Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4477–4480

TETRAHEDRON:
ASYMMETRY

First preparation of enantiomerically pure sibutramine and its major metabolite, and determination of their absolute configuration by single crystal X-ray analysis

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Received 25 October 1999; accepted 1 November 1999

Abstract

Racemic sibutramine was resolved with dibenzoyl-D-tartaric acid, and the absolute stereochemistry of sibutramine was determined by single crystal X-ray crystallography of its dibenzoyl D-tartrate. The major active metabolite (desmethylsibutramine) was obtained by demethylation of sibutramine with DEAD. Enantiomeric purity of sibutramine was determined by HPLC on an Ultron ES-OVM column.

Racemic sibutramine **1** (Fig. 1) is a new class of compounds for the treatment of obesity. It is a serotonin and noradrenaline re-uptake inhibitor[1] and is sold as the racemate form under the brand name Meridia® (HCl monohydrate salt). Sibutramine has one stereogenic center, resulting in the existence of two enantiomers. It is well documented that enantiomers often have different biological activities and metabolic profiles (pharmacokinetics). To date, however, there has been no report in the literature for the preparation of sibutramine (or desmethylsibutramine **2**) enantiomers by any one of the following general methods: (a) asymmetric synthesis; (b) resolution of the racemate with a chiral acid; (c) chiral column HPLC separation. In order to explore the biological and pharmacological activities of the enantiomers of sibutramine and its active metabolite, multigram quantities of these enantiomers are needed.[2] Here, we report the first efficient method for the preparation of both enantiomers of **1** and **2** by chiral acid resolution.

Racemic sibutramine was readily prepared by following the literature procedures.[3] Cycloalkylation of commercially available 4-chlorophenylacetonitrile with 1,3-dibromopropane yielded the 4-chlorophenylcyclobutylnitrile, which was treated with isobutylmagnesium bromide in toluene, followed by reduction with sodium borohydride to give the primary amine in 75% yield. The amine was then

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00511-X

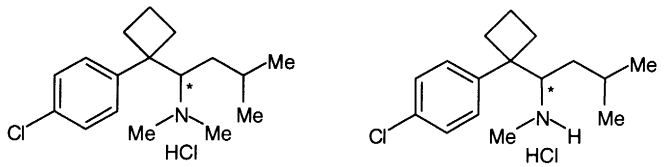
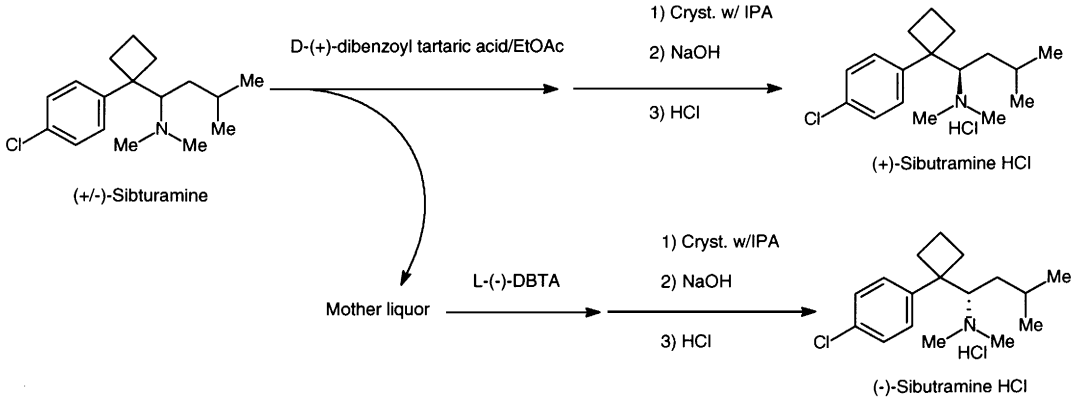


Fig. 1.

converted to sibutramine by Eschweiler–Clarke methylation. After a chiral analytical separation of sibutramine was achieved by HPLC with a chiral stationary phase column (ES-OVM),[4] screening of common resolving agents (e.g. tartaric acid, ditoluyl tartaric acid, dibenzoyl tartaric acid, and mandelic acid) in various solvents (methanol, ethyl acetate, toluene, and isopropyl alcohol) was conducted. Dibenzoyl tartaric acid in ethyl acetate was found to be an excellent choice to resolve racemic sibutramine, as outlined in Scheme 1.



Scheme 1.

Racemic sibutramine was treated with one equivalent of dibenzoyl-D-tartaric acid in ethyl acetate at 60°C for 30 min to give a crystalline solid. The solid was enriched (+)-sibutramine dibenzoyl-D-tartaric salt with 70 to 93% ee. Further crystallization in isopropyl alcohol yielded the diastereomeric salt with >99.5% ee in 40% overall yield ($[\alpha]_D$=+71.2, c 0.9, MeOH). Sibutramine HCl salt ($[\alpha]_D$=+3.3, c 1.5, H_2O) was prepared from the diastereomerically pure dibenzoyl tartrate by treatment with sodium hydroxide, followed by the addition of HCl/Et_2O. The (−)-isomer of sibutramine was isolated from the enriched mother liquor, and further enriched with dibenzoyl-L-tartaric acid to give (−)-sibutramine dibenzoyl-L-tartrate.

By slow crystallization of (+)-sibutramine dibenzyl-D-tartrate (ee >99.5%) from ethanol, crystals suitable for X-ray structural analysis were obtained. The structure of the dibenzoyl-D-tartrate salt was found to have the *R* configuration corresponding to (+)-sibutramine dibenzoyl-D-tartrate (Fig. 2).

Since multigram enantiomerically pure sibutramine is available by this efficient resolution method, it would be convenient to obtain the enantiomers of its active metabolite **2** by demethylation provided no racemization occurs during the process. It was found that commonly used demethylation reagents (e.g. alkyl chloroformates) failed to yield any desmethylsibutramine, but gave a complex mixture of elimination and rearrangement products. However, we were delighted to discover that when sibutramine was treated with DEAD[5] (1.2 equiv.) in toluene at 50°C for 10 h, followed by treatment of hydrochloric acid in ethanol under reflux, desmethylsibutramine was isolated in a 70% yield as shown in Scheme 2.

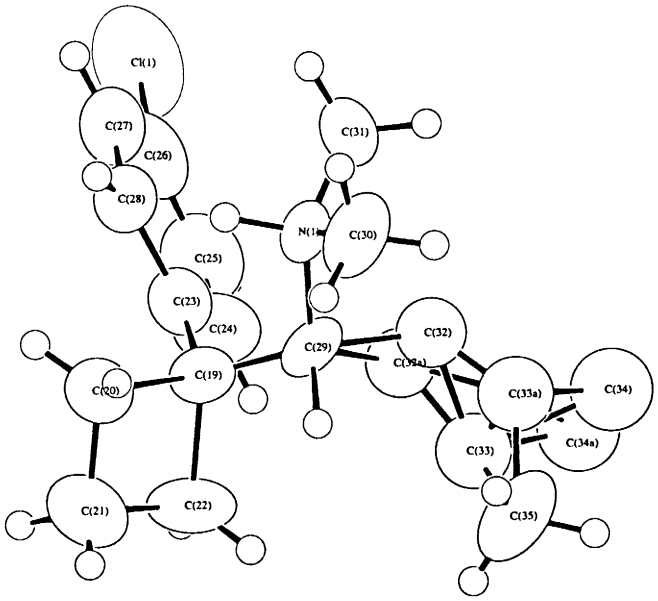
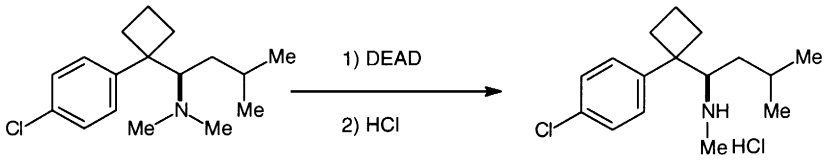


Fig. 2. X-Ray structure of the salt (dibenzoyl-D-tartaric acid was omitted in the figure)



Scheme 2.

Demethylation of sibutramine with DEAD was proven to proceed with retention of stereochemistry, and no racemization was observed. When (+)-desmethylsibutramine hydrochloride ($[\alpha]_D$=+5, c 0.5, H_2O), prepared from (*R*)-(+)-sibutramine (99% ee) with DEAD was alkylated under Eschweiler–Clarke methylation conditions, the product (sibutramine) had *R* configuration (99% ee).

In summary, an efficient resolution method for the preparation of both enantiomers of enantiomerically pure sibutramine was developed. Desmethylsibutramine was conveniently prepared in multigram quantity by demethylation of sibutramine with DEAD, with complete retention of the configuration. Based on single crystal X-ray structural analysis, the (+)-isomer of sibutramine HCl salt has the *R* configuration, as well as (+)-desmethylsibutramine HCl salt established by demethylation. Current efforts focus on the asymmetric synthesis of sibutramine and its derivatives.

Acknowledgements

We are grateful to Dr. Alex Jurgens from Sepracor Canada Limited for his involvement in this work, and to Ms. Susan Gillis for her contribution in the preparation of this manuscript.

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4. Ultron ES-OVM column, 5 μm, 15 cm×4.6 mm. Mobile phase: 0.01 M NaH_2PO_4 (pH 7)/MeCN=7:3. Retention time: *R*-isomer 4.6 min, *S*-isomer 5.4 min.
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