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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)

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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 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 sequential reaction with hydroperoxyl radical (HO_2), OH and O_2, which is then followed by the elimination of OH to yield a ~2:1 mixture of (2-methyloxirane-*cis*/*trans*-2,3-dilyl)dimethanol (*cis*/*trans*-β-IEPOX). The IEPOX isomers account for about 80% of the 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 affects 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.

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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; Chase et al., 2015; Bates et al., 2016), 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, 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-hydroxyperoxyl radicals (Hallquist et al., 2009). The major sink (>90%) for the peroxyl radicals is reaction with hydroperoxy 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 ~2:1 mixture of (2-methyloxirane-*cis*/*trans*-2,3-diyl)dimethanol (*cis*/*trans*-β-IEPOX). The IEPOX isomers account for about 80% of the closed-shell hydroxyperoxyl 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; Budisulistiorini et al. 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; Lin et al., 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*-/*trans*-β-IEPOX in high purity and in quantity.

2. Experimental

The esterification and 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 NMR spectra of isolated products are provided in the Supplement.

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

2.1.1. Mesaconic acid, dimethyl ester. To a solution of mesaconic acid (11.00 g, 84.5 mmol) in methanol (100 mL), conc. 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) and the reaction was the neutralized by addition of triethylamine (1.5 mL). Silica gel (11 g) was added and the resulting mixture was dried on a rotary evaporator under house vacuum. The residue was applied to a silica gel column and eluted with EtOAc/petroleum ether (1:1) to afford mesaconic acid dimethyl ester as a colorless oil (13.40 g, 96.5%), purity >98% by NMR. NMR (400 MHz, chloroform-*d*): δ 6.71 (d, *J* = 1.6 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.23 (d, *J* = 1.6 Hz, 3H), Figure S1.

2.1.2. E-2-Methyl but-2-ene-1,4-diol. A solution of mesaconic acid dimethyl ester (13.40 g, 84.72 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 dropwise, and the reaction mixture was stirred at 0°C for 1 h. The reaction was diluted with ether (100 mL) and quenched with water 16 mL (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

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magnesium sulfate. The aluminum salt was filtered out through a pad of Celite, and solid filtrant further washed with ethyl acetate (100 mL). The solvent was removed from filtrate on a rotary evaporator under house vacuum to yield *E*-2-methyl but-2-ene-1,4-diol as a colorless oil (6.12g, 70.7%), purity > 98% by NMR. NMR (400 MHz, D_2O): δ 5.54 – 5.43 (m, 1H), 4.06 (d, *J* = 7.0 Hz, 2H), 3.90 (s, 2H), 1.57 (s, 3H), Figure S2.

2.1.3. Trans-(2-Methyloxirane-2,3-diyl)dimethanol (trans-β-IEPOX). Epoxidation of *E*-2-methyl but-2-ene-1,4-diol followed a published procedure (Zhang et al., 2012). The butene diol (6.00 g, 58.8 mmol) was dissolved in acetonitrile (80 mL) and cooled in an ice-water bath. *m*-Chloroperoxybenzoic acid (15.53 g, 90 mmol) was added and the clear solution was stirred in the ice-water bath for 2 h, and then at room temperature until complete transformation of the starting material as monitored by TLC. The reaction mixture was cooled at 4°C and the resulting precipitate separated by filtration to remove the bulk of the 3-chlorobenzoic acid. The filtrate was concentrated under reduced pressure and the residue 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 colorless oil (6.24 g, 89%), purity > 98% by NMR. The ^1H NMR spectrum was identical to that reported in previous syntheses (Zhang et al. 2012). NMR (400 MHz, D_2O): δ 3.78 (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), 1.23 (s, 3H), Figure S3. Overall yield for the synthesis of *trans*-β-IEPOX from mesaconic acid was 62.5%.

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 (1.98 g, 15.2 mmol) in methanol (50 mL) conc. H_2SO_4 (0.8 mL) was added. The reaction mixture was refluxed for 8 h until complete conversion as determined by TLC and then neutralized by addition of triethylamine (0.5 mL). Silica gel (3 g) was added and the resulting mixture was concentrated *in vacuo.* The dry residue was applied to a silica gel column and eluted with EtOAc/petroleum ether (1:1) to afford the desired citraconic acid dimethyl ester (2.21g, 92.1%) as a colorless oil, purity > 98% by NMR. NMR (400 MHz, D_2O): δ 6.08 (d, *J* = 1.6 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 2.07 (d, *J* = 1.6 Hz, 3H), Figure S4.

2.2.2. Z-2-methyl but-2-ene-1,4-diol. A solution of citraconic acid dimethyl ester (2.21g, 14.0 mmol) in methylene chloride (25mL) under argon was cooled to 0°C and DIBAL-H (70 mL 1.0 M solution in toluene, 70.0 mmol) was added dropwise. 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 solid filtrant further washed with ethyl acetate (100 mL). The solvent was removed from filtrate and desired *Z*-2-methyl but-2-ene-1,4-diol (1.07 g, 74.9% yield) was obtained as a colorless oil, purity > 98% by NMR (Klimovica, et al., 2011). NMR (400 MHz, D_2O): δ 5.57 (t, J = 7.2 Hz, 1H), 4.16 (d, J = 7.2 Hz, 2H), 4.14 (s, 2H), 1.82 (s, 3H), Figure S5.

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 (1.07 g, 10.4 mmol) was dissolved in acetonitrile (25 mL) and cooled in an ice-water bath. *m*-Chloroperoxybenzoic acid (2.69 g, 15.6 mmol) was added and the clear solution was stirred in the ice-water bath for 1h, and then at room temperature until complete transformation of the starting material as monitored by TLC. The mixture was cooled at 0°C and the resulting precipitate separated by filtration to remove the bulk of the 3-chlorobenzoic acid. The filtrate was concentrated under reduced pressure, the residue dissolved in water (15 mL) and washed repeatedly with chloroform. The aqueous solution was lyophilized to give *Z*-(2-methyloxirane-2,3-dilyl)dimethanol as colorless oil isolated as the crude product (1.03 g, 82.9%), purity 88% by NMR. NMR (400 MHz, D_2O): δ 3.78 (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), 1.43 (s, 3H), Figure S6.

Overall yield for the synthesis of *cis*-β-IEPOX from citraconic acid was 57.1%.

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

2.3.1. Z-2-methyl but-2-ene-1,4-diol. A solution of 3-methyl-2(5H)-furanone (1.06 g, 10.8 mmol) in methylene chloride (30 mL) under argon was cooled to 0°C, and DIBAL-H (21 mL 1.0 M solution in toluene, 21.0 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 solid filtrant 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 (1.03 g, 94.1% yield) as a colorless oil, purity > 98% by NMR, Figure S5.

2.3.2. cis-(2-Methyloxirane-2,3-diyl)dimethanol (cis-β-IEPOX). Butene diol (0.9169 g, 8.99 mmol) was dissolved in acetonitrile (50 mL) and cooled in an ice-water bath. *m*-Chloroperoxybenzoic acid (1.92 g,13.5 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. The mixture was cooled at 0°C and the resulting precipitate 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 dissolved in water (30 mL). The aqueous solution was washed repeatedly with chloroform and lyophilized and isolated as the crude product to give *cis*-(2-methyloxirane-2,3-diyl)dimethanol as colorless oil (0.88 g, 82.9%), purity 88% by NMR, Figure S6.

Overall yield for the synthesis *cis*-β-IEPOX from 3-methyl-2(5H)-furanone was 69.2%.

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 Figures 1 – 3.

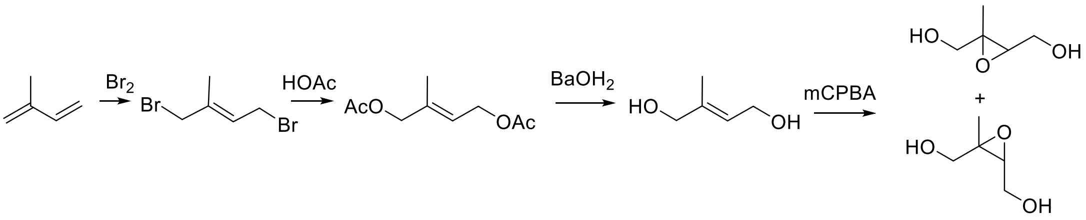

Figure 1. Synthesis of a *cis*-and *trans*-β-IEPOX mixture from isoprene.

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 required a double vacuum distillation for isolation of 1,4-dibromoisoprene and a further vacuum distillation for isolation of the 1,4-diol. The mixture of *cis*- and *trans* epoxides was not separated, and the combined overall yield was 11%.

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

The approach in Figure 2 (Zhang et al., 2012) has been used in most syntheses reported subsequent to its 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 spectrum. An overall yield of ~11% can be calculated for synthesis by the scheme in Figure 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 isolation of product is challenging and is most likely the source of the difference.

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

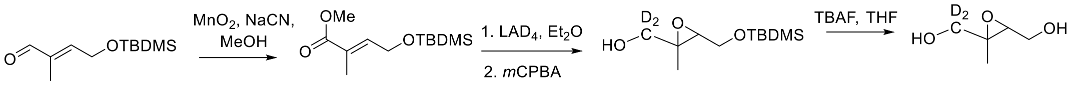

Figure 3. Synthesis of *trans*-β-IEPOX-d_2, adaptable to synthesis of protio analog.

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

Here we report a procedure for the synthesis of pure racemic *trans*-β-IEPOX that is efficient, simple and provides the target IEPOX in an overall yield of 62.5%. No protection/deprotection reactions, which add steps and can decrease yields are involved, and no specialized glassware or instrumentation is required. The strategy for synthesis follows the route in Figure 4, which is based on inexpensive, readily available mesaconic acid as starting material.

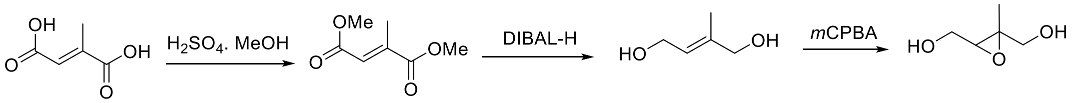

Figure 4. Newly developed route to trans-β-IEPOX starting with mesaconic acid.

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 recovery of the diol in 70% yield. The synthetic route in Figure 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.

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The isolation of *E*-2-methylbut-2-en-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; Bates et al., 2016; Zhang et al., 2012). In Figures 5 and 6, citraconic anhydride was the starting material and the reducing agent was DIBAL-H.

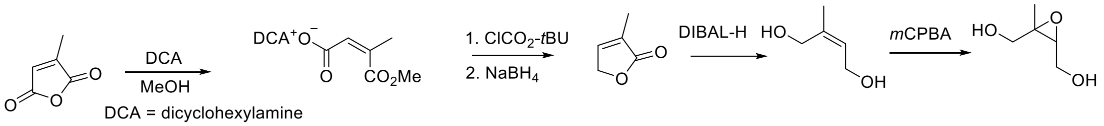

Figure 5. Synthesis of cis-β-IEPOX from citraconic anhydride.

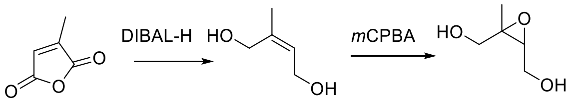

Figure 6. Streamlined route to cis-β-IEPOX from citraconic anhydride.

The reported overall yield of *cis*-β-IEPOX from synthetic route in Figure 5 was 12% (Bates et al., 2014). The reaction scheme in Figure 6 streamlined the synthesis through bypassing steps 2 and 3 of the reaction scheme in Figure 5 by 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 (5 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 the synthesis in Figure 5.

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

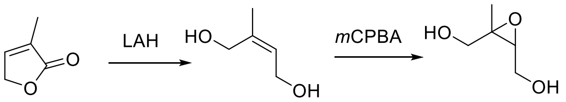

Figure 7. Synthesis of cis-β-IEPOX from 3-methylfuran-2(5H)-one.

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 synthesis of *cis*-β-IEPOX using either citraconic acid or 3-methylfuran-2(5H)-one as starting points (Figure 8). Because reduction of anhydrides to diols generally appears to be more difficult and require 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 is substantial.

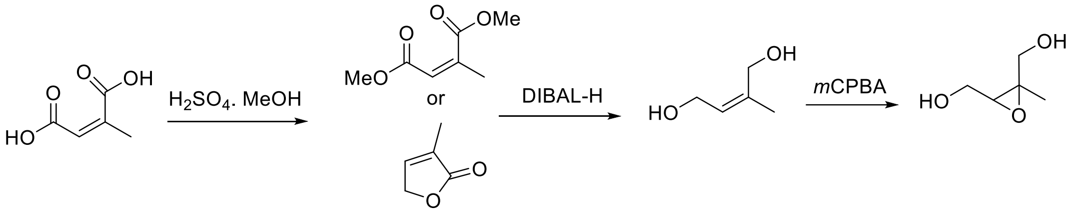

Figure 8. Synthesis of cis-β-IEPOX from citraconic acid.

Under the assumption that reduction of the *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 57.1%, which represents a significant improvement over the yields reported from the schemes in Figures 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*-β-IEPOX was > 98% by NMR (Figure S3). *Cis*-β-IEPOX invariably contained a small amount of hydrolysis product (Figure S6) which may be removed completely by column chromatography if required.

Supplement: The supplement related to this article is available online. Included in the supplement are ^{1}H NMR spectra of the target *cis*- and *trans*-β-IEPOX isomers, as well as the key intermediates in the synthetic routes.

Author contributions: MF, AG and ZZ contributed equally to planning and performing experiments and preparation of the manuscript. MF acquired spectroscopic data. J.D.S. helped with editing and manuscript preparation.

Competing interests: The authors declare that they have no conflict of interest.

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