

A Novel Scalable Synthesis of Pramipexole

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Abstract:

Pramipexole is a dopamine D₂ subfamily receptor agonist that is used for the treatment of Parkinson's disease. We report here on the successful application of the Fukuyama alkylation protocol to the development of a novel and scalable process for synthesis of pramipexole and its pharmaceutically acceptable salts. The synthesis consists of converting the crucial intermediate (S)-2,6-diamino-4,5,6,7-tetrahydrobenzothiazole to (6S)-N-(2-amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitrobenzenesulfonamide, which is in turn monoalkylated to (6S)-N-(2-amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitro-N-propylbenzenesulfonamide. Deprotection of the latter yields pramipexole base, which is finally converted to a crude pramipexole dihydrochloride monohydrate with a yield of over 50% over four steps. The process allows for the telescoping of the final three steps, has high conversion rates of intermediates, offers ease of purification, and preserves high optical purity throughout all of the stages.

Introduction

Pramipexole (Figure 1, **1**) has the chemical name of (S)-2-amino-6-N-propylamino-4,5,6,7-tetrahydrobenzothiazole, and it is a synthetic aminobenzothiazole derivative that has potent agonist activity for the D₂ subfamily of dopamine receptors, with a preference for the D₃ receptor. Pramipexole dihydrochloride monohydrate (**2**, Mirapex) was approved for treatment of signs and symptoms of idiopathic Parkinson's disease and restless-legs syndrome by the U.S. Food and Drug Administration in 1997. Additionally, studies have indicated its potential application for the treatment of some cognitive disorders.^{1–5}

Along with its salts, pramipexole was first defined in the European patent application EP 0186087.⁶ This presented three general routes for its synthesis (Scheme 1). All of these start with the protection of the amino group of 4-aminocyclohexanol (**3**) to form an N-protected 4-aminocyclohexanol (**4**), which

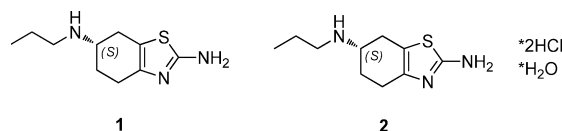
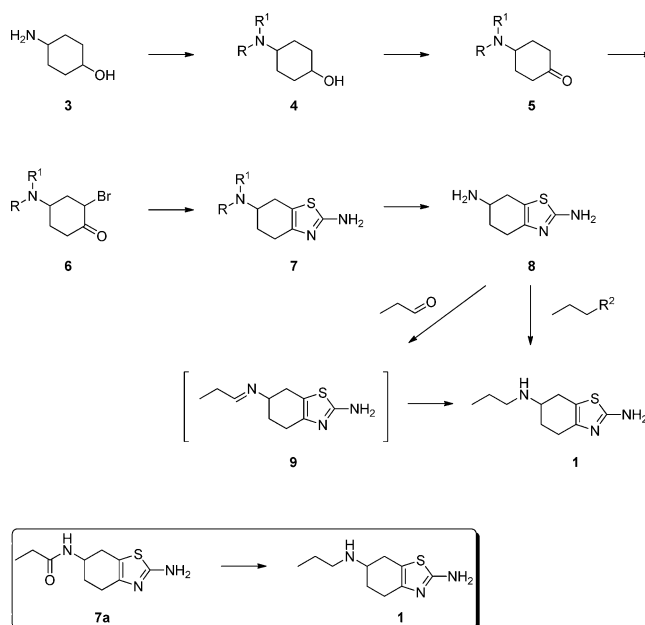


Figure 1. Pramipexole **1** and pramipexole dihydrochloride monohydrate **2**.

Scheme 1. Synthetic pathways of pramipexole, as reported in EP0186087^a



^a R = H, R¹ = protecting group, or R and R¹ together form a protecting group. R² can be a halide or a nucleophilically exchangeable group (such as OTs, OMs).

is then oxidized to an N-protected 4-aminocyclohexanone (**5**). This ketone **5** is then brominated to form α-bromo ketone (**6**), which is subsequently reacted with thiourea to obtain an N-protected 2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (**7**). In the case of intermediate **7a** (R = H, R¹ = CH₃CH₂CO), this can be directly reduced with a reducing agent to give racemic pramipexole (**1**). Alternatively, **7** can be deprotected to form the crucial intermediate 2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (**8**). From here on, **8** can be converted to pramipexole (**1**) by two possible routes:

- (1) by reductive amination with propionaldehyde and a suitable reducing agent, and
- (2) by direct alkylation with an alkyl, substituted by a nucleophilically exchangeable group, in the presence of a base

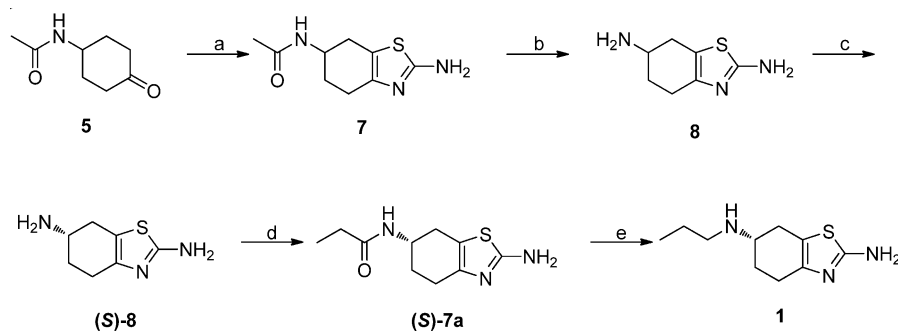
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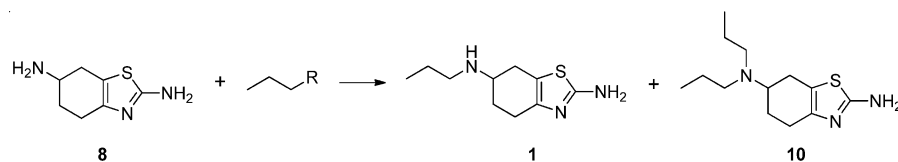
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Scheme 2. Synthetic pathway and resolution of pramipexole, as reported by Schneider and Mierau^a



^a Reagents and conditions: (a) first Br₂, AcOH, then thiourea; (b) 47% aqueous HBr, reflux; (c) resolution with tartaric acid; (d) propionic anhydride, triethylamine (TEA), tetrahydrofuran (THF); (e) borane–THF complex.

Scheme 3. Alkylation of 2,6-diamino-4,5,6,7-tetrahydrobenzothiazole 8 with an alkyl halide^a



^a R can be a halide or a nucleophilically exchangeable group (such as OTs, OMs).

Although (*S*)-pramipexole (**1**) was reported in EP0186087, no detailed information was given regarding its stereoselective synthesis or resolution.⁶ A possible resolution of the enantiomers was later presented by Schneider and Mierau.⁷ They used the same general route for the synthesis of racemic 2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (**8**), but added a resolution step using *L*-tartaric acid, which resulted in *S*-(–)-2,6-diamino-4,5,6,7-tetrahydrobenzothiazole (*S*)-**8**. This was then acylated to yield *S*-(–)-*N*-(2-amino-4,5,6,7-tetrahydrobenzothiazol-6-yl)propionamide (*S*)-**7a**, which was subsequently reduced to *S*-pramipexole (**1**) by a borane/tetrahydrofuran (THF) complex (Scheme 2).⁷

Since this report by Schneider and Mierau,⁷ studies have been focused on providing new synthetic routes for the synthesis of pramipexole and its pharmaceutically acceptable salts. Efforts were made in the attempt to find new synthetic strategies, or to improve the existing ones.^{8–17} Our aim was to develop a novel

and industrially acceptable process for the synthesis of pramipexole and its pharmaceutically acceptable salts. To achieve this, we investigated the possibility of improving the alkylation of intermediate **8** with alkyl halides. The major drawback of this method, which was first disclosed in the patent publication EP 0186087, was the formation of a dialkylated side product **10** (Scheme 3). This limits the yield to approximately 30% and requires tedious separation of the product using column chromatography, making the synthesis unsuitable for industrial purposes. In the present study, we report on the successful application of the Fukuyama protocol^{18,19} for monoalkylation of benzothiazole **8**, which resulted in the development of an industrially applicable process for the synthesis of pramipexole.²⁰

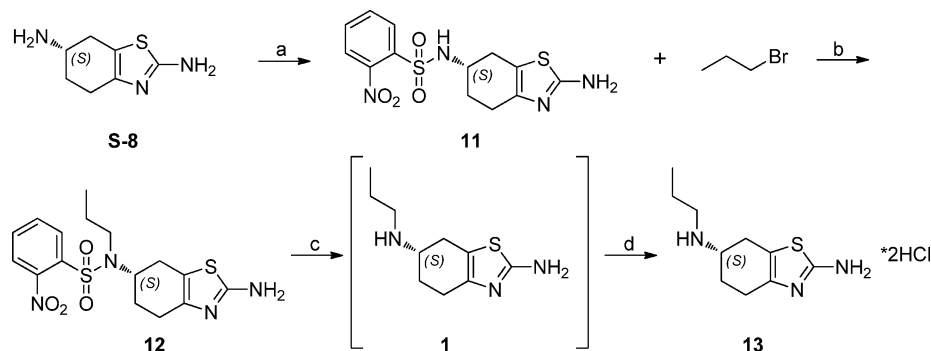
Results and Discussion

In the synthetic route of the present study, *S*-(–)-2,6-diamino-4,5,6,7-tetrahydrobenzothiazole ((*S*)-**8**) is converted to the sulfonamide (**11**) by reaction with 2-nitrosulfonyl chloride in the presence of excess TEA in THF at –10 °C. A simple workup gives sulfonamide **11** as a yellow solid. In a typical Fukuyama protocol, intermediate **11** is then dissolved in acetonitrile and treated with propyl bromide in the presence of K₂CO₃. The workup here gives *N*-propyl sulfonamide **12** as a pale-yellow solid, with almost quantitative conversion. The final step consists of selective removal of the sulfonamide protecting group with thioglycolic acid. The target *S*-pramipexole (**1**) is

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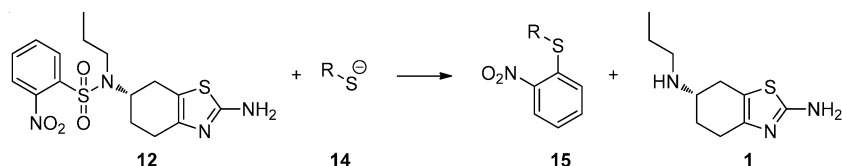
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Scheme 4. Synthetic route of pramipexole via the Fukuyama protocol^a



^a Reagents and conditions: (a) *o*-nitrobenzenesulfonyl chloride, TEA, THF, -10°C to room temperature over 1 h, 90%; (b) K_2CO_3 , AcCN, 60°C , 12 h, 90%; (c) Thioglycolic acid, LiOH, EtOH; (d) EtOH, $\text{HCl}_{(\text{g})}$, 70% over two steps.

Scheme 5. Deprotection of the sulfonamide protective group by a thiolate ion



obtained as a pale off-white solid. Optionally, the product can be converted to its dihydrochloride salt **13** by passing gaseous HCl through a solution of **1** in ethanol (Scheme 4). The process was successfully scaled up to a 25-kg scale, making it industrially acceptable for this low-dose drug. An important feature of this synthesis is also the possibility to telescope the last three steps.

The first reaction of this procedure is the formation of the sulfonamide **11**. This reaction was carried out in THF with the use of a small excess of the amine, which allowed complete use of the sulfonyl chloride, while at the same time providing a simple purification step. After the removal of precipitated triethylammonium chloride, intermediate **11** is precipitated from water, while the excess amine **8** remains dissolved in water due to its high hydrophilicity. The reaction is monitored by HPLC, and the reaction time is set accordingly.

The alkylation step consists of reacting sulfonamide **11** with excess propyl bromide in the presence of K_2CO_3 . The reaction was initially performed in dimethylformamide (DMF), which was later replaced with acetonitrile to facilitate the change of solvents during the purification step. The end point of the reaction was determined by HPLC, and the content of **11** was lower than 0.1%. Again, extraction was used for the purification of the intermediate. Excess propyl bromide was removed under reduced pressure, while traces of nonreacted starting material were removed by alkaline extraction. Sulfonamide **12** can be stored as an ethanolic solution for use in the next reaction step. To ensure that all propyl bromide is removed, GC carry-over analysis was performed on several consecutive batches. The content of propyl bromide was below the limit of detection (LOD = 100 ppm).

The final step was the removal of the sulfonamide protecting group. This reaction was initially carried out in DMF with thiophenol and K_2CO_3 . The reaction was initiated by activating the thiol used for the deprotection. This was achieved by adding a suitable base to a solution of the thiol and allowing for the formation of a thiolate ion **14** (Scheme 5). Failure in the

preparation of a thiolate resulted in a lower yield and a longer reaction time. After addition of the sulfonamide **12** to the reaction mixture, the conversion progress was relatively fast, with the end point determined by HPLC. As a result of this reaction, a stoichiometric amount of a thiol species **15** was formed along with the main product.

If thiophenol is used for the final deprotection, the thiophenolate byproduct would present a problem for the purification of the product, which would involve the use of chromatographic purification. Careful consideration of the reaction offered a solution to this problem: we replaced thiophenol with thioglycolic acid and thus successfully used this for deprotection of the sulfonamide **12** while at the same time allowing us to remove the byproduct thiolate **15** ($\text{R} = -\text{CH}_2\text{COOH}$) with alkaline extraction. Since the initial solvent must be replaced by dichloromethane prior to the extraction, DMF was inadequate for this process, and so it was replaced by ethanol. Experiments on a laboratory scale showed that the use of K_2CO_3 might produce additional side products (from TLC analysis). Thus LiOH was preferred in the development stage, leading to the replacement of K_2CO_3 with LiOH in the final protocol.

After completion of the reaction, ethanol was replaced by dichloromethane and the byproduct removed by alkaline extraction. The organic phases containing pramipexole **1** were collected and concentrated. Ethanol and water were added, followed by the passage of gaseous HCl through the solution. Crude pramipexole dihydrochloride monohydrate **2** (HPLC purity of 94.4%) was obtained with a 70% yield from **12**. To ensure that the quality of the final product conforms to the regulatory standards for API, two crystallizations rounds are needed. A first crystallization from methanol/ethanol gives a product with 99.6% HPLC purity with a yield of 77%. A second crystallization (yield is 84%, HPLC purity of 99.8%) is needed to ensure that all related substances are within the regulatory limits. The content of water in the final product is controlled, and humidification in a flow of air is performed to obtain the final pramipexole dihydrochloride monohydrate **2**. The quality

of the final product **2** is controlled by validated methods, utilizing potentiometric titration assay and HPLC of related substances. Related substances are characterized on the basis of reference standards of pramipexole and each individual impurity. To ensure the optical purity, both starting material and product are checked for the presence of the *R*-isomer, which is limited below 0.5%.

The whole synthetic process of the active substance was evaluated regarding genotoxic impurities. Starting materials, reagents, intermediates, and reaction byproducts were considered. Several compounds with genotoxic potential were identified, and safety limits were calculated on the base of TTC (Threshold of Toxicological Concern) and maximal daily dose or data from long-term carcinogenicity studies according to *EMA Guideline on the limits of genotoxic impurities CPMP/SW/5199/02*. The quantities of these impurities were determined by appropriate HPLC methods (using reference standards of these impurities), and the results of analyses show that all potential genotoxic impurities are absent or present at levels below 30% of the acceptable limits.

Conclusion

By using the Fukuyama protocol for the alkylation of diaminobenzothiazole (**S-8**), we were able to develop an efficient telescoped process for the synthesis of pramipexole. Although the number of steps needed to produce the final product is increased by one step if compared to the reductive alkylation method or the amide reduction method, this process still offers many advantages. First, transformation of the highly hydrophilic diamine ((**S-8**) to a more lipophilic sulfonamide (**11**) makes handling of the intermediates easier and enables the use of extraction as an efficient purification method. Second, the process provides high conversion rates of the intermediates (the overall yield of the synthesis of crude pramipexole starting from key intermediate (**S-8**) was 54%), and avoids the formation of undesired side products. Third, the process preserves high optical purity throughout all of the steps; racemisation does not occur at any of the steps in this process. Finally, the process uses inexpensive reagents, which are also comparatively safe and easy to handle, making it an industrially acceptable synthesis.

Experimental Section

Reagents and solvents were purchased and used as received. The ^1H and ^{13}C spectra were recorded in dimethylsulfoxide (DMSO) at 300 MHz on a VARIAN INOVA 300 MHz NMR spectrometer. The chemical shifts were reported as δ ppm relative to tetramethylsilane. The FT-IR spectra were obtained as a potassium bromide pellet using a Spectrum 100 Perkin-Elmer FT-IR spectrometer. Mass spectra were recorded on a Q-TOF Premier spectrometer, using electron-spray ionization. Melting points were determined on a Wagner & Munz hot-stage microscope and are uncorrected. Elemental analysis was performed on a Perkin-Elmer 2400 CHN Elemental Analyzer.

HPLC chromatographic purity was determined using a Gemini C-18 110A column (150 mm \times 4.6 mm, 5 μm particles) with a flow rate of 1.0 mL/min, detection at 263 nm, and an eluent system of: A = 0.01 M KH_2PO_4 (pH = 10); B =

$\text{CH}_3\text{CN}/\text{CH}_3\text{OH}/\text{H}_2\text{O}$ = 6:3:1 (pH = 10). The following gradient was applied: 0 min, 20% B; 0–18 min, 20% B \rightarrow 50% B; 18–24 min, 50% B \rightarrow 70% B; 24–40 min, 70% B; 40–41 min 70% B \rightarrow 20% B; 20% B re-equilibration 7 min; T = 25 $^\circ\text{C}$.

Enantiomeric purity was determined using a Chiralpack IA column (250 mm \times 4.6 mm, 5 μm particles) with a flow rate of 0.8 mL/min, detection at 263 nm, and a mobile phase of: hexane/ethanol/diethylamine = 75:25:0.05; T = 25 $^\circ\text{C}$. Retention times for the product and its enantiomer are 9.0 and 7.2 min, respectively. The content of the *R*-enantiomer is below 0.5%.

Preparation of (6S)-N-(2-Amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitrobenzenesulfonamide 11. 2-Nitrobenzenesulfonyl chloride (390 g, 1.76 mol) was dissolved in 4.0 L of THF, and the solution was cooled to approximately -10 $^\circ\text{C}$. TEA (740 g, 7.313 mol) and (6S)-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine (327 g, 1.932 mol) were added. The suspension was heated during mixing to approximately 25 $^\circ\text{C}$, and allowed to react for 1 h. Precipitated triethylammonium chloride was filtered off, and the filtrate was concentrated to about one-third of the volume. Water was added (2.0 L) and approximately half of the solvent was distilled off. Water was added again (2.0 L), and the mixture was cooled to 25 $^\circ\text{C}$ and mixed for about 1 h. The precipitated product was separated by filtration and dried under vacuum at 50 $^\circ\text{C}$, to obtain sulfonamide **11** (590 g, 1.665 mol) as a pale yellow solid with a yield of 94.6% and a HPLC purity of more than 98%. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 1.63–1.82 (m, 2H), 2.37–2.47 (m, 3H), 2.58–2.65 (m, 1H), 3.49–3.58 (m, 1H), 6.68 (s, 2H), 7.83–7.97 (m, 3H), 8.04–8.09 (m, 1H), 8.30 (bs, 1H). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$) δ 24.5, 29.3, 29.6, 50.0, 111.6, 124.2, 129.6, 132.6, 133.4, 134.1, 144.1, 147.6, 166.3. FT-IR (cm^{-1}): 3418 (NH_2 stretching), 3418 (N–H stretching of R- SO_2 –NH), 2944 (C–H stretching of CH_2), 1618 (C=N stretching), 1525 (heteroaromatic ring skeleton), 1328 (R- SO_2 –N asymmetric stretching), 1156 (R- SO_2 –N symmetric stretching), 741 (ArC–H out of plane). EI-MS m/z 355.1 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_4\text{S}_2$: C, 44.06; H, 3.89; N, 15.81. Found: C, 44.07; H, 4.25; N, 15.50. Melting point: 227–230 $^\circ\text{C}$.

Preparation of (6S)-N-(2-Amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitro-N-propylbenzenesulfonamide 12. Potassium carbonate (1890 g, 13.675 mol), (6S)-N-(2-amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitrobenzenesulfonamide (590 g, 1.665 mol) **11** and propyl bromide (1.09 L, 12 mol) were suspended in 4.1 L of acetonitrile. The mixture was heated during stirring to about 60 $^\circ\text{C}$, and left to react for approximately 12 h. The end point of the reaction was determined by HPLC (the content of **11** was less than 0.1%). The mixture was cooled off to 25 $^\circ\text{C}$, and the potassium bromide and potassium carbonate were removed by filtration. The solution was concentrated to about one-quarter of the volume (not exceeding 60 $^\circ\text{C}$) and cooled to room temperature. Methylene chloride (2.0 L) and 1.0 M aqueous NaOH (2.43 L) were added, and the mixture was mixed for about 30 min. The phases were separated, and the water phase was washed again with methylene chloride (1.46 L). The organic phases

were collected and concentrated to about one tenth of the volume. Ethanol (0.87 L) was added and the solution was again concentrated to one tenth of the volume. Ethanol (3.35 L) was added and the ethanolic solution of (6*S*)-*N*-(2-amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitro-*N*-propylbenzenesulfonamide **12** was stored for further reaction. The assay of **12** was determined by HPLC and the yield was 89%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.54–1.66 (m, 3H), 1.86–2.00 (m, 1H), 2.47 (m, 3H), 2.71–2.80 (m, 1H), 3.22–3.35 (m, 2H), 3.97–4.05 (m, 1H), 6.70 (s, 2H), 7.81–7.97 (m, 3H), 8.09–8.12 (m, 1H). ¹³C NMR (300 MHz, DMSO-*d*₆) 11.0, 24.6, 25.9, 27.3, 27.4, 45.6, 55.1, 112.0, 124.1, 130.0, 132.6, 133.4, 134.1, 143.8, 147.4, 166.5. FT-IR (cm⁻¹): 3367 (NH stretching), 3097 (ArC–H stretching), 2934 (C–H stretching of CH₂), 1617 (C=N stretching), 1543 (Heteroaromatic ring skeleton), 1340 (R–SO₂–N asymmetric stretching), 1220 (R–SO₂–N symmetric stretching), 742 (ArC–H out of plane). EI-MS *m/z* 397.1 (M⁺). Anal. Calcd for C₁₆H₂₀N₄O₄S₂ (× 0.5 H₂O): C, 47.39; H, 5.22; N, 13.82. Found: C, 47.21; H, 5.10; N, 13.54. Melting point: 101–105 °C.

Preparation of (S)-2-Amino-6-*N*-propylamino-4,5,6,7-tetrahydrobenzothiazole Dihydrochloride 13. Ethanol (2.35 L) and LiOH (288 g, 12 mol) were put into the reactor, and the suspension was cooled to about 0–5 °C. Over 30 min, thioglycolic acid (720 g, 7.816 mol) was added, maintaining the temperature below 25 °C. The suspension was heated to about 25 °C and mixed for about 45 min. The ethanolic solution of (6*S*)-*N*-(2-amino-4,5,6,7-tetrahydrobenzothiazole-6-yl)-2-nitro-*N*-propylbenzenesulfonamide **12** (3.45 L, containing 590 g of **12**) was added, and the air in the reactor was replaced by nitrogen. The mixture was heated to 50 °C and mixed for 4 h. The mixture was cooled to 25 °C and filtered. The filtrate was concentrated at 40 °C to about one-quarter of the volume, and cooled to room temperature. Methylene chloride (4.23 L) and

1.0 M aqueous NaOH (2.53 L) were added, and the mixture was mixed for about 30 min. The phases were separated, and the water phase was washed again with methylene chloride (4.23 L). The organic phases that contained pramipexole were collected and concentrated to one-quarter of the volume, and 5.0 L of ethanol was added. Water (27.6 mL, 1.53 mol) was added to this solution, and the mixture was cooled to about –10 °C. Gaseous HCl (200 g) was introduced into the solution; the temperature of the solution must not rise above 25 °C. After this addition, the suspension was heated to 40 °C and concentrated to two-thirds of the volume. Ethanol (2.65 L) was added and the suspension was concentrated to half of the volume. Ethanol (3.5 L) was again added, and the suspension was concentrated to half of the volume. The suspension was cooled to –15 °C and the solid was separated by filtration and dried at 25 °C and finally at 40 °C on air, to obtain pramipexole dihydrochloride monohydrate (315 g) with a yield of 70% (calculated from **12**) and an HPLC purity of 94.4%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.89 (t, *J* = 7.5 Hz, 3H), 1.62–1.75 (m, *J* = 7.6 Hz, 2H), 1.87–2.00 (m, 1H), 2.24–2.28 (m, 1H), 2.55–2.67 (m, 2H), 2.71–2.79 (m, 1H), 2.86–2.89 (m, 2H), 2.99–3.06 (m, 1H), 3.47 (m, 1H), 9.50 (m, 2H). ¹³C NMR (300 MHz, DMSO-*d*₆) 11.1, 19.1, 20.9, 23.5, 24.8, 46.0, 52.3, 111.0, 132.9, 168.7. FT-IR (cm⁻¹): 3150–3450 (NH₂ stretching), 2700–3000 (C–H stretching), 1600–1650 (C=N stretching), 1550–1600 (heteroaromatic ring skeleton).

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