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First practical synthesis of enantiomerically pure (*R*)- and (*S*)-desmethylsibutramine (DMS) and unambiguous determination of their absolute configuration by single-crystal X-ray analysis

Zhengxu Han,[a] Dhileepkumar Krishnamurthy,[a,*] Derek Pflum,[a] Qun K. Fang,[a] Hal Butler,[a] T. Stanley Cameron,[b] Stephen A. Wald[a] and Chris H. Senanayake[a,*]

[a]*Chemical Process Research and Development, Sepracor Inc., 111 Locke Drive, Marlborough, MA 01752, USA*
[b]*Department of Chemistry, Dalhousie University, Halifax, NS, Canada B3H 4J3*

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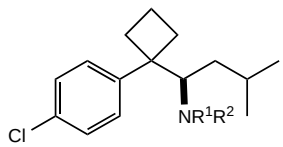
Abstract—A practical synthesis of enantiomerically pure (*R*)-desmethylsibutramine [(*R*)-DMS] and (*S*)-desmethylsibutramine [(*S*)-DMS] is outlined along with an improved synthesis of racemic desmethylsibutramine. This route was used for kilo-scale production of enantiomerically pure (*R*)- and (*S*)-DMS. Racemic desmethylsibutramine was resolved with either (*R*)- or (*S*)-mandelic acid, and the absolute stereochemistry of DMS was determined by single X-ray crystallography of its mandelate salt.

Desmethylsibutramine (DMS) **1** is a pharmacologically active metabolite of sibutramine **2**, a new class of compounds for the treatment of obesity.[1] It has been well documented that metabolites and/or enantiomers often exhibit different biological activities and pharmacokinetics. In order to evaluate the effectiveness of DMS towards attention deficit hyperactivity disorder (ADHD) and depression, kilo quantities of both (*R*)- and (*S*)-DMS in an enantiomerically pure form are required.[2] Recently, we reported the preparation of enantiomerically pure (*R*)-DMS by demethylation of corresponding (*R*)-sibutramine, which in turn was obtained by resolution of (±)-sibutramine.[3] Although this method was useful in the preparation of multigram quantities of enantiomerically pure sibutramine, due to the use of potentially explosive diethyl azodicarboxylate (DEAD), application of this method to the multi-kilo production of DMS was not desirable. Herein, we report a short and efficient synthesis of both enantiomers of DMS in enantiomerically pure form using a direct resolution of (±)-**1** with (*R*)- or (*S*)-mandelic acid (Fig. 1).

To develop a practical route for the synthesis of enantiomerically pure desmethylsibutramine, our synthetic efforts focused on the development of a high yielding scaleable process for the synthesis of (±)-**1** and identification of an inexpensive enantiomerically pure acid for resolution of the racemic mixture.

Previously reported procedures for the synthesis of (±)-**1** involve unoptimized and undesirable experimental conditions with long reaction times.[3–7] Therefore, this second-generation synthesis begins with the identification of a highly reproducible[8] and scaleable synthesis for (±)-DMS from the commercially available 1-(4-chlorophenyl)-1-cyclobutylcarbonitrile (CCBC) **3** (Scheme 1). The optimized procedure used the addition of *iso*-BuMgCl to **3** at >105°C for 2 h, followed by quenching with methanol. The intermediate imine **4** was reduced using 1 equiv. of sodium borohydride at 0–25°C for 1 h. Methylation of didesmethylsibutramine (DDMS) **5** was carried out using a two-step protocol



1 R^1=H, R^2=CH_3
2 R^1=R^2=CH_3

Figure 1.

* Corresponding authors.

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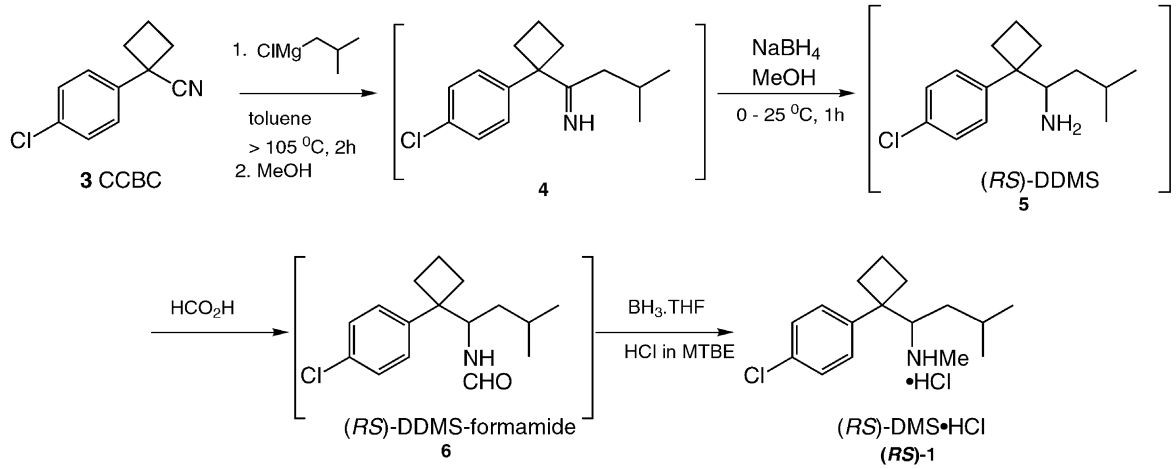


Scheme 1.

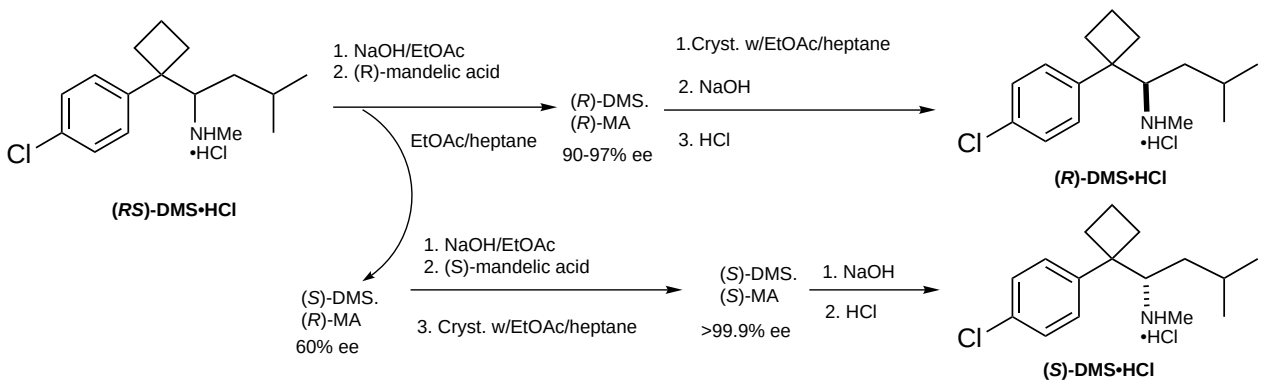
with the formation of formamide **6**, followed by reduction with borane to afford (±)-**1**. This four-step, streamlined process provided an overall yield of 72% of (±)-**1**·HCl from **3** at multi kilo scale. The key features in the synthesis follow. In the Grignard addition step, by increasing the temperature of the reaction from 92 to >105°C, the reaction time was reduced from 16 to 2 h. In the reduction step, the amount of sodium borohydride was reduced to 1 equiv. from 3 equiv., and the temperature of the reaction was reduced to 0–25°C from 90°C by replacing IPA with methanol.[9]

Once a scaleable method for the preparation of (±)-**1** was developed, screening of resolving agents for the resolution of (±)-DMS (e.g. tartaric acid, ditolyl tartaric acid, dibenzoyl tartaric acid, and mandelic acid) in various solvent systems (methanol, ethanol, ethyl acetate, acetonitrile, isopropyl alcohol, water, hexane, heptane and their combinations) was conducted. Mandelic acid in ethyl acetate and heptane (1/0.4, v/v) was found to be an excellent choice to resolve racemic desmethylsibutramine, as outlined in Scheme 2.

(±)-DMS was treated with 1 equiv. of (*R*)-mandelic acid in ethyl acetate and heptane at reflux for 1 h, then cooled to approximately 60°C, seeded and further cooled to 22°C. The resulting crystalline salt was collected and washed with EtOAc/heptane to give a white solid with 90–97% e.e. The salt was recrystallized from EtOAc/heptane (1:1, v/v) in 90% yield and >99% e.e.

(*R*)-DMS·HCl salt ($[\alpha]_D = +5$, *c* 0.5, H_2O) was prepared from the diastereomerically pure mandelate salt ($[\alpha]_D = +5.3$, *c* 5.8, CH_3OH) by treatment with sodium hydroxide followed by the addition of HCl/MTBE.[10] The enantiomeric excess (e.e.)[11] of the (*R*)-desmethylsibutramine·(*R*)-mandelic acid salt was >99.7% with a chemical purity of 99.8%. The overall yield for the resolution process was 37–40%. The (*S*)-DMS was isolated from the enriched mother liquor and was further enriched with (*S*)-mandelic acid to give (*S*)-desmethylsibutramine·(*S*)-mandalate (Scheme 2).[12] The overall yield for (*R*)-DMS from CCBC in this second-generation process was increased to 27 from 15%, with a reduced number of isolations and reduced cycle time.

By slow crystallization of the (*R*)-desmethylsibutramine·(*R*)-mandelate salt (e.e. >99.5%) from EtOAc/heptane, crystals suitable for X-ray structural analysis were obtained. The structure of the (+)-desmethylsibutramine·(*R*)-mandelate salt was found to have (*R*)-configuration as determined from the X-ray crystal structure (Fig. 2).



Scheme 2.

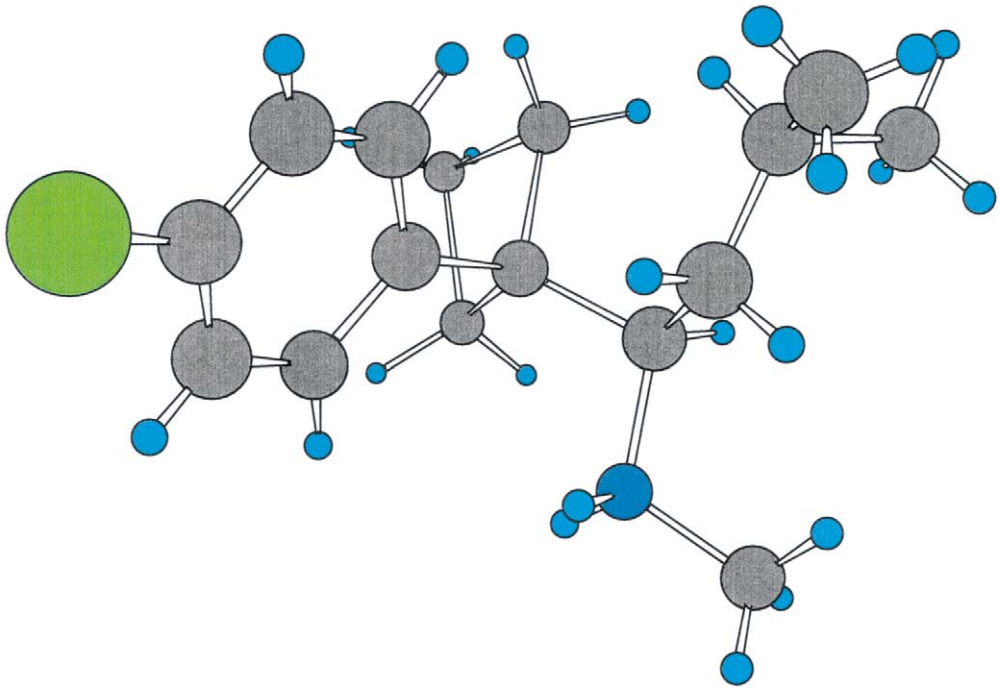


Figure 2. X-Ray structure of the (*R*)-DMS·(*R*)-mandelate salt ((*R*)-mandelic acid is omitted in the figure).

In summary, a practical resolution process for the preparation of both enantiomers of enantiomerically pure desmethylsibutramine was developed. This process was used to prepare multi kilo quantities of enantiomerically pure (*R*)-DMS and (*S*)-DMS. Based on single-crystal X-ray structural analysis, the (+)-isomer of the DMS·HCl salt has (*R*)-configuration. Current efforts focus on the asymmetric synthesis of desmethylsibutramine and its derivatives and the results will be reported in due course.

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9. Use of IPA instead of methanol in the imine reduction reaction requires vigorous reaction conditions with longer reaction time.
10. Gave satisfactory mp and $[\alpha]_D$ values as reported in a previous synthesis.[3]
11. Chirobiotic V column, 10 cm, 4.6 mm×25 cm. Mobil phase: 20 mM ammonium acetate/IPA, (65:35). Retention time: *R* isomer 13.2 min, *S* isomer 14.8 min.
12. (*S*)-DMS·HCl gave satisfactory elemental analysis. Anal. calcd for $C_{16}H_{25}Cl_2N$: C, 63.57; H, 8.34; N, 4.63. Found: C, 63.66; H, 8.39; N, 4.66%.