The First Enantioselective Synthesis of (2*R*,2′*R*)-*threo*-(+)-Methylphenidate Hydrochloride

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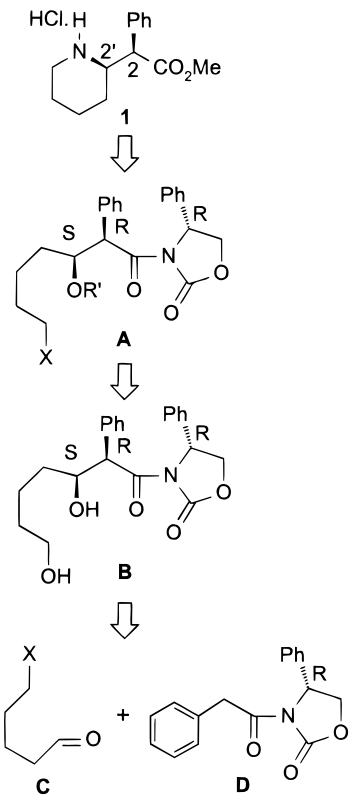
(±)-*threo*-Methylphenidate hydrochloride (Ritalin hydrochloride) is a mild nervous system stimulant marketed for the treatment of children with attention deficit hyperactivity disorder (ADHD). (2*R*,2′*R*)-(+)-*threo*-Methylphenidate hydrochloride (**1**) has been reported to be 5 times[1] to 38 times[2] more active than the corresponding (2*S*,2′*S*)-(−)-*threo*-methylphenidate hydrochloride. The clinical relevance of this difference to the use of racemate versus the pure eutomer is yet to be determined. We were therefore interested in developing a process that is suitable for manufacturing the active (2*R*,2′*R*)-enantiomer **1**. In the event that a ready supply of (±)-*threo*-methylphenidate hydrochloride is available, one must contrast the obvious choice of classical resolution to a total synthesis. We recently reported the resolution of (±)-*threo*-methylphenidate by an enzymatic hydrolysis,[3] which was followed by other patent literature.[4,5] Several classical resolution methods have been reported for the resolution of (±)-*threo*-methylphenidate free base or (±)-*threo*-ritalinic acid toward the preparation of **1**.[1,6−9] A synthesis of **1** has also been reported recently[10] that utilizes an enantiopure amino acid (D-pipecolic acid) as the starting material, which in turn was prepared by the resolution of (±)-pipecolic acid using tartaric acid, making this route unattractive for a scale-up in comparison to the direct resolution of (±)-*threo*-methylphenidate itself. Our goal was to develop an enantioselective synthesis of **1** that is suitable for manufacturing of this drug substance on a commercial scale. In this paper we report the first enantioselective synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride (**1**).

Our synthetic strategy toward **1** is depicted in Scheme 1. We rationalized that the piperidine ring system would be furnished by the cyclization of the stereoselectively substituted 1,5-diol such as **B** with an amine, after activation of the hydroxyl groups, as in **A**. The methyl ester functionality would be introduced by the displacement of the chiral auxiliary with methoxide. One possible method for accessing compounds such as **B** enantioselectively would be the asymmetric aldol condensation of an aldehyde (**C**) with the (*Z*)-boron enolate derived from *N*-phenylacetyl-(*R*)-4-substituted-2-oxazolidinone (**D**). The *erythro*-selective *syn* aldol addition of aldehydes with (*Z*)-boron enolates is well-known.[11]

Scheme 1



We opted to use (*R*)-4-phenyl-*N*-phenylacetyl-2-oxazolidinone (**3**) and 5-chlorovaleraldehyde (**4**) as the starting materials for the key aldol reaction (Scheme 2). Compound **3** was easily prepared by the new method developed in our laboratories,[12] a direct coupling of phenylacetic acid (**2**, 1.14 equiv) with the cheap and readily available (*R*)-4-phenyl-2-oxazolidinone in the presence of pivaloyl chloride and triethylamine, in 78% yield. The aldehyde **4** was prepared by the oxidation of commercially available 5-chloropentanol with NaOCl and TEMPO, using a known method.[13] The key aldol condensation of **3** with **4** was performed under known conditions,[11] which afforded the desired single diastereomer **5**, as confirmed by ^{1}H NMR, in 78% yield as an oil. ^{1}H NMR of the crude **5** did not indicate the presence of the undesired diastreomer. Similar results were obtained using either CH_2Cl_2 or toluene as the solvent. These results suggested that cheaper (*R*)-4-phenyl-2-oxazolidinone, which is not a

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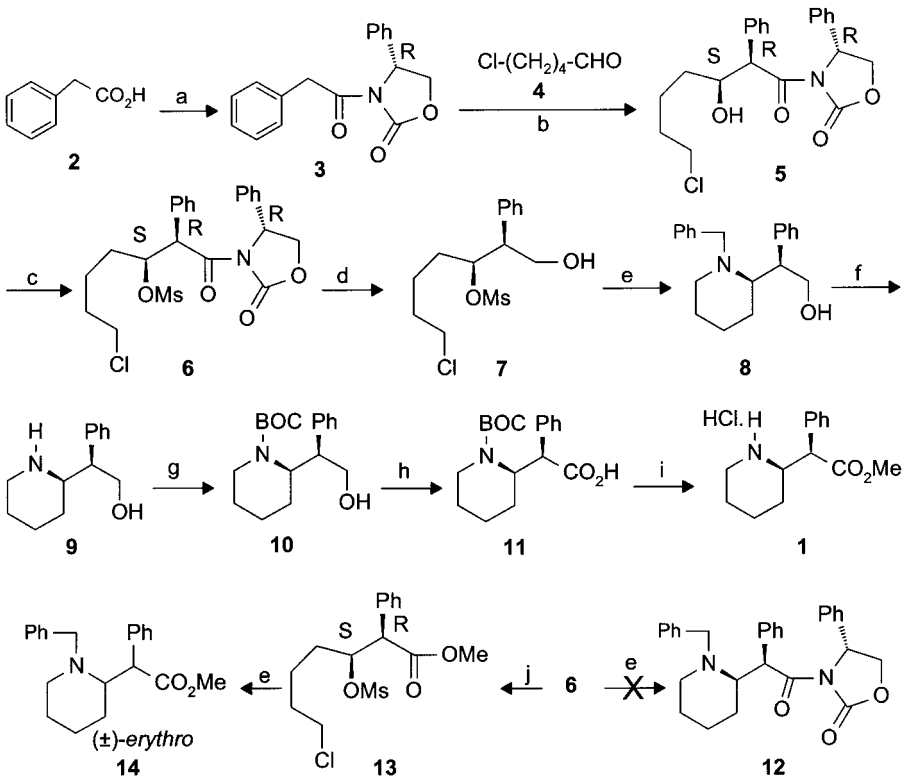
Scheme 2



Reagents and conditions: (a) (R)-4-phenyloxazolidinone, pivaloyl chloride,Et_3N, toluene (78%); (b) i) n-Bu_2BOTf, DIEA, CH_2Cl_2 or toluene, -20 °C to RT, ii) 30% H_2O_2, MeOH (78%); (c) Ms_2O, C_5H_5N, 0 °C or MsCl, Et_3N (92%); (d) $NaBH_4$, THF- H_2O, 0 °C to RT (91%); (e) $PhCH_2NH_2$ (10 eq.), 85 °C, 3 h (60%); (f) H_2, 10% Pd-C, EtOH (92%); (g) $(BOC)_2O$, THF (82%); (h) $NaIO_4$, $RuCl_3.H_2O$, CH_3CN, H_2O, CCl_4 (80%); (i) MeOH, HCl, 50 °C, overnight (70%); (j) MeOLi, MeOH, 0 °C (50 %).

commonly used auxiliary, is a suitable chiral auxiliary for the aldol reaction. Use of (*R*)-4-benzyl-2-oxazolidinone also gave the same diastereoselectivity in the aldol reaction. Mesylation of **5** with either methanesulfonic anhydride and pyridine in dichloromethane or methanesulfonyl chloride and triethylamine in toluene yielded the mesylate **6** in 92% yield. With **6** in hand, we were ready to construct the piperidine ring. We decided to use benzylamine, also used by Masamune to prepare a pyrrolidine ring,[14] to construct the piperidine ring. Reaction of **6** with benzylamine at 85 °C gave a complicated mixture, and no desired product **12** could be obtained. We postulated that the undesired ring opening of the 2-oxazolidinone by benzylamine and the steric bulk of this chiral auxiliary may be responsible for the unexpected outcome. To overcome this problem, we decided to replace the chiral auxiliary with the desired methyl ester functionality prior to the cyclization. The reaction of **6** with lithium methoxide[15] in methanol at 0 °C yielded the expected methyl ester **13**. Treatment of **13** with benzylamine yielded the cyclic product; however, it was characterized to be (±)-*erythro*-methylphenidate (**14**). These results could be explained based on the elimination of the mesylate, which destroyed both stereogenic centers; the α,*β*-unsaturated ester intermediate then underwent a Michael addition with benzylamine, followed by cyclization. To circumvent the elimination problem, we decided to replace the methyl ester group with the corresponding alcohol function prior to the cyclization step and oxidize it back to the desired carboxylic ester functionality afterward. The desired alcohol **7** was directly prepared from **6** in 91% yield by the reductive removal of the chiral auxiliary with sodium borohydride in THF and water[16] followed by a silica gel chromatography. This reductive removal was highly selective and no reduction of the chloride or the mesylate functionalities was observed. Treatment of alcohol **7** with benzylamine (10 equiv) at 85 °C and purification by a silica gel chromatography afforded the desired piperidine intermediate **8** in 60% yield. The optical purity of **8** was ascertained by a chiral HPLC method. No (2*S*,2′*S*)-enantiomer could be detected in **8**.

Having secured the two stereogenic centers and the piperidine ring in **8**, our next objective was to cleave the benzyl group and convert the alcohol group to the methyl ester. Oxidation of **8** with H_5IO_6 in the presence of catalytic amounts of CrO_3 in wet acetonitrile[17] yielded the corresponding acid in ∼35% yield. These poor yields may be due to side reactions such as *N*-benzylic oxidation and the oxidation of the tertiary amine in **8**. To circumvent this problem, we decided to replace the *N*-benzyl group with another protecting group which is stable

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under oxidative conditions. *tert*-Butyloxycarbonyl (BOC) group was our first choice. Thus, hydrogenation of **8** in the presence of Pd−C (10%) in ethanol yielded the amino alcohol **9** (92% yield), which was acylated with di-*tert*-butyl dicarbonate to afford N−BOC-protected alcohol **10** in 82% yield. Oxidation of **10** with $NaIO_4$ and $RuCl_3$ under reported conditions[18] furnished the acid **11** in 80% yield. Treatment of the acid **11** with methanol in the presence of HCl gas at 50 °C yielded the desired (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride (**1**) in 70% yield. Optical purity of crude as well as crystalline **1** was >99% as determined by a chiral HPLC method. All of the spectral and analytical data of **1** were identical to those of an authentic sample.[3]

In summary, we have described a novel and the first enantioselective synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride with >99% optical purity in a total of nine steps and 13.0% overall yield starting from phenylacetic acid. The key steps in the sequence are Evans's asymmetric aldol reaction, our own selective reductive removal of the 2-oxazolidinone chiral auxiliary, an extension of Masamune's method to piperidine ring formation, and Sharpless's oxidation of a primary alcohol to the carboxylic acid. This strategy would allow access to analogues of **1** and the corresponding (2*S*,2′*S*)-enantiomer by using (*S*)-4-phenyl-2-oxazolidinone as the chiral auxiliary.

Experimental Section

3-[7-Chloro-3-(*S*)-hydroxy-2-(*R*)-phenylheptanoyl]-4-(*R*)-phenyl-2-oxazolidinone (5). To a stirred solution of **3**[19] (8.5 g, 30.2 mmol) in 100 mL of CH_2Cl_2 (or toluene) was added di-*n*-butylboryl trifluoromethanesulfonate (33 mL, 1 M in CH_2Cl_2) dropwise to maintain the internal temperature at 0 °C. After stirring for 5 min at 0 °C, diisopropylethylamine (4.6 g, 35.6 mmol) was added dropwise, while maintaining the internal temperature at 0 °C. The solution turned from dark orange to light yellow after this addition. The reaction mixture was stirred for 30 min at 0 °C and then cooled to −20 °C. Aldehyde **4**[20] (4.02 g, 33.2 mmol) in 4 mL of CH_2Cl_2 was added at −20 °C. The reaction mixture was stirred at this temperature for 2 h and then allowed to warm to 22 °C. After stirring at 22 °C for 3 h, the reaction was quenched by addition of phosphate buffer (pH = 7.2, 20 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (40 mL), H_2O (40 mL), and brine (40 mL). The organic layer was concentrated in vacuo. The crude oil was dissolved in MeOH (90 mL) and cooled to an internal temperature at 0 °C, and 30% H_2O_2 (30 mL) was added. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to 22 °C. After 1 h at room temperature, the reaction was quenched by addition of H_2O (120 mL). The mixture was extracted with EtOAc (2 × 200 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (50 mL), H_2O (50 mL), and brine (50 mL) and then dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude aldol product, which was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:4) to give **5** (9.1 g, 78%) as an oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.34−6.91 (m, 10 H), 5.47 (dd, 1 H, J = 9.0, 5.0 Hz), 5.0 (d, 1 H, J = 5.0 Hz), 4.66 (t, 1 H, J = 9.0 Hz), 4.22−4.14 (m, 1 H), 4.09 (dd, 1 H, J = 9.0, 5.0 Hz), 3.50 (t, 2 H, J = 6.6 Hz), 2.66 (bs, 1 H), 1.82−1.36 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 152.7, 137.8, 132.8, 130.2, 129.0, 128.7, 128.3, 127.8, 125.7, 71.3, 69.6, 57.6, 54.4, 44.8, 33.5, 32.3, 23.1. Anal. Calcd for $C_{22}H_{24}NO_4Cl$: C, 65.75; H, 6.02; N, 3.49; Cl, 8.82. Found: C, 65.49; H, 6.34; N, 3.15; Cl, 8.68. $[\alpha]^{25}_D$ +11.80 (c = 0.61, MeOH); IR (neat, cm^{-1}) 1780, 1697, 1601.

3-[7-Chloro-3-(*S*)-(methylsulfonyl)oxy-2-(*R*)-phenylheptanoyl]-4-(*R*)-phenyl-2-oxazolidinone (6). Method A. To a stirred solution of **5** (19.0 g, 47.3 mmol) in toluene (150 mL) was added methanesulfonyl chloride (8.9 g, 77.7 mmol). Triethylamine (8.7 g, 86.0 mmol) was then added over 20 min while maintaining an internal temperature at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched by addition of 1 N HCl (20 mL), water (100 mL), and brine (50 mL). The mixture was extracted with EtOAc (2 × 125 mL), and combined organic layers were washed sequentially with 0.1 N HCl (100 mL), brine (100 mL), saturated $NaHCO_3$ solution (2 × 100 mL), and brine (100 mL) and then dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product, which was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:4) to give **6** (21.1 g, 93%) as an oil.

Method B. To a stirred solution of **5** (3 g, 7.7 mmol) in 30 mL of CH_2Cl_2 were added methanesulfonic anhydride (1.6 g, 9.2 mmol) and pyridine (0.91 g, 11.6 mmol) at 0 °C. After 3 h at 0 °C, the reaction mixture was quenched by addition of 1 N HCl (20 mL). The mixture was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), H_2O (30 mL), and brine (30 mL) and then dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product, which was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:4) to give **6** (3.39 g, 92%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.15 (m, 8 H), 6.93 (d, 2 H, J = 7.7 Hz), 5.50 (dd, 1 H, J = 8.9, 4.7 Hz), 5.37 (d, 1 H, J = 9.5 Hz), 5.35−5.20 (m, 1 H), 4.73 (t, 1 H, J = 8.9 Hz), 4.16 (dd, 1 H, J = 8.9, 4.7 Hz), 3.59 (t, 2 H, J = 6.5 Hz), 2.09 (s, 3 H), 1.95−1.60 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 153.3, 138.1, 134.3, 130.6, 130.5, 129.3, 129.1, 128.9, 126.1, 84.1, 70.1, 58.1, 53.7, 44.9, 37.8, 33.8, 32.3, 22.2. Anal. Calcd for $C_{23}H_{26}NSO_6Cl$: C, 57.55; H, 5.46; N, 2.92; S, 6.68; Cl, 7.38. Found: C, 57.28; H, 5.78; N, 3.15; S, 6.35; Cl, 6.65. $[\alpha]^{25}_D$ +9.83 (c = 0.84, MeOH); IR (neat, cm^{-1}) 1780, 1699.

α-(*S*)-(4-Chlorobutyl)-*β*-(*S*)-(hydroxymethyl)benzeneethanol Methanesulfonate (7). To a stirred solution of **6** (1.45 g, 3.1 mmol) in 25 mL of THF was added a solution of $NaBH_4$ (0.45 g, 11.8 mmol) in 4.5 mL of H_2O at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and allowed to warm to 22 °C. After stirring at 22 °C for 1 h, the reaction was quenched by addition of 2 N HCl solution (7 mL). The mixture was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL), H_2O (20 mL), and brine (20 mL) and then dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product, which was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:2) to give **7** (0.9 g, 91%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.38 (m, 5 H), 5.34−5.32 (m, 1 H), 4.15 (dd, 1 H, J = 11.5, 9.3 Hz), 3.94 (dd, 1 H, J = 11.5, 5.9 Hz), 3.64 (t, 2 H, J = 6.4 Hz), 3.23−3.19 (m, 1 H), 3.05 (s, 3 H), 1.92−1.68 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 129.3, 128.7, 127.7, 82.1, 62.8, 51.6, 44.5, 38.3, 32.4, 31.9, 22.6. Anal. Calcd for $C_{14}H_{21}ClO_4S$: C, 52.41; H, 6.6; S, 9.99; Cl, 11.05. Found: C, 52.47; H, 6.50; S, 9.69; Cl, 11.27. $[\alpha]^{25}_D$ +9.59 (c = 0.86, MeOH); IR (neat, cm^{-1}) 1495, 1454.

***β*-(*R*)-Phenyl-1-(phenylmethyl)-2-(*R*)-piperidineethanol (8).** A solution of **7** (10 g, 31.3 mmol) in benzylamine (34 g, 317 mmol) was stirred at 85 °C for 3 h. The reaction mixture was allowed to cool to 22 °C, and EtOAc (200 mL) was added. The mixture was washed with saturated $NaHCO_3$ solution (100 mL), H_2O (100 mL), and brine (100 mL) and then dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product, which was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **8** (5.5 g, 60%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−6.89 (m, 10 H), 3.98 (s, 2 H), 3.81 (t, 1 H, J = 10.3 Hz), 3.67 (dd, 1 H, J = 10.7, 3.5 Hz), 3.46 (td, 1 H, J = 10.7, 3.3 Hz), 3.31−3.16 (m, 2 H), 2.72 (bd, 1 H, J = 14.9 Hz), 1.80−0.88 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 138.5, 129.1, 128.6, 127.8, 127.4, 126.7, 70.0, 63.0, 57.2, 45.2, 44.9, 20.5, 20.0, 18.9. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.11; H, 8.82; N, 4.41. $[\alpha]^{25}_D$ −51.83° (c = 0.54, MeOH).

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The optical purity of **8** was determined by a chiral HPLC method on a Rainin Dynamax system using a Daicel Chiralpak AD column (4.6 × 250 mm) and a mixture of hexane/2-propanol/TFA (88:12:0.1 mL) as the mobile phase (isocratic at a flow rate of 1.0 mL/min and UV detector at 254 nm). The retention time of **8** was 15.8 min, and that of its corresponding (2*S*,2′*S*)-enantiomer was 19.7 min. No (2*S*,2′*S*)-enantiomer of **8** could be detected.

***β*-(*R*)-Phenyl-2-(*R*)-piperidineethanol (9).** To a solution of **8** (220 mg, 0.74 mmol) in ethanol (7 mL) in a Parr bottle was added 10% Pd/C (20 mg). The Parr bottle was flushed three times with H_2 (50 psi) and then vibrated at room temperature with H_2 (50 psi) for 4 h. The catalyst was filtered over a pad of Celite and washed with ethanol (2 × 5 mL). The filtrate was concentrated in vacuo to give crude **9** (140 mg, 92%), which was used in the next step without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.16 (m, 5 H), 4.03 (dd, 1 H, J = 11.0, 8.5 Hz), 3.86 (dd, 1 H, J = 11.0, 4.0 Hz), 3.7−3.3 (bs, 2 H), 3.12 (dd, 1 H, J = 13.3, 2.7 Hz), 3.01 (td, 1 H, J = 10.0, 2.4 Hz), 2.73 (td, 1 H, J = 8.7, 4.0 Hz), 2.63 (td, 1 H, J = 12.3, 3.1 Hz), 1.74−1.0 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 128.6, 128.1, 126.8, 68.3, 62.8, 51.8, 46.4, 31.7, 26.7, 24.2.

1-(*tert*-Butyloxycarbonyl)-*β*-(*R*)-phenyl-2-(*R*)-piperidineethanol (10). To a solution of **9** (130 mg, 0.63 mmol) in THF (5 mL) were added $(BOC)_2O$ (0.28 g, 1.26 mmol) and triethylamine (0.1 mL, 0.72 mmol). The solution was stirred at 22 °C for 19 h. The reaction mixture was concentrated in vacuo. The residue was purified by chromatography on SiO_2, to yield **10** (160 mg, 82%) as a white solid, mp 79−80 °C.[10]

1-(*tert*-Butyloxycarbonyl)-α-(*R*)-phenyl-2-(*R*)-piperidineacetic Acid (11). To a stirred solution of **10** (630 mg, 2.06 mmol) in a mixed solvent ($CCl_4/CH_3CN/H_2O$ = 8:8:12 mL) were added $NaIO_4$ (1.75 g, 8.2 mmol) and $RuCl_3 \cdot H_2O$ (10 mg, 0.05 mmol) at 22 °C. After stirring at 22 °C for 2 h, the mixture was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and then dried ($MgSO_4$). The solution was concentrated in vacuo to give the crude product, which was purified by column chromatography on SiO_2 (EtOAc/hexanes, 1:2) to give **11** (520 mg, 80%) as a white solid, mp 117−119 °C: ^{1}H NMR (300 MHz, CD_3OD) δ 7.46−7.25 (m, 5 H), 5.03−4.80 (bm, 1 H), 4.16 (d, 1 H, J = 11.8 Hz), 4.12−3.92 (bm, 1 H), 3.25−3.01 (bm, 1 H), 1.75−1.12 (m, 6 H), 1.50 (s, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.0, 156.9, 138.6, 130.3, 130.2, 129.2, 81.7, 56.1, 54.9, 52.7, 41.6, 40.1, 29.0, 26.8, 20.1. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.54; H, 7.97; N, 4.41. $[\alpha]^{25}_D$ −40.9 (c = 1.09, CH_2Cl_2).

(2*R*,2′*R*)-*threo*-(+)-Methylphenidate Hydrochloride (1). Into a solution of **11** (230 mg, 0.75 mmol) in MeOH (10 mL) was bubbled HCl gas, and the solution was stirred at 50 °C for 15 h. The reaction mixture was concentrated in vacuo to give a residue. The residue was treated with *tert*-butyl methyl ether (10 mL), and the resulting solid was collected by filtration and dried to give **1** (142 mg, 70%), mp 222−224 °C.[3]

The optical purity of crude as well as crystalline **1** was determined to be >99% (no other diastereomers could be detected) by a chiral HPLC method on a Rainin Dynamax system using a Daicel Chiralpak AD column (4.6 × 250 mm) and a mixture of hexane/ethanol/methanol/TFA (96:2:2:0.1 mL) as the mobile phase (isocratic at a flow rate of 0.8 mL/min and UV detector at 230 nm). The retention time of **1** was 15 min, and that of its corresponding (2*S*,2′*S*)-enantiomer was 13 min. The retention times of (2′*S*,2*R*)- and (2′*R*,2*S*)-*erythro*-methylphenidates were 13.5 and 16.5 min, respectively.

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