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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.

## 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

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

61  2014; Nguyen et al., 2014; Zhang et al., 2018; Riva et al., 2019; Armstrong et al., 2022; Cooke et

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

63  purity and in quantity.

64  **2. Experimental**

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

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

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

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

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

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

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

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

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

74  **2.1. *Trans*-β-IEPOX (*trans*-(2-methyloxirane-2,3-dilyl)dimethanol) from mesaconic acid**

75  *2.1.1. Mesaconic acid, dimethyl ester.* To a solution of mesaconic acid (11.00 g, 84.5 5 mmol,

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

77  mixture was refluxed for 8 h until a complete conversion was observed by thin layer

78  chromatography (TLC, SiO$_2$, 1:1 hexane: ethyl acetate) and the reaction was the neutralized by

79  addition of triethylamine (1.5 mL). Silica gel (11 g) was added and tThe resulting mixture was

80  dried on a rotary evaporator under house vacuum. The residue was applied to a silica gel column

81  and eluted with EtOAc/ (1:) to afford mesaconic acid dimethyl ester as a colorless oil (13.40 g,

82  96.57%), purity >98% by NMR. NMR (400 MHz, chloroform-*d*): δ 6.71 (d, *J* = 1.6 Hz, 1H), 3.74

83  (s, 3H), 3.71 (s, 3H), 2.23 (d, *J* = 1.6 Hz, 3H), Figure S1.

84  *2.1.2. E-2-Methyl but-2-ene-1,4-diol.* A solution of mesaconic acid dimethyl ester (13.40 g,

85  84.7285 mmol) in methylene chloride (120 mL) under argon was cooled to 0 °C and

86  diisobutylaluminum hydride (DIBAL-H; 400 mL 1.0 M solution in toluene, 400 mmol) was added

87  dropwise over 2 hours, and the reaction mixture was stirred at 0°C for 1 h. The reaction was diluted

88 with ether (100 mL) and quenched with water 16 mL (0.04 volume-equivalents of DIBAL-H),

89 followed by 16 mL 15% sodium hydroxide solution (0.04 volume-equivalents), and 40 mL water

90 (0.1 volume-equivalents). After quenching, the mixture was allowed to warm to room temperature

91 over 2 h and dried over magnesium sulfate. The aluminum salt was filtered under vacuum through

92 a pad of Celite, and solid filtrant further washed with ethyl acetate (100 mL). The solvent was

93 removed from filtrate on a rotary evaporator under house vacuum to yield *E*-2-methyl but-2-ene-

94 1,4-diol as a colorless oil (6.12g, 710.7%), purity > 98% by NMR. NMR (400 MHz, D$_2$O): δ 5.54

95 – 5.43 (m, 1H), 4.06 (d, *J* = 7.0 Hz, 2H), 3.90 (s, 2H), 1.57 (s, 3H), Figure S2.

96 *2.1.3. Trans-(2-Methyloxirane-2,3-diyl)dimethanol (trans-β-IEPOX).* Epoxidation of *E*-2-methyl

97 but-2-ene-1,4-diol followed a published procedure (Zhang et al., 2012). The butene diol (6.00 g,

98 58.89 mmol) was dissolved in acetonitrile (80 mL) and cooled in an ice-water bath. *m*-

99 Chloroperoxybenzoic acid (*m*-CPBA, 15.53 g, 90 mmol) was added and the clear solution was

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

101 transformation of the starting material as monitored by TLC (SiO$_2$, 1:1 hexane: ethyl acetate).

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

103 remove the bulk of the 3-chlorobenzoic acid. The filtrate was concentrated under reduced

104 pressurevacuum and the residue dissolved in water (30 mL), and washed repeatedly with

105 chloroform. The aqueous solution was lyophilized to yield *trans*-(2-methyloxirane-2,3-

106 diyl)dimethanol as colorless oil (6.24 g, 89%), purity > 98% by NMR. The ^{1}H NMR spectrum

107 was identical to that reported in previous syntheses (Zhang et al. 2012). NMR (400 MHz, D$_2$O):

108 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,

109 1H), 3.44 (d, J = 12.56 Hz, 1H), 3.15 (dd, *J* = 7.08, 4.29, 1H), 1.23 (s, 3H), Figure S3. ^{13}C NMR

110 (400 MHz, D$_2$O) δ 65.06, 62.35, 60.89, 59.78, 13.06, Figure S4. (-)ESI-HR-QTOF mass

111 spectrum is provided in Figure S5.

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

113 **2.2. *cis*-β-IEPOX (*cis*-(2-methyloxirane-2,3-diyl)dimethanol) from citraconic acid**

114 *2.2.1. Citraconic acid, dimethyl ester.* To a solution of citraconic acid (1.982.0 g, 15.2 mmol,

115 Sigma Aldrich, $46.10/5g) in methanol (50 mL) conc. H$_2$SO$_4$ (0.8 mL) was added. The reaction

116 mixture was refluxed for 8 h until complete conversion as determined by TLC (SiO$_2$, 1:1 hexane:

117 ethyl acetate) and then neutralized by addition of triethylamine (0.5 mL). ~~Silica gel (3 g) was added~~
118 ~~and t~~The resulting mixture was concentrated *in vacuo* ~~. The dry residue was applied to a silica gel~~
119 ~~column and eluted with EtOAc/petroleum ether (1:1)~~ to afford the desired citraconic acid dimethyl
120 ester (2.2 ~~1~~g, 92.~~1~~%) as a colorless oil, purity > 98% by NMR. NMR (400 MHz, $D_2O$): δ 6.08 (d,
121 *J* = 1.6 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 2.07 (d, *J* = 1.6 Hz, 3H), Figure S6~~4~~.

122 *2.2.2. Z-2-methyl but-2-ene-1,4-diol.* A solution of citraconic acid dimethyl ester (2.2 ~~1~~g, 14.~~0~~
123 mmol) in methylene chloride (25mL) under argon was cooled to 0°C and DIBAL-H (70 mL 1.0
124 M solution in toluene, 70.~~0~~ mmol) was added dropwise. Reaction mixture was stirred at 0°C for 1
125 h, diluted with ether (60 mL) and quenched with 2.8 mL water (0.04 of DIBAL-H volume
126 equivalents), followed by 2.8 mL 15% sodium hydroxide solution (0.04 volume equivalents) and
127 7.0 mL water (0.1 volume equivalents). After quenching, the mixture was allowed to warm to
128 room temperature over 2 h and dried over magnesium sulfate. The aluminum salt was removed by
129 filtration through a pad of Celite, and solid filtrant further washed with ethyl acetate (100 mL).
130 The solvent was removed from filtrate and desired *Z*-2-methyl but-2-ene-1,4-diol (1.1~~07~~ g, 75~~4.9~~%
131 yield) was obtained as a colorless oil, purity > 98% by NMR (Klimovica, et al., 2011). NMR (400
132 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
133 S7~~5~~.

134 *2.2.3. cis-(2-Methyloxirane-2,3-diyl)dimethanol (cis-β-IEPOX).* The epoxidation of the butene
135 diol was performed according to a published method (Zhang et al., 2012). The butene diol (1.1~~07~~
136 g, 10.~~4~~ mmol) was dissolved in acetonitrile (25 mL) and cooled in an ice-water bath. *m-*~~-~~
137 ~~Chloroperoxybenzoic acid~~CPBA (2.7~~69~~ g, ~~15.6~~16 mmol) was added and the clear solution was
138 stirred in the ice-water bath for 1h, and then at room temperature until complete transformation
139 of the starting material as monitored by TLC (SiO₂, 1:1 hexane: ethyl acetate). The mixture was
140 cooled at 0°C and the resulting precipitate separated by filtration to remove the bulk of the 3-
141 chlorobenzoic acid. The filtrate was concentrated under reduced pressure, the residue dissolved
142 in water (15 mL) and washed repeatedly with chloroform. The aqueous solution was lyophilized
143 to give *Z*-(2-methyloxirane-2,3-diyl)dimethanol as colorless oil isolated as the crude product
144 (1.0~~3~~ g, 83~~2.9~~%), purity 98% by NMR. NMR (400 MHz, $D_2O$): δ 3.78 (dd, *J* = 12.5, 3.9 Hz,
145 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

146    (dd, *J* = 7.35, 3.93 Hz, 1H), 1.43 (s, 3H), Figure S86. $^{13}$C NMR (500 MHz, D$_2$O) δ 64.68, 62.61,

147    62.48, 59.39, 18.82, Figure S9. (-)ESI-HR-QTOF mass spectrum is provided in Figure S10.

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

149    **2.3. *cis*-β-IEPOX (*cis*-(2-methyloxirane-2,3-diyl)dimethanol) from 3-methyl-2(5H)-furanone**

150    *2.3.1. Z-2-methyl but-2-ene-1,4-diol.* A solution of 3-methyl-2(5H)-furanone (1.106 g, 110.8

151    mmol) in methylene chloride (30 mL) under argon was cooled to 0°C, and DIBAL-H (21 mL 1.0

152

153 M solution in toluene, 21.0 mmol) was added dropwise. The reaction mixture was stirred at 0°C

154 for 1 h, diluted with ether (60 mL) and quenched with 0.85 mL water (0.04 of DIBAL-H volume-

155 equivalents), followed by 0.85 mL 15% sodium hydroxide solution (0.04 DIBAL-H volume-

156 equivalents), and 2.1 mL water (0.1 volume-equivalents). After quenching, the mixture was

157 allowed to warm to room temperature over 2 h, and dried over magnesium sulfate. The aluminum

158 salt was filtered out through a pad of Celite, and solid filtrant further washed with ethyl acetate

159 (100 mL). The solvent was removed on a rotary evaporator under house vacuum to yield *Z*-2-

160 methylbut-2-ene-1,4-diol (1.03 g, 94.1% yield) as a colorless oil, purity > 98% by NMR, Figure

161 S75.

162 *2.3.2. cis-(2-Methyloxirane-2,3-diyl)dimethanol (cis-β-IEPOX).* Butene diol (0.9169 92 g, 8.999.0

163 mmol) was dissolved in acetonitrile (50 mL) and cooled in an ice-water bath. *m*-

164 Chloroperoxybenzoic acidCPBA (1.92 g, 143.5 mmol) was added and the clear solution was

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

166 of the starting material as monitored by TLC (SiO$_2$, 1:1 hexane: ethyl acetate). The mixture was

167 cooled at 0°C and the resulting precipitate separated by filtration to remove the bulk of the 3-

168 chlorobenzoic acid. The filtrate was dried on a rotary evaporator under house vacuum and the

169 residue dissolved in water (30 mL). The aqueous solution was washed repeatedly with chloroform

170 and lyophilized and isolated as the crude product to give *cis*-(2-methyloxirane-2,3-diyl)dimethanol

171 as colorless oil (0.88 g, 832.9%), purity >9888% by NMR, Figures S8 and S96.

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

173 **3. Results and discussion**

174 Several synthetic routes to the β-IEPOX isomers have been published to date. Procedures for the

175 synthesis of *trans*-β-IEPOX followed the three strategies given in **Schemes 1 – 3**.

176 **Scheme 1**

7

177
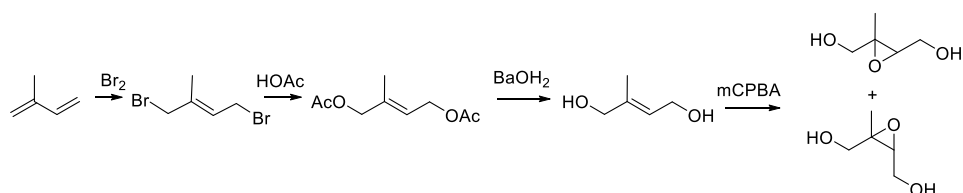
**Scheme 1**, the first published route to *trans*-β-IEPOX (Cole-Filipiak et al., 2010), yielded a
mixture of *cis* and *trans* products in four steps. The procedure is lengthy and required a double
vacuum distillation for isolation of 1,4-dibromoisoprene of the 1,4-diol were required. The mixture
was not separated, and the combined overall yield was 11%.

The approach in **Scheme 2** (Zhang et al., 2012) has been used in most syntheses reported
subsequent to publication in 2012. **Scheme 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 **Scheme 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.

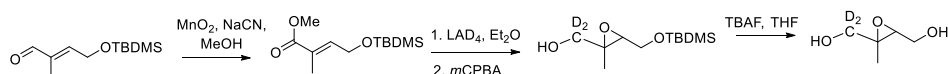**Scheme 2**



196
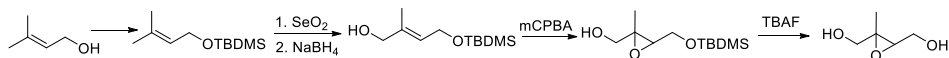
More recently, **Scheme 3**, a route to *trans*-β-IEPOX-*d$_2$*, has been reported that could also serve as
a route to the protio compound by substituting of LAH$_4$ for LAD$_4$ as reducing agent (Chase et al.,
2015).

200

**Scheme 3**



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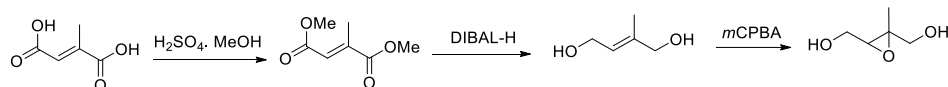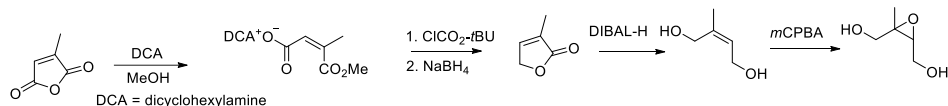
**Scheme 4**



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. **Scheme 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-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.,
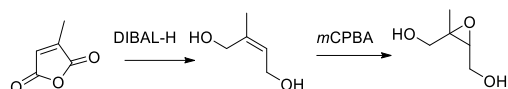
225 2012). In **Schemes 5** and **6**, citraconic anhydride was the starting material and the reducing agent
226 was DIBAL-H.

227 **Scheme 5**

228

229 **Scheme 6**

230

231 The reported overall yield of *cis*-β-IEPOX from **Scheme 5** was 12% (Bates et al., 2014). **Scheme**
232 **6** streamlined the synthesis through bypassing steps 2 and 3 of **Scheme 5** with direct reduction of
233 citraconic anhydride to *Z*-2-methylbut-2-en-1,4-diol (Bates et al., 2016). Reduction of the
234 anhydride required forcing conditions (5 equivalents of DIBAL-H were used) achieve reduction
235 of citraconic anhydride and possibly less efficient recovery of the diol resulted in the same overall
236 yield reported for **Scheme 5**.

237 3-Methylfuran-2(5H)-one was the starting material for **Scheme 7** and was reduced to directly *Z*-
238 2-methylbut-2-en-1,4-diol by LAH (Zhang et al., 2012).

239 **Scheme 7**
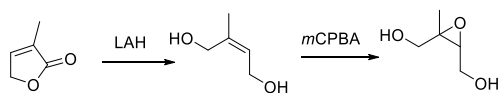
240

241 LAH is a powerful reducing agent leading to some unavoidable over-reduction of the furanone to
242 the saturated diol, and the overall yield was 19%. We repeated the synthesis of *cis*-β-IEPOX using
243 either citraconic acid or 3-methylfuran-2(5H)-one as starting points (**Scheme 8**). Because
244 reduction of anhydrides to diols generally appears to be more difficult and require forcing
245 conditions (Bloomfield and Lee, 1967), we selected citraconic acid rather than the anhydride as
246 the starting point for the synthesis. Citraconic acid requires esterification prior to reduction.

247  Although the dimethyl ester is commercially available, the esterification reaction is very
248  straightforward with a nearly quantitative yield and the savings in cost is substantial.

249  **Scheme 8**
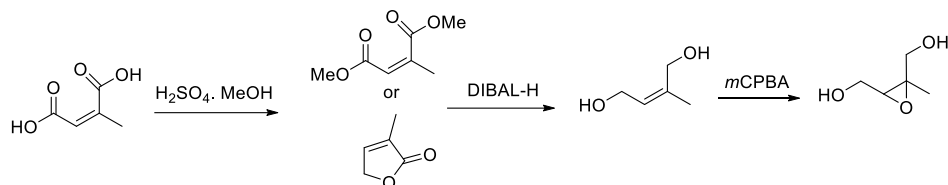


250  Under the assumption that sterically hindered *cis*-diester would nevertheless not proceed as readily
251  as reduction of the *trans*-diester, five equivalents of DIBAL-H were used for the reduction of
252  citraconic diester. With a yield of 74.9%, the reduction of the diester proved to be much more
253  efficient than that of citraconic anhydride, for which the reported yield was 28% (Bates et al.,
254  2016). The overall yield for this route was 57%, which represents a significant improvement over
255  **Scheme 5**.

256  3-Methylfuran-2(5H)-one is a more expensive starting compound than citraconic acid or citraconic
257  anhydride, but the procedure is streamlined to two steps and the overall yield, at 69%, is much
258  higher than for any of the published routes. Cost of reagents would largely dictate the choice of
259  citraconic acid or 3-methylfuran-2(5H)-one starting material. We note that *trans*- and *cis*-β-IEPOX
260  was isolated directly following lyophilization. The purity of *trans*- and *cis*-β-IEPOX were > 98%
261  by NMR (Figure S3-4, S8-9, respectively).

262  *Supplement:* The supplement related to this article is available online. Included in the supplement
263  are $^1$H NMR spectra of the target *cis*- and *trans*-β-IEPOX isomers and key intermediates in the
264  synthetic routes. Additional $^{13}$C and (-)ESI-HR-QTOF mass spectra are provided for the target *cis*-
265  and *trans*-β-IEPOX isomers.

266  *Author contributions:* All authors contributed equally into planning and performing experiments
267  and preparation of the manuscript. MF acquired spectroscopic data. J.D.S. helped with editing and
268  manuscript preparation.

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

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