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A Scalable Process for the Novel Antidepressant ABT-200

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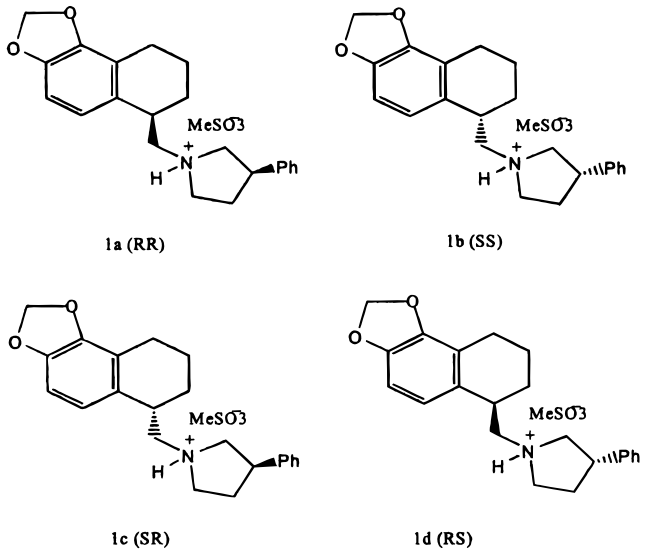
Abstract:

A scalable process for the novel antidepressant ABT-200, starting with 5,6-methylenedioxy-1-tetralone, is described. The new process improves the scale-up and safety concerns associated with the previously employed route to ABT-200. The scalable process eliminates the potential for HCN exposure to employees and produces ABT-200 in a stereospecific fashion. (TMS)CN was replaced by nitromethane as a reagent to introduce the nitrogen in the ABT-200 molecule. This stereospecific process employs an epimerization procedure which takes advantage of a key difference in the solubility of the two diastereomers of the succinimide intermediate, 9a/b and 10a/b. Balancing the rate of epimerization with the solubility of the diastereomers in the reaction medium was an essential factor in optimizing the yield and efficiency of this simple, one-pot reaction. The solubility-directed epimerization was demonstrated in both a predominantly aqueous and an organic solvent mixture. The succinimide derivative 10a/b was then converted to ABT-200. This improved procedure was used to prepare kilogram quantities of ABT-200.

Introduction

Inhibition of norepinephrine reuptake is the mechanism of action of many of the older and well-established antidepressant agents used in the clinic today, and research continues to focus on selective agents as well as ones working through multiple mechanisms.[2] An important regulatory mechanism of norepinephrine release is mediated through presynaptic α-2 receptors[3,4] which, when stimulated, inhibit the further neuronal release of the neurotransmitter norepinephrine. Reducing the effect of this negative feedback mechanism could potentially lead to a more effective antidepressant agent. An antidepressant agent possessing a combination of α-2 presynaptic antagonism and norepinephrine uptake inhibition has the potential to possess a more rapid onset of action. The effort to develop a compound with this property was reported by a group at Abbott Laboratories.[5] The compound chosen for further development was ABT-200. This compound possessed the fortuitous property of being a racemate, where the **1a** (*R*,*R*) enantiomer was a potent α-2 receptor antagonist and the **1b** (*S*,*S*) enantiomer was a norepinephrine uptake inhibitor. Since the optimal dose of each enantiomer was not known, a process for the racemate was developed. Our effort to develop a scalable synthesis to provide kilogram quantities of ABT-200 for further evaluation is described here.



Earlier syntheses[5a] (Scheme 1), although quite acceptable for making the initial quantities of ABT-200, required modifications before large-scale production of ABT-200 was attempted. The many steps and the use of trimethylsilylcyanide to convert 5,6-methylenedioxy-1-tetralone[6] (**2**) to unsaturated nitrile **3** were major concerns. The unsaturated nitrile **3** was a key intermediate in the initial procedures, and two approaches were used to introduce the side chain. In the first method, the nitrile **3** was converted to carboxylic acid **4** in two steps. DCC-mediated coupling of the acid **4** and 3-phenylpyrrolidine (**14**) afforded the amide **5** as a diastereomeric mixture. Since **14** was not commercially available, it was prepared separately in a three-step procedure from the benzylidenemalonic acid diethyl ester (**13**). The

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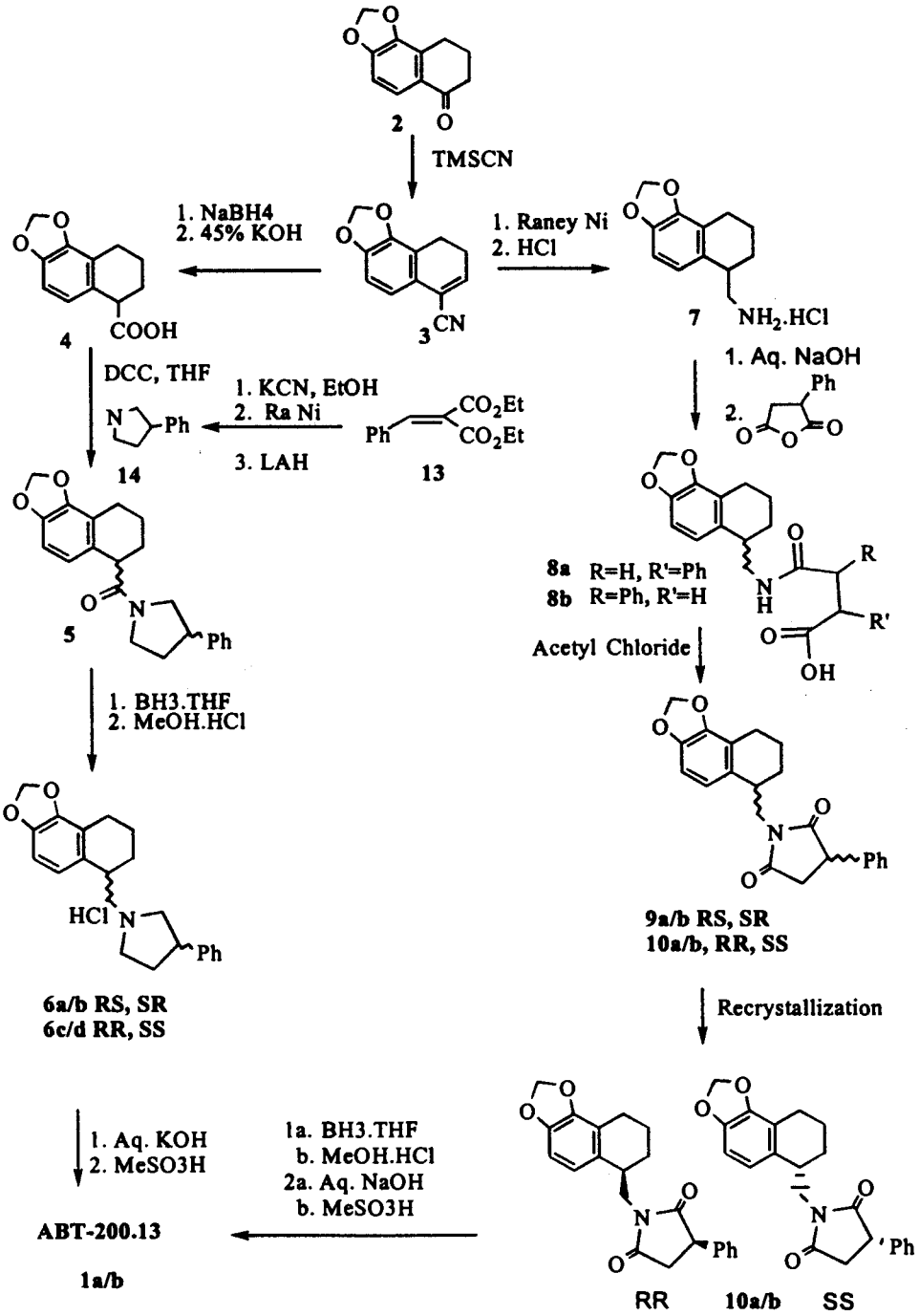
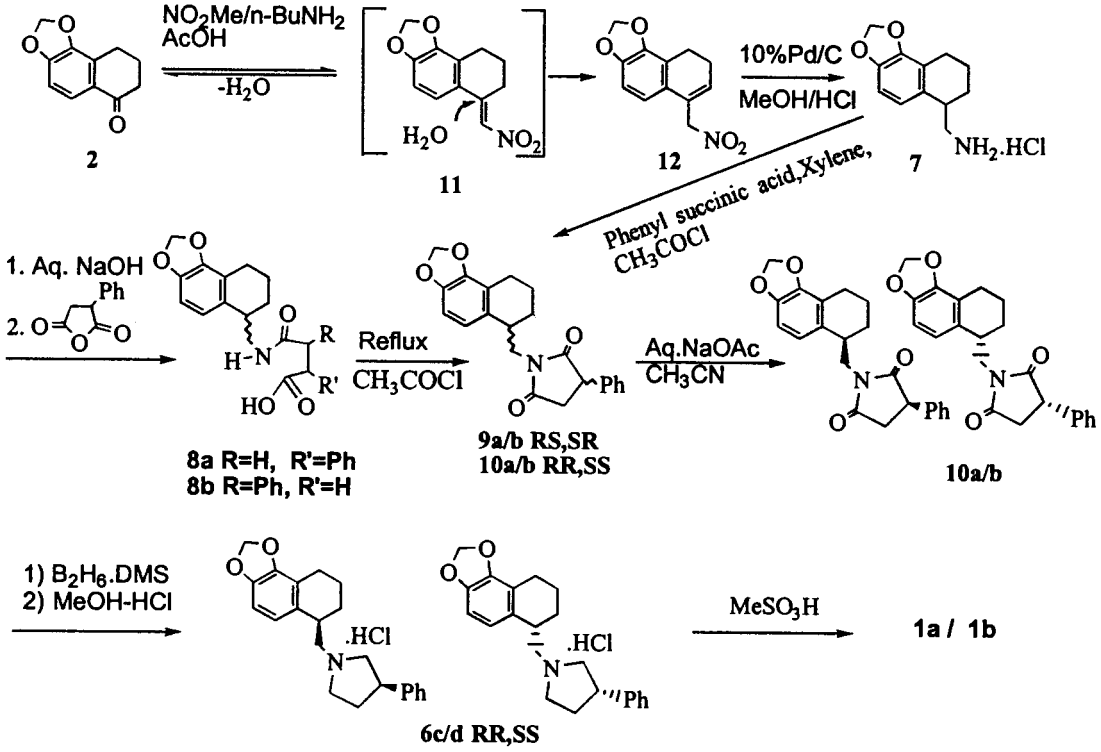
Scheme 1



diastereomers were not separated at this stage, and the amide was reduced with borane−tetrahydrofuran complex. The reaction mixture was quenched with methanolic−HCl to give a diastereomeric mixture of HCl salts of **6a**/**b** and **6c**/**d**. Fractional crystallization of the diastereomers as the hydrochloride salt was not successful. However, the HCl salt was converted to the methanesulfonate salt, which was crystallized to provide the desired racemate **1a**/**b** (*RR*,*SS*) without significant quantities of the other diastereomer **1c**/**d** (*RS*,*SR*). The low solubility and low bioavailability of the HCl salt of ABT-200 prompted the development of the methanesulfonate salt, with an improved bioavailability and solubility.

Scheme 1 also describes another method initially used to introduce the side chain of ABT-200. The unsaturated nitrile **3** was hydrogenated to provide the amine hydrochloride **7** in a straightforward fashion. This amine salt **7** was treated with aqueous sodium hydroxide and then condensed with phenylsuccinic anhydride to provide the acid-amide **8a**/**b** as a complex mixture of isomers. The isomers were not separated at this stage, and the cyclization to the succinimide intermediate **9a**/**b** and **10a**/**b** was completed when the acid-amide **8a**/**b** was refluxed with acetyl chloride. The desired succinimide diastereomer, **10a**/**b** (*RR*,*SS*) was obtained in about 25% yield after a series of fractional recrystallizations. The second synthetic route has the advantage over the first route in having the isomers separated at an earlier stage (the succinimide intermediate) rather than at the final product stage. The succinimide intermediate, **10a**/**b**, was reduced

Scheme 2



with borane−tetrahydrofuran complex, followed by a methanolic−HCl quench to afford ABT-200 as the HCl salt. In contrast to the first method described, this HCl salt consisted of mainly one diastereomer, **6c**/**d**. This salt was then converted to the desired ABT-200 methanesulfonate **1a**/**b**.

Fortunately, both procedures do have intermediates where the undesired stereochemistry could be epimerized under basic conditions to compounds with the desired stereochemistry. Of these two compounds, **5** and **9**, we focused our efforts on the succinimide **9**. Under the reaction conditions, both the diastereomers of the succinimide **9a**/**b** and **10a**/**b** are produced in approximately equal amounts, representing the approximately equal thermodynamic stability of these two diastereomers. Without an epimerization procedure, only half of the desired product could be recovered. The mother liquor was enriched with the succinimide with the undesired stereochemistry **9a**/**b**. Initial attempts to epimerize the undesired *RS*,*SR* succinimide isomers to the desired *RR*,*SS* isomers using NaH resulted in the formation of a 1:1 mixture of the diastereomers, accompanied by partial hydrolysis of the imide moiety to the acid-amide **8**. A procedure which converts a mixture enriched in the succinimide with the wrong stereochemistry to a 1:1 mixture represents only a small improvement and was, therefore, of little interest.

The expense and the toxic nature of (TMS)CN when used on a large scale made these earlier procedures unattractive. Moreover, the purification by fractional recrystallization led to a situation where half the material was lost because of the inappropriate stereochemistry. The reduced yield as a direct result of the fractional crystallizations rendered either of these procedures very cost inefficient. The need for further improvement was readily apparent. These challenges led to a process which was shorter and was capable of producing kilogram quantities of ABT-200 methanesulfonate for further development in clinical trials.

Results and Discussion

We continued to employ the strategy which included 5,6-methylenedioxy-1-tetralone (**2**) as a key raw material. An alternate procedure to the (TMS)CN method was sought. Nitromethane is known to condense with 1-tetralone[7] and 6-methoxy-1-tetralone[8] to form a nitro derivative containing an endocyclic double bond. Our group considered the safety issues associated with the use of nitromethane easier to control than a process generating large quantities of HCN during workup. The published reaction with 6-methoxy-1-tetralone[8] suggested that nitromethane could be a suitable alternative to (TMS)CN; however, early attempts to develop the nitromethane condensation with 5,6-methylenedioxy-1-tetralone (**2**, Scheme 2) led to mixed results. Small-scale laboratory reactions worked well; however, attempts to increase the scale of the reaction led to increased amounts of the tetralone starting material remaining at the end of the reaction. While the starting material never completely disappeared, the equilibrium shifted toward increased levels of the starting tetralone as the scale of the reaction increased. The difficulty encountered in the nitroaldol condensation could be due to the deactivation of the ketone by the methylenedioxy moiety present in **2**. A variety of reaction conditions and catalysts were evaluated to improve the conversion to the nitroalkene at larger scale. Several amines such as *N*,*N*-dimethylethylenediamine, benzylamine, mor-

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pholine, and *n*-butylamine were evaluated as catalysts to afford the nitroalkene **12** (Scheme 2). *n*-Butylamine was eventually chosen for use in the large-scale reactions. Acetic acid was also added. The addition of an acid proved to be essential for the success of the reaction. Reactions catalyzed by base alone were not effective in producing the desired product, and only starting material was seen. Compound **12** was obtained in 90% yield when *n*-butylamine and acetic acid were used. Efficient removal of water was very critical, especially when larger scale reactions were performed. Water, when present, would rapidly convert the nitroalkene **11** back to the starting tetralone **2**. Since significant quantities of the nitromethane were lost during the azeotropic removal of water, a large excess of nitromethane was used to drive the reaction to completion. Several solvents were evaluated, and a Dean−Stark-type water separator was used to aid with the separation of water. Toluene was eventually chosen as the solvent for the large-scale reactions; however, some decomposition and the formation of colored impurities were observed in refluxing toluene. Cyclohexane was used as a cosolvent with toluene, to remove water azeotropically at a lower temperature, which improved the color of the product formed in the reaction. Cyclohexane had an additional benefit in water removal. The distillate was enriched in cyclohexane, and this higher concentration of the nonpolar cyclohexane aided in the separation of water in the Dean−Stark water separator.

Catalytic hydrogenation of the nitroalkene **12** over Pd/C in methanolic−HCl solution afforded the amine hydrochloride **7**. Use of Raney nickel as a catalyst in hydrogenation resulted in the formation of several side products and incomplete reaction. This amine was treated in a variety of ways to obtain the succinimide intermediate (**9a**/**b** and **10a**/**b**, Scheme2). In one procedure, the salt was neutralized and then condensed with phenylsuccinic anhydride to form the acid-amide **8a**/**b** as a mixture of isomers. Treatment of acid-amide **8a**/**b** with acetyl chloride at about 60 °C resulted in the formation of succinimde intermediate as a mixture of isomers **9a**/**b** and **10a**/**b**. Alternatively, the succinimide was obtained by treating the amine hydrochloride **7** with phenylsuccinic acid in the presence of acetyl chloride in refluxing xylenes. This alternate procedure also avoids an independent preparation of phenylsuccinic anhydride and the isolation of the acid-amide **8a**/**b**. The formation of the succinimide is not stereospecific, and all isomers **9a**/**b** and **10a**/**b** are formed. Initially, the desired diastereomer **10a**/**b** was separated from **9a**/**b** via fractional crystallization using solvents such as toluene−heptane or ethanol−water. It was observed that the desired isomer **10a**/**b** was the first one to crystallize out, in 25% yield.

In theory, the undesired diastereomer could be epimerized to the desired diastereomer by taking advantage of the solubility difference between the two sets of diastereomers, **9a**/**b** and **10a**/**b**, in the same solvent system as employed in fractional recrystallization of these isomers. An epimerization procedure where both of the isomers are in solution would be totaly ineffective. The development of a procedure where the progress of epimerization is driven by the precipitation of product would greatly improve the yield of the reaction. Both the solvent and the temperature of the reaction would have a significant influence on the efficiency of the epimerization process. A room temperature procedure would be acceptable for the crystallization; however, the epimerization would proceed at a slow rate, which would render the process inefficient. Heating the mixture would allow the epimerization to occur at a reasonable rate; however, only a 1:1 mixture would be obtained if no product is precipitated at the elevated temperature due to the subsequent increase in solubility of the succinimide. Developing the appropriate epimerization conditions was crucial at this stage and is described in the following paragraph.

Our first attempts to develop this solubility-directed epimerization were initially started in toluene. Heptane was added until the succinimide was sufficiently insoluble in the reaction solvent to precipitate at the reflux temperature. Without the heptane addion, a homogeneous solution results, leading to a 1:1 mixture of diastereomers. Employing a solvent mixture of 10% heptane in toluene, the mixture **9a**/**b** and **10a**/**b** was subjected to a triethylamine-catalyzed epimerization at reflux, to provide **10a**/**b** in 80% yield and >99% diastereomeric purity. The 80% yield with the epimerization is a dramatic improvement over the 25% yield obtained by fractional crystallization.

Environmental concerns led to an interest in a predominantly aqueous procedure which would have a decreased organic solvent waste stream. In theory, a water-miscible organic solvent could be used, and water could be added to provide a solvent mixture with the desired succinimide solubility. The following solvent combinations were evaluated: methanol/water, acetonitrile/water, and water alone. In contrast to the epimerization employing strictly organic solvents, the aqueous procedure was more prone to the undesirable base-catalyzed ring-opening of the succinimide. The bases sodium bicarbonate and triethylamine led to significant quantities of the ring-opened product. Sodium acetate was chosen as the base for the scale-up because the rate of the ring-opening side reaction was sufficiently low. Among the several solvent mixtures evaluated, we chose acetonitrile/water. When the epimerization was carried out in an acetonitrile/water mixture in the presence of sodium acetate, an improved yield of 95% with >99% purity was obtained.

A variety of reducing agents such as Red-Al, $NaBH_4$, LAH, and DIBAL were used to reduce **10a**/**b** to **6c**/**d** (Scheme 2); however, none of these reducing agents gave satisfactory results. LAH and Red-Al could successfully reduce the imide **10a**/**b** but in low yields and with extensive re-epimerization forming unacceptable levels of **1c**/**d** (Scheme 2). Borane mediated reduction of **10a**/**b** followed by methanolic−HCl quench of the reaction mixture gave ABT-200 hydrochloride **6c**/**d** in an 88% yield. Borane−dimethyl sulfide complex was preferred over the THF complex because of its cost and stability. Since the bioavailability of the HCl salt **6c**/**d** was very poor, the hydrochloride was converted to ABT-200·$MeSO_3H$ (**1a** and **1b**). The HCl salt **6c**/**d** was converted to free base in isopropyl acetate in the

presence of aqueous NaOH solution and then treated with methanesulfonic acid to afford **1a** and **1b**. When the salt exchange process was carried out in ethyl acetate and aqueous NaOH solution, massive hydrolysis of ethyl acetate took place, producing **1a**/**b** as acetic acid solvate. Unfortunately, aqueous $NaHCO_3$ failed to work as well as aqueous NaOH. Isopropyl acetate is much more resistant to hydrolysis than ethyl acetate. The overall yield of this six-step synthesis was 54%.

The above process was carried out on a multikilogram scale in reproducible yield, with a purity of the final product **1a**/**b** of >99% (HPLC, Scheme 2). The current process has (1) eliminated toxic (TMS)CN, (2) utilized the undesired isomers **9a**/**b** by converting them to **10a**/**b**, and (3) eliminated the synthesis of the aminopyrrolidine moiety. In conclusion, we have developed a short, convenient, and cost-efficient synthesis of ABT-200 (**1a**/**b**).

Experimental Section

General. Progress of reactions and purities of intermediates were checked by analytical HPLC (reversed-phase columns, Waters C-18 microbondpac) and TLC (SiO_2). Diastereomeric purity was checked by a YMC AQ303 column using aqueous 0.067 M KH_2PO_4 and acetonitrile as mobile phase. Melting points were recorded using a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Elemental analyses were performed in-house. IR spectra were recorded on a Perkin-Elmer model 1650 IR. Mass spectra were obtained on a Hewlett-Packard 5971 MS system coupled to a Finnegan Mat SSQ-700 (DCI, NH_3). NMR spectra were recorded on a GE QE-300 instrument, and chemical shifts were reported in ppm downfield from TMS as an internal standard. ^{1}H and ^{13}CNMR were run in $CDCl_3$ or DMSO-d_6.

1-Nitromethyl-3,4-dihydro-5,6-methylenedioxynaphthalene (12). To a 1-L three-neck flask equipped with a mechanical stirrer, a Dean−Stark water separator with a condenser, and a thermometer were charged 5,6-methylenedioxy-1-tetralone (**2**, 50 g, 0.263 mol), nitromethane (85 mL), toluene (160 mL), methylcyclohexane (40 mL), and glacial acetic acid (17.2 g, 0.286 mol). *n*-Butylamine (11.5 g, 0.157 mol) was slowly added to the reaction mixture under N_2 atmosphere, maintaining temperature <40 °C. The reaction mixture was refluxed with vigorous stirring for approximately 24 h until tetralone **2** was <8% by HPLC. The reaction mixture was cooled to about 50 °C, and the solvents were evaporated under vacuum to dryness. The residue was triturated with 2-propanol (50 g) to give **12** as a yellowish-brown crystalline product: mp 82−84 °C (60 g, 98%); IR (KBr) 810, 1050, 1250, 1455, 1540, 2890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28−2.40 (m, 2H), 2.71 (t, J = 7.8 Hz, 2H), 5.67 (s, 2H), 5.90 (s, 2H), 6.12 (t, J = 4.5 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 19.85, 22.34, 78.42, 101.16, 105.74, 116.01, 116.85, 126.45, 127.42, 133.44, 144.76, 147.22 ppm; MS (CI, NH_3) 234 (M + 1). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.76; N,6.01. Found: C, 61.77; H, 4.77; N, 5.91.

1,2,3,4-Tetrahydro-5,6-methylenedioxynaphthyl-1-methylamine hydrochloride (7). 5% Palladium on carbon (7.5 g) and 1-nitromethyl-3,4-dihydro-5,6-methylenedioxy naphthalene (**12**) were placed in a 5-L hydrogenator, which was previously purged with nitrogen. Methanolic−HCl (34 g in 1230 mL of methanol) was charged to the hydrogenator. The reaction mixture was then hydrogenated under 50−65 psig pressure of hydrogen at 58−65 °C for about 40 h until there was <1% starting material present by HPLC or TLC. After the reaction mixture was cooled to ambient temperature, the insolubles were filtered and washed with methanol. The filtrate was concentrated under vacuum, and the crude product was refluxed in acetone (500 mL) for 1 h. The suspension was cooled to about 10 °C and filtered to give white crystalline product **7** (76 g, 71%): mp 248−250 °C; IR (KBr) 790, 1050, 1075, 1270, 1460, 1480, 1510, 2940 (br) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.60−1.81 (m, 3H), 1.85−1.97 (m, 1H), 2.42−2.68 (m, 2H), 2.83−3.21 (m, 3H), 5.90 (dd, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 8.40 (br s, 1H);^{13}C NMR (DMSO-d_6) 17.18, 22.28, 24.10, 34.70, 43.72, 100.78, 106.21, 119.18, 121.57, 130.34, 144.62, 144.68 ppm; MS (CI, NH3) 206 (M + 1, free base); HRMS calcd for $C_{12}H_{14}NO_2$ $(M + H)^+$ 206.1181, found 206.1178.

***(RR,SS,RS,SR)*-3-Phenyl-1-[(6,7,8,9-tetrahydronaphtho-[1,2-*d*]-1,3-dioxol-6-yl)methyl]pyrrole-2,5-dione (10a/b, 9a/b).** Amine hydrochloride **7** (300 g, 1.24 mol) and phenylsuccinic acid (241.2 g, 1.24 mol) were suspended in xylene (3 L) in a 5-L three-neck flask equipped with a mechanical stirrer and a Dean−Stark water separator with a condenser. The mixture was refluxed for 20 h with vigorous stirring until <3% starting material **7** was detected by HPLC or TLC. The reaction mixture was cooled to room temperature, and acetyl chloride (194.4 g, 2.48 mol) was added. The resulting solution was then refluxed for about 1 h until the intermediate, acid amide **8a**/**b**, completely disappeared, as monitored by TLC or HPLC. The solvent was removed under vacuum, and the crude product was stirred with methanol (1 L) for about 12 h. The product was filtered and dried to give a mixture of succinimide isomers **9a**/**b** and **10a**/**b** (406 g, 90%): IR (KBr) 1040, 1150, 1270, 1400, 1460, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) (mixture of diastereomers) δ 1.44−1.96 (m, 4H), 2.40−2.53 (m, 1H), 2.60−2.83 (m, 2H), 3.05−3.20 (m, 2H), 3.50−3.60 (m, 1H), 3.64−3.76 (m, 1H), 3.90−4.00 (m, 1H), 5.80−5.87 (m, 2H), 6.52−6.61 (m, 1H), 6.63−6.70 (m, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 17.05, 22.47, 24.68, 35.11, 35.28, 36.88, 36.91, 44.25, 44.32, 45.67, 45.77, 100.79, 106.06, 119.57, 119.60, 121.85, 127.28, 127.86, 129.12, 130.69, 130.72, 137.05, 137.10, 144.94, 144.99, 176.18, 177.79 ppm; HRMS calculated for $C_{22}H_{22}NO_4$ $(M + H)^+$ 364.1549; Found 364.1548 (M + 1).

***(RR,SS)*-3-Phenyl-1-[(6,7,8,9-tetrahydronaphtho[1,2-*d*]-1,3-dioxol-6-yl)methyl]pyrrole-2,5-dione (10a/b).** Succinimide intermediate **9** (406 g, 1.117 mol) and sodium acetate (458 g, 5.583 mol) were suspended in acetonitrile (650 mL) and distilled water (3.25 L). The resulting suspension was refluxed for 48 h with vigorous stirring until the undesired isomer, *RS*,*SR*, completely disappeared by HPLC. Most of the acetonitrile was removed by distillation, and the reflux was continued for another 24 h. The reaction mixture was

cooled to about 75 °C, and the product was filtered and washed thoroughly with water. After the product **10a**/**b** was dried at 55−60 °C under vacuum, the weight was 403 g (99% yield): mp 153.5−155 °C; IR (KBr) 1050, 1150, 1270, 1400, 1450, 1695, 2950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50−1.75 (m, 3H), 1.80−1.97 (m, 1H), 2.40−2.54 (m, 1H), 2.63−2.85 (m, 2H), 3.05−3.20 (m, 2H), 3.56 (dd, J = 12.6, 5.4 Hz, 1H), 3.7 (dd, J = 14.4, 10.5 Hz, 1H), 3.92−4.00 (m, 1H), 5.84 (m, 2H), 6.56 (d, J = 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) 17.05, 22.47, 24.70, 35.13, 36.93, 44.27, 45.69, 100.81, 106.08, 119.58, 121.86, 127.30, 127.88, 129.14, 130.71, 137.10, 144.96, 145.00, 176.18, 177.80 ppm. Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.72; H, 5.79; N, 3.76.

(*RR*,*SS*)-3-Phenyl-1-[(6,7,8,9-tetrahydronaphtho[1,2-*d*]-1,3-dioxol-6-yl)methyl]pyrrolidine Hydrochloride (6c/d). A 10.1 M solution of borane in dimethyl sulfide (100 mL, 1.0 mol) was slowly added over a period of 1 h to the solution of *RR*,*SS* succinimide derivative **10a**/**b** (130 g, 0.358 mol) in 650 mL of anhydrous THF at 35−60 °C. After the addition, the reaction mixture was stirred at 60−65 °C for 1 h and then refluxed for 21 h. The reaction was cooled to 0−5 °C, and methanol (250 mL) was added to the reaction mixture. Anhydrous hydrogen chloride (69.8 g, 1.92 mol) was addeded slowly, keeping the temperature below 20 °C. The solvents were removed under vacuum, and the crude product was triturated with acetone (600 mL) to give **6c**/**d** as a white crystalline soild (97 g, 80% yield): mp 260−263 °C; IR (KBr) 700, 1060, 1270, 1460, 1480, 2570, 2900 cm^{-1}; ^1H NMR ($CDCl_3$) (free base) δ 1.89−2.28 (m, 6H), 2.46−2.69 (m, 2H), 2.70−3.20 (m, 7H), 3.52−3.65 (m, 1H), 6.06−6.13 (m, 2H), 6.84 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) (free base) 18.05, 22.86, 25.51, 33.50, 36.13, 43.28, 54.70, 62.56, 62.83, 100.64, 105.79, 119.68, 121.52, 125.99, 127.25, 128.33, 133.54, 144.42, 144.75, 145.93 ppm. Anal. Calcd for $C_{22}H_{25}NO_2 \cdot HCl$: C, 71.05; H, 7.05; N, 3.77; Cl, 9.52. Found: C, 70.94; H, 6.98; N, 3.68; Cl, 9.68.

(*RR*,*SS*)-3-Phenyl-1-[(6,7,8,9-tetrahydronaphtho[1,2-*d*]-1,3-dioxol-6-yl)methyl]pyrrolidine Methanesulfonate (1a/b). To a suspension of **6c/d** (100 g, 0.27 mol) in isopropyl acetate (700 mL) at 5 °C was added slowly a solution of aqueous sodium hydroxide (48 g in 600 mL of water). The mixture was stirred until all solids dissolved. The layers were separated, and the aqueous layer was washed with isopropyl acetate (200 mL). The combined organic extracts were washed with brine and then dried over anhydrous sodium sulfate. Insolubles were removed by filtration, the filtrate was treated with methanesulfonic acid (26 g, 0.27 mol) at 5−10 °C, and the mixture was stirred for 2 h. The slurry was filtered and washed with isopropyl acetate to give white crystalline **1a**/**b** (108 g, 93% yield): mp 169−170 °C (absolute ethanol); IR (KBr) 1045, 1055, 1270, 1455, 1470, 1480, 2780, 2930, 3020 cm^{-1}; ^1H NMR ($CDCl_3$) (free base) δ 1.89−2.28 (m, 6H), 2.06−2.69 (m, 2H), 2.70−3.05 (m, 7H), 3.38−3.50 (m, 1H), 5.50−5.90 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) (free base) 18.05, 22.86, 25.51, 33.50, 36.13, 43.28, 54.70, 62.56, 62.83, 100.64, 105.79, 119.68, 121.52, 125.99, 127.25, 128.33, 133.54, 144.42, 144.75, 145.93 ppm. Anal. Calcd for $C_{23}H_{27}NO_5S$: C, 64.33; H, 6.29; N, 3.26; S, 7.46. Found: C, 64.17; H, 6.68; N, 3.23; S, 7.50.

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