1 **Technical Note: Improved synthetic routes to *cis*- and *trans*-(2-methyloxirane-**

2 **2,3-diyl)dimethanol (*cis*- and *trans*-β-isoprene epoxydiol)**

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9 **Abstract.** We report improved synthetic routes to the isomeric isoprene-derived β-epoxydiols (β-

10 IEPOX) in high yield (57-69%) from inexpensive, readily available starting compounds. The

11 syntheses do not require the protection/deprotection steps or time-consuming purification of

12 intermediates, and can readily be scaled up to yield the target IEPOX isomers in gram quantities.

13 Emissions of isoprene (2-methyl-1,3-butadiene, C_5H_8), primarily from deciduous vegetation,

14 constitute the largest source of nonmethane atmospheric hydrocarbons. In the gas phase under low-

15 nitric oxide (NO) conditions, addition of atmospheric hydroxyl radical (OH) followed by rapid

16 addition of O_2 yields isoprene-derived hydroxyperoxyl radicals. The major sink (>90%) for the

17 peroxyl radicals is sequential reaction with hydroperoxyl radical (HO_2), OH and O_2, which is then

18 followed by the elimination of OH to yield a ~2:1 mixture of (2-methyloxirane-*cis/trans*-2,3-

19 dilyl)dimethanol (*cis/trans*-β-IEPOX). The IEPOX isomers account for about 80% of the closed-

20 shell hydroxyperoxyl products, and are rapidly taken up into acidic aerosols to form secondary

21 organic aerosol (SOA). IEPOX-derived SOA makes a significant mass contribution to fine

22 particulate matter ($PM_{2.5}$), which is known to be a major factor in climate forcing as well as

23 adversely affects respiratory and cardiovascular systems of exposed populations. Prediction of

24 ambient $PM_{2.5}$ composition and distribution, both in regional- and global-scale atmospheric

25 chemistry models, crucially depends on the accuracy of identification and quantitation of uptake

26 product formation. Accessibility of authentic *cis*- and *trans*-β-IEPOX in high purity and in large

27 quantity for laboratory studies underpins progress in developing models as well as identification

28 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; 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-dilyl)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

59   mechanisms underlying PM$_{2.5}$ formation and aging (Lin et al., 2012; Lin et al., 2014; Gaston et al.,

60   2014; Nguyen et al., 2014; Zhang et al., 2018; Riva et al., 2019; Armstrong et al., 2022; Cooke et

61   al., 2022). Underpinning such efforts is the availability of authentic *cis-/trans*-β-IEPOX in high

62   purity and in quantity.

63   **2. Experimental**

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

65   The esterification and DIBAL-H reduction of mesaconic and citraconic acids generally followed

66   the procedure reported by Klimovica, et al. (2011). Epoxidation of the *E*- and *Z*-2-methylbut-2-

67   ene-1,4-diols followed the procedure reported by Zhang et al. (2012). ^{1}H NMR of all isolated

68   products, as well as ^{13}C NMR for target *cis-/trans*-β-IEPOX isomers are provided in the

69   Supplement. Mass spectra of *cis-/trans*-β-IEPOX, also provided in the Supplement, were

70   obtained using Agilent 134 6500 Series UPLC system equipped with an ESI source interfaced to

71   an Agilent 6250 Series 135 Accurate Mass Q-TOFMS operated in negative ion (–) mode using

72   instrumental conditions described elsewhere (Cui et al., 2018).

73   **2.1. *Trans*-β-IEPOX (*trans*-(2-methyloxirane-2,3-dilyl)dimethanol) from mesaconic acid**

74   *2.1.1. Mesaconic acid, dimethyl ester.* To a solution of mesaconic acid (11.00 g, 85 mmol, Sigma

75   Aldrich, $80.20/10g) in methanol (100 mL), conc. H$_2$SO$_4$ (3 mL) was added. The reaction mixture

76   was refluxed for 8 h until a complete conversion was observed by thin layer chromatography (TLC,

77   SiO$_2$, 1:1 hexane: ethyl acetate) and the reaction was the neutralized by addition of triethylamine

78   (1.5 mL). The resulting mixture was dried on a rotary evaporator under house vacuum to afford

79   mesaconic acid dimethyl ester as a colorless oil (13.4 g, 97%), purity >98% by NMR. NMR (400

80   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,

81   3H), Figure S1.

82   *2.1.2. E-2-Methyl but-2-ene-1,4-diol.* A solution of mesaconic acid dimethyl ester (13.4 g, 85

83   mmol) in methylene chloride (120 mL) under argon was cooled to 0 °C and diisobutylaluminum

84   hydride (DIBAL-H; 400 mL 1.0 M solution in toluene, 400 mmol) was added dropwise over 2

85   hours, and the reaction mixture was stirred at 0°C for 1 h. The reaction was diluted with ether (100

86   mL) and quenched with water 16 mL (0.04 volume-equivalents of DIBAL-H), followed by 16 mL

87 15% sodium hydroxide solution (0.04 volume-equivalents), and 40 mL water (0.1 volume-

88 equivalents). After quenching, the mixture was allowed to warm to room temperature over 2 h and

89 dried over magnesium sulfate. The aluminum salt was filtered under vacuum through a pad of

90 Celite, and solid filtrant further washed with ethyl acetate (100 mL). The solvent was removed

91 from filtrate on a rotary evaporator under house vacuum to yield *E*-2-methyl but-2-ene-1,4-diol as

92 a colorless oil (6.1g, 71%), purity > 98% by NMR. NMR (400 MHz, D_2O): δ 5.54 – 5.43 (m, 1H),

93 4.06 (d, *J* = 7.0 Hz, 2H), 3.90 (s, 2H), 1.57 (s, 3H), Figure S2.

94 *2.1.3. Trans-(2-Methyloxirane-2,3-diyl)dimethanol (trans-β-IEPOX).* Epoxidation of *E*-2-methyl

95 but-2-ene-1,4-diol followed a published procedure (Zhang et al., 2012). The butene diol (6.0 g,

96 59 mmol) was dissolved in acetonitrile (80 mL) and cooled in an ice-water bath. *m*-

97 Chloroperoxybenzoic acid (*m*-CPBA, 15.5 g, 90 mmol) was added and the clear solution was

98 stirred in the ice-water bath for 2 h, and then at room temperature for 1 h until complete

99 transformation of the starting material as monitored by TLC (SiO_2, 1:1 hexane: ethyl acetate).

100 The reaction mixture was cooled at 4°C and the resulting precipitate separated by filtration to

101 remove the bulk of the 3-chlorobenzoic acid. The filtrate was concentrated under vacuum and the

102 residue dissolved in water (30 mL), and washed repeatedly with chloroform. The aqueous

103 solution was lyophilized to yield *trans*-(2-methyloxirane-2,3-diyl)dimethanol as colorless oil (6.2

104 g, 89%), purity > 98% by NMR. The ^{1}H NMR spectrum was identical to that reported in

105 previous syntheses (Zhang et al. 2012). NMR (400 MHz, D_2O): δ 3.78 (dd, *J* = 12.49, 4.29 Hz,

106 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),

107 3.15 (dd, *J* = 7.08, 4.29, 1H), 1.23 (s, 3H), Figure S3. ^{13}C NMR (400 MHz, D_2O) δ 65.06, 62.35,

108 60.89, 59.78, 13.06, Figure S4. (-)ESI-HR-QTOF mass spectrum is provided in Figure S5.

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

110 **2.2. *cis*-β-IEPOX (*cis*-(2-methyloxirane-2,3-diyl)dimethanol) from citraconic acid**

111 *2.2.1. Citraconic acid, dimethyl ester.* To a solution of citraconic acid (2.0 g, 15 mmol, Sigma

112 Aldrich, $46.10/5g) in methanol (50 mL) conc. H_2SO_4 (0.8 mL) was added. The reaction mixture

113 was refluxed for 8 h until complete conversion as determined by TLC (SiO_2, 1:1 hexane: ethyl

114 acetate) and then neutralized by addition of triethylamine (0.5 mL). The resulting mixture was

115 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, D₂O): 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 S6.

2.2.2. Z-2-methyl but-2-ene-1,4-diol. A solution of citraconic acid dimethyl ester (2.2 g, 14 mmol)
in methylene chloride (25mL) under argon was cooled to 0°C and DIBAL-H (70 mL 1.0 M
solution in toluene, 70 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 (1.1 g, 75%
yield) was obtained as a colorless oil, purity > 98% by NMR (Klimovica, et al., 2011). NMR (400
MHz, D₂O): 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
S7.

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 1h, and then at
room temperature until complete transformation of the starting material as monitored by TLC
(SiO₂, 1:1 hexane: ethyl acetate). 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 (1.0 g, 83%), purity 98% by
NMR. NMR (400 MHz, D₂O): 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 S8. ¹³C NMR (500 MHz, D₂O) δ 64.68, 62.61, 62.48, 59.39, 18.82, Figure S9. (-
)ESI-HR-QTOF mass spectrum is provided in Figure S10.

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-methyl but-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 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 (1.0 g, 94% yield) as a colorless oil, purity > 98% by NMR, Figure 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 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, 83%), purity >98% by NMR, Figures S8 and S9.

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 **Figures 1 – 3**.

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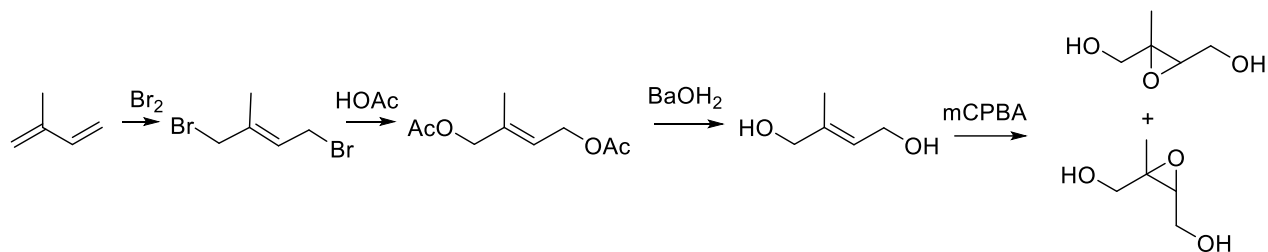
Figure 1. Synthesis of a *cis*-and *trans*-β-IEPOX mixture from isoprene.

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

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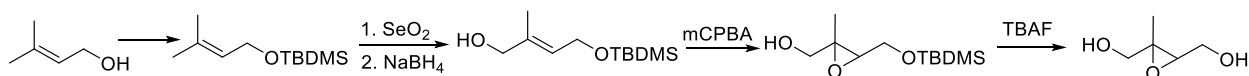
Figure 2. Synthesis of *trans*-β-IEPOX from prenol.

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The approach in **Figure 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 spectrum. An overall yield of ~11% can be calculated for synthesis by **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.

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More recently, **Figure 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 of LAH$_4$ for LAD$_4$ as reducing agent (Chase et al., 2015).

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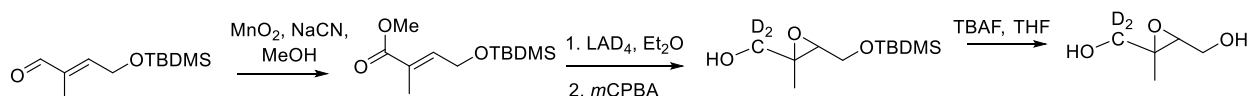
Figure 3. Synthesis of *trans*-β-IEPOX-d_2, adaptable to synthesis of protio analog.

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This route also involves a problematic metal hydride reduction step and an overall yield of 31% was reported. **Figure 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 **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%. 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 **Figure 4**, which is based on inexpensive, readily available mesaconic acid, as starting material.

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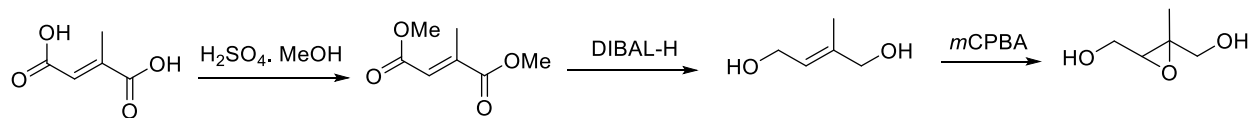
Figure 4. Newly developed route to *trans*-β-IEPOX starting with mesaconic acid.

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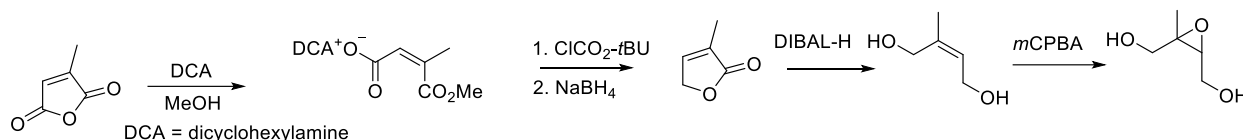
Mesaconic acid can be esterified to the dimethyl ester in high yield by refluxing in methanol containing 2% concentrated sulfuric acid. The diester is reduced by diisobutylaluminum hydride (DIBAL-H) in methylene chloride to *E*-2-methylbut-2-en-1,4-diol, which is epoxidized by *m*-CPBA in acetonitrile. 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

220 70% yield. The route in **Figure 4** will make *trans*-β-IEPOX readily available to laboratories
221 without sophisticated synthesis capabilities. The procedure is particularly attractive because it can
222 readily be scaled up to produce *trans*-β-IEPOX in gram quantities.
223   The isolation of *E*-2-methylbut-2-en-1,4-diol from the DIBAL-H reduction reaction in high
224 yield by extraction with ethyl acetate led us to revisit published syntheses of *cis*-β-IEPOX in which
225 metal hydrides were used as reduction reagents (Bates et al., 2014; Bates et al., 2016; Zhang et al.,
226 2012). In **Figures 5** and **6**, citraconic anhydride was the starting material and the reducing agent
227 was DIBAL-H.

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

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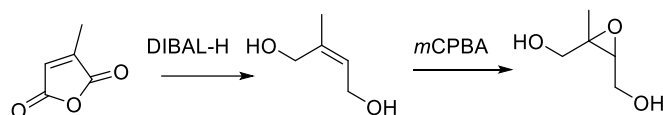
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232 **Figure 6.** Streamlined route to *cis*-β-IEPOX from citraconic anhydride.

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

240 3-Methylfuran-2(5H)-one was the starting material for **Figure 7** and was reduced to directly *Z*-2-
241 methylbut-2-en-1,4-diol by LAH (Zhang et al., 2012).

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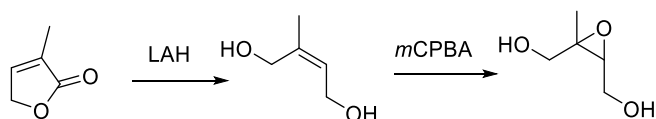
Figure 7. Synthesis of *cis*-β-IEPOX from 3-methylfuran-2(5H)-one.

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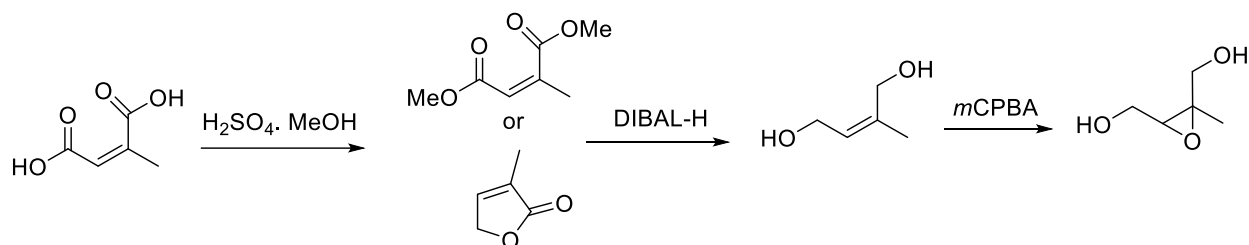
Figure 8. Synthesis of cis-β-IEPOX from citraconic acid.

Under the assumption that 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 **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 was isolated directly following lyophilization. The purity of *trans*- and *cis*-β-IEPOX were > 98% by NMR (Figure S3-4, S8-9, respectively).

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 and key intermediates in the synthetic routes. Additional ^{13}C and (-)ESI-HR-QTOF mass spectra are provided for the target *cis-* and *trans-*β-IEPOX isomers.

Author contributions: All authors contributed equally into 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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References

Armstrong, N. C., Chen, Y., Cui, T., Zhang, Y., Christensen, C., Zhang, Z., Turpin, B. J., Chan, M.N., Gold, A., Ault, A. P., Surratt, J. D.: Isoprene epoxydiol-derived sulfated and nonsulfated oligomers suppress particulate mass loss during oxidative aging of secondary organic aerosol, Environ. Sci. Technol., 56 (23), 16611 – 16620, https://doi.org/10.1021/acs.est.2c03200, 2022.

Bates, K.H., Crounse, J.D., St Clair, J.M., Bennett, N.B., Nguyen, T.B., Seinfeld, J.H., Stoltz B.M., Wennberg, P.O.: Gas phase production and loss of isoprene epoxydiols, J. Phys. Chem. A, 118(7), 1237-1246, https://doi.org/10.1021/jp4107958, 2014.

Bates, K.H., Nguyen, T.B., Teng, A.P., Crounse, J.D., Kjaergaard, H.G., Stoltz, B.M. Seinfeld, J.H., Wennberg, P.O.: Production and fate of C4 dihydroxycarbonyl compounds from isoprene oxidation, J. Phys. Chem. A, 120(1), 106−117, https://doi.org/10.1021/acs.jpca.5b10335, 2016.

Bloomfield, J.J., Lee, S.L.: Control of lithium aluminum hydride reduction of cyclic dicarboxylic acid anhydrides to produce 7-lactones or diols. J. Org. Chem., 32(12), 3919 – 3924, 1967.

295   Budisulistiorini, S. H., Li, X., Bairai, S. T., Renfro, J., Liu, Y., Liu, Y. J., McKinney, K. A., Martin,

296   S. T., McNeill, V. F., Pye, H. O. T., Nenes, A., Neff, M. E., Stone, E. A., Mueller, S., Knote, C.,

297   Shaw, S. L., Zhang, Z., Gold, A., and Surratt, J. D.: Examining the effects of anthropogenic

298   emissions on isoprene-derived secondary organic aerosol formation during the 2013 Southern

299   Oxidant and Aerosol Study (SOAS) at the Look Rock, Tennessee ground site, Atmos. Chem.

300   Phys., 15, 8871–8888, doi:10.5194/acp-15-8871-2015, 2015.

301

302   Budisulistiorini, S. H., Baumann, K., Edgerton, E. S., Bairai, S. T., Mueller, S., Shaw, S. L.,

303   Knipping, E. M., Gold, A., and Surratt, J. D.: Seasonal characterization of submicron aerosol

304   chemical composition and organic aerosol sources in the southeastern United States: Atlanta,

305   Georgia,   and   Look   Rock,   Tennessee,   Atmos.   Chem.   Phys.,   16,   5171–5189,

306   https://doi.org/10.5194/acp-16-5171-2016, 2016.

307

308   Chase, H.M., Psciuk, B.T., Strick, B.L., Thomson, R.J., Batista, V.S., Geiger, F.M.: Beyond local

309   group modes in vibrational sum frequency generation, J. Phys. Chem. A, 119(16), 3407- 3414.

310   https://doi.org/10.1021/jp511067d, 2015.

311

312   Cole-Filipiak, N. C., O'Connor, A. E., Elrod, M. J.: Kinetics of the hydrolysis of atmospherically

313   relevant isoprene-derived hydroxy epoxides, Environ. Sci. Technol., 44(17), 6718-6723,

314   https://doi.org/10.1021/es102631b, 2010.

315

316   Cooke, M. E., Armstrong, N. C., Lei, Z., Chen, Y., Waters, C. M., Zhang, Y., Buchenau, N. A.,

317   Dibley, M. Q., Ledsky, I. R., Szalkowski, T., Lee, J. Y., Baumann, K., Zhang, Z., Vizuete, W.,

318   Gold, A., Surratt, J. D., Ault, A. P.: Organosulfate formation in proxies for aged sea spray aerosol:

319   reactive uptake of isoprene epoxydiols to acidic sodium sulfate, ACS Earth Space Chem., 6 (12),

320   2790 – 2800, https://doi.org/10.1021/acsearthspacechem.2c00156, 2022.

321

322   Cui, T., Zeng, Z., dos Santos, E. O., Zhang, Z., Chen, Y., Zhang, Y., Rose, C. A.,

323   Budisulistiorini, S. H., Collins, L. B., Bodnar, W. M., de Souza, R. A. F., Martin, S. T.,

324   Machado, C. M. D., Turpin, B. J., Gold, A., Ault, A. P., Surratt, J. D. Development of a

Hydrophilic Interaction Liquid Chromatography (HILIC) method for the chemical characterization of water-soluble Isoprene Epoxydiol (IEPOX)-derived secondary organic aerosol. *Environ. Sci. Process. Impacts* 20 (11), 1524–1536. https://doi.org/10.1039/C8EM00308D, 2018.

Gaston, C. J., Riedel, T. P., Zhang, Z., Gold, A., Surratt, J. D., and Thornton, J. A.: Reactive uptake of an isoprene-derived epoxydiol to submicron aerosol particles, Environ. Sci. Technol., 48, 11178–11186, doi:10.1021/es5034266, 2014.

Guenther, A., Karl, T., Harley, P., Wiedinmyer, C., Palmer, P. I., and Geron, C.: Estimates of global terrestrial isoprene emissions using MEGAN (Model of Emissions of Gases and Aerosols from Nature), Atmos. Chem. Phys., 6, 3181–3210, doi:10.5194/acp-6-3181-2006, 2006.

Hallquist, M., Wenger, J. C., Baltensperger, U., Rudich, Y., Simpson, D., Claeys, M., Dommen, J., Donahue, N. M., George, C., Goldstein, A. H., Hamilton, J. F., Herrmann, H., Hoffmann, T., Iinuma, Y., Jang, M., Jenkin, M. E., Jimenez, J. L., Kiendler-Scharr, A., Maenhaut, W., McFiggans, G., Mentel, Th. F., Monod, A., Prevôt, A. S. H., Seinfeld, J. H., Surratt, J. D., Szmigielski, R., Wildt, J.: The formation, properties and impact of secondary organic aerosol: current and emerging issues, Atmos. Chem. Phys., 9 (14), 5155−5236, https://doi.org/10.5194/acp-9-5155-2009, 2009.

Jo, D. S., Hodzic, A., Emmons, L. K., Marais, E. A., Peng, Z., Nault, B. A., Hu, W., Campuzano-Jost, P., Jimenez, J. L.: A simplified parameterization of isoprene-epoxydiol-derived econdary organic aerosol (IEPOX-SOA) for global chemistry and climate models: A case study with GEOS-Chem V11-02-Rc. Geosci. Model Dev., 12, 2983−3000, 2019.

Kanakidou, M., Seinfeld, J. H., Pandis, S. N. Barnes, I., Dentener, F. J., Facchini, M. C., Van Dingenen, R., Ervens, B., Nenes, A., Nielsen, C. J., Swietlicki, E. Putaud, J. P., Balkanski, Y., Fuzzi, S., Horth, J., Moortgat, G. K., Winterhalter, R., Myhre, C. E. L., Tsigaridis, K., Vignati, E.,

354 Stephanou, E. G., Wilson, J.: Organic aerosol and global climate modelling: A review, Atmos.
355 Chem. Phys., 5 (4), 1053−1123, https://doi.org/10.5194/acp-5-1053-2005, 2005.

356

357 Klimovica, K., Grigorjeva, L., Maleckis, A., Popelis, J., Jirgensons, A.: C-quaternary
358 vinylglycinols by metal-catalyzed cyclization of allylic bistrichloroacetimidates, Synlett., 2849-
359 2851. https://doi.org/10.1055/s-00000083, 2011.

360

361 Lin, Y.-H., Zhang, Z., Docherty, K. S., Zhang, H., Budisulistiorini, S. H., Rubitschun, C. L., Shaw,
362 S. L., Knipping, E. M., Edgerton, E. S., and Kleindienst, T. E.: Isoprene epoxydiols as precursors
363 to secondary organic aerosol formation: acid-catalyzed reactive uptake studies with authentic
364 compounds, Environ. Sci. Technol., 46, 250–258, 2012.

365

366 Lin, Y.-H., Knipping, E. M., Edgerton, E. S., Shaw, S. L., and Surratt, J. D.: Investigating the
367 influences of SO_2 and NH_3 levels on isoprene-derived secondary organic aerosol formation using
368 conditional sampling approaches, Atmos. Chem. Phys., 13, 8457–8470, doi:10.5194/acp-13-8457-
369 2013, 2013.

370

371 Lin, Y.-H., Budisulistiorini, S. H., Chu, K., Siejack, R. A., Zhang, H., Riva, M., Zhang, Z., Gold,
372 A., Kautzman, K. E., and Surratt, J. D.: Light-absorbing oligomer formation in secondary organic
373 aerosol from reactive uptake of isoprene epoxydiols, Environ. Sci. Technol., 48, 12012–12021,
374 2014.

375

376 Marais, E. A., Jacob, D. J., Jimenez, J. L., Campuzano-Jost, P., Day, D. A., Hu, W., Krechmer, J.,
377 Zhu, L., Kim, P. S., Miller, C. C., Fisher, J. A., Travis, K., Yu, K., Hanisco, T. F., Wolfe, G. M.,
378 Arkinson, H. L., Pye, H. O. T., Froyd, K. D., Liao, J., McNeill, V. F.: Aqueous-phase mechanism
379 for secondary organic aerosol formation from isoprene: application to the southeast United States
380 and co-benefit of SO_2 emission controls, Atmos. Chem. Phys. 2016, 16, 1603−1618.

381

382 McNeill, V. F.: Aqueous organic chemistry in the atmosphere: Sources and chemical processing
383 of organic aerosols, Environ. Sci. Technol., 49, 1237–1244, 2015.

384

385 Nguyen, T. B., Coggon, M. M., Bates, K. H., Zhang, X., Schwantes, R. H., Schilling, K. A., Loza,
386 C. L., Flagan, R. C., Wennberg, P. O., and Seinfeld, J. H.: Organic aerosol formation from the
387 reactive uptake of isoprene epoxydiols (IEPOX) onto nonacidified inorganic seeds, Atmos. Chem.
388 Phys., 14, 3497–3510, doi:10.5194/acp-14-3497-2014, 2014.

389

390 Paulot, F., Crounse, J.D., Kjaergaard, H.G., Kürten, A., St. Clair, J.M., Seinfeld, J.H., Wennberg,
391 P.O.: Unexpected epoxide formation in the gas-phase photooxidation of isoprene, Science,
392 325(5941), 730 – 733, https://doi.org/10.1126/science.1172910, 2009.

393

394 Pope, C. A., 3rd, Dockery, D. W.: Health effects of fine particulate air pollution: lines that connect,
395 Journal of the Air & Waste Management Association, 56 (6), 709-42, ISSN 1047 – 3289, 2006.

396

397 Pye, H. O., Pinder, R. W., Piletic, I. R., Xie, Y., Capps, S. L., Lin, Y.-H., Surratt, J. D., Zhang, Z.,
398 Gold, A., and Luecken, D. J.: Epoxide pathways improve model predictions of isoprene markers
399 and reveal key role of acidity in aerosol formation, Environ. Sci. Technol., 47, 11056–11064, 2013.

400

401 Pye, H.O.T., Ward-Caviness, C.K., Murphy, B.N., Appel, K.W., Seltzer, K.M.: Secondary organic
402 aerosol association with cardiorespiratory disease mortality in the United States, Nat. Commun.,
403 12, 7215, https://doi.org/10.1038/s41467-021-27484-1, 2021.

404

405 Rattanavaraha, W., Chu, K., Budisulistiorini, S. H., Riva, M., Lin, Y.-H., Edgerton, E. S.,
406 Baumann, K., Shaw, S. L., Guo, H., King, L., Weber, R. J., Neff, M. E., Stone, E. A., Offenberg,
407 J. H., Zhang, Z., Gold, A., and Surratt, J. D.: Assessing the impact of anthropogenic pollution on
408 isoprene-derived secondary organic aerosol formation in $PM_{2.5}$ collected from the Birmingham,
409 Alabama, ground site during the 2013 Southern Oxidant and Aerosol Study, Atmos. Chem. Phys.,
410 16, 4897–4914, https://doi.org/10.5194/acp-16-4897-2016, 2016.

411

412 Riedel, T. P., Lin, Y.-H., Budisulistiorini, S. H., Gaston, C. J., Thornton, J. A., Zhang, Z., Vizuete,
413 W., Gold, A., and Surratt, J. D.: Heterogeneous reactions of isoprene-derived epoxides: reaction
414 probabilities and molar secondary organic aerosol yield estimates, Environ. Sci. Technol. Lett., 2,
415 38–42, 2015.

416

417 Riva, M., Chen, Y., Zhang, Y., Lei, Z., Olson, N. E., Boyer, H. C., Narayan, S., Yee, L D., Green,

418 H. S., Cui, T., Zhang, Z., Baumann, K., Fort, M., Edgerton, E., Budisulistiorini, S. H., Rose, C.

419 A., e Oliveira, I. O., Ribeiro, R. L., dos Santos, E. O., Machado, C. M. D., Szopa, S., Zhao, Y.,

420 Alves, E. G., de Sá, S. S., Hu, W., Knipping, E. M., Shaw, S. L., Junior, S. D., de Souza, R. A. F.,

421 Palm, B. B., Jimenez, J.-L., Glasius, M., Goldstein, A. H., Pye, H. O. T., Gold, A., Turpin, B. J.,

422 Vizuete, W., Martin, S. T., Thornton, J. A., Dutcher, C. S., Ault, A. P., Surratt, J. D.: Increasing

423 isoprene epoxydiol-to-inorganic sulfate aerosol ratio results in extensive conversion of inorganic

424 sulfate to organosulfur forms: Implications for aerosol physicochemical properties, Environ. Sci.

425 Technol., 53 (15), 8682 – 8694, https://doi.org/10.1021/acs.est.9b01019, 2019.

426

427 Sharpless, K.B., Lauer, R.F.: Selenium dioxide oxidation of olefins. Evidence for the intermediacy

428 of allylseleninic acids, J. Am. Chem. Soc., 94(20), 7154 – 7155, 1972.

429

430 St. Clair, J. M., Rivera-Rios, J. C., Crounse, J. D., Knap, H. C., Bates, K. H., Teng, A. P.,

431 Jorgensen, S., Kjaergaard, H. G., Keutsch, F. N., Wennberg, P. O.: Kinetics and products of the

432 reaction of the first-generation isoprene hydroxy hydroperoxide (ISOPOOH) with OH: J. Phys.

433 Chem. A, 120 (9), 1441−1451, https://doi.org/10.1021/acs.jpca.5b06532, 2016.

434

435 Surratt, J. D., Chan, A. W., Eddingsaas, N. C., Chan, M., Loza, C. L., Kwan, A. J., Hersey, S. P.,

436 Flagan, R. C., Wennberg, P. O., and Seinfeld, J. H.: Reactive intermediates revealed in secondary

437 organic aerosol formation from isoprene, P. Natl. Acad. Sci., 107, 6640–6645, 2010.

438

439 Trachtenberg, E.N., Nelson, C.H., Carver, J.R.: Mechanism of selenium dioxide oxidation of

440 Olefins, J. Org. Chem., 35(5), 1653 – 1658, 1970.

441

442 Wennberg, P.O., Bates, K.H., Crounse, J.D., Dodson, L.G., McVay. R.C., Mertens, L.A., Nguyen,

443 T.B., Praske, E., Schwantes, R.H., Smarte, M.D., St Clair, J.M., Teng, A.P., Zhang, X., Seinfeld,

444 J.H.: Gas-phase reactions of isoprene and its major oxidation products, Chem. Rev., 118(7),

445 3337−3390, https://doi.org/10.1021/acs.chemrev.7b00439, 2018.

446

447 Zhang, Z., Lin, Y.-H., Zhang, H., Surratt, J.D., Ball, L.M., Gold, A.: Technical note: synthesis of

448 isoprene atmospheric oxidation products: isomeric epoxydiols and the rearrangement products *cis*-

449 and *trans*-3-methyl-3,4-dihydroxytetrahydrofuran, Atmos. Chem. Phys., 12(18)*,* 8529–8535,

450 https://doi.org/10.5194/acp-12-8529-2012, 2012.

451

452 Zhang, Y., Chen, Y., Lambe, A. T., Olson, N. E., Lei, Z., Craig, R. L., Zhang, Z., Gold, A., Onasch,

453 T. B., Jayne, J. T., Worsnop, D. R., Gaston, C. J., Thornton, J. A., Vizuete, W., Ault, A. P., and

454 Surratt, J. D.: Effect of the aerosol-phase state on secondary organic aerosol formation from the

455 reactive uptake of isoprene-derived epoxydiols (IEPOX), Environ. Sci. Technol. Lett., 5, 167–

456 174, https://doi.org/10.1021/acs.estlett.8b00044, 2018

457