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PHENYLBUTAN-2-ONE β-D-GLUCOSIDES FROM RASPBERRY FRUIT

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Key Word Index—*Rubus idaeus*; Rosaceae; raspberry fruit; raspberry ketone glucoside; 4-(4′-hydroxyphenyl)butan-2-one 4′-*O*-β-D-glucopyranoside; 4-(3′,4′-dihydroxyphenyl)butan-2-one 3′-*O*-β-D-glucopyranoside; ^{13}C, ^{1}H NMR.

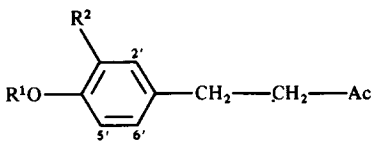
Abstract—From a methanolic extract of raspberry fruit, the 4′-*O*-β-D-glucopyranoside of 4-(4′-hydroxyphenyl)butan-2-one (raspberry ketone) and the 3′-*O*-β-D-glucopyranoside of 4-(3′,4′-dihydroxyphenyl)butan-2-one were isolated by liquid chromatography on XAD-2, Sephadex LH-20 and RP-18 as well as by HPLC on a diol phase. Identifications were carried out by ^{1}H and ^{13}C NMR spectroscopy, using synthetic reference compounds. Assignment of the carbon resonances was made by DEPT and INADEQUATE experiments. The effects of glucosylation on the ^{13}C NMR spectra of phenylbutanone derivatives are discussed.

INTRODUCTION

A recent finding that several aroma compounds of plant origin occur as 'precursors' in glycosidically conjugated forms raised considerable interest, especially in the field of grape/wine research [1–8]. In fact, 6-*O*-α-L-rhamnopyranosyl-β-D-glucopyranosides (β-rutinosides), and 6-*O*-α-L-arabinofuranosyl-β-D-glucopyranosides of geraniol, nerol, linalool [4], 2-phenylethanol and benzyl alcohol [5] have been identified in *Vitis vinifera* grapes, the two last alcohols also being present in the form of β-D-glucopyranosides [5]. Furthermore, it has been demonstrated that some grape monoterpenes are formed by acid hydrolysis/rearrangement of monoterpene diols and diol glycosides [7]. Isolation of glycosidic aroma precursors has been extended to other fruits such as papaya [9] in which benzyl alcohol glucoside and malonylated glucosides have been identified. In addition, octane-1,3-diol glucoside [10], and vomifoliol 1-*O*-β-D-xylopyranosyl-6-*O*-β-D-glucopyranoside [11] have been characterized in apple fruit. The recent identification in strawberries [12] of a glucoside of furaneol, one of the most important aroma compound of pineapples and strawberries, further demonstrated the widespread occurrence of bound forms of aroma substances in nature. In raspberries, an important constituent of the aroma is 4-(4′-hydroxyphenyl)butan-2-one, the so-called raspberry ketone [13–15]. In raspberry fruit, the presence of a glycosidically bound forms of raspberry ketone, the natural occurrence of which was probable, has not been demonstrated. In the present paper, we report on the first successful isolation of raspberry ketone glucoside and its related 4-(3′,4′-dihydroxyphenyl)butan-2-one 3′-glucoside from raspberry fruit.

RESULTS AND DISCUSSION

From an extract obtained from raspberry fruit by XAD adsorption and subsequent methanol elution, **1** was separated by LC on Sephadex LH-20 and RP-18, as well as HPLC on diol phase. Compound **1** gave raspberry ketone **3** upon enzymatic hydrolysis with a non-selective pectinase (Rohapect D5L). The presence on the DCI mass spectrum of **1** of a $[M+NH_4]^+$ ion at *m/z* 344 demonstrated that it was a raspberry ketone monoglycoside. The ^{1}H NMR spectrum of its acetylated derivative **1a** in benzene-d_6 (Table 1) confirmed the presence of a raspberry ketone moiety in the form of a Me-CO at δ 1.56, and of two adjacent methylene groups at δ 2.12 (CH_2-CO) and 2.69 (CH_2-Ar). Assignment of the methylene groups was made by means of a NOE experiment. Indeed, irradiation of the aromatic H-2′+H-6′ of raspberry ketone at δ 7.01 (C_6D_6) induced a higher effect on the methylene signal at δ 2.65, than on the 2.12 ppm one. On



	R¹	R²
1	Glc	H
1a	Glc(Ac)₄	H
2	H	OGlc
2a	Ac	OGlc(Ac)₄
3	H	H
4	H	OMe
5	H	OH

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Table 1. ^{1}H NMR data for ketones **1**, **1a** and **3**

H	Natural **1** D_2O* (400 MHz)	Natural **1** CD_3OD (400 MHz)	Synthetic **1** D_2O* (200 MHz)	**1a** $CDCl_3$ (200 MHz)	**1a** C_6D_6 (200 MHz)	**3** CD_3OD (400 MHz)	**3** $CDCl_3$ (200 MHz)	**3** C_6D_6 (200 MHz)
Aglucone								
1	2.18 *s*	2.10 *s*	2.18 *s*	2.11 *s*	1.56 *s*	2.10 *s*	2.12 *s*	1.53 *s*
3	*ca*	*ca*		*ca*	2.12 *t*		*ca*	2.12 *t*
	2.83–2.92	2.70–2.80	2.86	2.65–2.90	(7.4)	2.74	2.66–2.85	(7.4)
4			*s*		2.69 *t*	*s*		2.65 *t*
	m	*m*		*m*	(7.4)		*m*	(7.4)
2′	7.24 *d*	7.10 *d*	7.23 *d*	7.08 *d*		6.99 *d*	7.01 *d*	6.86 *d*
	(8.5)	(8.5)	(8.6)	(8.6)	*ca*	(8.4)	(8.5)	(8.5)
3′	7.07 *d*	6.99 *d*	7.06 *d*	6.88 *d*		6.67 *d*	6.73 *d*	6.67 *d*
	(8.5)	(8.5)	(8.6)	(8.6)	6.93	(8.4)	(8.5)	(8.5)
5′	7.07 *d*	6.99 *d*	7.06 *d*	6.88 *d*		6.67 *d*	6.73 *d*	6.67 *d*
	(8.5)	(8.5)	(8.6)	(8.6)	*s*	(8.4)	(8.5)	(8.5)
6′	7.24 *d*	7.10 *d*	7.23 *d*	7.08 *d*		6.99 *d*	7.01 *d*	6.86 *d*
	(8.5)	(8.5)	(8.6)	(8.6)		(8.4)	(8.5)	(8.5)
Glucose								
1	5.09 *d*	n.d.	5.08 *d*	*ca*	4.84 *d*			
	(7.5)		(7.3)		(7.8)			
2				4.89–	5.55 *dd*			
	ca	*ca*	*ca*		(8.9, 7.8)			
3				5.28	5.45 *dd*			
	3.40–	3.30–	3.40–		(9.1, 8.9)			
4				*m*	5.27 *dd*			
	3.65	3.62	3.65		(9.4, 9.1)			
5				3.83 *m*	3.17 *ddd*			
	m	*m*	*m*		(9.4, 4.8, 2.2)			
6	3.95 *dd*	3.87 *dd*	3.93 *dd*	4.27 *dd*	4.19 *dd*			
	(12.3, 1.8)	(12.0, 2.3)	(12.3, 1.8)	(12.2, 5.2)	(12.2, 4.8)			
	3.75 *dd*	3.68 *dd*	3.74 *dd*	4.14 *dd*	3.95 *dd*			
	(12.3, 5.7)	(12.0, 5.0)	(12.3, 5.3)	(12.2, 2.4)	(12.2, 2.2)			
Acetyl								
				2.01 *s*	1.65 *s*			
				2.03 *s*	1.67 *s*			
				2.04 *s*	1.69 *s*			
				2.06 *s*	1.71 *s*			
Phenol								5.42 *s*

*In ppm/TMSP.

the other hand, the spectrum of **1a** in benzene-d_6 clearly showed the presence of four alcoholic acetate groups, as well as a β-glucose chaining on the form of a doublet at δ 4.84 (Glc-1, $J = 7.8$ Hz), a *ddd* at δ 3.17 (Glc-5), a pair of *dd* at δ 3.95 and 4.19 (2 × Glc-6), and a series of *dd* at δ 5.27, 5.45 and 5.55 (Glc-4 to Glc-2) (Table 2).

The comparison of **1** with raspberry ketone-*O*-β-D-glucoside was confirmed by chemical synthesis. Natural and synthetic **1** displayed similar ^{1}H (Table 1) and ^{13}C NMR spectra (Table 3) in D_2O. Comparison of the ^{13}C NMR spectra (CD_3OD, Table 3) of raspberry ketone **3** and of its glucoside **1** demonstrated that the effects of glycosylation are quite unusual in this type of compounds (Table 4). In **1**, carbons *ortho* (C-3′ and C-5′) and *para* (C-1′) undergo usual downfield shifts of 1.68 and 3.22 ppm, respectively, as compared to **3**. The *ipso* carbon (C-4′) however, is not moved upfield as usually observed in polyphenols [18], but is shifted downfield by 0.86 ppm. On the other hand, examination of the ^{1}H NMR spectrum of **1** (CD_3OD, Table 1) shows that all aromatic protons are moved downfield as compared to **3**, H-3′ and H-5′ being more affected (0.32 ppm) than H-2′ and H-6′ (0.11 ppm).

In a similar procedure as for **1**, compound **2** was isolated in pure form from a glycosidic extract. The DCI mass spectrum of **2**, gave $[M + NH_4]^+$ m/z 360, indicating that this compound has one more oxygen atom than **1**. The presence in the ^{13}C NMR spectra of **2** (D_2O or CD_3OD), of carbohydrate signals at similar chemical shifts as for **1** (Table 3) demonstrated that this compound is also a monoglucoside. The ^{1}H NMR of the acetylated derivative **2a** in benzene-d_6 (Table 2) confirmed the presence of a β-glucose moiety. In addition, the presence of the methyl signal at δ 1.56 and of the two adjacent methylene groups at δ 2.10 and 2.69, indicated that the aglycone has a butan-2-one chain identical to that of

Table 2. ^{1}H NMR data for ketones **2**, **2a**, **4** and **5**

	2	**2a**		**4**	**5**
H	D_2O* (400 MHz)	$CDCl_3$ (200 MHz)	C_6D_6 (200 MHz)	CD_3OD (200 MHz)	CD_3OD (200 MHz)
Aglucone					
1	2.18 *s*	2.10 *s*	1.56 *s*	2.10	2.08 *s*
3	*ca*	*ca*	2.10 *t*		
	2.80–2.89	2.70–2.90	(7.0)	2.74 *s*	2.69 *s*
4			2.69 *t*		
	m	*m*	(7.0)		
2′	7.02 *s*	6.88 *d*	6.93 *d*	6.75 *d*	6.60 *d*
		(1.8)	(1.8)	(1.7)	(1.9)
5′	6.89 *s*	6.91 *d*	6.86 *d*	6.68 *d*	6.64 *d*
		(8.1)	(8.1)	(8.0)	(8.0)
6′	6.89 *s*	6.82 *dd*	6.54 *dd*	6.59 *dd*	6.47 *dd*
		(8.1, 1.8)	(8.1, 1.8)	(8.0, 1.7)	(8.0, 1.9)
OMe				3.81 *s*	
Glucose					
1	5.06 *d*	*ca*	4.85 *d*		
	(7.2)		(7.8)		
2	*ca*	5.00–5.30	5.54 *dd*		
			(9.3, 7.8)		
3	3.40–3.65		5.41 *t*		
			(9.3)		
4		*m*	5.23 *t*		
			(9.3)		
5	*m*	3.90 *ddd*	3.17 *dt*		
		(9.7, 4.7, 2.5)	(9.9, 3.5)		
6	3.94 *dd*	4.29 *dd*	4.17 *d*		
	(12.3, 1.8)	(12.3, 4.7)	(3.5)		
	3.76 *dd*	4.19 *dd*			
	(12.3, 5.7)	(12.3, 2.5)			
Acetyl					
		2.01 *s*	1.65 *s*		
		2.03 *s*	1.66 *s*		
		2.06 *s*	1.72 *s*		
		2.07 *s*			
		2.23 *s*	1.94 *s*		

* In ppm/TMSP.

raspberry ketone. The presence in **2a** of a more deshielded acetyl group at δ 1.94, suggested that the latter was esterifying a phenolic hydroxyl, and therefore that **2** differs from **1** by the presence of an additional phenolic substituent on the aromatic ring. This was further confirmed by the fact that the aglycone signals were similar in the ^{13}C NMR spectra of **2** and **1**, except for aromatic carbons (Table 3). The ^{1}H NMR spectrum of **2a** (in $CDCl_3$ or C_6D_6) (Table 2) demonstrated the presence of three aromatic protons on the form of one *dd* (J_{ortho} = 8.1 Hz and J_{meta} = 1.8 Hz), and of two doublets (J_{ortho} for the first and J_{meta} for the second). This established the aromatic ring as 1,2,4-trisubstituted. Irradiation of CH_2-Ar (H-4) in **2a** (solvent C_6D_6) produced a NOE on both the doublet at δ 6.93 (H-2′), and the *dd* at δ 6.54 (H-6′). This unequivocally demonstrated that the aglucone of **2** is 4-(3′,4′-dihydroxyphenyl)-butan-2-one. The position of attachment of glucose on the aglucone was established by means of a second NOE experiment. In fact, irradiation of H-1 of glucose in **2a** at δ 4.85 (C_6D_6) produced a NOE on H-2′, only, thus demonstrating that **2** is the 3′-*O*-β-glucoside of 4-(3′,4′-dihydroxyphenyl)-butan-2-one.

The ^{13}C NMR spectrum of **2** in methanol-d_4 (Table 3) was similar to that reported by Reyes *et al.* [19], except for the carbonyl resonance (C-2), which was obviously incorrectly assigned to δ 165.6. Although the carbon signals of C-1 and C-4 are close in the ^{13}C NMR spectra of phenylbutanone derivatives, the DEPT spectrum of **2** in methanol-d_4 allowed their immediate relative assignment. Interestingly, the DEPT spectrum in D_2O demonstrated that in the last solvent, the relative position of those two carbon atoms is reversed (Table 3). In addition, the DEPT spectrum of **2** in methanol-d_4, showed that the signal at δ 124.48 was due to a CH resonance, and therefore could not be assigned to C-1′, as reported in ref. [19]. This led us to undertake a complete reassignment of **2** carbons by comparison of its spectrum with that of its corresponding aglucone **5**. The latter compound was obtained through a three step synthesis. Condensation of vanillin with acetone gave dehydrozingerone which was subsequently hydrogenated to zingerone (**4**). Assignment

Table 3. ^{13}C NMR data for ketones **1**–**5**

	Natural 1		Synthetic 1	3	2		4	5
C	D_2O* (100 MHz)	CD_3OD (100 MHz)	D_2O* (50 MHz)	CD_3OD (100 MHz)	D_2O* (100 MHz)	CD_3OD 50 MHz)	CD_3OD (50 MHz)	CD_3OD (50 MHz)
Aglucone								
1	31.63	30.01	31.68	29.99	31.76	30.00	29.85	29.98
2	n.d.	211.02	218.23	211.31	n.d.	n.d.	211.03	211.59
3	46.70	46.00	46.72	46.25	46.88	45.99	46.80	46.14
4	30.66	30.01	30.72	30.05	30.98	30.18	30.15	30.26
1′	138.13	136.36	138.15	133.14	135.75	132.37	133.67	133.99
2′	131.81	130.21	131.81	130.18	119.01	118.97	112.86	116.43[b]
3′	118.98	117.83	119.03	116.15	146.97[a]	146.60	148.45	146.12
4′	157.18	157.48	157.18	156.62	146.75[a]	146.60	145.39	144.42
5′	118.98	117.83	119.03	116.15	118.95	116.97	115.93	116.38[b]
6′	131.81	130.21	131.80	130.18	125.91	124.48	121.43	120.50
OMe							56.19	
Glucose								
1	102.61	102.52	102.66		103.51	104.40		
2	75.18	74.94	75.22		75.18	74.93		
3	78.33	78.01	78.35		78.52	78.40		
4	71.68	71.42	71.73		71.77	71.49		
5	77.80	78.12	77.86		77.82	77.71		
6	62.79	62.54	62.86		62.87	62.58		

* In ppm/TMSP.
[a,b]Assignements may be reversed.

Table 4. ^{13}C NMR glucosylation shifts* for phenylbutanone glucosides (CD_3OD)

C	1	2	4-(3′,4′-dihydroxyphenyl)Butan-2-one 4′-glucoside. [21]†
Ipso	−0.86 (C-4′)	−0.48 (C-3′)	−0.38 (C-4′)
Ortho	−1.68 (C-3′ + 5′)	−2.54 (C-2′)	−2.08 (C-3′)
		−2.18 (C-4′)	−2.92 (C-5′)
Meta	−0.03 (C-2′ + 6′)	+1.62 (C-1′)	−0.57 (C-2′)
		−0.59 (C-5′)	−0.20 (C-6′)
Para	−3.22 (C-1′)	−3.98 (C-6′)	−4.31 (C-1′)

* Refers to $\delta_{aglycone} - \delta_{glucoside}$.
† After inversion of C-3′ and C-4′ assignments in ref. [21].

of carbon resonances on the ^{13}C NMR spectrum of **4** (Table 3) has been made by means of an INADEQUATE experiment. Demethylation of **4** using BBr_3 yielded **5**. Removal of the methyl group at position 3′ induced a 2.33 ppm upfield shift of C-3′ to 146.12 ppm in **5**. Substituted *ortho* carbon 4′ is moved upfield by 0.97 ppm to δ 144.42, while unsubstituted *ortho* carbon 2′ undergoes an important downfield shift of 3.57 ppm to δ 116.43. Such demethylation shifts are in accordance with those observed in unconjugated 3′,4′-dioxygenated aromatic systems such as in flavanones [20]. Assignments of carbons in **2** was finally made taking into account the glucosylation shifts observed in raspberry ketone glucoside (Table 4). 3′-Glucosylation led to a small downfield shift of 0.48 ppm to δ 146.6 for C-3′. *Ortho* carbons 2′ and 4′ were deshielded by 2.54 and 2.18 ppm to δ 118.97 and 146.60, respectively. Glucosylation at C-3′ is also shown by the important downfield shift of 3.98 ppm to δ 124.48 for C-6′. Application of similar glucosylation shift rules for the 4′-glucoside of **5**, which has been isolated from the leaves of *Vitex rotundifolia* [21], demonstrates that the assignment of the carbon atoms made by Kouno *et al.* [21] was right, except for the positions of C-3′ and C-4′ that need to be reversed (Table 4).

The UV spectral shifts obtained with phenylbutanone derivatives after the addition of usual reagents were quite unreliable and, therefore, should not be taken as structurally informative. In fact, considering the behaviour in the presence of NaOMe of compounds having a free 4′-hydroxyl group, raspberry ketone **3** gave a 10 nm bathochromic shift (λ_{max}^{MeOH}: 278 nm; + NaOMe: 288 nm), while zingerone **4** and compound **2** did not react (Experi-

mental). Similar inconsistent results were obtained in the case of *ortho* dihydroxylated compounds such as 4-(3',4'-dihydroxyphenyl)butan-2-one (**5**). A 5 nm bathochromic shift was recorded in presence of $NaOAc + H_3BO_3$, while no bathochromic shift was observed after the addition of $AlCl_3$.

Bound forms of raspberry ketone have been isolated from rhubarb, primarily as galloyl, cinnamoyl and/or *p*-coumaroyl esters of raspberry ketone glucoside [22–24]. Raspberry ketone glucoside **1** has been characterized in rhubarb root [24, 25] as well as in *Pinus* needles [17, 26]. Compound **2** has been identified in *Myzodendron punctulatum* only [19]. Both compounds are reported here for the first time in raspberry fruit.

EXPERIMENTAL

Plant material. Frozen raspberry fruit pulp (*Rubus idaeus* cv Heritage) was supplied by Pernod Ricard Research Center (Créteil, France).

General. TLC was carried out on silica gel F254 plastic sheets (Merck). After migration, the plates were sprayed with H_2SO_4–vanillin reagent and the coloured spots visualized at 100°. Centrifugal TLC was carried out using a Chromatotron apparatus (Harrison Research) using silica gel plates (2 mm thickness). CC (20 × 440 mm) was performed on silica gel 60 (70–230 mesh ASTM). MPLC was performed using a LiChroprep RP-18 column (Merck; 310 × 25 mm; 40–63 μm). Semi-prep. HPLC on Interchrom Diol bonded silica column (Interchim, France; 5 μm; 250 × 10 mm) was carried out using a Varian 9010 pump (flow rate 2 ml min^{-1}), and a Varian 9050 UV detector (detection at 280 nm). The following solvents were used: A, *n*-hexane–*n*-BuOH–MeOH–H_2O (55:35:9:1); B, CH_2Cl_2–MeOH–H_2O (80:19:1). Semi-prep. HPLC on Lichrosorb Si60 (Merck; 7 μm; 250 × 7 mm) was performed using a Waters 501 pump (flow rate 2 ml min^{-1}), a Waters 490E UV detector (detection 280 nm), and the following solvents: C, hexane–*iso*-PrOH–MeOH (7:2:1); D, $CHCl_3$. HRGC was carried out using (a) a CP-Wax-58-CB WCOT column (Chrompack; 30 m × 0.32 mm i.d.; df = 0.22 μm), and (b) a DB 1701 WCOT column (J&W; 30 m × 0.52 mm i.d.; df = 1 μm). In each case the column was programmed from 40 to 220° at 3° min^{-1}, and held at the upper temperature for 30 min. FID temperature was 250°. Injection was split-splitless (split ratio 1:9). Carrier gas was H_2 with a flow rate of 4 ml min^{-1} and 5 ml min^{-1}, respectively. NMR spectra were measured either at 400 (^1H) and 100 MHz (^{13}C) or at 200 (^1H) and 50 MHz (^{13}C). Spectra in D_2O were recorded using 3-(trimethylsilyl) propionic-2,2,3,3-d_4 acid Na salt (TMSP) as ref., while spectra in CD_3OD, $CDCl_3$ and C_6D_6 were calibrated from TMS. DCI mass spectra of compounds **1** and **2**: source pressure 0.3 Torr; source temp. 90°.

Localization of the phenylbutanone precursors in the fractions resulting from chromatographic separations. This was performed by hydrolysis of an aliquot in 0.2 M citrate–Pi buffer [16] pH 5 using Rohapect D5L pectinase (Röhm) at 35° overnight. The liberated aglycones were extracted in Et_2O and analysed by HRGC.

Extraction and isolation of compounds **1** and **2**. Lyophilized raspberry fruits (1.7 kg) (10.4 kg fr. wt) were homogenized with 2 × 3 l 80% aq. MeOH at room temp.; the pH was previously adjusted to 7 with NaOH to prevent hydrolysis of the glycosides. The extract was concd under red. pres., the aq. residue was diluted with 1 l H_2O and stirred with polyvinylpolypyrrolidone (PVPP) overnight for removal of pigments. After filtration, the extract was passed through a column of Amberlite XAD-2. The column was washed with H_2O and eluted with MeOH. The eluate was concd to dryness under red. pres., redissolved in H_2O and extracted with Et_2O to remove any remaining volatiles. The aq. extract was subjected to LC on a column of Sephadex LH-20 using H_2O, followed by a gradient of MeOH in H_2O. The phenylbutanone glucosides were present in the H_2O fraction of the Sephadex column. This fraction was chromatographed on a RP-18 medium pressure prep. column using gradients of MeOH in H_2O as solvent. The phenylbutanone glucosides were eluted in 30% aq. MeOH. Further fractionation was carried out by semi-preparative HPLC on a Diol column using solvent A. Complete purification of the glycosides was achieved by means of a second semi-prep. HPLC on Diol column using solvent B. This resulted in 2.8 mg **1** and 2.2 mg **2**.

Acetylation of **1** and **2**. Compounds **1** (2.8 mg) and **2** (2.2 mg) were acetylated using standard Ac_2O–pyridine procedure at room temp. for 2 days in the dark.

Purification of **1a** and **2a** was performed by semi-prep. HPLC on silica gel using solvent C for **1a** (yield 1.3 mg), and solvent D for **2a** (yield: 1.6 mg). Fractions from HPLC were analysed by TLC on silica gel using $CHCl_3$ as solvent (R_f **1a**: 0.25; R_f **2a**: 0.17).

4-(4'-hydroxyphenyl)Butan-2-one 4'-O-β-D-glucopyranoside (**1**). UV λ_{max}^{MeOH} nm: 282sh, 273; + NaOMe: 282sh, 273. IR ν_{max}^{KBr} cm^{-1}: 3367, 2924, 1709 (C=O), 1611, 1511, 1407, 1367, 1231, 1073, 1044, 820. DCIMS (NH_3) 90 eV, *m/z* 344 $[M+NH_4]^+$, 198 $[Glc+NH_4]^+$, 182 [raspberry ketone + $NH_4]^+$, 180 $[Glc+NH_4-H_2O]^+$.

Synthesis of **1**. To 30 mmol of 4-(4'-hydroxyphenyl)butan-2-one **3** in 50 ml CH_2Cl_2, 5 g drierite (Aldrich) and 21 mmol Ag_2O were added and the mixture stirred in the dark at room temp. for 30 min. Then 10 mmol α-D-acetobromoglucose in 50 ml CH_2Cl_2 were added. After stirring the reaction mixture in the dark at room temp. for 3 days, it was filtered through celite (Aldrich) and poured into ice water. The product was extracted with $CHCl_3$. Isolation of the 2,3,4,6-tetraacetyl glucoside of raspberry ketone **1a** was carried out by CC on silica gel using pentane–EtOAc (3:1) as solvent. To a soln of **1a** in 20 ml MeOH, 5 ml of 5% methanolic KOH were added. After 24 hr, the mixture was neutralized with HCl, concd and subjected to semi-prep. HPLC on Diol using solvent B. Final purification of synthetic **1** was carried out by centrifugal TLC on silica gel using $CHCl_3$–MeOH (17:3) as solvent.

4-(3',4'-dihydroxyphenyl)Butan-2-one 3'-O-β-D-glucopyranoside (**2**). UV λ_{max}^{MeOH} nm: 278; + NaOMe: 278. IR ν_{max}^{KBr} cm^{-1}: 3343, 2958, 2927, 1712 (C=O), 1515, 1438, 1365, 1277, 1164, 1118, 1072, 1042, 803. DCIMS (NH_3) 90 eV, *m/z* 360 $[M+NH_4]^+$, 198 $[Glc+NH_4]^+$, 180 $[Glc+NH_4-H_2O]^+$, 162 $[Glc+NH_4-2H_2O]^+$.

Synthesis of **5**. To 6.7 g vanillin in 30 ml Me_2CO were added 30 ml 10% aq. NaOH [17] and the mixture allowed to react for 48 hr at room temp. Acidification (6 M HCl) led to the crystallization of 6.85 g 4-(3'-hydroxy-4'-methoxyphenyl)-3-buten-2-one [27] (vanillalacetone or dehydrozingerone; % yield: 81%), which was recrystallized in aq. EtOH (yield: 5.35 g; % yield: 63%). R_f 0.22 (silica gel, hexane–EtOAc, 7:3). λ_{max}^{MeOH} nm: 336, 240. ^1H NMR (200 MHz, CD_3OD): δ 2.32 (3H, *s*, H-1), 3.86 (3H, *s*, OMe), 6.60 (1H, *d*, $J_{3,4}$ = 16.2 Hz, H-3), 6.80 (1H, *d*, $J_{5',6'}$ = 8.2 Hz, H-5'), 7.08 (1H, *dd*, $J_{5',6'}$ = 8.2 Hz and $J_{2',6'}$ = 1.9 Hz, H-6'), 7.17 (1H, *d*, $J_{2',6'}$ = 1.9 Hz, H-2'), 7.54 (1H, *d*, $J_{3,4}$ = 16.2 Hz, H-4). ^{13}C NMR (50 MHz, CD_3OD): 27.11 (C-1), 56.47 (OMe), 112.03 (C-2'), 116.58 (C-5'), 124.54 (C-6'), 125.00 (C-3), 127.75 (C-1'), 146.46 (C-4), 149.40 (C-3'), 150.94 (C-4'), 201.38 (C-2). Vanillalacetone (2 g) was hydrogenated with 680 mg Pd/C (10%) for 3 hr at room temp. The reaction medium was chromatographed on a column of silica gel using hexane–EtOAc (4:1) as solvent which led to the isolation of 0.87 g zingerone **4**

[17] (% yield = 43%). R_f 0.26 (silica gel, hexane–EtOAc, 7:3). λ_{max}^{MeOH} nm: 278; +NaOMe: 278; +NaOAc: 278. 500 mg **4** dissolved in 2 ml CH_2Cl_2 were demethylated using 3 ml 1.0 M BBr_3 in CH_2Cl_2 at −30°. The reaction medium was allowed to slowly warm up to room temp. Unreacted BBr_3 was destroyed by addition of 10 ml ice H_2O and the reaction products partitioned between EtOAc and 2% aq. $NaHCO_3$. The EtOAc extract was washed with H_2O, and purified by CC on silica gel using hexane–EtOAc (7:3) as solvent, to give **5** [28]. R_f 0.13 (silica gel, hexane–EtOAc, 7:3). λ_{max}^{MeOH} nm: 282; +NaOMe: 340sh, 287 (dec); +$AlCl_3$: 278; +$AlCl_3$+HCl: 280; +NaOAc: 340sh, 280; +NaOAc+H_3BO_3: 335sh, 287. EIMS 70 eV, *m/z* (rel. int.): 181 (6), 180 $[M]^+$ (69), 179 $[M-H]^+$ (26), 178 (3), 165 $[M-Me]^+$ (2), 162 $[M-H_2O]^+$ (3), 147 $[M-Me-H_2O]^+$ (5), 138 (3), 137 $[M-Ac]^{+\cdot}$ (37), 136 (9), 135 (2), 124 (6), 123 $[M-CH_2Ac]^+$ (100), 122 (15), 119 (16), 118 (2), 110 (12), 109 (3), 107 (2), 106 (2), 105 (4), 94 (2), 93 (2), 92 (2), 91 (26), 90 (6), 89 (5), 81 (3), 80 (3), 79 (4), 78 (4), 77 (17), 76 (2), 67 (3), 66 (4), 65 (11), 64 (4), 63 (7), 62 (2), 55 (8), 54 (2), 53 (8), 52 (6), 51 (16), 50 (4), 43 (72), 42 (6), 41 (3).

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