One-Pot Synthesis of 6-Hydroxyisochromans: The Example of Demethyl-oxa-coclaurine

Marcella Guiso,[a] Armandodoriano Bianco,[a] Carolina Marra,*[a] and Claudia Cavarischia[a]

Keywords: Natural products / Synthesis design / Isochroman

Using a modified oxa-Pictet Spengler reaction that we recently described, we synthesized 6-hydroxy-isochromans and their 7-hydroxy derivatives. The successful one step synthesis did not require protecting groups and provided high yields. The obtainment of 1-(4′-hydroxybenzyl)-6,7-dihydroxyisochroman (**1**) indicates that this protocol can be used to synthesize oxygenated analogues of benzyl-tetrahydroisoquinoline alkaloids, such as demethyl-coclaurine (**2**). This methodology could provide a general procedure for the synthesis of hydroxyisochromans.

Introduction

The benzyl-tetrahydro-isoquinoline moiety is present in the metabolic pattern of many plants and can undergo modifications to produce a wide range of substances.[1] Many of these substances are important drugs, including benzyl-tetrahydro-isoquinoline alkaloids, which are biosynthesized by an enzymatic Pictet−Spengler reaction.[2] In its simplest form, this reaction consists of the condensation of a β-phenyl-ethylamine with a carbonyl compound, generating an iminium salt which undergoes cyclization by means of an intramolecular electrophilic aromatic substitution. The oxygenated version of this reaction was reported for the first time by Wunsch and Zott in 1992 and denominated "the oxa-Pictet−Spengler reaction."[3] In previous work we proposed modifications to this reaction,[4] the results led us to hypothesize that this modified version could be generalized to obtain oxygenated analogues of benzyl-tetrahydroisoquinoline alkaloids (i.e. 1-benzyl-isochromans). To test this hypothesis, we used the modified oxa-Pictet−Spengler reaction to synthesize 1-(4′-hydroxybenzyl)-6,7-dihydroxyisochroman (**1**), the oxygenated analogue of the benzyl-tetrahydroisoquinoline alkaloid demethylcoclaurine (**2**, Figure 1).

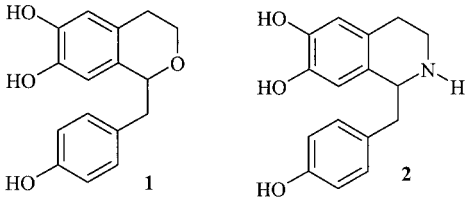


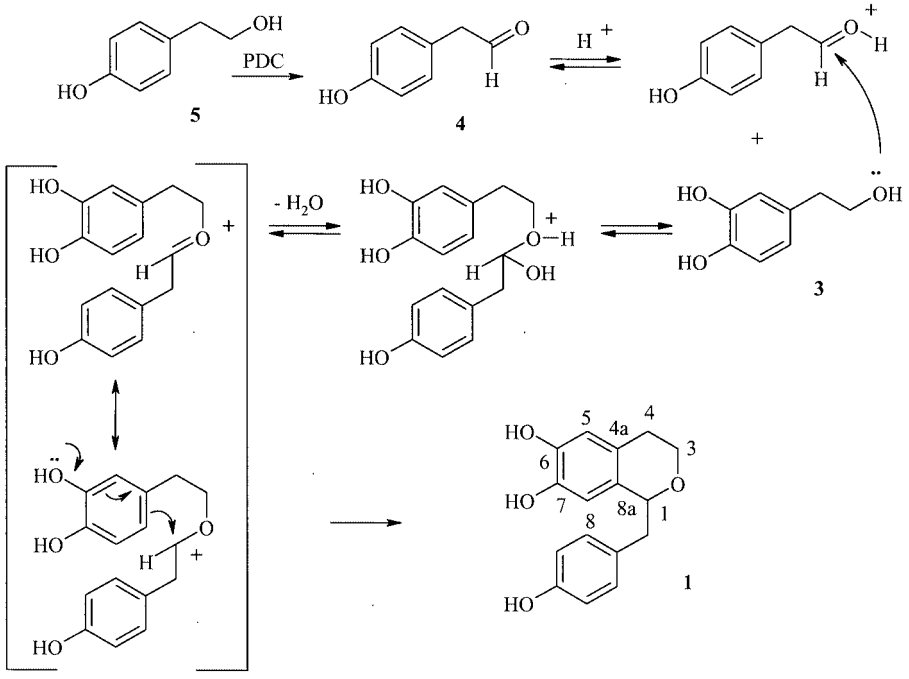
Figure 1. Demethyl-oxa-coclaurine (**1**) and demethylcoclaurine (**2**)

Results and Discussion

On the basis of a simple retrosynthetic analysis for the synthesis of the demethyl-oxa-coclaurine (**1**) [i.e., 1-(4′-hydroxybenzyl)-6,7-dihydroxyisochroman], hydroxytyrosol (**3**), and (*p*-hydroxyphenyl)ethanal (**4**) were identified as the starting compounds, as shown in Scheme 1. Aldehyde **4** is a non-commercial product which was prepared by the oxidation of tyrosol (**5**) with PDC.

The one-pot racemic synthesis of the target compound **1** was performed by a modified version of the protocol we recently described.[4] This modified procedure allows for the direct reaction between the two starting compounds, **3** and **4**, without requiring protecting groups. We proposed a three step mechanism[4] for the oxa-Pictet−Spengler reaction, as depicted in Scheme 1. The first step, the acid-catalyzed formation of the hemiacetal is followed by water loss, which provides the reactive intermediate that finally undergoes intramolecular electrophilic aromatic substitution, in the activated position *para* to the hydroxyl group. Under the mild experimental conditions adopted, we obtained a high regioselectivity for the aromatic electrophilic substitution, in the activated less hindered aromatic position. In our previous work[4] we found that aromatic aldehydes gave higher yields than aliphatic aldehydes, leading us to hypothesize that the water elimination step was fundamental. This step occurs more easily with a homobenzylic hemiacetal. To determine whether or not the water elimination step plays a key role in the proposed mechanism, we carried out reactions with and without dehydrating agents.

[a] Dipartimento di Chimica Università "La Sapienza",
Istituto di Chimica Biomolecolare del CNR
Piazzale Aldo Moro 5, 00185 Roma, Italy
Fax: (internat.) + 39-06/490631
E-mail: carolina.marra@uniroma1.it



Scheme 1. Proposed mechanism of oxa-Pictet−Spengler reaction

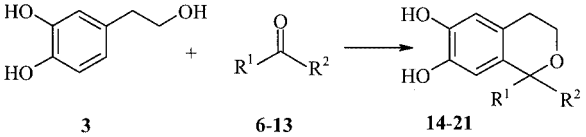
Specifically, we synthesized a series of 6,7-dihydroxyisochromans, some of which have been described previously,[4] with addition of one of two dehydrating agents to the reaction mixture: molecular sieves (protocol A) or anhydrous sodium sulfate (Na_2SO_4) (protocol B). The reaction yields were compared with those previous described by us without a dehydrating agent (protocol C). Hydroxytyrosol (**3**) and a series of selected carbonyl compounds (**6**−**13**) with aliphatic as well as aromatic structures were used. The carbonyl compounds used in our previous work and reused here (**6**−**10**) were those that had given the lowest yields of the corresponding isochromans (compounds **14**−**18**). The new isochromans (compounds **19**−**21**) were prepared using all three protocols.

The results of the modified oxa-Pictet−Spengler reaction with and without the dehydrating agents are reported in Table 1. The protocols using dehydrating agents gave higher yields compared to those without for all of the isochromans obtained (**14**−**21**). The highest yields were obtained when using molecular sieves as the dehydrating agent (protocol A). The reactions involving aliphatic carbonyl compounds generally gave higher increases in yield compared to those obtained for aromatic carbonyl compounds.

Finally, to determine whether or not the hydroxyl group at C-7 plays a role in the formation of the isochroman skeleton, we performed reactions using 2-(3′-hydroxyphenyl)ethanol (**25**) with pentanal (**7**) and three aromatic aldehydes: piperonal (**22**), *p*-chlorobenzaldehyde (**23**), and *p*-methoxycarbonylbenzaldehyde (**24**).

Table 2 shows the yields of the corresponding 6-hydroxyisochroman derivatives (**26**−**29**) obtained. As expected, aromatic aldehydes afforded the highest yields.

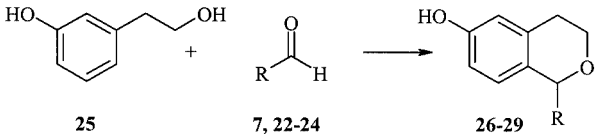
Table 1. Comparison of yields obtained from hydroxytyrosol (**3**) using protocols A, B, and C



3 **6-13** **14-21**

Reagents: **3** and	Yield (%) protocol A	Yield (%) protocol B	Yield (%) protocol C	Obtained product		
Acetone (**6**)	95	80	63	**14**	$R^1 = CH_3$	$R^2 = CH_3$
Pentanal (**7**)	80	60	50	**15**	$R^1 = H$	$R^2 = n$-butyl
m-OH-benzaldehyde (**8**)	98	90	80	**16**	$R^1 = H$	$R^2 = m$-OH-phenyl
p-OCH_3-benzaldehyde (**9**)	98	90	80	**17**	$R^1 = H$	$R^2 = p$-OCH_3-phenyl
Benzaldehyde (**10**)	95	80	60	**18**	$R^1 = H$	R^2 = phenyl
Isovaleraldehyde (**11**)	90	73	62	**19**	$R^1 = H$	R^2 = isobutyl
Propanal (**12**)	95	80	72	**20**	$R^1 = H$	R^2 = ethyl
Nonanal (**13**)	95	90	75	**21**	$R^1 = H$	$R^2 = n$-octyl

Table 2. Yields obtained from 2-(3′-hydroxy-phenyl)-ethanol (**25**) using protocol A



25 **7, 22-24** **26-29**

Reagents: **25** and	Yield (%)	Obtained product	
Pentanal (**7**)	80	**26**	R = *n*-butyl
Piperonal (**22**)	98	**27**	R = 3′,4′-(methylenedioxy)phenyl
p-chlorobenz-aldehyde (**23**)	95	**28**	R = *p*-Cl-phenyl
p-methoxycarbonyl-benzaldehyde (**24**)	90	**29**	R = *p*-$COOCH_3$-phenyl

The above results indicate that the hydroxyl in the *para* position to the reaction site controls the regioselectivity of the reaction.

To confirm the role of the C-6 hydroxyl group in the mechanism outlined in Scheme 1, we used 2-(4′-hydroxyphenyl)ethanol (**5**) instead of 2-(3′-hydroxyphenyl)ethanol (**25**), adopting the same experimental conditions described for the oxa-Pictet−Spengler reaction. The recovery of 2-(4′-hydroxyphenyl)ethanol unchanged suggests that the mechanism outlined in Scheme 1 is the only effective process under the conditions described in the reported protocols.

Given the yields obtained and the very simple experimental procedure, we propose that the modified oxa-Pictet−Spengler reaction can be used as a general procedure for synthesizing 6-hydroxyisochromans and oxygenated analogues of the benzyl-tetrahydroisoquinoline alkaloids. An objective of future studies could be to determine how substitution of the nitrogen atom with an oxygen atom would modify the biological activity.

Experimental Section

NMR spectra: Varian Mercury 300; NMR spectroscopic data marked with an asterisk (*) may be reversed. Micro-analyses: CE Instruments. Chromatography: Merck Silica gel 60, washed with 1 N HCl then with water until the chlorine test was negative, activated for 48 h at 120 °C, then equilibrated with 10% of water. TLC 5 × 20 Silica gel 60 F_{254} Merck.

IR spectra were performed by infrared spectrophotometer IR-470, Shimadzu using 1% concentration.

MS and MS\MS analyses were performed on a triple quadrupole PE-SCIEX API 365 (Perkin−Elmer Sciex Instruments Foster City, CA USA), equipped with Turboion Spray interface in negative ion mode. Melting point apparatus: Mettler FP 80. Reagents: Fluka. Solvents: Carlo−Erba.

Hydroxytyrosol (**3**) was prepared from 3,4-dihydroxyphenyl acetic acid, according to a previously described protocol.[5]

Oxidation of Tyrosol (5) to Give Compound 4: PDC (2.05 equiv.) was added in one portion to a solution of tyrosol **5** (100 mg) in CH_2Cl_2/EtOAc = 1:0.5 at room temperature, the mixture was allowed to stir for about 5 hours. The mixture was filtered through a short path of Celite and washed with the reaction solvent (CH_2Cl_2/EtOAc = 1:0.5; 70 mL). The pale yellow solution obtained was washed with brine and dried with anhydrous Na_2SO_4. Filtration and evaporation of the solvent yielded crude **4**, which was used in the following reaction without purification, to obtain **1**. ^{1}H NMR spectroscopic data of compound 4, partially reported in the literature (reference 6), are listed. ^{1}H NMR (CD_3COCD_3): 9.64 (t, J = 2.2 Hz, 1 H, 1-H); 7.05 (d, J = 8.1 Hz, 2 H, 2′-H and 6′-H); 6.82 (d, J = 8.1 Hz, 2 H, 3′-,5′-H); 3.62 (d, J = 2.2 Hz, 2 H, 2-H) ppm.

Isochroman Synthesis. General Procedure: We used three protocols to synthesize these compounds: **A**) with molecular sieves as dehydrating agent; **B**) with anhydrous Na_2SO_4 as dehydrating agent, and **C**) without dehydrating agent. Compounds **14**−**21** were prepared according to protocols **A**, **B**, and **C**; and compounds **26**−**29** according to protocol **A**.

A: Phenolic compound **3** or **25** (reaction scale about 20 mg) was dissolved in anhydrous methyl alcohol,and molecular sieves (about 100 mg) previously dried for one night at 150 °C were added. Carbonyl compound (**4**, **6**−**13**, **22**−**24**, 10% molar excess) and a catalytic amount of *p*-toluenesulfonic acid were added. The mixture was left to react at 4 °C for 24 h (aldehydes) or for 48 h (acetone). The molecular sieves were filtered off, the solution was concentrated at room temperature in vacuo, diluted with ethyl acetate, and washed with brine until the pH was neutral. The organic layer was dried with anhydrous Na_2SO_4, filtered, evaporated, and the residue purified by chromatography on a silica gel column eluting with $CHCl_3$/MeOH (9:1).

B: The solution was prepared as described in protocol **A** in the presence of anhydrous Na_2SO_4 (100 mg). After the reaction times reported above, the Na_2SO_4 was filtered off, the reaction was worked up, and the residue purified as described above.

C: The reaction was carried out in methyl alcohol without a dehydrating agent, as described in Reference 4.

1-(*p*-Hydroxybenzyl)-6,7-dihydroxyisochroman (1, racemic demethyloxacoclaurine): Yields: protocol A, 80% (28 mg); protocol B, 75% (26 mg); protocol C, 60% (21 mg). ^{1}H NMR ($CDCl_3$): 6.56 (s, 1 H, 5-H); 6.22 (s, 1 H, 8-H); 5.55 (s, 1 H, 1-H); 4.14 (m, 1 H, 3-H^1); 3.86 (m, 1 H, 3-H^2); 3.01 (m, 1 H, 4-H^1); 2.65 (m, 1 H, 4-H^2); *p*-OH phenyl moiety: 7.16 (d, J = 8.4 Hz, 2 H, 2′-,6′-H); 6.79 (d, J = 8.4 Hz, 2 H, 3′-,5′-H) ppm. ^{13}C NMR (C_3D_6O): 156.2 (C-4′); 144.2 (C-7*); 144.0 (C-6*); 131.3 (C-2′ and C-6′); 130.8 (C-1′*); 130.0 (C-8a*); 125.9 (C-4a); 115.7 (C-5); 115.4 (C-3′ and C-5′); 112.6 (C-8); 77.3 (C-1); 63.3 (C-3); 42.2 (Cα); 29.1 (C-4) ppm. IR ($CHCl_3$): ṽ = 3300, 2950, 1690, 1650, 1520, 1450, 1390, 1270, 1250, 1090, 1020 cm^{-1}. Elemental analysis: $C_{16}H_{16}O_4$ (272.29) calcd C 70.58, H 5.92; found C 70.45, H 6.01. $[M - H]^-$ = 271.0; product ions: 241.0.

1,1-Dimethyl-6,7-dihydroxyisochroman (14): See ref.[4] Yields: protocol A, 95% (24 mg); protocol B, 80% (20 mg); protocol C, 63%

(16 mg). m.p. 130−132 °C. ^{1}H NMR ($CDCl_3$): 6.59 (s, 1 H, 5*-H); 6.56 (s, 1 H, 8*-H); 3.94 (t, J = 5.5 Hz, 2 H, 3-H); 2.70 (t, J = 5.5 Hz, 2 H, 4-H); 1.49 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR ($CDCl_3$): 142.2 (C-7*); 142.0 (C-6*); 134.9 (C-8a); 124.9 (C-4a); 114.8 (C-5); 112.0 (C-8); 74.7 (C-1); 59.8 (C-3); 29.9 (C-1′); 28.9 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2970, 1690, 1660, 1610, 1520, 1450, 1370, 1290, 1130, 1090 cm^{-1}. Elemental analysis: $C_{11}H_{14}O_3$ (194.22) calcd C 68.02, H 7.27; found C 67.86, H 7.33. [M − H]$^-$ = 193.2; product ions: 123.0 and 163.2.

1-(1′-Butyl)-6,7-dihydroxyisochroman (15): See ref.[4] Yields: protocol A, 80% (23 mg); protocol B, 60% (17 mg); protocol C, 50% (14 mg). ^{1}H NMR ($CDCl_3$): 6.57 (s, 1 H, 5*-H); 6.56 (s, 1 H, 8*-H); 4.61 (dd, 1 H, J_1 = 7.1, J_2 = 3.0, H_2, 1-H); 4.07 (m, 1 H, 3-H^1); 3.70 (m, 1 H, 3-H^2); 2.82 (m, 1 H, 4-H^1); 2.52 (m, 1 H, 4-H^2); *n*-butyl moiety: 1.76 (m, 2 H, 1′-H); 1.38 (4 H, 2′-H and 3′-H); 0.90 (t, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 142.0 (C-7*); 141.9 (C-6*); 130.7 (C-8a); 126.1 (C-4a); 115.1 (C-5); 111.5 (C-8); 75.7 (C-1); 63.2 (C-3); 35.7 (C-1′); 28.5 (C-4); 27.4 (C-2′); 22.9 (C-3′); 14.1 C-4′ ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2940, 1720, 1650, 1610, 1520, 1460, 1380, 1290, 1160, 1090 cm^{-1}. Elemental analysis: $C_{13}H_{18}O_3$ (222.27) calcd C 70.24, H 8.16; found C 70.00, H 8.35; [M − H]$^-$ = 221.0; product ions: 162.2 and 191.2.

1-(*m*-Hydroxyphenyl)-6,7-dihydroxyisochroman (16): See ref.[4] Yields: protocol A, 98% (33 mg); protocol B, 90% (30 mg); protocol C, 80% (27 mg). m.p. 153−154 °C. ^{1}H NMR (CD_3OD): 6.73 (s, 1 H, 5-H); 6.15 (s, 1 H, 8-H); 5.49 (s, 1 H, 1-H); 4.06 (m, 1 H, 3-H^1); 3.81 (m, 1 H, 3-H^2); 2.91 (m, 1 H, 4-H^1); 2.60 (m, 1 H, 4-H^2); *m*-hydroxyphenyl moiety: 7.14 (t, J = 7.5 Hz, 1 H, 5′-H); 6.77 (d, J = 7.5 Hz, 1 H, 6′-H); 6.71 (m, 1 H, 4′-H); 6.70 (s*, 1 H, 2′-H) ppm. ^{13}C NMR ($CDCl_3$) 158.4 (C-3′); 145.4 (C-7*); 145.3 (C-6*); 144.6 (C-1′); 130.2 (C-5′); 129.5 (C-8a); 126.1 (C-4a); 121.3 (C-6′); 119.9 (C-2′); 116.8 (C-4′); 115.9 (C-5); 114.0 (C-8); 80.7 (C-1); 65.0 (C-3); 29.1 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2950, 1680, 1660, 1520, 1460, 1390, 1270, 1120, 1090 cm^{-1}. Elemental analysis: $C_{15}H_{14}O_4$ (258.26) calcd C 69.76, H 5.46; found C 69.56, H 5.58. [M − H]$^-$ = 257.0; product ions: 209.0; 227.0 and 212.1.

1-(*p*-Methoxyphenyl)-6,7-dihydroxyisochroman (17): See ref.[4] Yields: protocol A, 98% (35 mg); protocol B, 90% (32 mg); protocol C, 80% (28 mg). m.p. 173−174 °C. ^{1}H NMR ($CDCl_3$): 6.63 (s, 1 H, 5-H); 6.20 (s, 1 H, 8-H); 5.54 (s, 1 H, 1-H); 4.11 (m, 1 H, 3-H^1); 3.84 (m, 1 H, 3-H^2); 2.98 (m, 1 H, 4-H^1); 2.62 (m, 1 H, 4-H^2); *p*-methoxyphenyl moiety: 7.19 (2 H, 2′-,6′-H); 6.84 (2 H, 3′-,5′-H); 3.78 (OCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 159.7 (C-4′); 142.7 (C-7*); 141.7 (C-6*); 134.8 (C-1′); 130.4 (C-8a); 130.2 (C-2′ and C-6′); 127.0 (C-4a); 115.2 (C-5); 114.0 (C-3′ and C-5′); 113.8 (C-8); 79.0 (C-1); 64.1 (C-3); 55.5 (OCH_3); 28.4 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2950, 1680, 1660, 1520, 1460, 1390, 1290, 1240, 1140, 1080 cm^{-1}. Elemental analysis: $C_{16}H_{16}O_4$ (272.29) calcd C 70.58, H 5.92; found C 70.39, H 6.11. [M − H]$^-$ = 271.0; product ions: 241.0 and 226.1.

1-Phenyl-6,7-dihydroxyisochroman (18): See ref.[4] Yields: protocol A, 95% (30 mg); protocol B, 80% (25 mg); protocol C, 60% (19 mg). ^{1}H NMR ($CDCl_3$): 6.61 (s, 1 H, 5-H); 6.18 (s, 1 H, 8-H); 5.57 (s, 1 H, 1-H); 4.10 (m, 1 H, 3-H^1) 3.85 (m, 1 H, 3-H^2); 2.98 (m, 1 H, 4-H^1); 2.63 (m, 1 H, 4-H^2); phenyl moiety: 7.28 (5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.7 (C-7*); 141.8 (C-6*); 141.7 (C-1′); 128.9 (C-8a); 128.7 (C-6′ and C-2′); 128.3 (C-5′ and C-3′); 128.1 (C-4′); 115.9 (C-4a); 114.8 (C-5); 113.4 (C-8); 79.3 (C-1); 63.8 (C-3); 28.1 (C-4) ppm. IR (CCl_4): $\tilde{\nu}$ = 3800, 3500, 3100, 1700, 1560, 1420, 1330, 1250, 1160, 1100 cm^{-1}. Elemental analysis: $C_{15}H_{14}O_3$ (242.26) Calcd C 74.36, H 5.82; found C 74.13, H 5.93. [M − H]$^-$ = 241.2; product ions: 193.2 and 211.2.

1-Isobutyl-6,7-dihydroxyisochroman (19): Yields: protocol A, 90% (26 mg); protocol B, 73% (21 mg); protocol C, 62% (18 mg). ^{1}H NMR ($CDCl_3$): 6.57(s, 1 H, 5*-H); 6.54 (s, 1 H, 8*-H); 4.67 (d*, J = 8.7 Hz, 1 H, 1-H); 4.07 (m, 1 H, 3-H^1), 3.75 (m, 1 H, 3-H^2); 2.78 (m, 1 H, 4-H^1); 2.58 (m, 1 H, 4-H^2); isobutyl moiety: 1.93 (m, 1 H, 2′-H); 1.74 (m, 1 H, 1′-H^1); 1.47 (m, 1 H, 1′-H^2); 0.98 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H) methyl groups ppm. ^{13}C NMR ($CDCl_3$): 142.1 (C-6* and C-7*); 131.4 (C-8a*); 126.0 (C-4a*); 115.2 (C-5); 111.7 (C-8); 73.8 (C-1); 62.7 (C-3); 45.3 (C-1′); 28.3 (C-4); 24.5 (C-2′); 23.9 (C-3′); 21.5 (C-4′) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3580, 3300, 2950, 1650, 1610, 1520, 1460, 1380, 1290, 1160, 1090 cm^{-1}. Elemental analysis: $C_{13}H_{18}O_3$ (222.27) calcd C 70.24, H 8.16; found C 70.03, H 8.32. [M − H]$^-$ = 221.0; product ions: 176.2 and 205.2.

1-Ethyl-6,7-dihydroxyisochroman (20): Yields: protocol A, 95% (24 mg); protocol B, 80% (20 mg); protocol C, 72% (18 mg). ^{1}H NMR ($CDCl_3$): 6.56 (s, 1 H, 5-H); 6.54 (s, 1 H, 8-H); 4.57 (d, 1 H, 1-H); 4.08 (m, 1 H, 3-H^1) 3.72 (m, 1 H, 3-H^2), 2.81 (m, 1 H, 4-H^1); 2.53 (m, 1 H, 4-H^2); ethyl moiety: 1.72 and 1.84 (m, 2 H, 1′-H); 0.93 (t, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$) 142.1 (C-6*) and (C-7*); 130.3 (C-8a); 126.4 (C-4a); 115.0 (C-5); 111.5 (C-8); 77.0 (C-1); 63.5 (C-3); 28.6 (C-1′); 28.4 (C-4); 9.6 (C-2′) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2950, 1720, 1610, 1520, 1460, 1340, 1290, 1160, 1090 cm^{-1}. Elemental analysis: $C_{11}H_{14}O_3$ (194.22) calcd C 68.02, H 7.27; found C 67.88, H 7.40. [M − H]$^-$ = 193.2; product ions: 148.0 and 163.2.

1-(1′-Octyl)-6,7-dihydroxyisochroman (21): Yields: protocol A, 95% (34 mg); protocol B, 90% (32 mg); protocol C, 75% (27 mg). ^{1}H NMR ($CDCl_3$): 6.57 (s, 1 H, 5*-H); 6.56 (s, 1 H, 8*-H); 4.64 (m, 1 H, 1-H); 4.09 (m, 1 H, 3-H^1); 3.76 (m, 1 H, 3-H^2); 2.82 (m, 1 H, 4-H^1); 2.55 (m, 1 H, 4-H^2); octyl group: 1.77 (m, 2 H, 1′-H); 1.42 (m, 2 H, 2′-H); 1.26 (m, 10 H, 3′-,4′-,5′-,6′-,7′-H); 0.87 (t, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 142.2 (C-7*); 142.1 (C-6*); 130.8 (C-8a); 126.1 (C-4a); 115.1 (C-5); 111.6 (C-8); 75.7 (C-1); 63.1 (C-3); 35.9 (C-1′); 31.9 (C-7′); 29.7 (C-6′); 29.6 (C-5′); 29.3 (C-4′); 28.4 (C-4); 25.2 (C-3′); 22.7 (C-2′); 14.1 (C-8′) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2920, 1680, 1660, 1520, 1460, 1390, 1290, 1140, 1080 cm^{-1}. Elemental analysis: $C_{17}H_{26}O_3$ (278.38) calcd C 73.35, H 9.41; found C 73.14, H 9.56. [M − H]$^-$ = 277.0; product ions: 248.0.

2-(3′-Hydroxyphenyl)ethanol (25): 2-(3′-Hydroxyphenyl)acetic acid (0.5 g) was dissolved in anhydrous methanol (50 mL) and two drops of concentrated H_2SO_4 were added. After 2 h, the reaction was concentrated in vacuo, diluted with ethyl acetate, washed with brine until the pH was neutral, dried with anhydrous sodium sulfate, and the solvent evaporated under reduced pressure. The methyl ester (0.45 g; 82%) was obtained and immediately treated with an aqueous solution of excess $NaBH_4$. After 2 h, the solution was acidified with 2 N HCl, extracted with ethyl acetate, and worked up as reported above. The residue obtained was purified by silica gel column chromatography, eluting with $CHCl_3$/MeOH (9:1), gave pure **25** (0.37 g; 98%). ^{1}H NMR (CD_3OD): 7.15 (t, 1 H, 5′-H); 6.50−6.90 (3 H, 2′-,4′-,6′-H); 3.72 (t, 2 H, 1-H); 2.75 (t, 2 H, 2-H).

1-(1′-Butyl)-6-hydroxyisochroman (26): The reaction was only carried out according to protocol A. Yield: 80% (24 mg). ^{1}H NMR ($CDCl_3$): 6.94 (d, J = 8.1 Hz, 1 H, 8-H); 6.66 (dd, 1 H, J_1 = 8.1, J_2 = 2.7 Hz, 7-H); 6.57 (d, J = 2.7 Hz, 1 H, 5-H); 4.70 (dd, 1 H, J_1 = 8.0, J_2 = 3.0 Hz, 1-H); 4.12 (m, 1 H, 3-H^1); 3.76 (m, 1 H, 3-H^2); 2.94 (m, 1 H, 4-H^1); 2.64 (m, 1 H, 4-H^2); *n*-butyl moiety: 1.80 (m, 2 H, 1′-H); 1.45 (4 H, 2′-,3′-H); 0.93 (t, 3 H, 4′-H). ^{13}C NMR

($CDCl_3$): 153.6 (C-6); 135.4 (C-4a*); 130.8 (C-8a*); 126.0 (C-8); 114.9, 113.4 (C-5 and C-7); 75.8 (C-1); 63.0 (C-3); 35.8 (C-1′); 29.4 (C-4); 27.5 (C-2′); 22.9 (C-3′); 14.2 (C-4′) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2920, 1680, 1660, 1560, 1460, 1390, 1270, 1130, 1090 cm^{-1}. Elemental analysis: $C_{13}H_{18}O_2$ (206.27) calcd C 75.69, H 8.80; found C 75.57, H 8.94. $[M - H]^-$ = 205.2; product ions: 175.0.

1-[3′,4′-(Methylenedioxy)phenyl]-6-hydroxyisochroman (27): The reaction was only carried out according to protocol A. Yield: 98% (38 mg). ^1H NMR ($CDCl_3$) ppm: 6.83−6.73 and 6.65−6.51 (6 H, 8-,7-,5-,5′-,2′-,6′-H); 5.92 (2 H, dioxy-methylene group); 5.62 (br. s, 1 H, 1-H); 4.16 (m, 1 H, 3-H^1); 3.89 (m, 1 H, 3-H^2); 3.05 (m, 1 H, 4-H^1); 2.71 (m, 1 H, 4-H^2) ppm. ^{13}C NMR ($CDCl_3$): 154.3 (C-6); 147.6 and 147.3 (C-3′ and C-4′); 136.1 and 135.1 ($C\text{-}4_a$* and C-1′*); 129.0 ($C\text{-}8_a$*); 128.0 (C-8); 122.5 (C-6′); 114.7 (C-5); 113.4 (C-7); 109.0 (C-5′); 107.7 (C-2′); 100.9 (acetalic carbon); 79.2 (C-1); 63.5 (C-3); 28.9 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3350, 3000, 2900, 1720, 1620, 1500, 1450, 1380, 1300, 1240, 1140, 1090, 1040 cm^{-1}. Elemental analysis: $C_{16}H_{14}O_4$ (270.27) calcd C 71.10, H 5.22; found C 70.98, H 5.36. $[M - H]^-$ = 269.2; product ions: 239.0.

1-(*p*-Chlorophenyl)-6-hydroxyisochroman (28): The reaction was only carried out using protocol A. Yield: 95% (36 mg). ^1H NMR ($CDCl_3$): 7.40−7.25 (4 H, 2′-,3′-,5′-,6′-H); 6.70−6.50 (3 H, 5-,7-,-8-H); 5.70 (s, 1 H, 1-H); 4.18 (m, 1 H, 3-H^1); 3.90 (m, 1 H, 3-H^2); 3.10 (m, 1 H, 4-H^1); 2.75 (m, 1 H, 4-H^2) ppm. ^{13}C NMR ($CDCl_3$): 154.4 (C-6); 140.7 (C-1′); 135.3 (C-4a); 133.8 (C-4′); 130.0, (C-2′ and C-6′); 129.0 (C-8a); 128.5 (C-3′ and C-5′); 128.0 (C-8); 114.8 (C-5); 113.4 (C-7); 78.7 (C-1); 63.7 (C-3); 28.9 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2950, 1660, 1620, 1500, 1450, 1300, 1240, 1140, 1090 cm^{-1}. Elemental analysis: $C_{15}H_{13}ClO_2$ (260.70) calcd C 69.10, H 5.03, Cl 13.60; found C 68.98, H 5.24, Cl 13.42. $[M - H]^-$ = 259.0; product ions: 229.0.

1-(*p*-Methoxycarbonylphenyl)-6-hydroxyisochroman (29): The reaction was only carried out according to protocol A. Yield: 90% (37 mg). m.p. 147−148 °C. ^1H NMR ($CDCl_3$): 8.20 (2 H, 3′-,5′-H); 7.32 (2 H, 2′-,6′-H); 6.64−6.56 (3 H, 5-,7-,8-H); 5.73 (s, 1 H, 1-H); 4.18 (m, 1 H, 3-H^1); 3.99 (m, 1 H, 3-H^2); 3.97 (s, 3 H, OCH_3); 3.10 (m, 1 H, 4-H^1); 2.78 (m, 1 H, 4-H^2) ppm. ^{13}C NMR ($CDCl_3$) ppm: 167.0 (C=O), 154.4 (C-6); 147.2 (C-1′); 135.1 (C-4a); 129.7 (C-3′ and C-5′); 128.7 (C-2′* and C-6′*); 128.7 (C-8a*); 128.4 (C-4′); 127.8 (C-8); 114.9 (C-5); 113.5 (C-7); 78.9 (C-1); 63.8 (C-3); 52.2 (OCH_3), 28.9 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3400, 2950, 1720, 1620, 1510, 1450, 1280, 1130, 1090 cm^{-1}. Elemental analysis: $C_{17}H_{16}O_4$ (284.30) calcd C 71.82, H 5.67; found C 71.77, H 5.71. $[M - H]^-$ = 283.1; product ions: 193.0 and 89.0.

Acknowledgments

Financial support was provided by Ministero dell′Istruzione dell′Università e della Ricerca (MIUR) and Consiglio Nazionale delle Ricerche (CNR).

[1] P. M. Dewick, *Medicinal Natural Products*, **1998**, Wiley, Chichester.
[2] A. Pictet, T. Spengler, *Ber.* **1911**, *44*, 2030−2036.
[3] B. Wunsch, M. Zott, *Liebigs Ann. Chem.* **1992**, 39−45.
[4] M. Guiso, C. Marra, C. Cavarischia, *Tetrahedron Lett.* **2001**, *42*, 6531−6534.
[5] A. Bianco, G. Righi, P. Passacantilli, *Synth. Commun.* **1988**, *18(5)*, 1765−1771.
[6] S. L. Hazen, F. F. Hsu, J. W. Heinecke, *J. Biol. Chem.* **1996**, *271*, 1861−1867.

Received March 17, 2003

