



Simple and cost-effective synthesis of 5,7,8-deuterium-labelled 1,1,6-trimethyl-1,2-dihydronaphthalene (TDN-D₃)

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ABSTRACT

We report an economical and readily scalable synthesis of 1,1,6-trimethyl-1,2-dihydronaphthalene-5,7,8-D₃ (TDN-D₃), a novel deuterium-labeled specimen for stable isotope dilution assay. TDN-D₃ was obtained in four simple steps with 25% overall yield and > 99% chemical purity, starting from commercially available and inexpensive reagents. The described method does not require additional purification procedures (e.g. HPLC or even column chromatography), and the complete synthesis can be performed in three part-time working days.

Introduction

1,1,6-Trimethyl-1,2-dihydronaphthalene (TDN, **1**) belongs to C₁₃-norisoprenoids (Fig. 1), which represent one of the main groups of varietal aromas in wine. C₁₃-Norisoprenoids originate from the breakdown of carotenoids in grapes, and their content depends strongly on the grape varieties. Among the wines produced from international grape varieties, particularly high concentrations of TDN have been found in Riesling wines. Unlike β-ionone (**2**) and β-damascenone (**3**), TDN is rarely present in significant concentrations in young wines, but its content increases with wine aging. The recognition sensory threshold of 10–12 μg/L is often reached by TDN after three-five years of bottle storage [1]. The kerosene/petrol aroma of TDN enriches the Riesling wine bouquet and provides complexity. However, further accumulation of this compound above 70–80 μg/L (rejection threshold) can result in an overwhelming intensity of the kerosene/petrol odor [1]. Therefore, the analysis and management of TDN content in Riesling wines is of great importance to wine producers. Especially nowadays, when global warming tends to increase the breakdown of carotenoids and formation of TDN precursors in grapes at higher concentrations. As for TDN

management, various strategies are being studied including viticulture, winemaking and bottling aspects: e.g. Riesling clones and rootstock options [2], vine canopy and soil management [3–5], selection of fermenting yeasts [6], application of various bottle closures [7], bottling and wine storage conditions [8].

The determination of TDN in wine along with other wine C₁₃-norisoprenoids is usually carried out by GC-MS analysis. The application of isotopically labeled internal standards (stable isotope dilution assay (SIDA) approach) is state-of-the-art for this type of analysis. This improves the accuracy of quantification and reduces the wine matrix effects. Among the commercially available deuterated C₁₃-norisoprenoids, for example, β-ionone-D₃ is readily accessible, but this is not the case for deuterated TDN.

The pioneering work (to the best of our knowledge only one so far) on the synthesis of deuterium-labeled TDN and its use in SIDA-based analysis was published in 2019 by Peter Winterhalter's group [9]. According to their method, the introduction of deuterium labels into the TDN structure was achieved using toluene-D₈ as the starting compound. In this way, the six-step synthetic pathway combined with chromatographic purification allowed the preparation of 1,1-dimethyl-6-(methyl-

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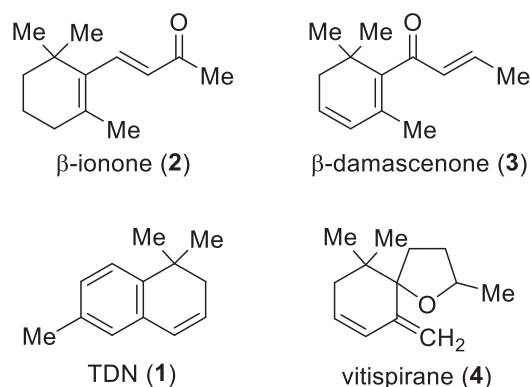


Fig. 1. Selected C_{13} -norisoprenoids responsible for wine aroma.

D_3 -1,2-dihydronaphthalene-5,7,8- D_3 (TDN- D_6 , **5**) (Scheme 1). The overall yield of the target TDN- D_6 was about 8% and 91% purity (by GC).

Taking into consideration the particularities and limitations of the proposed TDN- D_6 synthesis along with the fact [10] that isotopic analogs with three deuterium atoms are usually considered as effective internal standards for GC-MS analysis, we aimed at developing an alternative deuterium-labeled TDN specimen. At the same time, we strived for using readily accessible and inexpensive starting reagents, fewer synthetic steps, as well as higher overall yield of the final deuterium-labeled TDN. As a result, the target 1,1,6-trimethyl-1,2-dihydronaphthalene-5,7,8- D_3 (TDN- D_3 , **6**) was synthesized in four simple steps with 25% overall yield and > 99% chemical purity avoiding chromatographic purification procedures. The sample was stored in a glass vial flushed with Argon at -20°C and demonstrated no changes in the composition after one year (please, see Supplementary data). The isotopic composition of TDN- D_3 was also studied and discussed in the next section.

Results and discussion

We initiated our study with the literature survey on the deuteration methods of (hetero)aromatic compounds [11–17]. As a result, we found acid-mediated conditions to be the most appropriate and D_2O as a cheap and environmentally friendly source of deuterium atoms. At the same time, the substrate must tolerate these reaction conditions as well as expected heating.

Since TDN is unstable in strong acidic media because of the presence

of the conjugated exocyclic $C=C$ bond, its direct precursor ionene (**7**) turned out to be a suitable substrate for deuteration at the aromatic ring. In this way, D_2SO_4 and ionene were the reagents of choice.

Ionene (**7**) was obtained following the literature methods (Scheme 2) [18,19], whereas D_2SO_4 was prepared from SO_2Cl_2 and D_2O (Supplementary data). With these compounds in hand, we attempted to find the most favorable reaction conditions for the introduction of deuterium labels into the aromatic ring. We started our investigation by screening the D_2SO_4 concentration and reaction temperature (Table 1). The best outcome was obtained using 65% D_2SO_4 as the reaction medium at 90°C (Table 1, entry 4). Next, we determined the optimal ionene : D_2SO_4 ratio, which was 1 g of ionene (**7**) per 8 g of 65% D_2SO_4 (solution in D_2O). The H/D exchange occurred in a two-phase system eventually affording ionene- D_3 (**8**) in 78% isolated yield (Scheme 2).

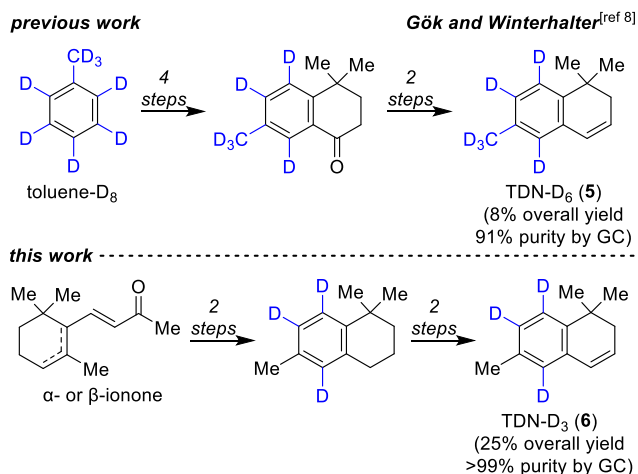
In the final step, ionene- D_3 (**8**) was converted into the target TDN- D_3 adopting previously described method [18]. Thus, **8** was subjected to benzoyl peroxide (BPO)-initiated radical bromination with NBS followed by the Hünigs base-induced dehydrobromination (Scheme 2). To our great delight, this step not only proceeded with higher yield (61% versus 56% for the non-deuterated counterpart) and purity (>99% versus 96%), but also resulted in extra depletion of protium content in the aromatic ring. These effects likely arise from the greater susceptibility of non-/partially deuterated ionene to participate in the side reactions while converting into TDN. Such particularities allow avoiding additional purification procedures and enables using the specimen directly from the synthetic laboratory. The GC-MS spectrum of the obtained TDN- D_3 is shown in Fig. 2.

Based on the more detailed GC-MS analysis, we established the isotopic composition of the specimen which was about as follows: TDN- D_3 (82%), TDN- D_2 (16%), TDN- D_1 (1%), and TDN (1%). Despite the incomplete deuteration of the aromatic core, our specimen meets the requirements of analytical standards since the ratio of its components is established and remained stable.

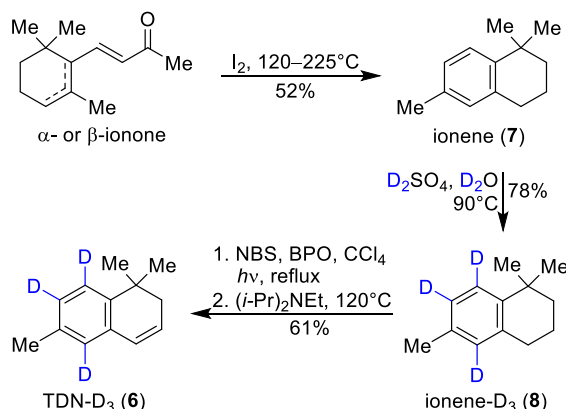
Finally, the stability of the deuterium labels was confirmed by adding the deuterated TDN standard to water, model wine and Riesling wine. After 24 h, one week, and one month of storage, no H/D exchange was observed, that confirms the suitability of TDN- D_3 as an internal standard in GC-MS analysis of wine.

Conclusion

To sum up, we have developed a simple, viable, and economically profitable synthesis of the novel deuterium-labeled TDN specimen (TDN- D_3) for stable isotope dilution assay. The synthetic pathway consists of four simple steps with the ordinary work-up procedures (no column chromatography or HPLC are required) and provides the target compound in 25% overall yield and > 99% chemical purity (isotopic composition: about 82% of TDN- D_3). The procedures are readily scaled



Scheme 1. Approaches to the synthesis of deuterium-labelled TDN.



Scheme 2. The synthesis of TDN- D_3 .

Table 1

Optimization of the deuteration reaction conditions for ionene (7) on the aromatic ring.

Entry	Conditions	Outcome
1.	50% D ₂ SO ₄ in D ₂ O, rt, 48 h	no reaction
2.	50% D ₂ SO ₄ in D ₂ O, 50 °C, 24 h	partial deuteration (~40%) ^a
3.	65% D ₂ SO ₄ in D ₂ O, 50 °C, 24 h	incomplete deuteration (~75%) ^a
4.	65% D ₂ SO ₄ in D ₂ O, 90 °C, 24 h	complete deuteration (>95%) ^a
5.	80% D ₂ SO ₄ in D ₂ O, 90 °C, 24 h	sulfonylation
6.	100% D ₂ SO ₄ , rt, few hours	decomposition

^a Controlled by ¹H NMR spectroscopy by monitoring the decrease in intensity of aromatic signals.

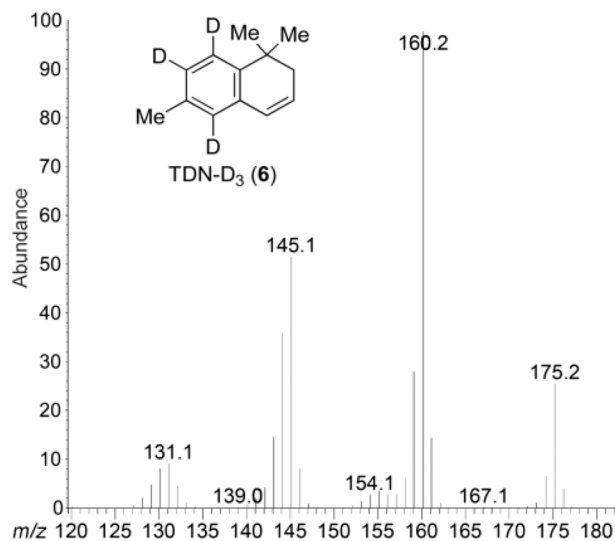


Fig. 2. Mass spectrum of TDN-D₃ (6).

up and allowed the preparation of multigram amount of ready-to-use TDN-D₃ specimen in three part-time working days.

The stability of the introduced deuterium labels makes TDN-D₃ a promising and inexpensive deuterium-labeled internal standard for GC-MS analysis of Riesling and other wines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Data availability

The analytical data is presented in the [Supplementary data file](#).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2023.154692>.

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