

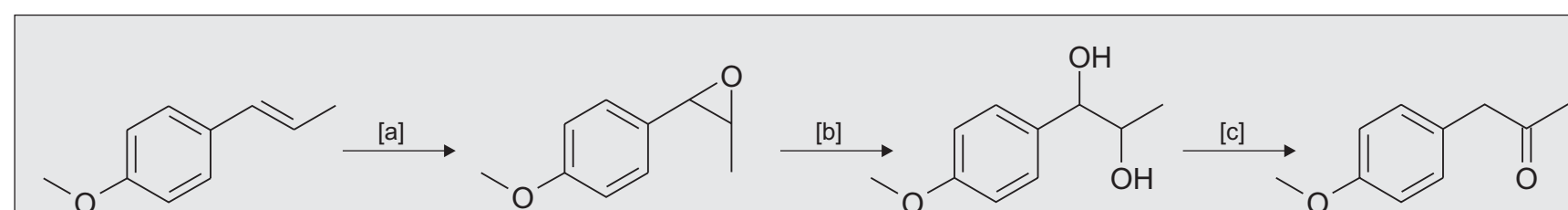
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## INTRODUCTION:

The profiling of synthesis impurities is of utmost importance in forensic chemistry. This poster presents an overview of impurities formed during the peracid oxidation of anethole (the major component of anise oil) in the synthesis of PMA.

## SYNTHESIS:

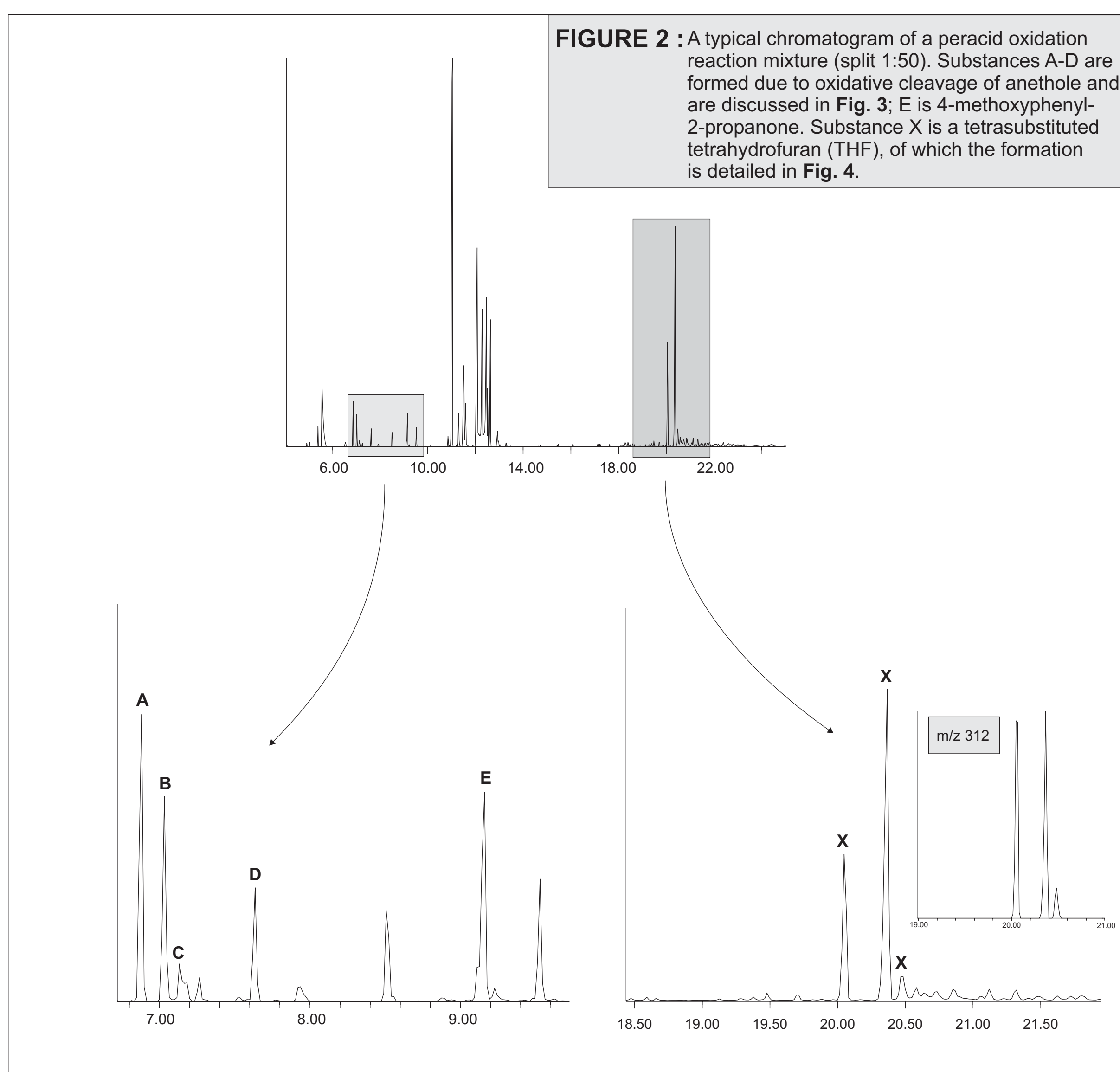
- **Performic acid:** created by adding 6.8 g 30% H<sub>2</sub>O<sub>2</sub> to 24.0 g HCOOH.
- **Peracid oxidation:** the performic acid was added to a solution of 6.0 g anise oil in 30 mL acetone at such a rate that the temperature did not exceed 38°C. After addition, reaction was allowed to continue for 12 hours. Extracting the reaction mixture with 2 x 50 mL dichloromethane and washing the organic phase with 50 mL water yielded 8.2 g of a yellow oil. (cf reaction scheme **Fig. 1**)



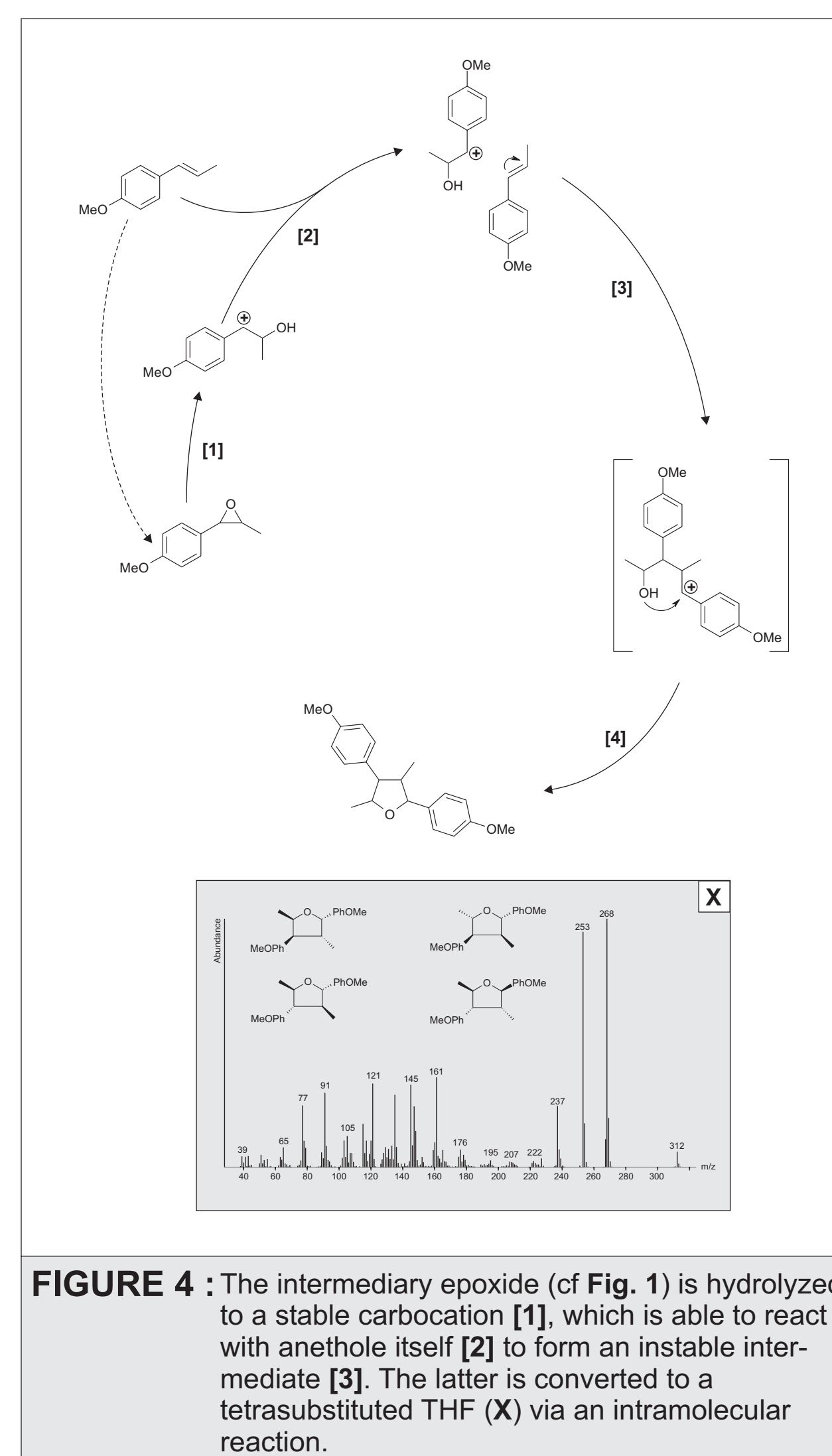
**FIGURE 1:** Anethole is reacted with a peracid (typically performic acid) to form an intermediary epoxide [a], which is hydrolyzed to a glycol (and its esters) [b]. The glycol (esters) are refluxed in a mixture of methanol and dilute sulfuric acid to obtain the ketone 4-methoxyphenyl-2-propanone, a precursor of 4-methoxyamphetamine (PMA) in the Leuckart reaction [c].

## INSTRUMENTATION:

GC/MS analysis by Agilent 6890 Plus GC coupled to Agilent 5973N MSD:  
- **column:** VF-5MS factorFour (30 m x 0.250 mm x 0.25 µm); **carrier gas:** He, flow rate of 1 mL/min.  
- **oven programming:** 50°C (1 min), 35°C/min to 100°C, 10°C/min to 270° (20 min).  
- **MSD:** EI mode (70 eV), 36-500 amu, 4.00 min solvent delay.



**FIGURE 2:** A typical chromatogram of a peracid oxidation reaction mixture (split 1:50). Substances A-D are formed due to oxidative cleavage of anethole and are discussed in **Fig. 3**; E is 4-methoxyphenyl-2-propanone. Substance X is a tetrasubstituted tetrahydrofuran (THF), of which the formation is detailed in **Fig. 4**.



**FIGURE 4:** The intermediary epoxide (cf **Fig. 1**) is hydrolyzed to a stable carbocation [1], which is able to react with anethole itself [2] to form an unstable intermediate [3]. The latter is converted to a tetrasubstituted THF (X) via an intramolecular reaction.

## DISCUSSION:

### IMPURITY FORMATION

#### 1. Oxidative cleavage of anethole

The oxidative cleavage of anethole will yield anisaldehyde, which in turn is converted to O-formyl-4-methoxyphenol according to the Baeyer-Villiger reaction. The latter substance is hydrolyzed to 4-methoxyphenol. Screening of the reaction mixture also demonstrates the presence of methyl chavicol (also present in anise oil and MS similar to anethole). (cf. reaction scheme and MS in **Fig. 3**)

#### 2. 2,4-Dimethyl-3,5-bis(4'-methoxyphenyl) tetrahydrofuran

This substituted tetrahydrofuran (THF) is formed during the peracid oxidation of anethole. The anethole epoxide (cf **Fig. 1**) can convert spontaneously to a carbocation intermediate, which in turn can react with anethole to form the tetrasubstituted THF (cf **Fig. 4**)

Theoretically, this THF can have 4 different diastereomers (cf MS **Fig. 4**, denominated as X). The chromatogram and extracted ion chromatogram for *m/z* 312 in **Fig. 2** illustrates that the applied capillary column separates the THF in 3 diastereomers (cf **Fig. 2**).

## CONCLUSION:

Peracid oxidation impurities are formed *via* different routes. Both 4-methoxyphenol (**Fig. 3B**) and the tetrasubstituted THF (**Fig. 4X**) are specific for the peracid oxidation of anethole and are utile markers for forensic chemists.

### FIGURE 3:

The reaction scheme shows the oxidative cleavage of anethole, yielding anisaldehyde (a); the latter is converted to O-formyl-4-methoxyphenol due to the presence of performic acid (Baeyer-Villiger reaction, b). Hydrolysis of this formyl ester yields 4-methoxyphenol (c).

**Mass spectra:** methyl chavicol (A), 4-methoxyphenol (B), O-formyl-4-methoxyphenol (C) and anisaldehyde (D)

