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An efficient large scale resolution of (±)-*threo*-methylphenidate hydrochloride (Ritalin® hydrochloride)

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Abstract

An efficient and large scale preparation of (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**3**) by the resolution of (±)-*threo*-methylphenidate hydrochloride (**1**) salt with *O*,*O*′-dibenzoyl-D-(+)-tartaric acid in the presence of 4-methylmorpholine is described. © 1999 Elsevier Science Ltd. All rights reserved.

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1. Introduction

(±)-*threo*-Methylphenidate hydrochloride (**1**, Ritalin® hydrochloride) is a mild nervous system stimulant. It is marketed for the treatment of children with attention deficit hyperactivity disorder (ADHD). (2*R*,2′*R*)-(+)-*threo*-Methylphenidate hydrochloride (**3**) has been reported to be five[1] to 38 times[2] more active than the corresponding (2*S*,2′*S*)-(−)-*threo*-methylphenidate hydrochloride (**5**). We recently reported the first enantioselective synthesis of **3**.[3] Original synthesis of **3** utilized the resolution of (±)-*erythro*-α-phenyl-α-(2-piperidyl)acetamide to obtain enantiomerically pure *l*-*erythro*-α-phenyl-α-(2-piperidyl)acetamide, which was subjected to epimerization, hydrolysis, and esterification to afford **3**.[1,4] A recent synthesis of **3** also utilized an enantiopure amino acid (D-pipecolic acid) as the starting material, which in turn was prepared by the resolution of (±)-pipecolic acid with tartaric acid.[5] Both of these routes were unattractive for a scale-up in comparison to the direct resolution of (±)-methylphenidate itself. Resolution of **1** by enzymatic hydrolysis has also been investigated.[6–8] A classical resolution method was reported for the resolution of (±)-*threo*-methylphenidate free base using expensive (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate as the resolving agent.[9] Recently, patent literature disclosed the use of *O*,*O*′-di-*p*-toluoyl-D-(+)-tartaric acid and (−)-menthoxyacetic acid to give satisfactory resolution,[10,11] however, they require the preparation and isolation of the (±)-*threo*-methylphenidate free base, which makes large scale preparation cumbersome. Also, further details on the conversion of the

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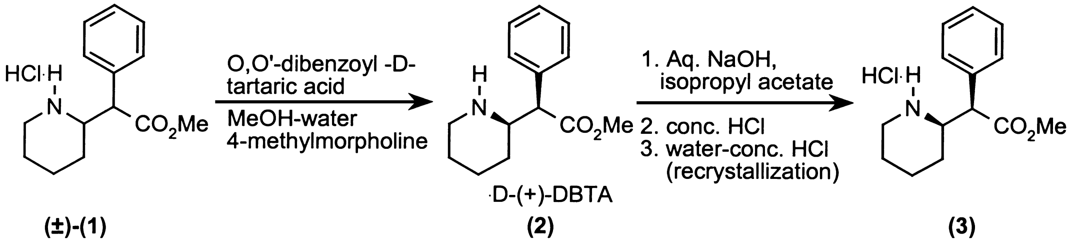
diastereomeric salt to **3** were not disclosed. Thus, the necessity of a more efficient method for the preparation of **3** on a commercial scale prompted us to investigate the resolution of (±)-*threo*-methylphenidate hydrochloride (**1**) in detail. In this paper we describe an efficient and large scale preparation of (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**3**) by the resolution of (±)-*threo*-methylphenidate hydrochloride (**1**) with *O*,*O*′-dibenzoyl-D-(+)-tartaric acid in the presence of 4-methylmorpholine, which avoids the isolation of (±)-*threo*-methylphenidate free base (Scheme 1).



Scheme 1.

2. Results and discussion

Our objective was to develop a process for the direct resolution of (±)-*threo*-methylphenidate hydrochloride salt, thus eliminating the necessity for the preparation and isolation of the corresponding free base. Because (±)-*threo*-methylphenidate hydrochloride (**1**) was soluble in a mixture of methanol and water, we selected this solvent system for the direct resolution of the salt. To test this solvent mixture, we initially studied the resolution of the free base with different diaroyl-D-tartaric acids (1 equivalent). The crystalline diastereomeric salts were isolated by filtration and the enantiopurities were determined by HPLC using a Daicel Chiralpak AD column. The results are summarized in Table 1. The resolution of the free base was most satisfactory with di-*p*-isopropylbenzoyl-D-tartaric acid in a 2:1 mixture of methanol and water, and with dibenzoyl-D-tartaric acid in a 1:1 mixture of these solvents. Because dibenzoyl-D-tartaric acid is a cheap and commercially available material, it was chosen to study the direct resolution of the hydrochloride salt. *O*,*O*′-Diaroyltartaric acids are well documented resolving agents for amines.[12,13]

Intuitively, the presence of a base should be necessary for the direct resolution of the HCl salt (**1**) with dibenzoyl-D-tartaric acid, however, this is not always the case when thermodynamics are favorable. Thus, interestingly, resolution of **1** in a 1:1 mixture of methanol and water at 0°C, without any base, yielded the diastereomeric salt with excellent enantiopurity but in only 18% yield. Use of aqueous sodium hydroxide

Table 1
Resolution of (±)-methylphenidate free base

Entry	Resolving agent	MeOH : H_2O ratio	Temp. (°C)	Enantiopurity of diastereomeric salt (2S,2'S) : (2R,2'R)	Yield (%)
1	Di-*p*-toluoyl-D-tartaric acid	2 : 1	22	31.6 : 68.4	62
2	Di-*m*-toluoyl-D-tartaric acid	2 : 1	22	7.1 : 92.9	44
3	Di-*o*-toluoyl-D-tartaric acid	2 : 1	22	49.7 : 50.3	30
4	Di-*p*-isopropylbenzoyl-D-tartaric acid	2 : 1	22	2.4 : 97.6	33
5	Dibenzoyl-D-tartaric acid	1 : 1	22	3.75 : 96.25	42
6	Di-phenylacetyl-D-tartaric acid	1 : 1	22	No solids	-

Table 2
Optimization of direct resolution of (±)-methylphenidate hydrochloride salt

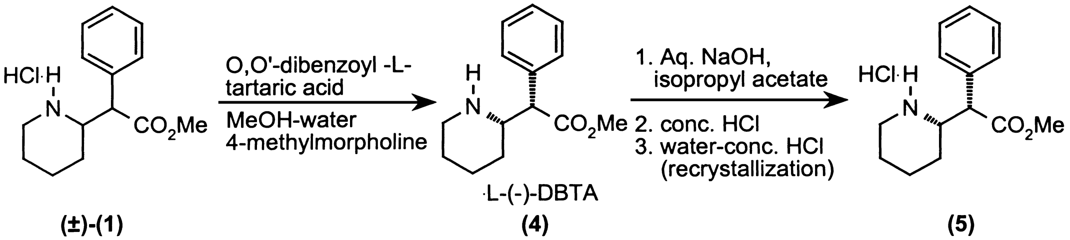
Entry	MeOH : H_2O ratio	Total Volume (MeOH + H_2O)	Temp. (°C)	Enantiopurity of diastereomeric salt (2S,2'S) : (2R,2'R)	Yield (%)
1	1 : 1	40 mL	45 → 21	41.9 : 58.1	75.3
2	1 : 1	60 mL	45 → 21	38.0 : 62.0	67.7
3	1.25 : 1	31.5 mL	45 → 21	40.0 : 60.0	71.7
4	1.25 : 1	45 mL	45 → 21	35.0 : 65.0	65.3
5	1.33 : 1	17.5 mL	45 → 21	41.0 : 59.0	70.7
6	1.5 : 1	22.5 mL	45 → 21	0.44 : 99.56	40.6
7	1.5 : 1	30 mL	45 → 21	0.49 : 99.51	37.7
8	1.5 : 1	30 mL	45 → 21→ 0	33.7 : 66.3	66.5
9	1.6 : 1	25 mL	45 → 21→ 0	6.3 : 93.7	46.2
10	1.67 : 1	20 mL	45 → 21	0.46 : 99.54	40.6
11	1.7 : 1	24.3 mL	45 → 21→ 0	0.53 : 99.47	41.45
12	1.8 : 1	28 mL	45 → 21→ 0	0.45 : 99.55	41.3
13	**2 : 1**	**19.5 mL**	**45 → 21**	**0.65 : 99.35**	**38.0**
14	2 : 1	15 mL	45 → 21	0.46 : 99.54	38.0
15	2 : 1	30 mL	45 → 21→ 0	0.63 : 99.37	40.1
16	2 : 1	27 mL	45 → 21→ 0	0.5 : 99.5	41.4
17	2 : 1	22.5 mL	45 → 21→ 0	0.5 : 99.5	41.4
18	**2 : 1**	**19.5 mL**	**45 → 21→ 0**	**0.46 : 99.54**	**44.0**

as a base yielded the diastereomeric salt with poor enantiopurity. Use of ammonium hydroxide and triethylamine, while leading to good enantiopurity, always contaminated the diastereomeric salt with ammonium or triethylammonium salt of the resolving agent and was undesirable for scale-up puposes. We found that 4-methylmorpholine gave the diastereomeric salt which was not contaminated with the 4-methylmorpholinium salt of the resolving agent. Thus, the resolution of **1** was studied using varying compositions of methanol and water at different temperatures in the presence of 1 equivalent of 4-methylmorpholine as a base to afford crystalline diastereomeric salts which were isolated by filtration. The results are summarized in Table 2. A 1.5:1 ratio of methanol and water gave satisfactory resolution at room temperature. Further cooling to 0°C led to poor enantiopurity of the diastereomeric salt **2** (entries 7 and 8). A 2:1 ratio of methanol and water was optimal for this resolution. With this ratio the resolution was satisfactory at room temperature as well as at 0°C. Cooling to 0°C increased the yield from 38% to 44% (entries 13 and 18). These conditions were selected for a further scale-up. A preformed salt of 4-methylmorpholine with dibenzoyl-D-tartaric acid also led to a satisfactory resolution of **1**.

With successful resolution conditions in hand, our next objective was to convert the D-(+)-DBTA salt (**2**) to **3**. Basification of the salt (**2**) with aqueous sodium hydroxide in isopropyl acetate yielded a solution of the (2*R*,2′*R*)-(+)-*threo*-methylphenidate free base in isopropyl acetate. Treatment of this solution with concentrated hydrochloric acid furnished the crude (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride. Finally, the crude material was recrystallized from water and concentrated hydrochloric acid and isolated by filtration to afford 40.3% of crystalline **3** with 99.9% enantiopurity (it contained <0.1% of the (2*S*,2′*S*)-enantiomer).

The resolving agent was also recovered by combining the filtrate from the resolution step and the aqueous layer from the basification step of the diastereomeric salt **2**, treatment with aqueous sodium hydroxide to basify the combined solution, extraction with isopropyl acetate and acidifying the aqueous layer with concentrated hydrochloric acid, extraction with isopropyl acetate, followed by recrystallization from isopropanol and heptane. The recovered *O*,*O*′-dibenzoyl-D-(+)-tartaric acid was of comparable purity to that of the commercial material. A resolution of **1** with the recovered material yielded the D-(+)-DBTA salt (**2**) with the desired enantiopurity ((2*R*,2′*R*):(2*S*,2′*S*)=95.5:0.5). These results indicate that the resolving agent is recyclable, making this process even more economical.

We also needed to prepare the (2*S*,2′*S*)-(−)-*threo*-enantiomer of methylphenidate (**5**) as a reference standard (Scheme 2). Compound **5** was prepared in 38% yield using the same procedure but replacing *O*,*O*′-dibenzoyl-D-(+)-tartaric acid with *O*,*O*′-dibenzoyl-L-(−)-tartaric acid in the resolution step.



Scheme 2.

In summary, an efficient and large scale synthesis of (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**3**) by direct resolution of (±)-*threo*-methylphenidate hydrochloride (**1**) with *O*,*O*′-dibenzoyl-D-(+)-tartaric acid in the presence of 4-methylmorpholine was developed. The resolving agent was recyclable. (2*S*,2′*S*)-(−)-*threo*-Methylphenidate hydrochloride (**5**) was also prepared by the resolution of (±)-*threo*-methylphenidate hydrochloride with *O*,*O*′-dibenzoyl-L-(−)-tartaric acid.

3. Experimental

Melting points were measured on a Büchi 535 melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker 300 instrument. The enantiopurities were determined either by capillary electrophoresis on a Beckman P/ACE 5000 series instrument (capillary: fused silica, 75 μm (ID)×361 μm (OD)×77 cm (70 cm effective separation length), 800 μm aperture; detection: 214 nm; injection: 4.5 seconds, run voltage: 28 kV (363 V/cm); run time: 32 min; polarity: positive; temperature: 23°C; current: 115–130 μamps; 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). *O*,*O*′-Dibenzoyl-D-(+)-tartaric acid and *O*,*O*′-di-*p*-toluoyl-D-(+)-tartaric acid were commercially available. The other diaroyl-D-tartaric acids were prepared from D-tartaric acid using a reported procedure.[14]

*3.1. (2*R*,2′*R*)-(+)-*threo*-Methylphenidate hydrochloride (**3**)*

A 3 L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and heating mantle was charged with (±)-methylphenidate hydrochloride (129.5 g; 0.48 mol), *O*,*O*′-dibenzoyl-D-(+)-tartaric acid (172.0 g; 0.48 mol), and methanol (624 mL). The mixture was stirred at room temperature (23–25°C) and to the resulting solution was added 4-methylmorpholine (48.55 g; 0.48 mol) over a period of 5–10 min while maintaining an internal temperature of 29–31°C. The resulting clear solution was heated to an internal temperature of 40–45°C, and water (312 mL) was added over a period of 10 min while maintaining the same internal temperature to obtain a clear solution. To this solution were added seeds of *O*,*O*′-dibenzoyl-D-(+)-tartrate salt (**2**) of (2*R*,2′*R*)-methylphenidate (60 mg). The reaction mixture was allowed to cool to room temperature (23–25°C) over a period of 1 h, and the stirring was continued at the same temperature for an additional 1 h. The heterogeneous mixture was cooled to an internal temperature of 0–5°C over a period of 15 min and stirred at 0–5°C for an additional 2 h (at the 25 kg scale this cooling step was eliminated). The solids were collected by filtration, washed with a precooled mixture (0–5°C) of methanol and water (2:1 v/v) in three equal 70 mL portions, and dried at 50–55°C (100 mmHg) to afford 125.5 g of *O*,*O*′-dibenzoyl-D-(+)-tartrate salt of (2*R*,2′*R*)-methylphenidate (**4**): mp=138–140°C; $[\alpha]_D^{25}$ +107.7 (c=1.0, MeOH); (2*S*,2′*S*):(2*R*,2′*R*)=99.54:0.46.

O,*O*′-Dibenzoyl-D-(+)-tartrate salt of (2*R*,2′*R*)-(+)-*threo*-methylphenidate (**2**, 125.3 g) was suspended in isopropyl acetate (400 mL), and a solution of sodium hydroxide (21.2 g) in water (400 mL) was added over a period of 15 min while maintaining an internal temperature of 20–25°C. The addition funnel was washed with water (5 mL), which was added to the mixture. The suspension was stirred efficiently until all the solids dissolved (15–20 min). The organic layer was separated, and the aqueous layer was extracted with isopropyl acetate (200 mL). The aqueous layer was saved to recover the resolving agent. The combined organic layers were washed with water (30 mL) and filtered. The filtrate was cooled to 0–2°C (internal temperature), and concentrated hydrochloric acid (34.9 g; 31%) was added over a period of 10 min while maintaining an internal temperature of <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 mm Hg) to afford 55.2 g of crude (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride. This solid was added to hot water (64 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 (24.0 g; 31%) over a period of 10 min while maintaining an internal temperature of <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 (2×7.5 mL; precooled to 0–5°C) and dried at 50–55°C (100 mmHg) for 16 h to obtain a constant weight of 52.2 g of pure (2*R*,2′*R*)-(+)-*threo*-methylphenidate hydrochloride (**3**) as a white powder. Yield 40.3%; mp=222–224°C; $[\alpha]_D^{25}$ +84 (c=1.0, MeOH); (2*R*,2′*R*):(2*S*,2′*S*)=99.9:<0.1). Lit.[1] mp=210–211°C; $[\alpha]_D^{25}$ +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.

3.2. (2S,2′S)-(−)-threo-Methylphenidate hydrochloride (5)

Compound **5** was prepared in a similar manner as described above for **3** except *O*,*O*′-dibenzoyl-L-(−)-tartaric acid was used for the resolution step. This afforded the *O*,*O*′-dibenzoyl-L-(−)-tartrate salt of (2*S*,2′*S*)-(−)-*threo*-methylphenidate (**4**) in 41.7% yield; mp=138–140°C; $[\alpha]_D^{25}$ −107 (c=1.0, MeOH); (2*S*,2′*S*):(2*R*,2′*R*)=99.73:0.27.

Compound **5**: Yield 38%; mp=222–224°C; $[\alpha]_D^{25}$ −87 (c=1.0, MeOH); (2*S*,2′*S*):(2*R*,2′*R*)=99.9:0.1. Lit.[1] mp=209–210°C; $[\alpha]_D^{20}$ −75 (1% in MeOH); IR (KBr, cm^{-1}) 1739; ^{1}H NMR (CD_3OD, δ) 1.33–1.55 (m, 3H), 1.64–1.92 (m, 3H), 3.1 (dt, 1H, J=3.5 and 12.6 Hz), 3.4–3.5 (m, 1H), 3.7 (s, 3H), 3.83 (dt, 1H, J=3.5 and 10.0 Hz), 3.96 (d, 1H, J=10.0 Hz), 7.25–7.44 (m, 5H); ^{13}C NMR (CD_3OD, δ) 22.79, 23.27, 27.58, 46.64, 53.4, 55.23, 59.2, 129.59, 129.64, 130.38, 135.25, 173.24; 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, 62.21; H, 7.32; N, 5.44; Cl, 13.16.

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