Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **XLI**, 465-475 (1998)

SYNTHESIS OF (*S*)-1-(1H-INDOL-4-YLOXY)-3-[4-(3-METHOXYPHENYL)-4-HYDROXYPIPERIDIN-1-YL]-PROPAN-2-OL (LY333068) SUCCINATE, AND ITS 3-[^{14}C]-ISOTOPOMER BASED ON CHIRAL GLYCEROL-[^{14}C] DERIVATIVES†

Boris A. Czeskis

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285

SUMMARY

The 3-[^{14}C]-isotopomer of (*S*)-1-(1H-indol-4-yloxy)-3-[4-(3-methoxyphenyl)-4-hydroxypiperidin-1-yl]-propan-2-ol (LY333068), a 5HT$_{1A}$ antagonist, was prepared in 10 steps and 8.2% radiochemical yield from (*L*)-serine-[3-^{14}C]. Deamination, esterification, and protection of the resulting diol gave methyl (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate-[3-^{14}C], as a chiral and radiolabeled building block, which then was subsequently coupled with 4-hydroxyindole and 4-(3-methoxyphenyl)-4-hydroxypiperidine to give the titled product with 99.4% radiochemical purity.

Key words: 5HT$_{1A}$ antagonist, LY333068 succinate, carbon 14 labeled

INTRODUCTION

Over the past several years, due to extensive research into receptors influenced by the neurotransmitter 5-hydroxytryptamine (serotonin, 5-HT), several 5-HT receptor subtypes have been found.[1] Even within certain subtypes some receptors show preferential binding for various agonists and antagonists.[2] LY333068 succinate (**1a**) has been identified as a potent antagonist of 5-HT which acts specifically at the 5-HT$_{1A}$ receptor.[3] For the pre-clinical drug metabolism studies in laboratory animals radiolabeled material was needed. The established synthetic route for the preparation of **1a** offered no

CCC 0362–4803/98/060465–11$17.50

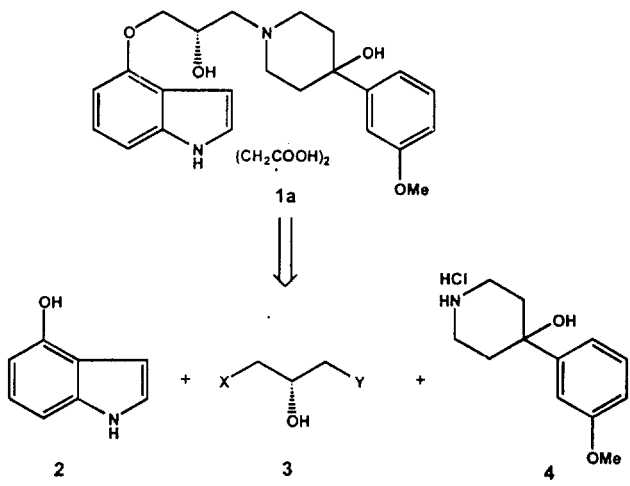
Received 24 July 1997
Accepted 19 January 1998

convenient steps for the introduction of the C-14 label, so an alternate method has been developed which converges with the established route in the penultimate step. We report herein this novel synthesis of the chiral compound **1a** and its corresponding [^{14}C]-isotopomer **1b**.

DISCUSSION

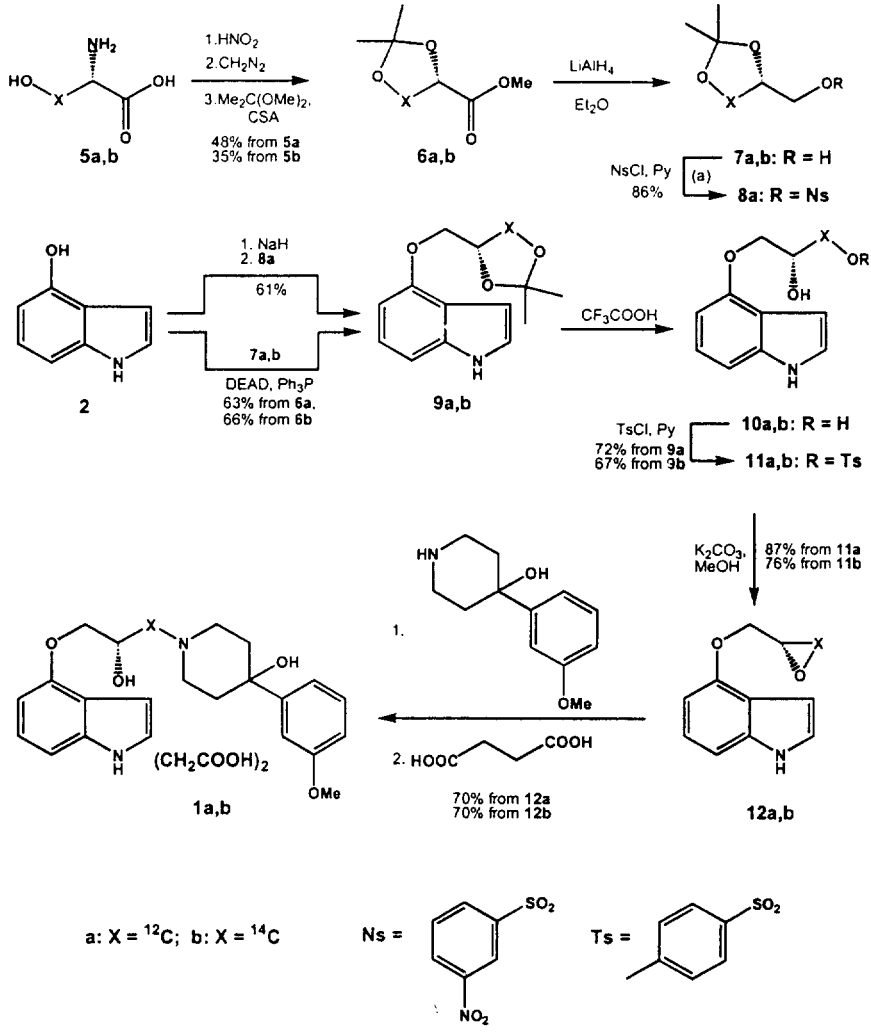
Retrosynthetic analysis of target molecule **1a** showed the possibility of its construction from three fragments **2-4** (Scheme 1). The key question was the preparation of the chiral building block **3**, suitable for the insertion of [^{14}C]-label. For this purpose we have chosen the optically active glycerol derivatives which are easily available and widely used in organic synthesis.[4]

Scheme 1



Thus (*S*)-acetonide **6a** was prepared starting from (*L*)-serine (**5a**) in three consecutive steps: deamination with retention of configuration using nitrous acid,[5-7] esterification of crude α-hydroxy acid with diazomethane,[8] and immediate protection of the resulted diol with 2,2-dimethoxypropane (Scheme 2). Attempts to use 2-methoxypropene for the protection,[5] or to protect the dihydroxyacid before esterification as well as esterification of the acid with trimethyl orthoformate[9] afforded lower yields of the desired products.

Scheme 2



Reduction of ester **6a** with lithium aluminum hydride gave glycerol acetonide **7a**, which then was coupled with 4-hydroxyindole **2** in two alternative ways. In the first case alcohol **7** was converted into corresponding nosylate **8a**, which was in turn reacted with phenolate, generated from **2** and sodium hydride.[10] Use of sodium methoxide or potassium carbonate[11] for deprotonation of 4-hydroxyindole resulted in a lower yield of coupling product. The second and more effective approach was based on direct Mitsunobu coupling of alcohol **7a** with phenol **2** in the presence of diethyl

azodicarboxylate (DEAD) and triphenylphosphine.[12] The order of addition of reagents appeared to be important in this case. The best result was achieved when triphenylphosphine and DEAD were reacted first to form a complex, followed by addition of a mixture of alcohol **7a** and hydroxyindole **2**.[13] The resultant acetonide **9a** was hydrolyzed using trifluoroacetic acid[14] to give diol **10a**, which upon reaction with one equivalent of *p*-toluenesulfonyl chloride in pyridine[15] selectively afforded the primary monotosylate **11a**. Its treatment with potassium carbonate in methanol[16] led to the (*S*)-epoxide **12a**, which after coupling with the amine free base, generated from hydrochloride **4**, furnished the desired chiral aminoalcohol LY333068, and, subsequently, its succinate **1a**. The product, obtained in 10 steps and 13.2% overall yield from (*L*)-serine (**5a**), had the same physico-chemical properties as an authentic sample.

The method described above was also used for the preparation of [^{14}C]-labeled compound **1b** with 99.4% radiochemical purity and a specific activity of 67.49 μCi/mg (34.76 mCi/mmol) from readily available (*L*)-serine-[3-^{14}C] (**5b**) in 8.2% chemical and radiochemical yields.

EXPERIMENTAL

The (*L*)-serine-3-[^{14}C] was purchased from Amersham Life Science. The NMR spectra were obtained on a General Electric QE-300 at 300 (^{1}H) and 75 (^{13}C) MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Microanalytical, IR, UV, MS, and optical rotation data were provided by the Physical Chemistry Research Department of the Lilly Research Laboratories.
Flash chromatography was performed on silica gel as described by Still *et al.*,[17] using silica gel 60 (230-400 mesh). Unless otherwise noted, the organic extracts were dried over anhydrous sodium sulfate.
HPLC was conducted on a Hitachi instrument with a UV detector at 217 nm. Analysis of the final product was performed using a Zorbax RX-C8 column (4.6 mm x 25 cm); eluting with mobile phase consisting of 81% of 0.02M monobasic potassium phosphate buffer (pH 2.7) and 19% of acetonitrile at 1.5 mL/min.

Methyl (*S*)-2,3-isopropylidenedioxypropionate, 6a:

To a solution of (*L*)-serine (**5a**) (2.1 g, 20.0 mmol) in 1*M* sulfuric acid (26 mL, 26 mmol) at 0°C (ice bath) was added a solution of sodium nitrite (2.2 g, 31.9 mmol) in water (8 mL) over the period of 30 min. The reaction mixture was allowed to reach room temperature, and after 4 days was neutralized to pH 2-3 with sodium bicarbonate (~1.6 g, 19 mmol), and concentrated *in vacuo*. The residue was diluted with methanol and

filtered. The filtrate was evaporated *in vacuo*, and twice reevaporated with toluene to remove the rest of the water. The resulting crude dihydroxyacid was diluted with methanol (100 mL) and treated with an ethereal solution of diazomethane [prepared by addition of 1-methyl-3-nitro-1-nitrosoguanidine (~10 g, 69 mmol) into a mixture of 40% aqueous potassium hydroxide (80 mL, 0.57 mol) and ether (300 mL) at 0°C] until the light yellow color persisted. The reaction mixture was evaporated *in vacuo*, the residue was diluted with 2,2-dimethoxypropane (25 mL), *d*-10-camphorsulfonic acid (300 mg, 1.3 mmol) was added, and the resulting solution was stirred for 36 hr at room temperature. The solvent was carefully evaporated *in vacuo* at 40°C, and the residue subjected to flash chromatography (40% ether in pentane) to give acetonide **6a** (1.54 g, 48%): R_f 0.48 (ether/hexane, 1:1); $[\alpha]_D^{20}$= -18.07° (c 0.57, $CHCl_3$), Lit.[5]: $[\alpha]_D^{20}$= -17.4° (c 3.02, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.78 (s, 3H, CH_3O), 4.11 (dd, J = 8.2, 5.3 Hz, 1H, H-3), 4.24 (t, J = 7.5 Hz, 1H, H-2), 4.60 (dd, J = 7.2, 5.3 Hz, 1H of H-3).

Methyl (*R*)-2,3-isopropylidenedioxypropionate-3-[^{14}C], 6b:[18]

In the same manner as described above, starting from (*L*)-serine-3-[^{14}C] (**5b**) (350 mCi, 56 mCi/mmol, 6.25 mmol) and (*L*)-serine (**5a**) (394 mg, 3.75 mmol), acetonide **6b**-[^{14}C] (565 mg, 35%) was obtained.

(*S*)-2,3-Isopropylidenedioxyprop-1-yl 3-nitrobenzenesulfonate, 8a:

To a solution of ester **6a** (1.535 g, 9.58 mmol) in ether (50 mL) was added lithium aluminum hydride (0.5 g, 13.2 mmol) in portions. The reaction mixture was stirred for 1 hr at room temperature, and subsequently treated with water (0.5 mL), 15% aqueous potassium hydroxide (0.5 mL), and again with water (1.5 mL). The ether solution was dried, decanted, and carefully concentrated *in vacuo* at 40°C. Flash chromatography of the residue (10% pentane in ether) gave an alcohol **7a** (R_f 0.38, ethyl acetate/hexane, 1:1). The solvent was not completely evaporated, so **7a** was used in the next step as a concentrated solution in the eluent.

To a solution of above alcohol **7a** in pyridine (5 mL) at 0°C (ice bath) was added 3-nitrobenzenesulfonyl chloride (2.5 g, 11.28 mmol). The reaction mixture was stirred for 1 hr at 0°C, diluted with ether, and washed with saturated aqueous sodium bisulfate and

brine, then dried, and evaporated *in vacuo*. Flash chromatography of the residue (40% ethyl acetate in hexane) gave nosylate **8a** (2.62 g, 86%): R_f 0.48 (ether/hexane, 1:1); mp 51-52°C; $[\alpha]_D^{20}$= 14.81° (c 1.03, $CHCl_3$); IR (KBr): 598, 670, 735, 897, 983, 1188, 1354, 1545 cm^{-1}; UV (EtOH) $\lambda_{max}(\varepsilon)$: 250 nm (7046), 210 nm (21688); ^{1}H-NMR ($CDCl_3$) δ 1.30 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.78 (dd, J = 8.8, 5.3 Hz, 1H, H-3), 4.04-4.16 (m, 3H, H-1, H-3), 4.31 (m, 1H, H-2), 7.81 (t, J = 8.0 Hz, 1H, arom. H), 8.26 (d, J = 6.9 Hz, 1H, arom. H), 8.52 (d, J = 8.0 Hz, 1H, arom. H), 8.78 (s, 1H, arom. H); MS (FD) m/z(%): 302 (M^+-CH_3, 100), 288 (10), 278 (89), 216 (33), 203 (86), 186 (60). Analysis calc'd for $C_{12}H_{15}NO_7S$: C, 45.42; H, 4.77; N, 4.41; S, 10.10. Found: C, 45.20; H, 4.74; N, 4.76.

(*S*)-1-(1H-Indol-4-yloxy)-2,3-isopropylidenedioxypropane, 9a from nosylate 8a: To a suspension of sodium hydride (238 mg, 5.95 mmol, 60% dispersion in oil, washed with pentane) in DMF (8 mL) was added 4-hydroxyindole (**2**) (720 mg, 5.407 mmol) in portions. After 20 min to the resulting blue solution was added a solution of nosylate **8a** (1.373 g, 4.326 mmol) in DMF (5 mL) *via* cannula. The reaction mixture was stirred for 3.5 hr at room temperature, then diluted with water and extracted with ether. The extract was washed with water, 5% aqueous lithium chloride, and brine, then dried, and evaporated *in vacuo*. Flash chromatography of the residue (40% ethyl acetate in hexane) gave ether **9a** (655 mg, 61%): R_f 0.43 (ether/hexane, 1:1); $[\alpha]_D^{20}$= -31.10° (c 0.55, $CHCl_3$); IR (KBr): 846, 1058, 1086, 1242, 1362, 1504, 1590, 2991 cm^{-1}; UV (EtOH) $\lambda_{max}(\varepsilon)$: 288 nm (5366), 265 nm (10193), 219 nm (31273); ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 4.05 (dd, J = 8.5, 5.9 Hz, 1H, H-3), 4.11-4.30 (m, 3H, H-1, H-3), 4.61 (m, 1H, H-2), 6.56 (d, J = 7.8 Hz, 1H, indole H), 6.67 (br. s, 1H, indole H), 7.01-7.26 (m, 3H, indole H), 8.29 (br. s, 1H, NH); MS (FD) m/z(%): 247 (M^+, 100). Analysis calc'd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.75; H, 6.92; N, 5.41.

(*S*)-1-(1H-Indol-4-yloxy)-2,3-isopropylidenedioxypropane, 9a from alcohol 7a: To a solution of ester **6a** (355 mg, 2.216 mmol) in ether (10 mL) was added lithium aluminum hydride (120 mg, 3.162 mmol) in portions. The reaction mixture was stirred for 0.5 hr at room temperature and then sequentially treated with water (0.15 mL), 15%

aqueous potassium hydroxide (0.15 mL), and again with water (0.45 mL), dried, decanted, and carefully evaporated *in vacuo* at 40°C. Flash chromatography of the residue (10% pentane in ether) gave an alcohol **7a** (R_f 0.38, ethyl acetate/hexane, 1:1). The solvent was not completely evaporated, so **7a** was used in the next step as a concentrated solution in the eluent.

To a solution of triphenyphosphine (500 mg, 1.906 mmol) in THF (1.5 mL) at 0°C (ice bath) was added a solution of DEAD (332 mg, 1.906 mmol) in THF (1 mL) dropwise over the period of 5 min. The light yellow mixture was stirred for 30 min at 0°C, and a solution of alcohol **7a** and hydroxyindole **2** in THF (2.5 mL) was added dropwise. The reaction mixture was allowed to reach room temperature, then heated to 50°C, and kept at this temperature for 15 hr. The resulting mixture was evaporated *in vacuo*, and subjected directly to flash chromatography (45% ether in hexane) to give adduct **9a** (346 mg, 63%), which was identical (TLC, HPLC, NMR) to **9a** obtained by the method described above.

(*R*)-1-(1H-Indol-4-yloxy)-2,3-isopropylidenedioxypropane-3-[^{14}C], 9b:

In the same manner as described above, starting from ester **6b** (565 mg, 3.51 mmol), alcohol-[^{14}C] **7b**, and then ether-[^{14}C] **9b** (573 mg, 66%) were obtained.

(*R*)-1-(1H-Indol-4-yloxy)-2-hydroxypropyl *p*-toluenesulfonate, 11a:

To a solution of acetonide **9a** (300 mg, 1.213 mmol) in THF (4 mL) and water (1 mL) at 0°C (ice bath) was added trifluoroacetic acid (0.3 mL). The reaction mixture was allowed to reach room temperature, after 1 hr it was heated to 50°C and stirred at this temperature for 3 h. The resulting solution was then diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine, then dried over magnesium sulfate, and evaporated *in vacuo* to give crude diol **10a** (245 mg).

To a solution of the above diol in pyridine (4 mL) at 0°C (ice bath) was added *p*-toluenesulfonyl chloride (250 mg, 1.31 mmol). The reaction mixture was kept at 0-4°C for 15 hr, then diluted with ethyl acetate, and poured into a mixture of 1*N* HCl (50 mL) with ice. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried, and evaporated *in vacuo*. Flash chromatography of the residue (50% of ethyl acetate in hexane) gave tosylate **11a** (315 mg, 72%): R_f 0.43 (ethyl acetate/hexane, 1:1); $[\alpha]_D^{20}$= -11.01° (c 0.53,

$CHCl_3$); IR (KBr): 831, 990, 1087, 1178, 1243, 1362, 1504, 1599, 3483 cm^{-1}; UV (EtOH) $\lambda_{max}(\varepsilon)$: 288 nm (4010), 265 nm (7900), 219 nm (42539); ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.63 (br. d, J = 5.2, 1H, OH), 4.05-4.35 (m, 5H, H-1, H-2, H-3), 6.43 (br. d, J = 6.8 Hz, 1H, indole H), 6.50 (br. s, 1H, indole H), 7.00-7.27 (m, 5H, arom. H), 7.79 (m, 2H, arom. H), 8.28 (br. s, 1H, NH); MS (FAB) m/z(%): 361 (M^+, 100), 229 (17), 207 (27), 190 (11), 172 (50), 155 (26), 146 (23), 133 (68); HRMS (FAB): calc'd for $C_{18}H_{19}NO_5S$: 361.0984. Found: 361.1000.

(*R*)-1-(1H-Indol-4-yloxy)-2-hydroxypropyl *p*-toluenesulfonate-3-[^{14}C], 11b:

In the same manner as described above, starting from acetonide **9b** (573 mg, 2.31 mmol), diol-[^{14}C] **10b** was obtained and subsequently converted to its monotosylate-[^{14}C] **11b** (560 mg, 67%).

(*S*)-1-(1H-Indol-4-yloxy)-2,3-epoxypropane, 12a:

To a solution of tosylate **11a** (314 mg, 0.87 mmol) in methanol (20 mL) was added potassium carbonate (550 mg, 3.98 mmol). The reaction mixture was stirred for 1.5 hr at room temperature, most of the solvent was evaporated *in vacuo*; the residue was diluted with ether, washed with water and brine, dried, and evaporated *in vacuo*. Flash chromatography of the residue (50% ether in hexane) gave epoxide **12a** (144 mg, 87%), which was identical (TLC, NMR) to an authentic sample.

For **12a:** R_f 0.45 (ether/hexane, 1:1); mp 77-78°C; $[\alpha]_D^{20}$= 25.61° (c 0.99, MeOH); IR (KBr): 750, 868, 910, 1055, 1089, 1246, 1364, 1511, 1586 cm^{-1}; UV (EtOH) $\lambda_{max}(\varepsilon)$: 288 nm (4227), 265 nm (8064), 218 nm (29625); ^{1}H-NMR ($CDCl_3$) δ 2.83 (m, 1H, H-3), 2.94 (m, 1H, H-3), 3.46 (m, 1H, H-2), 4.15 (dd, J = 11.1, 5.5 Hz, 1H, H-1), 4.36 (dd, J = 11.1, 3.3 Hz, 1H, H-1), 6.53 (d, J = 7.4, 1H, indole H), 6.70 (br. s, 1H, indole H), 7.02-7.13 (m, 3H, indole H), 8.20 (br. s, 1H, NH); MS (FD) m/z(%): 189 (M^+, 100).

(*R*)-1-(1H-Indol-4-yloxy)-2,3-epoxypropane-3-[^{14}C], 12b:

In the same manner as described above, starting from tosylate **11b** (560 mg, 1.547 mmol), epoxide-[^{14}C] **12b** (223 mg, 76%) was obtained.

(*S*)-1-(1H-Indol-4-yloxy)-3-[4-(3-methoxyphenyl)-4-hydroxypiperidin-1-yl]-propan-2-ol (LY333068) Succinate, 1a:

To a solution of amine hydrochloride 4 in methanol (1.5 mL) was added 5*N* sodium hydroxide (0.18 mL, 0.9 mmol), and after 15 min the resulting solution of amine free base was added to a solution of epoxide **12a** (139 mg, 0.735 mmol) in methanol (1.5 mL). The reaction mixture was heated at 60°C for 2 hr, then diluted with water and extracted with ethyl acetate. The extract was washed with brine, dried, evaporated *in vacuo*, and subjected to flash chromatography (5% methanol in ethyl acetate followed by ethyl acetate/methanol/ammonium hydroxide, 80:20:4) to give **LY333068** (242 mg, 83%): R_f 0.52 (ethyl acetate/methanol, 4:1); mp 58-61°C; $[\alpha]_D^{20}$= -16.31° (c 0.97, $CHCl_3$); IR (KBr): 743, 1045, 1091, 1245, 1289, 1364, 1431, 1510, 1586, 2832, 2924, 3409 cm^{-1}; UV (EtOH) $\lambda_{max}(\varepsilon)$: 288 nm (4266), 266 nm (9053), 218 nm (43206), 202 nm (37738); ^{1}H-NMR ($CDCl_3$) δ 1.78 (d, J = 13.3 Hz, 2H, piperidine H), 2.11-2.28 (m, 2H, piperidine H), 2.52-3.03 (m, 6H, H-3, piperidine H), 3.83 (s, 3H, CH_3), 4.09-4.28 (m, 3H, H-1, H-2), 6.55 (d, J = 7.6, 1H, indole H), 6.68 (br. s, 1H, indole H), 6.83 (m, 1H, arom. H), 7.01-7.17 (m, 5H, indole and arom. H), 7.31 (t, J = 7.7, 1H, arom. H), 8.19 (br. s, 1H, NH); MS (FAB) m/z(%): 397 (M^+, 100), 220 (40), 119 (14); HRMS (FAB): calc'd for $C_{23}H_{29}N_2O_4$: 397.2127 Found: 397.2150.

To a vigorously stirred solution of **LY333068** (228 mg, 0.575 mmol) in ethyl acetate (2.5 mL) at 60°C was added a solution of succinic acid (68 mg, 0.576 mmol) in methanol (0.3 mL) in one portion. The reaction mixture was allowed slowly to reach room temperature, then cooled to 0°C (ice bath), and kept at this temperature for 1h. The precipitate was collected by filtration, washed with ethyl acetate and ether, and dried *in vacuo* to give succinate **1a** (248 mg, 84%), identical (mp, $[\alpha]_D^{20}$, HPLC, NMR) to an authentic sample. For **1a:** mp 152-154°C; $[\alpha]_D^{20}$= -10.0° (c 0.6, MeOH); ^{1}H-NMR (CD_3OD) δ 1.90 (m, 2H, pyperidine H), 2.25-2.48 (m, 2H, piperidine H), 2.50 (s, 4H, succinate H), 3.21-3.54 (m, 6H, H-3, piperidine H), 3.78 (s, 3H, CH_3), 4.17 (m, 2H, H-1), 4.47 (m, 1H, H-2), 6.50 (d, J = 6.3, 1H, indole H), 6.56 (br. s, 1H, indole H), 6.82 (m, 1H, arom. H), 7.00-7.15 (m, 5H, indole and arom. H), 7.27 (t, J = 7.8, 1H, arom. H).

(*R*)-1-(1H-Indol-4-yloxy)-3-[4-(3-methoxyphenyl)-4-hydroxypiperidin-1-yl]-propan-2-ol-3-[^{14}C] {(LY333068)-[^{14}C]} Succinate, 1b:

In the same manner as described above, starting from epoxide **12b** (223 mg, 1.17 mmol), **(LY333068)-[^{14}C]** (419 mg, 90%) was obtained and subsequently converted to its succinate salt **1b** (28.75 mCi, 426 mg, 78%): radiochemical purity 99.4% (radio-HPLC), specific activity 67.49 mCi/mg (34.76 mCi/mmol).

REFERENCES

† A portion of this work was presented at the Sixth International Symposium on the Synthesis and Applications of Isotopes and Isotopically Labeled Compounds, Philadelphia, PA, September 14-18, 1997

1. Humphrey, P. P. A. In: *5-Hydroxytryptamines Receptors and Drug Discovery*; Langer, S. Z.; Brunello, N.; Racagni, G.; and Mendlevicz, J., Eds.; Karger: Basel, 1992; Vol. 1, pp 129-139.
2. Audia, J. E. and Cohen, M. L. - *Ann. Rep. Med. Chem.* **26**: 103 (1991), and references therein.
3. Krushinski, J. H., Jr.; Rasmussen, K.; Rocco, V. P.; Schaus, M.; and Thompson, D. C. - *U. S. Pat.* 5,576,321 (1996).
4. Reviews: a) Chiral Glyceraldehyde: Jurczak, J.; Pikul, S.; and Bauer, T. - *Tetrahedron* **42**: 447 (1986); b) Chiral Glycidol: Hanson, R. M. - *Chem. Rev.* **91**: 437 (1991).
5. Hirth, G. and Walther, W. - *Helv. Chim. Acta* **68**: 1863 (1985).
6. Schrotter, E.; Hauser, A.; Hamann, H.-J.; Schick, H.; and Schonecker, B. - *J. prakt. Chem.* **328**: 705 (1986).
7. De Witt, P.; Misiti, D.; and Zappia, G. - *Tetrahedron Lett.* **30**: 5505 (1989).
8. Block, T. H. - *Aldrichimica Acta* **16**: 3 (1983).
9. Anzalone, L. and Hirsch, J. A. - *J. Org. Chem.* **50**: 2607 (1985).
10. Klunder, J. M.; Onami, T.; and Sharpless, K. B. - *J. Org. Chem.* **54**: 1295 (1989).
11. Dewick, P. M. - *Synth. Commun.* 11: 853 (1981).
12. Manhas, M. S.; Hoffman, W. H.; Lal, B.; and Bose, A. K. - *J. Chem. Soc. Perkin Trans. 1* 461 (1975).

13. Smith, A. B. III; Hale, K. J.; and Rivero, R. A. - *Tetrahedron Lett.* **27**: 5813 (1986).

14. Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; and Rokach, J. - *J. Org. Chem.* **51**: 789 (1986).

15. Takano, S.; Goto, E.; Hirama, M.; and Ogasawara, K. - *Heterocycles* **16**: 381 (1981).

16. Molander, G. and Swallow, S. - *J. Org. Chem.* **59**: 7148 (1994).

17. Still, W. C.; Kahn, M.; and Mitra, A. - *J. Org. Chem.* **43**: 2923 (1978).

18. The change from *S* to *R* in the C-14 isotopomer is a consequence of the higher priority of the ^{14}C-substituent as opposed to the ^{12}C-substituent in the Cahn-Ingold-Prelog convention.

ACKNOWLEDGEMENT

The author is grateful to Dr. Bill Wheeler for helpful discussions and suggestions, and to Dr. Alex Godfrey of Chemical Process Research and Development for the authentic samples of epoxide **12a** and final product **1a**.