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TETRAHEDRON: *ASYMMETRY*

A concise synthesis of (*S*)-(+)-1-(4-{2-[bis-(4-fluorophenyl)methoxy]-ethyl}piperazin-1-yl)-2-phenylpropan-2-ol dimaleate

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Abstract—(*S*)-(+)-1-(4-{2-[Bis-(4-fluorophenyl)methoxy]-ethyl}piperazin-1-yl)-2-phenylpropan-2-ol dimaleate was prepared in several steps from (*S*)-(+)-atrolactic acid by a process permitting synthesis of multigram quantities. With the information provided by asymmetric synthesis, the X-ray crystal structure was solved.
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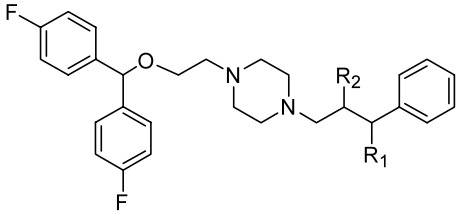
1. Introduction

The abuse of cocaine continues to cause serious public health problems in many countries.[1] Numerous studies have indicated that the reinforcing properties of cocaine are mainly mediated by the binding of cocaine to the dopamine transporter (DAT);[2–4] thus, DAT ligands that might block its binding have been sought as potential treatment agents for cocaine abuse.[5,6] Previous work in this laboratory has shown that acute introduction of analogues of the disubstituted piperazine GBR12909 (1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine) **1** (Fig. 1) could decrease cocaine-maintained responding in rhesus monkeys at lower doses than those affecting food-maintained responding,[7,8] an important characteristic for a potential treatment agent.

Recently, in an effort to develop long-acting cocaine abuse therapeutic agents, we prepared benzylic hydroxyl analogues, (±)-**2**, (*S*)-(−)-**2**, and (*R*)-(+)-**2**.[9,10] The pharmacological profiles of these compounds were found to be similar to that of **1**. In addition, the decanoate ester of (±)-**2** was shown to be successful in suppressing cocaine-maintained responding in rhesus monkeys without affecting food intake for up to 30 days.[11] Further explorations discovered that their structural isomers, (*R*)-**3** and (*S*)-**3**, are also able to reduce cocaine self-administration while not affecting food-maintained responding in rhesus monkeys.[11]

In an effort to identify other compounds with potential use as cocaine abuse therapeutics, ligands with higher affinity and greater selectivity for DAT than **1**–**3**, we



1: $R_1 = R_2 = H$
2: $R_1 = OH$, $R_2 = H$
3: $R_1 = H$, $R_2 = OH$

Figure 1. Structure of GBR 12909 and its hydroxyl analogues.

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synthesized several additional hydroxyl-containing analogues.[12] One of these compounds, (+)-**4**, had a pharmacological profile similar to that of **1**. The hydroxyl substituent in (+)-**4**, which would allow conversion to an oil-soluble prodrug, makes it a good candidate for further development as a potential stimulant abuse therapeutic. Moreover, the presence of the α-methyl group in **4** suggests its use as a potential ultra long-acting therapeutic due to its possible resistance to metabolism. Given the promising pharmacological and chemical properties of **4**, we selected this compound for further behavioral studies in rhesus monkeys. Multigram quantities of the compound are required for such studies.

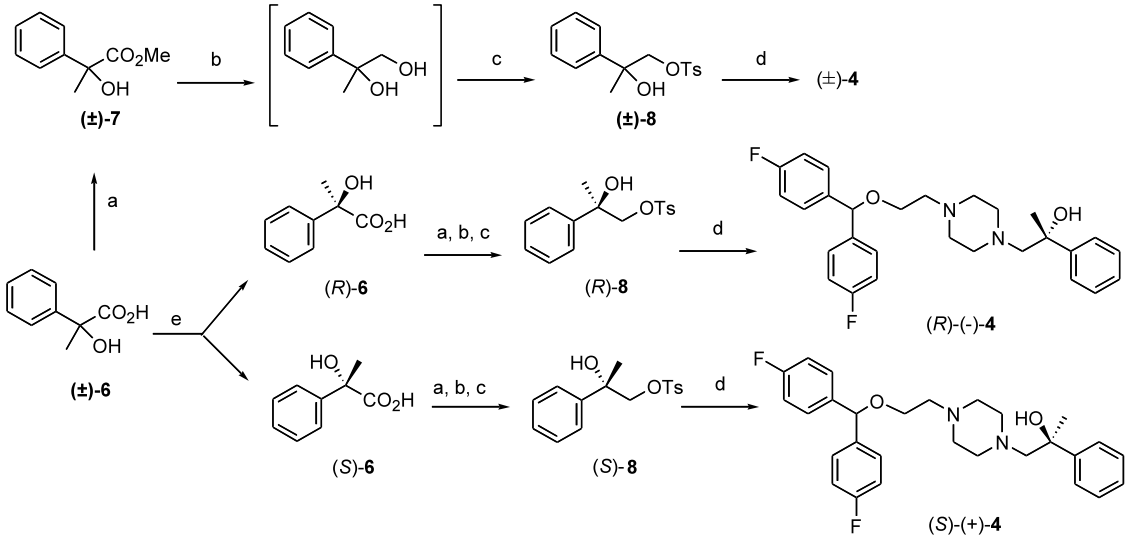
Our previously described synthesis of (+)-**4**[12] is not readily amendable for the preparation of large quantities, based on the requirement for chiral HPLC in its preparation. We have now designed a new synthetic approach that gave (+)-**4** with the *S* absolute configuration. Although X-ray crystallographic analysis might establish the absolute configuration of the compound, we knew that a similar molecule, GBR 12909, showed the presence of twinned forms.[13] Since there was considerable molecular similarity between (+)-**4** and GBR 12909, we felt that there was a high probability for twinning, and if twinning were to also occur with (+)-**4** (which it did, as we later found), this would increase the difficulty of the structural analysis. We decided to find a method for the resynthesis of (+)-**4** that would both directly provide enantiopure material and would easily allow the preparation of multigram quantities. This was achieved through the use of a molecule of known absolute configuration in the synthesis. We herein describe the synthesis of (+)-**4** starting from the readily available (±)-atrolactic acid.

2. Results and discussion

Our initial focus was the resynthesis of (±)-**4**. It was decided that rather than consume valuable homochiral material, an improved method for the preparation of (±)-**4** would be sought first. Once this route had been established, the methodology would then be applied to the preparation of a homochiral homoderivative. Our efforts focused on coupling the previously described 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]piperazine **5** with a derivative of (±)-atrolactic acid **6**. In particular, we chose to explore a way to improve the coupling of **5** with a hydroxyl-containing alkylating agent derived from **6**. We set out then to convert **6** into a derivative suitable for coupling.

The reaction of (±)-atrolactic acid **6** with iodomethane under basic conditions afforded methyl ester **7** (Scheme 1), avoiding the previously described use of diazomethane.[14] We prepared methyl ester **7** for two reasons. First, direct reduction of **6**, with LAH[15] or BH_3, in our hands led to poor yields of the corresponding diol. We thought that the reduction of **7** with LAH might lead to higher yields of the diol. Second, the ester could be used to determine the enantiomeric excess of the chiral atrolactic acids by an NMR method.[16] Reduction of **7** with LAH cleanly gave the desired diol. As a result, this intermediate was not isolated but directly treated with *p*-toluenesulfonyl chloride in pyridine to afford the previously described tosylate **8**.[17] The reaction of piperazine **5** and tosylate **8** under basic condition gave (±)-**4** in 74% yield.

The synthesis of (−)-**4** and (+)-**4** required (−)- and (+)-atrolactic acid. Rather than enantioselectively[14] synthesizing these compounds, (±)-atrolactic acid **6** was separated into its isomers, (*R*)-(−)-**6** and (*S*)-(+)-**6**, using fractional crystallization with α-methylbenzylamine (Scheme 1).[18,19] (*R*)-**6** and (*S*)-**6** were then sub-



Scheme 1. *Reagents and conditions*: (a) MeI, K_2CO_3, acetone; (b) LAH, THF; (c) *p*-TsCl, pyridine; (d) **5**, Na_2CO_3, EtOH; (e) (i) fractional crystallization with α-methylbenzylamine; (ii) conc. H_2SO_4, Et_2O.

jected to a sequence of ester formation, reduction and selective tosylation to gave (*R*)-**8**[20] and (*S*)-**8**.[21] The reaction of (*R*)-**8** and (*S*)-**8** with piperazine **5** under basic conditions gave (*R*)-(−)-**4** and (*S*)-(+)-**4**, respectively.

The specific rotations in MeOH at 365 nM of (−)-**4** and (+)-**4** prepared from (*R*)-(−)-**6** and (*S*)-(+)-**6** were found to be −10.4 and +10.4, respectively. The determined rotation was higher than that obtained from (−)-**4** previously isolated by chiral HPLC ($[\alpha]_{365}^{20}=-9.4$ in MeOH at this wavelength). The melting points of (+)-**4** and (−)-**4** prepared from (+)-**6** and (−)-**6** were identical to those prepared previously.[12] Since (−)-**4** was prepared from (*R*)-(−)-**7**, and (+)-**4** from (*S*)-(+)-**7**, and the stereogenic center was not modified by the synthesis, (−)-**4** and (+)-**4** must be (*R*)-(−)-**4** and (*S*)-(+)-**4**, respectively.

The stereoselective synthesis of (*S*)-(+)-**4** permitted us to resolve the configuration of the molecule by X-ray crystallographic analysis. As we expected, the crystal of (*S*)-(+)-**4** (Fig. 2) was twinned. The X-ray diffraction analysis indicated the *S* configuration but the level of uncertainty made this indication unreliable. However, with the information provided by our asymmetric synthesis, the structure could definitively be assigned the *S* configuration.

3. Conclusions

(*S*)-(+)-**4** was prepared in several steps from (*S*)-(+)-atrolactic acid in 71% yield by a process permitting synthesis of multigram quantities. Research is currently underway to examine its ability to suppress cocaine self-administration in rhesus monkeys.

4. Experimental

4.1. Single-crystal X-ray diffraction analysis of (*S*)-(+)-4

A clear colorless 0.33×0.21×0.01 mm crystal was used for data collection with a Bruker SMART[22] 6K CCD detector on a Platform goniometer. The Rigaku rotating Cu anode source was equipped with incident beam Gobel mirrors. Lattice parameters were determined using SAINT[22] from 3666 reflections within $2.91<\theta<65.02°$ Data were collected to $2\theta=133.9°$. A set of 12588 reflections was collected in the ω scan mode. All of the collected data was treated as unique in the twinned refinement. Empirical formula, $C_{28}H_{34}F_2N_2O_2{}^{2+}2(C_4H_3O_4{}^-)$; F_w (g/mmol), 698.70; temperature (K), 294(2); wavelength (λ, Å), 1.54178; crystal system, triclinic; space group, *P*1; unit cell dimensions, $a=10.0316(10)$ Å; $\alpha=101.3690(10)°$; $b=11.7507(2)$ Å; $\beta=105.0830(10)°$; $c=16.1968(2)$ Å; $\gamma=96.8850(10)°$; volume (Å^3), 1778.31(4); *Z*, 2; density (calculated); 1.305 mg/mm^3; absorption coefficient (mm^{-1}), 0.860; *F*(000), 736; crystal size (mm^3), 0.33×0.21×0.01; θ range, 2.91–66.92°; index ranges, $-11\leq h\leq 11$, $-13\leq k\leq 13$, $-18\leq l\leq 19$; reflections collected, 12588; independent reflections, 12588 [*R*(int) = 0.0000]; completeness to $\theta=66.94°$; 89.1%; absorption correction, multiscan; max. and min. transmission, 0.991 and 0.753; refinement method, full-matrix least-squares on F^2; data/restraints/parameters, 12588/3/843; goodness-of-fit on F^2, 0.858; final *R* indices [$I>2\sigma(I)$], $R_1=0.0635$, $wR_2=0.1603$; *R* indices (all data), $R_1=0.0953$, $wR_2=0.1770$; absolute structure parameter, −0.2(2); extinction coefficient, 0.0159(13); largest diff. peak and hole (e Å^{-3}), 0.239 and −0.271; corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved with SHELXTL[23] and refined with

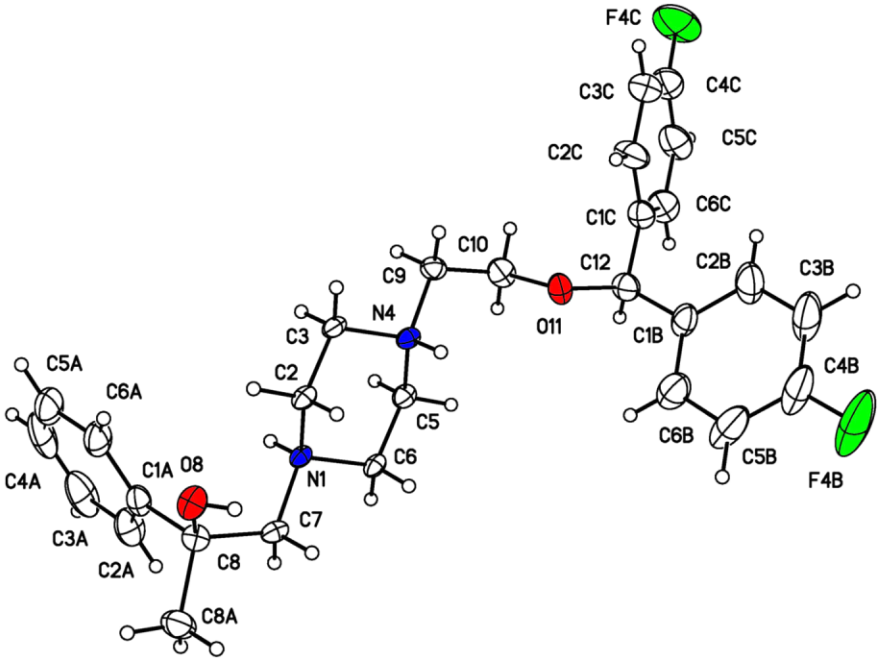


Figure 2. Displacement ellipsoid plot of one of the two unique molecules of (*S*)-(+)-**4** drawn at 20% probability levels.

the aid of the SHELX97 system of programs. The full-matrix least-squares refinement on F^2 used three restraints and varied 843 parameters including atom coordinates and anisotropic thermal parameters. H atoms were included using a riding model [coordinate shifts of C applied to attached H atoms, C–H distances set to 0.96 to 0.93 Å, H angles idealized, U_{iso}(H) were set to 1.2 to 1.5 U_{eq}(C). Final residuals were $R_1 = 0.064$ for the 6903 observed data with $F_o > 4\sigma(F_o)$ and 0.095 for all data. Final difference Fourier excursions of 0.24 and −0.27 e Å^{-3}. The data crystal was twined but was resolved with the aid of the program Gemini. The assignment as (*S*)-(+)-**4** was on the basis of the asymmetric synthesis. While the Flack parameter[24] indicates the (*S*)-configuration, the level of uncertainty makes this indication unreliable due both to the twinning and the weak anomalous scattering of the fluorines. Coordinates of each of the twinned compounds have been deposited with the Cambridge Crystallographic Data Centre (Cambridge University Chemical Laboratory, Cambridge CB2 1EW, UK). CDCC number: 203142.

4.2. General remarks

Optical rotations were determined on a Perkin–Elmer 341 polarimeter at 365 nM and 20°C. All melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 instrument using $CDCl_3$ or DMSO-d_6 as solvent, δ values in ppm (TMS as internal standard), J (Hz) assignments of ^{1}H resonance coupling. Thin layer chromatography (TLC) was performed on 250 mm Analtech GHLF silica gel plates using either *n*-hexanes/EtOAc, 7:3 or $CHCl_3$/MeOH, 19:1 as eluent. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

4.3. Methyl 2-hydroxy-2-phenylpropionate, 7

A suspension of **6** (2.0 g, 12.0 mmol), iodomethane (1.9 g, 13.2 mmol), and K_2CO_3 (1.8 g, 13.2 mmol) in acetone (30 mL) was heated at reflux overnight. The solvent was removed under reduced pressure and H_2O (100 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (75 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 2.2 g (97%) of **7** as a clear oil: ^{1}H NMR ($CDCl_3$): δ 7.2–7.6 (m, 5H); 3.7 (m, 4H); 1.8 (s, 3H).

4.4. 2-Phenyl-1-tosyloxy-2-propanol, 8

A solution of **7** (5.0 g, 27.7 mmol) in dry THF (50 mL) was added in a dropwise manner to a suspension of LAH (1.2 g, 30.5 mmol) in dry THF (100 mL) at 0°C. The mixture was stirred vigorously at room temperature for 2 h. The mixture was cooled to 0°C and then cautiously treated with H_2O (1.2 mL) and 10% NaOH (1.2 mL). After warming to room temperature, Celite was added and the mixture was filtered and the solid material was washed with CH_2Cl_2 (150 mL). The filtrate was evaporated under reduced pressure to afford 4.0 g of a crude oil that was used without further purification. A solution of the crude oil in dry pyridine (25 mL) was cooled to 0°C and treated with *p*-toluenesulfonyl chloride (5.3 g, 27.6 mmol). The resulting mixture was stirred vigorously and allowed to warm to room temperature overnight. The mixture was poured in an ice (200 g), H_2O (100 mL) mixture and the resulting aqueous mixture was extracted with Et_2O (3×100 mL). The combined Et_2O portion was washed successively with 2N HCl (3×50 mL), H_2O (100 mL), and saturated NaCl (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 7.6 g of **8** (93%) as a tan solid, mp 44–48°C (lit.[17] mp 54–55°C).

4.5. 1-(4-{2-[Bis-(4-fluorophenyl)methoxy]-ethyl}piperazin-1-yl)-2-phenylpropan-2-ol dimaleate, (±)-4

A suspension of 1-{2-[bis-(4-fluorophenyl)-methoxy]-ethyl}piperazine (1.1 g, 3.3 mmol), **8** (1.1 g, 3.5 mmol), Na_2CO_3 (1.0 g, 9.9 mmol) in absolute EtOH (30 mL) was heated at reflux overnight. The solvent was removed under reduced pressure to afford a crude oil. H_2O (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (75 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded an oily residue that was purified by flash chromatography (eluent: $CHCl_3$/MeOH, 19:1) to afford a pale yellow oil. The oil was dissolved in MeOH (50 mL) and maleic acid (2.2 equiv.) was added. The precipitate was collected by filtration and dried to afford 1.6 g (70%) of (±)-**4** as a white solid, mp 183–184°C (lit.[12] mp 182–183°C).

4.6. (*S*)-(+)-1-(4-{2-[Bis-(4-fluorophenyl)methoxy]-ethyl}-piperazin-1-yl)-2-phenylpropan-2-ol dimaleate, (*S*)-(+)-4

A suspension of 1-{2-[bis-(4-fluorophenyl)-methoxy]-ethyl}piperazine (1.1 g, 3.3 mmol), (*S*)-**8**[21] (1.1 g, 3.5 mmol), Na_2CO_3 (1.0 g, 9.9 mmol) in absolute EtOH (30 mL) was heated at reflux overnight. The solvent was removed under reduced pressure to afford a crude oil. H_2O (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (75 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded an oily residue that was purified by flash chromatography (eluent: $CHCl_3$/MeOH, 19:1) to afford a pale yellow oil. The oil was dissolved in MeOH (40 mL) and maleic acid (2.2 equiv.) was added. The precipitate was collected by filtration and dried to afford 1.7 g (74%) of (*S*)-(+)-**4** as a white solid, mp 187–188°C: ^{1}H NMR (DMSO-d_6): δ 7.1–7.5 (m, 13H); 6.1 (s, 4H); 5.5 (s, 1H); 2.4–3.6 (m, 18H); 1.4 (s, 3H); $[\alpha]_{365}^{20} = +10.4$ ($c = 0.68$, MeOH); Anal. calcd for ($C_{28}H_{32}F_2N_2O_2 \cdot 2C_4H_4O_4$): C, 61.88; H, 5.77; N, 4.01. Found: C, 61.98; H, 5.77; N, 3.96.

4.7. (*R*)-(−)-1-(4-{2-[Bis-(4-fluorophenyl)methoxy]-ethyl}piperazin-1-yl)-2-phenylpropan-2-ol dimaleate, (*R*)-(−)-4

This compound was synthesized in a manner similar to (*S*)-(+)-**4** using (*R*)-**8**[20] to afford (*R*)-(−)-**4** as a white solid, mp 181–182°C: ^{1}H NMR (DMSO-d_6): δ 7.1–7.5 (m, 13H); 6.1 (s, 4H); 5.5 (s, 1H); 2.4–3.6 (m, 18H); 1.4 (s, 3H); $[\alpha]_{365}^{20} = -10.4$ (*c* 0.68, MeOH); Anal. calcd for ($C_{28}H_{32}F_2N_2O_2 \cdot 2C_4H_4O_4$): C, 61.88; H, 5.77; N, 4.01. Found: C, 61.85; 5.79; N, 3.99.

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