Prep, 60/40 acetonitrile/aqueous buffer (v/v, 0.2% TEA/phosphoric acid, pH 7.3)]. The eluent fraction containing either [^{11}C](+)-**1** or [^{11}C](-)-**1** was collected, and the product was concentrated on a Waters C8 SepPak Plus cartridge, which was subsequently eluted with 1 mL of 100% ethanol. This solution was passed through a 0.22 μm syringe filter and placed in 9 mL of 0.9% NaCl in a sealed sterile vial. The time required for the radiosynthesis of [^{11}C](+)-**1** or [^{11}C](-)-**1** was approximately 25 min from the end of bombardment (EOB). The chemical and radiochemical purities of [^{11}C](+)-**1** and [^{11}C](-)-**1** were ≥ 95%, as determined by analytical HPLC [k′ 6.4 on a Prodigy ODS(3) column eluted with 70/30 acetonitrile/aqueous buffer (v/v, 0.2% TEA/phosphoric acid, pH 7.3)]. Chiral HPLC analysis (Chiralcel OD-H eluted with hexane/*i*-PrOH/DEA 99.3/0.5/0.2) demonstrated that the k′ values of compounds [^{11}C](+)-**1** and [^{11}C](-)-**1** were identical to those of authentic (+)-McN 5652 and (-)-McN 5652 (k′ 1.3 and 2.0, respectively). In addition, reverse phase and chiral HPLC analyses indicated that compounds [^{11}C](+)-**1** and [^{11}C](-)-**1** were obtained in > 98% de and ee. The isolated radiochemical yields achieved at EOB and the final product specific activities and yields obtained at EOS are summarized in the table below (n = 6 for each).

Radiochemical Yields, Product Specific Activities, and Product Yields of [^{11}C](+)-McN 5652 and [^{11}C](-)-McN 5652

Product	Radiochemical Yield (at EOB) (% of [^{11}C]CH_3I incorporated)	Product Specific Activity (Ci/mmol at EOS)	Product Yield (mCi at EOS)
[^{11}C](+)-**1**	29.0 ± 3.0	3840 ± 1170	131 ± 14
[^{11}C](-)-**1**	29.6 ± 7.3	4720 ± 1410	123 ± 30

Acknowledgments

The authors thank S. Kendro, J. Perevuznik, D. Holt, and B. Mui for experimental assistance. This work was supported by grants from the National Institutes of Health (NS-22899, MH-52247, and MH-49815).

References

1. Szabo Z., Kao P.F., Scheffel U., Suehiro M., Mathews W.B., Ravert H.T., Musachio J.L., Marenco S., Kim S.E., Ricaurte G.A., Wong D.F., Wagner H.N. Jr., and Dannals R.F. - Synapse 20:37 (1995)
2. Suehiro M., Ravert H.T., Dannals R.F., Scheffel U., and Wagner H.N. Jr. - J. Label. Compd. Radiopharm. 31:841 (1992)
3. Suehiro M., Musachio J.L., Dannals R.F., Mathews W.B., Ravert H.T., Scheffel U., and Wagner H.N. Jr. - Nucl. Med. Biol. 22:543 (1995)
4. Rane A.M., Miranda E.I., and Soderquist J.A. - Tetrahedron Lett. 35:3225 (1994)
5. Sorgi K.L., Maryanoff C.A., McComsey D.F., Graden D.W., and Maryanoff B.E. - J. Am. Chem. Soc. 112:3567 (1990)
6. Maryanoff C.A., McComsey D.F., Gardocki J.F., Shank R.P., Costanzo M.J., Nortey S.O., Schneider C.R., and Setler P.E. - J. Med. Chem. 30:1433 (1987)
7. Maryanoff C.A. and McComsey D.F. - J. Heterocyclic Chem. 22:911 (1988)
8. Miranda E.I., Diaz M.J., Rosado I., and Soderquist J.A. - Tetrahedron Lett. 35:3221 (1994)
9. Shank R.P., Vaught J.L., Pelley K.A., Setler P.E., McComsey D.F., and Maryanoff B.E. - J. Pharmacol. Exp. Ther. 247:1032 (1988)
10. Dannals R.F., Ravert H.T., Wilson A.A., Wagner H.N. Jr. - Int. J. Appl. Radiat. Isot. 37:433 (1986)

