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Technical note: Improved synthetic routes to *cis*- and *trans*-(2-methyloxirane-2,3-diyl)dimethanol (*cis*- and *trans*-β-isoprene epoxydiol)

Molly Frauenheim[1], Jason D. Surratt[1,2], Zhenfa Zhang[1], and Avram Gold[1]

[1]Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7431, USA
[2]Department of Chemistry, College of Arts and Sciences, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3290, USA

Correspondence: Avram Gold (golda@email.unc.edu)

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Abstract. We report improved synthetic routes to the isomeric isoprene-derived β-epoxydiols (β-IEPOX) in high yield (57 %–69 %) from inexpensive, readily available starting compounds. The syntheses do not require the protection/deprotection steps or time-consuming purification of intermediates and can readily be scaled up to yield the target IEPOX isomers in gram quantities. Emissions of isoprene (2-methyl-1,3-butadiene, C_5H_8), primarily from deciduous vegetation, constitute the largest source of nonmethane atmospheric hydrocarbons. In the gas phase under low-nitric-oxide (NO) conditions, addition of the atmospheric hydroxyl radical (OH) followed by rapid addition of O_2 yields isoprene-derived hydroxyperoxyl radicals. The major sink (> 90 %) for the peroxyl radicals is a sequential reaction with the hydroperoxyl radical (HO_2), OH, and O_2, which is then followed by the elimination of OH to yield a $\sim 2:1$ mixture of *cis*- and *trans*-(2-methyloxirane-2,3-diyl)dimethanol (*cis*- and *trans*-β-IEPOX). The IEPOX isomers account for about 80 % of closed-shell hydroxyperoxyl products and are rapidly taken up into acidic aerosols to form secondary organic aerosol (SOA). IEPOX-derived SOA makes a significant mass contribution to fine particulate matter ($PM_{2.5}$), which is known to be a major factor in climate forcing as well as adversely affecting respiratory and cardiovascular systems of exposed populations. Prediction of ambient $PM_{2.5}$ composition and distribution, both in regional- and global-scale atmospheric chemistry models, crucially depends on the accuracy of identification and quantitation of uptake product formation. Accessibility of authentic *cis*- and *trans*-β-IEPOX in high purity and in large quantity for laboratory studies underpins progress in developing models as well as identification and quantitation of $PM_{2.5}$ components.

1 Introduction

We report here straightforward procedures for the synthesis of isomeric isoprene β-epoxydiols (β-IEPOX) in high yield from inexpensive, readily available starting compounds. The syntheses do not require the protection/deprotection steps or time-consuming purification of intermediates as used in past studies (Cole-Filipiak et al., 2010; Zhang et al., 2012; Bates et al., 2014, 2016; Chase et al., 2015) and can readily be scaled up to yield the target IEPOX isomers in gram quantities.

Yearly global emissions of isoprene (2-methyl-1,3-butadiene, C_5H_8), primarily from deciduous vegetation, are estimated to be between 500 and 600 Tg and constitute the largest source of nonmethane atmospheric hydrocarbons (Kanakidou et al., 2005; Guenther et al., 2006; Hallquist et al., 2009; St. Clair et al., 2016). In the gas phase under low-nitric-oxide (NO) conditions, the atmospheric hydroxyl radical (OH) adds rapidly to isoprene almost exclusively at C1 and C4, followed by addition of O_2 to yield β- or δ-hydroperoxyl radicals (Hallquist et al., 2009). The major sink (> 90 %) for the peroxyl radicals is reaction with

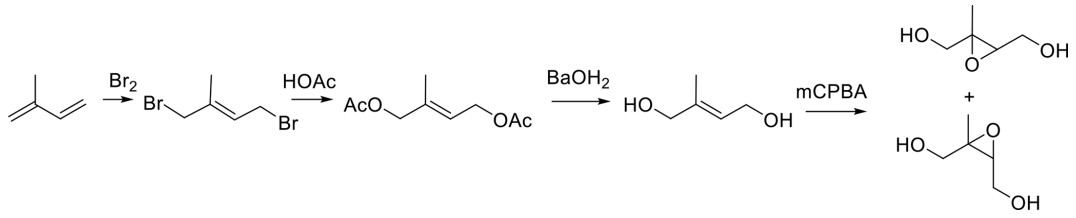

Figure 1. Synthesis of a *cis*- and *trans*-β-IEPOX mixture from isoprene.

Figure 2. Synthesis of *trans*-β-IEPOX from prenol.

the hydroperoxyl radical (HO_2) to give closed-shell isoprene hydroxyhydroperoxides (ISOPOOHs). ISOPOOHs then undergo sequential addition with OH and O_2, followed by the elimination of OH to yield a $\sim 2:1$ mixture of *cis*- and *trans*-(2-methyloxirane-2,3-diyl)dimethanol (*cis*- and *trans*-β-IEPOX). The IEPOX isomers account for about 80 % of the closed-shell hydroxyperoxy products (St. Clair et al., 2016; Wennberg et al., 2018; Paulot et al., 2009) and are rapidly taken up onto acidic aerosols (Lin et al., 2012; Gaston et al., 2014; Riedel et al., 2015). IEPOX isomers thus make a significant mass contribution to secondary organic aerosol (SOA) (Surratt et al., 2010; Riva et al., 2019) and the resulting atmospheric fine particulate matter ($PM_{2.5}$) (Lin et al., 2013; Budisulistiorini et al., 2015, 2016; Rattanavaraha et al., 2016). $PM_{2.5}$ is known to be a major factor in climate forcing (Hallquist et al., 2009) and adversely affects respiratory and cardiovascular systems of exposed populations (Pope and Dockery, 2006; Pye et al., 2021). Advancing the understanding of the impacts of $PM_{2.5}$ requires the ability to predict $PM_{2.5}$ composition and distribution, both in regional- and global-scale atmospheric chemistry and climate models (Pye et al., 2013; McNeill et al., 2015; Marais et al., 2016; Jo et al., 2019), which in turn depends crucially on the accuracy of identification and quantitation of uptake product formation. As major precursors of $PM_{2.5}$, *cis*- and *trans*-β-IEPOX have been the focus of considerable effort to elucidate mechanisms underlying $PM_{2.5}$ formation and aging (Lin et al., 2012, 2014; Gaston et al., 2014; Nguyen et al., 2014; Zhang et al., 2018; Riva et al., 2019; Armstrong et al., 2022; Cooke et al., 2022). Underpinning such efforts is the availability of authentic *cis*- and *trans*-β-IEPOX in high purity and in quantity.

2 Experimental methods

The reactions described below should be performed under a fume hood.

The esterification and diisobutylaluminum hydride (DIBAL-H) reduction of mesaconic and citraconic acids generally followed the procedure reported by Klimovica et al. (2011). Epoxidation of the *E*- and *Z*-2-methylbut-2-ene-1,4-diols followed the procedure reported by Zhang et al. (2012). ^{1}H nuclear magnetic resonance (NMR) spectra of all isolated products, as well as ^{13}C NMR for target *cis*- and *trans*-β-IEPOX isomers, are provided in the Supplement. Mass spectra of *cis*- and *trans*-β-IEPOX, also provided in the Supplement, were obtained using the Agilent 1200 Series HPLC (high-performance liquid chromatography) system equipped with an ESI (electrospray ionization) source interfaced to an Agilent 6250 Series Accurate-Mass Q-TOF MS (quadrupole time-of-flight mass spectrometer) operated in negative ion (–) mode using instrumental conditions described elsewhere (Cui et al., 2018).

2.1 *trans*-β-IEPOX (*trans*-(2-methyloxirane-2,3-diyl)dimethanol) from mesaconic acid

2.1.1 Mesaconic acid, dimethyl ester

To a solution of mesaconic acid (11.00 g, 85 mmol, Sigma Aldrich, USD 80.20/10 g) in methanol (100 mL), concentrated H_2SO_4 (3 mL) was added. The reaction mixture was refluxed for 8 h until a complete conversion was observed by thin-layer chromatography (TLC; SiO_2, 1 : 1 hexane : ethyl acetate), and the reaction was neutralized by addition of triethylamine (1.5 mL). The resulting mixture was dried on a rotary evaporator under house vacuum to afford mesaconic acid dimethyl ester as a colorless oil (13.4 g, 97 %), purity > 98 %, by NMR. NMR (400 MHz, chloroform-*d*): δ6.71 (d, $J = 1.6$ Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), and 2.23 (d, $J = 1.6$ Hz, 3H); see Fig. S1 in the Supplement.

2.1.2 *E*-2-Methylbut-2-ene-1,4-diol

A solution of mesaconic acid dimethyl ester (13.4 g, 85 mmol) in methylene chloride (120 mL) under argon was cooled to 0 °C, and diisobutylaluminum hydride (DIBAL-H; 400 mL 1.0 M solution in toluene, 400 mmol) was added

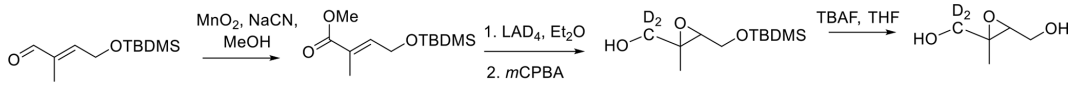

Figure 3. Synthesis of *trans*-β-IEPOX-d_2, adaptable to synthesis of protio analog.

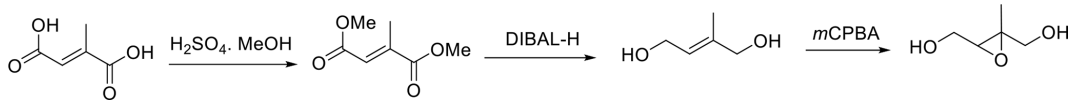

Figure 4. Newly developed route to *trans*-β-IEPOX starting with mesaconic acid.

dropwise over 2 h. The reaction mixture was stirred at 0 °C for 1 h. The reaction was diluted with ether (100 mL) and quenched with 16 mL water (0.04 volume equivalents of DIBAL-H), followed by 16 mL 15 % sodium hydroxide solution (0.04 volume equivalents) and 40 mL water (0.1 volume equivalents). After quenching, the mixture was allowed to warm to room temperature over 2 h and dried over magnesium sulfate. The aluminum salt was filtered under vacuum through a pad of Celite, and the collected solid was further washed with ethyl acetate (100 mL). The solvent was removed from the filtrate on a rotary evaporator under house vacuum to yield *E*-2-methylbut-2-ene-1,4-diol as a colorless oil (6.1 g, 71 %), purity > 98 %, by NMR. NMR (400 MHz, D_2O): δ5.54–5.43 (m, 1H), 4.06 (d, $J = 7.0$ Hz, 2H), 3.90 (s, 2H), and 1.57 (s, 3H); see Fig. S2.

2.1.3 *trans*-(2-Methyloxirane-2,3-diyl)dimethanol (*trans*-β-IEPOX)

Epoxidation of *E*-2-methylbut-2-ene-1,4-diol followed a published procedure (Zhang et al., 2012). The butene diol (6.0 g, 59 mmol) was dissolved in acetonitrile (80 mL) and cooled in an ice-water bath. *m*-Chloroperoxybenzoic acid (*m*-CPBA; 15.5 g, 90 mmol) was added, and the clear solution was stirred in the ice-water bath for 2 h and then at room temperature for 1 h until complete transformation of the starting material as monitored by TLC (SiO_2, 1 : 1 hexane : ethyl acetate). The reaction mixture was cooled at 4 °C, and the resulting precipitate was separated by filtration to remove the bulk of the 3-chlorobenzoic acid. The filtrate was concentrated under vacuum, and the residue was dissolved in water (30 mL) and washed repeatedly with chloroform. The aqueous solution was lyophilized to yield *trans*-(2-methyloxirane-2,3-diyl)dimethanol as a colorless oil (6.2 g, 89 %), purity > 98 %, by NMR. The ^{1}H NMR spectrum was identical to that reported in previous syntheses (Zhang et al., 2012). NMR (400 MHz, D_2O): δ3.78 (dd, $J = 12.49$, 4.29 Hz, 1H), 3.59 (d, $J = 12.56$ Hz, 1H), 3.58 (dd, $J = 12.49$, 7.08 Hz, 1H), 3.44 (d, $J = 12.56$ Hz, 1H), 3.15 (dd, $J = 7.08$, 4.29, 1H), and 1.23 (s, 3H); see Fig. S3. ^{13}C NMR (400 MHz, D_2O): δ65.06, 62.35, 60.89, 59.78, and 13.06; see Fig. S4. The (–)ESI-Q-TOF mass spectrum is provided in Fig. S5.

The overall yield for the synthesis of *trans*-β-IEPOX from mesaconic acid was 62. %.

2.2 *cis*-β-IEPOX (*cis*-(2-methyloxirane-2,3-diyl)dimethanol) from citraconic acid

2.2.1 Citraconic acid, dimethyl ester

To a solution of citraconic acid (2.0 g, 15 mmol, Sigma Aldrich, USD 46.10/5 g) in methanol (50 mL), concentrated H_2SO_4 (0.8 mL) was added. The reaction mixture was refluxed for 8 h until complete conversion as determined by TLC (SiO_2, 1 : 1 hexane : ethyl acetate) and then neutralized by addition of triethylamine (0.5 mL). The resulting mixture was concentrated in vacuo to afford the desired citraconic acid dimethyl ester (2.2 g, 92 %) as a colorless oil, purity > 98 %, by NMR. NMR (400 MHz, D_2O): δ6.08 (d, $J = 1.6$ Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), and 2.07 (d, $J = 1.6$ Hz, 3H); see Fig. S6.

2.2.2 *Z*-2-Methylbut-2-ene-1,4-diol

A solution of citraconic acid dimethyl ester (2.2 g, 14 mmol) in methylene chloride (25 mL) under argon was cooled to 0 °C, and DIBAL-H (70 mL 1.0 M solution in toluene, 70 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, diluted with ether (60 mL), and quenched with 2.8 mL water (0.04 of DIBAL-H volume equivalents), followed by 2.8 mL 15 % sodium hydroxide solution (0.04 volume equivalents) and 7.0 mL water (0.1 volume equivalents). After quenching, the mixture was allowed to warm to room temperature over 2 h and dried over magnesium sulfate. The aluminum salt was removed by filtration through a pad of Celite, and the collected solid was further washed with ethyl acetate (100 mL). The solvent was removed from filtrate, and the desired *Z*-2-methylbut-2-ene-1,4-diol (1.1 g, 75 % yield) was obtained as a colorless oil, purity > 98 %, by NMR (Klimovica, et al., 2011). NMR (400 MHz, D_2O): δ5.57 (t, $J = 7.2$ Hz, 1H), 4.16 (d, $J = 7.2$ Hz, 2H), 4.14 (s, 2H), and 1.82 (s, 3H); see Fig. S7.

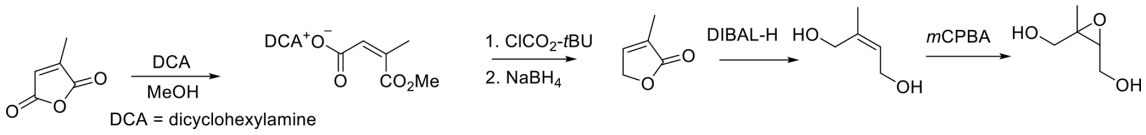

Figure 5. Synthesis of *cis*-β-IEPOX from citraconic anhydride.

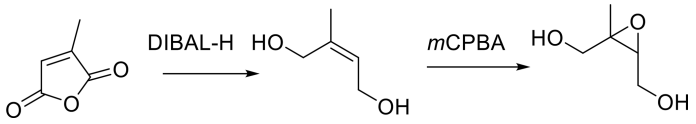

Figure 6. Streamlined route to *cis*-β-IEPOX from citraconic anhydride.

2.2.3 *cis*-(2-Methyloxirane-2,3-diyl)dimethanol (*cis*-β-IEPOX)

The epoxidation of the butene diol was performed according to a published method (Zhang et al., 2012). The butene diol (1.1 g, 10 mmol) was dissolved in acetonitrile (25 mL) and cooled in an ice-water bath. *m*-CPBA (2.7 g, 16 mmol) was added, and the clear solution was stirred in the ice-water bath for 1 h and then at room temperature until complete transformation of the starting material, as monitored by TLC (SiO_2, 1 : 1 hexane : ethyl acetate). The mixture was cooled at 0 °C, and the resulting precipitate was separated by filtration to remove the bulk of the 3-chlorobenzoic acid. The filtrate was concentrated under reduced pressure, and the residue was dissolved in water (15 mL) and washed repeatedly with chloroform. The aqueous solution was lyophilized to give *Z*-(2-methyloxirane-2,3-diyl)dimethanol as a colorless oil isolated as a crude product (1.0 g, 83 %), purity 98 %, by NMR. NMR (400 MHz, D_2O): δ3.78 (dd, $J = 12.5$, 3.9 Hz, 1H), 3.61 (d, $J = 12.3$ Hz, 1H),3.54 (dd, $J = 12.6$, 7.35 Hz, 1H), 3.52 (d, $J = 12.3$ Hz, 1H), 3.10 (dd, $J = 7.35$, 3.93 Hz, 1H), and 1.43 (s, 3H); see Fig. S8. ^{13}C NMR (500 MHz, D_2O): δ64.68, 62.61, 62.48, 59.39, and 18.82; see Fig. S9. The (–)ESI-Q-TOF mass spectrum is provided in Fig. S10.

The overall yield for the synthesis of *cis*-β-IEPOX from citraconic acid was 57 %.

2.3 *cis*-β-IEPOX (*cis*-(2-methyloxirane-2,3-diyl)dimethanol) from 3-methyl-2(5H)-furanone

2.3.1 *Z*-2-Methylbut-2-ene-1,4-diol

A solution of 3-methyl-2(5H)-furanone (1.1 g, 11 mmol) in methylene chloride (30 mL) under argon was cooled to 0 °C, and DIBAL-H (21 mL 1.0 M solution in toluene, 21 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, diluted with ether (60 mL), and quenched with 0.85 mL water (0.04 of DIBAL-H volume equivalents), followed by 0.85 mL 15 % sodium hydroxide solution (0.04 DIBAL-H volume equivalents) and 2.1 mL water (0.1 volume equivalents). After quenching, the mixture was allowed to warm to room temperature over 2 h and dried over magnesium sulfate. The aluminum salt was filtered out through a pad of Celite, and the collected solid was further washed with ethyl acetate (100 mL). The solvent was removed on a rotary evaporator under house vacuum to yield *Z*-2-methylbut-2-ene-1,4-diol (1.0 g, 94 % yield) as a colorless oil, purity > 98 %, by NMR; see Fig. S7.

2.3.2 *cis*-(2-Methyloxirane-2,3-diyl)dimethanol (*cis*-β-IEPOX)

Butene diol (0.92 g, 9.0 mmol) was dissolved in acetonitrile (50 mL) and cooled in an ice-water bath. *m*-CPBA (1.9 g, 14 mmol) was added, and the clear solution was stirred in the ice-water bath for 1 h and then at room temperature until complete transformation of the starting material, as monitored by TLC (SiO_2, 1 : 1 hexane : ethyl acetate). The mixture was cooled at 0 °C, and the resulting precipitate was separated by filtration to remove the bulk of the 3-chlorobenzoic acid. The filtrate was dried on a rotary evaporator under house vacuum, and the residue was dissolved in water (30 mL). The aqueous solution was washed repeatedly with chloroform and lyophilized and isolated as a crude product to give *cis*-(2-methyloxirane-2,3-diyl)dimethanol as a colorless oil (0.88 g, 83 %), purity > 98 %, by NMR; see Figs. S8 and S9.

The overall yield for the synthesis *cis*-β-IEPOX from 3-methyl-2(5H)-furanone was 69 %.

3 Results and discussion

Several synthetic routes to the β-IEPOX isomers have been published to date. Procedures for the synthesis of *trans*-β-IEPOX followed the three strategies given in Figs. 1–3.

Figure 1, the first published route to *trans*-β-IEPOX (Cole-Filipiak et al., 2010), yielded a mixture of cis and trans products in four steps. The procedure is lengthy, and consecutive vacuum distillations for isolation of 1,4-dibromoisoprene

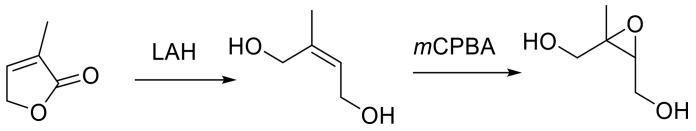

Figure 7. Synthesis of *cis*-β-IEPOX from 3-methylfuran-2(5H)-one.

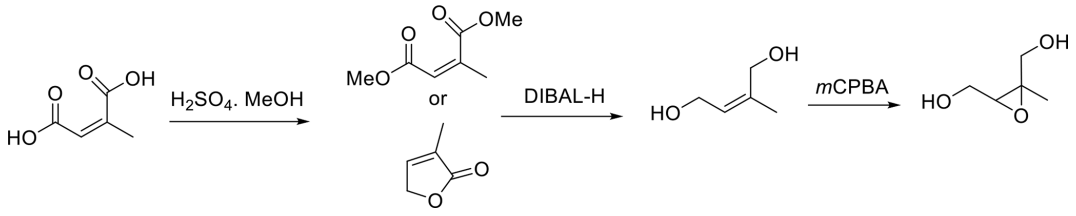

Figure 8. Synthesis of *cis*-β-IEPOX from citraconic acid.

from the 1,4-diol were required. The mixture was not separated, and the combined overall yield was 11 %.

The approach in Fig. 2 (Zhang et al., 2012) has been used in most syntheses reported subsequent to publication in 2012. Figure 2 targets synthesis of the trans isomer starting with prenol (3-methyl-2-buten-1-ol). SeO_2 oxidation of the trisubstituted olefin yielded *E*-2-methylbut-2-ene-1,4-diol. Deprotection of the diol, followed by epoxidation with *m*-CPBA gave the target *trans*-β-IEPOX in an overall yield of 43 %. The expected trans geometry of the ultimate IEPOX isomer (Trachtenberg, et al., 1970; Sharpless and Lauer, 1972) was confirmed by the absence of a nuclear Overhauser effect correlation between the methyl group and the oxirane proton in the 1D NOESY (nuclear Overhauser effect spectroscopy) spectrum. An overall yield of $\sim$ 11 % can be calculated for synthesis by Fig. 2 in the only other report citing yields (Bates et al., 2014). The SeO_2 oxidation–$NaBH_4$ reduction sequence to generate 2-methylbut-2-ene-1,4-diol appears largely responsible for the discrepancy in yields. Isolation of the diol from the $NaBH_4$ reduction step yields a mixture from which the isolation of a product is challenging and is most likely the source of the difference.

More recently, Fig. 3, a route to *trans*-β-IEPOX-d_2, has been reported that could also serve as a route to the protio compound by substituting LAH_4 for LAD_4 as the reducing agent (Chase et al., 2015).

This route also involves a problematic metal hydride reduction step, and an overall yield of 31 % was reported. Figures 1–3 have steps that are difficult to accomplish in common, such as vacuum distillation, or they require carefully controlled conditions for the protection/deprotection of labile substituents, with the best reported yield being 43 % for Fig. 2 (Zhang et al., 2012).

Here we report a procedure for the synthesis of pure racemic *trans*-β-IEPOX that is efficient and simple and provides the target IEPOX with an overall yield of 62 %. No protection/deprotection steps, which add steps and can decrease yields, are involved, and no specialized glassware or instrumentation is required. The strategy for synthesis follows Fig. 4, which is based on inexpensive, readily available mesaconic acid as the starting material.

Mesaconic acid can be esterified to the dimethyl ester in high yield by refluxing in methanol containing 2 % concentrated sulfuric acid. The diester is reduced by diisobutylaluminum hydride (DIBAL-H) in methylene chloride to *E*-2-methylbut-2-en-1,4-diol, which is epoxidized by *m*-CPBA in acetonitrile. Key to the procedure is the efficient extraction of *E*-2-methylbut-2-ene-1,4-diol from the DIBAL-H reduction reaction with ethyl acetate, which allows for recovery of the diol in 70 % yield. The route in Fig. 4 will make *trans*-β-IEPOX readily available to laboratories without sophisticated synthesis capabilities. The procedure is particularly attractive because it can readily be scaled up to produce *trans*-β-IEPOX in gram quantities.

The isolation of *E*-2-methylbut-2-ene-1,4-diol from the DIBAL-H reduction reaction in high yield by extraction with ethyl acetate led us to revisit published syntheses of *cis*-β-IEPOX in which metal hydrides were used as reduction reagents (Bates et al., 2014, 2016; Zhang et al., 2012). In Figs. 5 and 6, citraconic anhydride was the starting material, and the reducing agent was DIBAL-H.

The reported overall yield of *cis*-β-IEPOX from Fig. 5 was 12 % (Bates et al., 2014). Figure 6 streamlined the synthesis through bypassing steps 2 and 3 of Fig. 5 with direct reduction of citraconic anhydride to *Z*-2-methylbut-2-en-1,4-diol (Bates et al., 2016). Reduction of the anhydride required forcing conditions (five equivalents of DIBAL-H were used) to achieve reduction of citraconic anhydride, and possibly less efficient recovery of the diol resulted in the same overall yield reported for Fig. 5.

3-Methylfuran-2(5H)-one was the starting material for Fig. 7 and was reduced directly to *Z*-2-methylbut-2-en-1,4-diol by LAH (Zhang et al., 2012).

LAH is a powerful reducing agent leading to some unavoidable over-reduction of the furanone to the saturated diol, and the overall yield was 19 %. We repeated the syn-

thesis of *cis*-β-IEPOX using either citraconic acid or 3-methylfuran-2(5H)-one as the starting point (Fig. 8). Because reduction of anhydrides to diols generally appears to be more difficult and requires forcing conditions (Bloomfield and Lee, 1967), we selected citraconic acid rather than the anhydride as the starting point for the synthesis. Citraconic acid requires esterification prior to reduction. Although the dimethyl ester is commercially available, the esterification reaction is very straightforward with a nearly quantitative yield, and the savings in cost are substantial.

Under the assumption that sterically hindered cis diester would nevertheless not proceed as readily as reduction of the trans diester, five equivalents of DIBAL-H were used for the reduction of citraconic diester. With a yield of 74.9 %, the reduction of the diester proved to be much more efficient than that of citraconic anhydride, for which the reported yield was 28 % (Bates et al., 2016). The overall yield for this route was 57 %, which represents a significant improvement over the yields reported by the routes in Figs. 5 and 6.

3-Methylfuran-2(5H)-one is a more expensive starting compound than citraconic acid or citraconic anhydride, but the procedure is streamlined to two steps, and the overall yield, at 69 %, is much higher than for any of the published routes. Cost of reagents would largely dictate the choice of citraconic acid or 3-methylfuran-2(5H)-one starting material. We note that *trans*- and *cis*-β-IEPOX were isolated directly following lyophilization. The purity of *trans*- and *cis*-β-IEPOX was > 98 % by NMR (Figs. S3–S4 and S8–S9, respectively).

Data availability. Unprocessed free induction decay signals (FIDs) and mass spectral data files are available on request from the corresponding author (golda@email.unc.edu).

Supplement. Included in the Supplement are ^{1}H NMR spectra of the target *cis*- and *trans*-β-IEPOX isomers and key intermediates in the synthetic routes. Additional ^{13}C and (–)ESI-Q-TOF mass spectra are provided for the target *cis*- and *trans*-β-IEPOX isomers. The supplement related to this article is available online at: https://doi.org/10.5194/acp-23-7859-2023-supplement.

Author contributions. All authors contributed equally to the planning and performing of the experiments and the preparation of the manuscript. MF acquired spectroscopic data. JDS helped with editing and manuscript preparation.

Competing interests. At least one of the (co-)authors is a member of the editorial board of *Atmospheric Chemistry and Physics*. The peer-review process was guided by an independent editor, and the authors also have no other competing interests to declare.

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