AN ASYMMETRIC SYNTHESIS OF (*R*)-5-(METHYLAMINO)-5,6-DIHYDRO-4*H*-IMIDAZO-[4,5,1-*ij*]QUINOLIN-2(1*H*)-ONE (1) AND ITS [2-^{14}C]- AND [6,7-$^{3}H_2$]-LABELED FORMS.

Richard F. Heier,[†] Malcolm W. Moon,[†] Wayne T. Stolle,[‡] John A. Easter[‡] and Richard S. P. Hsi.[‡*]

Departments of Structural, Analytical and Medicinal Chemistry[†] and Drug Metabolism Research,[‡] Pharmacia and Upjohn, Inc., Kalamazoo, MI 49001.

SUMMARY

(*R*)-5-(Methylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one (**1**) is a dopamine agonist which shows selectivity for the D2 receptor subtype, and is of interest as a potential drug for the treatment of Parkinson's disease. An asymmetric epoxidation approach has been used to prepare **1** in eleven steps (15% overall yield) from 8-nitroquinoline. An advanced intermediate in this synthesis, *tert*-butyl (*R*)-methyl(8-amino-1,2,3,4-tetrahydro-3-quinolinyl)carbamate (**10**), has been reacted with [^{14}C]phosgene to provide a two-step synthesis of **1** labeled with carbon-14 at the C-2 position (236 μCi/mg). Bromination of **1** gave the dibromo analogue **12b** which was reduced in the presence of tritium gas to give **1** labeled with tritium at the C-6 and C-7 positions (28.5 Ci/mmol). In addition to providing syntheses for labeled forms of the drug which are useful in drug disposition and receptor binding studies, this approach also provides a convenient synthesis for the unlabeled form of drug.

Key words: asymmetric synthesis, imidazoquinolinone, D2 dopamine agonist, tritium, carbon-14, radioligand.

INTRODUCTION

We have previously reported the preparation of a series of imidazoquinolinones and related heterocyclic amines which are potent dopamine agonists.[1,2] We have recently found that imidazoquinolinone **1** also shows good biological activity.[3] This compound differs from previously reported analogues and other literature dopamine agonists as it is selective for the dopamine D2 receptor subtype, showing low activity at other dopaminergic (D1, D3 and D4) receptors.[3] The compound may find use in the treatment of Parkinson's disease. To further the development of this compound, an improved procedure for its synthesis was required, and

*Author to whom correspondence should be addressed.

CCC 0362–4803/96/121087–12

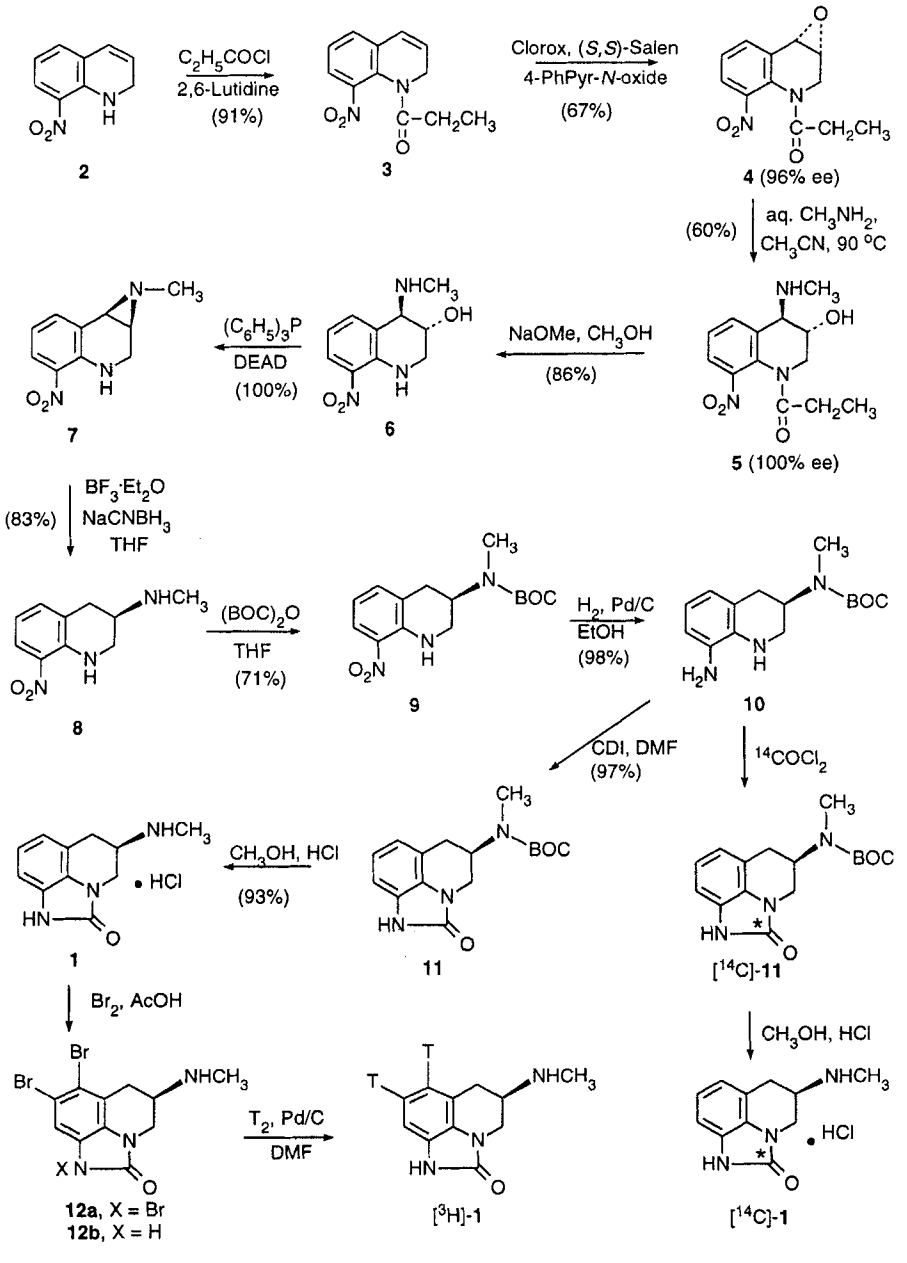
Received 14 May 1996
Revised 17 July 1996

radiolabeled forms of the drug were needed. This report describes an efficient synthesis of **1** from 8-nitroquinoline, the preparation of the carbon-14 labeled drug which is useful for drug disposition studies, and the preparation of a high specific activity tritium-labeled form useful for receptor binding studies.

RESULTS AND DISCUSSION

The procedure for preparing compound **1** is shown in Scheme 1. Sodium borohydride reduction of 8-nitroquinoline in acetic acid afforded the dihydroquinoline **2** in 94% yield[4] Attempts to epoxidize this somewhat unstable, crystalline solid with a variety of reagents gave 8-nitroquinoline as the only product, and it was necessary to derivatize the compound before epoxidation. The compound was refluxed with propionyl chloride in the presence of 1.2 equiv of 2,6-lutidine to scavenge hydrogen chloride generated in the reaction to give **3**. Asymmetric epoxidation of **3** with sodium hypochlorite (Clorox®) as the oxidant, (*S,S*)-(+)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride as the chiral catalyst and with 4-phenylpyridine-*N*-oxide as a co-catalyst[5] afforded a good yield of **4** (67% with 96% ee); we were unable to crystallize the product to optical purity at this stage.[6,8] When the epoxide was reacted with methylamine in aqueous acetonitrile at 90 °C for 2 h, **5** was obtained as the major product (79%), and this was recrystallized to remove the minor enantiomer and other impurities.[9] Compound **5** was hydrolyzed with excess aqueous methanolic sodium hydroxide solution to give the non-crystalline amino alcohol **6**. This was reacted with triphenylphosphine/diethyl azodicarboxylate (DEAD)[10] to give the aziridine **7**. While this compound had good stability in the reaction solution, it was too reactive to be isolated and decomposed on attempted silica gel chromatography or in water in the presence of acids.[11] It was therefor reduced directly with boron trifluoride etherate and sodium cyanoborohydride to give the amine **8**. This was separated from neutral, triphenylphosphine/DEAD-derived byproducts either by extraction into hydrochloric acid or by chromatographing the crude product on silica gel. Compound **8** was converted to the BOC-derivative **9** by reaction with di-*tert*-butyl dicarbonate and this was reduced to **10**. Cyclization of **10** with 1,1'-carbonyldiimidazole (CDI) afforded **11** which was deprotected by

Scheme 1. Synthesis of 1 and its Carbon-14 and Tritium Labelled Forms.[a]



[a] * is ^{14}C, T is ^{3}H

heating in methanolic hydrogen chloride to give the hydrochloride salt of **1** in 15% overall yield from 8-nitroquinoline.

For the preparation of [^{14}C]-labeled drug, compound **10** was reacted with [^{14}C]phosgene[12] (Scheme 1) to give [^{14}C]**11** which was deprotected with methanolic hydrogen chloride to give [^{14}C]**1** as the hydrochloride salt with a specific activity (SA) of 236 μCi/mg (44.3 mCi/mmol) and a radiochemical purity (RCP) of >98%. This product was also converted by ion exchange chromatography to the free base and then into the maleate salt, the preferred pharmaceutical form of this drug.

To provide high specific activity radiolabeled drug for conducting receptor binding studies, we prepared the tritium labeled compound. Bromination of **1** in acetic acid with excess bromine afforded an unstable solid, tentatively assigned structure **12a**, which upon refluxing in methanol and treatment with sodium bisulfite gave the stable dibromo analogue **12b**. This was reduced with carrier-free tritium gas[13] at room temperature in dimethylformamide with 3 eq triethylamine in the presence of 10% Pd/C catalyst to give [^{3}H]**1** labeled with tritium at the C-6 and C-7 positions. The product was purified by preparative reverse-phase HPLC to give the tritium-labelled drug (140.3 mCi/mg, 28.5 Ci/mmol) with a radiochemical purity of 98.3%.

In summary, we have developed an asymmetric synthesis for the dopamine D2-selective agonist **1** and applied this route to the synthesis of carbon-14 and tritium labeled forms of the drug. In additon to providing a convenient route to the unlabeled compound, this work provides labeled forms which are useful in drug development and mode of action studies.

EXPERIMENTAL

General Methods

Thin layer chromatographic (TLC) analysis was done on 2.5 x 10 cm glass plates precoated with a 250 μm layer of silica gel GF (Analtec) with mixtures of ethyl acetate/hexane (E/H) or methanol/chloroform (M/C) being used to develop the plates. Developed zones were visualized by UV light or by using iodine. Radioactive zones were detected with a Bioscan System 200 Imaging Scanner. For non-labeled synthetic work, HPLC data were obtained with a set-up consisting of two Waters 6000A pumps, a Waters 660 gradient programmer, a

Waters 486 variable wavelength UV detector set at 215 nM, a Hewlett-Packard 3390A recorder and a Waters C18 reverse-phase column (25 cm x 0.45 cm i.d.). Aqueous buffer was prepared by adding 5.22 g of sodium dihydrogen phosphate and 0.76 mL of 85% phosphoric acid to water (4 L). A linear, 15 min, solvent program from 10% acetonitrile/aqueous buffer to 85% acetonitrile/aqueous buffer and a flow rate of 2.0 mL/min was used for all analyses. Chiral HPLC data were obtained with Beckman Instruments equipment (Beckman 112 solvent delivery module, 165 model UV detector set at 215 nM, 340 model integrator, and 421 model controller), with Regis Whelk-O or Chiral Technologies Chiralcel OD and OJ columns (25 cm x 0.4 cm id), with isopropanol/hexane mixtures as the mobile phase and a flow rate of 1.0 mL/min. Radioactive determinations were carried out with a Pharmacia Wallac 1410 Liquid Scintillation counter using the external standard method with Ultima Gold (Packard) as the scintillation cocktail. In the radiolabeled work, HPLC analyses were carried out with a Spectra Physics model 8700 Solvent Delivery System. The eluate was analyzed with a LCD/Milton Roy SpectroMonitor D variable wavelength UV detector set at 254 nm and, where appropriate, a Radiomatic Model Flo-One Beta A280 radiodetector in series with the UV detector. ^{3}H-NMR spectra were obtained using an IBM 300 MHz instrument at 300 MHz in methanol-d_4. Elemental analyses were obtained through the Structural, Analytical and Medicinal Chemistry Department of Pharmacia and Upjohn, Inc.

1,2-Dihydro-8-nitro-1-propionylquinoline (3).

2,6-Lutidine (134 g, 1.25 mol) was added dropwise over 5 min to a stirred solution of **2**[4] (176 g, 1.0 mol) in propionyl chloride (1.7 L), during which time a precipitate of the lutidine/propionyl chloride complex separated from the reaction solution. The mixture was heated under reflux for 1 h, and the precipitate of 2,6-lutidine hydrochloride was then filtered off and washed with propionyl chloride. The propionyl chloride filtrate was evaporated to afford a solid. This was dissolved in methanol (200 mL) and triethylamine (30 g) was added to destroy residual propionyl chloride. After 15 min, the solvents were removed and the residue was partitioned between methylene chloride (400 mL) and water (300 mL). The aqueous phase was re-extracted with methylene chloride (100 mL), and the combined organic extracts were evaporated. The residual solid was dissolved in hot ethyl acetate (500 mL), hexane (300 mL) was added, and the solution was cooled and filtered to afford 210.2 g (91%)

of product, mp 75-79 °C. HPLC Rt = 8.71 min; TLC Rf = 0.64 (50% E/H). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.99; H, 5.20; N, 12.06.

(1a*R*)-1a,2,3,7b-Tetrahydro-4-nitro-3-propionyloxireno[*c*]quinoline (4).

Compound **3** (21.6 g, 93 mmol), (*S,S*)-(+)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride [(*S,S*-Salen, 1.36 g, 2.0 mmol] and 4-phenylpyridine-*N*-oxide (4.28 g, 25 mmol) were dissolved in methylene chloride (100 mL). A mixture of Clorox (125 mL) and 0.05 M sodium hydrogen phosphate (50 mL, buffered to pH 10.5 by addition of 1 N sodium hydroxide solution) was added and the 2-phase system was stirred at 20 °C until reaction was complete (2 h). Additional methylene chloride was added and the solution was filtered to remove insoluble material. The aqueous phase was re-extracted with methylene chloride and the combined organic phases were evaporated to afford 25.7 g of crude product. This was chromatographed on silica gel with 20% ethyl acetate/hexane as the initial eluant to give 15.4 g (67%, 96% ee) of product. A sample was crystallized twice from ethyl acetate/hexane for analysis; mp 116-118 °C. HPLC Rt = 7.80 min (4-phenylpyridine-*N*-oxide Rt = 7.06 min); chiral HPLC [(*R,R*)-Whelk-O column, 50% isopropanol/hexane] Rt = 20.0 min (96.7%, 94% ee) and 50.8 min (3.3%). Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.95; H, 4.83; N, 11.35. $[\alpha]_D$ (MeOH, c = 1.0) + 627 °.

(3*R-trans*)-1,2,3,4-Tetrahydro-4-(methylamino)-8-nitro-1-propionyl-3-quinolinol (5)

A solution of **4** (20.0 g, 80.3 mmol) in acetonitrile (200 mL) and 40% aqueous methylamine (20 mL) was stirred in a Paar bomb at 95 °C for 120 min. After cooling, the solvent was evaporated, methanol (50 mL) was added, and the precipitate of **5** (13.3 g, 60%) was filtered off. It was recrystallized from methanol (130 mL) to give 12.2 g of product, mp 155-157 °C. HPLC Rt = 4.6 min. Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.04. Found: C, 55.80; H, 6.19; N, 14.87. $[\alpha]_D$ (MeOH, c = 1.0) + 108 °.

To determine optical purity, the product (50 mg) was derivatized with propionic anhydride (0.5 mL)/pyridine (0.1 mL) at 140 °C for 30 min to give the dipropionyl derivative of **5**. After removal of volatile materials, the crude product was analyzed on a Chiralcel OJ column (50% isopropanol/hexane as the mobile phase) and showed a single peak at 13.5 min (enantiomer has a Rt of 9.5 min).

(3*R-trans*)-1,2,3,4-Tetrahydro-4-(methylamino)-8-nitro-3-quinolinol (6).

A mixture of sodium methoxide in methanol (100 mL of 25%) and **5** (55.8 g, 0.20 mol) in methanol (500 mL) was heated under reflux for 1 h. The solvent was evaporated, the excess base was neutralized by addition of 4 N hydrochloric acid, and the product was extracted into ethyl acetate. The product was chromatographed on silica gel with 1% methanol/chloroform as the initial eluant to give 4.5 g of 1,2,3,4-tetrahydro-4-(propionylamino)-8-nitro-3-quinolinol. Continued elution of the column with 10-15% methanol/chloroform gave 38.5 g (86%) of **6** as an oil; HPLC Rt = 2.4 min. An aliquot (1.1 g) was dissolved in methanol and excess methanolic hydrogen chloride was added to afford the hydrochloride salt (1.1 g), mp 247 °C (dec). Anal. Calcd for $C_{10}H_{13}N_3O_3$ HCl: C, 46.25; H, 5.43; Cl, 13.66; N, 16.18. Found: C, 46.01; H, 5.45; Cl, 13.32; N 15.90. $[\alpha]_D$ (H_2O, c = 1.0) - 189°.

(*R*)-*N*-Methyl-1,2,3,4-tetrahydro-8-nitro-3-quinolinamine (8).

Diethyl azodicarboxylate (5.2 g, 30 mmol) was added to a stirred solution of **6** (4.46 g, 20 mmol) and triphenylphosphine (7.86 g, 30 mmol) in anhydrous THF (40 mL) at 10 °C. TLC in 5% methanol/chloroform after 45 min indicated complete conversion of **6** (Rf = 0.32) into the aziridine **7** (Rf = 0.74). Boron trifluoride etherate (4.2 g, 30 mmol) and additional THF (40 mL) were added. The reaction was stirred for 15 min and sodium cyanoborohydride (5.0 g, 80 mmol) was added over a period of 5 min. After 30 min, solvents were removed to give an oil which contained **8** (HPLC Rt = 4.52 min) and its cyanoborane adduct (HPLC Rt = 9.8 min). This was dissolved in ethyl acetate (200 mL), cooled and stirred while sodium hydroxide solution (40 mL of 5 N) was slowly added to destroy residual boron trifluoride etherate. The phases were separated and the aqueous phase was further extracted with ethyl acetate (2 x 100 mL). Evaporation of the organic extracts gave an oil which was dissolved in methanol (100 mL) and 4 N sodium hydroxide solution (15 mL) was added. The resulting solution was refluxed for 1 h to destroy the cyanoborane adduct of **8**, evaporated, and the residue was partitioned between ethyl acetate and water. The crude product obtained on evaporation of the ethyl acetate was chromatographed on silica gel with chloroform as the initial eluant to give 3.42 g (83%) of **8** as an oil. ^{1}H NMR ($CDCl_3$) δ 1.27 (br s, 1 H), 2.53 (s, 3 H), 2.74 (dd, 1 H), 3.06 (m, 2 H), 3.34 (m, 1 H), 3.62 (m, 1 H), 6.53 (dd, 1 H), 7.15 (dd, 1 H), 7.99 (dd, 1 H) and 8.24 (br s, 1 H).

***tert*-Butyl (*R*)-Methyl(1,2,3,4-tetrahydro-8-nitro-3-quinolinyl)carbamate (9).**

Di-*tert*-butyl dicarbonate (24.0 g, 110 mol) was added to **8** (18.9 g, 91 mmol) in THF (300 mL). The solution was stirred at room temperature for 20 min and was then evaporated and the product was chromatographed on silica gel with 10% ethyl acetate/hexane as the initial eluant to give 22.0 g of product. This was crystallized from ethyl acetate to give 19.9 g (71%) of **9**, mp 81-83 °C. $[\alpha]_D$ (c = 1.0, MeOH) -40.5°. Chiral HPLC (Chiralcel OJ column, 50% isopropanol/hexane) Rt = 11.5 min (100%; enantiomer has Rt of 9.5 min) Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.51; H, 6.89; N, 13.70.

***tert*-Butyl (*R*)-Methyl(8-amino-1,2,3,4-tetrahydro-3-quinolinyl)carbamate (10).**

A suspension of **9** (16.0 g, 52 mmol) and 10% palladium on charcoal (1.4 g) in ethanol (200 mL) was hydrogenated (50 psi hydrogen pressure) for 1 h. The catalyst was filtered off and the solvent evaporated to give 14.2 g (98%) of **10**. A saple of the solid was recrystallized from ethyl acetate/hexane for analysis; mp 139-141 °C. $[\alpha]_D$ (c =1.0, MeOH) -39.8°. HPLC Rt = 8.23 min; chiral HPLC (Chiralcel OD, 50% isopropanol/hexane) Rt = 18.4 min (enantiomer has Rt of 10.6 min). Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.95; H, 8.36; N, 15.15. Found: C, 64.79; H, 8.26; N, 14.94.

***tert*-Butyl (*R*)-Methyl(1,2,5,6-tetrahydro-2-oxo-4*H*-imidazo[4,5,1-*ij*]quinolin-5-yl)-carbamate (11).**

Carbonyldiimidazole (9.5 g, 58.6 mmol) was added to a stirred solution of **10** (14.7 g, 53 mmol) in DMF (75 mL) at 0 °C. The solution was allowed to warm to room temperature and was then heated at 90 °C for 20 min. The stirred solution was diluted with water (200 mL), the precipitate was filtered off, washed with water and air dried to give 15.7 g (97%) of **11**; TLC Rf = 0.15 (50% E/H); HPLC Rt = 9.17 min (100%); chiral HPLC (*R,R*-Whelk-O column, 50% isopropanol/hexane) Rt = 13.0 min (enantiomer has Rt of 8.2 min). A sample was recrystallized from ethyl acetate for analysis; mp 205-207 °C. $[\alpha]_D$ (c = 1.0, MeOH) +52.9°; Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.40; H, 6.96; N, 13.84.

(*R*)-5-(Methylamino)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one Hydrochloride (1).

A suspension of **11** (10.0 g, 33 mmol) in methanolic hydrogen chloride (150 mL of 5 N)

was stirred at 60 °C for 30 min. The starting material had all dissolved within 10 min, and after 25 min the product started to precipitate. After cooling to -10 °C, the precipitate was filtered off, washed with methanol/ether and dried to give 7.3 g (93%) of the hydrochloride salt of **1**, mp 308 °C (dec). $[\alpha]_D$ (c = 1.0, MeOH) -35.1°. Anal. Calcd for $C_{11}H_{13}N_3O$ HCl: C, 55.12; H, 5.89; Cl, 14.79; N, 17.53. Found: C, 55.13; H, 5.91; Cl, 14.48; N, 17.61. HPLC Rt = 2.70 min; TLC Rf = 0.32 (10% M/C); ^{1}H NMR (D_2O) δ 2.75 (s, 3 H), 3.15 (dd, *J* = 4.3, 17.2 Hz, 1 H), 3.15 (dd, *J* = 3.9, 17.2 Hz, 1 H), 3.93 (dd, *J* = 3.2, 13.6 Hz, 1 H), 4.03 (m, 1 H), 4.16 (dd, *J* = 3.6, 13.6 Hz, 1 H) and 6.95-7.10 (m, 3 H).

***tert*-Butyl (*R*)-Methyl(1,2,5,6-tetrahydro-2-oxo-4*H*-[2-^{14}C]imidazo[4,5,1-*ij*]quinolin-5-yl)-carbamate ([^{14}C]11).**

[^{14}C]Phosgene (0.86 mmol of 58 mCi/mmol) in toluene (5 mL)[12] was added dropwise over 5 min to a stirred solution of **10** (277 mg, 1.0 mmol) and triethylamine (2.0 mL of 1.0 M in THF) in THF (18 mL). After 3.5 h at room temperature, the solvents were evaporated and the residue was dissolved in 1% methanol/ methylene chloride (4 mL) and chromatographed on silica gel (60 g). Elution of the column with 2 % methanol/ methylene chloride gave 222 mg of pure product, identical to the unlabeled product **11** by TLC, which was used without further purification in the next step.

(*R*)-5-(Methylamino)-5,6-dihydro-4*H*-[2-^{14}C]imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one, Hydrochloride Salt ([^{14}C]1).

The above compound was dissolved in methanol (3 mL), saturated methanolic hydrogen chloride (2 ml) was added and the solution was stirred at 70 °C under reflux. A precipitate began to form after 10 min. Heating was continued for 3.5 h and the solution was then cooled to -10 °C and filtered to give 123 mg of [^{14}C]**1** with SA of 236 μCi/mg (58% RCY from [^{14}C]phosgene, 98.6% RCP by HPLC analysis and 98.2% RCP by TLC analysis).

(*R*)-5-(Methylamino)-5,6-dihydro-4*H*-[2-^{14}C]imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one, Maleate Salt ([^{14}C]1).

The above product was dissolved in water (2 mL) and was passed through a 5 mL SAX ion exchange resin (hydroxide form) cartridge (Worldwide Monitoring). The column was washed with 25 mL of water and the eluate was lyophilized. The resulting free base was dissolved in methanol (2 mL), filtered and maleic acid in methanol (0.4 mL of 1 M) was

added. The solution was cooled to 0 °C, ether (10 mL) was added and the precipitate was filtered off to give 89 mg of the maleate salt of [^{14}C]**1** with SA 138.8 μCi/mg (99% RCP by HPLC and TLC analyses).

(*R*)-7,8-Dibromo-5,6-dihydro-5-(methylamino)-4*H*-imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one [(*R*)-12b].

Bromine (2.8 g, 17.5 mmol) was added to a stirred solution of **1** (1.0 g, 5.0 mmol) in acetic acid. The solution was stirred at room temperature for 20 min and was then heated at 50 °C for 30 min. The solution was cooled and the solid product was filtered to give 2.59 g of solid which, by reason of its instability in methanol and in presence of base, appeared to contain active bromine species such as **12a**. The bulk of the solid (2.0 g) was refluxed in methanol (100 mL) for 30 min and the red-colored methanol solution was evaporated under reduced pressure. The residue was dissolved in methanol and reevaporated; this procedure was repeated twice more until the distillate was colorless. The product was dissolved in methanol (20 mL), sodium bisulfite (0.4 g) in water (5.0 mL) was added followed by sodium hydroxide solution (5.0 mL of 4 N). Chloroform (100 mL) was added and, after vigorous shaking, the two-phase solution was filtered, the solid was washed with water and air dried to afford 1.1 g of crude product as a white solid. This was dissolved in methanol/chloroform and was chromatographed on silica gel with 2% methanol/chloroform as the eluant to give 820 mg of material which was crystallized from ethyl acetate (100 mL) to give 610 mg of **12b**, mp 218-220 °C. HPLC Rt = 6.6 min (>99%). Anal. Calcd for $C_{11}H_{11}Br_2N_3O$: C, 36.59; H, 3.07; Br, 44.27; N, 11.64. Found: C, 36.62; H, 3.03; Br, 44.11; N, 11.56. $[\alpha]_D$ (MeOH, c = 1.0) + 3.1 °.

(*R*)-5,6-dihydro-5-(methylamino)-4*H*-[6,7-$^3H_2$]imidazo[4,5,1-*ij*]quinolin-2(1*H*)-one ([^{3}H]1).

A solution of **12b** (36.8 mg, 0.1 mmol) in 1.0 M triethylamine in DMF (0.5 mL) was reduced at room temperature with carrier-free tritium gas (initial pressure 710 mm Hg) in the presence of 10% Pd/C catalyst (10 mg).[13] Uptake of tritium ceased at 30 min, and the reaction was stopped after 2.5 h. The solution was evaporated, methanol (1 mL) was added and the solution was evaporated under vacuum. The methanol addition was repeated twice to remove exchangeable tritium, the product was dissolved in methanol and filtered through a Supelclean silica gel Sep-Pak attached to a Gelman Acrodisc (0.45μm) filter to remove the

catalyst. The solution was evaporated to give 3.92 Ci of crude [^{3}H]**1** which was dissolved in methanol (3.0 mL). An aliquot of this solution (1.0 mL) was divided into four portions and was purified on a Phenomenex Ultramex 5μm C-18 column (250 mm x 4.6 mm ID) eluted with a mobile phase of 480:520:5 v/v methanol/water/triethylamine pumped isocratically at 1.0 mL/min with UV detection at 254 nm. The peak at 4-5 min was collected from each application, pooled and lyophilized to give 516 mCi of product with good RCP (93.6%). This product was again purified by preparative HPLC on a Phenomenex Ultramex 5μm C-18 column (250 mm x 21.5 mm ID) with the mobile phase used previously (20 mL/min flow rate with UV detection at 282 nm). The peak at 5.8-8 min was collected and lyophilized to give 215.5 mCi of [^{3}H]**1** which was stored as a solution of 2.07 mCi/mL in methanol (SA 140.3 mCi/mg; 98.3% RCP by HPLC analysis and 97.3% RCP by TLC analysis). ^{3}H-NMR analysis of the product showed tritium labels at the expected adjacent ring positions C-7 [δ 6.93 (d, $^3J_{T\text{-}T}$ = 8.6 Hz); 6.94 (s)] and C-8 [δ 7.026 (s); 7.027 (d, $^3J_{T\text{-}T}$ = 8.6 Hz)].

REFERENCES

(1) Moon, M. W.; Morris, J. K.; Heier, R. F.; Hsi, R. S. P.; Manis, M. O.; Royer, M. E.; Walters, R. R.; Lawson, C. F.; Smith, M. W.; Lahti, R. A.; Piercey, M. F.; Sethy, V. H. *Drug Design and Discovery,* **1992**. *9*, 313-322.

(2). Moon M. W.; Hsi, R. S. P. *Journal of Labelled Compounds and Radiopharmaceuticals*, **1992**, *31*, 933-943.

(3) Heier, R. F.; Dolak, L. A.; Duncan, J, N.; Hyslop, D.K.; Lipton, M. J.; Martin, I. J.; Mauragis, M. A.; Piercey, M. F.; Smith, M. W.; Nichols, N. F.; Schreur, P. J. K. D.; Moon, M. W. *J. Med. Chem.,* submitted

(4) Rao, K. V.; Jackman, D. *J. Het. Chem.,* **1970**, *10*, 213-215.

(5) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima. I, Ed.; VCH Publishers, Inc., New York, NY (1993). pp 159-202.

(6) The racemic epoxide, prepared by reaction of **3** with acetonitrile/hydrogen peroxide in acetonitrile[7] has a higher melting point (153-156 °C) than the enantiomer. Crystallization of the chiral epoxide (96% ee) did not improve its optical purity.

(7) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.*, **1961**, *26*, 659-663.

(8) The enantiomeric series of compounds has also been prepared by the same procedure from **3** by using (*R,R*)-(+)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride as the catalyst; chiral HPLC retention times of the various intermediates are presented in the experimental section.

(9) Byproducts in the synthesis arise by intramolecular rearrangement of the propionyl group to the 3-hydroxy position [(3*R-trans*)-1,2,3,4-tetrahydro-*N*-methyl 8-nitro-3-(propionyloxy)-4-quinolinamine, 8%) and to the 4-methylamine position [(3*R-trans*)-1,2,3,4-tetrahydro-4-propionylamino-8-nitro-3-quinolinol, 3%); a small amount of the hydroysis product **6** is also formed in this reaction. Intramolecular rearrangement to the 4-position is also encountered in the base-induced hydrolysis of **5** (see experimental section).

(10) Pfister, J. R. *Synthesis*, **1984**, 969.

(11) Treatment of **7** in aqueous THF with 1.5 eq of perchloric acid immediately opened the aziridine ring giving a 1:2 mixture of amino alcohols [(3*S-cis*)- and (3*R-trans*)-1,2,3,4-tetrahydro-3-methylamino-8-nitro-4-quinolinol].

(12) Supplied by Amersham Corporation, Arlington Heights, IL (Lot No. CFQ 8282)

(13) Reduction was carried out at the National Tritium Labeling Facility (NTLF), Lawrence Berkeley Laboratory, University of California, Berkeley, CA.

ACKNOWLEDGEMENT

We are indebted to Mr Hiromi Morimoto of the NTLF for collaboration in carrying out the tritiation and to Dr Philip Williams of NTLF for providing the ^{3}H-NMR spectra.