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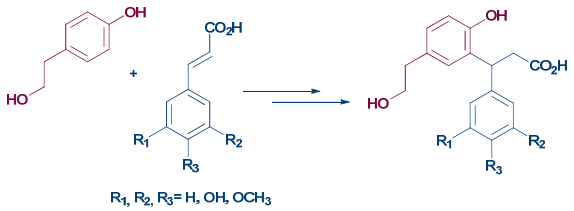
Synthesis and DPPH radical scavenging activity of novel compounds obtained from tyrosol and cinnamic acids derivatives

Maurizio Barontini,[†] Roberta Bernini, [†,*] Isabella Carastro,[†] Patrizia Gentili [≠] and Annalisa Romani [§]

Novel compounds exhibiting DPPH radical scavenging activity were synthesised. Key step was the trifluoroacetic acid-mediated hydroarylation of cinnamic ester with tyrosol.



Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis and DPPH radical scavenging activity of novel compounds obtained from tyrosol and cinnamic acids derivatives

Maurizio Barontini,[†] Roberta Bernini, [†,*] Isabella Carastro,[†] Patrizia Gentili [≠] and Annalisa Romani [§]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Tyrosol, a naturally phenolic compound poorly attractive as antioxidant for its weak efficacy, was used as starting material to obtain novel compounds. The synthesis is based on a trifluoroacetic acid-mediated hydroarylation of cinnamic esters with tyrosol to produce 4-aryl-3,4-dihydrocoumarins, molecules of biological interest, followed by a basic hydrolysis to give the corresponding opening products. Unreported mechanistic investigations confirmed that the first step resulted from an electrophilic aromatic substitution and an intramolecular transesterification. Final products exhibited a DPPH radical scavenging activity significantly higher than tyrosol.

Introduction

It is well known that the human body is susceptible to the attack of free radicals and reactive oxygen species (ROS) showing harmful effects for human health. Under normal conditions, this action is controlled by endogenous defence systems which intercept ROS or repair the damage that has already occurred by them. On the contrary, if there is an imbalance between these systems because of an overproduction of free radicals in the organism or a deficit in the defence system, a pathological mechanism called *oxidative stress* ensues.[1] Epidemiological studies demonstrated that this condition is related to the occurrence of many chronic degenerative diseases including neurovegetative pathologies,[2] cancer,[3] cerebral ischemia,[4] hypertension,[5] diabetes,[6] rheumatic diseases,[7] and multiple sclerosis.[8] In addition to endogenous defence systems, exogenous antioxidants taken up from the diet may counteract the dangerous effects of ROS. Among them, phenolic compounds are well-recognized powerful antioxidants present in plant food.[9] Representative compounds are 2-(3,4-dihydroxyphenyl)ethanol **1** (hydroxytyrosol), present in extra-virgin olive oil;[10] 4-hydroxycinnamic acid **3** (*p*-coumaric acid), 4-hydroxy-3-methoxycinnamic acid **4** (ferulic acid); 3,4-dihydroxycinnamic acid **5** (caffeic acid) and 4-hydroxy-3,5-dimethoxycinnamic acid **6** (sinapic acid), responsible for the beneficial health effects associated with cereal consumption (Figure 1).[11] In contrast, 2-(4-hydroxyphenyl)ethanol **2** (tyrosol) shows a weak anti-oxidative efficacy.[12] Despite this property, in the last few years tyrosol has attracted the attention of organic chemists and pharmacologists being a versatile substrate for the synthesis of a variety of esters exhibiting diverse biological effects including antioxidant, anti-cancer, antimicrobial and antileishmania activities.[13] In this context, in our laboratory we utilized tyrosol for the preparation of biologically and industrially-relevant catechols that showed antioxidant and antiproliferative effect on human colon cancer cells.[14] Continuing this research, we describe here the synthesis of novel DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavengers. As shown in Scheme 1, key step of our strategy is the preparation of 4-aryl-3,4-dihydrocoumarins. In the literature several synthetic methods have been described for the synthesis of this class of compounds including catalytic hydrogenation of coumarins,[15] reaction of alkenyl carbene chromium(0) complexes with ketene acetals,[16] reaction of Meldrum's acid or 5-alkylidene Meldrum's acid with phenols,[17] rhodium-mediated reaction of 3-(2-hydroxyphenyl)-cyclobutanones,[18] Lewis acid catalyzed reaction of acrylonitrile with phenols,[19] hydroarylation of cinnamic acid derivatives with alkyl phenols under acidic conditions [20] or microwave irradiation.[21] Among them, hydroarylation reaction seems of interest allowing the formation of C-C bonds with high atom economy from simple phenol substrates.[22] A mild and convenient version is the trifluoroacetic acid-mediated hydroarylation.[23] On the basis of these literature data, we firstly explored the potentiality of this procedure using tyrosol and cinnamic acid derivatives as starting materials in order to obtain novel 4-aryl-3,4-dihydrocoumarins, precursors of our target compounds.

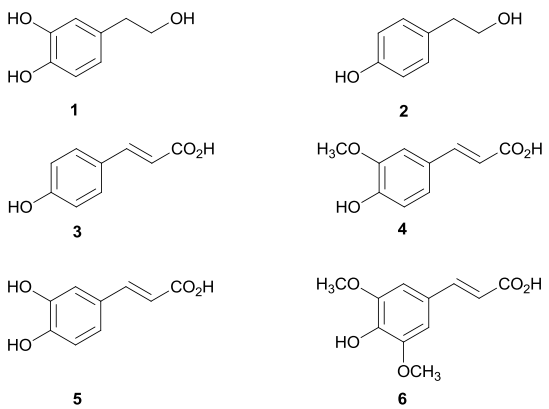
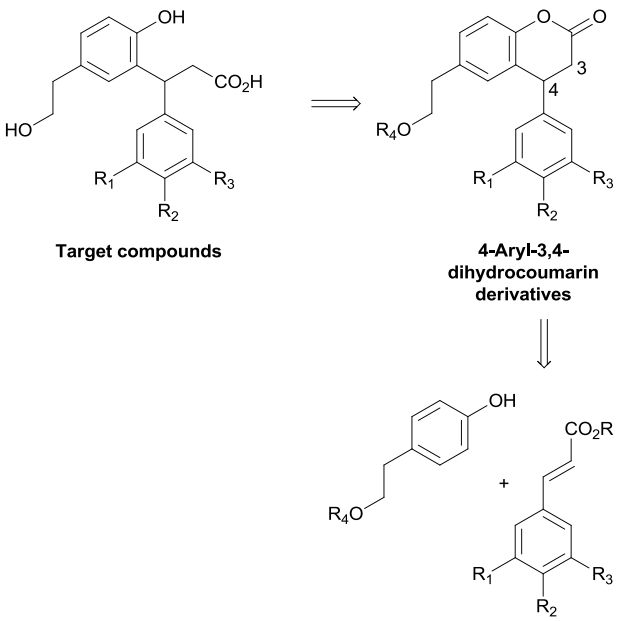


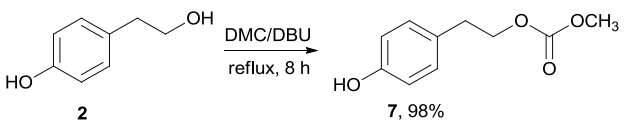
Fig. 1. Representative naturally occurring phenolic compounds.



Scheme 1. Synthetic strategy to obtain novel tyrosol derivatives.

Results and discussion

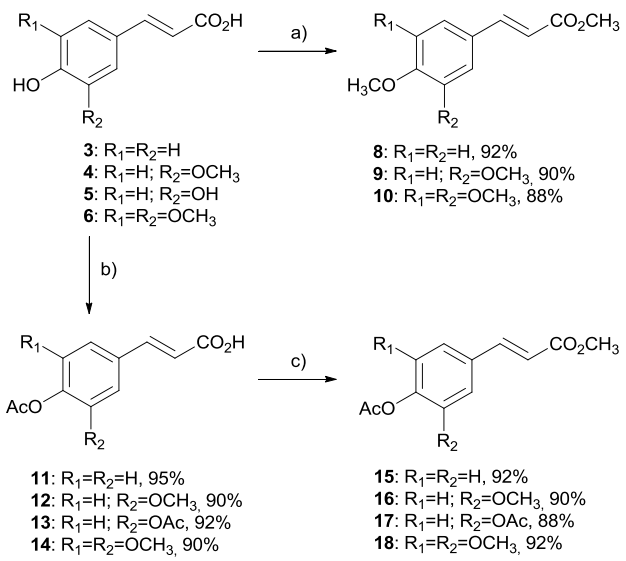
Firstly, we selectively protected the alcoholic functionality of tyrosol **2**, the carboxylic and phenolic moieties of cinnamic acids **3-6**. Thus, tyrosol was converted in the corresponding tyrosol methyl carbonate **7** by an efficient and simple procedure using dimethyl carbonate (DMC) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), as shown in Scheme 2.[24]



2 **7**, 98%

Scheme 2. Carboxymethylation of tyrosol **1** with DMC/DBU.

Cinnamic acids **3-6** were converted into the corresponding methyl cinnamates **8-10** by reaction with potassium carbonate and an excess of dimethyl sulfate. The yields of the final products were comparable to those obtained by the Wittig reactions between the corresponding benzaldehydes and the appropriate phosphorane derivatives.[25,26,27] Finally, cinnamic acids **3-6** were converted into *p*-acetoxy methyl cinnamates **15-18** by reaction of the phenolic moiety with acetic anhydride in dry pyridine followed by methylation of the carboxylic group with potassium carbonate and dimethyl sulfate (Scheme 3).



3: R_1=R_2=H
4: R_1=H; R_2=OCH_3
5: R_1=H; R_2=OH
6: R_1=R_2=OCH_3

8: R_1=R_2=H, 92%
9: R_1=H; R_2=OCH_3, 90%
10: R_1=R_2=OCH_3, 88%

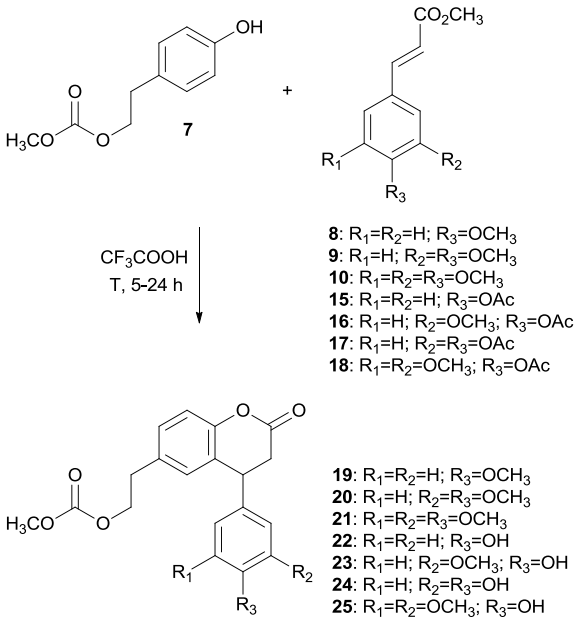
11: R_1=R_2=H, 95%
12: R_1=H; R_2=OCH_3, 90%
13: R_1=H; R_2=OAc, 92%
14: R_1=R_2=OCH_3, 90%

15: R_1=R_2=H, 92%
16: R_1=H; R_2=OCH_3, 90%
17: R_1=H; R_2=OAc, 88%
18: R_1=R_2=OCH_3, 92%

a) $(CH_3)_2SO_4/K_2CO_3$, acetone, rt, 24 h
b) Ac_2O, dry Py, rt, 24 h
c) $(CH_3)_2SO_4/K_2CO_3$, acetone, rt, 8 h

Scheme 3. Methylation and acetylation reactions of cinnamic acids **3-6**.

Hydroarylation reactions of cinnamic esters **8-10** and **15-18** with tyrosol methyl carbonate **7** in trifluoroacetic acid are depicted in Scheme 4. Experimental results showed that 4-aryl-3,4-dihydrocoumarins **19-21** deriving from cinnamic esters bearing electron-donating groups were obtained in satisfactory yields both at room temperature and reflux temperature (Table 1, entries 1-6); 4-aryl-3,4-dihydrocoumarins **22-25** deriving from cinnamic esters bearing an electron-withdrawing group at *para*-position (an acetoxy group) were isolated in lower yields also at reflux temperature (Table 1, entries 7-14).



Scheme 4. TFA-mediated reaction of tyrosol methyl carbonate **7** with cinnamic esters **8**-**10** and **15**-**18**.

Table 1. Experimental conditions of the reaction depicted in Scheme 4.

Entry	Cinnamic ester	Experimental conditions [a]	Product (Yield %)[b]
1	**8**	25 °C, 24 h	**19**: 76
2	**8**	Reflux, 5 h	**19**: 78
3	**9**	25 °C, 24 h	**20**: 70
4	**9**	Reflux, 5 h	**20**: 74
5	**10**	25 °C, 24 h	**21**: 68
6	**10**	Reflux, 5 h	**21**: 64
7	**15**	25 °C, 24 h	**22**: 42
8	**15**	Reflux, 6 h	**22**: 52
9	**16**	25 °C, 24 h	**23**: 40
10	**16**	Reflux, 6 h	**23**: 50
11	**17**	25 °C, 24 h	**24**: 38
12	**17**	Reflux, 6 h	**24**: 42
13	**18**	25 °C, 24 h	**25**: 40
14	**18**	Reflux, 5 h	**25**: 44

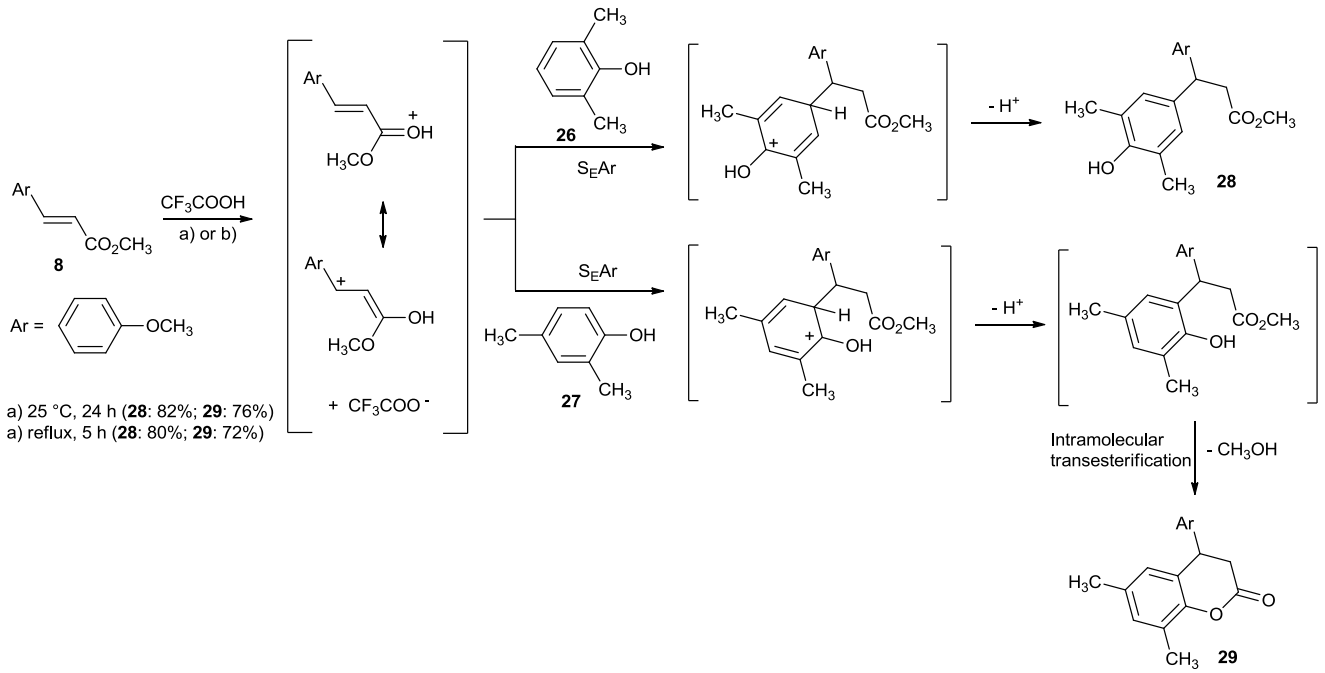
[a] Tyrosol methyl carbonate **7** (0.5 mmol); ester **8**-**10**, **15**-**18** (0.5 mmol); trifluoroacetic acid: 2 ml; [b] Calculated after chromatographic purification.

In the literature the *hypothesized* mechanism of the TFA-hydroarylation reaction, suggested on the basis of the electronic substituents effects on cinnamic ester derivatives, consists in the aromatic electrophilic substitution by the protonated cinnamic ester on phenolic substrate, followed by the intramolecular transesterification to afford the dihydrocoumarin.[20] In order to confirm this hypothesis, we carried out the reactions of ester **8** in combination with 2,6-dimethylphenol **26** and 2,4-dimethylphenol **27** in trifluoroacetic acid (Scheme 5). According to the proposed mechanism, phenol **26**, exhibiting two methyl groups in *both* the *ortho*-positions and the free *para*-position, gave **28** as the only product; in contrast, phenol **27**, showing one free *ortho*-position, produced the dihydrocoumarin **29**. Both at 25 °C and reflux temperature, compounds **28** and **29** were obtained as the only reaction products.

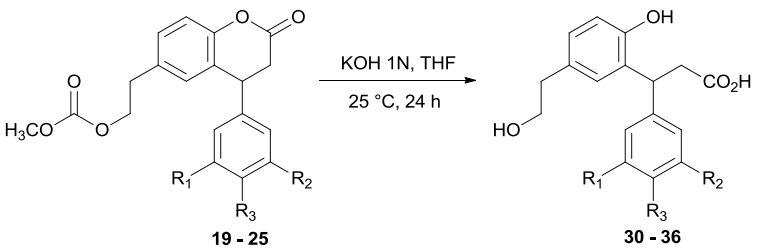
Novel 4-aryl-3,4-dihydrocoumarins **19-25** appear interesting molecules from the biological point of view. As a matter of fact, several compounds of these class have been shown to possess many biological properties such as antiherpetic,[25] estrogenic,[26] antimicrobial,[27] anti-inflammatory,[28] cytotoxic,[29] and antifungal activities.[30] In addition, many dihydrocoumarins are used as synthetic intermediates of pharmaceuticals and flavoring agents of foods such as drinks, yogurt, cakes.[31]

Finally, we carried out the basic hydrolysis of compounds **19-25**. Under these conditions both the opening of the lactonic ring and deprotection of the carbonate moiety of tyrosol skeleton was observed to produce tyrosol derivatives **30**, **31**, **32**, **33**, **34** and **36** (Scheme 6). Unfortunately, we were not able to isolate pure sample of tyrosol derivative **35**, probably for its high polarity.

Compounds **30**, **31**, **32**, **33**, **34** and **36** were evaluated about their radical scavenging capacity by using the DPPH radical test assay.[32] The antioxidant activity was defined as the amount of compound necessary to decrease the initial DPPH concentration by 50% and expressed as EC_{50} (Efficient Concentration=mmol tyrosol derivative/mmol DPPH). As showed in Table 2, all novel products showed a significant radical-scavenging activity. Among them, the most active was compound **36**; as a general trend, the substitution of a methoxy group with an hydroxyl group in the acidic frame produced an increase of activity (compare compound **30** with **33**; **31** with **34**; **32** with **36**) as already reported in the literature and also observed by us.[14]



Scheme 5. Mechanistic investigations with cinnamic ester **8** and phenols **26** and **27**.

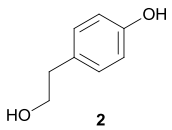
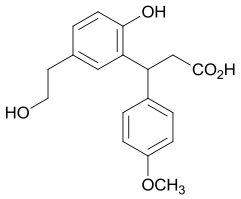
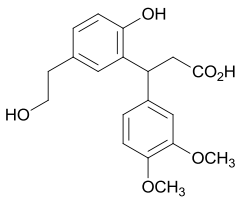
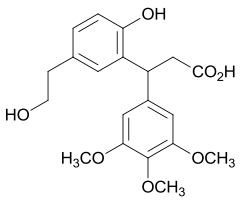
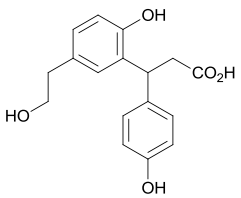
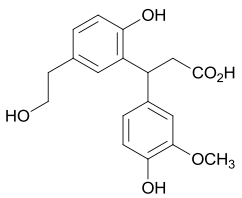
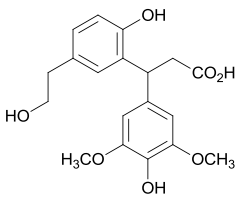


19: R_1=R_2=H; R_3=OCH_3
20: R_1=H; R_2=R_3=OCH_3
21: R_1=R_2=R_3=OCH_3
22: R_1=R_2=H; R_3=OH
23: R_1=H; R_2=OCH_3; R_3=OH
24: R_1=H; R_2=R_3=OH
25: R_1=R_2=OCH_3; R_3=OH

30: R_1=R_2=H; R_3=OCH_3 (90%)
31: R_1=H; R_2=R_3=OCH_3 (92%)
32: R_1=R_2=R_3=OCH_3 (92%)
33: R_1=R_2=H; R_3=OH (88%)
34: R_1=H; R_2=OCH_3; R_3=OH (90%)
35: R_1=H; R_2=R_3=OH (traces)
36: R_1=R_2=OCH_3; R_3=OH (92%)

Scheme 6. Basic hydrolysis of 4-aryl-3,4-dihydrocoumarins **19-25**.

Table 2. DPPH radical-scavenging effect of tyrosol **2** and compounds **30**-**34** and **36**.

Compound	 **2**	 **30**	 **31**	 **32**
EC_{50} [a]	21 ± 1.0	2.32 ± 0.03	2.49 ± 0.03	3.00 ± 0.03
Compound		 **33**	 **34**	 **36**
EC_{50} [a]		2.04 ± 0.02	0.86 ± 0.01	0.24 ± 0.01

[a] Mmol isochroman/mmol DPPH radical.

Conclusions

Tyrosol, a naturally phenolic compound poorly attractive as antioxidant for its weak efficacy, was used as starting material for the preparation of novel bioactive compounds by a two-steps procedure: 1) a trifluoroacetic acid-mediated hydroarylation of cinnamic esters; 2) a basic hydrolysis of the corresponding 4-aryl-3,4-dihydrocoumarins. Unreported mechanistic investigations confirmed that the hydroarylation process proceeded by an electrophilic substitution followed by an intramolecular esterification. Pure samples of final compounds were evaluated about the DPPH radical scavenging activity. Experimental results demonstrated that all compounds showed an effect significantly higher than tyrosol and their efficacy increased with the presence of one hydroxyl group into the aromatic ring of the acidic frame.

Experimental section

Materials and methods

Reagents and solvents were supplied from Sigma Aldrich (Milan, Italy) and used without further purification. Tyrosol methyl carbonate **7** was prepared according to already reported by us.[24] Silica gel 60 F254 plates and silica gel 60 were obtained from Merck (Milan, Italy). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 200 MHz spectrometer using $CDCl_3$ and CD_3OD as solvents. Chemical shifts are expressed in parts per million (δ scale) and coupling constants in Hertz. GC-MS analyses were performed on a Shimadzu VG 70/250S apparatus equipped with a Supelco SLB™-5ms column (30 m, 0.25 mm and 0.25 μm film thickness). The analyses were performed using an isothermal temperature profile of 100 °C for 2 min, followed by a 10 °C/min temperature gradient until 280 °C for 15 min. The injector temperature was 280 °C. High Resolution Mass Spectrometry (HRMS) analyses were recorded with Micromass Q-TOF micro Mass Spectrometer (Waters).

Synthesis

Methylation of cinnamic acids (3)-(6)

Cinnamic acid **3**, **4** or **6** (1.0 mmol) was solubilized in acetone (5 mL) at room temperature; then, potassium carbonate (2.0 mmol) and dimethyl sulfate (2.0 mmol) were added. The mixture was kept under magnetic stirring at room temperature for 24 h. After the work-up, final product (**8**, **9** or **10**) was purified on silica gel chromatographic column using hexane/ethyl acetate=9/1 as eluent.

(*E*)-Methyl 3-(4-methoxyphenyl)acrylate (8)

Yield: 92%; colorless oil; spectroscopic data are according to the literature.[33]

(*E*)-Methyl 3-(3,4-dimethoxyphenyl)acrylate (9)

Yield: 90%; colorless oil; spectroscopic data are according to the literature.[34]

(*E*)-Methyl 3-(3,4,5-trimethoxyphenyl)acrylate (10)

Yield: 88%; colorless oil; spectroscopic data are according to the literature.[35]

Acetylation of cinnamic acids (3)-(6)

To a solution of cinnamic acid **3**, **4**, **5** or **6** (1.0 mmol) into dry pyridine (1.5 mL) was added acetic anhydride (1.5 mL). The mixture was stirred at room temperature overnight. Then, the reaction mixture was poured into the ice-water (5 ml) and treated with 3M HCl. The precipitated product was filtered and washed with water and diethyl ether. Pure sample of compound (**11, 12, 13, 14**) was obtained after silica gel chromatographic column using hexane/ethyl acetate=8/2 as eluent.

(*E*)-3-(4-Acetoxyphenyl)acrylic acid (11)

Yield: 95%; colorless oil; spectroscopic data are according to the literature.[36]

(*E*)-3-(4-Acetoxy-3-methoxyphenyl) acrylic acid (12)

Yield: 90%; colorless oil; spectroscopic data are according to the literature.[37]

(*E*)-3-(3,4-Diacetoxyphenyl) acrylic acid (13)

Yield: 92%; colorless oil; spectroscopic data are according to the literature.[38]

(*E*)-3-(4-Acetoxy-3,5-dimethoxyphenyl)acrylic acid (14)

Yield: 90%; colorless oil; spectroscopic data are according to the literature.[37]

Methylation of cinnamic acid derivatives (11)-(14)

Cinnamic acid **11**, **12**, **13** or **14** (1.0 mmol) was solubilized in acetone (5 mL) at room temperature. Then potassium carbonate (1.0 mmol) and dimethyl sulfate (1.0 mmol) were added and the mixture was kept under magnetic stirring at room temperature for 8 h. After the work-up, final product (**11**, **12**, **13**, **14**) was purified by silica gel chromatographic column using hexane/ethyl acetate=8/2 as eluent.

(*E*)-Methyl 3-(4-acetoxyphenyl)acrylate (15)

Yield: 92%; colorless oil; spectroscopic data are according to the literature.[39]

(*E*)-Methyl 3-(4-acetoxy-3-methoxyphenyl)acrylate (16)

Yield: 90%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.66 (d, *J*= 16.0 Hz, 1H, CH=CH), 6.96-7.09 (m, 3H, Ph-H), 6.34 (d, *J*= 16.0 Hz, 1H, CH=CH), 3.84 (s, 3H, OCH_3), 3.77 (s, 3H, CO_2CH_3), 2.29 (s, 3H, $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.7, 167.2, 151.4, 144.1, 141.4, 133.2, 123.2, 121.1, 118.0, 111.3, 55.8, 51.7, 20.6; GC-MS: 250 (M^+), 208, 177, 145. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64; found: C, 62.45; H, 5.60.

(*E*)-Methyl 3-(3,4-diacetoxyphenyl)acrylate (17)

Yield 88 %; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.57 (d, *J*= 16.0 Hz, 1H, CH=CH), 7.14 -7.37 (m, 3H, Ph-H), 6.33 (d, *J*= 16.0 Hz, 1H, CH=CH), 3.74 (3H, s, CO_2CH_3), 2.25 (6H, s, 2x$OCOCH_3$);^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.0 (2C), 166.9, 143.5, 142.8, 142.4, 133.2, 126.3, 123.9, 122.6, 118.9, 51.7, 20.5 (2C); GC-MS: 278 (M^+), 236, 194, 163, 134. $C_{14}H_{14}O_6$ requires C, 60.43; H, 5.07; found C, 60.54; H, 5.10.

(*E*)-Methyl 3-(4-acetoxy-3,5-dimethoxyphenyl)acrylate (18)

Yield 92 %; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.54 (d, *J*= 16.0 Hz, 1H, CH=CH), 6.70 (s, 2H, Ph-H), 6.32 (d, *J*= 16.0 Hz, 1H, CH=CH), 3.76 (s, 6H, 2xOCH_3), 3.74 (s, 3H, CO_2CH_3), 2.23 (s, 3H, $OCOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.4, 167.1, 152.4 (2C), 144.5, 132.6, 130.4, 118.0, 104.6 (2C), 56.1 (2C), 51.6, 20.3; GC-MS: 280 (M^+), 238, 207, 175, 163, 147, 135, 119. $C_{14}H_{16}O_6$ requires C, 59.99; H, 5.75; found C, 60.19; H 5.70.

Reaction of tyrosol methyl carbonate (7) with cinnamates (8)-(10) or (15)-(18)

Tyrosol methyl carbonate **7** (0.3 mmol) and the appropriate cinnamate derivative **8**, **9**, **10**, **15**, **16**, **17** or **18** (0.5 mmol) were kept in trifluoroacetic acid (2.5 mL) under magnetic stirring at room or reflux temperature for 5-24 h depending on the experiment. At the end, the crude was neutralized with aqueous $NaHCO_3$ and extracted with ethyl acetate. Organic phases were washed with a saturated NaCl solution and dried on anhydrous Na_2SO_4. After evaporation of the solvent, final product (**19**, **20**, **21**, **22**, **23**, **24**, **25**) was purified by silica gel chromatographic column using hexane/ethyl acetate (8/2 or 7/3) as eluent depending on the substrate.

2-[4-(4-Methoxyphenyl)-2-oxochroman-6-yl]ethyl methyl carbonate (19)

Yield 76 and 78%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.02-7.16 (4H, m, Ph-H), 6.72-6.87 (m, 3H, Ph-H), 4.20-4.27 (m, 3H, CH_2 and CH), 3.78 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 2.87-3.00 (m, 2H, CH_2), 2.86 (t, *J*= 6.7 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.7, 159.0, 155.6, 150.5, 133.8, 132.1, 130.1, 129.1, 128.7, 128.6, 126.2, 117.2, 115.4, 114.5, 68.1, 55.3, 54.7, 39.9, 37.2, 34.4; GC-MS: 356 (M^+), 280, 262, 237, 207. $C_{20}H_{20}O_6$ requires C, 67.41; H, 5.66; found C, 67.50; H, 5.60.

2-[4-(3,4-Dimethoxyphenyl)-2-oxochroman-6-yl]ethyl methyl carbonate (20)

Yield 70 and 74%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.02-7.16 (m, 2H, Ph-H); 6.63-6.83 (m, 4H, Ph-H), 4.20-4.27 (m, 3H, CH_2 and CH), 3.81 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 2.96-3.01 (m, 2H, CH_2), 2.88 (t, *J*= 7.1 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.6, 155.6, 150.5, 149.5, 148.6, 133.8, 132.6, 129.2, 128.6, 126.1, 119.7, 117.2, 111.6, 110.5, 68.1, 55.9 (2C) , 54.7, 40.4, 37.1, 34.4; GC-MS: 386 (M^+), 310, 292, 277, 237. $C_{21}H_{22}O_7$ requires C, 65.28; H 5.74; found C, 65.42; H, 5.84.

Methyl [2-(2-oxo-4-(3,4,5-trimethoxyphenyl)chroman-6-yl-]ethyl carbonate (21)

Yield 68 and 64%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.87-7.17 (m, 3H, Ph-H), 6.32 (s, 2H, Ph-H), 4.19-4.29 (m, 3H, CH_2 and CH), 3.84 (s, 3H, 2xOCH_3), 3.78 (s, 3H, OCH_3), 3.71 (3H, s, CO_2CH_3), 2.97-3.03 (m, 2H, CH_2), 2.81 (2H, t, *J*= 6.8 Hz, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.7, 155.6, 150.5 (2C), 146.9, 145.1, 133.8, 132.0, 129.2, 128.7, 126.2, 120.5, 117.2,

114.9, 109.7, 68.1, 55.9, 54.7, 40.5, 37.2, 34.4, 29.7; GC-MS: 416 (M^+), 340, 322, 307, 281, 267. $C_{22}H_{24}O_8$ requires C, 63.45; H, 5.81; found C 65.08; H, 5.80.

2-[4-(4-Hydroxyphenyl)-2-oxochroman-6-yl]ethyl methyl carbonate (22)

Yield 42 and 52%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.93-7.15 (m, 5H, Ph-H), 6.71-6.83 (m, 2H, Ph-H), 4.19-4.27 (m, 3H, CH_2 and CH), 3.72 (s, 3H, CO_2CH_3), 2.94-2.99 (m, 2H, CH_2), 2.86 (t, J= 6.9 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.2, 155.4, 150.4, 148.2, 133.9, 131.9, 129.1, 128.7 (2C), 128.5, 126.2, 117.2, 116.0 (2C), 68.1, 54.1, 39.8, 37.2, 34.3; GC-MS: 342 (M^+), 266, 248, 223, 207. $C_{19}H_{18}O_6$ requires C, 66.66; H, 5.30; found C, 66.46; H 5.20.

2-[4-(4-Hydroxy-3-methoxyphenyl)-2-oxochroman-6-yl]ethyl methyl carbonate (23)

Yield 40 and 50%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.02-7.16 (m, 2H, Ph-H); 6.83-6.88 (m, 2H, Ph-H), 6.60-6.65 (m, 2H, Ph-H), 5.60 (s, br, 1H, OH), 4.18-4.27 (m, 3H, CH_2 and CH), 3.82 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 2.98-3.01 (m, 2H, CH_2), 2.87 (t, J= 6.9 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.7, 155.6, 150.4, 146.9, 145.1, 133.8, 132.0, 129.1, 128.6, 126.1, 120.5, 117.2, 114.8, 109.7, 68.1, 55.9, 54.7, 40.4, 37.2, 34.4. GC-MS: 386 (M^+), 372, 296, 278, 253, 223. $C_{20}H_{20}O_7$ requires C, 64.51; H, 5.41; found C, 64.61; H, 5.31.

2-[4-(3,4-Dihydroxyphenyl)-2-oxochroman-6-yl]ethyl methyl carbonate (24)

Yield 38 and 42%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.78-7.14 (m, 4H, Ph-H), 6.57 (d, J= 6.7 Hz, 2H, Ph-H), 4.05-4.34 (m, 3H, CH_2 and CH), 3.72 (s, 3H, CO_2CH_3), 2.85-3.03 (m, 2H, CH_2), 2.87 (t, J= 6.8 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.2, 155.6, 150.4, 144.1, 143.4, 133.8, 132.7, 128.9, 128.7, 125.9, 119.9, 117.0, 115.6, 114.4, 68.3, 54.9, 39.8, 36.9, 34.4; GC-MS: 358 (M^+), 382, 296, 278, 253, 194. $C_{19}H_{18}O_7$ requires C, 63.68; H, 5.06; found C, 63.88; H, 5.16.

2-[4-(4-Hydroxy-3,5-dimethoxyphenyl)-2-oxochroman-6-yl]ethyl methyl carbonate (25)

Yield 40 and 44%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 6.73-7.02 (m, 3H, Ph-H), 6.34 (s, 2H, Ph-H), 4.17-4.28 (m, 3H, CH_2 and CH), 3.80 (6H, s, 2xOCH_3), 3.71 (3H, s, CO_2CH_3), 2.90-3.01 (m, 2H, CH_2), 2.86 (t, J= 6.8 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 167.6, 155.6, 150.5, 147.4 (2C), 134.2, 133.9, 131.2, 130.1, 129.2, 128.7, 126.1, 117.2 (2C), 104.3 (2C), 68.1, 56.3, 54.7, 40.9, 37.1; GC-MS: 402 (M^+), 326, 308, 293, 253. $C_{21}H_{22}O_8$ requires C, 62.68; H, 5.51; found C, 62.48; H, 5.59.

Methyl 3-(4-hydroxy-3,5-dimethylphenyl)-3-(4-methoxyphenyl)propanoate (28)

Yield 80 and 82%; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.16-7.19 (d, J= 8.0 Hz, 2H, Ph-H), 6.83-6.86 (m, 4H, Ph-H), 4.42 (t, J= 8.0 Hz, 1H, CH), 4.01 (s, br, 1H, OH), 3.98 (s, 3H, OCH_3), 3.61 (s, 3H, CO_2CH_3), 3.02 (d, J= 8.0 Hz, 2H, CH_2), 2.22 (6H, s, 2xCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.2, 157.5, 150.3, 135.7, 134.9, 127.9 (2C), 127.1 (2C), 122.6, 113.4 (2C), 54.7, 51.2, 44.9, 40.5, 15.7, 15.6 (2C) ; GC-MS: 314 (M^+), 299, 281, 271, 254, 241. $C_{19}H_{22}O_4$ requires C, 72.59; H, 7.05; found C, 72.37; H, 7.15.

4-(4-Methoxyphenyl)-6,8-dimethylchroman-2-one (29)

Colorless oil. Spectroscopic data are according to the literature.[20a]

Hydrolysis of compounds (19)-(25)

Dihydrocoumarin **20**, **21**, **22**, **23**, **24** or **25** (0.2 mmol) was treated with 1N KOH in THF (2 ml) at room temperature. After the work-up and chromatographic purification by silica gel chromatographic column using dichloromethane/methanol (8/2, 7/3 or 6/4 depending on the polarity of product), compounds **30**, **31**, **32**, **33**, **34** and **36** were isolated as pure samples.

3-(2-Hydroxy-5-(2-hydroxyethyl)phenyl)-3-(4-methoxyphenyl)propanoic acid (30)

Yield 90%; colorless oil; ^{1}H NMR ($CDCl_3$/CD_3OD, 200 MHz) δ: 7.1 (d, J= 7.1 Hz, 2H, Ph-H), 6.61-6.84 (m, 5H, Ph-H), 4.72 (t, J= 7.5 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.63 (t, J= 6.9 Hz, 2H, CH_2), 2.94-3.02 (m, 2H, CH_2), 2.70 (t, J= 6.7 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.6, 159.0, 151.8, 133.1, 130.6 (2C), 129.2, 130.1, 126.2, 123.2, 117.5 (2C), 115.9, 63.0, 54.2, 42.4, 39.2, 38.5. $C_{18}H_{20}O_5$ requires C, 68.34; H, 6.37; found C, 68.42; H, 6.45.

3-(3,4-Dimethoxyphenyl)-3-(2-hydroxy-5-(2-hydroxyethyl)phenyl)propanoic acid (31).

Yield 92%; colorless oil; ^{1}H NMR ($CDCl_3$/CD_3OD, 200 MHz) δ: 6.63-6.85 (m, 6H, Ph-H), 4.71 (t, J= 7.8 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.63 (t, J= 6.9 Hz, 2H, CH_2), 2.85-3.10 (m, 2H, CH_2), 2.62 (t, J= 6.6 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.6, 151.7, 149.6, 147.6, 130.6, 129.4, 128.5, 126.2, 123.8, 123.0, 115.9, 115.0, 112.0, 63.0, 56.0 (2C), 42.4, 39.7, 39.2. $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40; found C, 68.48; H, 6.32.

3-(2-Hydroxy-5-(2-hydroxyethyl)phenyl)-3-(3,4,5-trimethoxyphenyl)propanoic acid (32)

Yield 92%; colorless oil; ^{1}H NMR ($CDCl_3$/CD_3OD, 200 MHz) δ: 6.77-6.86 (m, 2H, Ph-H), 6.65 (d, J= 8.0 Hz, 1H, Ph-H), 6.45 (s, 2H, Ph-H), 4.68 (t, J= 7.8 Hz, 1H, CH), 3.70 (s, 6H, 2xOCH_3), 3.68 (s, 3H, OCH_3), 3.59 (t, J= 6.7 Hz, 2H, CH_2), 2.81-3.07 (m, 2H, CH_2), 2.61 (t, J= 6.7 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.6, 151.5, 152.2, 151.4, 140.4, 137.0, 131.4, 130.1, 126.2, 124.0, 115.9, 108.0 (2C), 63.0, 60.6, 56.1 (2C), 42.4, 40.9, 39.2. $C_{20}H_{24}O_7$ requires C, 63.82; H, 6.43; found C, 63.72; H, 6.38.

3-(2-Hydroxy-5-(2-hydroxyethyl)phenyl)-3-(4-hydroxyphenyl)propanoic acid (33)

Yield 88%; colorless oil; ^{1}H NMR ($CDCl_3$/CD_3OD, 200 MHz) δ: 7.12 (d, J= 8.7 Hz, 2H, Ph-H), 6.51-6.73 (m, 5H, Ph-H), 4.65 (t, J= 7.6 Hz, 1H, CH), 3.57 (t, J= 6.7 Hz, 2H, CH_2), 2.78-3.01 (m, 2H, CH_2), 2.56 (t, J= 6.7 Hz, 2H, CH_2); ^{13}C NMR (50 MHz,

$CDCl_3$) δ: 177.6, 154.0, 151.8, 139.7, 130.2 (2C), 130.1, 129.3, 126.2, 123.2, 117.9 (2C), 115.9, 63.0, 42.4, 39.2, 38.5. $C_{17}H_{18}O_5$ requires C, 67.54; H, 6.00; found C, 67.74; H, 6.10.

3-(4-Hydroxy-3-methoxyphenyl)-3-(2-hydroxy-5-(2-hydroxyethyl)phenyl)propanoic acid (34)

Yield 90%; colorless oil; ^{1}H NMR ($CDCl_3/CD_3OD$, 200 MHz) δ: 6.59-6.86 (m, 6H, Ph-H), 4.70 (t, *J*= 7.5 Hz, 1H, CH), 3.66 (t, *J*= 6.6 Hz, 2H, CH_2), 2.88-3.10 (m, 2H, CH_2), 2.58 (t, *J*= 6.6 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.6, 151.7, 149.2, 143.6, 135.1, 130.1, 129.5, 128.2, 124.7, 123.0, 117.9, 115.9 (2C), 63.0, 55.9, 42.4, 39.7, 39.5. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.07; found: C, 65.25; H, 6.12.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-3-(2-hydroxy-5-(2-hydroxyethyl)phenyl)propanoic acid (36)

Yield 92%; colorless oil; ^{1}H NMR ($CDCl_3/CD_3OD$, 200 MHz) δ: 6.58-6.95 (m, 4H, Ph-H), 6.43 (s, 2H, Ph-H), 4.65 (t, *J*= 7.5 Hz, 1H, CH), 3.75 (s, 6H, 2xOCH_3), 3.66 (t, *J*= 6.6 Hz, 2H, CH_2), 2.87-2.96 (m, 2H, CH_2), 2.61 (t, *J*= 6.6 Hz, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.6, 151.5, 148.4 (2C), 136.5, 133.8 (2C), 131.5, 130.1, 126.2, 124.0, 115.9, 108.2 (2C), 63.0, 56.1, 42.4, 40.9, 39.2. $C_{19}H_{22}O_7$ requires C, 62.97; H, 6.12; found: C, 63.42; H, 6.10.

Determination of the antioxidant activity

The antioxidant activity of tyrosol **1** and compounds **30**, **31**, **32**, **33**, **34** and **36** was determined using DPPH as free radical in methanol.[32] This ability was expressed as Efficient Concentration (EC_{50}= mmol of antioxidant/mmol DPPH that is the concentration of antioxidant needed to decrease the initial DPPH concentration by 50%. Aliquots of methanol solution containing different concentrations of the tested compound (expressed as the number of mmoles of antioxidant/mmol DPPH were added to a 2.8 mL of 6 x 10^{-5} M methanolic DPPH solution. The decrease in absorbance was determined at 25 °C at selected λ=516 nm (ε_{516}= 10357 ± 162 $M^{-1}cm^{-1}$) for different ranges of time until the reaction reached a plateau. For each concentration tested, the reaction kinetics was plotted. From these graphs the percentage of remaining DPPH at the steady state was determined and corrected with respect to a control DPPH solution. The percentage of remaining DPPH values was transferred onto another graph showing the percentage of residual DPPH at the steady state as a function of molar ratio of tyrosol and cinnamic acid derivatives to DPPH. EC_{50} values were then extrapolated.

Notes and references

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