Alternative Formal Synthesis of the Potent D_1 Dopamine Agonist Dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline: Dinapsoline

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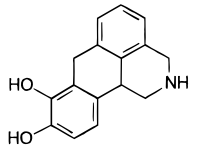
Introduction

We have previously reported the synthesis and pharmacological evaluation of 8,9-dihydroxy-2,3,7,11b-tetrahydro-1*H*-naphth[1,2,3-*de*]isoquinoline, dinapsoline (**1**),[1] a potent full dopamine D_1 agonist containing a rigid *β*-phenyldopamine pharmacophore, with potential antiparkinsonian activity. The original synthesis was rather long and unsuitable for production of large quantities. This note describes the highly efficient preparation of key intermediate **2** in the original synthetic pathway for dinapsoline comprising therefore an alternative formal synthesis of dinapsoline.



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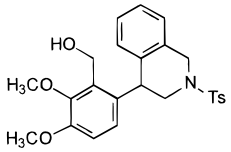

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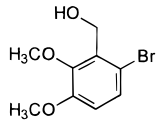

(3)

Results and Discussion

The new retrosynthetic route is illustrated in Scheme 1. In 1994 Miller and Svoboda[2] described the synthesis of a 4-phenyl-1,2,3,4-tetrahydroisoquinoline from 4-bromoisoquinoline based on the Miyaura−Suzuki cross-coupling reaction (more commonly known as the Suzuki cross-coupling reaction) for the preparation of diaryl compounds.[3,4] Their report provided the elements for an improved synthesis of dinapsoline, with the challenge being in our case to prepare the necessary boronic acid. This synthesis is illustrated in Scheme 2.

The benzyl alcohol **3** was previously prepared through a five-step synthesis.[5,6] As illustrated in Scheme 2, we were able to obtain the same intermediate by brominating commercially available 2,3-dimethoxybenzyl alcohol with *N*-bromosuccinimide. The reaction proceeded regioselectively and in high yield at room temperature. The benzylic hydroxyl group was protected as the methoxymethyl (MOM) ether using a procedure described by Kluge et al.[7] to afford **4** in excellent yield. Lithium−bromine exchange proceeded smoothly at −78 °C. Quenching with trimethyl borate followed by slow neutralization with aqueous 1 M sodium hydrogen sulfate solution furnished the boronic acid **5** in essentially quantitative yield. An NMR spectrum of the crude boronic acid from this reaction showed it to be sufficiently pure to be used in the next step without further purification.

Using typical conditions for the Suzuki cross-coupling reaction, a mixture of 4-bromoisoquinoline, the arylboronic acid, degassed aqueous sodium carbonate, and a catalytic amount of tetrakis(triphenylphosphine)palladium-(0) was heated to reflux in degassed 1,2-dimethoxyethane.[8] After extraction and evaporation of the solvents, the crude residue was treated with trifluoroacetic acid in dichloromethane to afford the desired product **6** in very good yield as an off-white solid. Reduction using sodium cyanoborohydride in methanolic-HCl gave the 1,2,3,4-tetrahydroisoquinoline **7** in quantitative yield, as shown in Scheme 3. The amine **7** was then treated with *p*-toluenesulfonyl chloride in the presence of *N*,*N*-diisopropylethylamine to afford *N*-*p*-toluenesulfonylamide **2** in excellent yield.

Conclusions

This synthesis proved to be highly efficient to prepare large quantities of intermediate **2**. This intermediate will be used to obtain dinapsoline and other dinapsoline analogues.

Experimental Section

General Comments. Melting points are uncorrected. High-resolution CI and EI mass spectra were obtained within 0.0015 *m*/*z*, unless otherwise noted. The ionization gas for CIMS and high-resolution CIMS was isobutane.

6-Bromo-2,3-dimethoxybenzyl Alcohol (3). To a solution of 45 g (0.268 mol) of 2,3-dimethoxybenzyl alcohol in 200 mL of THF was added 47.6 g (0.268 mol) of *N*-bromosuccinimide (NBS). The suspension was stirred until all the NBS had dissolved. The THF was then evaporated, and the residue was taken up in 500 mL of diethyl ether. The insoluble succinimide was removed by filtration, and the ethereal layer was washed twice with 2 N aqueous NaOH. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated. The residue was crystallized from ethyl acetate−hexane to yield 61.47 g (93%) as a white solid: mp 76 °C (lit. 74−75 °C). ^{1}H NMR: *δ* 2.32 (t, 1H, −OH, *J* = 7 Hz); *δ* 3.84 (s, 3H, O−CH_3); *δ* 3.89 (s, 3H, O−CH_3); *δ* 4.81 (d, 2H, Ar−CH_2−O, *J* = 7 Hz); *δ* 6.76 (d, 1H, Ar−H, *J* = 9 Hz); *δ* 7.25 (d, 1H, Ar−H, *J* = 9 Hz). CIMS *m*/*z*: (M, M + 2) 246 and 248, ((M + H) − 18) 229, ((M + H + 2) − 18) 231.

6-Bromo-2,3-dimethoxy(methoxymethoxy)methylbenzene (4). Sodium hydride (8.55 g; 60% suspension in mineral oil; 0.213 mol) was rinsed with hexane several times and then suspended in 250 mL of dry THF, and the mixture was placed under argon and cooled in an ice bath. A solution of 44 g (0.178 mol) of **3** in 250 mL of dry THF was added, and the mixture

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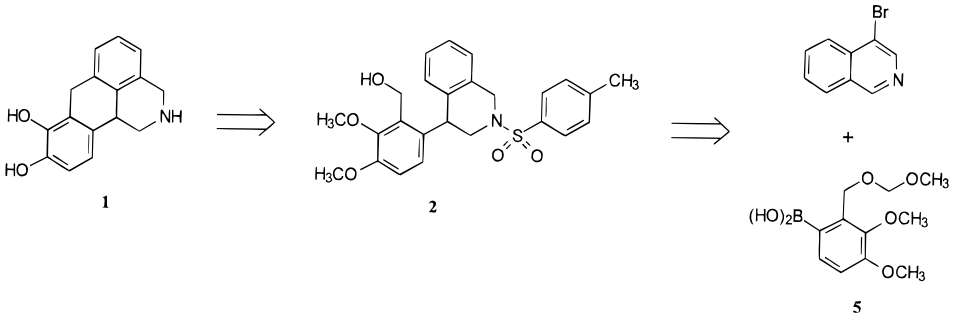
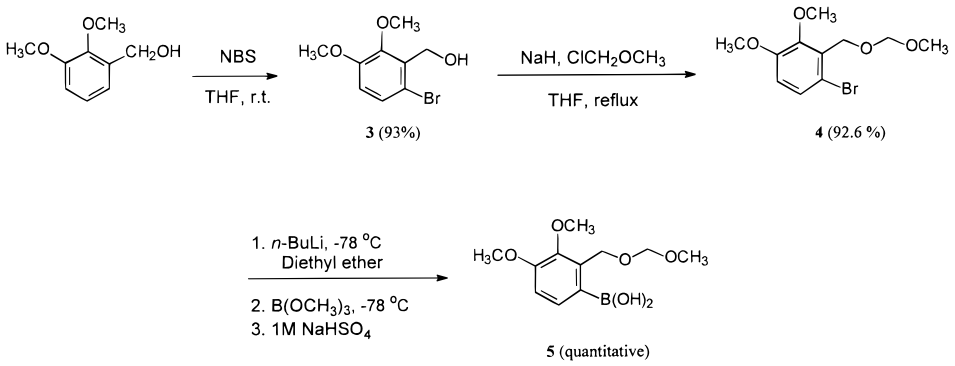
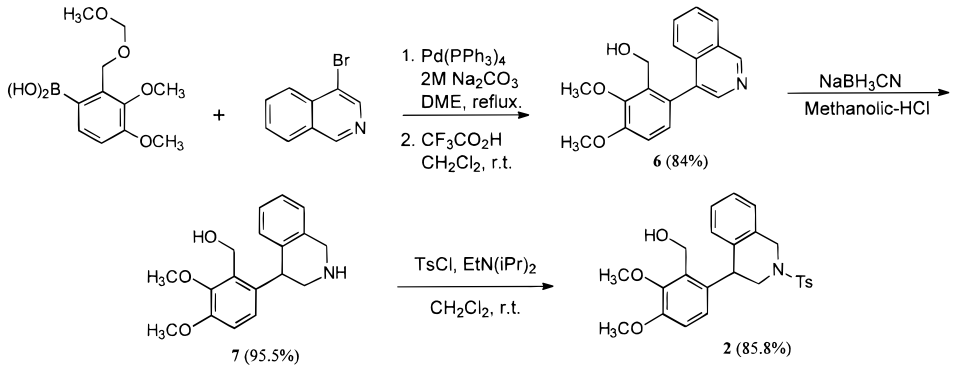
Scheme 1



Scheme 2



Scheme 3



was heated at reflux for 1 h. The reaction was left to cool to room temperature, and then 13.5 mL (14.33 g, 0.178 mol) of methoxymethyl chloride was added and the solution was stirred at reflux for another 1 h. After cooling to room temperature the mixture was added slowly to 500 mL of ice−water, and the THF was then evaporated. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$), filtered, and then concentrated. The oily residue was distilled (95 °C, 60 mmHg) to afford 48.0 g of a colorless oil (92.6%). NMR: δ 3.44 (s, 3H, O−CH_3); δ 3.83 (s, 3H, O−CH_3); δ 3.855 (s, 3H, O−CH_3); δ 4.719 (s, 2H, Ar−CH_2−O); δ 4.744 (s, 2H, O−CH_2−O); δ 6.767 (d, 1H, Ar−H, J = 8.5 Hz); δ 7.27 (d, 1H, Ar−H, J = 8.5 Hz). CIMS m/z: 290, 292 (M^+, 52; M + 2, 50); 229, 231 (M^+ − 61, 98; M^+ + 2 − 61, 100). Anal. Calcd for $C_{11}H_{15}BrO_4$: C, 45.38; H, 5.19. Found: C, 45.54; H, 5.19.

3,4-Dimethoxy-2-(methoxymethoxy)methylboronic Acid (5). The methoxymethyl ether **4** (48 g; 0.165 mol) was dissolved in 300 mL of dry diethyl ether and stirred under argon at −78 °C. A solution of *n*-butyllithium (123.8 mL of 1.6 M) was cooled to −78 °C, then cannulated into the solution of **4**, and the mixture was left to stir for 15 min. Trimethyl borate 56.2 mL (51.43 g, 0.495 mol) was added rapidly to the cold reaction. The mixture was left to stir and allowed to warm to room temperature over 4 h. The reaction was neutralized by dropwise addition of 200 mL of 1 M aqueous $NaHSO_4$. The ethereal layer was dried ($MgSO_4$), filtered, and concentrated. An oily residue was obtained in essentially quantitative yield (42.2 g) that was used for the subsequent reaction without further purification. A sample for NMR was recrystallized from diethyl ether−hexane, but drying the crystals under high vacuum led to apparent desolvation with the formation of a white gum. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.39 (s, 3H, OCH_3); δ 3.81 (s, 3H, O−CH_3); δ 3.87 (s, 3H, O−CH_3); δ 4.7 (s, 2H, Ar−CH_2−O); δ 4.8 (s, 2H, O−CH_2−O); δ 6.5 (s, 2H, (B−$(OH)_2$); δ 6.9 (d, 1H, Ar−H, J = 8.5 Hz); δ 7.6 (d, 1H, Ar−H, J = 8.0 Hz).

4-(3,4-Dimethoxy-2-hydroxymethylphenyl)isoquinoline (6). To 25 g (0.120 mol) of 4-bromoisoquinoline (Aldrich) in 200 mL of dimethoxyethane (DME) under an atmosphere of argon were added all the crude product, **5** (0.165 mol), from the previous reaction and 165 mL of aqueous 2 M sodium carbonate solution. To this mixture was added 5 g (3.6 mol %) of tetrakis-(triphenylphosphine)palladium(0), and the reaction was heated at reflux for 10 h. The biphasic mixture was allowed to cool, and the layers were separated. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with cold 2 N sodium hydroxide solution, then water, and finally dried (Na_2SO_4). The solvent was filtered and evaporated, the residue was taken up into trifluoroacetic acid (TFA) solution in dichloromethane (20 mL of TFA in 100 mL of CH_2Cl_2), and the solution was stirred overnight. The reaction was then diluted with 300 mL of water, carefully basified with 2 N sodium hydroxide solution, and then extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and filtered, and the solvent was

evaporated. The residue was crystallized from diethyl ether to afford 30.4 g (84%) of an off-white powder: mp 128−130 °C. ^{1}H NMR: δ 3.96 (s, 3H, O−CH_3); δ 4.02 (s, 3H, O−CH_3); δ 4.34 (d, 1H, Ar−CH_2−O, J = 12.5 Hz); δ 4.4 (d, 1H, Ar−CH_2−O, J = 12.0 Hz); δ 7.01 (s, 2H, Ar−H); δ 7.56 (d, 1H, Ar−H, J = 8.5 Hz); δ 7.63 (m, 2H, Ar−H); δ 7.79 (d, 1H, Ar−H, J = 8.5 Hz); δ 8.40 (s, 1H, Ar−H); δ 9.23 (s, 1H, Ar−H). CIMS m/z: 296 (M^+ + H, 100); 278 (M^+ + H − 18, 76). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.02; H, 5.82; N, 4.70.

4-(3,4-Dimethoxy-2-hydroxymethylphenyl)-1,2,3,4-tetrahydroisoquinoline (7). The isoquinoline **6** (30 g; 101.6 mmol) was dissolved in 250 mL of anhydrous methanol under an atmosphere of argon. To that solution was added 38.4 g (0.611 mol) of powdered sodium cyanoborohydride in portions. A few drops of methanolic bromocresol green solution were added, which turned the color of the reaction blue. The reaction was acidified (the color of the reaction turned yellow) and maintained acidic by adding 10% methanolic-HCl solution though a dropping funnel. When the yellow color persisted, the solution was basified with 2 N NaOH solution, and the methanol was evaporated. The residue was partitioned between 200 mL of water and 200 mL of dichloromethane, and the aqueous layer was reextracted with dichloromethane. The organic layers were dried (Na_2SO_4), and the solvent was filtered and evaporated. The residue was triturated with diethyl ether to afford 29.04 g (95.5%) of the amino alcohol **7** as a white solid: mp 160−162 °C. ^{1}H NMR (500 MHz NMR, DMSO): δ 2.8 (dd, 1H, ArCH−CH_2−N, J = 7.5, 12.5 Hz); δ 3.19 (dd, 1H, ArCH−CH_2−N, J = 5.5, 13.0 Hz); δ 3.74 (s, 6H, O−CH_3); δ 3.87 (d, 1H, Ar−CH_2−N, J = 16.0 Hz); δ 3.99 (d, 1H, Ar−CH_2−N, J = 16.0 Hz); δ 4.32 (t, 1H, Ar−CH−CH_2N, J = 6.5 Hz); δ 4.64 (m, 3H, Ar−CH_2−OH and −NH); δ 6.55 (d, 1H, Ar−H, J = 8.5 Hz); δ 6.76 (d, 1H, Ar−H, J = 8.0 Hz); δ 6.9 (d, 1H, Ar−H, J = 8.5 Hz); δ 6.99 (t, 1H, Ar−H, J = 7.5 Hz); δ 7.05 (m, 2H, Ar−H). CIMS m/z: 300 (M^+ + 1, 45); 282 (M^+ + 1 − 18, 100). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.00; H, 7.04; N, 4.60.

4-(3,4-Dimethoxy-2-hydroxymethylphenyl)(*N*-*p*-toluenesulfonyl)-1,2,3,4-tetrahydroisoquinoline (2). The amino alcohol **7** (20 g; 66.8 mmol) was dissolved in 250 mL of dichloromethane under an atmosphere of argon. To that solution 12.74 g (66.79 mmol) of *p*-toluenesulfonyl chloride was added, followed by 15.13 mL (11.23 g; 86.85 mmol) of *N*,*N*-diisopropylethylamine, which was added slowly via syringe. The solution was stirred at room temperature for 13 h. The dichloromethane solution was washed with 2 N HCl and then dried ($MgSO_4$). After filtration, the solvent was evaporated, and the residue was crystallized from ethyl acetate to afford 25.95 g (85.8%) of the *N*-*p*-tosyl amido alcohol as a white solid: mp 158−160 °C (lit. 166−168 °C). ^{1}H NMR and chemical ionization MS were identical to material prepared by the method of Ghosh et al.[1]

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