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Atmospheric Chemistry and Physics

Technical Note: Synthesis of isoprene atmospheric oxidation products: isomeric epoxydiols and the rearrangement products *cis*- and *trans*-3-methyl-3,4-dihydroxytetrahydrofuran

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Abstract. Isoprene epoxydiol (IEPOX) isomers are key gas-phase intermediates of isoprene atmospheric oxidation. Secondary organic aerosols derived from such intermediates have important impacts on air quality and health. We report here convergent and unambiguous pathways developed for the synthesis of isomeric IEPOX species and the rearrangement products *cis*- and *trans*-3-methyl-3,4-dihydroxytetrahydrofuran in good yield. The availability of such compounds is necessary to expedite research on isoprene atmospheric oxidation mechanisms and subsequent aerosol formation as well as the toxicological properties of the aerosols.

1 Introduction

Isoprene (2-methyl-1,3-butadiene, **1**), the most abundant non-methane biogenic hydrocarbon emitted into the Earth's atmosphere (Guenther et al., 2006), undergoes extensive atmospheric oxidation. The resulting secondary organic aerosol (SOA) contributes significantly to the overall atmospheric aerosol budget (Claeys et al., 2004; Carlton et al., 2009), which affects regional air quality and global climate. Isoprene-derived SOA is also a major contributor to fine particulate matter ($PM_{2.5}$), which adversely impacts respiratory and cardiovascular systems of exposed populations (Pope III and Dockery, 2006). Under low nitric oxide (NO) conditions, gas-phase oxidation of isoprene yields four epoxydiol (IEPOX) isomers (Eddingsaas et al., 2010; Lin et al., 2012; Paulot et al., 2009; Surratt et al., 2010; Wang et al., 2005) (Fig. 1; **IEPOX-1–4**). Although epoxides have been suggested as possible precursors for SOA (Paulot et al., 2009; Surratt et al., 2010), the reaction pathways leading to aerosol formation are unknown. The gas-phase formation of the IEPOX isomers in high yield can provide suitable precursors for SOA and elucidation of the reaction pathways involved in this chemistry will contribute to resolving an outstanding puzzle in atmospheric aerosol chemistry. Recently, we have synthesized the four IEPOX isomers and in a series of controlled dark chamber studies have demonstrated that their reactive uptake onto pre-existing acidic seed aerosols yielded SOA (Lin et al., 2012). We have in addition, identified two previously unreported direct rearrangement products of the IEPOX isomers on uptake by acidic seed particles, *cis*- and *trans*-3-methyl-3,4-dihydroxytetrahydrofuran (Lin et al., 2012; Chan et al., 2010). Comparison of the chemical composition of the IEPOX-derived SOA with that of fine aerosol samples collected from the rural Southeastern US has confirmed the atmospheric relevance of our chamber findings, providing substantial support for the role of IEPOX in forming organic aerosol in the troposphere (Lin et al., 2012).

Our published study (Lin et al., 2012) demonstrates that availability of authentic, pure and rigorously-characterized intermediates and standards is critical for investigations into the generation and subsequent reactions of the IEPOX isomers leading to SOA and the identification and quantitation of aerosol components. In addition, availability of these compounds is essential for evaluation of their toxicological properties in order to assess the impact of isoprene-derived aerosols on human health. The IEPOX isomers and

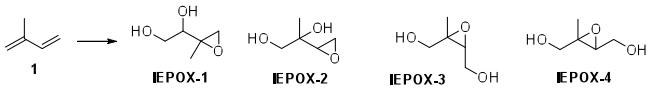

Fig. 1. Structures and abbreviations for IEPOX isomers.

other putative components of isoprene-derived SOA are not at present commercially available and no streamlined synthetic routes to these compounds in quantity and high purity have yet been reported. Investigation into the chemistry of IEPOX has to date relied upon the simpler surrogate butadiene epoxydiol (Eddingsaas et al., 2010; Paulot et al., 2009; Surratt et al., 2010) to explore reaction pathways, and on surrogate standards for quantitation of key isoprene tracers. We report here the convenient synthesis of regioisomers **IEPOX-1–4**, and the isomeric tetrahydrofurans that are the immediate rearrangement products of IEPOX isomers on contact with acidic seed aerosols (Lin et al., 2012).

2 Experimental section

2.1 Instrumentation

All the nuclear magnetic resonance (NMR) spectra were recorded on a Varian INOVA 400 MHz spectrometer, with chemical shifts reported in ppm relative to tetramethylsilane. Splitting patterns are reported as: m (multiplet), s (singlet), d (doublet), t (triplet) and dd (doublet of doublets). Gas chromatography/electron impact ionization mass spectrometry (GC/EI-MS) was performed with prior trimethylsilylation. Samples were trimethylsilylated by treatment with *N*, *O*-bis(trimethylsilyl)trifluoroacetamide and trimethylchlorosilane (BSTFA + TMCS) (99 : 1, 100 µl v/v, Supelco) and pyridine (50 µl anhydrous, 99.8 %, Sigma-Aldrich) at 70 °C for 1 h, and analyzed on a Hewlett-Packard (HP) 5890 Series II Gas Chromatograph with an Econo-Cap™-EC™ Capillary Column (30 m × 0.25 mm i.d.; 0.25 µm film thickness) coupled to an HP 5971A Mass Selective Detector. Operating conditions and temperature program were as described previously (Surratt et al., 2010).

2.2 IEPOX-1 (*erythro*- and *threo*- 1-(2-methyloxiran-2-yl)ethane-1,2-diol)

To 2-methyl-2-vinyloxirane (**2**, 1.3 g, 14.8 mmol, Alfa Aesar) in acetone (50 ml, Fisher Scientific), OsO_4 (2 ml, 1 % in water, Aldrich) and *N*-methylmorpholine *N*-oxide (3.46 g. 29.6 mmol, Aldrich) were added and the reaction stirred at room temperature (RT) until the starting material was completely consumed. Progress was monitored by the disappearance of the three-proton vinylic signals (5.64 ppm, dd, $J = 17.6$, 10.7 Hz; 5.35 ppm, dd, $J =$ 17.6, 1.1 Hz; 5.23 ppm, dd, $J = 10.7$, 1.1 Hz) in the ^{1}H NMR spectrum of reaction mixture aliquots. Upon completion, the reaction mixture was diluted with ethyl acetate (50 ml, Acros), quenched with saturated $Na_2S_2O_3$ (2 ml, Aldrich), dried over anhydrous Na_2SO_4 (Acros) and filtered. The filtrate was concentrated under reduced pressure, and the residue purified by flash chromatography (SiO_2 – Aldrich, diethyl ether – Fisher) to give the mixture of enantiomeric **IEPOX-1** diastereomers as a colorless oil (1.19 g, 68 %). **IEPOX-1** is a racemic mixture of diasteromers *erythro*-**IEPOX-1** ([(2′R)-1S]/[(2′S)-1R]-1-(2-methyloxiranyl)-1,2-ethanediol) and *threo*-**IEPOX-1** ([(2′S)-1S]/[(2′R)-1R]-1-(2-methyloxiranyl)-1,2-ethanediol). (*erythro*/*threo*, 2 : 1). GC/EI-MS. m/z, 231, 217, 205, 191, 177, 159, 147. *erythro*-**IEPOX-1**: ^{1}H NMR (400 MHz, $CDCl_3$, Cambridge Isotope Laboratories): 3.87–3.58 (m, 3H, H1 + $C2H_2$); 2.96 (d, 1H, $J = 4.6$ Hz, $C1'H_2$); 2.65 (d, 1H, $J = 4.6$ Hz, $C1'H_2$); 1.38 (s, 3H, CH_3) ppm (Fig. S1). ^{13}C NMR (100 MHz, $CDCl_3$): 72.4, 63.5, 57.3, 50.6, 18.5 ppm (Fig. S2). *threo*-**IEPOX-1**: ^{1}H NMR (400 MHz, $CDCl_3$): 3.87–3.58 (m, 3H, H1 + $C2H_2$); 2.89 (d, 1H, $J = 4.7$ Hz, $C1'H_2$); 2.63 (d, 1H, $J = 4.7$ Hz, $C1'H_2$); 1.35 (s, 3H, CH_3) ppm (Fig. S1). ^{13}C NMR (100 MHz, $CDCl_3$): 74.0, 63.7, 58.0, 51.5, 17.43 ppm (Fig. S2).

2.3 IEPOX-2 (*erythro*- and *threo*-2-(oxiran-2-yl) propane-1,2-diol)

Compound **2** (210 mg, 2 mmol) was dissolved in water acidified with HCl (0.1 N, 2 ml, Fisher) and the mixture was heated in a water bath at 50 °C for 30 min and then lyophilized. The residue was dissolved in acetonitrile (ACN, Fisher) (5 ml), cooled in an ice-water bath and *m*-chloroperoxybenzoic acid (*m*CPBA) (540 mg, 70 %, 2.4 mmol, Aldrich) was added. The clear solution was stirred in the ice-water bath for 2 h and then at RT until transformation of the starting material as monitored by thin layer chromatography (TLC) was complete. The 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 was purified by flash chromatography (SiO_2, diethyl ether) to afford **IEPOX-2** (150 mg, 62 %). The ^{1}H NMR spectrum (Fig. S3) is identical to published spectra (Adam and Nestler, 1993; Adam et al., 1997).

2.4 IEPOX-3 (*cis*-2-methyl-2,3-epoxy-1,4-butanediol)

3-Methyl furan-2(5*H*)-one (**7**) (2.11 g, 21.5 mmol) in diethyl ether (10 ml) was added to a suspension of lithium aluminum hydride (LAH) (1.02 g, 31.6 mmol, Aldrich) in diethyl ether (50 ml) at 0 °C. Following the completion of addition, the mixture was stirred at RT for 2 h and quenched with water (1 ml) followed by the addition of 15 % (w/w) NaOH (1 ml, Fisher) and water (3 ml) and stirred at RT for 0.5 h. The organic layer was filtered, then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure.

The residue was purified by chromatography (SiO_2, hexane (Acros)/diethyl ether, 1 : 1) to afford 2-methyl-2-butene-1,4-diol (**8**) (0.6 g, 27 %) (Duvold et al., 1997). ^{1}H NMR (400 MHz, $CDCl_3$): 5.65 (t, $J = 7.6$ Hz, 1H), 4.19–4.09 (m, 4H), 1.84 (s, 3H) ppm (Fig. S4).

Compound **8** (0.6 g, 5.9 mmol) was dissolved in ACN (20 ml) and cooled in an ice-water bath. *m*CPBA (1.6 g, 70 %, 7.2 mmol) was added and the clear solution was stirred in the ice-water bath for 2 h and then at RT until complete transformation of the starting material as monitored by TLC. The 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 (20 ml) and washed repeatedly with chloroform until no 3-chlorobenzoic acid was detected by TLC. The aqueous solution was lyophilized to give **IEPOX-3** as colorless oil (488 mg, 70 %). GC/EI-MS: m/z 244, 231, 217, 205, 191, 159, 147. ^{1}H NMR (400 MHz, D_2O): 3.94 (dd, 1H, $J = 12.2$, 6.0 Hz, H4), 3.82–3.74 (m, 2H, H1 and H4), 3.68 (d, 1H, $J = 11.9$ Hz, H1), 3.09 (t, 1H, $J = 5.8$ Hz, H3), 1.44 (s, 3H, CH_3) ppm (Fig. S5); ^{13}C NMR (100 MHz, D_2O): 64.4, 63.4, 61.4, 61.1, 20.5 ppm (Fig. S6).

2.5 *trans*-4-((*t*-Butyldimethylsilyl)oxy)-2-methyl-2-buten-1-ol (11)

SeO_2 (0.85 g, 7.7 mmol, Aldrich) was added to a solution of **9** (3.06 g, 16.4 mmol) in dichloromethane (DCM) (100 ml, Aldrich) cooled in ice-water. A solution of *t*-BuOOH (3 ml, 5.5 M in decane, 16.5 mmol, Aldrich) was added and the reaction mixture was stirred at 0 °C for an additional 2 h before being warmed to RT and stirred for an additional 1 h at RT. The reaction was then quenched with saturated $NaHCO_3$ (25 ml, Fisher), separated and the organic layer washed with brine and evaporated to dryness. The residue was taken up in ethanol (50 ml, Fisher) and cooled in an ice bath. $NaBH_4$ (0.5 g, 9.2 mmol, Aldrich) was added portionwise and the reaction mixture stirred for 15 min. Acetone (1 ml, Acros) was added and the reaction was stirred for another 15 min. Bulk solvent was then removed under reduced pressure; the residue was partitioned between water (25 ml) and ethyl acetate (50 ml), and the aqueous layer extracted with ethyl acetate (2×25 ml). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was purified by flash chromatography (SiO_2, hexane/ethyl acetate, 10 : 1) to give **11** (1.76 g, 8.7 mmol, 53 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): 5.53–5.59 (m, 1H), 4.25 (dd, 2H, $J = 6.3$, 0.8 Hz), 4.03 (d, 2H, $J = 5.2$ Hz), 1.68 (s, 3H), 0.92 (s, 9H); 0.87 (s, 6H) ppm (Fig. S9); ^{13}C NMR (100 MHz, $CDCl_3$): 136.35, 125.44, 68.49, 60.09, 26.19, 18.62, 14.00, 4.93 ppm.

2.6 (3-(((*t*-Butyldimethylsilyl)oxy)methyl)-2-methyloxiran-2-yl)methanol (12)

Compound **11** (0.7 g, 3.5 mmol) was dissolved in DCM (20 ml), *m*CPBA (0.9 g, 77 %, 3.9 mmol) was added and the mixture stirred at RT over night. The reaction mixture was then concentrated under reduced pressure and the residue dissolved in diethyl ether (80 ml) and washed with saturated solutions of $Na_2S_2O_3$, Na_2CO_3 (Fisher) and brine consecutively, and dried over anhydrous $MgSO_4$ (Fisher). Following filtration and concentration, the residue was purified by chromatography (SiO_2, hexane/ethyl acetate, 10 : 1) to provide **12**. ^{1}H NMR (400 MHz, $CDCl_3$): 3.82 (dd, 1H, $J = 11.7$, 4.8 Hz), 3.76 (dd, 1H, $J = 11.7$, 5.8 Hz), 3.64 (dd, 2H, $J = 12.6$ Hz), 3.20 (dd, 1H, $J = 5.7$, 4.8 Hz), 1.30 (s, 3H), 0.92 (s, 9H); 0.09 (s, 6H) ppm (Fig. S10).

2.7 IEPOX-4 (*trans*-2-methyl-2,3-epoxybutane-1,4-diol)

Compound **12** was dissolved in tetrahydrofuran (THF) (6 ml, Aldrich), cooled in ice water, then Bu_4NF (6 ml, 1 M, Aldrich) was added and the mixture was stirred for 1 h, concentrated and the residue purified by chromatography (SiO_2, diethyl ether) to afford **IEPOX-4** (308 mg, 82 %). GC/EI-MS: 24.44 min m/z 244, 205, 191, 159, 147. ^{1}H NMR (400 MHz, $CDCl_3$); 3.92 (dd, 1H, $J = 12.5$, 4.5 Hz, H4), 3.75–3.68 (m, 2H, H4+H1), 3.58 (d, 1H, $J = 12.6$ Hz, H1), 3.28 (dd, 1H, $J = 7.1$, 4.5 Hz, H3), 1.36 (s, 3H, CH_3) ppm (Fig. S11). ^{13}C NMR (100 MHz, $CDCl_3$): 65.2, 61.4, 61.1, 59.9, 14.4 ppm (Fig. S12).

2.8 *cis*-3-Methyltetrahydrofuran-3,4-diol (14) and *trans*-3-methyltetrahydrofuran-3,4-diol (15): method 1

IEPOX-1 (200 mg, 1.7 mmol) in water (4 ml) was stirred at 80 °C for 4 h with *p*-toluenesulfonic acid (6 mg, Aldrich) to give a mixture of diastereomeric 2-methylbutane tetrols. The reaction mixture was lyophilized and the residue mixed with toluene (15 ml, Fisher) and refluxed overnight. Following removal of the solvent under reduced pressure, the residue was purified by column chromatography (SiO_2, hexane/diethyl ether, 2 : 1) to give **14** as the early-eluting isomer and **15** as the late-eluting isomer: **14** (25 mg, 14 %). GC/EI-MS: m/z 262, 247, 231, 218, 204, 147. ^{1}H NMR (400 MHz, $CDCl_3$): 4.04 (dd, 1H, $J = 9.8$, 5.8 Hz, H5), 3.92–3.86 (m, 1H, H4), 3.76 (d, 1H, $J = 9.2$ Hz, H2), 3.73 (dd, 1H, $J = 9.8$, 4.3 Hz, H5). 3.62 (d, 1H, $J = 9.2$ Hz, H2), 1.35 (s, 3H, CH_3) ppm (Fig. S19). ^{13}C NMR (100 MHz, $CDCl_3$): 77.43, 76.92, 76.50, 73.87, 23.48 ppm (Fig. S20). **15** (49 mg, 29 %): GC-EIMS. m/z 262, 247, 231, 218, 204, 147. ^{1}H NMR (400 MHz, D_2O): 4.27 (dd, $J = 10.1$, 4.5 Hz, 1H, H5), 3.99 (dd, $J = 4.6$, 1.8 Hz, 1H, H4), 3.75–3.68 (m, 3H, $C2H_2$ + H5), 1.35 (s, 3H, CH_3) ppm (Fig. S22). ^{13}C NMR

(100 MHz, $CDCl_3$): 80.54, 79.13, 75.26, 74.56, 18.30 ppm (Fig. S23).

2.9 *cis*-3-Methyltetrahydrofuran-3,4-diol (14) and *trans*-3-methyltetrahydrofuran-3,4-diol (15): method 2

2.9.1 4-(Benzyloxy)tetrahydrofuran-3-ol (17)

1,4-Anhydroerythritol (**16**) (3.1 g, 29.8 mmol, Aldrich) was added to a solution of Bu_2SnO (7.6 g, 30.5 mmol, Aldrich) and Bu_4NI (12.2 g, 33.1 mmol, Aldrich) in toluene (150 ml) and heated at reflux for 1 h. After the reaction mixture was cooled to RT, BnBr (4 ml, 33.7 mmol, Aldrich) was added and the mixture was maintained at $\sim 100\,^{\circ}C$ for 4 h and then cooled to RT. After dilution with diethyl ether, the mixture was washed with aqueous $Na_2S_2O_3$, water and brine successively and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue purified by column chromatography (SiO_2, hexane/ethyl diethyl ether, 2 : 1) to give **17** (5.1 g, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.28 (m, 5H, phenyl-H), 4.61 (s, 2H, benzyl-CH_2) 4.29–4.22 (m, 1H), 4.11–4.04 (m, 1H), 3.93–3.84 (m, 2H), 3.82–3.71 (m, 2H), 2.81–2.74 (m, 1H, OH) ppm (Fig. S15). ^{13}C NMR (100 MHz, $CDCl_3$): 137.34, 128.79, 128.37, 128.06, 78.45, 73.61, 72.74, 70.52, 70.16 ppm (Fig. S16).

2.9.2 4-(Benzyloxy)dihydrofuran-3(2*H*)-one (18)

To a mixture of pyridine (14.0 ml, Aldrich) and Ac_2O (8.25 ml, Aldrich) in DCM (50 ml) cooled in an icewater bath, CrO_3 (8.4 g, 84 mmol, Aldrich) was added, followed by **17** (5.1 g, 26.3 mmol). The mixture was stirred at RT for 1.5 h, poured in to ethyl acetate (300 ml) and filtered through silica gel. The filtrate was concentrated under reduced pressure and the residue purified by chromatography (SiO_2, hexane/diethyl ether, 2:1) to give **18** (1.4 g, 28 %). ^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.29 (m, 5H, phenyl-H), 4.92 (d, 1H, $J = 11.8$ Hz, benzyl-CH) 4.68 (d, 1H, $J = 11.8$ Hz, benzyl-CH) 4.29 (dd, 1H, $J = 9.8$, 7.5 Hz), 4.06 (t, 1H, $J = 7.5$ Hz), 4.03, 3.98 (q, 2H, $J_{AB} = 17.6$ Hz, $COCH_2$), 3.871 (dd, 1H, $J = 9.8$, 7.6 Hz) ppm (Fig. S17). ^{13}C NMR (100 MHz, $CDCl_3$): 213.07, 137.08. 128.73, 129.39, 129.32, 76.22, 72.80, 70.93, 70.18 ppm (Fig. S18).

Compound **18** (1.2 g, 6.3 mmol) was added to a solution of CH_3MgCl in THF (3 M, 1.5 eq, Aldrich) cooled in an icewater bath. The reaction mixture was stirred at RT for 1 h, quenched with saturated NH_4Cl (Aldrich) and diluted with diethyl ether. The organic layer was separated and the aqueous layer extracted with diethyl ether. The combined organic phases were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure, the residue was dissolved in methanol (50 ml, Fisher). Pd-C (10 %, 200 mg, Aldrich) was added and the reaction mixture was hydrogenated overnight. The reaction mixture was filtered through silica gel, concentrated under reduced pressure and the residue purified by chromatography (SiO_2, hexane/diethyl ether, 2 : 1) to give **14** (190 mg, 27 %) and **15** (300 mg, 41 %). The ^{1}H and ^{13}C NMR spectra were identical to those obtained by method 1.

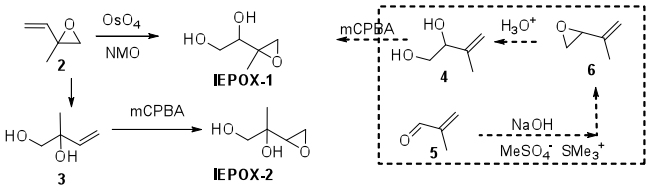

Fig. 2. Scheme for synthesis of **IEPOX-1** and **IEPOX-2**. The scheme within the box represents a multi-step procedure (Cole-Filipiak, 2010) for synthesis of **IEPOX-1** in lower overall yield than in the present work. (Abbreviations: NMO, *N*-methylmorpholine oxide; *m*CPBA, *m*-chloroperbenzoic acid.)

3 Results and discussion

3.1 Synthesis

Syntheses of the mixtures of racemic *erythro* and *threo* diastereomers of **IEPOX-1** (1-(2-methyloxiran-2-yl)ethane-1,2-diol) and **IEPOX-2** (2-oxiranyl-propane-1,2-diol) have been reported in different contexts (Cole-Filipiak et al., 2010; Adam et al., 1997; Chiappe et al., 2000), all based on the epoxidation of butendiol **4** or **3**, respectively (Scheme 1). Compound **3** is readily available through hydrolysis of commercially available 2-methyl-2-vinyloxirane (**2**). An excellent yield of a 9 : 1 *erythro*/*threo* mixture of **IEPOX-1** has been reported via a titanium-catalyzed epoxidation of precursor **4** (Adam et al., 1997) obtained through hydroxylation of 2-(prop-1-en-2-yl)oxirane (**6**). Although there are a number of methods for the preparation of **6**, including catalytic epoxidation of isoprene (Sheng and Zajacek, 1970; Brill and Indictor, 1964; Indictor et al., 1965; Rasmussen et al., 1995), methylene addition to methacrolein (Welzel et al., 1987; Harwood et al., 1990), and a multi-step pathway starting from isoprene (Suzuki et al., 1986), these routes all suffer from poor yield and lack of convenience, limiting the overall yield for the preparation of **IEPOX-1**. Using **2** as starting material, we have designed a convergent synthesis for **IEPOX-1** and **IEPOX-2** as diastereomeric mixtures (Fig. 2) which significantly simplifies preparation and improves overall yields. **IEPOX-1** was obtained as a mixture of diastereomers in 68 % yield through direct dihydroxylation of **2** with OsO_4. Acid hydrolysis of **2** followed by epoxidation with *m*CPBA gave the diastereomeric mixture **IEPOX-2** in 62 % yield. The ^{1}H NMR spectrum of **IEPOX-1** is identical to published spectra (Chiappe et al., 2000; Adam and Nestler, 1993) in which assignment of NMR signals was based on the spectral characteristics of close structural analogs (Adam

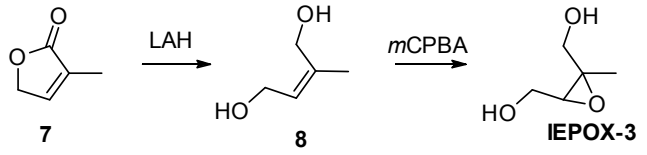

Fig. 3. Scheme for synthesis of **IEPOX-3**. (Abbreviation: LAH, lithium aluminium hydride.)

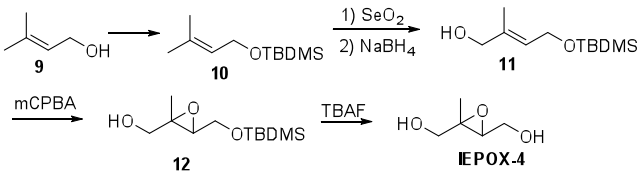

Fig. 4. Scheme for synthesis of **IEPOX-4**. (Abbreviations: TBDMS, *tert*-butyldimethylsilyl; TBAF, tetrabutylammonium fluoride.)

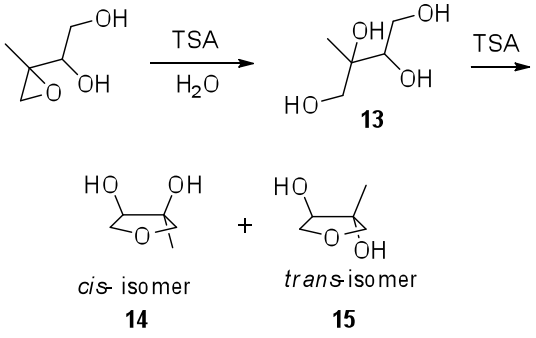

Fig. 5. Scheme for preparation of a mixture of **14** and **15** (method 1). (Abbreviation: TSA, toluenesulfonic acid.)

and Nestler, 1993). In the ^{13}C NMR spectrum of **IEPOX-1**, two sets of signals in a 2 : 1 ratio are assigned to the *erythro* and *threo* diastereomers, respectively, based on the ^{13}C NMR shifts which are in accord with the published report. Correspondingly, in the ^{1}H NMR, the resolved signals with higher intensity were assigned to *erythro* diastereomer. For **IEPOX-2**, the ^{1}H NMR spectrum of the mixture was identical to the reported spectrum in which, however, the *erythro* and *threo* diastereomers were not assigned. The tentative assignment for the two sets of NMR signals to *erythro* and *threo* diastereomers in this work is based on the NMR spectrum of the close structural analog linalool epoxide for which the absolute stereochemistry has been established (Morales et al., 2011; Khomenko et al., 2002).

Synthesis of a mixture of **IEPOX-3** and **IEPOX-4** in 11 % overall yield starting with isoprene has been reported (Cole-Filipiak et al., 2010). Since the authors did not specify that their product was a mixture, we have deduced the composition by comparison of the published ^{1}H NMR spectrum with the ^{1}H NMR spectra of the racemates of the pure geometric isomers from our syntheses described below. The *cis* isomer **IEPOX-3** was prepared by the unambiguous pathway shown in Fig. 3. Commercially available 3-methyl furan-2(5*H*)-one (**7**) was reduced with LAH to afford *cis*-2-methyl-2-butene-1,4-diol (**8**), which was then epoxidized with *m*CPBA to give **IEPOX-3**. While some over-reduction of **7** to the corresponding butanediol appears difficult to avoid, isolation of **8** could be achieved through chromatographic separation. To ensure the purity of the target **IEPOX-3**, the fully reduced butanediol side product was more efficiently removed following treatment of **7** with LAH, rather than following the epoxidation. The overall yield for this sequence was 19 %, further optimization was not attempted. The *cis* geometry of **IEPOX-3** was confirmed by 1D nuclear Overhauser effect spectroscopy (1D NOESY) (Fig. S8), which showed strong dipolar coupling between the methyl group and the oxirane proton.

IEPOX-4 was prepared according to the scheme in Fig. 4. 3-Methyl-2-buten-1-ol (**9**) was protected with TBDMS and a hydroxyl group introduced by SeO_2 oxidation followed by reduction with $NaBH_4$. The resulting 2-buten-1-ol (**11**) was epoxidized and deprotected to give **IEPOX-4** in 43 % yield. The *trans*-configuration was confirmed by the absence of a nuclear Overhauser effect correlation between the methyl group and the oxirane proton in the 1D NOESY spectrum (Fig. S14).

The preparation of *cis*-3-methyltetrahydrofuran-3,4-diol (**14**) has been reported in two steps starting with 4-methyl-1,2-dioxine (Robinson et al., 2009). Since this route leads only to the *cis* isomer and the overall yield, taking into account the photolytic synthesis of the dioxine from isoprene (Motsumoto et al., 1985), is moderate, we devised two routes to a the synthesis of **14** and **15** as a readily separable mixture. First, taking advantage of **IEPOX-1** on hand, we prepared the mixture according to the scheme in Fig. 5 by acid-catalyzed hydrolysis of **IEPOX-1** to the 2-methyl-erythritol/threitol mixture **13** followed by a second acid-catalyzed cyclization of **13** to the desired mixture isolated as the pure targets by column chromatography. It is worth noting that while the process is simple and can be carried out in one-pot, the isolation is complicated by side products. The combined yield for the purified isomers **14** and **15** (1 : 2, respectively) was 43 % starting from **IEPOX-1**. Alternatively, the isomers **14** and **15** can be obtained via the scheme in Fig. 6. Dihydroxytetrahydrofuran **16** was partially protected by benzylation (**17**) and oxidized to dihydrofuranone **18**. The methyl substituent was introduced by a Grignard reaction, and following deprotection, purified isomers **14** and **15** (1 : 1.6, respectively) were obtained in a combined yield of 68 % from **18**. Through the latter method, the purification of the final products to a high standard was facilitated.

In the ^{1}H NMR of **14** and **15**, the signal for H4 displays a broadened pattern, distinct from other non-exchanging protons, which display well-resolved first order doublet-of-doublet signal patterns. The ^{1}H NMR of **14** was identical to

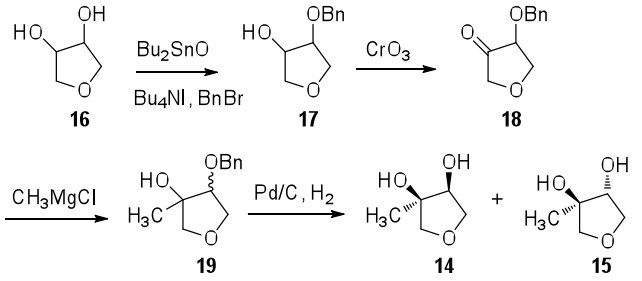

Fig. 6. Scheme for preparation of a mixture of **14** and **15** (method 2). (Abbreviation: Bu_2SnO, dibutyltin oxide; Bu_4NI, tetrabutylammonium iodide; BnBr, benzyl bromide.)

that reported for the *cis* isomer (Robinson et al., 2009), and the *cis*-isomeric structure was further confirmed by the 1D NOESY spectrum (Fig. S21), in which the signal for carbinyl H4 is strongly enhanced on irradiation of the neighboring 3-methyl signal. In the case of **15**, irradiation of the methyl signal produces a much smaller enhancement of the H4 signal in the 1D NOESY spectrum in accordance with expectation for the *trans*-geometry. The GC/EI-MS of the *bis*-TMS derivatives of **14** and **15** provides additional evidence supporting the assignment of **14** as the *cis* isomer. Fragmentation to the product ion $[Me_3Si\text{-}O=SiMe_2]^+$ (m/z 147) is significantly more pronounced for **14** than for **15**, as would be expected for the *cis* isomer (Diekman et al., 1968; Pierce et al., 1968).

3.2 Purity of synthetic targets

The purity of the **IEPOX** and 3-methyl-3,4-dihydroxytetrahydrofuran isomers was evaluated by both the GC/EI-MS spectra and total ion chromatograms (TICs) of the TMS-derivatized standards and the ^{1}H- and ^{13}C NMR traces. The TICs and GC/EI-MS spectra of the TMS-derivatized standards demonstrate high purity (Lin et al., 2012). No extraneous resonances were observed in the NMR spectra. Since a proton signal integrating to $> 1\,\%$ of a proton signal of the target compounds would have been detectable in the NMR spectra, the targets were isolated in $> 99\,\%$ purity.

3.3 Stability of stock solutions

The stability of the isomeric **IEPOX** and tetrahydrofuran isomers is of interest with regard to the preparation and storage of stock solutions. Stock solutions of **IEPOX-1**, **IEPOX-3** and the THF isomers in ethyl acetate ($100\,ng\,\mu l^{-1}$) were prepared and stored at $-20\,^{\circ}C$ for use in chamber experiments and as standards. Over a period of 1 yr, no deterioration was observed for any of the compounds in analyses of the stock solutions by derivatization GC/EI-MS (Figs. S26, S27). Thus, both the IEPOX and THF isomers can be stored for long periods at subambient temperature in an aprotic solvent.

4 Conclusions

We have reported convenient synthetic routes to the IEPOX isomers that are key intermediates in the formation of isoprene-derived SOA, as well as to the 3-methyl-3,4-dihydroxytetrahydrofuran isomers that are the initial rearrangement products of IEPOX on contact with acidic seed aerosols. The availability of these compounds will be critical in further investigation into the influence of environmental conditions on SOA formation and composition and will also be important in assessing the impact of isoprene SOA on human health.

Supplementary material related to this article is available online at: http://www.atmos-chem-phys.net/12/8529/2012/acp-12-8529-2012-supplement.pdf.

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