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Identification of a precursor to naturally occurring β-damascenone†

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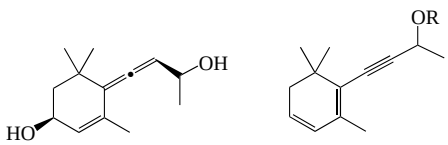
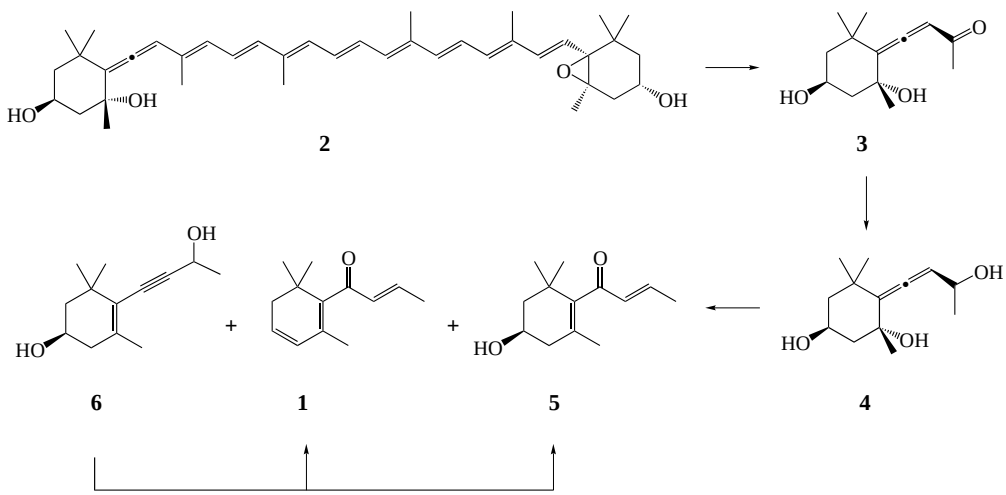
Abstract—9-Hydroxymegastigma-3,5-dien-7-yne **8a** was synthesised and shown to be identical to an intermediate found in the acid-catalysed conversion of 3,5,9-trihydroxymegastigma-6,7-diene **4** to β-damascenone **1**, 3-hydroxydamascone **5** and megastigma-5-en-7-yne-3,9-diol **6**. When subjected to acid hydrolysis, **8a** produced β-damascenone **1**, in high yield. Importantly, the hydrolysate was completely free of 3-hydroxydamascone **5**.

1. Results and discussion

β-Damascenone **1** is one of the most important flavour compounds known to science;[1] it is found in many fruit and vegetable products, and tonne quantities are produced commercially for the perfume and flavouring industries. It is believed to be formed in nature from the hydrolytic breakdown of complex secondary metabolites[2–6] derived from carotenoids such as neoxanthin **2**. Recent studies of wine grapes have indicated that β-damascenone **1** can be formed in vivo, as shown in Scheme 1.



7 **8a**, R=H **8b**, R=Ac



2 **3** **6** **1** **5** **4**

Scheme 1.

Keywords: β-damascenone; flavour precursors; wine; carotenoid metabolites.

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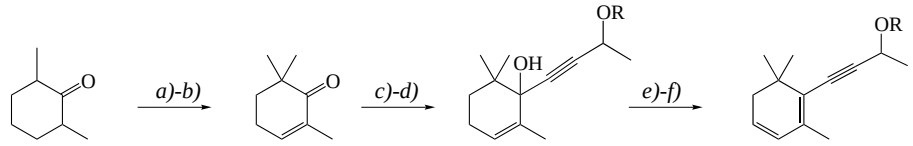


9 **10** **11a**, R=H **11b**, R=Ac **8a**, R=H **8b**, R=Ac

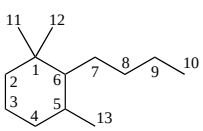
Scheme 2. (a) LDA, MeI (84%); (b) i. Br_2, ii. pyr, Δ (79%); (c) LiC≡CCH(CH_3)OLi (99%); (d) Ac_2O, THF, Δ (88%); (e) P_2O_5/Celite, $PhCH_3$, Δ (54%); (f) KOH (78%).

Both the so-called 'grasshopper ketone' **3**[7] and the allenic triol **4**[6] have been identified as components of wine grape extracts treated with a glycosidase enzyme preparation. Hydrolytic studies[8] have shown that triol **4** is converted rapidly to the products **1**, **5** and **6** at room temperature and pH 3.0 in an aqueous environment. Furthermore, the ratio of these three products in at least some grape samples[9] was broadly similar to that found in the hydrolysates of the triol **4**. β-Damascenone **1**, 3-hydroxydamascone **5** and enyne diol **6** are apparently formed by competing pathways from the triol **4**, as no significant interconversion of these products takes place at room temperature. The diol **6** (and also its C_9 glucopyranoside)[‡] will form both **1** and **5** extremely slowly under these conditions, and therefore may generate β-damascenone **1** in wine over several years of bottle ageing, but is not a significant precursor to **1** in either grapes or young wines.

In the early stages of hydrolysis, two intermediates in the conversion of **4** to **1**, **5** and **6** were observed by GC/MS and tentatively identified as **7** and **8a**. The latter has also been reported (without presentation of evidence) as a constituent of rum.[10] We now wish to report the successful synthesis and characterisation of **8a** and its role as an intermediate in the formation of β-damascenone.

The synthesis of **8a** was accomplished in six steps (Scheme 2) from 2,6-dimethylcyclohexanone **9**. Methylation, then bromination followed by dehydrobromination gave the enone **10**, which underwent reaction with the dilithio derivative[11] of 2-hydroxybut-3-yne. Acetylation of the secondary hydroxy group in **11a** gave **11b**, which was dehydrated with P_2O_5 on Celite.[12] Treatment of **8b**[13] with potassium hydroxide under mild conditions produced the free alcohol **8a**,[14] which was shown by GC/MS (retention time, fragmentation pattern and co-injection) to be identical with one of the two compounds observed as intermediates in the hydrolysis of the triol **4**.

‡ The numbering scheme is that employed for the megastigmane skeleton.



Hydrolysis of **8a** was effected in model wine,[15] and produced β-damascenone **1** as the major product (>90%) by GC/MS. The absence of 3-hydroxydamascone **5** and the enyne diol **6** in the hydrolysate confirms the hypothesis that **1**, **5** and **6** are formed from the triol **4** by competing pathways.

Compounds **3**–**6** are known to accumulate in grapes and other fruits as glycoconjugates. Studies of the reactivity of allylic and propargyllic alcohols and their corresponding β-D-glucopyranosides have shown that the glucopyranosyl moiety retards the acid-catalysed hydrolysis of these compounds. Thus, in plant products containing glycoconjugated forms of the allenic triol **4**, the position of glycoconjugation has the capacity to steer hydrolysis either towards or away from β-damascenone formation by promoting or suppressing formation of the intermediate **8a** in competition with other products.[4,5]

Acknowledgements

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13. Selected spectral data for (**8b**): ^{1}H NMR ($CDCl_3$, 300 MHz), 5.88–5.76 (2H, m, H_3, H_4); 5.66 (1H, q, $J=6.7$ Hz, H_9); 2.10–2.07 (2H, m, H_2); 2.08 (3H, s, OAc); 1.92 (3H, br s, H_{13}); 1.54 (3H, d, $J=6.7$ Hz, H_{10}); 1.06 (3H, s, H_{11}); 1.05 (3H, s, H_{12}). ^{13}C NMR ($CDCl_3$, 75.5 MHz), 169.9 (CO); 137.4, 127.6, 126.8, 122.6 (C_3, C_4, C_5, C_6); 94.7, 83.2 (C_7, C_8); 61.3 (C_9); 38.2 (C_2); 32.7 (C_1); 26.9, 26.9 (C_{11}, C_{12}); 21.8 (C_{10}); 21.2 (CH_3CO); 20.5 (C_{13}).
14. Selected spectral data for (**8a**): 5.86–5.76 (2H, m, H_3, H_4); 4.75 (1H, q, $J=6.6$ Hz, H_9); 2.11–2.07 (2H, m, H_2); 1.93 (3H, br s, H_{13}); 1.52 (3H, d, $J=6.6$ Hz, H_{10}); 1.06 (6H, s, H_{11}, H_{12}). ^{13}C NMR ($CDCl_3$, 75.5 MHz), 136.5, 127.6, 126.4, 122.9 (C_3, C_4, C_5, C_6); 98.5, 82.1 (C_7, C_8); 58.8 (C_9); 38.2 (C_2); 32.6 (C_1); 26.8, 26.8 (C_{11}, C_{12}); 24.7 (C_{10}); 20.3 (C_{13}).
15. Model wine: 10% (v/v) EtOH in H_2O, buffered at pH 3.0. Hydrolysis was conducted at 45°C overnight.