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Improved Synthesis of Stable Isotope Labeled and Carbon-14 Labeled (S)-(-)-3-[3-(methylsulfonyl) phenyl]-1-propylpiperidine Hydrochloride; (-)-OSU-6162

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Summary

(-)OSU-6162, ((*S*)-(-)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride), **1**, is a dopamine autoreceptor antagonist with potential atypical antipsychotic properties. The synthesis of stable labeled and carbon-14 labeled (-)-OSU-6162 was achieved by an alkylation of the anion of (*S*)-3-(1-propylpiperidine-3-yl)-benzenethiol, **5**, with either [^{13}C, $^{2}H_3$]methyl iodide or [^{14}C]methyl iodide to provide the corresponding methyl sulfide. Selective oxidation of the methyl sulfide to the sulfone and conversion to its hydrochloride salt gave either stable isotope labeled (-)-OSU-6162 or carbon-14 labeled (-)-OSU-6162. The overall radiochemical yield was 36% with chemical and radiochemical purity exceeding 99% by HPLC analysis. The precursor thiol (5) was provided by a modified synthetic route from commercially available (*S*)-(-)-3-(3-(hydroxyphenyl)-1-propylpiperidine); ((*S*)-(-)-PPP), **2**, in three steps *via* the triisopropylsilanethiolate intermediate (7).

Key Words: (-)-OSU-6162, Dopamine autoreceptor antagonist

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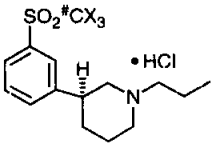
Introduction

The neurotransmitter dopamine plays a very important role in CNS related disorders such as Schizophrenia and Parkinson's disease. These diseases may be treated with agents that interact with dopamine receptors (i.e. D_2, D_3). One group of compounds which shows dopamine (DA) presynaptic mixed agonist /antagonistic properties are the (-)-phenylpiperidines (e.g.(S)-(-)-3-(3-hydroxyphenyl)-1-propylpiperidine, preclamol, **2**) reported by Hjorth (1). The analog ((*S*)-(-)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride), (-)-OSU-6162; **1**, shows preferential dopamine (DA) autoreceptor antagonist activity (2).



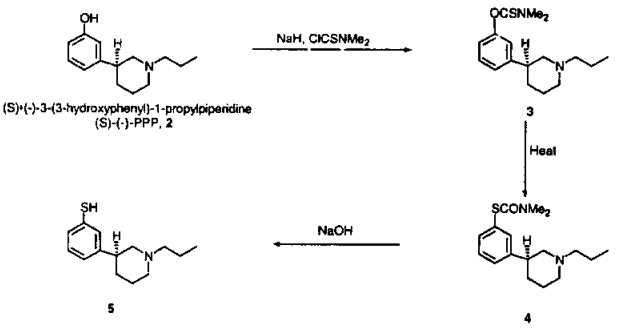
(S)-(-)-3-(3-Methylsulfonylphenyl)-1-propylpiperidine hydrochloride

(-)-OSU6162, 1; # = ^{12}C, X = H
1a; # = ^{13}C, X = D
1b; # = ^{14}C, X = H

It has been shown that (-)-OSU-6162 efficiently increased the synthesis and release of DA in rats, and this compound displayed potential antipsychotic properties without signs of extrapyramidal side effects in several animal models (2, 3). Drug absorption, distribution, excretion, and metabolism studies required the preparation of stable isotope labeled and radioisotope labeled (-)-OSU-6162. This report describes the synthesis of stable isotope labeled (-)-OSU-6162, **1a**, with incorporation of carbon-13 and three deuterium atoms and the synthesis of carbon-14 labeled (-)-OSU-6162, **1b**, both labeled at the methyl sulfone group. Various synthetic routes to prepare (-)-OSU-6162, **1** have been explored (2, 4). One approach reported by Neu (4b) starting with commercially available (*S*)-(-)-PPP, **2**, (See Scheme 1) failed to give consistent and reproducible results for the formation of the carbamoylthio derivative **4**. Subsequent hydrolysis of the *N,N*-dimethylcarbamoyl group gave multiple products and a low yield of the desired

thiol **5**. Hence, based on these results, we decided to pursue an alternative synthesis of **5**.

SCHEME 1



Arnould (5) has recently reported a mild conversion of phenols to aryl sulfides. In this general procedure, a phenol is first converted to its aryl triflate derivative. The triflate is then displaced with a silylated thiol by reacting it with sodium triisopropylsilanethiolate (NaSTIPS) using a palladium catalyst to obtain the silylated aryl thiol. The aryl silylthiol can then be easily hydrolyzed under mild conditions to obtain the desired aryl thiol. Thus, this approach presented an attractive alternative to the previous method of obtaining thiol, **5**, in good yield.

Efforts were initiated in which (*S*)-(-)-3-(3-hydroxyphenyl)-1-propylpiperidine, **2**, was treated with trifluoromethanesulfonic anhydride in the presence of triethylamine to obtain (*S*)-(-)-trifluoromethanesulfonic acid 3-(1-propylpiperidin-3-yl)phenyl ester, **7**, in 77% yield using the procedures reported by Sonesson (4a) (See Scheme 2). The triflate derivative **7**, in the presence of tetrakis(triphenylphosphine)palladium (0), was treated with a solution of freshly prepared sodium triisopropylsilanethiolate (6) in dry toluene at 120°C to give the silylated thiol **8**. Compound **8** was not stable on silica gel with methanol in methylene chloride as the eluent. To circumvent this problem, crude product **8** was not purified but hydrolyzed directly with 10% Conc. HCl in methanol to obtain the corresponding thiol, **5**, whose structure was confirmed by mass spectrometry and ^{1}H NMR analysis. Thiol **5**, could then be used as an intermediate in the preparation of either stable labeled (-)-OSU-6162, **1a**, or radiolabeled (-)-OSU-6162, **1b**.

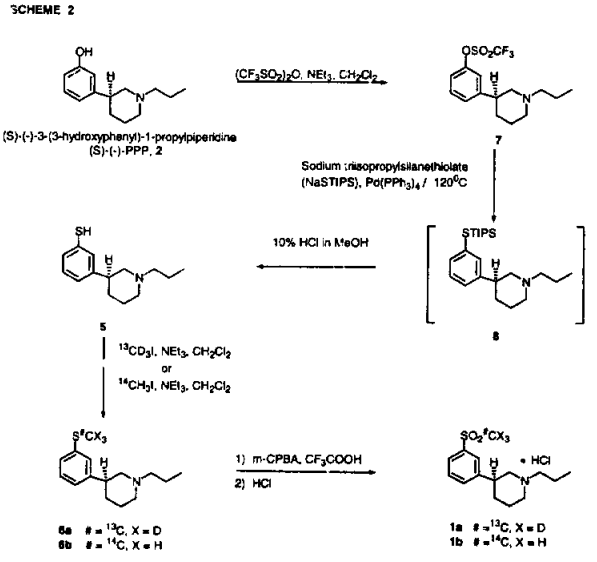
The next step was to introduce the isotopic label on the thiol moiety by alkylation of the aryl thiol with the appropriately labeled methyl iodide. In order to avoid dimerization of thiol **5** to the disulfide, it was used without further purification (4b). Thiol **5**, was treated with [^{13}C, $^{2}H_3$]methyl iodide in the presence of triethylamine to yield methyl sulfide **6a**. Analysis by mass spectrometry, as well as ^{1}H NMR, confirmed the structure. The overall chemical yield of **6a** was 49%, starting from **2**. The final step was the oxidation of the methyl sulfide **6a** to methyl sulfone and conversion to the hydrochloride salt, **1a**. Compound **6a** was treated with m-chloroperoxybenzoic acid in the presence of trifluoroacetic acid at room temperature for 3 hours to give crude **1a**. The crude product was purified by preparative silica gel TLC (70% ethyl acetate: 30% pentane) to obtain pure **1a** as its free base. The free base was dissolved in methylene chloride and treated with dry HCl gas in order to get the corresponding HCl salt. The solids were separated and dried to yield (-)-[^{13}C, $^{2}H_3$-methyl]OSU-6162, **1a,** in 45% yield. The purity of the product obtained was 99.93% (UV at 254 nm) by HPLC and mass spectrometry analysis showed the $(M+H)^+$ peak at 286 amu (100%). The ^{1}H NMR and TLC (10% methanol in methylene chloride, $R_f = 0.65$) data were in accordance with an authentic (-)-OSU-6162 sample.

Similarly, the synthesis of (-)-[^{14}C-methyl]OSU-6162, **1b,** was carried out by alkylation of the common intermediate thiol, **5**, with [^{14}C]methyl iodide (100 mCi, nominally 55 mCi/mmol) in the presence of triethylamine. The crude [^{14}C]methyl sulfide was purified by preparative silica gel TLC to obtain **6b** in 69% yield. The oxidation of **6b** was carried out with *m*-chloroperoxybenzoic acid in trifluoroacetic acid and the crude product was purified by preparative silica gel TLC (70% ethyl acetate: 30% pentane). The purified free base was treated with dry HCl gas and recrystalized from methylene chloride to yield 35.7 mCi of (-)-[^{14}C-methyl]OSU-6162, **1b**, in 77% yield with 98.17% UV (at 254 nm) purity and 99.78% radiochemical purity by HPLC. The TLC showed 100% radiochemical purity. Mass spectral analysis showed a $(M+H)^+$ peak at 284 amu (100%). ^{1}H-NMR data was in accordance with the authentic sample of (-)-OSU-6162. The

total activity remaining in the aqueous phase was 11 mCi, which was believed to contain the *N*-oxide of (-)-[^{14}C-methyl]OSU-6162 (2), but no further efforts were made to either isolate or characterize the material nor convert it to sulfone **1b**.

Conclusions

We have successfully synthesized both carbon-14 and stable isotope labeled OSU-6162 for ADME studies and have demonstrated the utility of the triflate displacement reaction to prepare thiophenols from phenols.



Experimental

General Methods: Reagents and solvents were purchased from common commercial sources and used as received. Reactions requiring anhydrous conditions were run under an atmosphere of dry nitrogen. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 400 MHz. ^{13}C-NMR spectra were recorded in $CDCl_3$ at 100.6 MHz. Chemical shifts are reported in ppm relative to TMS. EI or FAB recorded Mass spectra at an ionizing voltage 70 eV.

Sodium triisopropylsilanethiolate (NaSTIPS) was prepared according to the procedure described in reference 6, using sodium hydride (60% suspension in oil) and triisopropyl silylthiol.

(*S*)-(-)-Trifluoromethanesulfonic acid 3-(1-propylpiperidine-3-yl)phenyl ester, **7**

A solution of (*S*)-(-)-3-(3-hydroxyphenyl)-1-propylpiperidine, **2**, free base (660.15 mg, 3.01 mmol) and triethylamine (3 mL, excess) in 10 mL of dry methylene chloride was cooled to -30 °C under a nitrogen atmosphere. Triflic anhydride (3.31 mmol, 1 mL) in 5 mL dry methylene chloride was added dropwise. The reaction mixture was allowed to reach room temperature and stirred for 3 hr. The reaction was quenched with cold water and the organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The crude product was purified by silica gel column chromatography (70-230 mesh, 100 g) using 10% methanol in methylene chloride as an eluent. The collected fractions containing pure **7** were evaporated under reduced pressure to yield pure **7** as a pale yellow oil (822.3 mg, 77.7%).

^{1}H NMR ($CDCl_3$) δ: 0.9 (t, 3H), 1.35-2.1 (m, 8H), 2.33 (m, 2H), 2.82-3.2 (m, 3H), 7.1-7.4 (m, 4H). Mass (ESI $^+$) 352.2 $(M+H)^+$, (100%).

(*S*)-(-)- 3-(1-Propylpiperidine-3-yl)benzenethiol , **5**

A solution of freshly prepared sodium triisopropylsilanethiolate (NaSTIPS)(161.42 mg, 0.759 mmol) in 10 mL of dry toluene was added to a stirred solution of **7** (242.75 mg, 0.69 mmol) and tetrakis(triphenylphosphine)palladium (0) (63.81 mg, 0.053 mmol) in 6 mL of dry tetrahydrofuran under a nitrogen atmosphere. The reaction flask was protected from light and heated at 120°C. TLC analysis (70% ethyl acetate in pentane) after 7-8 hours showed a faster moving spot with no trace of starting material. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure to yield crude **8** as a dark yellow oil. The crude silyl sulfide, **8**, was dissolved in 5 mL of methanol and a solution of 10% conc. HCl in methanol (10 mL) was added at 0^0C. The reaction mixture was stirred for 2 hours and the organic solvent was removed under reduced pressure to yield crude aryl thiol, **5**, in about 70-80% yield which was used without further purification for the

next reaction. Mass spectral analysis showed a peak at 236.2 $(M+H)^{+}$. This product has been characterized elsewhere (4b).

(*S*)-(-)-3-(3-([^{13}C,$^{2}H_3$]Methylsulfonyl)phenyl)-1-propylpiperidine, **6a**

A solution of compound **5** (120 mg, 0.51 mmol) and triethylamine (0.3 mL) in 5 mL dry methylene chloride was cooled to 0°C under a nitrogen atmosphere. A solution of 0.06 mL of (^{13}C $^{2}H_3$)methyl iodide (Isotec Inc.) in 2 mL of methylene chloride was slowly added. The reaction mixture was stirred at room temperature for 3 hours and diluted with 20 mL of methylene chloride. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product was purified by preparative silica gel TLC (70% ethyl acetate in pentane) to yield (*S*)-(-)-3-(3-([^{13}C, $^{2}H_3$]methylsulfonyl)phenyl)-1-propylpiperidine **6a** (100.8 mg, 79%).

^{1}H NMR ($CDCl_3$) δ: 0.9 (t, 3H), 1.45-1.65 (m, 3H), 1.78-1.85 (m, 2H), 1.9-2.1 (m, 3H), 2.4 (m, 2H), 2.8-3.1(m, 3H), 7.0(d, 1H), 7.1-7.3 (m, 3H)

Mass (ESI) 254.3$(M+H)^{+}$, 100%

(*S*)-(-)-3-(3-([^{14}C]Methylsulfonyl)phenyl)-1-propylpiperidine, **6b**

A similar procedure was followed to synthesize (*S*)-(-)-3-(3-([^{14}C]methylsulfonyl)phenyl)-1-propylpiperidine, **6b**, in which [^{14}C]methyl iodide(100 mCi, 55 mCi/ mmol, American Radiolabeled Chemicals., Inc.) was used to alkylate thiol **5**. The progress of the reaction was monitored by TLC. After 6 hours, the reaction mixture was worked up and purified as described above to obtain **6b** (286.45 mg, 63.28 mCi, 69.05%).

(*S*)-(-)-3-(3-([^{13}C, $^{2}H_3$]Methylsulfonyl)phenyl)-1-propylpiperidine, hydrochloride **1a**

(*S*)-(-)-3-(3-([^{13}C, $^{2}H_3$]Methylsulfonyl)phenyl)-1-propylpiperidine, **6a**, (87.9 mg, 0.355 mmol) was dissolved in trifluoroacetic acid (2 mL) and cooled to 0°C. To this solution was added, a solution of m-chloroperoxybenzoic acid (134.02 mg,

0.77 mmol) in 2 mL of trifluoroacetic acid under a nitrogen atmosphere. The reaction mixture was stirred for 3 hours and then poured into ice water. The resulting mixture was made alkaline with 15% NaOH and extracted with methylene chloride (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, concentrated and purified by preparative silica gel TLC to yield the free amine of **1a**. The free amine was dissolved in methylene chloride (10 mL) and dry HCl gas was bubbled through it for 10 min to yield (*S*)-(-)-3-(3-([^{13}C, $^{2}H_3$]methylsulfonyl)phenyl)-1-propylpiperidine, **1a**, ((-)-[^{13}C,$^{2}H_3$]OSU-6162 (45.5 mg, 45%). ^{1}H NMR ($CDCl_3$) (free base) δ 0.9 (t, 3H), 1.45-1.65 (m, 3H), 1.75-1.85 (m, 2H), 1.9-2.2 (m, 3H), 2.35-2.5 (m, 2H), 2.9-3.1 (M, 3H), 7.5-7.6 (m, 2H), 7.8-7.9(m, 2H). Mass (ESI) 286.2 $(M+H)^+$, 100%.

(*S*)-(-)-3-(3-([^{14}C]Methylsulfonyl)phenyl)-1-propylpiperidine, hydrochloride **1b,** ((-)-[^{14}C]OSU-6162)

(*S*)-(-)-3-(3-([^{14}C]Methylsulfonyl)phenyl)-1-propylpiperidine, **6b**, (286.48 mg, 63.28 mCi, 1.15 mmol) was dissolved in 3 mL of trifluoroacetic acid and a solution of m-chloroperoxybenzoic acid (134.02 mg, 0.77 mmol) in 3 mL of trifluoroacetic acid, under a nitrogen atmosphere was added at 0°C. The reaction mixture was stirred for 3 hours and then poured into ice water. The resulting mixture was made alkaline with 15% NaOH and extracted with methylene chloride (3 x 25 mL). The combined organic extracts were dried over sodium sulfate and purified by silica gel preparative TLC to yield the free amine, which was converted into its HCl salt as described above to obtain, (*S*)-(-)-3-(3-([^{14}C]methylsulfonyl)phenyl)-1-propylpiperidine, (-)-[^{14}C]OSU-6162, **1b**, as an off-white solid (251.1 mg, 77.6%). The radiochemical and UV purity were determined by HPLC to be 99.78% and 98.17% respectively. The total activity obtained was 35.75 mCi, and the specific activity was 45.5 mCi/mmol or 0.142 mCi/mg. ^{1}H NMR ($CDCl_3$)(HCl Salt) δ: 1.0 (t, 3H), 1.6-1.8 (m, 3H), 1.9-2.1 (m, 3H), 2.5-2.8 (m, 2H), 2.9 (m, 2H), 3.05(s, 3H), 3.55-3.7(m, 2H), 3.8-3.9(m, 1H), 7.55 (m, 2H), 7.85(m, 2H). Mass (ESI $^+$) 284 $(M+H)^+$, 100%.

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