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Tetrahedron: *Asymmetry* 14 (2003) 3553–3556

TETRAHEDRON: *ASYMMETRY*

New resolution approach for large-scale preparation of enantiopure didesmethylsibutramine (DDMS)

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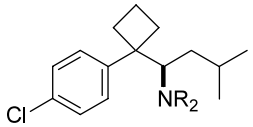
Received 15 July 2003; accepted 28 August 2003

Abstract—An improved synthesis and efficient resolution method to prepare both enantiopures of DDMS using crystallization of enantiomerically pure tartaric acid salts of racemic DDMS are disclosed.

1. Introduction

Didesmethylsibutramine (DDMS) **1b** represents one of the sibutramine **1a** metabolites (Fig. 1)[1–3] that was reported to be a more potent noradrenaline and serotonin reuptake inhibitor than the parent sibutramine itself.[4] Preliminary studies showed that the two enantiomers of DDMS exhibit different biological activities.[5] In order to support the preclinical studies, larger quantities of both enantiomers of DDMS were required. To meet this requirement, an efficient and scalable process leading to the production of multi-kilograms of enantiomeric pure (*R*)- and (*S*)-DDMS was needed.



1a: R = CH_3 (*R*)-Sibutramine
1b: R = H (*R*)-DDMS

Figure 1.

Traditionally, in the preparation of enantiopure chiral amines using resolution methods, fractional crystallization was commonly used to separate the two diastereomeric salts that were formed by treatment of racemic amine with a homochiral acid in a solvent system.[6] Due to the fact that resolutions normally are highly sensitive to both solvent systems and impurities,[1] amines should be purified before use either by distillation, precipitation, or crystallization. Furthermore, this method is not desirable because additional steps have to be conducted, and it is limited if the purification of amine by distillation or precipitation is not successful, as in the case for DDMS free-base.

Herein, we disclose a new strategy for efficient production of both enantiomers of DDMS by combining isolation, purification, and salt formation resolution in one-step, in which chemically pure racemic DDMS is isolated from the reaction mixture as a salt of enantiomerically pure tartaric acid to perform simple crystallizations, to provide both enantiopure (*R*)- and (*S*)-DDMS.

2. Results and discussion

Initial efforts were focused on the development of a feasible method for the large-scale production of racemic DDMS. Previously reported procedures for the synthesis of DDMS involved unoptimized and undesirable experimental conditions.[1,7] The reaction was performed by Grignard addition to 1-(4-chlorophenyl)-1-cyclobutylcarbonitrile (CCBC) **2** in toluene at 90–95°C for 18 h, followed by reduction using 3 equiv. of $NaBH_4$ in *iso*-propanol under reflux-

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doi:10.1016/j.tetasy.2003.08.042

ing for >20 h, and the reaction was quenched with water to furnish the product. This protocol proved unsatisfactory for large-scale production with the following associated problems: (1) long reaction time; (2) moderate yield (<80%); and (3) inefficient reaction quenching after reduction process, in which conglomeration occurred in the reaction mixture making the agitation difficult, and the hydrogen evolution uncontrollable. Therefore, a practical and reliable process was desired for large-scale production of racemic DDMS.

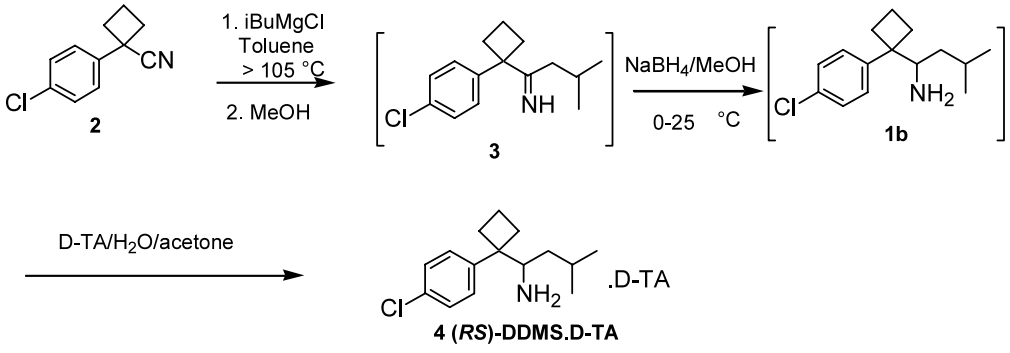
After a series of experiments an optimum procedure was established, which uses the addition of iBuMgCl to **2** at >105°C for 2 h, followed by quenching with methanol. The imine intermediate **3** was reduced using one equivalent of $NaBH_4$ at 0–25°C for 1 h. An efficient quenching process was identified by adding the reaction mixture to a 2 M HCl aqueous solution at 0°C, which generated a homogeneous reaction mixture that can be easily stirred. After work-up, this optimized process afforded a crude racemic DDMS **1b** in toluene with excellent yield (>95%), The optimized experimental conditions proved highly desirable for large-scale production (Scheme 1).

Once a scalable method for the preparation of racemic DDMS was developed, our efforts were directed toward the isolation of DDMS free-base from the reaction mixture. Isolation of DDMS by salt formation with inorganic acids proved unsatisfactory. The salts were either soluble in toluene, or precipitates were not formed. With this problem, we sought a different strategy for the isolation by using enantiomerically pure acid.

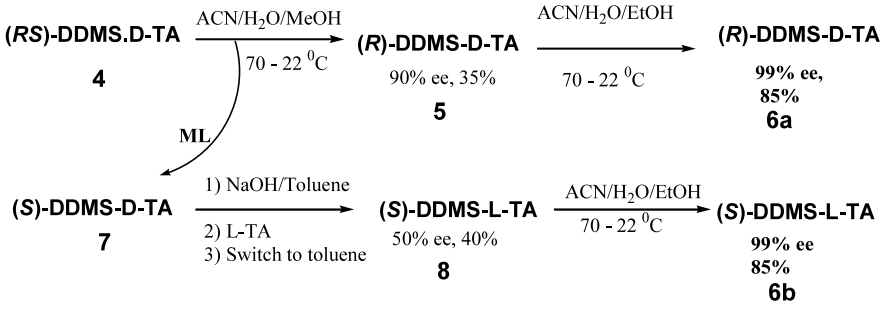
The acid used should also meet the requirement of a typical resolving reagent. Isolation of the salt in a racemic form is important for producing both enantiomers in a high chemical purity and yield.

After screening a number of enantiomerically pure acids (e.g. tartaric acid, mandelic acid, ditolyl tartaric acid), tartaric acid was found to be an excellent choice for the isolation of DDMS from the reaction mixture. Racemic DDMS in toluene was treated with D-tartaric acid (D-TA) in a water/acetone (2:1, v/v) mixture by slow addition at 60–70°C, and the mixture was then distilled under azeotropic condition to remove the water, which included the salt formation with 0% de.[8] The key features for this process follow. The addition of acetone with water and controlling the addition temperature allows the generation of a homogeneous reaction mixture, and facilitates the salt formation. Removal of water from the reaction mixture gradually also benefits the salt formation and the yield. This three-step streamline process (Scheme 1) provides an overall yield of 95% of DDMS·D-TA **4** with 98% chemical purity in a multi-kilogram scale.[8,9]

With **4** in hand, we focused on developing a solvent system to separate the two diastereomers for (*R*)-DDMS·D-TA **6a** and (*S*)-DDMS·L-TA **6b** by crystallization (Scheme 2). Screening of different solvents and solvent mixtures led to the discovery that the ACN/H_2O/MeOH combination was an excellent choice for the resolution, which afforded **6a** in optically enriched form **5**.[8] Detailed studies show that the ratio of solvents, the amount of water used, and the isolation temperature have an impact on the diastereopurity and



Scheme 1.



Scheme 2.

yield of the product (see below). An optimized system gave crude product **5** in 90% ee and 35% yield on a multi-kilogram scale, in which ACN/H_2O/MeOH was used in a ratio of 8:1.3:0.5 (v/v/v)/ g salt, and the isolation temperature was 20–25°C. Diastereomerically pure (*R*)-DDMS·D-TA (>99.5% ee, $[\alpha]_D^{20}=+58.7$, *c* 1.0, DMF) **6a**[10] was obtained by one additional crystallization of **5** from the optimized solvent system of ACN/H_2O/EtOH (16:2:1, v/v/v) in 85% yield. The addition of ethanol to the system was found to be crucial for obtaining diastereopure product with single minimum crystallization.

As mentioned above, while the solvent ratio and amount of solvents used are crucial for high yield and high de of the final product in the crystallization process, water content also has a high impact. To investigate this effect, we undertook a systematic study, and the result is shown in Figure 2. In this study, 80% ee of (*R*)-DDMS·D-TA was used as the starting material, and the solvent ratio of ACN/EtOH of 16:1 (v/v) and the total amount of solvent (19 mL/g salt) were kept constant. The result shows that ee increases with the increase % of water, peaks at approx. 10.5% of water, and then decreases slightly. The yield, on the other hand is very sensitive to water, and decreases dramatically as the % of water is increased. With only one recrystallization, this procedure affords the final product with excellent ee and yield.

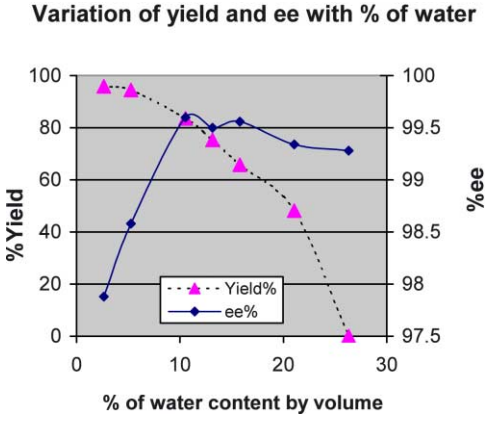


Figure 2.

The (*S*)-DDMS was isolated from the mother liquor containing enriched (S)-DDMS·D-TA, which was treated with base and then switched to the L-TA salt to afford crude (*S*)-DDMS·L-TA **8** in 50% ee and 40% yield. After two crystallizations, using the same solvent system as described above gave the final product (*S*)-DDMS·L-TA **6b**, $[\alpha]_D^{20}=-53.4$, (*c* 1.0, DMF) in >99.5% de and 85% yield.

In summary, a new and efficient resolution method for the preparation of both enantiomers of enantiomerically pure didesmethylsibutramine (DDMS) was developed by simple crystallization of racemic DDMS·TA salt. This process was used to prepare multi-kilogram quantities of (*R*)-DDMS and (*S*)-DDMS in an enantiomerically pure form. Current efforts are focused on the asymmetric synthesis of DDMS and the results will be reported in due course.

3. Experimental

3.1. Preparation of (*RS*)-DDMS·D-TA

A 1 L three-necked round-bottomed flask was charged with 1-(4-chlorophenyl)-1-cyclobutylcarbonitrile (CCBC, 50.0 g, 261 mmol) and toluene (150 mL), followed by *iso*-butyl magnesium chloride (395 mL, 1.0 M in MTBE), and the resulting mixture was distilled until the internal temperature reached ≥105°C. After stirring at that temperature for 2 h, the mixture was cooled to 0°C and methanol was added slowly (295 mL), followed by sodium borohydride (10.4 g, 1.06 equiv.) portion-wise. The resulting mixture was stirred at rt for 15 min and was added to a 2N HCl solution (330 mL) slowly, stirred for 15 min and the phases were separated. The aqueous phase was extracted with toluene (300 mL), the combined organic phases were distilled to remove methanol, and then washed with aqueous NaOH solution (1.5 M, 100 mL) and water (100 mL) twice. The resulting organic phase was heated to 50–60°C, followed by an addition of D-tartaric acid (40.0 g) in water (80 mL) and acetone (40 mL) slowly. The reaction mixture was azeotrope distilled until the internal temperature reached ≥92°C and then cooled to ambient temperature in 1–2 h. The slurry was filtered, and the wet cake was washed with MTBE (100 mL) and dried at 40–45°C under reduced pressure to afford (*RS*)-DDMS·D-TA (100.5 g) in 95.8% yield.

3.2. Preparation of (*R*)-DDMS·D-TA

A mixture of (*RS*)-DDMS·D-TA (50 g), acetonitrile (400 mL), water (70 mL) and methanol (33 mL) was heated to reflux for 30 min and then cooled to 64–66°C. The reaction mixture was seeded with (*R*)-DDMS·D-TA (0.5 g, >99% ee) and stirred for 15 min. After being cooled to 25°C in about 60 min, the slurry was filtered and the wet cake washed with the solvent mixture (30 mL), acetonitrile (50 mL×2), and then dried to afford crude (*R*)-DDMS·D-TA (17.5 g) in 90% ee. After one recrystallization of the above product from acetonitrile/water/ethanol (280 mL/43.7 mL/18 mL) provided diastereomerically pure (*R*)-DDMS·D-TA (14.8 g) in 99% ee[10] and 30% overall yield. $[\alpha]_D^{20}=+58.7$, (*c* 1.0, DMF). ^{1}H NMR (DMSO-d_6): δ 0.7–0.9 (m, 6H), 0.9–1.05 (t, 1H), 1.1–1.24 (b, 1H), 1.5–1.8 (b, 2H), 1.8–2.02 (b, 1H), 2.1–2.4 (3, 3H), 2.4–2.6 (b, 1H), 3.5 (m, 1H), 4.0 (s, 2H), 7.1–7.6 (m, 4H, with 6H from NH_2, OH and COOH). ^{13}C NMR δ: 15.4, 21.5, 22.0, 22.2, 32.0, 32.2, 38.4, 49.0, 54.0, 72.8, 128.8, 130.0, 132.0, 143.0, 175.5. Anal. calcd for $C_{19}H_{28}ClNO_6$, C, 56.78; H, 7.02; Cl, 8.82; N, 3.49. Found: C, 56.08, H, 6.98, N, 3.61, Cl, 8.86.

3.3. Preparation of (*S*)-DDMS·L-TA

The mother liquor from the preparation of (*R*)-DDMS was treated with NaOH and after work-up, the free-base was treated with L-tartaric acid to afford L-tartrate salt with 50% ee and in 40% yield, using the same method described above. After one crystallization of the salt from acetonitrile/water/ethanol (16:2:1), the solvent mixture afforded (*S*)-DDMS·L-TA in 99% ee and 34% overall yield. $[\alpha]_D^{20} = -53.4$, (*c* 1.0, DMF). NMR (DMSO-d_6): ^{1}H NMR δ 0.7–0.9 (m, 6H), 0.9–1.05 (m, 1H), 1.1–1.3 (b, 1H), 1.52–1.8 (b, 2H), 1.84–2.05 (b, 1H), 2.15–2.4 (b, 3H), 2.4–2.6 (b, 1H), 3.65–3.58 (m, 1H), 4.0 (s, 2H), 6.7–7.3 (b, 6H from NH_2, OH and COOH) 7.1–7.6 (m, 4H). ^{13}C NMR δ: 15.4, 21.5, 22.0, 22.2, 32.0, 32.2, 38.4, 49.0, 54.0, 72.8, 128.8, 130.0, 132.0, 143.0, 175.5. Anal. calcd for $C_{19}H_{28}ClNO_6$, C, 56.78; H, 7.02; Cl, 8.82; N, 3.49. Found: C, 56.12; H, 7.00; N, 3.57; Cl, 8.77.

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8. Enantiopurity of DDMS was based on chiral HPLC analysis with Chiralpak AD-RH column, 5 μm, 4.6 mm× 15 cm; mobile phase, 20 mM sodium borate (pH 9)/ACN (25:75); 1.0 mL/min; 222 nm; (*R*)-DDMS, $r_t = 9.46$ min; (*S*)-DDMS, $r_t = 7.53$ min.
9. Chemical purity analysis for DDMS was performed on achiral HPLC with agilent SB-CN column, 5 μm, 4.6×150 mm; mobile phase, 0.05 M NaH_2PO_4–0.01 M sodium octyl sulfate buffer, pH 3/THF, 60:40; 1.0 mL/min; 222 nm.
10. Determination of the absolute configuration of (*R*)-DDMS or (*S*)-DDMS was achieved by converting DDMS to desmethylsibutramine (DMS) by methylation, followed by chiral HPLC analysis with known compound as reported.[2]