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IMPROVED SYNTHESIS OF ANTIPSYCHOTIC DRUG BIFEPRUNOX

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Abstract – A new and efficient six-step synthesis of the antipsychotic drug bifeprunox is reported. The key step is azidation of a lithiated phenol ether. Subsequent reduction of the azide, removal of phenol protecting group, and cyclization lead to the desired benzoxazolinone.

The investigational drug bifeprunox mesylate is a partial dopamine agonist with a unique receptor-binding profile and potential antipsychotic properties.[1] Patented processes involve multi-step reaction sequences with low over-all yields.[2] For example, a proposed Hartwig-Buchwald coupling as a single reaction step in a multi-step synthesis reportedly gave a prohitive yield of only 9%. Our earlier attempts to prepare 3-aminobenzoxazolinone as a key intermediate from 3-nitrosalicylic acid[3] was found to be prone to formation of by-products.[4] Therefore, we were looking for an improved synthesis of the title compound with a limited number of steps and increased yield.

Commercial 2-(piperazin-1-yl)phenol (**1**) was assumed to be a convenient starting material. The resulting synthesis of the title compound is outlined in Scheme 1. We used Pd(*N*,*N*-dimethyl-β-alaninate)$_2$ as an inexpensive, yet highly efficient catalyst[5] for palladium-catalyzed cross-coupling and obtained an almost quantitative yield of 3-phenylbenzaldehyde (**2**). By reductive amination of **2** with **1** we obtained the biphenyl derivative **3** in excellent yield and purity. This product crystallized readily, thus allowing the determination of its crystal structure (Figure 1) without additional purification. Protection of the phenolic hydroxy group using bis(chloromethyl) ether-free methoxymethyl (MOM) chloride[6] yielded the MOM ether **4** in high yield. Directed ortho-metalation[7] of the MOM ether by butyllithium in diethyl ether,

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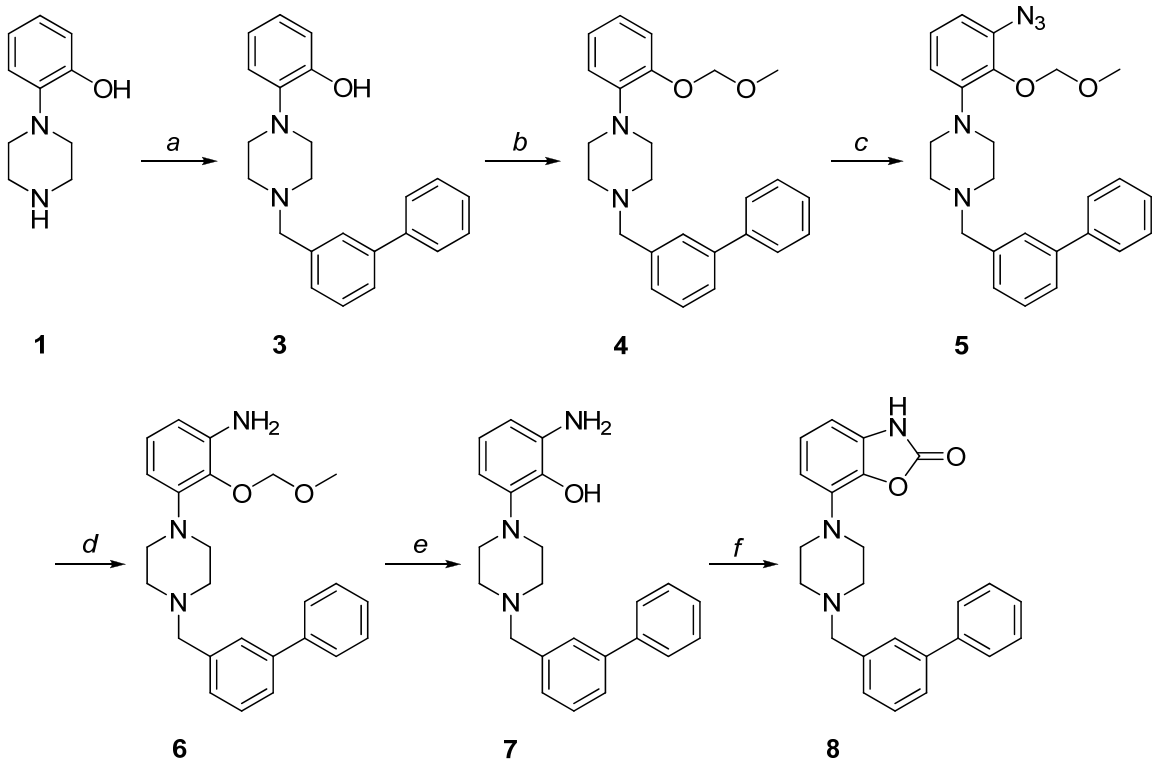
This paper is dedicated with friendship to Professor Victor Snieckus on occasion of his 77th birthday and in recognition for his many significant contributions in carbanion and heterocyclic chemistry.

followed by electrophilic azidation was assessed for the introduction of a nitrogen functionality into the aromatic ring. Trisyl azide[8] as a safe azidation reagent was found to be too unreactive. We developed 2-ethylimidazole-1-sulfonyl azide as an improved, but still safe reagent.[9] However, this reagent gave only a moderate yield of **5**. For small scale preparations we judged use of the more reactive tosyl azide[10] to be acceptable. The crude azide **5** was employed without further purification, as we intended to avoid chromatography. A small amount of unreacted **4** could be removed at a later stage. Reduction of the azide using magnesium metal in methanol[11] produced the aminophenyl ether **6** in a straightforward manner. Subsequent cleavage of the MOM ether by hydrochloric acid yielded the aminophenol **7**. At this stage, the phenolic impurity **3** (after deprotection) could be removed due to its insolubility in hydrochloric acid, whereas the aminophenol was soluble in aqueous acid. Finally, cyclization using 1,1'-carbonyldiimidazole (CDI) in hot THF gave the desired product, bifeprunox (**8**), as the free base.



Scheme 1. Reagents and conditions: (a) 3-Ph-PhCHO (**2**), $Na(OAc)_3BH$, CH_2Cl_2, rt; (b) NaH, THF, MOMCl, rt; (c) BuLi, Et_2O, TMEDA, then TsN_3, –20 °C to rt; (d) Mg, MeOH, rt; (e) HCl, CH_2Cl_2, rt; (f) CDI, THF, reflux.

Fortunately, the ^1H NMR signals of the phenol ring in **3**, the phenyl ether **4**, the azidophenyl ether **5**, the aminophenyl ether **6**, the aminophenol **7**, and the benzoxazolinone **8** are well separated from those of the biphenyl system and allowed monitoring the progress of the synthesis. The free base can be converted to the known mesylate as described in several patents.[2,12]

In conclusion, we have demonstrated that a target-oriented, efficient synthesis of bifeprunox is possible.

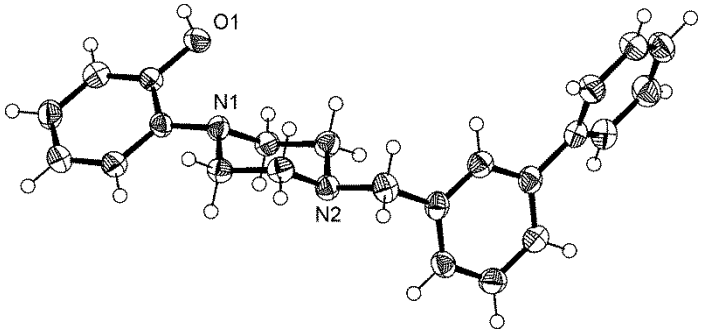


Figure 1. X-Ray crystal structure of **3**

EXPERIMENTAL

NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer. IR spectra were obtained with a Bruker Alpha FT-IR instrument. High-resolution mass spectra were measured with a Finnigan MAT 95S mass spectrometer (Cs gun, 3-nitrobenzyl alcohol matrix). Single-crystal diffraction intensity data were recorded by the rotation method with a Stoe IPDS-II diffractometer using Mo-*K*α radiation.

Starting Materials. 2-(Piperazin-1-yl)phenol (**1**) was purchased from Alfa Aesar, *N*,*N*-dimethyl-β-alanine hydrochloride from ABCR. All other chemicals used in this study were obtained from Sigma-Aldrich.

3-Phenylbenzaldehyde (2). Benzeneboronic acid (15.3 g, 0.126 mol), 3-bromobenzaldehyde (20.0 g, 0.105 mol) and finely powdered K_3PO_4 (29.0 g, 0.210 mol) were added to EtOH (100 mL) and H_2O (100 mL). After addition of Pd(*N*,*N*-dimethyl-β-alaninate)$_2$ (44 mg, 0.13 mmol) the mixture was stirred for 3 h at 60 °C. The mixture was allowed to cool to 20 °C, mixed with aqueous NaOH (200 mL 0.5 M), and extracted twice with hexanes (200 + 50 mL). The combined extracts were washed with saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and taken to dryness under reduced pressure at 50 °C to yield a colorless liquid (19.0 g; 99%). IR (neat) 1693, 750, 693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.52 (m, 3H), 7.59-7.65 (m, 3H), 7.87 (dd, *J* = 1.8, 7.7 Hz, 2H), 8.11 (t, *J* = 1.7 Hz, 1H), 10.09 (s, 1H).

2-(4-(3-Phenylbenzyl)piperazin-1-yl)phenol (3). Sodium triacetoxyborohydride (24.4 g, 0.115 mol) was added within 2 h at 20 °C to a solution of 2-(piperazin-1-yl)phenol (9.8 g, 0.055 mol) and 3-phenylbenzaldehyde (10.5 g, 0.058 mol) in CH_2Cl_2 (150 mL). The mixture was stirred for 12 h at rt. Aqueous HCl (100 mL 1 M) was added to give a crystalline precipitate in the organic phase. The aqueous phase was discarded, and the precipitate was stirred with H_2O (100 mL). The aqueous phase was again removed, and the precipitate was stirred with saturated aqueous $NaHCO_3$ (150 mL) until the evolution of gas had ceased. The organic phase was separated, dried over $MgSO_4$, and taken to dryness. The residue was stirred with Et_2O (40 mL) to yield the crystalline product (17.6 g, 93%) which was filtered off and dried. Single crystals from hot MeOH; mp 128 °C; IR 762, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (m, 4H), 2.93 (m, 4H), 3.67 (s, 2H), 6.87 (td, *J* = 7.5, 1.4 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.08 (td, *J* = 7.5, 1.4

Hz, 1H), 7.19 (dd, J = 7.8, 1.4 Hz, 1H), 7.34-7.64 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7 (2C), 54.0 (2C), 63.3, 114.2, 120.3, 121.7, 126.4, 126.7, 127.4 (2C), 127.6, 128.3, 128.5, 129.0 (2C), 139.2, 141.3, 141.6, 151.7; HRMS (FAB) *m/z* 345.1996 (calcd 345.1961 for $C_{23}H_{25}N_2O$, $[M+H]^+$).

Single-crystal diffraction: T = 173(2) K; θ_{max} = 24.6°; indices $-6 \le h \le 8$, $-16 \le k \le 16$, $-16 \le l \le 21$; D_x = 1.26 g cm^{-3}; 4752 reflections measured, 2589 independent with R_{int} = 0.047, $F(000)$ = 736, μ = 0.08 mm^{-1}. Crystal data for **3**, $C_{23}H_{24}N_2O$ (M = 344.45 g mol^{-1}): orthorhombic, $P2_1ca$, a = 7.0719(6), b = 14.1111(9), c = 18.2548(15) Å, V = 1821.7 (2) Å^3, Z = 4. R_1 = 0.046 and wR_2 = 0.066 for 2053 reflections with $I > 2\sigma(I)$, R_1 = 0.068 and wR_2 = 0.072 for all data; S = 1.10; $\Delta\rho_{max}$ = 0.13 and $\Delta\rho_{min}$ = –0.13 e Å^{-3}. CCDC reference number 966654. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

4-(2-(Methoxymethoxy)phenyl)-1-(3-phenylbenzyl)piperazine (4). Sodium hydride (1.46 g 60% suspension, washed with hexanes (20 mL), 0.037 mol) was suspended in anhydrous THF (100 ml) under argon. A solution of **3** (10.0 g, 0.029 mol) in THF (100 mL) was added within 15 min. After 1 h methoxymethyl chloride (2.5 mL, 0.033 mol) was added, and the mixture was stirred for 26 h at 20 °C. The solvent was evaporated, and the residue was treated with aqueous NaOH (100 mL 0.1 M). The mixture was extracted with Et_2O (100 + 20 mL). The combined extracts were dried over $MgSO_4$, and the volatiles were removed under reduced pressure at 50 °C to yield a viscous oil (10.8 g, 96%). IR (neat): 2812, 752, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69 (m, 4H), 3.13 (m, 4H), 3.51 (s, 3H), 3.66 (s, 2H), 5.23 (s, 2H), 6.97 (m, 3H), 7.07 (m, 1H), 7.33-7.53 (m, 6H), 7.60-7.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.9 (2C), 53.7 (2C), 56.5, 63.4, 95.4, 116.8, 118.9, 123.0, 126.2, 127.4 (2C), 127.5, 128.3, 128.5, 129.0 (2C), 138.7, 141.4, 141.5, 142.7, 150.2; HRMS (FAB) *m/z* 389.2226 (calcd 389.2224 for $C_{25}H_{29}N_2O_2$, $[M+H]^+$).

4-(3-Azido-2-(methoxymethoxy)phenyl)-1-(3-phenylbenzyl)piperazine (5). To a stirred solution of **4** (1.0 g, 2.6 mmol) and TMEDA (0.77 mL, 5.1 mmol) in Et_2O (20 mL) at –20 °C was added BuLi (1.6 M in hexanes, 5.1 mmol). The mixture was stirred for 1 h, then a solution of tosyl azide (1.02 g, 5.1 mmol) in Et_2O (10 mL) was added at the same temperature. The suspension was allowed to attain room temperature and was stirred overnight. A solution of $Na_4P_2O_7$ (1.37 g, 5.1 mmol) in H_2O (30 mL) was added, and stirring was continued for 5 h. The organic phase was separated, washed with H_2O, and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded the crude azide **5** as a brown oil (1.1 g). IR (neat): 2106, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (m, 4H), 3.11 (m, 4H), 3.63 (s, 5H), 5.19 (s, 2H), 6.72 (dd, J = 8.2, 1.3 Hz, 1H), 6.74 (dd, J = 8.2, 1.3 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 7.33-7.51 (m, 6H), 7.59-7.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4 (2C), 53.7 (2C), 58.1, 63.3, 97.9, 114.0, 115.6, 125.1, 126.3, 127.4 (2C), 127.5, 127.7, 128.2, 128.4, 128.9 (3C), 130.5, 134.4, 141.3, 141.5, 146.6; HRMS (FAB) *m/z* 430.2217

(calcd 430.2238 for $C_{25}H_{28}N_5O_2$, $[M+H]^+$).

4-(3-Amino-2-(methoxymethoxy)phenyl)-1-(3-phenylbenzyl)piperazine (6). A solution of **5** (1.0 g, 2.3 mmol) in MeOH (20 mL) was treated with Mg turnings (0.45 g) and stirred for 18 h. The temperature of the mixture temporarily rose to 50 °C. The solvent was removed under reduced pressure, and the residue was extracted twice with CH_2Cl_2 (15 mL each). Evaporation of the solvent yielded the the product **6** (0.60 g, 64%) as a brown oil. IR (neat): 1476, 1140, 961, 754, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (m, 4H), 3.09 (m, 4H), 3.57 (s, 3H), 3.63 (s, 2H), 5.19 (s, 2H), 6.37 (dd, J = 8.1, 1.4 Hz, 1H), 6.44 (dd, J = 7.9, 1.4 Hz, 1H), 6.84 (t, J = 7.9 Hz, 1H), 7.35-7.52 (m, 6H), 7.60-7.63 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.5 (2C), 54.0 (2C), 57.9, 63.4, 98.3, 109.0, 110.9, 124.9, 126.1, 127.4 (2C), 128.1, 128.3, 128.9 (2C), 138.9, 141.2, 141.4, 145.5; HRMS (FAB) *m/z* 404.2323 (calcd 404.2333 for $C_{25}H_{30}N_3O_2$, $[M+H]^+$).

4-(3-Amino-2-hydroxyphenyl)-1-(3-phenylbenzyl)piperazine (7). A solution of **6** (0.50 g, 1.2 mmol) in CH_2Cl_2 (10 mL) was vigorously stirred with HCl (6 M, 10 mL) for 48 h at room temperature. After removal of the organic solvent H_2O (10 mL) was added, and the mixture was heated at 100 °C for 1 h. Insoluble material was removed by filtration, and the hot filtrate was neutralized by addition of solid $NaHCO_3$ until the gas evolution ceased. This mixture was extracted with CH_2Cl_2 (10 mL); the extract was dried over anhydrous $MgSO_4$ and the solvent evaporated to give **7** (0.28 g, 63%) as a brown oil. IR (neat): 755, 728, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (m, 4H), 2.93 (m, 4H), 3.70 (s, 2H), 6.56 (dd, J = 7.4, 1.8 Hz, 1H), 6.65 (dd, J = 7.9, 1.8 Hz, 1H), 6.70 (t, J = 7.7 Hz, 1H), 7.33-7.54 (m, 6H), 7.61-7.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.6 (2C), 54.0 (2C), 63.2, 111.4, 113.1, 120.0, 126.4, 127.4 (2C), 127.5, 128.3, 128.5, 129.0 (2C), 134.0, 139.0, 139.4, 141.2, 141.5; HRMS (FAB) *m/z* 360.2099 (calcd 360.2070 for $C_{23}H_{26}N_3O$, $[M+H]^+$).

Bifeprunox (8). A solution of **7** (100 mg, 0.28 mmol) and 1,1'-carbonyldiimidazole (68 mg, 0.4 mmol) in THF (5 mL) was refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5 mL). The solution was stirred with H_2O (5 mL) for 1 h, and the aqueous phase was discarded. The organic phase was repeatedly washed with H_2O, dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to yield **8** (103 mg, 96%) as a tan solid. IR (neat): 1767, 1008, 753, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (m, 4H), 3.32 (m, 4H), 3.68 (s, 2H), 6.57 (d, J = 7.4 Hz, 1H), 6.96-7.61 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.5 (2C), 53.1 (2C), 63.2, 110.6, 117.6, 126.3, 127.4 (2C), 127.5, 128.4, 128.9 (2C), 131.3, 137.6, 141.2, 141.5, 144.7, 155.2; HRMS (FAB) *m/z* 386.1878 (calcd 386.1863 for $C_{24}H_{24}N_3O_2$, $[M+H]^+$).

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