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Scalable synthesis of the aroma compounds d_6-β-ionone and d_6-β-cyclocitral for use as internal standards in stable isotope dilution assays

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ABSTRACT

C_{13} Norisoprenoids are important aroma compounds in wine, giving positive attributes to the overall wine aroma even when found at very low levels. β-Ionone is considered one of the most important aroma compounds giving violet, woody and raspberry aromas to wine, fruits and vegetables in which it is found. Due to its potent aroma at low levels, precise analytical methods are desired for its quantification. Stable isotope dilution assay (SIDA) is one of the most important of these methods but requires the use of isotopically labelled standards. Herein, we describe the scalable synthesis of d_6-β-ionone and d_6-β-cyclocitral, another aroma compound with smokey and fruity notes, starting from the relatively inexpensive deuterated starting material d_6-acetone.

Introduction

Aroma is considered to be one of the key factors in determining the quality of a wine [1–3]. Aroma compounds can be present in grapes during ripening as free volatile species or as non-volatile precursors [4]. Monoterpenes, norisoprenoids, benzenoids, and lactones are examples of classes of compounds that contribute to the varietal aroma of wine and are present in grapes as odourless precursors or glycosides [5]. C_{13} Compounds are the most abundant natural norisoprenoids and are thought to contribute favourable aroma in wines, even at very low concentrations [6–8]. C_{13}-Norisoprenoids constitute an essential component of the aroma profile in non-floral grapes such as Cabernet sauvignon [9], Syrah [10], Sauvignon blanc [11] and Pinot noir [7].

β-Ionone [(2,2,6-trimethyl-1,3-cyclohexen-1-yl)-3-buten-2-one] is considered as one of the most important volatile C_{13}-norisoprenoids from an aroma point of view [12]. The structure of this aroma compound consists of the megastigmane backbone with a keto group at C(9) (Fig. 1) [13]. β-Ionone and its derivatives are widely present in fruits, vegetables and grains containing β-carotene [14]. It was first isolated in 1929 from Boronia megastigma and identified in Tokaj Aszu wines made from white grapes by Schreier and co-workers in 1976 [12]. β-Ionone has been associated with violet, woody and raspberry sensory descriptors and has an odour threshold of 30 ng L^{-1} in water [15]. Studies have demonstrated that β-ionone and its derivatives can exhibit anti-inflammatory, antifungal, antibacterial, anti-proliferative, anti-metastatic and anti-cancer pharmaceutical properties [16].

Due to the important contribution of β-ionone to the aroma profile of wines, a number of sensitive analytical techniques have been developed for the quantification of this compound. These methods, with a focus on the wine matrix, include stir bar sorptive extraction with liquid desorption followed by large volume injection coupled to gas chromatography–quadrupole mass spectrometry (SBSE-LD/LVI-GC–qMS) [17], headspace solid phase microextraction (SPME) coupled with gas-chromatography/mass-spectrometry (GC–MS) [18], stable isotope dilution assay (SIDA) [18], stir bar sorptive extraction (SBSE) followed by a thermal desorption-gas chromatography–mass spectrometry analysis [19], automated headspace solid-phase microextraction (HS-SPME) combined with gas chromatography-ion trap/mass spectrometry (GC-IT/MS) [20], chromatography–olfactometry (GC-O) [21] and stir bar sorptive extraction gas chromatography mass spectrometry (SBSE-GC–MS) [7]. The development of SIDA has contributed significantly to improving the accuracy and ease of determination of trace concentrations of compounds by limiting variability related to the sample preparation and the matrix [18,22,23]. This

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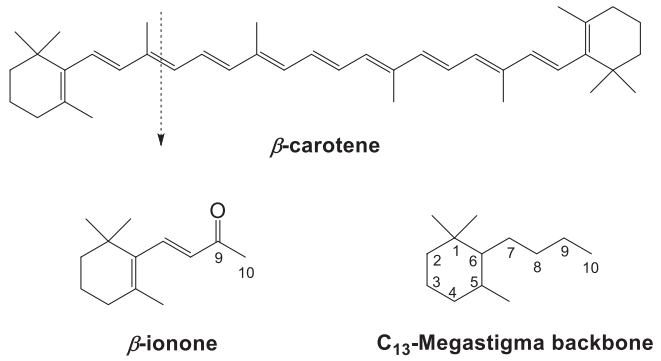


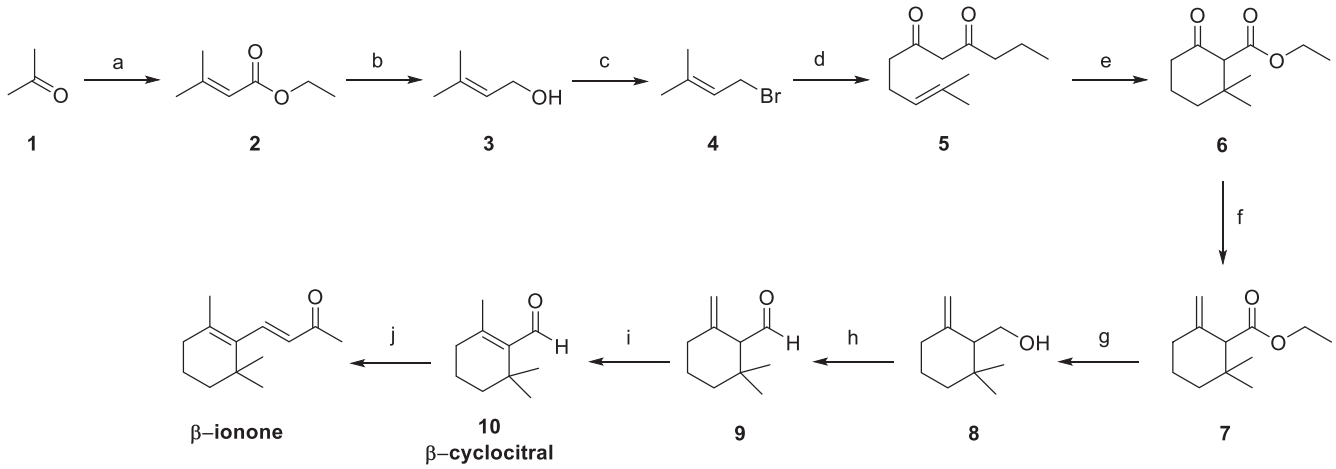
Fig. 1. β-Ionone structure.

approach is based on using isotopically labelled compounds as analytical standards. In previously reported synthetic methods, β-ionone has been converted to a deuterated analogue through the inclusion of three deuterium atoms at the C-10 methyl group [24]. This approach tends to require long reaction times and/or results in low yields. However, more importantly, the deuterium atoms at this position can be readily lost during mass spectrometry fragmentation, which poses a hindrance to some experimental designs [23,25]. In another reported method, the toxic and highly volatile reagent d_3-iodomethane is employed as the source of deuterium; this reaction results in deuteration of the methyl groups on the cyclohexene ring [26,27].

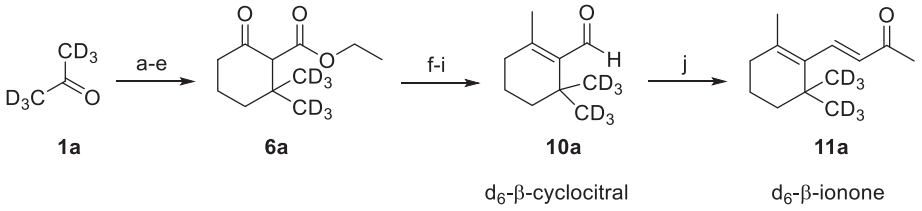
It was envisaged that deuterated β-ionone could be prepared using the inexpensive and readily available deuterated solvent d_6-acetone, which would have the added benefit of introducing six deuterium atoms. In addition, the use of d_6-acetone versus d_3-iodomethane as the source of deuteration is approximately ten times more cost efficient.

Result and discussion

The proposed synthesis was first investigated using unlabeled acetone to establish the methodology. Acetone (**1**) was converted to unsaturated ester **2** in 88% yield using triethyl phosphonoacetate (Scheme 1). Reduction of ester **2** with $LiAlH_4$ gave allylic alcohol **3**, which was immediately converted to dimethylallyl bromide **4** in 70% yield using HBr. The dianion of ethyl acetoacetate was formed using NaH and *n*-BuLi, which was reacted with dimethylallyl bromide **4** to give β-ketoester **5** in 60% yield [28]. Cyclisation of β-ketoester **5** was achieved easily using tin-(IV) chloride, providing cyclic β-ketoester **6** in 88% yield [29]. Following formation of the required cyclohexane ring in cyclic β-ketoester **6**, a Wittig reaction, using methylene(triphenyl)phosphorane, afforded methylenecyclohexane ester **7** in 85% yield [30]. Reduction of ester **7** using DIBAL-H provided primary alcohol **8** in a moderate 62% yield [31]. $LiAlH_4$ was less effective than DIBAL-H at yielding **7** from **8**; even when excess $LiAlH_4$ was used, starting material consistently remained. Alcohol **8** was oxidised using Dess-Martin periodinane (DMP) to give the desired aldehyde **9**. Rearrangement of the alkene in aldehyde **9** using DBU gave conjugated aldehyde **10**, which itself



Scheme 1. Synthesis of β-cyclocitral and β-ionone. Reagents and conditions: (a) triethyl phosphonoacetate (1.3 equiv.), NaH (1.2 equiv.), THF, 0 °C, 24 h, 88%; (b) $LiAlH_4$ (1.5 equiv.), Et_2O, 0 °C, 3 h, 72%; (c) HBr 48% (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 70%; (d) NaH (2 equiv.), ethyl acetoacetate (1 equiv.), 1.6 M *n*-BuLi (1.6 equiv.), THF, 0 °C, 21 h, 60%; (e) $SnCl_4$ (1.6 equiv.), CH_2Cl_2, 0 °C, 24 h, 88%; (f) KO^{t}Bu (2.3 equiv.), $Ph_3P^+MeBr^-$ (2.2 equiv.), THF, 60 °C, 23 h, 85%; (g) 1 M DIBAL-H (2.5 equiv.), CH_2Cl_2, −78 °C, 2 h, 62%; (h) DMP (1.1 equiv.), CH_2Cl_2, rt, 2 h, 75%; (i) DBU (3 equiv.), CH_2Cl_2, 0 °C, 24 h, 60%; (j) 10% aqueous KOH (8 equiv.), acetone, 60 °C, 22 h, 40%.



Scheme 2. Synthesis of d_6-β-ionone. Reagents and conditions; (a) triethyl phosphonoacetate (1.3 equiv.), NaH (1.2 equiv.), THF, 0 °C, 24 h, 85%; (b) $LiAlH_4$ (1.5 equiv.), Et_2O, 0 °C, 3 h, 77%; (c) HBr 48% (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, 69%; (d) NaH (2 equiv.), ethyl acetoacetate (1 equiv.), 1.6 M *n*-BuLi (1.6 equiv.), THF, 0 °C, 21 h, 58%; (e) $SnCl_4$ (1.6 equiv.), CH_2Cl_2, 0 °C, 24 h, 86%; (f) KO^{t}Bu (2.3 equiv.), $Ph_3P^+MeBr^-$ (2.2 equiv.), THF, 60 °C, 23 h, 82%; (g) 1 M DIBAL-H (2.5 equiv.), CH_2Cl_2, −78 °C, 2 h, 68%; (h) DMP (1.1 equiv.), CH_2Cl_2, rt, 2 h, 71%; (i) DBU (3 equiv.), CH_2Cl_2, 0 °C, 24 h, 65%; (j) 10% aqueous KOH (8 equiv.), acetone, 60 °C, 22 h, 38%.

is a well-known aroma compound, commonly known as β-cyclocitral. Finally, an aldol reaction of **10** with acetone, afforded the desired β-ionone in 40% yield in a single step [32]. Whilst this yield is only moderate it is a significant improvement on previously reported procedures which have used three steps to synthesise **11** from **10** [33,34].

With the synthesis of β-ionone achieved, the same procedure was subsequently performed for the synthesis of deuterated β-ionone. Using d_6-acetone **1a** rather than acetone **1** gave d_6-β-ionone (Scheme 2).

In conclusion, a robust, easily scalable and efficient synthetic procedure for the syntheses of d_6-β-ionone and d_6-β-cyclocitral has been established. These isotopically labelled analogues can be used as analytical standards for accurate quantitative analyses of these important aroma compounds.

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.

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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.2020.152642.

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