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Isochromans from 2-(3′,4′-dihydroxy)phenylethanol

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Abstract—A facile method to obtain an isochromanic structure was achieved by the oxa-Pictet–Spengler reaction using 2-(3′,4′-dihydroxy)phenylethanol as starting material. The reaction was performed in very mild conditions on a series of carbonylic compounds. Yields were always satisfactory. © 2001 Elsevier Science Ltd. All rights reserved.

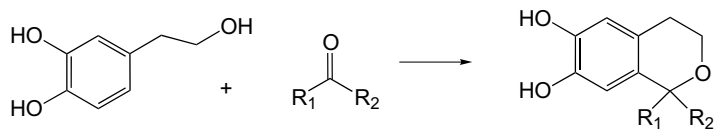
The oxa-Pictet–Spengler reaction is a variation of the Pictet–Spengler reaction. While in the Pictet–Spengler reaction a compound with a phenethylamine structure reacts with an aldehyde or a ketone to give a Schiff base and subsequently the Friedel–Crafts cyclization of the iminium salt gives an isoquinoline derivative,[1] in the oxa-Pictet–Spengler reaction, a compound such as a 2-phenylethanol reacts with an aldehyde or a ketone to give a 3,4-dihydro-1*H*-benzo[*c*]pyranic (isochromanic) structure. This reaction was described in 1992[2] and was accomplished under difficult operative conditions. The authors used $ZnCl_2$\HCl gas, or *p*-toluenesulfonic acid, etc. as Friedel–Crafts catalyst, and high reaction temperatures. It has been reported[3] that activated substrates needed moderately milder conditions.

We performed the oxa-Pictet–Spengler reaction in very mild operative conditions and in this paper we report that an activated substrate such 2-(3′,4′-dihydroxy)phenylethanol **1** undergoes the oxa-Pictet–Spengler reaction even using a very mild acid catalyst, such as a fatty acid. Compound **1**, whose trivial name is hydroxytyrosol, is characterised by an *ortho*-diphenolic structure, which is responsible for its very high reactivity in redox and non redox reactions. In addition, hydroxytyrosol is a widespread natural product, mainly in the Oleaceae family, both as a free compound and glycosilate or esterified as in oleuropein.[4]

Isochromanic structures seem to be very rare in nature, and until now only a few examples have been described,[5–7] among which is compound **2**.[5]

By our method we carried out a series of reactions using 16 different carbonyl compounds (compounds **3**–**18** in Table 1 and Scheme 1) both aldehydes and ketones, obtaining the corresponding isochromans (compounds **2**, **19**–**33** in Table 1 and Scheme 1). This series of reactions was carried out at low temperature; generally at 4°C, using *p*-toluenesulfonic acid as a catalyst. From a synthetic point of view, our procedure constitutes a significant improvement of the oxa-Pictet–Spengler reaction, it does not give side-products and it may be useful to synthesise, with satisfactory yields, a set of hydroxysubstituted isochromans. The yields of the reactions are summarised in Table 1.

Hydroxytyrosol **1** reacts with carbonylic compounds, giving at first an hemiacetalic linkage between its primary alcoholic function and the carbonylic function of the aldehyde or ketone, as reported in Scheme 2. Then the hemiacetalic intermediate loses a water molecule



1 **3-18** **2, 19-33**

Scheme 1.

Keywords: isochromans; oxa-Pictet–Spengler reaction; hydroxytyrosol.

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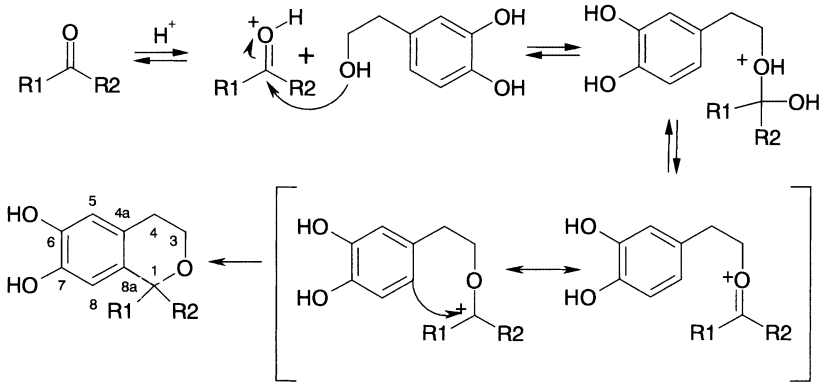
Table 1.

Reagents	Yield (%)	Obtained product[a]		NMR[b] data (solvent): chemical shift in ppm from TMS, J in Hz
1 Acetone, **3**	63	**2** $R_1=CH_3$	$R_2=CH_3$	^{1}H NMR (CD_3OD): 6.58 (1H, s, H-5);6.50 (1H, s, H-8); 3.80 (2H, t, $J=5.5$ 2H-3); 2.65 (2H, t, $J=5.5$, 2H-4); 1.45 (6H, s, $2CH_3$)
1 Methylpropyl ketone, **4**	48	**19** $R_1=CH_3$	$R_2=n$-propyl	^{1}H NMR ($CDCl_3$): 6.54 (2H, H-5, H-8); 3.87 (2H, m, 2H-3); 2.53 and 2.73 (2H, m, 2H-4); 1.41 (3H, s, CH_3 in C-1); R_2 moiety: 1.71 (2H, m, CH_2); 1.05 and 1.38 (2H, m, CH_2 at C-1). 0.81 (3H, t, $J=7.2$, CH_3); ^{13}C NMR: 142.2 C-6; 141.8 C-7; 134.6 C-8a; 126.0 C-4a; 114.9 C-5;112.2; C-8; 76.8 C-1; 59.7 C-3; 28.9 C-4; 16.8 CH_3 at C-1; R_2 moiety at C-1. 45.2; 27.8; 14.32
1 Isopropylmethyl ketone, **5**	35	**20** $R_1=CH_3$	$R_2=iso$-propyl	^{1}H NMR ($CDCl_3$): 6.64 (1H, s, H-5); 6.59 (1H, s, H-8); 3.93 (2H, t, $J=6$ 2H-3); 2.71 (2H, t, $J=6.0$ 2H-4); 1.64 (3H, s, R_1); R_2 moiety: 1.40–1.60 (7H)
1 Vanillin, **6**	76	**21** $R_1=H$	$R_2=$4-OH, 3-OCH_3-phenyl	^{1}H NMR (CD_3OD): 6.47 (1H, s, H-5); 6.06 (1H, s, H-8); 5.41 (1H, s, H-1); 4.00 and 3.72 (2H, m, 2H-3); 2.84 and 2.52 (2H, m, 2H-4); R_2 moiety: 6.6–6.8 (3H); 3.68 (3H, s, OCH_3). ^{13}C NMR: 145.3 C-6; 144.5 C-7; 135.3 C-8a; 126.1 C-4a; 115.9 C-5; 114.6 C-8; 80.9 C-1; 65.1 C-3; 29.1 C-4; R_2 moiety: 148.9; 147.5; 129.9; 123.1; 113.3; 115.6;.56.3
1 *p*-OH benzaldehyde, **7**	87	**22** $R_1=H$	$R_2=p$-OH phenyl	^{1}H NMR (CD_3OD): 6.55 (1H, s, H-5); 6.11 (1H, s, H-8); 5.50 (1H, s, H-1); 4.05 and 3.80 (2H, m, 2H-3); 2.91 and 2.59 (2H, m, 2H-4); R_2 moiety: 7.08 (2H, d*) and 6.74 (2H, d*). ^{13}C NMR: 145.2 C-6; 144.5 C-7; 134.8 C-8a; 126.1 C-4a; 115.8 C-5; 114.6 C-8; 80.5 C-1; 64.9 C-3; 29.1 C-4; R_2 moiety: 158.4; 131.4; 129.9; 115.9
1 Cyclohexan-carbaldehyde, **8**	82	**23** $R_1=H$	$R_2=$cyclohexyl	^{1}H NMR ($CDCl_3$): 6.57 (2H, s, H-5 and H-8); 4.50 (1H, s, H-1); 4.11 and 3.63 (2H, m, 2H-3); 2.40 and 2.83 (2H, m, 2H-4); 1.0–1.9 (R_2 moiety). ^{13}C NMR: 142.0 C-6; 141.8 C-7; 129.8 C-8a; 127.4 C-4a; 115.1 C-5; 111.7 C-8; 79.9 C-1; 64.1 C-3; 30.2 C-4; R_2 moiety: 43.6; 28.7; 26.9; 26.5; 26.4; 25.5
1 *o*-OH benzaldehyde, **9**	42	**24** $R_1=H$	$R_2=o$-OH phenyl	^{1}H NMR ($CDCl_3$): 6.65 (1H, s, H-5); 6.27 (1H, s, H-8); 5.71 (1H, s, H-1) 4.22 and 3.92 (2H, m, 2H-3); 3.00 and 2.73 (2H, m, 2H-4); R_2 moiety: 6.7–7.1 (4H)
1 *m*-OH benzaldehyde, **10**	80	**25** $R_1=H$	$R_2=m$-OH phenyl	^{1}H NMR (CD_3OD): 6.73 (1H, s, H-5); 6.15 (1H, s, H-8), 5.49 (1H, s, H-1); 3.81 and 4.06 (2H, m, 2H-3); 2.60 and 2.91 (2H, m, 2H-4); R_2 moiety: 7.14 (1H, t, $J=7.5$, H-5′); 6.77 (1H, d, $J=7.5$, H-6′); 6.71 (1H, m, H-4′); 6.70 (1H, s*, H-2); ^{13}C NMR 145. (C-6); 145.3 (C-7); 129.5 (C-8a); 126.1 (C-4a); 115.9 (C-5); 114.5 (C-8); 80.7 (C-1); 65.0 (C-3); 29.1 (C-4); R_2 moiety: 158.4; 144.5; 116.8; 115.9; 130.2; 121.3
1 *m*-NO_2 benzaldehyde, **11**	95	**26** $R_1=H$	$R_2=m$-NO_2 phenyl	^{1}H NMR ($CDCl_3$): 6.62 (1H, s, H-5); 6.13 (1H, s, H-8); 5.68 (1H, s, H-1); 4.11 and 3.87 (2H, m, 2H-3), 2.99 and 2.65 (2H, m, 2H-4); R_2 moiety: 8.12 (2H, m, H-2′,4′); 7.62 (1H, d*, H-6′); 7.48 (1H, t, $J=7.8$, H-5′); ^{13}C NMR: 143.0 (C-6); 142.1 (C-7); 127.8 (C-8a); 126.2 (C-4a); 115.2 (C-5); 113.1 (C-8); 78.2 (C-1); 64.1 (C-3); 27.8 (C-4); R_2 moiety: 148.2; 144.2; 134.9; 129.4; 123.6; 123.1
1 *o*-NO_2 benzaldehyde, **12**	58	**27** $R_1=H$	$R_2=o$-NO_2 phenyl	^{1}H NMR ($CDCl_3$): 6.63 (1H, s, H-5); 6.27 (1H, s, H-8); 6.17 (1H, s, H-1); 4.07 and 3.84 (2H, m, 2H-3); 2.95 and 2.2 (2H, m, 2H-4); R_2 moiety: 7.81 (1H, dd, $J=8.2$, 1.8, H-3′); 7.38-7.55 (3H, H-4′, H-5′, H-6′)
1 *p*-OCH_3 benzaldehyde, **13**	80	**28** $R_1=H$	$R_2=p$-OCH_3 phenyl	^{1}H NMR ($CDCl_3$): 6.63 (1H, s, H-5); 6.20 (1H, s, H-8); 5.54 (1H, s, H-1); 3.84 and 4.11 (2H, m, 2H-3); 2.62 and 2.98 (2H, m, 2H-4); R_2 moiety: 7.19 (2H, d, $J=8.4$, H-2′, H-6′); 6.84 (2H, d, $J=8.4$, H-3′, H-5′); 3.78 (OCH_3); ^{13}C NMR: 142.7 (C-6); 141.7 (C-7); 130.4 (C-8a); 127.0 (C-4a); 115.2 (C-5); 113.8 (C-8); 79.0 (C-1); 64.1 (C-3); 28.4 (C-4); R_2 moiety: 159.7; 134.7; 130.2; 114.0; 55.5
1 *p*-Cl benzaldehyde, **14**	90	**29** $R_1=H$	$R_2=p$-Cl phenyl	^{1}H NMR ($CDCl_3$): 6.55 (1H, s, H-5); 6.09 (1H, s, H-8); 5.53 (1H, s, H-1); 3.82 and 4.07 (2H, m, 2H-3); 2.59 and 2.92 (2H, m, 2H-4); R_2 moiety: 7.25 (2H, d, $J=8.4$, C-3′ and C-5′), 7.16(2H, d, $J=8.4$, C-2′ and C-6′).^{13}C NMR: 142.9 (C-6); 141.9 (C-7); 128.7 (C-8a); 126.1 (C-4a); 114.9 (C-5); 113.2 (C-8); 78.5 (C-1); 63.9 (C-3); 27.9 (C-4); R_2 moiety 133.9; 130.2; 128.5
1 Pentanal, **15**	50	**30** $R_1=H$	$R_2=n$-butyl	^{1}H NMR ($CDCl_3$): 6.57 (1H, s, H-5); 6.56 (1H, s, H-8); 4.61 (1H, dd, $J=7.1$, 3.0, H-1); 4.07 and 3.70 (2H, m, 2H-3); 2.82 and 2.52 (2H, m, 2H-4) R_2 moiety: 1.76 (2H, m, 2H C-1′); 1.38 (4H, 2H C-2′ and 2H C-3′); 0.90 (3H, t, $J=6.9$, CH_3)
1 Benzaldehyde, **16**	60	**31** $R_1=H$	$R_2=$phenyl	^{1}H NMR ($CDCl_3$): 6.61 (1H, s, H-5); 6.18 (1H, s, H-8); 5.57 (1H, s, H-1); 4.10 and 3.85 (2H, m, 2H-3); 2.98 and 2.63 (2H, m, 2H-4); R_2 moiety 7.28 (5H)
1 Butanal, **17**	64	**32** $R_1=H$	$R_2=n$-propyl	^{1}H NMR ($CDCl_3$): 6.58 (1H, s, H-5); 6.57 (1H, s, H-8); 4.65 (1H, t, $J=5.5$, H-1); 4.09 and 3.75 (2H, m, 2H-3), 2.82 and 2.55 (2H, m, 2H-4); R_2 moiety: 1.75 (2H, m, 2H-1′); 1.48 (2H, m, 2H-2′); 0.93 (3H, t, $J=7.2$, CH_3)
1 (*E*)-2-methyl-2-butenal, **18**	57	**33** $R_1=H$	$R_2=$2-(*E*)-2-butenyl	^{1}H NMR ($CDCl_3$): 4.94 (1H, s, H-1); 4.18 and 3.75 (2H, m, 2H-3); 2.90 and 2.45 (2H, m, 2H-4); 6.59 (1H, s, H-5); 6.47 (1H, s, H-8); R_2 moiety: 1.43 (3H, s, CH_3); 1.65 (3H, d, $J=6.3$, CH_3); 5.61 (1H, m, H-10)

[a] Safisfactory microanalyses obtained: C±0.35, H±0.16).
[b] Varian, Mercury 300.
* Unshaped signal.



Scheme 2.

and gives an isochroman, closing a six-membered ring at the position, on the phenyl moiety, which results in activation by the *para* hydroxyl group.

The reaction time necessary to obtain the isochroman with satisfactory yields is different for aldehydes and ketones, indeed **1** reacts faster with aldehydes (generally 1 day at 4°C) than with ketones (2 days at 4°C). In our experiments, we observed that the more hindered ketones give, in the usual operative conditions, the isochroman with lower yields (see Table 1), as shown by the different reaction yields of isopropyl-methyl-ketone **5** and acetone **3**. This effect increases when the steric crowding increases; and very hindered ketones, such as benzophenone or acetophenone, do not react at all with **1**. It is also possible to point out a different reactivity between aromatic and aliphatic aldehydes. In fact, the aromatic aldehydes generally give the corresponding isochroman with higher yields than aliphatic ones, probably because in the aromatic aldehydes the positive charge present on the reaction intermediate (see Scheme 2) may give a resonance on the aromatic ring, so increasing the stability of the intermediate cation,[8] or because these aldehydes can not undergo enolisation. We have selected the carbonylic compounds reported in Table 1 to also investigate the effects of substituents on aromatic ring, but as shown by data of Table 1, we have noted only steric effects. In fact, the aromatic aldehydes with a substituent in the *ortho* position give lower yields than those with substituents in the *para* or *meta* positions.

As previously reported, *p*-toluenesulfonic acid was used as a catalyst in the first series of reactions. Afterwards we tried to verify if the reaction could also be performed by using a weaker acid, such as a fatty acid. We selected oleic acid because it is present in the same natural matrix as the hydroxytyrosol **1**, olives and olive oil.

It has been noted that **1** reacts in the presence of oleic acid with carbonylic compounds, but in this case it is necessary to have a longer reaction time (1 week), and an increase in the temperature (room temperature, about 21°C), nevertheless lower yields are observed than when using *p*-toluenesulfonic acid as a catalyst.

We selected aldehydes and ketones for these experiments that were present in olive oil together with hydroxytyrosol **1** and oleic acid[9] and also successively investigated the presence of isochromans in this foodstuff. The obtained compounds in this second set of reactions and their yields are reported in Table 2.

As some isochromans were isolated from natural matrices[5–7] and we demonstrated the possibility that **1** can react with carbonylic compounds in very mild conditions (low temperature, mild acid catalysis) by an oxa-Pictet–Spengler reaction, the doubt is if all the isochromans that were isolated until now are true natural compounds or artefacts arising from the isolation procedure.

We are convinced that some of these may be natural products, while others could arise from a spontaneous acid-catalysed reaction. An example could be the isochroman **2** isolated from the leaves of *Tectaria subtriphylla*[5] by an acetone extraction.

So it is necessary to look for these products in the natural matrices, having in mind the possibility of an oxa-Pictet–Spengler reaction.

Experimental procedures

First series (*p*-toluenesulfonic acid): 20 mg of **1** was dissolved in methyl alcohol (1 ml) together with the selected carbonylic compound (**3**–**18**) in a 1:1 molar ratio. A catalytic amount of *p*-toluenesulfonic acid was added. The mixture was left to react at 4°C for the required period of time (about 24 h for aldehydes and 48 h for ketones). After a chromatographic control on a silica gel plate, the volume of the reaction mixture is

Table 2.

Reagents	Yield (%)	Obtained product[a]
1 Acetone, **3**	40	**2**
1 Benzaldehyde, **16**	30	**31**
1 Pentanal, **15**	35	**30**
1 Methyl isopropylketone, **5**	20	**20**

[a] Satisfactory microanalyses obtained: C±0.35, H±0.16.

cut in half under reduced pressure at low temperature, diluting with ethyl acetate (25 ml). The organic layer is washed with a saturated solution of NaCl until neutrality, dried with anhydrous Na_2SO_4, concentrated and the residue purified by chromatography on silica gel, by eluting usually with 9:1 $CHCl_3$/MeOH.

Second series (oleic acid): 20 mg of **1** is dissolved in methyl alcohol (1 ml) together with the selected carbonylic compound (**3**, **5**, **14**, **15**) in a 1:1 molar ratio. A catalytic amount of oleic acid was successively added. The mixture was left to react at 21°C for a week. After chromatographic control on silica gel plate, the oleic acid was extracted with hexane, methanol was evaporated under reduced pressure and the residue was purified as above.

Acknowledgements

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