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Precursors to oak lactone: synthesis of gallate ester derivatives of 3-methyl-4-hydroxyoctanoic acid

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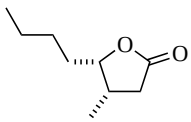
Abstract—(3*R*,4*R*- and 3*S*,4*S*)-3-Methyl-4-(3′-*O*-methylgalloyloxy)octanoic acid (**2b**), the corresponding methyl ester (**2c**) and the straight galloyl derivative, (3*R*,4*R*- and 3*S*,4*S*)-3-methyl-4-galloyloxyoctanoic acid (**2a**) were synthesised from *cis*-oak lactone (**1**). Analysis by TLC and mass spectrometry established that the original assignment of structure (**2c**) to a methylated natural oak component was in error.

Results and discussion

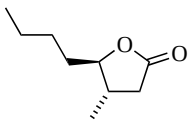
The 4*S*,5*S*-(*cis*) and 4*S*,5*R*-(*trans*) isomers of 5-*n*-butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone (**1**), also known as 'oak lactone' or 'whisky lactone', are natural oak components, extracted into wine and spirits during oak barrel maturation. Of the two, the *cis*-isomer is considered to be the more important in sensory terms, and is thought to impart coconut and vanilla-like nuances to wine.[1,2] Despite their importance, the origin of these compounds remains unclear. *cis*- and *trans*-Oak lactone are already present in green oakwood, but additional quantities of these compounds can be generated in the wood during the drying (seasoning) and coopering processes,[1] in model wine oak extracts heated to 50°C,[3] and even in the injector block of a gas chromatograph during analysis of oak extracts.[2]

These observations indicate the presence of one or more precursor forms of oak lactone in oak. Several potential precursors have been observed: Otsuka et al.[4] isolated, from oak wood powder, a compound which they termed a precursor to oak lactone. On the basis of rather limited degradation studies, they assigned a structure to this compound. Although the structure of the natural species was claimed as (**2b**), the compound which was actually isolated was thought to be the corresponding methyl ester (**2c**), formed as an artefact of the isolation process. Despite the limited evidence presented, this compound as a precursor to oak lactone has gained credence through literature citation.[1]

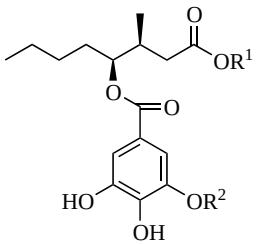
More recently Tanaka and co-workers[5] isolated several interesting compounds from the wood of *Platycarya strobilacea*, a member of the walnut (Juglandaceae)



cis-**1**



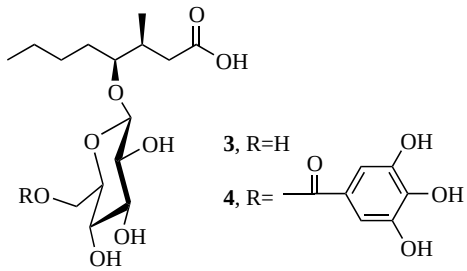
trans-**1**



2a, R^1=H R^2=H

2b, R^1=H R^2=Me

2c, R^1=Me R^2=Me



3, R=H

4, R=

Keywords: oak lactone; flavour precursors; wine; gallate esters.

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family of trees. Among this collection of compounds were two which could conceivably serve as precursors to oak lactone, viz. (**3**) and (**4**). Hydrolysis of the glycosides (**3**) and (**4**), albeit under strongly acidic conditions, did indeed produce the (4*S*,5*S*) *cis*-oak lactone.[5,6] The identification of the galloyl glucoside (**4**) in this wood, and its subsequent isolation from oak[6] is of particular interest, as the structural similarity to (**2b**) allows the possibility of the misidentification of this compound by Otsuka et al. Our interest was aroused by this potential ambiguity and, therefore, we set out to synthesise (**2b**) and (**2c**) in an unambiguous fashion. Because of the possibility that *O*-methylation on the aromatic ring might also have occurred as an artefact of the isolation by Otsuka et al., the straight gallate ester (**2a**) was also synthesised; 3-*O*-methylgallic acid derivatives are relatively uncommon in nature, whereas gallate esters are major constituents of oak and other woods.

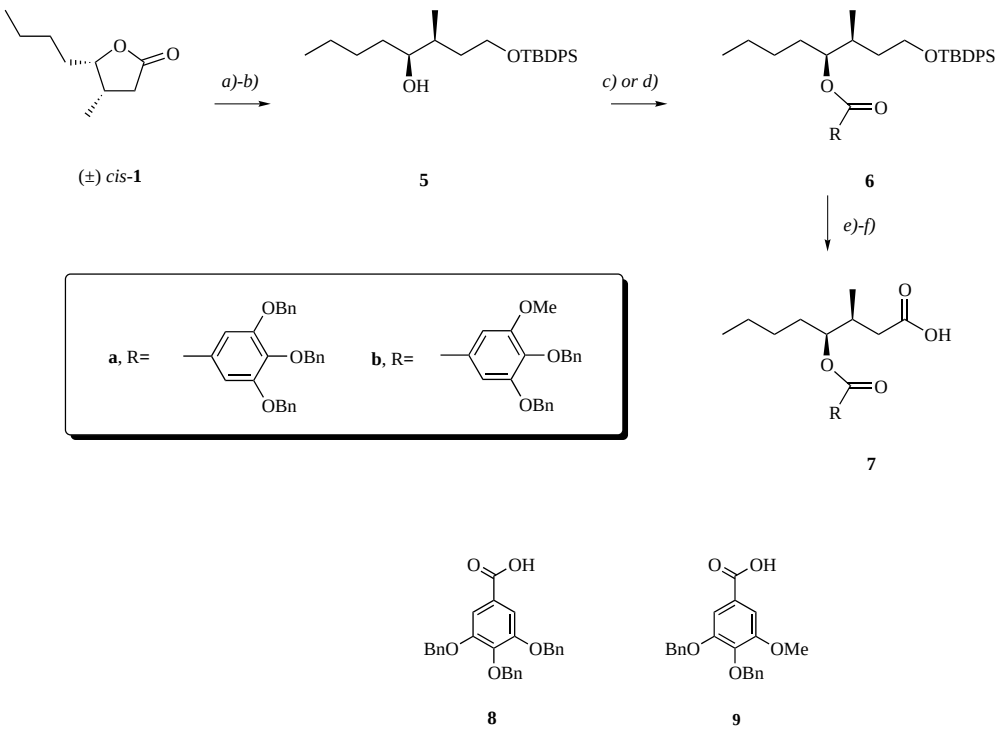
Initial attempts involved ring-opening of the oak lactone and protection of the acid functionality as its isopropyl ester.[7] Our attempts at coupling this ester with various substituted gallic acid chlorides were, on the whole unsuccessful; the major problem appeared to be the overwhelming preference for the ester to undergo relactonisation to the oak lactone, even when strongly buffered the oak lactone was the major product. To overcome this lactonisation problem, an alternative strategy was employed (Scheme 1) which involved initial reduction of the ester function with lithium aluminium hydride.[8] Coupling of the protected species (**5**) with the gallic acid derivatives (**8**) and (**9**) in the presence of DCC and 4-DMAP[9] gave (**6a**) and (**6b**), respectively. Deprotection with fluoride regenerated the primary alcohols which were oxidised to the acids by the use of the free radical TEMPO and bis-acetoxyiodobenzene (BAIB) in aqueous acetonitrile.[10] The acid (**7b**) was esterified to give the corresponding methyl ester in 97% yield. Removal of the benzyl protecting groups to produce the desired gallic acid derivatives (**2a–c**)[11] was effected in excellent yields by hydrogenolysis over palladium in acetone.[12,13]

Because of the absence of any definitive structural evidence in the original report concerning the role of (**2b**) as precursor to oak lactone, it was necessary to repeat the TLC work of Otsuka et al. on the corresponding methyl ester (**2c**) as this was the crux of his argument. The results are collected in Table 1. Notwithstanding the difficulty in reproducing exactly the conditions reported by Otsuka,[4] it is clear that the R_f values for the compound reported by him as (**2c**), are not in agreement with those of the authentic sample

Table 1. Comparison of R_f values between this work and Ref. 4

	This work		Otsuka Ref. 4	
	Gallic acid	**2c**	Gallic acid	**2c**
Solvent system A	0.39	0.64	0.51	0.40
Solvent system B	0.13	0.69	0.25	0.19

A: 40:10:2:10 (benzene:dioxane:acetic acid:methanol).
B: 50:30:20:0.2 (chloroform:ethyl acetate:methanol:1N NH_4OH).



Scheme 1. *Reagents and conditions*: (a) $LiAlH_4$, THF, Δ, 97%; (b) TBDPSCl, pyr., 92%; (c) DCC, DMAP, **8**, CH_2Cl_2, 88%; (d) DCC, DMAP, **9**, CH_2Cl_2, 96%; (e) TBAF, THF (**a** 88%, **b** 94%); (f) TEMPO, BAIB, CH_3CN/H_2O (**a** 84%, **b** 92%).

prepared in this study. In both solvent systems the authentic (**2c**) elutes much more rapidly than gallic acid, whereas in the original report the converse was found to be the case. In addition to the non-congruence of the TLC data, the mass spectral data for the authentic sample in no way matches the reported spectrum. The spectrum of authentic (**2c**) is dominated by ions due to aromatic fragments; the base peak (m/z 167) for this compound appears as a very minor peak in the published spectrum, whereas the published base peak (m/z 99) does not appear at all in the spectrum of authentic (**2c**).

These results indicate that the compound isolated from oakwood by Otsuka et al.[4] did not have the structure (**2c**) as proposed by these authors. It is possible that their compound was an artefactually methylated analogue of the known oak compound (**4**), or was some other galloylated derivative of 3-methyl-4-hydroxyoctanoic acid. The status of the simple gallate ester (**2a**) as a possible oak component is under investigation.

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11. *Selected spectral data for* ***2a***: ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.18 (2H, s, ArH), 5.07 (1H, ddd, $J=8.5$, 4.7 and 3.8 Hz, H_4), 2.46 (1H, dd, $J=15.2$ and 5.4 Hz, H_{2a}), 2.39–2.28 (1H, m, H_3), 2.20 (1H, dd, $J=15.2$ and 8.1 Hz, H_{2b}), 1.78–1.64 (2H, m, H_5), 1.44–1.28 (4H, m, H_6, H_7), 1.08 (3H, d, $J=6.8$ Hz, Me), 0.91 (3H, t, $J=6.7$ Hz, H_8); ^{13}C NMR (acetone-d_6, 75.5 MHz): δ 173.2 (C_1), 165.9 (C=O), 145.4, 138.1, 121.5, 109.2 (Ar), 76.4 (C_4), 37.8 (C_2), 33.9 (C_3), 31.2 (C_5), 28.3 (C_6), 22.7 (C_7), 14.3 (Me), 13.8 (C_8).
    Selected spectral data for ***2b***: ^{1}H NMR (acetone-d_6): δ 7.29 (1H, d, $J=1.8$ Hz, ArH), 7.23 (1H, d, $J=1.8$ Hz, ArH), 5.10 (1H, ddd, $J=8.6$, 4.6 and 3.8 Hz, H_4), 3.91 (3H, s, OMe), 3.35 (3H, br s, OH), 2.48 (1H, dd, $J=15.2$ and 5.5 Hz, H_{2a}), 2.40–2.30 (1H, m, H_3), 2.20 (1H, dd, $J=15.2$ and 8.0 Hz, H_{2b}), 1.82–1.64 (2H, m, H_5), 1.44–1.28 (4H, m, H_6, H_7), 1.10 (3H, d, $J=6.8$ Hz, Me), 0.92 (3H, t, $J=6.7$ Hz, H_8); ^{13}C NMR (acetone-d_6): δ 173.3 (C_1), 165.9 (C=O), 148.1, 145.3, 139.2, 121.4, 111.1, 105.4 (Ar), 76.7 (C_4), 56.1 (OMe), 37.9 (C_2), 34.0 (C_3), 31.2 (C_5), 28.4 (C_6), 22.8 (C_7), 14.5 (Me), 13.9 (C_8).
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13. All intermediates gave satisfactory spectral and elemental data.