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An Efficient Synthesis of the Novel Dopamine Autoreceptor Antagonist S-(-)-OSU6162, *via* Palladium Catalyzed Cross-Coupling Reaction.

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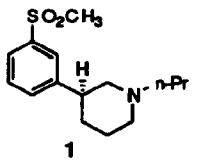
Abstract: *Optically active S-(-)-OSU6162 ((-)-1) has been synthesized in 4 steps with an overall yield of 48 %. The four steps consists of palladium catalyzed cross-coupling, catalytic hydrogenation, classical resolution with tartaric acid and reductive amination.*

Recently our group reported a series of substituted phenylpiperidines as selective dopamine autoreceptor antagonists. Compound **1** (S-(-)-OSU6162) was found to be one of the most interesting in this respect.[1] Unlike classical neuroleptics, these agents show a preference for the autoreceptors and produce a weak behavioral activation when the baseline activity is low. However, when the baseline activity is pushed very high by means of dopaminergic agents such as apomorphine, amphetamine or cocaine, compound **1** counteracts the behavioral stimulation, decreasing it to the normal baseline activity. Thus, this compound might have potential for therapeutic intervention in central nervous system disorders such as schizophrenia and drug addiction.



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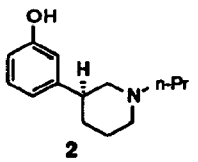
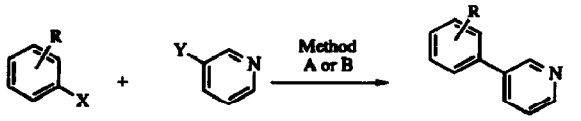


2

The synthesis of **1** has been reported.[1] In this procedure, the phenol group in S-(-)-3-(3-hydroxyphenyl)-1-propylpiperidine (preclamol, **2**) was converted in several steps and low overall yield to the corresponding methylsulfonyl group.[1] Requiring large amounts of **1**, we developed a new synthetic procedure to obtain this compound, resulting in the synthesis of optically active **1** in 48 % overall yield .

In the synthesis of **2** the coupling of the two rings to each other was accomplished by Ni-catalyzed coupling of the Grignard reagent from 3-bromoanisole with 3-bromopyridine in 76.5 % yield (Scheme 1, Table 1).[2] However, this procedure is tedious and limited in scope as demonstrated by the fact that 2-bromoanisole failed to couple.[3] Ishikura et al., reported that diethyl-(3-pyridyl)-borane (commercial available) and heteroaryl- or aryl halides yield cross-coupling products when reacted in the presence of a palladium catalyst and a base.[4, 5] We found this reaction to be an efficient and simple method to prepare compounds **3-5** (Scheme 1, Table 1).

Scheme 1



X = Br or I Y = Br or BEt_2

3: R = *m*-OMe
4: R = *o*-OMe
5: R = *m*-SO_2Me

Reagents and conditions: Method A: (i) Mg / THF (ii) $Cl_2Ni(PPh_3)_2$ / THF. Method B: $Pd(PPh_3)_4$, KOH, TBAI, THF, Δ

Table 1. Isolated yields obtained from method A and B, Scheme 1

comp.	R	X	Y	Method	Yield (%)
3	*m*-OMe	Br	Br	A	76.5[a]
3	*m*-OMe	I	BEt_2	B	79
4	*o*-OMe	Br	Br	A	3[b]
4	*o*-OMe	Br	BEt_2	B	50[c]
4	*o*-OMe	I	BEt_2	B	67
5	*m*-SO_2Me	Br	BEt_2	B	84

Footnotes: [a] Data taken from ref. 2 [b] Data taken from ref. 3. [c] Data taken from ref. 5

As shown in Table 1 compounds **3-5** were prepared in high yields with the palladium catalyzed cross-coupling reaction. Compound **4** was prepared by Ishikura *et* al. in 50% yield when using *m*-bromoanisole.[5] However, using the corresponding iodide analog seems to slightly improve the yield. In the synthesis of **5**, we have modified the workup procedure to remove all triphenylphosphine, which was found to be important for the next step (catalyst poisoning).

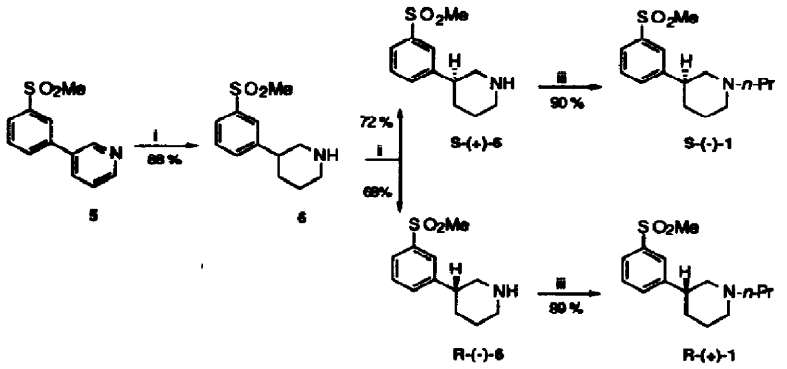
Thus, 1-bromo-3-methanesulfonyl-benzene[6] (15 g, 63.86 mmol), diethyl-(3-pyridyl)-borane (7.5 g, 51.06 mmol), powdered KOH (136 g, 204 mmol), tetra-*n*-butylammonium iodide (9.4 g, 25.5 mmol) and tetrakis[triphenylphosphine]-palladium (2.95 g, 2.55 mmol) in 300 ml THF were refluxed under an argon atmosphere for 12 h. The reaction mixture was then poured into a 10 % sulfuric acid solution (250 ml) and extracted several times with dichloromethane. The combined organic phases were extracted with two portions of 10 % sulfuric acid. The combined aqueous phases were basified with 15 % sodium hydroxide solution and extracted several times with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane / methanol (15/1, v/v) as eluent, affording pure **5** (10.0 g, 84 %). Compound **5** was then converted to the hydrochloride salt by treating the free amine with an ethanol solution, saturated with HCl (g). The resulting salt was recrystallized from ethanol:*iso*-propylether to afford **5** x HCl as a white powder.

The piperidine **6** was obtained by catalytic hydrogenation (Scheme 2) of the pyridine ring (**5**·HCl, 11 g, 40.82 mmol) in acidic solution (MeOH 125 ml, H_2O 20 ml, conc. HCl 25 ml) over $PtO_2 \cdot H_2O$.(800 mg).[3] Owing to problems with poisoning of the catalyst, the PtO_2 was filtered off and the procedure was repeated 2

times with fresh PtO_2. The solvents were evaporated and the residue was basified with 10 % Na_2CO_3 and subsequently extracted with dichloromethane several times. The combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane/methanol (5/1, v/v) with 1 % diethylamine as eluent, affording pure **6** (8.6 g, 88 %).

Enantiomerically pure **6** was obtained by classical resolution with tartaric acid in the following manner:[7] A solution of racemic **6** (8.3 g, 34.7 mmol) in methanol (20 ml) was heated to 50 °C and combined with a solution of (+)-tartaric acid (5.3 g, 35.3 mmol) in refluxing methanol (15 ml). The mixture was stirred at 50 °C for 1.0 h then cooled to room temperature. After 2 days the resulting salt (8 g) was filtered off. To increase the enantiomeric purity the tartaric salt was recrystallized three times using 40-50 ml methanolic water solution (30 % water in methanol). Recovery of the free amine was accomplished by dissolving the tartrate salt in 10 % Na_2CO_3 solution and extracting with dichloromethane. On average, an overall yield of 72 % (3.0 g) of S-(+)-**6** with enantiomeric purity[8] > 94 % ee was obtained using this procedure. Repeating the above procedure with the combined mother liquors enriched with the (-)-enantiomer (and using (-)-tartaric acid) gave R-(-)-**6** (2.8 g, 68 %) with enantiomeric purity > 94 % ee.

Scheme 2



Reagents and conditions: (i) $PtO_2 \cdot H_2O$, MeOH, conc. HCl, H_2O, H_2, 50 psi, 12 h. (ii) (+)- or (-)-tartaric acid, H_2O, MeOH, 3 recrystallizations. (iii) CH_3CH_2CHO (1.1 eq.), $NaB(O_2CCH_3)_3H$ (1.5 eq.) CH_3CO_2H, (1 eq.) $ClCH_2CH_2Cl$

The tertiary amines S-(-)-**1** and R-(+)-**1** were prepared from the corresponding secondary amines (**6**) by reductive amination using propionaldehyde and sodium triacetoxyborohydride according to the method described in the literature.[9] The residue was purified by flash chromatography using dichloromethane / methanol (9/1, v/v) as eluent, affording pure S-(-)-**1** and R-(+)-**1** in 90 and 89 % yield, respectively. The free amines were then converted to the hydrochloride salt by treatment with a ethanol solution saturated with HCl(g). The resulting salt was recrystallized from ethanol / *iso*-propylether.

In conclusion, optically active S-(-)-**1** has been synthesized in 4 steps with an overall yield of 48%. The four steps consists of: 1. palladium catalyzed cross-coupling, 2. catalytic hydrogenation, 3. classical resolution with tartaric acid, and 4. reductive amination. All compounds synthesized have been fully characterized and display satisfactory elemental analysis (± 0.4 %).[10]

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5. Ishikura, M.; Kamada, M.; Terashima, M. *Heterocycles* **1984**, *22 (2)*, 265-268.
6. 1-Bromo-3-methanesulfonyl-benzene has been made from commercially available 3-bromothiophenol by methylation with methyl iodide (3 eq.) and powdered potassium carbonate (3 eq.) in refluxing acetonitrile. It was then further oxidized efficiently with *m*-CPBA (2.3 eq) in methylene chloride to give the desired compound in an overall yield of 90 %. After extractive workup 1-bromo-3-methanesulfonyl-benzene was recrystallized from toluene/hexane (m.p 76°C).
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8. Enantiomeric purity was determined by ^{1}H-NMR. Using 1 eq of S-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate ((+)-BNPPA) in $CDCl_3$ affected the protons in the methylsulfonyl moiety ($\Delta\delta$ 0.023).
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10. All NMR spectra were recorded at 300 MHz (^{1}H) and 75.47 MHz (^{13}C) in $CDCl_3$: (**5**): (^{1}H)-NMR δ 3.1 (s, 3 H), 7.43 (dd, J = 7.9 Hz, J = 4.8 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 1 H), 7.93 (dt, J = 7.9 Hz, J = 1.75 Hz, 1 H), 7.99 (d, J = 7.8 Hz, 1 H), 8.16 (t, J = 1.71 Hz, 1 H), 8.68 (dd, J = 4.8 Hz, J = 1.47 Hz, 1 H), 8.88 (d, J = 2.25 Hz, 1 H); ^{13}C-NMR δ 44.6, 123.8, 126.0, 126.8, 130.3, 132.2, 134.5, 134.7, 139.5, 141.6, 148.2, 149.6; MS m/z (relative intensity, 70 eV) 233.15 (M^+, 51.3), 154.15 (100); m.p. 180-185 °C (HCl, recryst. from ethanol / *iso*-propylether). (**6**): (^{1}H)-NMR δ 1.5-2.1 (m, 5 H), 2.5-2.9 (m, 3 H), 3.0-3.2 (m, 5 H), 7.5 (m, 2 H), 7.8 (m, 2 H); ^{13}C-NMR δ 26.6, 31.9, 44.0, 44.4, 46.4, 53.6, 125.1, 125.6, 129.4, 132.6, 140.5, 146.6; MS m/z (relative intensity, 70 eV) 239.15 (M^+, 83.3), 115.0 (100); m.p. 234-238 °C (HCl, recryst. from ethanol / *iso*-propylether). (S-(+)-**6**): m.p. 212-217 °C (HCl, recryst. from methanol / diethylether), $[\alpha]_D^{25}$ + 8.1 (c 1.04, MeOH). (R-(-)-**6**): m.p. 210-216 °C (HCl, recryst. from methanol / diethylether), $[\alpha]_D^{25}$ - 8.9 (c 1.13, MeOH). (S-(-)-**1**): (^{1}H)-NMR δ 0.9 (t, 3H), 1.45-1.6 (m, 3 H), 1.7-1.85 (m, 2 H), 1.9-2.1 (m, 3 H), 2.35 (m, 2 H), 2.9-3.1 (m, 6 H), 7.5 (m, 2 H), 7.8 (m, 2 H); ^{13}C-NMR δ 11.8, 19.8, 25.2, 31.4, 42.5, 44.4, 53.5, 60.5, 60.9, 125.2, 125.6, 129.3, 132.8, 140.5, 146.4; MS m/z (relative intensity, 70 eV) 281.2 (M^+, 2.9), 252.15 (100); m.p. 179-181 °C (HCl, recryst. from ethanol / *iso*-propylether), $[\alpha]_D^{25}$ - 6.2 (c 1.0, MeOH lit[1] -6.1). (R-(+)-**1**): m.p. 180-182 °C (HCl, recryst. from ethanol / *iso*-propylether), $[\alpha]_D^{25}$ +5.9 (c 1.0, MeOH).

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