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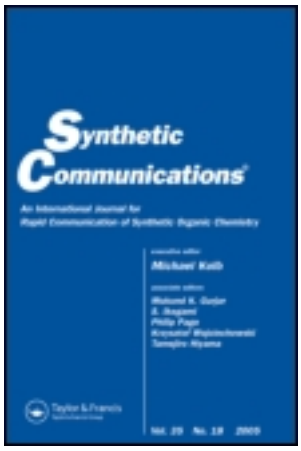

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# MULTIGRAM-SCALE STEREOSELECTIVE SYNTHESIS OF MESO-1,3-BUTADIENE BISEPOXIDE

David J. Claffey [a]

[a] Dept. of Pharmaceutical Sciences , University of Colorado Health Sciences Center , 4200 E. Ninth Avenue, Box C238, Denver, CO, 80262, U.S.A.

Published online: 16 Aug 2006.

To cite this article: David J. Claffey (2002) MULTIGRAM-SCALE STEREOSELECTIVE SYNTHESIS OF MESO-1,3-BUTADIENE BISEPOXIDE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:19, 3041-3045, DOI: 10.1081/SCC-120012996

To link to this article: http://dx.doi.org/10.1081/SCC-120012996

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SYNTHETIC COMMUNICATIONS
Vol. 32, No. 19, pp. 3041–3045, 2002

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# MULTIGRAM-SCALE STEREOSELECTIVE SYNTHESIS OF *MESO*-1,3-BUTADIENE BISEPOXIDE

**David J. Claffey**

University of Colorado Health Sciences Center,
Dept. of Pharmaceutical Sciences, 4200 E.
Ninth Avenue, Box C238, Denver, CO 80262, USA
E-mail: david.claffey@uchsc.edu

## ABSTRACT

*meso*-1,3-Butadiene bisepoxide, a potential building block for natural product synthesis and of interest as a toxic metabolite of butadiene, was synthesized in multi-gram scale in two steps from *meso*-erythritol in good overall yield.

*Key Words:* Mesobutadiene bisepoxide; Synthesis; Metabolite; Butadiene

## INTRODUCTION

*meso*-1,3-Butadiene bisepoxide (*meso*-BBO) is a small symmetrical reactive compound that has significant potential as a building block for natural product synthesis.[1] It, along with its diastereoisomers, is also of great interest to toxicologists at present.[2,3] BBO is a highly toxic metabolite of butadiene, a widely used monomer in the polymer industry. Several epidemiological studies have suggested an excess mortality for lymphatic and hematopoetic cancers in the 65,000 workers that are potentially



DOI: 10.1081/SCC-120012996 0039-7911 (Print); 1532-2432 (Online)
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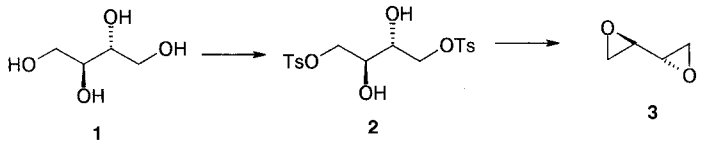
exposed to butadiene in the United States.[4] A range of oxygenated butadiene metabolites, including *meso*-BBO were synthesized in our laboratory by Sharpless epoxidation of 1-tosyloxy-2-hydroxy-3-butene, followed by treatment with base.[5,6] This procedure sufficed for the milligram quantities of *meso*-BBO needed for in vitro studies.[6,7] However, it was not practical to scale-up these reactions for the multi-gram quantities needed for in vivo inhalation exposure studies, or indeed for multistep organic syntheses. A suitable alternative synthesis of *meso*-BBO could not be found in the literature. It has been produced as an isomeric mixture, generally through the epoxidation of butadiene[8] or butadiene monoxide,[9] or from base catalyzed cyclization of dichlorobutanediol.[10] This communication will describe a practical synthesis of gram quantities of *meso*-BBO in good yield starting from *meso*-erythritol.

## RESULTS AND DISCUSSION

*meso*-Erythritol **1** was treated with 1.9 equivalents of tosyl chloride in pyridine. Larger amounts of tosylate generally gave reduced yields. The reaction easily afforded a mixture of the *bis*-tosylate **2** in good yield and adequate purity along with small amounts of mainly mono-, tri-, and tetratosylate (Sch. 1). The reaction mixture did not require any further purification, as these by-products would ultimately give non-volatile products upon reaction with potassium hydroxide. The final step was safely carried out, by suspending the *bis*-tosyl reaction mixture in dichloromethane, and adding 2 equivalents of freshly powdered potassium hydroxide. The resulting insoluble potassium tosylate was easily filtered to give a dichloromethane solution of the *bis*-epoxide. The former was concentrated by evaporation in a fumehood, leaving a more manageable volume of the epoxide, with trace dichloromethane. The remaining solvent was removed from the reaction mixture by fractional distillation. The product distilled as a clear liquid. Its diastereomeric purity (95%) was determined by integration of the $^{13}C$ signals of the *meso*-BBO with those of the diastereomeric D,L-BBO at $\delta$ 43.9 and 50.9 ppm. The identity of the signals of its diaste-




*Scheme 1.*

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reoisomers were confirmed by comparison with an NMR spectrum of D,L-butadiene *bis*epoxide (Aldrich Chemical Co., Milwaukee, WI). Much of the D,L-BBO may have been produced as a result of the reaction of the by-product, 1,3-*O*-tosyl-erythritol, with KOH. If higher diastereomeric purity is required, the crude *bis*-tosylate could be further purified by recrystallization before reaction with base. *meso*-BBO required storage at −20°C.

Though established synthetic steps were used in this synthesis,[11,12] the strength of this procedure is that it allows for the synthesis and isolation to a high degree of physical and optical purity of this highly volatile and toxic compound to be achieved relatively economically, in good yield, and with a relatively high degree of safety.

## EXPERIMENTAL

Note: *meso*-BBO is a suspected carcinogen. All operations must be conducted with adequate safety precautions.

A solution of *meso*-erythritol (100 g, 0.82 mol) in pyridine (3000 mL) was cooled to 5°C with stirring (magnetic). Tosyl chloride (296 g, 1.56 mol) was added portionwise over 4 h while maintaining the temperature at 5–7°C. A clear solution resulted which became opaque, 30 min after the last portion of chloride was added. The mixture was stirred for 12 h at 3–5°C then was allowed to warm to room temperature. The resulting thick suspension was evaporated under reduced pressure at 50°C to give a thick orange syrup (ca. 500 mL). This was dissolved in ethyl acetate (2000 mL) and 5 M HCl was added dropwise with vigorous stirring (magnetic) until the aqueous solution became acidic. The mixture was poured into a separating funnel, the organic portion was removed and washed once with distilled water (200 mL). The ethyl acetate solution was dried over magnesium sulfate, filtered, and evaporated under reduction pressure to give the crude *bis*-tosylate as a thick orange syrup (223 g). This was suspended in dichloromethane (1500 mL) and freshly powdered KOH (56 g, 1 mol) was added over 30 min with vigorous stirring (magnetic). The mixture was stirred for 2 h until TLC (silica; ethyl acetate : hexanes 1 : 1) showed that no *bis*-tosylate (**2**) remained ($R_f$ 0.5). The suspension was filtered and the solid washed with dichloromethane. The dichloromethane was allowed to evaporate in a fume hood (under a dry ice trap) to give an orange liquid. This material was distilled under reduced pressure with vigorous stirring using a fractionating column. *meso*-BBO (**3**) distilled as a clear liquid between 26 and 28°C (30 mmHg) (26 g, 37% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.57 (2H, m), 2.70 (2H, m), 2.86 (2H, m). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 44.5, 50.42.

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## ACKNOWLEDGMENTS

This work was supported in part by agreement 99-5 from the Health Effects Institute and Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87185, USA.

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Received in the USA September 18, 2001

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