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The Oxa-Pictet–Spengler Reaction: A Highlight on the Different Efficiency between Isochroman and Phthalan or Homoisochroman Derivative Syntheses

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Recently we reported that 6-hydroxy- and 6,7-dihydroxyisochromans can be obtained under very mild conditions and with very good yield by a one-pot synthesis based on a modified oxa-Pictet–Spengler reaction. In this paper, we demonstrate that the above reaction is also useful for the synthesis of hydroxyphthalans, and we discuss the effects of the substituents on the alcoholic aromatic ring on the course of the reaction, as well as those on the aldehydic structure. We also report a synthesis of hydroxyhomoisochromans performed by the same method.

Introduction

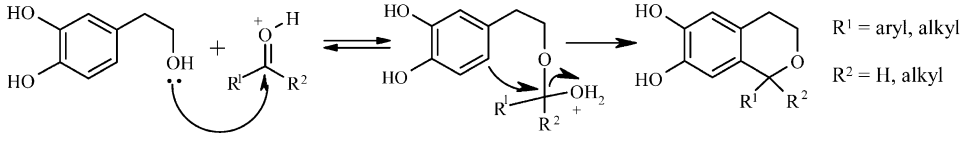
In previous papers,[1,2] we reported the high-yield synthesis, performed under very mild conditions, of a series of 1-substituted hydroxyisochromans from suitable hydroxyphenylethyl alcohols and carbonyl compounds. This one-pot synthesis is based on a modified oxa-Pictet–Spengler reaction,[3–5] in which the aromatic carbon atom involved in the heterocyclic ring closure is strongly activated by a *para*-hydroxy or a *para*-methoxy functionality and thus acts as a nucleophile. Here we report the synthesis of 1-substituted hydroxyphthalans and 1-substituted hydroxyhomoisochromans performed by the same reaction in order to verify if this synthetic pathway could still be successfully applied to obtain different heterocyclic ring structures.

In the cited papers,[1,2] we rationalized the course of our modified oxa-Pictet–Spengler reaction, which afforded hydroxyisochromans, according to Scheme 1 and we pointed out the following reaction features: (1) the presence an activating group, such as a hydroxy group, in the *para* position to the carbon atom involved in the heterocyclic ring closure is compulsory on the alcoholic reagent aromatic ring; (2) there was no difference in yield by using 3-hydroxy- over 3,4-dihydroxyphenylethyl alcohol; (3) a yield of ≥90% was obtained when the reaction was performed with aromatic aldehydes and a yield of about 70% was obtained with aliphatic aldehydes; (4) steric hindrance in the heterocyclic ring closure is of importance: *ortho*-substituted aromatic aldehydes or aliphatic ketones afforded the corresponding isochromans in about 60% yield, whereas aromatic ketones were unreactive; (5) the yield was improved when a dehydrating agent was added to the reaction mixture; (6) the reaction temperatures ranged from 4 to 25 °C according to the reagents used; (7) it is possibility to perform this reaction with a very mild acid catalyst, such as oleic acid, and also by using extra virgin olive oil as the solvent, which is a very different medium than methanol (the solvent usually employed).

In addition we proved that hydroxyisochromans could spontaneously form in extra virgin olive oil by the isolation, from this matrix,[4] of small amounts of 1-phenyl-6,7-dihydroxyisochroman and 1-(4-hydroxy-3-methoxy-phenyl)-6,7-dihydroxyisochroman.

Results and Discussion

The phthalan (1,3-dihydroisobenzofuran) structure is important (Figure 1), not only because it is present in some natural compounds[5] but also because it is a good synthon for obtaining complex molecules.[6–18] In recent years, these compounds were studied for their antihistamine,[21] antidepressant,[22–24] and other biological or pharmacological activities.[19,20] Moreover, some phthalan derivatives are uti-



Scheme 1. Synthesis of isochromans.

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lized in the agricultural industry as herbicides[25] and fungicides;[26–28] other uses include colorants[29] and perfumes.[30] Many methods to synthesize phthalans have been reviewed.[31,32] Most of these are based on a nucleophilic substitution reaction, which results in intramolecular cyclization. Starting compounds are, for example, *o*-phthalyl alcohol[33–37] or *o*-phthalyl halides.[38–43]

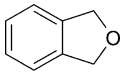
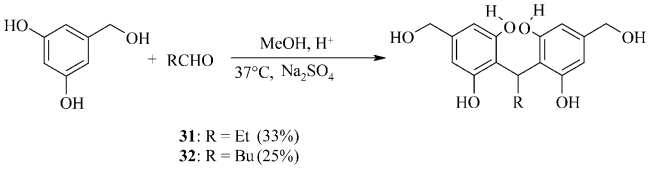


Figure 1. 1,3-Dihydroisobenzofuran.

We synthesized hydroxyphthalans under the same conditions used for the synthesis of isochromans (see Experimental Section), but in some cases the temperature was increased to 38 °C. We used 3-hydroxybenzyl alcohol (**1**), 3,5-dihydroxybenzyl alcohol (**2**), and 3,5-dimethoxybenzyl alcohol (**3**) and a group of aromatic, as well as aliphatic, aldehydes chosen from those successfully used for the synthesis of isochromans. The use of 3,4-dihydroxybenzyl alcohol, which has the same substitution pattern of hydroxytyrosol used in the synthesis of isochromans, was obviously impossible owing to the quick formation of its stable benzylic carbocation, which subsequently afforded an ether derivative. The use of an aprotic solvent instead of methanol did not increase the yield of phthalan, but lowered it instead. A possible reaction pathway is shown in Scheme 2.

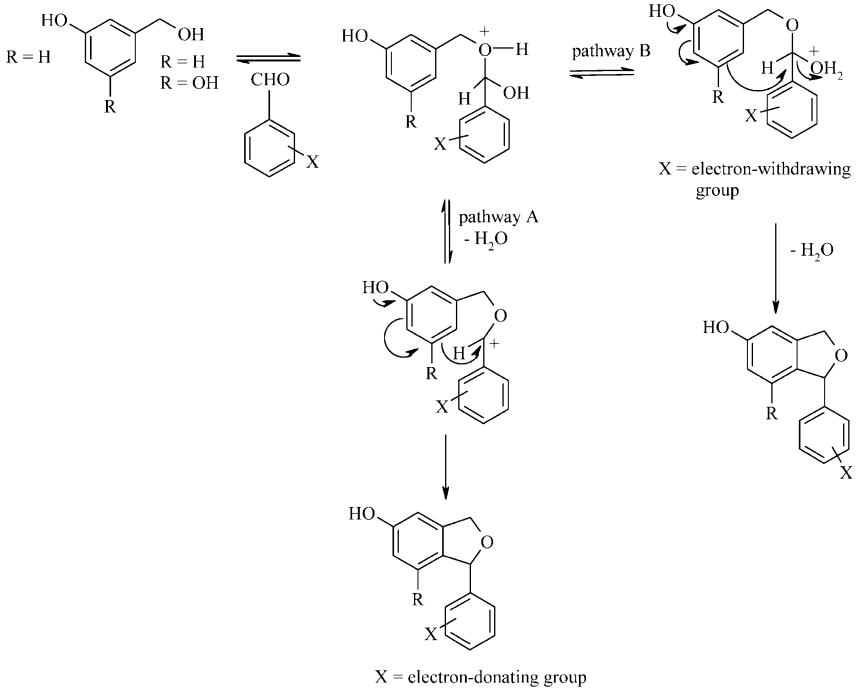
Phthalans obtained from the above benzyl alcohols were always accompanied by aldehyde acetals (methyl and mixed acetals that we omitted in this paper for brevity) and those prepared from **2** and **3** were also accompanied by side products arising from electrophilic aromatic substitution on the strongly activated alcoholic ring, mainly if aliphatic or *para*-donor substituted aromatic aldehydes were used. The formation of these last by-products was generally prevented by using chloroacetic acid as the catalyst instead of *p*-toluenesulfonic acid. Obtained phthalans and relative yield are listed in Table 1.

The data shown in Table 1 show that: (1) Phthalan derivatives were always obtained with a lower yield than those of the isochromans prepared from the same aldehyde, mainly when an aliphatic aldehyde was used. (2) Best yields were achieved by using 3-hydroxybenzylalcohol (**1**). When we tried to react **2** with an aliphatic aldehyde only the diarylation product arising from the electrophilic aromatic substitution at C-4 was obtained. No phthalan derivative was detected (Scheme 3).



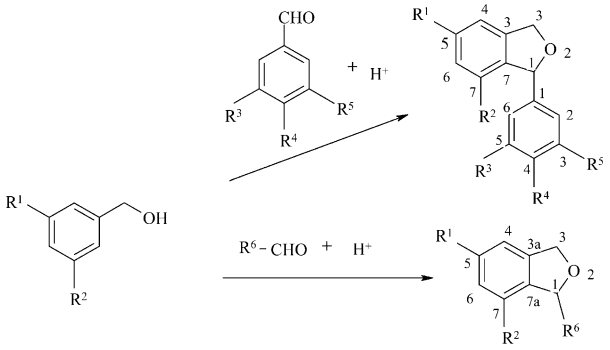
Scheme 3. Reaction involving the use of aliphatic aldehydes.

In addition, the reaction times were strongly dependent on the structures of both reagents. When we used alcohol **1**, the reaction with any aldehyde went on for about a week at 37 °C; therefore, these reactions were performed under an atmosphere of argon to avoid aldehyde oxidation. When we used alcohol **2**, reaction times and temperatures were dependent on the aldehyde structure. The reaction performed with electron-withdrawing-substituted aromatic aldehydes required (with *para*-toluenesulfonic acid as a cata-



Scheme 2. Synthesis of phthalans.

Table 1. Oxa-Pictet–Spengler synthesis of phthalans.



R^1	R^2	R^3	R^4	R^5	Yield [%]	T [°C]	t [h]	Product
OH	H	H	H	H	60	38	48	**7**
OH	H	H	Cl	H	56	38	48	**8**
OH	H	H	OCH_3	H	62	38	48	**9**
OH	H	H	OCH_3	OCH_3	55	38	48	**10**
OH	H	H	OCH_2O		50	38	48	**11**
OH	H	H	OH	OCH_3	55	38	48	**12**
OH	H	H	NO_2	H	61	38	48	**13**
OH	H	H	H	NO_2	61	38	48	**14**
OH	H	OCH_3	OCH_3	OCH_3	55	38	48	**15**
OH	H	$R^6 = CH_3(CH_2)_3$			25	38	48	**16**
OH	OH	H	NO_2	H	61	38	48	**17**
OH	OH	H	Cl	H	57	38	48	**18**
OH	OH	H	H	NO_2	61	38	48	**19**
OH	OH	H	H	H	50	4	2	**20**
OH	OH	H	OH	H	15/29[a]	4/38[a]	2/48[a]	**21**
OH	OH	H	OCH_3	H	27/48[a]	4/38[a]	2/48[a]	**22**
OH	OH	OCH_3	H	OCH_3	33/57[a]	4/38[a]	2/48[a]	**23**
OH	OH	OCH_3	OCH_3	OCH_3	33/58[a]	4/38[a]	2/48[a]	**24**
OH	OH	H	OH	OCH_3	17/33[a]	4/38[a]	2/48[a]	**25**
OH	OH	H	OCH_2O		25/45[a]	4/38[a]	2/48[a]	**26**
OH	OH	H	$N(CH_3)_2$	H	32	4	2	**27**
OCH_3	OCH_3	H	NO_2	H	45	38	48	**28**
OCH_3	OCH_3	H	OCH_2O		43	38	48	**29**
OCH_3	OCH_3	OCH_3	H	OCH_3	47	38	48	**30**

[a] Data obtained by using chloroacetic acid as the catalyst.

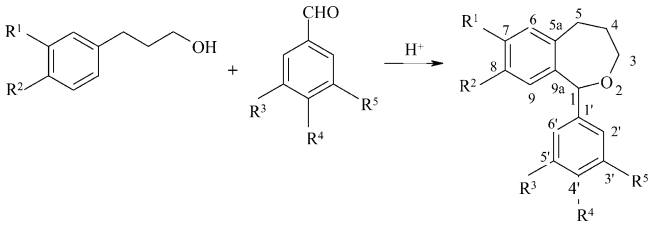
lyst), at least 2 d and 37 °C, whereas those performed with electron-donating-substituted aromatic aldehydes required only a few minutes to a few hours at 4 °C. In this case, to avoid the simultaneous electrophilic aromatic substitution reaction, a milder catalyst, such as chloroacetic acid, was used. The reaction time obviously increased.

As previously reported, the hypothetical reaction pathway for the synthesis of hydroxyisochromans could proceed by preliminary carbocation formation at the C-1 aldehydic carbon atom; in addition, the attack could happen at the protonated hemiacetalic or acetalic structure (Scheme 1). This synthetic way is also in accordance with the Baldwin rules,[44,45] which favor *6-endo-trig* and the *6-exo-tet* ring closure. The synthesis of the phthalans could follow the same pathway, but in this case, the *5-endo-trig* path is not favored. In addition, the steric hindrance shown by the substituents at the aldehydic C-1 atom during the closure of the unsaturated five-membered ring could hamper the compound from adopting the correct orientation. Therefore, in the synthesis of isochromans, the great ease with which the six-membered ring could undergo closure avoided the possibility of side reactions, as demonstrated by the formation of isochroman **33** (90% yield) by treating 2-(3,5-dimethoxyphenyl)ethanol with piperonal. In this reaction, in fact, no byproduct was detected. On the contrary, when aliphatic aldehydes are involved, the difficult closure of the phthalan ring shifts the equilibrium to the formation of the less-hindered acetals and of the arylation products. The formation of only **31** and **32** could support this hypothesis. The aromatic aldehydes may provide some minor steric hindrance in the closure of the phthalan ring. Among these, the ones having electron-donating substituents contemporaneously form also the arylation products, probably by the great stability of the intermediate carbocation. On the contrary, those with electron-withdrawing substituents give only the oxa-Pictet–Spengler reaction.

The synthesis of hydroxyhomoisochromans, performed under the same conditions, gave poor yield (see Table 2). In this case, the seven-membered ring closure is hampered by the relatively low probability of achieving the required mo-

lecular orientation. It should be noted that the yield obtained by using 3-(3,4-dihydroxyphenyl)-1-propanol (**5**) is generally higher than that obtained with 3-(3-hydroxyphenyl)-1-propanol (**6**).

Table 2. Oxa-Pictet–Spengler synthesis of homoisochromans.[a]



R^1	R^2	R^3	R^4	R^5	Yield [%]	Product
OH	OH	H	H	H	45	**34**
OH	OH	H	OCH_3	H	44	**35**
OH	OH	H	Cl	H	41	**36**
OH	OH	H	NO_2	H	43	**37**
OH	OH	H	OCH_2O		45	**38**
OH	OH	H	OH	OCH_3	42	**39**
OH	OH	H	OCH_3	OCH_3	40	**40**
OH	OH	OCH_3	H	OCH_3	45	**41**
OH	OH	OCH_3	OCH_3	OCH_3	45	**42**
OH	OH	H	$COOCH_3$	H	35	**43**
OH	H	H	H	H	21	**44**
OH	H	H	OCH_3	H	20	**45**
OH	H	H	Cl	H	25	**46**
OH	H	H	NO_2	H	21	**47**
OH	H	H	H	NO_2	21	**48**
OH	H	H	OCH_2O		22	**49**
OH	H	H	$N(CH_3)_2$	H	22	**50**

[a] The reactions were carried out at 37 °C for one week.

Conclusions

The above-reported results show that our modification of the oxa-Pictet–Spengler reaction may be useful to synthesize hydroxyphthalans and hydroxyhomoisochromans even if the yields are less satisfactory than those for hydroxyisochromans. It is noteworthy, in this case, that the closure of a five-membered ring appears more difficult than that of γ-lactone rings,[46] but the double bond presence in the intermediate and the steric hindrance of the aldehydic residue may hamper the closure. The low yields found in the synthesis of hydroxyhomoisochromans are in agreement with the difficulties involved in achieving the required molecular orientation. Therefore, this synthetic way is less interesting with the use of the described experimental conditions and could hamper the spontaneous formation of both kinds of compounds, contrary to what was found for hydroxyisochromans.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were measured with a Varian Mercury 300 MHz spectrometer, chemical shifts are expressed in ppm relative to TMS and *J* values are quoted in Hz. NMR spectroscopic data marked with an asterisk (*) may be reversed. Purification of the products was achieved by solid-liquid column chromatography on Merck 0.063–0.20 nm silica gel treated with diluted HCl, then washed with hot water to eliminate Cl^- ions, dried and activated at 120 °C for 24 hrs. Silica gel was treated with 10% of water before using. The eluting solutions were determined on a case by case basis. TLC was performed on Silica gel 60 F_{254} Merck plates and visualized by spraying with 2 N H_2SO_4 and heating. Microanalyses were performed with a CE Instrument. MS analyses were performed with a triple quadrupole PE-SCIEX API 365 (Perkin–Elmer Sciex Instruments Foster City, CA USA), equipped with Turboin Spray interface in negative-ion mode. Melting points were determined with a Mettler FP 80 apparatus. All reagents were purchased from Fluka, and all solvents were purchased from Carlo Erba. IR spectra were obtained with a infrared spectrophotometer IR-470, Shimadzu by using 1% concentration; $CHCl_3$ was used as the solvent, and it was passed through a Al_2O_3 column before use.

***m*-Hydroxybenzyl Alcohol (1):** *m*-OH benzaldehyde (100 mg, ca. 0.82 mmol) was suspended in water (3 mL) and then an excess amount of $NaBH_4$ (63 mg, ca. 1.7 mmol) was added over the course of 30 min at room temperature. The excess amount of $NaBH_4$ was destroyed by slowly adding HCl (6 N) to the chilled solution until it reached pH = 5. The water solution was extracted with EtOAc, 3 × 20 mL), and the combined organic layer was washed with a brine solution until neutrality. The residue obtained after evaporation in vacuo of the volatile material (110 mg) contained pure **1** as checked by its ^1H NMR spectrum in $CDCl_3$.

General Synthesis of 1,3-Dihydroisobenzofuran-5-ol, 1,3-Dihydroisobenzofuran-5,7-diol, 1,3-Dihydro-5,7-dimethoxyisobenzofuran, 6,8-Dimethoxyisochroman, Benzo-2-oxacycloheptene-7,8-diol, and Benzo-2-oxacycloheptene-7-ol Derivatives: Alcohol **1**, **2**, **3**, **4**, **5**,or **6** (30 mg, respectively, 0.24 mmol, 0.21 mmol, 0.16 mmol, 0.17 mmol, 0.19 mmol, 0.18 mmol), was dissolved in anhydrous methanol (1 mL) and an equimolar quantity of aldehyde was added together with catalytic amounts of *p*-toluenesulfonic acid and anhydrous Na_2SO_4 (100 mg) or molecular sieves. Reaction times and temperatures were different according to the utilized aldehydes (Tables 1 and 2). Reactions requiring longer periods were performed under an atmosphere of Ar. After chromatographic control on a silica-gel plate, the volume of the reaction mixture was cut in half under reduced pressure at low temperature and then diluted with EtOAc, 25 mL). The organic layer was washed with a brine solution until neutrality, and the residue obtained after evaporation in vacuo of the volatile material was purified on a silica-gel (ratio 1:100) column by eluting with different solvents mixture. The reactions were also carried out by using a greater concentration (1 g of **1**, **2**, **3**, **4**, **5**, or **6** dissolved in 9 mL of anhydrous MeOH), and the obtained products and yields were unchanged.

1-Phenyl-1,3-dihydroisobenzofuran-5-ol (7): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **7** (31 mg, 0.15 mmol, 60%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.36 (5 H, ArH), 6.84 (d, J = 8.1 Hz, 1 H, 7-H), 6.68 (br. s, 1 H, 4-H), 6.66 (dd, $J_{6,7}$ = 8.1 Hz, $J_{6,4}$ = 2.1 Hz, 1 H, 6-H), 6.09 (br. s, 1 H, 1-H), 5.24 (dd, $J_{3b,3a}$ = 12.0 Hz, $J_{3b,1}$ = 2.4 Hz, 1 H, 3b-H), 5.11 (d, $J_{3a,3b}$ = 12.0 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHZ, $CDCl_3$): δ = 155.6 (C-5), 142.0 (C-3a),; 140.7 (C-1′), 133.8 (C-7a), 128.4 (C-2′ and C-6′), 128.0 (C-4′), 126.9 (C-3′ and C-5′), 123.1 (C-7), 114.9 (C-6), 107.6 (C-4), 85.9 (C-1), 72.9 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3320, 2980, 1610, 1460, 1370, 1250, 1120, 1020 cm^{-1}. MS: m/z = 213.2 $[M - H]^-$. $C_{14}H_{12}O_2$ (212.25): calcd. C 79.23, H 5.70; found C 79.04, H 5.75.

1-(4′-Chlorophenyl)-1,3-dihydroisobenzofuran-5-ol (8): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 9:1) to afford pure **8** (33 mg, 0.13 mmol, 56%). ^{1}H NMR (300 MHZ, $CDCl_3$): δ = 7.30 (d, $J_{3',5'}$ = 8.4 Hz, 2 H, 3′-H, 5′-H), 7.23 (d, $J_{2',6'}$ = 8.4 Hz, 2 H, 2′-H, 6′-H), 6.82 (d, $J_{7,6}$ = 8.2 Hz, 1 H, 7-H), 6.71 (br. s, 1 H, H-4), 6.67 (br. d, $J_{6,7}$ = 8.2 Hz, 1 H, 6-H), 6.05 (br. s, 1 H, 1-H), 5.23 (dd, $J_{3b,3a}$ = 12.3 Hz, $J_{3b,1}$ = 2.1 Hz, 1 H, 3b-H), 5.12 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7 (C-5), 141.1* (C-3a), 140.9* (C1′), 134.0 (C-4′), 133.8* (C-7a), 128.7 and 128.3 (C-2′, C-3′, C-5′, C-6′), 123.1 (C-7), 115.0 (C-6), 107.8 (C-4), 85.2 (C-1), 73.0 (C-3). IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2850, 1660, 1600, 1500, 1460, 1360, 1290, 1190, 1080, 1020 cm^{-1}. MS: *m*/*z* = 245.7 [M – H]$^-$. $C_{14}H_{11}ClO_2$ (246.69): calcd. C 68.16, H 4.49, Cl 14.37; found C 67.84, H 4.57, Cl 14.20.

1-(4′-Methoxyphenyl)-1,3-dihydroisobenzofuran-5-ol (9): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **9** (36 mg, 0.15 mmol, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, $J_{2',6'}$ = 8.8 Hz, 2 H, 2′-H and 6′-H), 6.87 (d, $J_{3',5'}$ = 8.8 Hz, 2 H, 3′-H and 5′-H), 6.85 (d, $J_{6,7}$ = 7.8 Hz, 1 H, 7-H), 6.70 (d, $J_{6,7}$ = 7.8 Hz, 1 H, 6-H), 6.73 (s, 1 H, 4-H), 6.08 (br. s, 1 H, 1-H), 5.24 (dd, $J_{3a,3b}$ = 12.2 Hz, $J_{3b,1}$ = 2.2 Hz, 1 H, 3b-H), 5.12 (d, $J_{3a,3b}$ = 12.2 Hz, 1 H, 3a-H), 3.79 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0 (C-4′), 155.9 (C-5), 141.2 (C-3a), 134.5 (C-1′), 131.2 (C-7a), 128.6 (C-7), 123.3 (C-2′ and C-6′), 115.0* (C-6), 114.1* (C-4), 107.8 (C-3′ and C-5′), 85.7 (C-1), 72.7 (C-3), 55.4 (methoxy carbon) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3320, 2960, 1650, 1520, 1480, 1280, 1130 cm^{-1}. MS: *m*/*z* = 241.2 [M – H]$^-$. $C_{15}H_{14}O_3$ (242.27): calcd. C 74.36, H 5.82; found C 74.28, H 5.90.

1-(3′,4′-Dimethoxyphenyl)-1,3-dihydroisobenzofuran-5-ol (10): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **10** (36 mg, 0.13 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.7–6.9 (6 H, ArH), 6.09 (s*, 1 H, 1-H), 5.25 (d*, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H), 5.12 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3b-H), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4 (C-5), 149.1 (C3′ and C-4′), 141.2 (C-3a), 134.6 (C-1′), 134.3 (C-7a), 123.2 (C-7), 119.5 (C-6′), 114.8 (C-6), 110.9 (C-2′), 110.2 (C-5′), 107.7 (C-4), 85.8 (C-1), 72.7 (C-3), 56.0 and 55.9 (methoxy carbons). IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2950, 1660, 1520, 1460, 1280, 1130 cm^{-1}. MS: *m*/*z* = 271.3 [M – H]$^-$. $C_{16}H_{16}O_4$ (272.30): calcd. C 70.58, H 5.92; found C 70.22, H 6.07.

1-(3′,4′-Methylenedioxyphenyl)-1,3-dihydroisobenzofuran-5-ol (11): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **11** (31 mg, 0.12 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (d, $J_{6',5'}$ = 7.8 Hz, 1 H, 6′-H), 6.83 (d, $J_{7,6}$ = 8.4 Hz, 1 H, 7-H), 6.78 (d, $J_{5',6'}$ = 7.8 Hz, 1 H, 5′-H), 6.71 (br. s, 2 H, 4-H, 2′-H), 6.69 (d, $J_{6,7}$ = 8.4 Hz, 1 H, 6-H), 6.02 (br. s, 1 H, 1-H), 5.93 (s, 2 H, OCH_2O), 5.22 (dd, $J_{3b,3a}$ = 12.6 Hz, $J_{3b,1}$ = 1.8 Hz, 1 H, 3b-H), 5.09 (d, $J_{3a,3b}$ = 12.6, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8 (C-5), 155.4 (C-3′), 147.4 (C-4′), 141.5 (C-3a), 140.9 (C-7a), 136.1 (C-1′), 123.1 (C-7), 120.6 (C-6′), 114.8 (C-6), 107.9* (C-2′), 107.5* (C-5′), 107.4* (C-4), 100.9 (dioxymethylene carbon), 85.7 (C-1), 72.6 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2950, 1660, 1520, 1480, 1360, 1130 cm^{-1}. MS: *m*/*z* = 255.3 [M – H]$^-$. $C_{15}H_{12}O_4$ (256.26): calcd. C 70.31, H 4.72; found C 70.03, H 4.81.

1-(4′-Hydroxy-3′-methoxyphenyl)-1,3-dihydroisobenzofuran-5-ol (12): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 9:1) to afford pure **12** (34 mg, 0.13 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68–6.94 (6 H, ArH), 6.05 (br. s, 1 H, 1-H), 5.25 (dd, $J_{3b,3a}$ = 12.4 Hz, $J_{3b,1}$ = 2.2 Hz, 1 H, 3b-H), 5.13 (d, $J_{3a,3b}$ = 12.4 Hz, 1 H, 3a-H), 3.84 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3 (C-5), 156.2 (C-4′), 149.3 (C-3′), 141.2 (C-3a), 135.3 (C-1′), 131.3 (C-7a), 128.4 (C-7), 119.3 (C-6′), 115.3* (C-6), 111.2 (C-2′), 108.7 (C-5′), 107.3 (C-4), 85.5 (C-1), 72.5 (C-3), 55.4 (OCH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2950, 1670, 1530, 1470, 1350, 1130 cm^{-1}. MS: *m*/*z* = 257.3 [M – H]$^-$. $C_{15}H_{14}O_4$ (258.27): calcd. C 69.76, H 5.46; found C 69.38, H 5.55.

1-(4′-Nitrophenyl)-1,3-dihydroisobenzofuran-5-ol (13): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 95:5) to afford **13** (38 mg, 0.15 mmol, 61%). ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 8.22 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.67 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 6.94 (d, $J_{6,7}$ = 8.4 Hz, 1 H, 7-H), 6.82 (d, $J_{6',4'}$ = 2.4 Hz, 1 H, 4-H), 6.73 (dd, $J_{6,7}$ = 8.4 Hz, $J_{6,4}$ = 2.4 Hz, 1 H, 6-H), 6.21 (s*, 1 H, 1-H), 5.29 (dd, $J_{3b,3a}$ = 12.6 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3b-H), 5.11 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 158.4 (C-5), 151.7 (C-4′), 141.4 (C-3a), 132.8 (C-7a), 127.9 (C-7′ and C-6′) 124.2 (C-3′), 123.4 (C-7), 115.7 (C-6), 124.2 (C-3′ and C-5′), 85.0 (C-1), 73.9 (C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3300, 2850, 1660, 1600, 1500, 1460, 1360, 1290, 1190, 1080, 1020 cm^{-1}. MS: *m*/*z* = 256.23 [M – H]$^-$. $C_{14}H_{11}NO_4$ (257.25): calcd. C 65.37, H 4.31, N 5.44; found C 64.80, H 3.93, N 5.13.

1-(3′-Nitrophenyl)-1,3-dihydroisobenzofuran-5-ol (14): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 95:5) to afford **14** (38 mg, 0.15 mmol, 61%). ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 8.21 (t, *J* = 1.8 Hz, 1 H, 2′-H), 8.15 (dm, 1 H, 4′-H), 7.83 (d*, 1 H, 6′-H), 7.65 (t, *J* = 8.1 Hz, 1 H, 5′-H), 6.94 (d, *J* = 8.1 Hz, 1 H, 7-H), 6.82 (s*, 1 H, 4-H), 6.73 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 6-H), 6.22 (s*, 1 H, 1-H), 5.29 (dd, $J_{3a,3b}$ = 12.6 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3b-H), 5.11 (d, $J_{3a,3b}$ = 12.6 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 157.9 (C-5), 148.7 (C-3′), 146.1 (C-1′), 141.0 (C-3a), 132.3 (C-2′), 132.9 (C-7a) 129.9 (C-4′), 123.0 (C-7), 122.5 (C-6′), 121.0 (C-5′), 115.1 (C-6), 107.9 (C-4), 84.4 (C-1), 73.1 (C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3300, 2850, 1660, 1600, 1500, 1460, 1360, 1290, 1190, 1080, 1020 cm^{-1}. MS: *m*/*z* = 256.3 [M – H]$^-$. $C_{14}H_{11}NO_4$ (257.25): calcd. C 65.37, H 4.31, N 5.44; found C 64.90, H 3.97, N 5.10.

1-(3′,4′,5′-Trimethoxyphenyl)-1,3-dihydroisobenzofuran-5-ol (15): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford **15** (36 mg, 0.13 mmol, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.89 (d, $J_{6,7}$ = 8.1 Hz, 1 H, 7-H), 6.72 (s*, 1 H, 4-H), 6.70 (dd, $J_{7,6}$ = 8.1 Hz, $J_{6,4}$ = 2.1 Hz, 1 H, 6-H), 6.54 (s, 2 H, 2′-H and 6′-H), 6.03 (s*, 1 H, 1-H), 5.24 (dd, $J_{3b,3a}$ = 12.0 Hz, $J_{3b,1}$ = 2.4, 1 H, 3b-H), 5.12 (d, $J_{3a,3b}$ = 12.0 Hz, 1 H, 3a-H), 3.81and 3.82 (s, 9 H, 3 OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8 (C-5), 153.2 (C-3′ and C-5′), 140.9 (C-3a and C-4′), 137.7 (C-1′), 133.3 (C-7a), 123.0 (C-7), 114.9 (C-6), 107.7 (C-4), 104.0 (C-2′and C-6′), 86.0 (C-1), 72.8 (C-3), 60.8 (OCH_3), 56.1 (2 OCH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3300, 2950, 1660, 1520, 1460, 1280, 1130 cm^{-1}. MS: *m*/*z* = 301.3 [M – H]$^-$. $C_{17}H_{18}O_5$ (302.33): calcd. C 67.54, H 6.00; found C 67.15, H 5.89.

1-Butyl-1,3-dihydroisobenzofuran-5-ol (16): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **16** (12 mg, 0.06 mmol, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 8.4 Hz, 1 H, 7-H), 6.72 (d, *J* = 8.4 Hz, 1 H, 6-H), 6.70 (s, 1 H, 4-H), 5.35 (t, *J* = 7.2 Hz, 1 H, 1-H), 4.43 (d, $J_{3a,3b}$ = 12.6 Hz, 1

H, 3a-H), 4.09 (d, $J_{3a,3b}$ = 12.6 Hz, 1 H, 3b-H), 2.82–1.83 (9 H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0 (C-5), 141.8 (C-3a), 132.9 (C-7a), 123.1 (C-7), 114.6 (C-6), 107.6 (C-4), 84.9 (C-1), 72.5 (C-3), 35.8 (C-1′), 27.4 (C-2′), 22.9 (C-3′9, 14.2 (C-4′) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2920, 1680, 1660, 1560, 1460, 1390, 1270, 1130, 1090 cm^{-1}. MS: *m*/*z* = 191.2 $[M - H]^-$. $C_{12}H_{16}O_2$ (192.26): calcd. C 74.97, H 8.39; found C 74.77, H 8.45.

1-(4′-Nitrophenyl)-1,3-dihydroisobenzofuran-5,7-diol (17): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel (Et_2O/hexane, 8:2) to afford pure **17** (35 mg, 0.13 mmol, 61%). ^1H NMR (300 MHz, CD_3OD): δ = 8.12 (d, $J_{3',5'}$ = 8.7 Hz, 2 H, 3′-H and 5′-H), 7.54 (d, $J_{2',6'}$ = 8.7 Hz, 2 H, 2′-H and 6′-H), 6.23 (m, 1 H, 4-H), 6.16 (d, $J_{1,3b}$ = 2.4 Hz, 1 H, 1-H), 6.14 (m, 1 H, 6-H), 5.21 (dd, $J_{3b,3a}$ = 12.3 Hz, $J_{3b,1}$ = 2.4 Hz, 1 H, 3b-H), 5.03 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 160.9 (C-5), 154.3 (C-7), 151.5 (C-4′), 148.7 (C-1′), 143.2 (C-3a), 129.2 (C-3′ and C-5′), 124.2 (C-2′ and C-6′), 119.4 (C-7a), 102.7 (C-4), 99.9 (C-6), 85.2 (C-1), 74.8 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3050, 2900, 1660, 1530, 1470, 1360, 1250, 1130 cm^{-1}. MS: *m*/*z* = 272.2 $[M - H]^-$. $C_{14}H_{11}NO_5$ (273.24): calcd. C 61.54, H 4.06, N 5.13; found C 61.41, H 4.15, N 5.01.

1-(4′-Chlorophenyl)-1,3-dihydroisobenzofuran-5,7-diol (18): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel (Et_2O) to afford pure **18** (26 mg, 0.10 mmol, 50%). ^1H NMR (300 MHz, CD_3OD): δ = 7.25 (s, 4 H, 2′-H, 3′-H, 5′-H, 6′-H), 6.21 (s, 1 H, 4-H), 6.14 (s, 1 H, 6-H), 6.05 (d, $J_{1,3b}$ = 1.8 Hz, 1 H, 1-H), 5.13 (dd, $J_{3b,3a}$ = 12.3 Hz, $J_{3b,1}$ = 1.8 Hz, 1 H, 3b-H), 4.97 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6 (C-5), 152.2 (C-7), 141.3 (C-3a), 140.6 (C-1′), 132.3 (C-6′), 128.0 (C-2′ and C-6′), 127.2 (C-3′ and C-5′), 117.9 (C-7a), 100.8 (C-6), 83.6 (C-1), 72.4 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2950, 1700, 1610, 1500, 1420, 1380, 1270, 1080, 1020 cm^{-1}. MS: *m*/*z* = 261.7 $[M - H]^-$. $C_{14}H_{11}ClO_3$ (262.69): calcd. C 64.01, H 4.22, Cl 13.50; found C 63.84, H 4.33, Cl 13.42.

1-(3′-Nitrophenyl)-1,3-dihydroisobenzofuran-5,7-diol (19): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel (Et_2O/hexane, 8:2) to afford pure **19** (25 mg, 0.09 mmol, 45%). ^1H NMR (300 MHz, CD_3OD): δ = 8.17 (t, *J* = 2.1 Hz, 1 H, 2′-H), 8.08 (d*, *J* = 8.1 Hz, 1 H, 4′-H), 7.73 (d*, *J* = 8.1 Hz, 1 H, 2′-H), 7.50 (t, *J* = 8.1 Hz, 1 H, 5′-H), 6.24 (d*, *J* = 0.9 Hz, 1 H, 4-H), 6.18 (d*, $J_{1,3b}$ = 1.5 Hz, 1 H, 1-H), 6.15 (d*, 1 H, 6-H), 5.20 (dd, $J_{3a,3b}$ = 12.6 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3b-H), 5.04 (d, $J_{3a,3b}$ = 12.6 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 160.6 (C-5), 153.4 (C-7), 149.3 (C-3′), 146.2 (C-1′), 143.1 (C-3a), 134.4 (C-6′), 130.1 (C-5′), 122.8 (C-2′), 123.2 (C-4′), 119.2 (C-7a), 102.6 (C-4), 99.8 (C-6), 85.0 (C-1), 74.6 (C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3050, 2900, 1660, 1530, 1470, 1360, 1250, 1130 cm^{-1}. MS: *m*/*z* = 272.1 $[M - H]^-$. $C_{14}H_{11}NO_5$ (273.24): calcd. C 61.54, H 4.06, N 5.13; found C 61.18, H 3.95, N 4.97.

1-Phenyl-1,3-dihydroisobenzofuran-5,7-diol (20): The reaction was carried out as reported in the general procedure. The residue was purified on silica gel ($CHCl_3$/MeOH, 95:5) to afford pure **20** (25 mg, 0.11 mmol, 50%). ^{1} H NMR (300 MHz, CD_3OD): δ = 7.26–7.19 (5 H, ArH), 6.23 (m, 1 H, 4-H), 6.14 (m, 1 H, 6-H), 6.08 (m, 1 H, 1-H), 5.13 (dd, $J_{3a,3b}$ = 12.0 Hz, $J_{3a,1}$ = 2.4 Hz, 1 H, 3a-H), 4.97 (d, $J_{3b,3a}$ = 12.0 Hz, 1 H, 3b-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 160.2 (C-5), 154.0 (C-7), 143.4* (C-1′), 143.1* (C-3a), 128.9 (C-2′ and C-6′), 128.5 (C-4′), 128.3 (C-3′ and C-5′), 119.9 (C-7a), 102.6 (C-4), 99.6 (C-6), 86.4 (C-1), 74.1 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3600, 3300, 2970, 1610, 1470, 1370, 1250, 1130, 1020 cm^{-1}. MS: *m*/*z* = 227.2 $[M - H]^-$. $C_{14}H_{12}O_3$ (228.25): calcd. C 73.67, H 5.30; found C 73.59, H 5.37.

1-(4′-Hydroxyphenyl)-1,3-dihydroisobenzofuran-5,7-diol 21: The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel (Et_2O/hexane, 8:2) to afford pure **21** (8 mg, 0.03 mmol, 15%). The reaction was also carried out by using chloroacetic acid to afford pure **21** (17 mg, 0.07 mmol, 29%). ^1H NMR (300 MHz, CD_3OD): δ = 7.05 (d, *J* = 8.4 Hz, 2 H, 2′-H, 6′-H), 6.69 (d, *J* = 8.4 Hz, 2 H, 3′-H, 5′-H), 6.21 (d*, *J* = 1.5 Hz, 1 H, 4-H), 6.14 (d*, *J* = 1.8 Hz, 1 H, 6-H), 6.01 (d*, *J* = 2.1 Hz, 1 H, 1-H), 5.08 (dd, $J_{3b,3a}$ = 12.0 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3b-H), 4.92 (d, $J_{3a,3b}$ = 12.0 Hz, 1 H, 3a-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3300, 2950, 1690, 1520, 1450, 1390, 1270, 1250, 1090, 1020 cm^{-1}. MS: *m*/*z* = 242.1 $[M - H]^-$. $C_{14}H_{12}O_4$ (243.1): calcd. C 68.48, H 4.95; found C 68.25, H 4.97.

1-(4′-Methoxyphenyl)-1,3-dihydroisobenzofuran-5,7-diol (22): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 96:4) to afford pure **22** (15 mg, 0.06 mmol, 27%). The reaction was also carried out by using chloroacetic acid to afford pure **22** (30 mg, 0.10 mmol, 48%). ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.20 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 6.82 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 6.30 (m, 1 H, 4-H), 6.25 (d*, *J* = 1.8 Hz, 1 H, 6-H), 6.05 (d*, *J* = 1.8 Hz, 1 H, 1-H), 5.09 (dd, $J_{3a,3b}$ = 12.3 Hz, $J_{3b,1}$ = 2.1 Hz, 1 H, 3a-H), 4.91 (d, $J_{3b,3a}$ = 12.3 Hz, 1 H, 3b-H), 3.75 (s, 3 H, OCH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3429, 2963, 1610, 1511, 1463, 1303, 1247, 1173, 1107, 1030, 802, 757, 553 cm^{-1}. MS: *m*/*z* = 257.1 $[M - H]^-$. $C_{15}H_{14}O_4$ (258.28): calcd. C 69.76, H 5.46; found C 69.52, H 5.58.

1-(3′,5′-Dimethoxyphenyl)-1,3-dihydroisobenzofuran-5,7-diol (23): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 96:4) to afford pure **23** (21 mg, 0.07 mmol, 33%). The reaction was also carried out by using chloroacetic acid to afford pure **23** (40 mg, 0.10 mmol, 48%). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.46 (d, *J* = 2.4 Hz, 2 H, 6′-H, 2′-H), 6.35 (t, *J* = 2.4 Hz, 1 H, 4′-H), 6.22 (m, 1 H, 4-H), 6.16 (d*, $J_{5,4}$ = 1.8 Hz, 1 H, 6-H), 6.02 (d*, $J_{1,3b}$ = 1.8 Hz, 1 H, 1-H), 5.11 (dd, $J_{3a,3b}$ = 12.0 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3a-H), 4.96 (d, $J_{3a,1}$ = 12.0 Hz, 1 H, 3b-H), 3.71 (s, 6 H, 2 OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2 (C-3′ and C-5′), 158.5 (C-5), 152.2 (C-7), 141.5 (C-3a), 144.0 (C-1′), 118.0 (C-7a), 104.5 (C-2′ and C-6′), 100.9 (C-4), 98.7 (C-4′), 97.9 (C-6), 84.3 (C-1), 72.2 (C-3), 53.8 (2 CH_3O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3300, 2950, 1700, 1610, 1470, 1370, 1260 1150, 1070, 940 cm^{-1}. MS: *m*/*z* = 287.8 $[M - H]^-$. $C_{16}H_{16}O_5$ (288.30): calcd. C 66.66, H 5.59; found C 66.02, H 5.11.

1-(3′,4′,5′-Trimethoxyphenyl)-1,3-dihydroisobenzofuran-5,7-diol (24): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 94:6) to afford pure **24** (22 mg, 0.07 mmol, 33%). The reaction was also carried out by using chloroacetic acid to afford pure **24** (39 mg, 0.1 mmol, 58%). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.57 (s, 2 H, 2′-H, 6′-H), 6.28 (s*, 1 H, 4-H), 6.12 (s*, 1 H, 6-H), 6.05 (s*, 1 H, 1-H), 5.57 (br. s, 2 H, 2 OH), 5.17 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H), 5.02 (d, $J_{3b,3a}$ = 12.3 Hz, 1 H, 3b-H), 3.75 (s, 6 H, 2 CH_3O), 3.80 (s, 3 H, CH_3O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (C-5), 142.1 (C-4′), 153.3 (C-3′ and C-5′), 151.4 (C-7), 142.7 (C-3a), 136.4 (C-1′), 118.9 (C-7a), 104.4 (C-2′ and C-6′), 102.3 (C-4), 100.3 (C-6), 84.7 (C-1), 73.3 (C-3), 60.8 (CH_3O), 56.1 (2 CH_3O) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3300, 2950, 1700, 1610, 1470, 1370, 1260 1150, 1070, 940 cm^{-1}. MS: *m*/*z* = 317.2

[M – H]⁻. $C_{17}H_{18}O_6$ (318.33): calcd. C 64.14, H 5.70; found C 64.02, H 5.18.

1-(4′-Hydroxy-3′-methoxyphenyl)-1,3-dihydroisobenzofuran-5,7-diol (25): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 85:15) to afford pure **25** (10 mg, 0.03 mmol, 17%). The reaction was also carried out by using chloroacetic acid to afford pure **25** (18 mg, 0.07 mmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (s, 1 H, 6′-H), 6.70 (s, 2 H, 2′-H, 5′-H), 6.22 (m, 1 H, 4-H), 6.14 (d*, J = 2.1 Hz, 1 H, 6-H), 6.02 (d*, J = 1.8 Hz, 1 H,1-H), 5.06 (dd*, $J_{3a,3b}$ = 12.3 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3b-H), 4.93 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H), 3.77 (s, 3 H, OCH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3550, 3350, 2950, 1660, 1500, 1465, 1360, 1300, 1160 cm^{-1}. MS: m/z = 259.2 [M – H]⁻. $C_{14}H_{12}O_5$ (260.24): calcd. C 64.61, H 4.65; found C 64.58, H 4.52.

1-(3′,4′-Methylenedioxyphenyl)-1,3-dihydroisobenzofuran-5,7-diol (26): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford a pure **26** (12 mg, 0.05 mmol, 25%). The reaction was also carried out by using chloroacetic acid to afford pure **26** (26 mg, 0.09 mmol, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.90 (dd, $J_{6',5'}$ = 7.8 Hz, $J_{6',2'}$ = 1.5 Hz, 1 H, 6′-H), 6.80 (d, $J_{5',6'}$ = 7.8 Hz, 1 H, 5′-H), 6.78 (s*, 1 H, 2′-H), 6.34 (s*, 1 H, 4-H), 6.20 (br. s*, 1 H, 6-H), 6.03 (s*, 1 H, 1-H), 5.96 (s, 2 H, OCH_2O), 5.19 (dd*, $J_{3b,3a}$ = 12.3 Hz, $J_{3b,1}$ = 2.4 Hz, 1 H, 3b-H), 5.05 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5 (C-5), 152.2 (C-7), 147.0 (C-4′), 146.7 (C-3′), 141.5 (C-3a), 135.7 (C-1′), 120.1 (C-6′), 118.1 (C-7a), 106.7 (C-2′ and C-5′), 100.9 (C-4), 100.3 (OCH_2O) 97.9 (C-6), 84.3 (C-1), 72.0 (C-3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3550, 3300, 2900, 2050, 1860, 1625, 1510, 1450, 1380, 1260, 1240, 1160, 1130, 1110, 1080, 1040, 940, 880 cm^{-1}. MS: m/z = 271.2 [M – H]⁻. $C_{15}H_{12}O_5$ (272.26): calcd. C 66.17, H 4.44; found C 65.58, H 4.02.

1-(4′-*N*,*N*-Dimethylaminophenyl)-1,3-dihydroisobenzofuran-5,7-diol (27): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/MeOH, 95:05) to afford pure **27** (12 mg, 0.07 mmol, 32%). ^{1}H NMR (300 MHz, CD_3OD): δ = 7.07 (d, J = 8.7 Hz, 2 H, 2′H, 6′H), 6.71 (d, J = 8.7 Hz, 2 H, 3′-H and 5′-H), 6.22 (m, 1 H, 4-H), 6.14 (d*, J = 2.1 Hz, 1 H,6-H), 6.02 (d*, J = 1.8 Hz, 1 H, 1-H), 5.07 (dd, $J_{3b,3a}$ = 12.0 Hz, $J_{3b,1}$ = 2.7 Hz, 1 H, 3b-H), 4.92 (d, J = 12.0 Hz, 1 H, 3a-H), 3.29 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 160.0 (C-5), 153.8 (C-7), 151.9 (C-4′), 143.2 (C-3a), 131.5 (C-1′), 129.2 (C-2′ and C-6′), 113.7 (C-3′ and C-5′), 120.0 (C-7a), 102.6 (C-4), 99.6 (C-6), 86.3 (C-1), 73.6 (C-3), 41.4 (CH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3443), 2920, 2852, 1651, 1557, 1456, 1353, 1105, 978, 812 cm^{-1}. MS: m/z = 270.2 [M – H]⁻. $C_{16}H_{17}NO_3$ (271.32): calcd. C 70.83, H 6.32, N 5.16; found C 70.75, H 6.43.

5,7-Dimethoxy-1-(4′-nitrophenyl)-1,3-dihydroisobenzofuran (28): The reaction was carried out as reported in the general procedure. The obtained solid product was purified on silica gel (hexane/Et_2O, 6:4) to afford **28** (22 mg, 0.072 mmol, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, J = 7.7 Hz, 2 H, 3′-H and 5′-H), 7.51 (d, J = 7.7 Hz, 2 H, 2′-H and 6′-H), 6.42 (m, 1 H, 4-H), 6.32 (s, 1 H, 6-H), 6.25 (m, 1 H, 1-H), 5.35 (dd, $J_{3b,3a}$ = 12.3 Hz, $J_{3b,1}$ = 2.4 Hz, 1 H, 3b-H), 5.05 (d, $J_{3a,3b}$ = 12.3 Hz, 1 H, 3a-H), 3.81 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3620, 3050, 2900, 1660, 1525, 1470, 1355, 1250, 1220, 1130, 1060 cm^{-1}. MS: m/z = 300.2 [M – H]⁻. $C_{16}H_{15}NO_5$ (301.30): calcd. C 63.78, H 5.02, N 4.65; found C 63.62, H 5.15, N 4.39.

5,7-Dimethoxy-1-(3′,4′-methylenedioxyphenyl)-1,3-dihydroisobenzofuran (29): The reaction was carried out as reported in the general procedure. The obtained solid product was purified on silica gel (hexane/Et_2O, 6:4) to afford pure **29** (20 mg, 0.07 mmol, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70–6.85 (m, 3 H, 2′-H, 5′-H, 6′-H), 6.40 (s*, 1 H, 4-H), 6.34 (d*, J = 2.1 Hz, 1 H, 6-H), 6.12 (m, 1 H, 1-H), 5.92 (s, 2 H, OCH_2O), 5.25 (dd, $J_{3b,3a}$ = 12.0 Hz, $J_{3b,1}$ = 2.4 Hz, 1 H, 3b-H), 5.08 (d, $J_{3a,3b}$ = 12.0 Hz. 1 H, 3a-H), 3.82 (s, 1 H, OCH_3), 3.66 (s, 1 H, OCH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3550, 3300, 2950, 2050, 1855, 1625, 1505, 1450, 1380, 1260, 1240, 1155, 1135, 1110, 1080, 1030 cm^{-1}. MS: m/z = 299.2 [M – H]⁻. $C_{17}H_{16}O_5$ (300.31): calcd: C 67.99, H 5.37; found C 67.67, H 5.44.

5,7-Dimethoxy-1-(3′,5′-dimethoxyphenyl)-1,3-dihydroisobenzofuran (30): The reaction was carried out as reported in the general procedure. The obtained solid product was purified on silica gel (hexane/Et_2O, 6:4) to afford **30** (23 mg, 0.08 mmol, 47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.50 (d, J = 2.3 Hz, 2 H, 6′-H and 2′-H), 6.39 (s, 1 H, 4-H), 6.33 (d*, J = 1.8 Hz,1 H, 6-H), 6.34 (d*, J = 2.4 Hz, 1 H, 4′-H), 6.50 (d, J = 2.4 Hz, 2 H, 2′-H and 6′-H), 6.14 (d*, 1 H, 1-H), 5.27 (dd, $J_{3a,3b}$ = 12.4 Hz, $^{3b,1}J$ = 2.7 Hz, 1 H, 3a-H), 5.09 (d, $^{3a,1}J$ = 12.4 Hz,1 H, 3b-H), 3.82 (s, 3 H, OCH_3), 3.76 (s, 6 H, 2 OCH_3), 3.72 (s, 3 H, OCH_3) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3300, 2950, 1700, 1610, 1470, 1370, 1250, 1220, 1150, 1060, 1070, 940 cm^{-1}. MS: m/z = 315.2 [M – H]⁻. $C_{18}H_{20}O_5$ (316.36): calcd. C 68.34, H 6.37; found C 68.03, H 6.42.

1,1-Bis[1-(2′,6′-dihydroxy-4′-hydroxymethylphenyl)]ethane (31): The reaction was carried out as reported in the general procedure at 4 °C for 2 h. The residue was purified on silica gel (Et_2O) to afford pure **31** (12 mg, 0.04 mmol, 33%). ^{1}H NMR (300 MHz, CD_3OD): δ = 6.39 (s, 4 H, 3′-H and 5′-H), 4.58 (t, J = 8.1 Hz, 1 H, 1-H), 4.41 (s, 4 H, 2 CH_2OH), 2.30 (m, 2 H, 2-H), 0.86 (t, J = 7.2 Hz, 3 H, 3-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.5 (C-2′ and C-6′), 142.4 (C-4′), 116.6 (C-1′), 107.8 (C-3′ and C-5′), 64.8 (hydroxymethyl carbon), 57.4 (C-1), 25.0 (C-2), 14.0 (C-3) ppm. MS: m/z = 319.3 [M – H]⁻. $C_{17}H_{20}O_6$ (320.35): calcd. C 63.74, H 6.29; found C 63.66, H 6.33.

1,1-Bis[1-(2′,6′-dihydroxy-4′-hydroxymethylphenyl)]butane (32): The reaction was carried out as reported in the general procedure at 38 °C for 48 h by using chloroacetic acid as the catalyst. The residue was purified on silica gel (Et_2O/hexane, 8:2) to afford pure **32** (9 mg, 0.03 mmol, 25%). ^{1}H NMR (300 MHz, CD_3OD): δ = 6.39 (s, 4 H, 3′-H and 5′-H), 4.68 (t, J = 7.8 Hz, 1 H, 1-H), 4.41 (s, 4 H, 2 CH_2OH), 2.27 (m, 2 H, 2-H), 1.26 (m, 4 H, 3-H and 4-H), 0.85 (t, J = 7.2 Hz, 3 H, 3 5-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.4 (C-3 and C-7), 142.4 (C-5), 116.8 (C-2), 107.9 (C-4 and C-6), 64.8 (hydroxymethyl carbon), 33.1 (C-1), 32.4 (C-1′), 31.6 (C-3), 23.6 (C-4), 14.4 (C-5) ppm. MS: m/z = 347.4 [M – H]⁻. $C_{19}H_{24}O_6$ (348.40): calcd. C 65.50, H 6.94; found C 65.38, H 7.02.

1-(3′,4′-Methylenedioxyphenyl)-6,8-dimethoxyisochroman (33): The reaction was carried out as reported in the general procedure at 4 °C for 24 h. The residue was purified on silica gel ($CHCl_3$/hexane, 8:2) to afford pure **33** (44 mg, 0.14 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.6–3.1 (m, 2 H, 4-H), 3.59 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.9–3.7 (m, 2 H, 3-H), 5.79 (s, 1 H, 1-H), 5.92 (s, 2 H, OCH_2O), 6.27 (d*, J = 2.2 Hz, 1 H, 7-H), 6.33 (d*, J = 2.2 Hz, 1 H, 5-H), 6.63 (dd, J = 7.8 Hz, J = 2.0 Hz, 1 H, 6′-H), 6.71 (d, J = 2.0 Hz, 1 H, 2′-H), 6.72 (d, J = 7.8 Hz, 1 H, 5′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8 (C-4), 55.2 (2 OCH_3), 59.3 (C-3), 73.4 (C-1) 96.6 (C-7), 100.8 (OCH_2O), 104.2 (C-5), 107.5 (C-2′), 108.9 (C-5′), 117.5 (C-8a), 121.9 (C-6′), 136.1 (C-1′), 136.4 (C-4a), 146.7 (C-3′), 147.3 (C-4′), 157.1 (C-6), 159.5 (C-8)

ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3300, 2935, 1650, 1480, 1340, 1148 cm^{-1}. MS: *m/z* = 313.3 $[M - H]^-$. $C_{18}H_{18}O_5$ (314.34): calcd. C 68.72, H 5.77; found C 68.32, H 5.42.

1-Phenylbenzo-2-oxacycloheptene-7,8-diol (34): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 93:7) to afford pure **34** (16 mg, 0.06 mmol, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.88 (m, 2 H, 4-H), 2.88 (m, 1 H, 5a-H), 3.10 (m, 1 H, 5b-H), 3.96 (m,1 H, 3a-H), 4.30 (m, 1 H, 3b-H), 5.08 (br. s, 1 H, OH), 5.27 (br. s, 1 H, OH), 5.67 (s, 1 H, 1-H), 6.08 (s, 1 H, 9-H), 6.74 (s, 1 H, 6-H), 7.25 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.2 (C-5), 34.2 (C-4), 55.3 (OCH_3), 73.2 (C-3), 83.2 (C-1), 127.4 (C-3 and C-5′), 116.0 (C-9), 117.0 (C-6), 128.4 (C-2′′ and C-6′), 141.1 (C-1′), 135.5 (C-5a), 135.5 (C-9a), 140.6 (C-7), 142.6 (C-8), 127.5 (C-4′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3629, 1718, 1613, 1500, 1448, 1232, 1097, 1028 cm^{-1}. MS: *m/z* = 255.2 $[M - H]^-$. $C_{16}H_{16}O_3$ (256.30): calcd. C 74.98, H 6.29; found C 74.65, H 6.34.

1-(4′-Methoxyphenyl)benzo-2-oxacycloheptene-7,8-diol (35): The reaction was carried out as reported in the general procedure The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 93:7) to afford pure **35** (17 mg, 0.06 mmol, 34%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (m, 2 H, 4-H), 2.86 (m, 1 H, 5a-H), 3.05 (m, 1 H, 5b-H), 3.82 (s, 3 H, OCH_3), 3.93 (m, 1 H, 3a-H), 4.26 (m, 1 H, 3b-H), 5.08 (br. s, 1 H, OH), 5.27 (br. s, 1 H, OH), 5.60 (s, 1 H, 1-H), 6.11 (s, 1 H, 9-H), 6.71 (s, 1 H, 6-H), 6.90 (d, *J* = 9.0 Hz, 2 H, 3′-H and 5′-H), 7.23 (d, *J* = 9.0 Hz, 2 H, 2′-H and 6′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1 (C-5), 34.2 (C-4), 55.4 (OCH_3), 72.9 (C-3), 82.8 (C-1), 113.6 (C-3′ and C-5′), 115.8 (C-9), 116.8 (C-6), 128.3 (C-2′ and C-6′), 133.0 (C-1′), 135.0 (C-5a), 135.3 (C-9a), 140.4 (C-7), 142.4 (C-8), 158.7 (C-4′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3300, 2950, 1680, 1660, 1520, 1460, 1390, 1290, 1240, 1140, 1080 cm^{-1}. MS: *m/z* = 285.10 $[M - H]^-$. $C_{17}H_{18}O_4$ (286.33): calcd. C 71.31, H 6.34; found C 71.04, H 6.42.

1-(4′-Chlorophenyl)benzo-2-oxacycloheptene-7,8-diol (36): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/MeOH, 93:7) to afford pure **36** (16 mg, 0.05 mmol 31%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (m, 2 H, 4-H), 2.84 (m, 1 H, 5a-H), 3.09 (m, 1 H, 5b-H), 3.94 (m, 1 H, 3a-H), 4.27 (m, 1 H, 3b-H), 5.08 (br. s, 2 H, 2 OH), 5.62 (s, 1 H, 1-H), 6.03 (s, 1 H, 9-H), 6.72 (s, 1 H, 6-H), 7.27 (d, *J* = 8.4 Hz, 2 H, 2′-H and 6′-H), 7.4 (d, *J* = 8.4 Hz, 2 H, 3′-H and 5′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3383, 2938, 2847, 1607, 1515, 1490, 1455, 1344, 1294, 1214, 1089, 1014, 938, 886, 757 cm^{-1}. MS: *m/z* = 289.5 $[M - H]^-$. $C_{16}H_{15}ClO_3$ (290.75): calcd. C 66.10, H 5.20; found C 65.99, H 5.38.

1-(4′-Nitrophenyl)benzo-2-oxacycloheptene-7,8-diol (37): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 95:5) to afford pure **37** (18 mg, 0.06 mmol, 33%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (m, 2 H, 4-H), 2.85 (m, 1 H, 5a-H), 3.12 (m, 1 H, 5b-H), 3.96 (m, 1 H, 3a-H), 4.32 (m, 1 H, 3b-H), 5.20 (br. s, 2 H, 2 OH) 5.74 (s, 1 H, 1-H), 5.93 (s, 1 H, 9-H), 6.74 (s, 1 H, 6-H), 7.53 (d, *J* = 8.7 Hz, 2 H, 2′-H and 6′-H), 8.20 (d, *J* = 8.7 Hz, 2 H, 3′-H and 5′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3441, 2944, 2360, 1607, 1517, 1456, 1346, 1295, 1205, 1085, 1044, 891, 742 cm^{-1}. MS: *m/z* = 300.2 $[M - H]^-$. $C_{16}H_{15}NO_5$ (301.30): calcd. C 63.78, H 5.02, N 4.65; found C 63.53, H 5.13.

1-(3′,4′-Methylenedioxyphenyl)benzo-2-oxacycloheptene-7,8-diol (38): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 95:5) to afford pure **38** (19 mg, 0.06 mmol, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.83 (m, 2 H, 4-H), 2.87 (m, 1 H, 5a-H), 3.04 (m, 1 H, 5b-H), 3.92 (m, 1 H, 3a-H), 4.25 (m, 1 H, 3b-H), 5.14 (br. s, 2 H, 2 OH), 5.57 (s, 1 H, 1-H), 5.96 (s*, 2 H, CH_2), 6.16 (s, 1 H, 9-H), 6.71 (s, 1 H, 6-H), 6.77 (d*, *J* = 8.4 Hz, 1 H, 6′-H), 6.80 (d*, *J* = 8.4 Hz, 1 H, 5′-H-5′), 6.85 (1 H, 2′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3350, 3000, 2900, 1720, 1620, 1500, 1450, 1380, 1240, 1140, 1090, 1040 cm^{-1}. MS: *m/z* = 299.2 $[M - H]^-$. $C_{17}H_{16}O_5$ (300.31): calcd. C 67.99, H 5.37; found C 67.68, H 5.44.

1-(4′-Hydroxy-3′-methoxyphenyl)benzo-2-oxacycloheptene-7,8-diol (39): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 93:7) to afford pure **39** (17 mg, 0.06 mmol, 32%). ^1H NMR (300 MHz, CD_3OD): δ = 1.80 (m, 2 H, 4-H), 2.80 (m, 1 H, 5a-H), 3.07 (m, 1 H, 5b-H), 3.94 (m, 1 H, 3a-H), 4.18 (m, 1 H, 3b-H), 3.88 (s, 3 H, OCH_3), 5.60 (s, 1 H, 1-H), 6.08 (s, 1 H, 9-H), 6.62 (s, 1 H, 6-H), 6.70 (dd, *J* = 8.1 Hz, *J* = 2.1 Hz, 1 H, 6′-H), 6.78 (d, *J* = 8.1 Hz, 1 H, 5′-H), 6.89 (d, *J* = 2.1 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 31.6 (C-5), 35.0 (C-4), 56.3 (CH_3O), 73.9 (C-3), 84.6 (C-1), 117.8 (C-2′), 115.6 (C-9), 117.0 (C-6), 118.0 (C-5′), 121.0 (C-6′), 134.0 (C-1′), 134.9 (C-5a), 135.4 (C-9a), 143.1 (C-6′), 144.7 (C-8), 146.6 (C-4′), 148.6 (C-3′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3430, 2950, 1690, 1650, 1520, 1450, 1390, 1275, 1247, 1090, 1060, 1020, 784 cm^{-1}. MS: *m/z* = 301.3 $[M - H]^-$. $C_{17}H_{18}O_5$ (302.38): calcd. C 67.54, H 6.00; found C 67.49, H 6.12.

1-(3′,4′-Dimethoxyphenyl)benzo-2-oxacycloheptene-7,8-diol (40): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/MeOH, 93:7) to afford pure **40** (17 mg, 0.05 mmol, 30%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.84 (m, 2 H, 4-H), 2.86 (m, 1 H, 5a-H), 3.08 (m, 1 H, 5b-H), 3.85 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.92 (m, 1 H, 3a-H), 4.29 (m, 1 H, 3b-H), 5.28 (br. s, 1 H, OH), 5.35 (br. s,1 H, OH), 5.61 (s, 1 H, 1-H), 6.12 (s*, 1 H, 9-H), 6.74 (s, 1 H, 6-H), 6.78–6.88 (2 H, 5′-H and 6′-H), 6.91 (s*, 1 H, 2′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3440, 2935, 2840, 1600, 1515, 1455, 1423, 1345, 1295, 1204, 1150, 1065, 1027, 840, 752 cm^{-1}. MS: *m/z* = 315.3 $[M - H]^-$. $C_{18}H_{20}O_5$ (316.36): calcd. C 68.34, H 6.37; found C 68.12, H 6.41.

1-(3′,5′-Dimethoxyphenyl)benzo-2-oxacycloheptene-7,8-diol (41): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **41** (20 mg, 0.06 mmol, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (m, 2 H, 4-H), 2.86 (m, 1 H, 5a-H), 3.11 (m, 1 H, 5b-H), 3.78 (s, 6 H, 2 OCH_3), 3.95 (m, 1 H, 3a-H), 4.31 (m, 1 H, 3b-H), 4.86 (br. s, 1 H, OH), 5.13 (br. s, 1 H, OH), 5.58 (s, 1 H, 1-H), 6.15 (s, 1 H, 9-H), 6.41 (d, *J* = 2.1 Hz, 1 H, 4′-H), 6.52 (d, *J* = 2.1 Hz, 2 H, 2′-H and 6′-H), 6.74 (s, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.2 (C-5), 34.3 (C-4), 55.0 (2 CH_3O), 73.7 (C-3), 82.0 (C-1), 99.6 (C-4′), 105.0 (C-2′ and C-6′), 115.6 (C-9), 116.8 (C-9), 135.4 (C-5a), 135.3 (C-9a), 140.3 (C-7), 142.4 (C-8), 143.2 (C-1′), 160.5 (C-3′ and C-5′) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3447), 2938, 2847, 1598, 1515, 1456, 1428, 1347, 1295, 1204, 1154, 1065, 1027, 839, 752 cm^{-1}. MS: *m/z* = 315.3 $[M - H]^-$. $C_{18}H_{20}O_5$ (316.36): calcd. C 68.34, H 6.37; found C 68.12, H 6.10.

1-(3′,4′,5′-Trimethoxyphenyl)benzo-2-oxacycloheptene-7,8-diol (42): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **42** (22 mg, 0.06 mmol, 35%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (m, 2 H, 4-H), 2.84 (m, 1 H, 5a-H), 3.12 (m, 1 H, 5b-H), 3.78 (s, 6 H, 2 OCH_3), 3.81 (s, 3 H, OCH_3), 3.95 (m, 1 H, 3a-H), 4.32 (m, 1 H, 3b-H), 5.44 (br. s, 1 H, OH), 5.57 (s, 1 H, 1-H), 6.13 (s, 1 H, 9-H), 6.60 (s, 2 H, 2′-H and 6′-H), 6.74 (s, 1 H, 6-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3445, 2930, 2845, 1598,

1515, 1454, 1428, 1340, 1295, 1204, 1154, 1065, 1027, 839, 752 cm^{-1}. MS: *m*/*z* = 345.2 [M – H]$^-$. $C_{19}H_{22}O_6$ (346.38): calcd. C 65.88, H 6.40; found C 64.98, H 6.02.

1-(4′-Methoxycarbonylphenyl)benzo-2-oxacycloheptene-7,8-diol (43): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOH, 95:5) to afford pure **43** (16 mg, 0.05 mmol, 30%). ^{1}H NMR (300 MHz, CD_3OD): δ = 1.81 (m, 2 H, 4-H), 2.79 (m, 1 H, 5a-H), 3.12 (m, 1 H, 5b-H), 3.94 (m, 1 H, 3a-H), 3.90 (s, 3 H, OCH_3), 4.22 (m, 1 H, 3b-H), 5.74 (s, 1 H, 1-H), 5.90 (s, 1 H, 9-H), 6.63 (s, 1 H, 6-H), 7.42 (d, *J* = 8.4 Hz, 2 H, 6′-H and 2′-H), 8.00 (d, *J* = 8.4 Hz, 2 H, 3′-H and 5′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 3400, 2950, 1720, 1620, 1510, 1450, 1280, 1130, 1090 cm^{-1}. MS: *m*/*z* = 299.2 [M – H]$^-$. $C_{17}H_{16}O_5$ (300.31): calcd. C 67.99, H 5.35; found C 67.77, H 5.44.

1-Phenylbenzo-2-oxacycloheptene-7-ol (44): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/EtOAc, 8:2) to afford pure **44** (10 mg, 0.04 mmol, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.89 (m, 2 H, 4-H), 2.94 (m, 1 H, 5a-H), 3.16 (m, 1 H, 5b-H), 3.97 (m, 1 H, 3a-H), 4.29 (m, 1 H, 3b-H), 5.70 (s, 1 H, 1-H), 6.45 (s*, 2 H, 8-H and 9-H), 6.70 (s*, 1 H, 6-H): 7.30–7.40 (m, 5 H, ArH) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3631, 2980, 1684, 1604, 1497, 1448, 1248, 1097, 1028, 803 cm^{-1}. MS: *m*/*z* = 239.2 [M – H]$^-$. $C_{16}H_{16}O_2$ (240.30): calcd. C 79.97, H 6.71; found C 79.78, H 6.74.

1-(4′-Methoxyphenyl)benzo-2-oxacycloheptene-7-ol (45): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/MeOH, 95:5) to afford pure **45** (11 mg, 0.04 mmol, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (m, 2 H, 4-H), 2.94 (m, 1 H, 5a-H), 3.11 (m, 1 H, 5b-H), 3.90 (s, 3 H, OCH_3), 3.95 (m, 1 H, 3a-H), 4.26 (m, 1 H, 3b-H), 4.70 (br. s, 1 H, OH), 5.66 (s, 1 H, 1-H), 6.45 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 8-H), 6.49 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.69 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.92 (d, *J* = 9.0 Hz, 2 H, 3′-H and 5′-H) 7.26 (d, *J* = 9.0 Hz, 2 H, 2′-H and 6′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3620, 2835, 1636, 1604, 1448, 1247, 1040, 784 cm^{-1}. MS: *m*/*z* = 269.3 [M – H]$^-$. $C_{17}H_{18}O_3$ (270.33): calcd. C 75.53, H 6.71; found C 75.41, H 6.65.

1-(4′-Chlorophenyl)benzo-2-oxacycloheptene-7-ol (46): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel (Et_2O/hexane, 8:2) to afford pure **46** (14 mg, 0.05 mmol, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (m, 2 H, 4-H), 2.93 (m, 1 H, 5a-H), 3.14 (m, 1 H, 5b-H), 3.95 (m, 1 H, 3a-H), 4.28 (m, 1 H, 3b-H), 5.67 (s, 1 H, 1-H), 6.41 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.46 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 8-H), 6.70 (d, *J* = 2.4 Hz, 1 H, 6-H), 7.28 (d, *J* = 8.7 Hz, 2 H, 2′-H and 6′-H), 7.35 (d, *J* = 8.7 Hz, 2 H, 3′-H and 6′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3600, 1684, 1636, 1604, 1567, 1447, 1246, 1090, 1028, 803 cm^{-1}. MS: *m*/*z* = 273.7 [M – H]$^-$. $C_{16}H_{15}ClO_2$ (274.75): calcd. C 69.95, H 5.50; found C 69.72, H 5.40.

1-(4′-Nitrophenyl)benzo-2-oxacycloheptene-7-ol (47): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel (Et_2O/hexane, 75:25) to afford pure **47** (12 mg, 0.04 mmol, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (m, 2 H, 4-H), 2.92 (m, 1 H, 5a-H), 3.17 (m, 1 H, 5b-H), 3.97 (m, 1 H, 3a-H), 4.32 (m, 1 H, 3b-H), 4.79 (br. s, 1 H, OH), 5.79 (s, 1 H, 1-H), 6.31 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.46 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 8-H), 6.73 (d, *J* = 2.4 Hz, 1 H, 6-H), 7.55 (d, *J* = 8.7 Hz, 2 H, 2′-H and 6′-H), 8.25 (d, *J* = 8.7 Hz, 2 H, 3′-H and 5′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3630, 2944, 2360, 1604, 1520, 1347, 1248, 1097, 852 cm^{-1}. MS: *m*/*z* = 284.2 [M – H]$^-$. $C_{16}H_{15}NO_4$ (285.30): calcd. C 67.36, H 5.30, N 4.91; found C 64.20, H 5.03, N 4.70.

1-(3′-Nitrophenyl)benzo-2-oxacycloheptene-7-ol (48): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel (Et_2O/hexane, 75:25) to afford pure **48** (12 mg, 0.04 mmol, 21%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (m, 2 H, 4-H), 2.94 (m, 1 H, 5a-H), 3.17 (m,1 H, 5b-H), 3.97 (m, 1 H, 3a-H), 4.32 (m, 1 H, 3b-H), 4.79 (br. s, 1 H, OH), 5.80 (s, 1 H, 1-H), 6.34 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.46 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 8-H), 6.73 (d, *J* = 2.4 Hz, 1 H, 6-H), 7.56 (t, *J* = 8.1 Hz, 1 H, 5′-H), 7.70 (d*, *J* = 8.1 Hz, 1 H, 6′-H), 8.19 (dm, *J* = 8.1 Hz, 1 H, 4′-H), 8.25 (1 H, 2′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3444, 3100, 1609, 1525, 1457, 1347, 1297, 1095, 1014, 852 cm^{-1}. MS: *m*/*z* = 284.2 [M – H]$^-$. $C_{16}H_{15}NO_4$ (285.30): calcd. C 67.36, H 5.30, N 4.91; found C 67.18, H 5.12.

1-(3′,4′-Methylenedioxyphenyl)benzo-2-oxacycloheptene-7-ol (49): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/MeOH, 95:5) to afford pure **49** (12 mg, 0.04 mmol, 22%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (m, 2 H, 4-H), 2.94 (m, 1 H, 3a-H), 3.12 (m, 1 H, 3b-H), 3.94 (m, 1 H, 5a-H), 4.26 (m, 1 H, 5b-H), 4.69 (br. s, 1 H, OH), 5.62 (s, 1 H, 1-H), 5.96 (d, *J* = 4.2 Hz, 2 H, OCH_2O), 6.48 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 8-H), 6.53 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.68 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.77 (d, *J* = 8.1 Hz, 1 H, 6′-H), 6.81 (d, *J* = 8.1 Hz, 1 H, 5′-H), 6.86 (d, *J* = 1.5 Hz, 1 H, 2′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3300, 2947, 1653, 1604, 1520, 1480, 1352, 1130 cm^{-1}. MS: *m*/*z* = 283.2 [M – H]$^-$. $C_{17}H_{16}O_4$ (284.31): calcd. C 71.82, H 5.67; found C 71.60, H 5.77.

1-(4′-*N*,*N*-Dimethylaminophenyl)benzo-2-oxacycloheptene-7-ol (50): The reaction was carried out as reported in the general procedure. The obtained oil product was purified on silica gel ($CHCl_3$/MeOH, 95:5) to afford pure **50** (12 mg, 0.04 mmol, 22%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (m, 2 H, 4-H), 2.94 (m, 1 H, 5a-H), 2.96 (s, 6 H, 2 CH_3), 3.10 (m, 1 H, 5b-H), 3.93 (m, 1 H, 3a-H), 4.25 (m, 1 H, 3b-H), 4.79 (br. s, 1 H, OH), 5.63 (s, 1 H, 1-H), 6.45 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1 H, 8-H), 6.56 (d, *J* = 8.4 Hz, 1 H, 9-H), 6.68 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.76 (d, *J* = 8.4 Hz, 2 H, 3′-H and 5′-H), 7.19 (d, *J* = 8.4 Hz, 2 H, 2′-H and 6′-H) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3420, 2920, 2349, 2260, 1604, 1448, 1353, 1097, 1028 cm^{-1}. MS: *m*/*z* = 282.3 [M – H]$^-$. $C_{18}H_{21}NO_2$ (283.37): calcd. C 76.30, H 7.47, N 4.94; found C 76.15, H 7.15, N 4.66.

[1] M. Guiso, C. Marra, C. Cavarischia, *Tetrahedron Lett.* **2001**, *42*, 6531–6534.
[2] M. Guiso, A. Bianco, C. Marra, C. Cavarischia, *Eur. J. Org. Chem.* **2003**, 3407–3411.
[3] B. Wunsch, M. Zott, *Liebigs Ann. Chem.* **1992**, 39–45.
[4] E. A. Markariyan, A. G. Samodurova, *Russ. Chem. Rev.* **1989**, *58*, 479.
[5] E. L. Larghi, T. S. Kaufman, *Synthesis* **2006**, *187*, 220.
[6] A. Bianco, F. Coccioli, M. Guiso, C. Marra, *Food Chem.* **2001**, *77*, 405–411.
[7] A. A. Qureshi, R. W. Rickards, A. Kamal, *Tetrahedron* **1967**, *23*, 3801–3808.
[8] B. A. Keay, R. Rodrigo, *J. Am. Chem. Soc.* **1982**, *104*, 4725–4727.
[9] E. J. Corey, J. Das, *J. Am. Chem. Soc.* **1982**, *104*, 5551–5553.
[10] J. E. McMurry, M. D. Erion, *J. Am. Chem. Soc.* **1985**, *107*, 2712–2720.
[11] R. Camenzind, B. Rickborn, *J. Org. Chem.* **1986**, *51*, 1914–1916.
[12] M. Yus, J. Gomis, *Eur. J. Org. Chem.* **2002**, 1989–1995.
[13] M. Yus, C. Gomez, P. Candela, *Tetrahedron* **2002**, *58*, 6207–6210.

[14] M. C. Elliott, C. J. Mood, *Synlett* **1993**, 909–910.
[15] J. G. Smith, D. E. Fogg, I. J. Munday, R. E. Sandborn, P. W. Dibble, *J. Org. Chem* **1988**, *53*, 2942–2953.
[16] Y. Nagao, A. Ueki, K. Asano, S. Tanaka, S. Sano, M. Shiro, *Org. Lett.* **2002**, *4*, 455–457.
[17] F. Foubelo, C. Gomez, A. Gutierrez, M. Yus, *J. Heterocycl. Chem.* **2000**, *37*, 1061–1064.
[18] M. Barfield, R. J. Spear, S. Sternhell, *J. Am. Chem. Soc.* **1975**, *97*, 5160–5167.
[19] U. Azzena, S. Demartis, G. Melloni, *J. Org. Chem.* **1996**, *61*, 4913–4919.
[20] U. Azzena, S. Demartis, M. G. Fiori, G. Melloni, L. Pisano, *Tetrahedron Lett.* **1995**, *36*, 8123–8126.
[21] R. R. Fraser, R. N. Renaud, *Can. J. Chem.* **1971**, *49*, 46–54.
[22] S. Ram, A. K. Saxena, G. K. Patnaik, P. C. J. Jain, *Ind. J. Chem. Sect. B* **1984**, *23B*, 1261–1267.
[23] D. A. Oparin, T. Zimatkina, S. M. Zimatkina, *Farmakol. Toksikol. (Moscow)* **1985**, *48*, 115–119.
[24] F. J. McEvoy, G. R. Allen Jr, GB 1225216 19710317, **1971** [*Chem. Abstr.* **1971**, *75*, 76600].
[25] J. F. De Bernardis, *J. Med. Chem.* **1987**, *30*, 178–184.
[26] W. J. Houlihan, J. Nadelson, US 3745165 19710317, **1973** [*Chem. Abstr.* **1973**, *79*, 66201].
[27] Y. F. Kulibaba, E. A. Ignatova, *Khim. Sel. Khoz.* **1973**, *11*, 600–602.
[28] H. Feichtinger, H. Linden, (Ruhrchemie A.-G.), US 3176024 19650330, **1965** [*Chem. Abstr.* **1965**, *62*, 16192].
[29] H. Feichtinger, H. Linden, (Ruhrchemie A.-G.), DE 1170963 19640527, **1964** [*Chem. Abstr.* **1964**, *61*, 6992].
[30] D. D. Phillips, S. B. Soloway, (Shell Oil Co.), US 3036092 19620522 [*Chem. Abstr.* **1962**, *57*, 13724].
[31] D. A. Oparin, *Ser. Chim. Navuk* **1988**, *5*, 113–114.
[32] M. Grimberg, *Seifen, Oele, Fette,. Wachse* **1965**, *91*, 826–827.
[33] W. Friedrichsen, *Adv. Heterocycl. Chem.* **1999**, *73*, 1–96.
[34] B. Rickborn in *Advances in Theoretically Interesting. Molecules* (Ed.: R.P. Thummel), JAI Press, Greenwich, **1989**, vol. 1, pp. 1–134.
[35] W. E. Parham, Y. A. Sayed, *Synthesis* **1976**, 116–117.
[36] N. Meyer, D. Seebach, *Chem. Ber.* **1980**, *113*, 1304–1319.
[37] U. Azzena, S. Demartis, *J. Org. Chem.* **1996**, *61*, 4913–4919.
[38] J. G. Smith, R. T. Wikmen, *J. Org. Chem.* **1974**, *39*, 3648–3650.
[39] E. J. Corey, A. Palani, *Tetrahedron Lett.* **1995**, *36*, 3485–3488.
[40] M. Mihara, Y. Ishino, S. Minakata, M. Komatsu, *Synlett* **2002**, 1526–1528.
[41] W. Kirmse, K. Kund, *J. Org. Chem.* **1990**, *55*, 2325–2332.
[42] Jpn Kokai Tokkyo Koho, JP 59139375 A 19840810 Showa, **1984** [*Chem. Abstr.* **1985**, *102*, 6189].
[43] J. Renga, US 4336195 A 19820622, **1982** [*Chem. Abstr.* **1982**, *97*, 144751].
[44] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
[45] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas, *J. Chem. Soc., Chem. Commun.* **1976**, 736–738.
[46] L. Mandolini, *J. Am. Chem. Soc.* **1978**, *100*, 550.

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