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Resolution of (±)-*threo*-Methylphenidate with (*R*)-(−)-Binaphthyl-2,2′-diyl Hydrogen Phosphate: 0.5 M Equiv of Resolving Agent Is Better than 1 M Equiv

Mahavir Prashad,* Bin Hu, Oljan Repič, Thomas J. Blacklock, and Peter Giannousis

Process Research & Development, Chemical & Analytical Development, Novartis Institute for Biomedical Research, 59 Route 10, East Hanover, New Jersey 07936, U.S.A.

Abstract:

Resolution of (±)-*threo*-methylphenidate (1) with 0.5 M equiv of (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (4) is described. Use of 0.5 M equiv of 4 was found to be better than 1 M equiv for the resolution of (±)-*threo*-methylphenidate (1) under different conditions to yield diastereomeric (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (3) with excellent enantiopurity. The diastereomeric salt 3 afforded pure (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (2) in high enantiopurity and yield.

Introduction

Resolutions provide a speedy access to enantiopure compounds and could result in a practical method in those cases where the racemic material is readily available. Usually 1 M equiv of the resolving agent is used to resolve a racemic compound. However, theoretically and of course ideally, only 0.5 M equiv of the resolving agent is required to form the diastereomeric salt with one enantiomer from the racemic mixture. Use of 0.5 or 1 equiv of the same resolving agent is known to give the similar resolution.[1] But to the best of our knowledge, it has not been reported that use of 1 equiv of the resolving agent gives poorer resolution compared to 0.5 equiv of the same resolving agent. In this paper, we would like to report such a rare example of the resolution of (±)-*threo*-methylphenidate hydrochloride (**1**, Ritalin hydrochloride) with (R)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**).

(±)-*threo*-Methylphenidate hydrochloride (**1**, 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 (**2**) has been reported to be 5[2] to 38 times[3] more active than the corresponding (2*S*,2′*S*)-(−)-*threo*-methylphenidate hydrochloride. Whereas the original synthesis[2,4] of (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**2**), reported in 1958 by Rometsch, utilized the resolution of (±)-*erythro*-α-phenyl-α-(2-piperidyl)acetamide to obtain enantiopure *l*-*erythro*-α-phenyl-α-(2-piperidyl)acetamide, which was subjected to epimerization, hydrolysis, and esterification, the resolution of (±)-*threo*-methylphenidate hydrochloride (**1**) was first reported with (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**) in 1987 by Patrick et al., to afford **2**.[5] Several classical resolution as well as enzymatic hydrolysis methods for the resolution of (±)-*threo*-methylphenidate hydrochloride (**1**) and its precursors have been reported recently by us[6,7] and by others.[8−13] A synthesis of **2** has also been reported recently[14] that utilized 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. We recently reported[15] the first enantioselective synthesis of **2** in >99% enantiomeric purity, which has been followed by several reports.[16−18] Enantioselective synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate has also been reported recently by us[19] and in a patent[20] because it could potentially be epimerized to **2**.

At the onset of this project in our laboratories, we were interested in the preparation of **2** by the resolution of (±)-**1** free base with (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**; BNDHP) in an acetone−methanol (95:5) mixture, reported by Patrick et al,[5] although **4** was an expensive reagent. Recently, these conditions were found to be nonreproducible and yielded **2** with only 92.6% enantiopurity (2*R*,2′*R*:2*S*,2′*S* = 96.3:3.7), even after an additional recrystallization,[10] compared to 99% enantiopurity reported by

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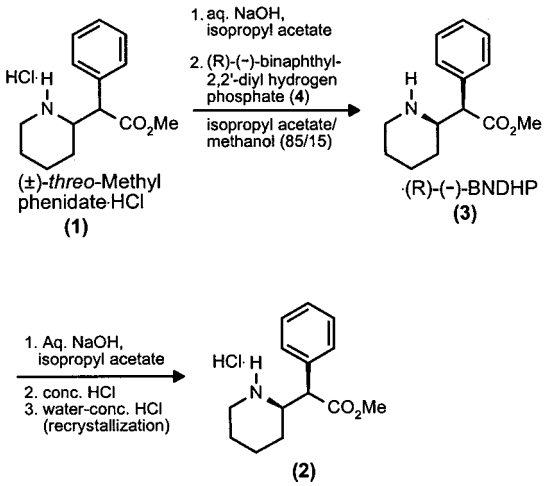
Table 1. **Resolution of (±)-*threo*-methylphenidate free base (0.7 g) in acetone−methanol**

entry	molar equiv of **4**	solvent (ratio)	total (mL)	temp (°C)	time (h)	enantiopurity of **3** (2*R*,2′*R*):(2*S*,2′*S*)	yield (%) of **3**
1	1.0	acetone−MeOH (95.0:5.0)	15	r.t.	16	55.5:44.5	66.7
2	0.8	acetone−MeOH (95.0:5.0)	15	65 → r.t. → 0	12	62.8:37.2	40.1
3	0.8	acetone−MeOH (95.0:5.0)	10	65 → r.t. → 0	12	56.4:43.6	58.5
4	0.7	acetone−MeOH (95.0:5.0)	15	65 → r.t. → 0	12	92.0:8.0	38.4
5	0.7	acetone−MeOH (95.0:5.0)	10	65 → r.t. → 0	12	61.0:39.0	52.7
6	0.6	acetone−MeOH (95.0:5.0)	15	r.t.	16	98.9:1.1	33.8
7	0.52	acetone−MeOH (95.0:5.0)	15	r.t.	16	97.9:2.1	28.6
8	0.5	acetone−MeOH (98.0:2.0)	15	r.t.	16	100: 0	30.9
9	0.52	acetone	15	r.t.	16	97.4:2.6	37.8

Scheme 1



Patrick et al.[5] However, both of these reports lacked critical experimental details, in particular the volume of the solvent used in the resolution step and the recrystallization step. In our hands, the resolution of (±)-**1** free base with **4** under literature conditions (except unknown solvent volume) gave diastereomeric salt (**3**) with poor enantiopurity (2*R*,2′*R*:2*S*,2′*S* = 62.8:37.2). This prompted us to investigate the resolution of (±)-**1** free base with **4** in detail. Herein, we describe our results on the resolution of (±)-**1** with 0.5 M equiv of **4**, which clearly demonstrated that 0.5 M equiv of **4** is better than 1 M equiv. Our newly developed conditions (Scheme 1) are highly reproducible and are suitable for scale-up, if necessary, because **4** is now cheaper and available in bulk amounts.

Results and Discussion

We reasoned that the molar ratio of (±)-**1** and **4** and/or solvent volume may be critical parameters in this resolution. We investigated the resolution of (±)-**1** free base, which was generated by treatment of (±)-**1**·HCl salt with aqueous sodium hydroxide in isopropyl acetate followed by complete removal of solvent, with variable amounts of **4** in a mixture of acetone and methanol at different concentrations. The diastereomeric salt was isolated by filtration in each case and the enantiopurity was determined by a chiral HPLC method using a Daicel Chiralpak AD column. The results are summarized in Table 1. With 1 M equiv of **4**, the (2*R*,2′*R*:2*S*,2′*S*) ratio in the diastereomeric salt **3** was only 55.5:44.5 (entry 1). Interestingly, a decrease in the amount of **4** led to an improved resolution. Excellent results were obtained when the resolution was carried out using close to 0.5 equiv of **4**. With 0.6 or 0.52 equiv of **4** (entries 6 and 7), the (2*R*,2′*R*:2*S*,2′*S*) ratios in **3** were 99:1 and 98:2, respectively. Furthermore, the yield of **3** under these conditions was also good. Good resolution with higher yield was also achieved with less methanol (acetone−methanol = 98:2) or in pure acetone with 0.5 equiv of **4** (entries 8 and 9). However, a clear solution was never observed in case of pure acetone as solvent. These results clearly demonstrated that 0.5 M equiv of **4** gave better resolution than 1 equiv. In fact, since the theoretical yield is 50%, the high yields (over 25%; entries 6−9) were especially interesting. This suggested that a quick exchange between the (2*S*,2′*S*)-*threo*-methylphenidate·(*R*)-BNDHP salt and (2*R*,2′*R*)-*threo*-methylphenidate free base in the solution was taking place.

Because preparation of the (±)-**1** free base from the hydrochloride salt required an extra step and a solvent exchange, we decided to investigate the resolution of (±)-**1**·HCl salt directly in a mixture of methanol and water as solvent in the presence of 4-methylmorpholine as a base. Such a direct resolution of (±)-**1**·HCl salt has been developed in our laboratories using di-benzoyl-D-tartaric acid as the resolving agent.[7] The direct resolution of (±)-**1**·HCl salt with 0.5 equiv of **4** in methanol−water mixture in the presence of 4-methylmorpholine was studied under various conditions. The results are summarized in Table 2. Poor results were obtained with a methanol−water ratio of 1.2:1 (Table 2, entry 1). Excellent resolution was achieved with a methanol−water ratio from 1.6:1 to 2:1 (entries 5, 14, and 15), affording **3** with undetectable amounts of the undesired (2*S*,2′*S*)-enantiomer. A comparison of entries 5 with 6, and 15 with 16,

Table 2. **Direct resolution of (±)-*threo*-methylphenidate·HCl (3.0 mmol) with 4 (1.5 mmol) in the presence of 4-methylmorpholine (3.0 mmol)**

entry	MeOH (mL)	H_2O (mL)	ratio (MeOH−H_2O)	total (mL)	temp (°C)	time (h)	enantiopurity of **3** (2*R*,2′*R*):(2*S*,2′*S*)	yield (%) of **3**
1	8.4	7	1.2:1	15.4	r.t.	3	74.9:25.1	38.4
2	6	5	1.2:1	11	r.t.	16	69.6:30.4	42.4
3	9	6	1.5:1	15	r.t.	16	69.6:30.4	35.5
4	4.4	3	1.5:1	7.5	r.t.	16	61.8:38.2	39.5
5	9.6	6	1.6:1	15.6	r.t.	3	99.1:0.9	26.0
6	9.6	6	1.6:1	15.6	r.t.	16	68.6:31.4	32.1
7	6.4	4	1.6:1	10.4	r.t.	3	73.7:26.3	32.1
8a	9.6	6	1.6:1	15.6	r.t.	3	75.8:24.2	28.7
9a	9.6	6	1.6:1	15.6	r.t.	16	65.3:34.7	32.1
10b	9.6	6	1.6:1	15.6	r.t.	3	78.2:21.8	24.1
11	9.6	6	1.6:1	15.6	0	3	94.2:5.8	27.5
12	7.2	4	1.8:1	11.2	r.t.	3	68.4:31.6	33.2
13	7.2	4	1.8:1	11.2	r.t.	16	64.1:35.9	33.2
14	9.9	5.5	1.8:1	15.4	r.t.	3	100: 0	24.6
15	10	5	2.0:1	15	r.t.	3	100: 0	29.8 (2 crops)
16	10	5	2.0:1	15	r.t.	16	73.6:26.4	21.8
17	5	2.5	2.0:1	7.5	r.t.	3	62.6:37.4	35.0
18	10	5	2.0:1	15	0	3	97.8:2.2	20.1
19	5	2.5	2.0:1	7.5	r.t.	16	59.4:40.6	37.3

[a] With 1.65 mmol of 4-methylmorpholine. [b] With 6.0 mmol of 4-methylmorpholine.

Table 3. **Resolution of (±)-*threo*-methylphenidate free base (3.0 mmol) in isopropyl acetate−methanol**

entry	molar equiv of **4**	solvent (ratio)	total (mL)	temp (°C)	time (h)	enantiopurity of **3** (2*R*,2′*R*):(2*S*,2′*S*)	yield (%) of **3**
1	0.5	i-PrOAc-MeOH (95.0:5.0)	15	r.t.	72	86.2:13.8	43.6
2	0.5	i-PrOAc-MeOH (92.5:7.5)	15	r.t.	16	89.8:10.2	40.1
3	0.5	i-PrOAc-MeOH (90.0:10.0)	15	r.t.	3	100: 0	35.5
4	0.5	i-PrOAc-MeOH (90.0:10.0)	15	r.t.	16	99.1:0.9	39.5
5	0.5	i-PrOAc-MeOH (90.0:10.0)	15	0	16	100: 0	39.0
6	0.5	i-PrOAc-MeOH (90.0:10.0)	11	r.t.	16	98.2:1.8	40.1
7	0.5	i-PrOAc-MeOH (90.0:10.0)	7.5	r.t.	16	80.7:19.3	43.6
8	1.0	i-PrOAc-MeOH (90.0:10.0)	25	r.t.	72	55.9:44.1	75.1
9	0.5	i-PrOAc-MeOH (87.5:12.5)	15	r.t.	16	100: 0	35.5
10	0.5	i-PrOAc-MeOH (87.5:12.5)	11	r.t.	16	98.4:1.6	36.0
11	0.5	i-PrOAc-MeOH (85.0:15.0)	7.5	r.t.	72	89.3:10.7	39.5
12	0.5	i-PrOAc-MeOH (85.0:15.0)	15	r.t.	72	100: 0	32.1
13	0.5	i-PrOAc-MeOH (80.0:20.0)	15	r.t.	16	100: 0	26.4
14	1.0	i-PrOAc-MeOH (80.0:20.0)	15	r.t.	16	65.4:34.6	62.5

suggested that under these conditions longer resolution time led to a poor resolution. When the reaction was continued for a longer time, the (2*S*,2′*S*)-*threo*-methylphenidate·(*R*)-BNDHP salt also crystallized in the end. Again use of 1 equiv of **4** under these conditions gave poor results (2*R*,2′*R*:2*S*,2′*S* = 60.0:40.0). A comparison of entries 5 with 7, and 15 with 17, indicated that lower solvent amounts also afforded **3** with significantly lower enantiopurity. In addition, further cooling of the mixture to 0 °C also led to slightly lower enantiopurity of **3** (compare entries 5 with 11, and 15 with 18). These results suggested that long reaction time, low solvent amounts, and lower temperature have adverse effects on the direct resolution of (±)-**1**·HCl salt with 0.5 M equiv of **4** in methanol−water solvent system. In addition, using more or less of 4-methylmorpholine also led to unsatisfactory resolution (entries 8−10). This led us to believe that although using (±)-**1**·HCl salt directly is convenient, the narrow window for all these parameters to achieve a good resolution may prove difficult to control at a large scale in the pilot plant. Therefore, we decided to go back to the (±)-**1** free base approach.

Because (±)-**1** free base from the hydrochloride salt was generated with aqueous NaOH in isopropyl acetate as the solvent, we decided to investigate the resolution in isopropyl acetate and methanol mixture. This would avoid the solvent exchange step after the free base generation, which was necessary for the acetone−methanol conditions. In fact, it was found that the combination of isopropyl acetate and methanol was the best solvent mixture we discovered so far for the resolution of (±)-**1** free base with 0.5 M equiv of **4**. These results are summarized in Table 3. The resolution of (±)-**1** free base with different ratios of isopropyl acetate and methanol and different total volumes of this solvent system was first studied in detail. A comparison of entries 1−3

suggested that an increase in the amount of methanol (from 95:5 to 90:10) in the isopropyl acetate−methanol mixture led to an increase in the enantiopurity of **3**. With isopropyl acetate−methanol ratio from 90:10 to 80:20, **3** was obtained with excellent enantiopurity and no undesired (2*S*,2′*S*)-enantiomer could be detected (entries 3, 9, 12, and 13). A decrease in the total volume of the solvent mixture led to a slight decrease in the enantiopurity of **3** (entries 6 and 10), although if only half the volume of the solvent was used, the enantiopurity was significantly lower (compare entries 11 and 12, 3 and 7). As expected, an increase in the amount of methanol in this solvent mixture led to a lower yield of **3**. In contrast to the methanol−water solvent system as observed previously, the longer resolution time or cooling to 0 °C did not affect the enantiopurity of **3** under these new conditions involving an isopropyl acetate−methanol mixture (entries 3−5). Even after 72 h (entry 12) or cooling to 0 °C (entry 5), no undesired (2*S*,2′*S*)-enantiomer could be detected in **3**. Once again use of 1 equiv of **4**, even with large amount of solvent (entry 8) or with an isopropyl acetate−methanol ratio of 80:20 (entry 14), led to poor resolution. The solubilities of (2*R*,2′*R*)- and (2*S*,2′*S*)-*threo*-methylphenidate·(*R*)-BNDHP diastereomeric salts at 25 °C were 2.4 and 10.3 mg/mL, respectively, in a 90:10 mixture of isopropyl acetate−methanol, and 3.4 and 24.4 mg/mL, respectively, in a 80:20 mixture of isopropyl acetate−methanol. The conditions utilizing a 85:15 ratio of isopropyl acetate−methanol over 90:10 were selected for further scale-up to allow a wider margin, which should further increase the robustness of the process in the pilot plant. These conditions (Table 3; entry 12) were selected for a scale-up. Actually, a scale-up to 0.27 mol of (±)-**1** gave a better yield of the diastereomeric salt **3** (36%) compared to 32% on a smaller scale (3.0 mmol; entry 12).

The (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-BNDHP diastereomeric salt (**3**) was treated with NaOH in isopropyl acetate to yield a solution of (2*R*,2′*R*)-*threo*-methylphenidate free base. Treatment of this solution with aqueous HCl gave crude **2**, which was recrystallized from water−HCl mixture to afford crystalline **2**. No (2*S*,2′*S*)-enantiomer (by HPLC) or resolving agent (by ^{1}H NMR) could be detected in **2**. The overall yield of recrystallized **2** was 31.4%. The resolving agent **4** was also recovered in 83% yield and was recyclable.

Conclusions

A detailed investigation on the preparation of (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**2**) by the resolution of (±)-*threo*-methylphenidate (**1**) with (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**) is described. Resolution with 1 M equiv of this resolving agent did not give satisfactory results. However, 0.5 M equiv led to an excellent resolution under various conditions in high yields. Such a resolution is unique in that there are no reports where 1 equiv of the resolving agent leads to poor resolution, while .05 equiv gives such excellent results. These results suggested that in addition to using the recently reported "family approach" to the resolution of racemates,[21] one must also consider to use 0.5 M equiv of the resolving agent in cases where the resolution is cumbersome. The diastereomeric salt **3** yielded **2** in excellent enantiopurity and yield.

Experimental Section

Melting points were measured on a Buchi 535 melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker 300 instrument. Enantiopurities were determined after generating the free base from the salts either by capillary electrophoresis on a Beckman P/ACE 5000 series instrument (capillary: fused silica, 75 μm (i.d.) × 361 μm (o.d.) × 77 cm (70 cm effective separation length), 800 μm aperture; detection: 214 nm; injection: 4.5 s, pressure; run voltage: 28 kV (363 V/cm); run time: 32 min; polarity: positive; temperature: 23 °C; current: 115−130 (μA); separation electrolyte: 100 mM phosphate, pH 2.0, 10% methanol, 5 mM heptakis (2,6-di-*O*-methyl)-β-cyclodextrin, or by chiral HPLC 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) as the mobile phase (isocratic at a flow rate of 0.8 mL/min and UV detector at 230 nm).

Preparation of (2*R*,2′*R*)−(+)-*threo*-Methylphenidate Hydrochloride (2) by Resolution of (±)-1 Free Base in Isopropyl Acetate−Methanol Mixture. A 1-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and heating cooling bath was charged with (±)-*threo*-methylphenidate hydrochloride (**1**, 72.85 g; 0.27 mol) and isopropyl acetate (450 mL). The mixture was stirred at room temperature (23−25 °C), and to the suspension was added a solution of NaOH (18.0 g) and NaCl (72.0 g) in water (315 mL) over a period of 5 min while maintaining an internal temperature 20−25 °C. The suspension was allowed to stir for 30 min until all the solids dissolved, to obtain a two-phase mixture. The organic layer (∼500 mL), containing (±)-*threo*-methylphenidate free base, was separated, filtered to remove any suspended particles, and saved for the resolution step.

A 3-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, heating mantle, and addition funnel was charged with (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**; 47.02 g, 0.135 mol), methanol (202.5 mL), and isopropyl acetate (652.5 mL). The suspension was stirred and heated to an internal temperature at 65 °C, and the above-prepared organic layer (∼500 mL, containing (±)-**1** free base) was added over a period of 15 min while maintaining an internal temperature of 60−65 °C to obtain a clear solution. To this solution were added seeds of (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (**3**, 50 mg). The reaction mixture was allowed to cool to room temperature (23−25 °C) over a period of 2 h, and the stirring was continued at the same temperature for an additional 2 h. The heterogeneous mixture was cooled to an internal temperature of 0−5 °C over a

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period of 15 min and stirred at the same temperature for an additional 2 h. The solids were collected by filtration, washed with a precooled mixture (0−5 °C) of isopropyl acetate−methanol (85:15 v/v) in two equal portions of 75 mL each, and dried at 50−55 °C (100 mmHg) to afford (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (**3**, 56.85 g; 36.2%); mp = 246−247 °C decomp; $[\alpha]^{25}_{D}$ −316.7 (*c* = 1.0, MeOH); (2*R*,2′*R*):(2*S*,2′*S*) = 99.2:0.8.

To a suspension of (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (**3**, 56.85 g) in isopropyl acetate (853 mL) and water (942 mL) was added a solution of sodium hydroxide (23.46 g) in water (195 mL) over a period of 5−10 min while maintaining an internal temperature at 20−25 °C. All of the solids dissolved, and another solid precipitated immediately. The three-phase mixture was stirred for 30 min and filtered. The biphasic filtrate was saved. The solids were washed with isopropyl acetate (3 × 285 mL) in another filtration flask. The solids were saved to recover the resolving agent. The organic layer was separated from the biphasic filtrate. The aqueous layer was extracted with the second filtrate (855 mL). The aqueous layer was saved to recover the resolving agent. The combined organic layers were washed with water (50 mL) and filtered. The filtrate was cooled to 0−2 °C (internal temperature), and to it was added concentrated hydrochloric acid (14.45 g; 37%) over a period of 10 min while maintaining an internal temperature <10 °C. The heterogeneous mixture was warmed to room temperature over a period of 45 min. The solids were collected by filtration, washed with isopropyl acetate (2 × 50 mL), and dried at 50−55 °C (100 mmHg) to afford crude (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**2**, 24.62 g).

Crude (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**2**, 24.62 g) was added to hot water (29.0 g; preheated to an internal temperature of 74−75 °C). The mixture was heated to an internal temperature of 80−82 °C to obtain a clear solution. The solution was cooled to room temperature (20−22 °C) over a period of 45 min to obtain a suspension. To the resulting suspension was added concentrated hydrochloric acid (9.0 g; 37%) over a period of 10 min while maintaining an internal temperature <25 °C. The mixture was cooled to 0−5 °C over a period of 15 min and was allowed to stir at this temperature for an additional 30 min. The solids were collected by filtration, washed with cold water (2 × 4.0 mL; precooled to 0−5 °C) and dried at 50−55 °C (100 mmHg) for 16 h to obtain pure (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**2**, 22.89 g) as a white crystalline solid; yield 31.4%; mp = 222−224 °C; $[\alpha]^{25}_{D}$ +84 (*c* = 1.0, MeOH); (2*R*,2′*R*):(2*S*,2′*S*) = 99.9:<0.1. Lit.[2] mp = 210−211 °C; $[\alpha]^{25}_{D}$ +88 (1% in MeOH); IR (KBr, cm^{-1}) 1739; ^{1}H NMR (CD_3OD, δ) 1.35−1.58 (m, 3H), 1.65−1.93 (m, 3H), 3.11 (dt, 1H, *J* = 3.5 and 12.6 Hz), 3.4−3.5 (m, 1H), 3.7 (s, 3H), 3.84 (dt, 1H, *J* = 3.5 and 10.0 Hz), 3.99 (d, 1H, *J* = 10.0 Hz), 7.25−7.44 (m, 5H); ^{13}C NMR (CD_3OD, δ) 22.78, 23.23, 27.54, 46.63, 53.4, 55.2, 59.18, 129.59, 129.62, 130.36, 135.25, 173.22; MS (*m*/*e*) 234 (MH^+). Anal. Calcd for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.31; H, 7.36; N, 5.15; Cl, 13.11.

Resolution of (±)-*threo*-Methylphenidate Free Base with 4 in Acetone−Methanol. A suspension of (±)-*threo*-methylphenidate free base (0.7 g; 3.0 mmol) and (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**; 0.52 g; 1.5 mmol) in a mixture of acetone−methanol (98:2 v/v; 15 mL) was heated to an internal temperature at 65 °C over 15 min, to achieve a gentle reflux. All of the solids dissolved, and another solid separated out. The heterogeneous mixture was refluxed for an additional 10 min. The reaction mixture was cooled to 22 °C over 1 h and was stirred at this temperature overnight (16 h). The solids were collected by filtration, washed with acetone−methanol mixture (98:2 v/v; 2 mL), and dried to afford (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (**3**, 0.54 g; 31%). (2*R*,2′*R*:2*S*,2′*S*) = 100:0.

Direct Resolution of (±)-*threo*-Methylphenidate Hydrochloride with 4 in the Presence of 4-Methylmorpholine. A clear solution of (±)-*threo*-methylphenidate hydrochloride (**1**, 0.81 g; 3.0 mmol), (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (**4**; 0.52 g; 1.5 mmol), and 4-methylmorpholine (0.3 g; 3.0 mmol) in methanol (9.6 mL) was heated to an internal temperature at 40−50 °C. To this solution was added water (6.0 mL), followed by (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (**3**, 2 mg) seeds. The reaction mixture was cooled to 20−25 °C over a period of 1 h and allowed to stir at this temperature for an additional 3 h. The solids were collected by filtration, washed with a precooled (0 °C) mixture of methanol−water (1.6:1, v/v, 2 mL), and dried to afford (2*R*,2′*R*)-*threo*-methylphenidate·(*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate salt (**3**, 0.47 g; 27%). (2*R*,2′*R*:2*S*,2′*S*) = 99.1:0.9.

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