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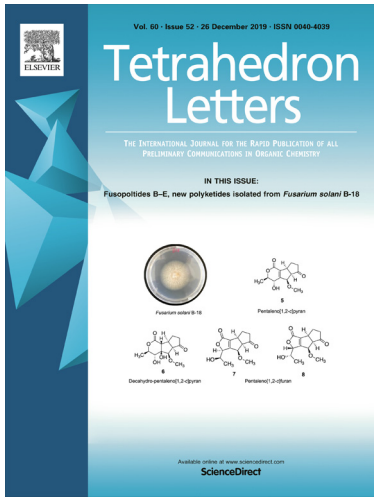


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# A convenient synthesis of amino acid-derived precursors to the important wine aroma 3-sulfanylhexan-1-ol (3SH)

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**Abstract**

A convenient, straightforward synthesis of the important amino acid-derived aroma precursors, 3-*S*-cysteinylhexan-1-ol (Cys-3SH) and 3-*S*-glutathionylhexan-1-ol (GSH-3SH) from commercially available butan-1-ol is reported. The versatility of this approach to include deuterium labelling is also demonstrated.

**Keywords**

Wine aroma; Aroma precursors; 3-sulfanylhexan-1-ol (3SH); Isotopic labelling.

## Introduction

The varietal thiol 3-sulfanylhexan-1-ol (3SH, **1**) is an important aroma compound responsible for the desirable fruity notes associated with white wines, particularly Sauvignon Blanc. Two key amino acid-derived precursors to **1** have previously been identified, namely 3-*S*-cysteinylhexan-1-ol (Cys-3SH, **2**) and 3-*S*-glutathionylhexan-1-ol (GSH-3SH, **3**).[1,2] The bioconversion of these amino acid-derived precursors, **2** and **3**, to 3SH (**1**), which is known to occur during fermentation, is therefore of considerable interest as it becomes desirable to maximise the concentration of 3SH (**1**) in wine for its sought after sensory properties. Studies of these transformations often require the use of deuterated analogues followed by mass spectrometry detections.[3]

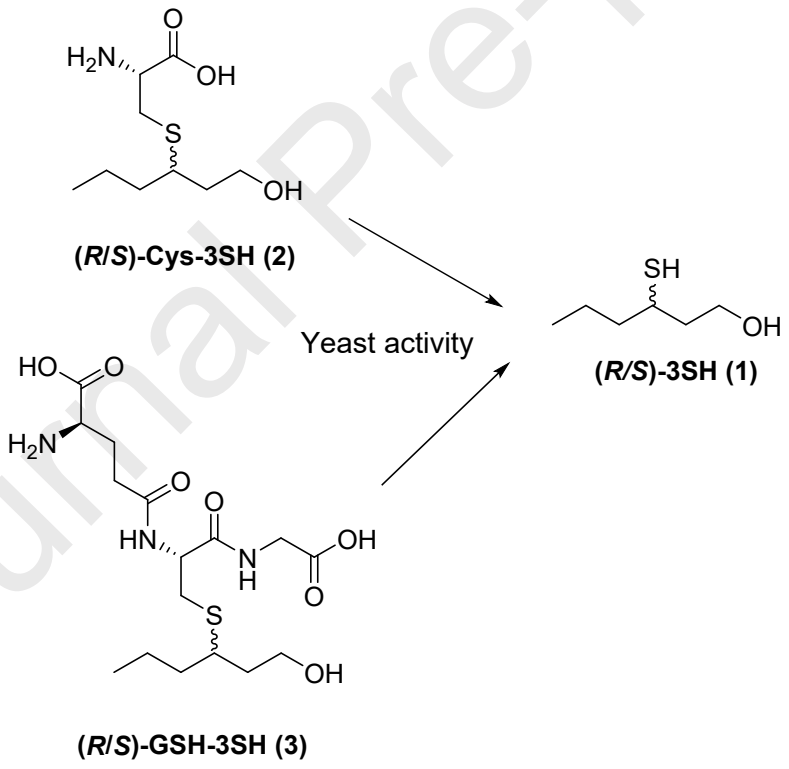



**Figure 1.** Structures of the amino acid-derived precursors to the aroma compound **1**.

Previous approaches to the synthesis of these amino acid-derived precursors involve the conjugate addition of glutathione or cysteine to a very reactive species, hex-2-enal (**4**).[1,2,4,5] In addition to the difficulties arising from the susceptibility of volatile **4** to readily oxidise, it has been documented that the addition reaction does not stop at the mono-adduct but proceeds to the di-adduct giving an unwanted side product containing a thiazolidine moiety **5** and under some conditions thiazepane **6** (Fig. 2).[5,6]

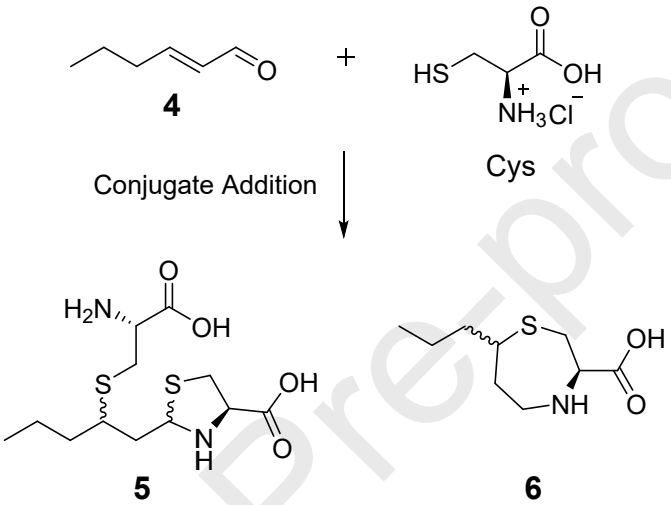



**Figure 2.** Structures of reported byproducts obtained during the conjugate addition of **4** and cysteine.[5,6]

Changes to this approach involved the inclusion of protecting groups on cysteine before the conjugate addition with hex-2-enal (**4**), to prevent the unwanted cyclisation.[7,8] However, this adds further synthetic steps. We encountered difficulties with the reproducibility of the aforementioned strategies to obtain GSH-3SH (**3**), as did Roland and co-workers.[9] Therefore, in an attempt to improve the reproducibility of the syntheses of these compounds, avoiding the problematic use of hex-2-enal (**4**) and protecting amino acid derivatives, it was envisaged that the two aroma precursors could be prepared from a common starting material derived from commercially available butan-1-ol (**7**). This approach follows those of Luisier and co-workers,[10] Pardon and co-workers,[4] and Duhamel and co-workers,[11] where the intermediate

ethyl hex-2-enoate (**8**) has been employed, and can provide access to both aroma precursors with the inclusion of up to eight deuterium labels, depending on the degree of deuteration of butan-1-ol (**7**) (Fig. 3).

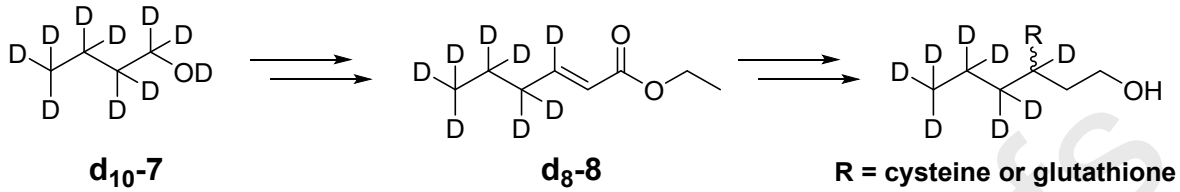



**Figure 3.** Proposed pathway to deuterated Cys-3SH (**2**) and GSH-3SH (**3**) from commercially available deuterated butan-1-ol (**7**).

## Results and Discussion

Butanal (**9**) was obtained from the Swern oxidation of butan-1-ol (**7**) using oxalyl chloride and DMSO and the crude aldehyde **9**, retained in the reaction solvents, was used immediately without further purification due to its high volatility. Butanal (**9**) was then converted to ethyl (*E*)-hex-2-enoate in 88% yield (from butan-1-ol), through a Wittig reaction using $Ph_3P{=}CHCO_2Et$.[11] This gave exclusive formation of the desired (*E*)-alkene product, which was confirmed by NMR analysis. In contrast to hex-2-enal (**4**), (*E*)-hex-2-enoate (**8**) could be easily purified using normal-phase silica gel chromatography under ambient conditions as it is not readily oxidised.

A conjugate addition was then employed to add the desired amino acid to α,β-unsaturated ester **8** using similar reported reaction conditions,[10] for the synthesis of Cys-3SH (**2**). However, difficulties were encountered when the reported purification procedure was followed. Purification was found to be improved through the use of reversed-phase C18 column chromatography using pre-packed cartridges, especially when working on smaller scales.

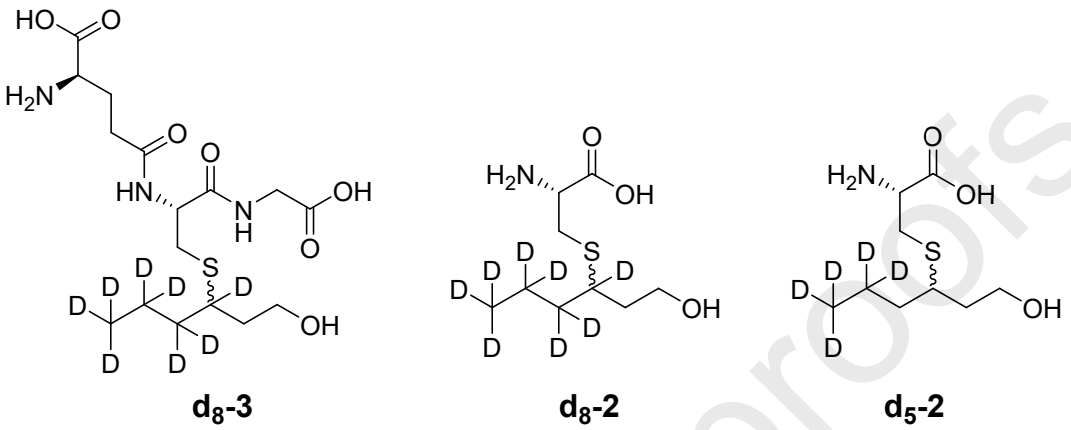
Addition of single enantiomers of cysteine or glutathione to ethyl (*E*)-hex-2-enoate (**8**) gave an inseparable mixture of two diastereomers (of **10** and **11**), in an approximately 1:1 mixture in both cases, as determined by NMR analysis.

The reduction of an ester in the presence of a carboxylic acid moiety is potentially problematic, particularly when the compound of interest has poor solubility in organic solvents. The most commonly used reducing agents, sodium borohydride and lithium aluminium hydride, exhibit different reactivities towards the reduction of esters; the former is often unreactive towards esters, while reduction of both the ester and the carboxylic acid is generally observed with the latter.[10] However, additives have been shown to enhance the reactivity of $NaBH_4$ towards esters,[12,13] and a simple one-pot sodium borohydride-MeOH system in THF has been shown to be effective for a range of different esters.[13]

This methodology was therefore employed and proved to be successful in selectively reducing the ethyl esters of both Cys-3SH and GSH-3SH to their desired alcohol functionality. This approach utilised less expensive regents and solvents than those employed previously to reduce **8**.[10] By employing reversed-phase C18 column chromatography, using pre-packed cartridges, to purify the final products, the issues with removing the inorganic salts from the products were eliminated.

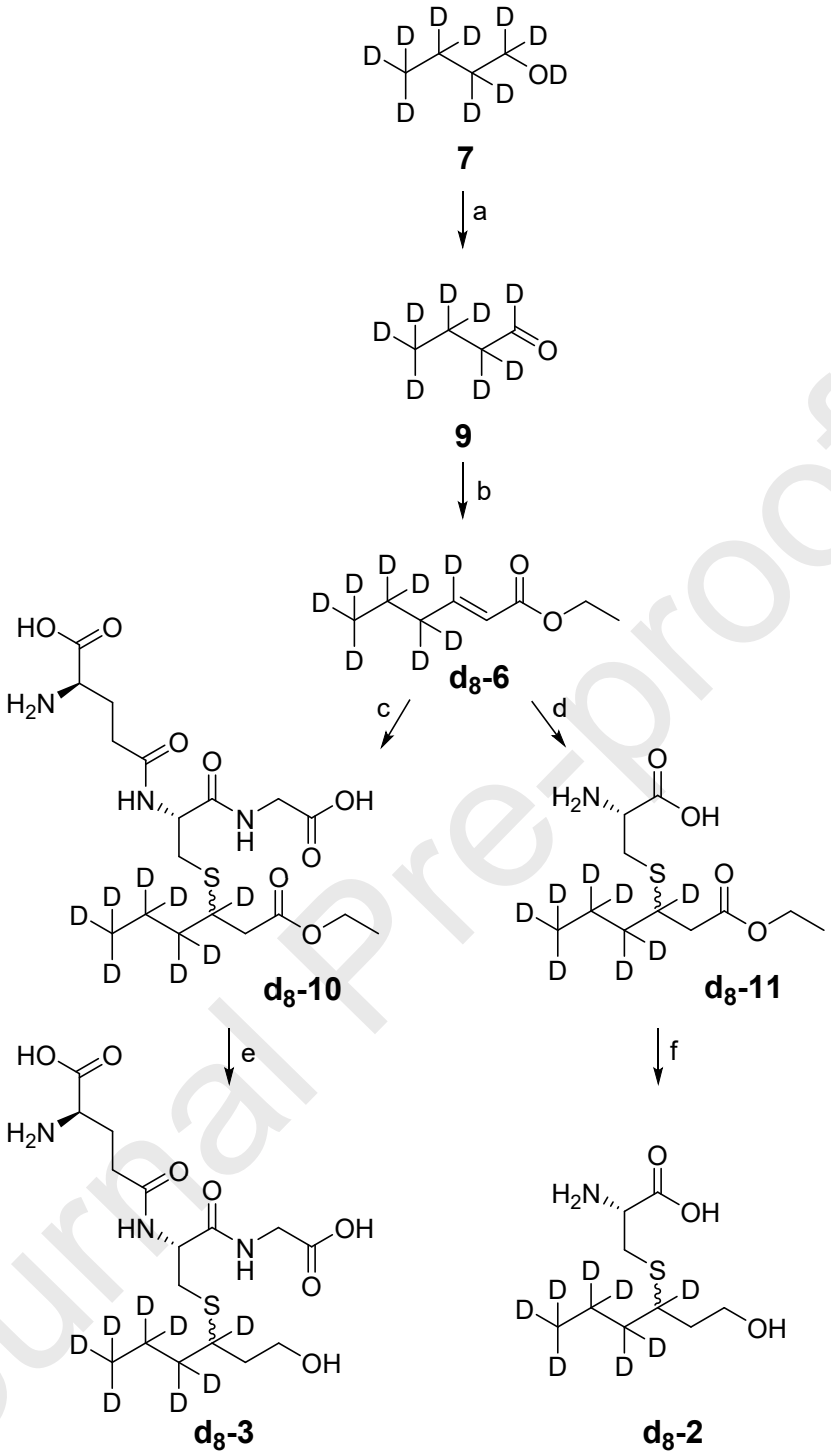
Following optimisation of the above synthetic procedures, they were then used to prepare $d_8$-Cys-3SH (**$d_8$-2**) and $d_8$-GSH-3SH (**$d_8$-3**), and $d_5$-Cys-3SH (**$d_5$-2**), from $d_{10}$-butan-1-ol and 3,3,4,4,4-$d_5$-butan-1-ol respectively (Fig. 3). The general reaction pathway, conditions and yields (for both labelled and unlabelled compounds) are shown in Scheme 1. All products and intermediates were fully characterised using NMR spectroscopy and high resolution mass spectrometry. $^1$H NMR analysis of the deuterated deuterated final products provided no evidence that unwanted deuterium-proton exchange occurred during the synthetic

transformations. Therefore, **$d_8$-2**, **$d_8$-3** and **$d_5$-2** retain the >99% labelling found in the commercial precursors.




**$d_8$-3** **$d_8$-2** **$d_5$-2**

**Figure 3.** Structures of the deuterated analogues prepared of precursors **2** and **3**.




**Scheme 1** Synthesis of $d_8$-Cys 3SH **$d_8$-2** and $d_8$-GSH-3SH **$d_8$-3.** Reagents and conditions; (a) oxalyl chloride, DMSO, $CH_3Cl$, −78 °C; (b) $Ph_3P{=}CHCO_2Et$, $CH_3Cl$, room temperature, 50% yield over two steps; (c) glutathione; $H_2O$, pH 7.5, 3 days, room temperature, 44% yield; (d) cysteine; $H_2O$, pH 7.5, 3 days, room temperature, 43% yield; (e) $NaBH_4$, MeOH, THF, reflux, 1 h, 49% yield; (f) $NaBH_4$, MeOH, THF, reflux, 1 h, 47% yield. Yields for synthetic steps to

the unlabelled precursors, **2** and **3**, were as follows; (b) 88% over two steps; (c) 50%; (d) 69%; (e) 33%; (f) 48%. Yields for synthetic steps to **$d_5$-2** were as follows; (b) 62% over two steps; (c) 42%; (e) 58%.

In conclusion, a convenient, versatile and reproducible synthetic procedure to access the important aroma precursors Cys-3SH (**2**) and GSH-3SH (**3**) has been established. Three new deuterated analogues of these precursors were synthesised and fully characterised using this methodology, $d_5$-Cys-3SH, $d_8$-Cys-3SH and $d_8$-GSH-3SH. Isotopically labelled analogues of the natural aroma precursors, allow for mass spectrometry based stable isotope dilution analyses (SIDA) to be developed. In this case, such analogues can be employed in studies to better understand the accumulation of these precursors in different grape and grapevine tissues as well as to study their bioconversion into the desirable wine aroma compound, 3-sulfanylhexan-1-ol (3SH).

**Acknowledgements**

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**Supplementary Information**

Full experimental procedures, characterisation and NMR spectra can be found in the Supplementary Information document.

**References**


1. Tominaga T, Peyrot des Gachons C, Dubourdieu D. *J Agric Food Chem*. 1998; 46: 5215–5219.
2. Peyrot des Gachons C, Tominaga T, Dubourdieu D. *J Agric Food Chem*. 2002; 50: 4076–4079.
3. Roland A, Schneider R, Razungles A, Cavelier F. *Chem Rev*. 2011; 111: 7355–7376.
4. Pardon KH, Graney SD, Capone DL, Swiegers JH, Sefton MA, Elsey GM. *J Agric Food Chem*. 2008; 56: 3758–3763.
5. Starkenmann C. *J Agric Food Chem*. 2003; 51: 7146–7155.
6. Wakabayashi H, Wakabayashi M, Eisenreich W, Engel K-H. *J Agric Food Chem*. 2004; 52: 110–116.
7. Grant-Preece PA, Pardon KH, Capone DL, Cordente AG, Sefton MA, Jeffery DW, Elsey GM. *J Agric Food Chem*. 2010; 58: 1383–1389.
8. Roland A, Schneider R, Le Guerneve C, Razungles A, Cavelier F. *Food Chem*. 2010; 121: 847–855.
9. Roland A, Schneider R, Razungles A, Le GC, Cavelier F. *J Agric Food Chem*. 2010; 58: 10684–9.
10. Luisier J-L, Veyrand J, Piantini U. *Chim Int J Chem*. 2007; 61: 533–535.
11. Duhamel N, Piano F, Davidson SJ, Larcher R, Fedrizzi B, Barker D. *Tetrahedron Lett*. 2015; 56: 1728–1731.
12. Periasamy M, Thirumalaikumar M. *J Organomet Chem*. 2000; 609: 137–151.
13. da Costa JCS, Pais KC, Fernandes EL, de Oliveira PSM, Mendonca JS, de Souza MVN, Peralta MA, Vasconcelos TRA. *Arkivoc*. 2005; 2006: 128.


Highlights

- Convenient and reproducible synthetic route to Cys-3SH and GSH-3SH
- Method easily adapted to allow for the preparation of deuterium-labelled compounds
- Straightforward purification of products using SPE pre-packed C18 cartridges

**Declaration of interests**

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: