

### Response to Referee #3

Thank you for the valuable comments and suggestions. Our answers are in bullet points below the original referee comments in **bold**, changes to the manuscript are in *italics*.

**This review is submitted with the benefit of having read reviews of anonymous Reviewers 1 and 2. As stated in the previous reviews, this work contributes procedures for synthesis of a number of vicinal hydroxynitrate esters derived from a monoterpene. The esters can serve as much needed authentic standards for characterizing components of SOA and therefore the work should be published. There are a number of comments that the authors need to address prior to publication.**

Thank you for acknowledging the critical need for these standards. We hope that our work will help fill this gap in the literature.

**Most important: the authors should include  $^1\text{H}$  and  $^{13}\text{C}$  NMR traces for all compounds that have not been previously reported, and should also include HSQC and HMBC spectra where this is critical for structural elucidation. In particular, the assignment of quaternary carbons is readily evident from the absence of C–H cross peaks in the HSQC spectra. Since the authors had access to high-resolution mass spectrometry, exact mass measurements and fragmentation patterns should be provided either in the experimental section of the text or the SI for all compounds not previously reported.**

- We have included all  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and HSQC spectra in the SI for all compounds not previously reported. We have also added HRMS data in the experimental section for all compounds not previously reported.

**Globally, there is considerable carelessness with regard to the presentation of this manuscript. Conventionally, solvent names do not begin with upper case letters and in the case of deuterated solvents, the notation “d” is italicized (e.g., chloroform-[*italics*]d). This convention is adhered to randomly throughout.**

**The use of abbreviations for solvents is also not consistent (e.g. EtOAc:Hex and ethyl acetate:hexanes (solvent and compound names are inappropriately capitalized in the text)).**

- We have fixed the minor typos and inconsistent abbreviations.

**Several citations are only partially given in the text (e.g. Cocker, 1969 on p. 4, l. 8) and in one case, a citation in the text is missing from the bibliography (Charbonneau, 2018; Charbonneau was misspelled).**

- We have amended the partial citations to full citations at first instance.
- Charbonneau, 2018 has been added to the bibliography.

**There are mistakes in nomenclature: trans-3-carene (not trans-(3)-carene). Synthetic targets are referred to as “title” compounds. However, “target compound” would be preferable, since compounds do not appear in titles.**

- Corrected instances of extraneous parentheses.
- Replaced “title compound” with the names compounds and compound numbers.

**Reaction/synthetic schemes should be separated from tables and figures and appropriately designated.**

- Sometimes it may be appropriate to separate a table from a reaction scheme, we do not believe that it is appropriate in this case. The tables are communicating different reaction conditions of the connected reaction scheme and would be meaningless if separated.
- 1. The authors might note that products having two or more asymmetric carbons were isolated and characterized as mixtures of diastereomers. Visual inspection of the NMR spectra does not appear to show any resolution of the mixture by NMR. Did the authors look for any such result?**
    - We have indicated in the text and by using line bonds (not wedged or dashed) the cases where we generated mixtures of diastereomers. For example, the perillal alcohol epoxides **15**, 8,9-limonene oxide (**9**), nitrate ester **10**, oxazoline **10a**, and aldehyde **11** are the only mixtures of diastereomers. All other compounds are drawn, characterized and reported as single diastereomers.
  - 2. For the preparation of trans-carene oxide (p. 3, starting with l. 17), did the authors start with optically pure (+)-carene or a racemic mixture? This is important, since epoxidation with mCPBA will give an enantiomerically pure epoxide from enantiomerically pure starting material. The synthesis of the cis oxide described below apparently starts with (+)-carene.**
    - The starting material was corrected to (+)-carene.
  - 3. Preferred nomenclature for cpd 20 would be 2-methyl-5-(propan-2-ylidene)cyclohex-2-en-1-ol.**
    - Amended to “5-isopropylidene-2-methyl-2-cyclohexen-1-ol”
  - 4. Visual inspection of the <sup>1</sup>H NMR trace of cpd 24 appears to be consistent with the signal at 5.31 ppm as a poorly resolved doublet-of-doublets. It is not clear how the authors interpreted this signal as a doublet-of-doublets-of-doublets.**
    - The expansion of the NMR trace clearly shows the reported doublet-of-doublets-of-doublets. This is corroborated by gCOSY correlation to the adjacent methylene as well as long-range, 4-bond coupling to the methyne (-*CHOH*). This type of 4-bond coupling ( $J = 1-2$  Hz) is quite common in substituted cyclohexane derivatives (see: Crews, P., et al. *Organic Structure Analysis*, Oxford University Press, 1998, pages 142-143).
  - 5. p. 7, l. 16 and following; p. 13, l. 3 and following: As pointed out by Reviewer 1, there is a problem with the structural assignment of limonene 8,9-dihydrodiol (**10**) to the crude product of Bi(NO<sub>3</sub>)<sub>3</sub> treatment of limonene 8,9-oxide (**9**). This is true as well for the rearrangement product 2-(4-methylcyclohex-3-en-1-yl)propanal (preferred nomenclature) (**11**). The <sup>1</sup>H NMR data provided do not match published data for either proposed structure (diol: *J. Am. Chem. Soc.* **2018**, *140*, 1502–1507; aldehyde: *Phytochemistry* **2017**, *144*, 208 – 215). This reviewer notes that the reported <sup>1</sup>H NMR of the diol was acquired at a spectrometer frequency of 600 MHz, although the only expected difference would be improved resolution of the proton splittings.**
    - Thank you for bringing this to our attention. We revisited the reaction of **9** in acetonitrile & dioxane. Upon full characterization we determined that the product formed in acetonitrile is actually a 1:1 diastereomeric mixture of oxazolidine **10a**. Of note were <sup>13</sup>C signals at: 162.62, 162.55 ppm (carbonyl carbon), 72.77, 72.62 ppm (tetrasubstituted C), 13.87, 13.86 ppm (*CH*<sub>3</sub>C). The structure was further confirmed by an IR stretch at 1674

cm<sup>-1</sup> and an *m/z* 193.8 (M<sup>+</sup>). This type of reactivity with bismuth nitrate and acetonitrile opening epoxides was also observed by Pinto, et al., 2007.

- We have added tabulated <sup>1</sup>H and <sup>13</sup>C NMR for aldehyde 11 in the supplemental information to show the comparison to both Uehara, et al., 2017 and a second reference, Reid and Watson, 2018. The data are in agreement within expected error.
- 6. On p. 11, starting with line 12: The authors should provide additional discussion justifying the structural assignments of cpds 27 and 29. Neither of these compounds appears to have been structurally characterized by NMR in the literature. In the <sup>1</sup>H NMR spectrum of 27, the signal at ~5.6 ppm appears to be a broad doublet. It is unclear why the authors have used the designation “multiplet”. In the <sup>1</sup>H NMR spectrum of 29, which is a racemic mixture, the lowest field signal (H attached to the nitrate-substituted C) should be a singlet, as it appears to be. Why is it described as a doublet?**
    - The structural assignments of 27 and 29 are in the body of the text (after figure 8) and bear distinct similarities to the related nitrate esters 23 and 24. The signal at 5.6 appears as a poorly resolved doublet-of-doublet-of doublets, i.e. multiplet. As with 24, this is due to long-range, 4-bond coupling.
    - For 29, the <sup>1</sup>H NMR signal is a doublet with the reported 1.6 Hz coupling constant. Again, this is due to apparent long-range, 4-bond coupling and is corroborated by gCOSY data.
  - 7. Figure 2: The authors should add the diol and aldehyde structures to this scheme. There is sufficient space and this gives the true picture of reaction products.**
    - Included diol and aldehyde structures in figure 2.
  - 8. p. 12, l. 15: The phrase, “. . .assigned to the methyne adjacent to the alcohol...” should be rewritten as “. . .assigned to the alcohol methyne carbon...” As written, the statement “adjacent to” is confusing. Where heteronuclear correlations are important in verifying structure, the 2D spectra should be added to the SI. As pointed out above, it would be helpful if all the NMR data were included in SI.**
    - Phrase was amended to “*assigned to the alcohol methyne carbon*”
    - gHSQC spectra for all compounds not previously characterized have been added to the SI.
  - 9. p. 12, l. 17: The rationale for assigning the quaternary carbon would be better explained by stating that no C–H cross peak was observed for the <sup>13</sup>C signal at 95.6 ppm in the HSQC experiment.**
    - Amended to “A tetrasubstituted carbon, with no correlations in the gHSQC, at 95.6 ppm was consistent with the tertiary nitrate ester.”
  - 10. p. 16, l. 12: “Epimer” is misused here. Platydiol (the name “platydiol” automatically designates the the di-endo geometry of the diol) has a plane of symmetry, and there are no optical isomers.**
    - Replaced “its epimer” with “its *trans* diastereomer.” We note that the *trans*-diastereomer is epimeric at one stereocenter from platydiol.
  - 11. p.17, l. 14: In discussing the structural verification of nitrate ester 27, it would be helpful to include the HSQC spectrum. As presented in the text, there is not enough data to be convincing regarding the structural assignment.**
    - gHSQC spectra for all compounds not previously characterized have been added to the SI.
  - 12. p. 17, bottom: The table of spectral data should have the heading at the top.**
    - table heading moved to the top.