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Regiospecific synthesis of 3-(2,6-dihydroxyphenyl)phthalides: application to the synthesis of isopestacin and cryphonectric acid

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Abstract—DBU catalyzed condensation of phthalaldehydic acids and 1,3-diketones has been developed to be a general method for the synthesis of 3-substituted phthalides. This method, in combination with mercuric acetate mediated oxidative aromatization has been utilized for the regiospecific synthesis of isopestacin (**9**) and cryphonectric acid (**10**).
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1. Introduction

1(3*H*)-Isobenzofuranones (phthalides) are a prominent class of natural products by virtue of their significantly varied biological properties.[1] In particular, 3-substituted phthalide moieties are embodied in numerous natural products. Typical examples are fuscinarin (**1**),[2a] typhaphthalide (**2**),[2b] catalpalactone (**3**),[2c] alcyopterosin E (**4**),[2d] (+)-spirolaxine (**5**),[2e] vermistatin (**6**),[2f] rubiginone-H (**7**),[2g] (−)-hydrastine (**8**),[2h] isopestacin (**9**),[2i] and cryphonectric acid (**10**).[2j] They possess a wide range of biological activities, which include antibacterial,[3a] anticonvulsant,[3b] and anti-HIV.[2a] Phthalides also serve as valuable synthetic intermediates.[4]

The newer members, isopestacin (**9**) and cryphonectric acid (**10**), are distinguished in having a resorcinol moiety attached at the C-3 position of phthalides (Fig. 1). Isopestacin (**9**) was isolated in 2002 by Strobel et al.[2i] from culture broths of the endophytic fungus *Pestalopsis microspore*. It shows antifungal activity and acts as an antioxidant toward both superoxide radical and hydroxyl free radicals, the activity being comparable to that of vitamin C. Cryphonectric acid (**10**) was isolated by Arnone et al.[2j] from cultures of a hypovirulent strain of *Cryphonectrica parasitica*. It has been shown to inhibit the formation of tomato seedlings.

Both the phthalides **9** and **10** have a resorcinol moiety attached through C-2 to the C-3 of the isobenzofuranone unit. In addition, the resorcinolyl carboxylic acid moiety of **10** strongly resembles the aromatic subunit of balanol, well-known PKC inhibitor.[5] The potential biological activity along with unusual structural features prompted us to develop a synthesis of **9**,[6] which was published in a communication. We now report a full account of the investigation as well as its extension to the first synthesis of cryphonectric acid (**10**).

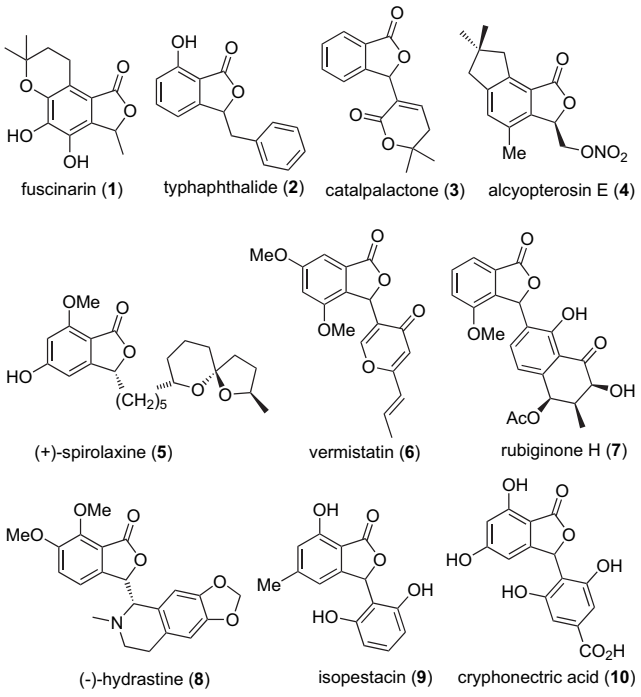

Figure 1. Examples of 3-substituted isobenzofuranone natural products.

Keywords: Isopestacin; Cryphonectric acid; Isobenzofuranone; Oxidative aromatization.
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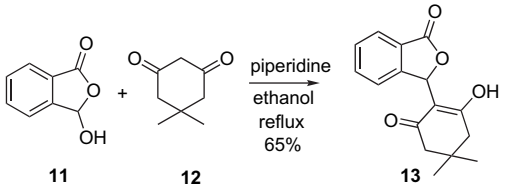
2. Synthetic strategy

Since the classical work by Bistrzycki et al.,[7a] many methods have been reported for the synthesis of phthalides. These include preparation of phthalides by acid catalyzed condensation of phthalaldehydic acids with arenes,[7b] base catalyzed reaction of appropriate nucleophiles with substituted phthalides,[7c] oxidation of *ortho*-alkyl substituted benzoic acids,[7d] electrophilic addition of aldehydes with *ortho*-metallated esters, amides, or protected benzaldehydes,[7e] nucleophilic addition of alkyl or aryl metals on properly substituted phthalaldehydic acids and its derivatives,[7f] metallic or microbial hydrogenation of 4-oxo carboxylic esters,[7g,h,j] photochemical rearrangements,[7i] intramolecular cyclization,[7j] Tischenko reaction, etc.[7k]

For the present target molecules **9** and **10**, the development of a newer method was warranted for ensuring regiospecificity in the synthesis of their 3-(2,6-dihydroxyphenyl)phthalide backbone. Acid catalyzed condensation of resorcinol with phthalaldehydic acid is not suitable, as it produces 3-(2,4-dihydroxyphenyl)isobenzofuran-1-one arising from substitution at undesired position.[8] Similarly, formylation or bromination of 3,5-dihydroxybenzoic acid leads to formation of 2- and 6-substituted products.[9] Mindful of this problem, we envisaged an application of condensation of phthalaldehydic acid **11** with dimedone **12** in the presence of piperidine giving 1:1 condensation product **13** (Scheme 1).[10a]



Scheme 1.

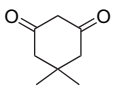
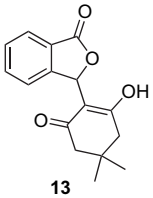
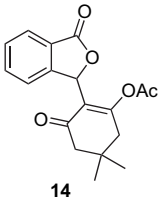
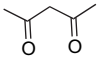
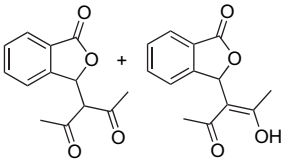
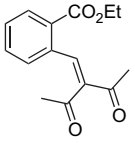
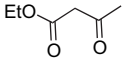
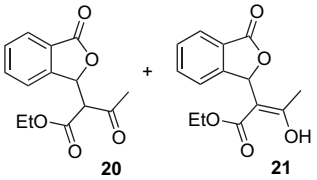
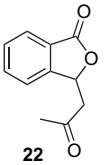
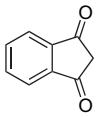
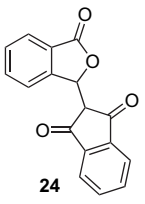
Base catalyzed aldol reaction of 1,3-cyclohexanedione with phthalaldehydic acid followed by aromatization of the condensation product was expected to furnish the resorcinol unit present in the target molecules. The chemistry of lithiated resorcinol derivatives was considered but not pursued in view of the presence of a –COOH group in **10**.[10b]

3. Results and discussion

3.1. Reaction of phthalaldehydic acid with β-keto carbonyl compounds

First we studied the reported[10] aldol reaction of phthalaldehydic acid (**11**) with dimedone (**12**) and noted that the same reaction could be effected more efficiently in shorter time if DBU was used as a base. It took place at room temperature in excellent yield (95%). The product **13** was characterized by comparison of its spectroscopic data with the reported values as well as by conversion to its acetate derivative **14**. The

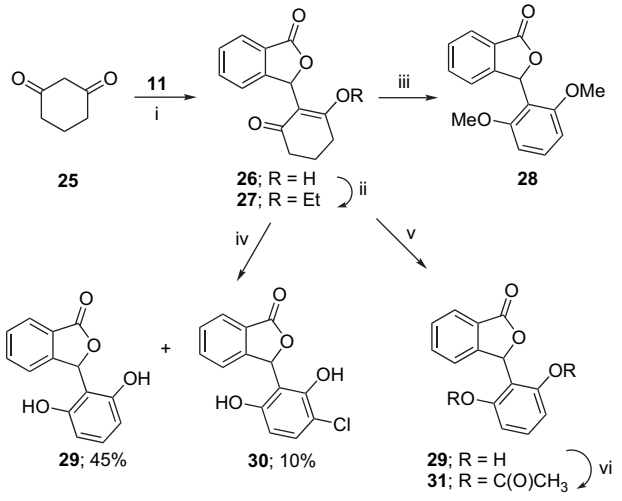
Table 1. Reaction of phthalaldehydic acid (**11**) with few 1,3-dicarbonyl compounds in the presence of DBU

Entry	1,3-Diketone	Product(s)	Yield (%)	Derivative
1	 **12**	 **13**	95	 **14**
2	 **15**	 **16** **17**	81	 **18**
3	 **19**	 **20** **21**	55	 **22**
4	 **23**	 **24**	86	

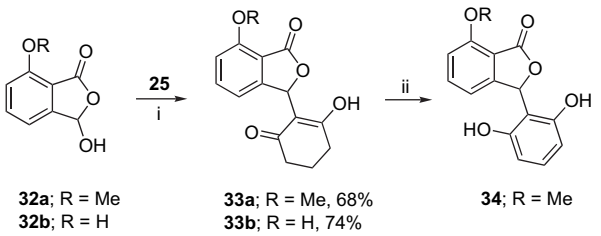
increased efficiency of the reaction with DBU led to the generalization of the process with some cyclic and open chain 1,3-diones. The results are summarized in Table 1. Unlike cyclic 1,3-diketones, product of the open chain diones (entries 2 and 3) existed as inseparable mixture of both keto and enol forms. The yield of the reaction appeared to depend upon the acidity of the methylene proton of 1,3-diketones. For acetylacetone (**15**), the yield of the products **16** and **17** was 81% requiring lesser reaction time (10–12 h), whereas for ethyl acetoacetate (**19**), the yield of the products **20** and **21** was 55% and the reaction required 20–24 h for completion. When we tried to prepare the ethoxy derivative of **16** by treatment with EtOH, *p*-toluenesulfonic acid (PTSA), and benzene, a ring opened product **18** was formed, contrary to the enol ether[6] earlier reported by us. Attempted conversion of **20** to its acetate derivative (pyridine, Ac_2O, reflux) led to decarboxylation to compound **22**. Indane-1,3-dione (**23**) gave product **24** at room temperature. Attempted preparation of ethoxy derivative of **24** using EtOH, C_6H_6, and PTSA failed to give any product.

3.2. Synthesis of model compounds 29 and 34

Having worked out the condensation, we focused our attention to assemble the phthalides and resorcinol units of isopestacin (**9**). Initially, we targeted the synthesis of unsubstituted model compound **29** (Scheme 2) and 7-methoxy substituted model compound **34** (Scheme 3). The reaction of phthalaldehydic acid (**11**) with cyclohexane-1,3-dione (**25**) in the presence of DBU furnished the expected product **26** in 70% yield. The compound **26** existed in the enol form and there was no trace of the keto form as evident from its ^{1}H NMR spectrum. The ethoxy derivative **27** was prepared by EtOH/PTSA (Scheme 2). Next most important task was to aromatize the adduct **26**. Although initial attempt with Pd/C mediated oxidative aromatization in refluxing *p*-cymene or diphenylether failed, we could aromatize the compound by the treatment with I_2 in refluxing MeOH[11] and obtained the dimethoxy compound **28**. However, subsequent didemethylation to



Scheme 2. (i) DBU, CH_3CN, reflux; 70%. (ii) EtOH, PTSA, C_6H_6, reflux; 73%. (iii) I_2, MeOH, reflux; 77%. (iv) $CuCl_2$, LiCl, DMF, reflux. (v) $Hg(OAc)_2$, NaOAc, AcOH, reflux; 95%. (vi) Ac_2O, concd H_2SO_4 (cat.), reflux; 75%.



Scheme 3. Model synthetic study of **34**. (i) CH_3CN, DBU, reflux. (ii) $Hg(OAc)_2$, NaOAc, AcOH, reflux; 86%.

the corresponding phenol **29** by $AlCl_3$ or BBr_3 proved to be a serious problem. Alternatively, we examined $CuCl_2$/LiCl[12] system. Its reaction with the compound **26** in DMF produced our desired phenol **29** in 45% yield along with a nuclear chlorinated product **30**. Remarkable improvement of the yield (up to 95%) of our desired phenol **29** was observed when compound **26** was heated at reflux in acetic acid in the presence of $Hg(OAc)_2$ and NaOAc.[13] To prove the presence of two hydroxyl groups, we converted **29** to its diacetate derivative **31**. The structures of all new products **26**, **27**, **28**, **29**, **30**, and **31** were confirmed by analysis of their IR, ^{1}H NMR, ^{13}C NMR, MS spectra, and CHN analysis data. The structure of compound **31** was re-confirmed by an X-ray crystallographic analysis (Fig. 2).

Next we targeted compound **34**, which resembled pestacin (**9**) with respect to the position of methoxy group. Accordingly, 3-hydroxy-7-methoxy-1(3*H*)-isobenzofuranone (**32a**)[14] was condensed with **25** in the presence of DBU to produce **33a** (68%), which was then aromatized with $Hg(OAc)_2$/NaOAc to compound **34** (Scheme 3). Similarly, 3,7-dihydroxy-1(3*H*)-isobenzofuranone (**32b**) produced condensation product **33b** (74%) containing both keto and enol forms, aromatization of which proved to be difficult. The structures of **33a**, **33b**, and **34** were confirmed by analysis of their IR, ^{1}H NMR, ^{13}C NMR spectrum, and CHN analysis data. The presence of characteristic 2H doublet at δ 6.19 corresponded to resorcinol moiety of the product (**34**).

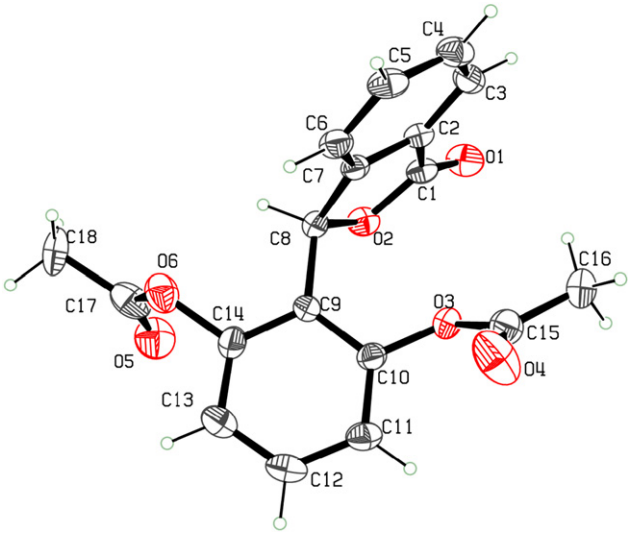
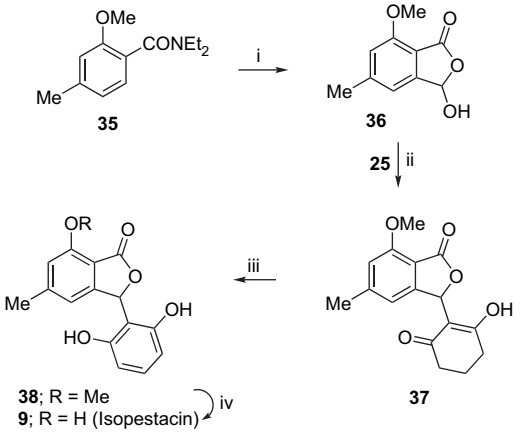


Figure 2. X-ray crystal structure of compound **31**.

3.3. Synthesis of isopestacin (9)

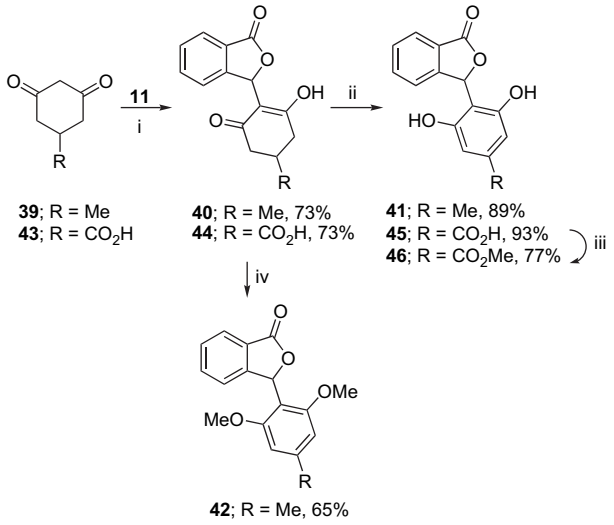
With the synthesis of the model compounds **29** and **34** standardized, we focused our attention to the synthesis of isopestacin (**9**). The required phthalaldehydic acid **36** was prepared from *N*,*N*-diethyl-2-methoxy-4-methylbenzamide (**35**) by *ortho*-metallation (*s*-BuLi, tetramethylethylenediamine) followed by formylation with dimethylformamide, which, in turn, was prepared from 2,5-dimethylanisole by the three-step reported procedure.[15] Condensation of phthalaldehydic acid **36** with 1,3-cyclohexanedione (**25**) gave desired product **37** in moderate yield (60%), aromatization ($Hg(OAc)_2$/NaOAc) of which gave phenol **38** in 93% yield. Room temperature demethylation of **38** with anhydrous $AlCl_3$ in dichloromethane solvent provided isopestacin (**9**) in 65% yield (Scheme 4). The spectroscopic data of the synthetic material were identical with that of the reported values for natural product. There was, however, some discrepancy in melting point (mp: 269–270 °C; lit.[2g] 218–220 °C), although the TLC behavior of the synthetic compound matched well with that of an authentic natural sample provided by Professor G. Strobel. Briefly, we also examined the preparation of enantiopure analogs using L-proline as chiral base. However, the study was not encouraging as the compound **26** prepared by this route did not show any optical rotation.



Scheme 4. Synthesis of isopestacin (**9**). (i) (a) *s*-BuLi, TMEDA, DMF; 59%; (b) AcOH/HCl, reflux; 64%. (ii) CH_3CN, DBU, reflux; 60%. (iii) $Hg(OAc)_2$, NaOAc, AcOH, reflux; 93%. (iv) $AlCl_3$, CH_2Cl_2, rt; 65%.

3.4. Model study for cryphonectric acid (10)

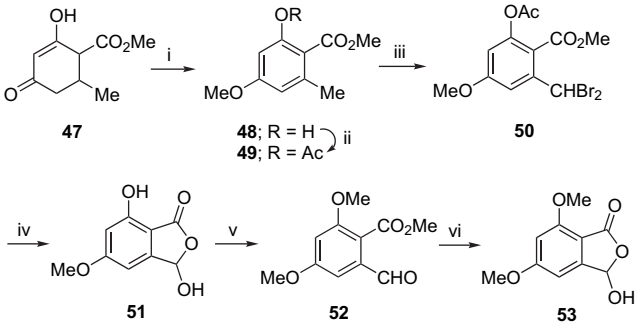
In extending the above strategy to the synthesis of cryphonectric acid (**10**) that has a nuclear carboxylic acid in the resorcinol moiety, we considered oxidation of methyl group of **41** or **42** for incorporation of a carboxylic acid (Scheme 5). To this end, we prepared compound **40** from commercially available 5-methyl-1,3-cyclohexanedione (**39**) and phthalaldehydic acid (**11**). Aromatization of **40** with $Hg(OAc)_2$/NaOAc and I_2/MeOH produced **41** (89%) and **42** (65%), respectively (Scheme 5). Attempted oxidation of the methyl group of **41** or **42** by various literature precedents like ZnO/DMF,[16a] PCC,[16b] $Ce(NH_4)_2(NO_2)_6$,[16c] NBS/O_2,[16d] and $KMnO_4$/pyridine[16e] did not work. Consequently, we avoided the oxidation step and prepared carboxylic acid **43**, albeit low yield, by the Birch reduction of 3,4,5-trimethoxybenzoic acid.[17a] This, in turn, was synthesized from commercially available gallic acid in two steps by methylation followed by ester hydrolysis.[17b] Condensation of **43** with phthalaldehydic acid (**11**) produced adduct **44** in 73% yield. $Hg(OAc)_2$/NaOAc mediated aromatization of **44** followed by conversion of the carboxylic acid group to the corresponding ester by $SOCl_2$/MeOH produced **46** (Scheme 5). The new compounds of the sequence were duly characterized by spectroscopic means.



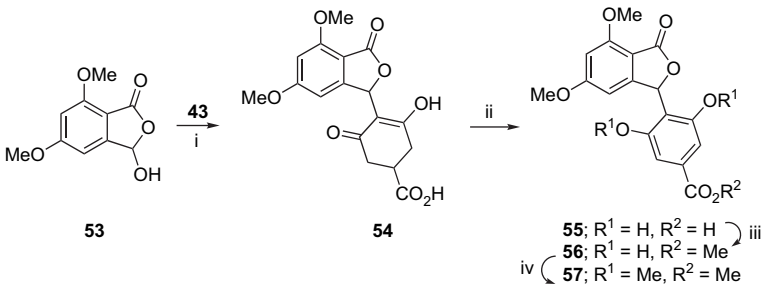
Scheme 5. Model synthetic study of cryphonectric acid (**10**). (i) DBU, CH_3CN, reflux. (ii) $Hg(OAc)_2$, NaOAc, AcOH, reflux. (iii) $SOCl_2$, MeOH, rt. (iv) I_2, MeOH, reflux.

3.5. Synthesis of cryphonectric acid (10)

Application of the preceding strategy to the synthesis of cryphonectric acid (**10**) called for 5,7-dimethoxyphthalaldehydic acid **53**, the preparation of which is known in the literature.[18] However, due to inconvenience in the adaptation of Diels–Alder process described by Freskos et al.[18a] or the difficulty in reproducing the *ortho*-lithiation process described by Trost et al.,[18b] we sought to develop a new method. 4-Carbomethoxy-3-hydroxy-5-methyl-cyclohexenone (**47**)[19] prepared by base catalyzed condensation of methyl acetoacetate with methyl crotonate was aromatized with I_2/MeOH to give **48**. Instead of commonly conceivable *O*-methyl derivative, we prepared the acetate **49**, since 2,4-dimethoxy-6-methylbenzoate is known to produce nuclear



Scheme 6. (i) I_2, MeOH, reflux; 56%. (ii) CH_3COCl, Et_3N, CH_2Cl_2; 68%. (iii) NBS (2 equiv), AIBN, CCl_4, reflux. (iv) AcOH, HCl, reflux; overall 38% for two steps from **49**. (v) K_2CO_3, MeI, acetone; 73%. (vi) aq NaOH (10%), MeOH; 83%.

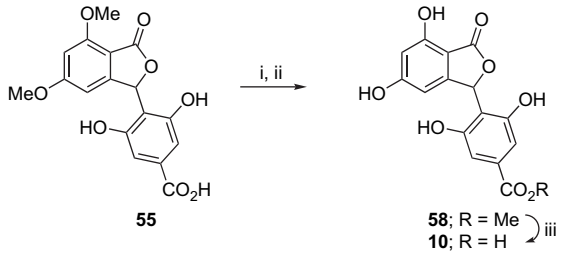


Scheme 7. (i) DBU, CH_3CN, reflux; 30%. (ii) $Hg(OAc)_2$, NaOAc, AcOH, reflux; 60%. (iii) $SOCl_2$, MeOH, rt; 73%. (iv) K_2CO_3, MeI, acetone; 77%.

brominated products on reaction with NBS.[20] Benzylic bromination of **49** with NBS (2 equiv) followed by hydrolysis of the resultant dibromo compound in refluxing AcOH/HCl/H_2O produced 7-dihydroxy-4-methoxyphthalaldehydic acid **51**. Methylation of **51** with MeI and K_2CO_3 followed by ester hydrolysis with NaOH gave the desired phthalaldehydic acid **53** (Scheme 6). All the new compounds gave satisfactory spectral data, and those of **52** and **53** agreed well with the reported[21] values.

Attempted condensation of phthalaldehydic acid **51** with 3,5-diketohexahydrobenzoic acid (**43**) in the presence of DBU provided an intractable mixture of products. Possibly due to the presence of free hydroxyl group in **51** and the resulting diminished electrophilicity of the latent formyl group, the condensation was disfavored. On the other hand, corresponding permethylated phthalaldehydic acid **53** when condensed with **43** in the presence of DBU (2 equiv) produced **54**, but the yield of the reaction was low (30%). Base catalyzed destruction of **43** could be a major side reaction, since the starting phthalaldehydic acid **53** was recovered after the reaction. $Hg(OAc)_2$/NaOAc promoted aromatization of **54** to **55**, followed by esterification by MeOH/$SOCl_2$ produced **56**. Both the compounds **55** and **56** were duly characterized. The presence of four singlets in the aromatic region of their ^{1}H NMR spectrum was indicative of their fully aromatized structures. Methylation (K_2CO_3/MeI) of **56** produced permethylated cryphonectric acid methyl ester **57** (Scheme 7). Spectral data of compound **57** were identical to the reported values.[2j]

Attempted demethylation of compound **55** by refluxing in HBr/AcOH provided a solid compound, which defied purification. Consequently, the crude mixture was submitted to esterification with $SOCl_2$/MeOH. The resulting solid compound was identified as the methyl ester of cryphonectric acid, i.e., **58**, spectroscopic data of which matched well with the literature values.[2j] Alkaline hydrolysis (dil NaOH) of **58** gave cryphonectric acid (**10**) in 79% yield (Scheme 8). The analysis of its spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS) left no doubt about the structural identity.



Scheme 8. Synthesis of cryphonectric acid (**10**). (i) HBr, AcOH, reflux, 12 h. (ii) $SOCl_2$, MeOH, rt; overall 42% for two steps. (iii) aq NaOH (10%), MeOH; 79%.

4. Conclusion

In conclusion, we have developed a generalized regiospecific synthetic route to the 3-(2,6-dihydroxyphenyl)isobenzofuranones. It has been applied to the synthesis of isopestacin (**9**) and cryphonectric acid (**10**) in completely regiospecific manners. Furthermore, its simplicity and brevity appear to be suitable for generating a wide variety of analogs of the natural products.

5. Experimental

5.1. General

Melting points are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus 870 FTIR spectrophotometer using KBr pellet. ^{1}H and ^{13}C NMR spectra of the samples in the indicated solvents were recorded on 200 MHz, 300 MHz, or 400 MHz spectrometer (Brücker) as solution in $CDCl_3$ or DMSO-d_6 or mixture of $CDCl_3$ and DMSO-d_6 or MeOH-d_4 or in acetone-d_6 with TMS as the internal standard. Chemical shifts are expressed in δ unit and coupling constant in hertz. Mass spectra were taken using a VG Autospec M mass spectrometer. Elemental analyses were carried out by using an elemental analyzer VARIO EL instrument. Dry solvents used for reactions were purified, before use, according to the standard protocols. All solvents for chromatography were distilled prior to use. Columns were prepared with silica gel (60–120 or 230–400 mesh).

5.1.1. Isopestacin (9).[2i] To a stirred solution of compound **38** (90 mg, 0.31 mmol) in dichloromethane (5 mL), $AlCl_3$ (84 mg, 0.62 mmol) was added. The mixture was stirred for 5–6 h, and after completion of the reaction as judged by TLC, it was quenched by dropwise addition of H_2O (5 mL). The mixture was extracted with ethyl acetate (2×50 mL) and the combined organic layer was washed with 10% HCl (5 mL), H_2O (2×20 mL), and brine (5 mL) and dried (Na_2SO_4). Concentration of the organic layer and chromatographic separation (1:1 ethyl acetate/petroleum ether) of the resulting residue produced compound **9** (55 mg) as a light brown crystalline solid. Yield: 65%;

R_f: 0.8 (1:1 ethyl acetate/petroleum ether); mp: 269–270 °C (lit.[2i] 218–220 °C); ν_{max} (KBr, cm^{-1}): 3415 (br), 2936, 1723, 1615, 1319, 1041, 772; ^1H NMR (300 MHz, MeOH-d_4): δ 6.97 (t, 1H, J=8.1 Hz), 6.93 (s, 1H), 6.66 (s, 1H), 6.53 (s, 1H), 6.29 (d, 2H, J=8.1 Hz), 2.32 (s, 3H); ^{13}C NMR (75 MHz, MeOH-d_4): δ 173.7, 158.8, 157.2, 154.8, 148.8, 131.4, 116.4, 114.4, 111.6, 110.1, 107.8, 77.0, 22.0; MS ESI (70 eV): 272 (40), 254 (55), 239 (60), 227 (100). Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.34; H, 4.50.

5.1.2. Cryphonectric acid (10).[2j] An aqueous solution of NaOH (2 mL, 10%) was added to a solution of compound **58** (20 mg, 0.06 mmol) in methanol (1 mL) and stirred at room temperature for 4 h. The reaction was acidified by addition of 6 N HCl (5 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), concentrated, and purified by flash column chromatography (ethyl acetate) to produce compound **10** (15 mg) as a light brown crystalline solid. Yield: 79%; R_f: 0.2 (ethyl acetate); mp: >350 °C; ν_{max} (KBr, cm^{-1}): 3350 (br), 1733, 1718, 1617, 1436, 1051, 804; ^1H NMR (400 MHz, acetone-d_6): δ 9.32 (s, 1H, OH), 9.09 (s, 2H, OH), 8.41 (s, 1H, OH), 7.11 (s, 2H), 6.91 (s, 1H), 6.34 (s, 1H), 6.24 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): δ 171.8, 167.2, 165.8, 158.3, 154.6, 133.4, 132.1, 115.0, 109.1, 106.1, 102.7, 101.4, 75.5.

5.1.3. 3-(2-Hydroxy-4,4-dimethyl-6-oxo-cyclohexen-1-yl)-3*H*-isobenzofuran-1-one (13). To a stirred solution of dimedone (**12**) (500 mg, 3.57 mmol) in $CHCl_3$ (5 mL), DBU (0.53 mL, 3.57 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid (**11**) (535 mg, 3.57 mmol) was added to it and the mixture was allowed to stir for 5 h at room temperature. The reaction was quenched with 10% HCl (5 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated and washed with H_2O (2×20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from ethyl acetate to give **13** (922 mg) as a white solid. Yield: 95%; R_f: 0.1 (ethyl acetate); mp: 207–208 °C (lit.[10] mp: 208–210 °C); ν_{max} (KBr, cm^{-1}): 3506 (br), 2962, 1770, 1575, 1381, 1318, 1294; ^1H NMR (200 MHz, DMSO-d_6+$CDCl_3$): δ 7.71 (d, 1H, J=7.3 Hz), 7.53 (t, 1H, J=7.3 Hz), 7.38 (t, 1H, J=7.3 Hz), 7.19 (d, 1H, J=7.3 Hz), 6.60 (s, 1H), 2.22 (s, 4H), 0.98 (s, 6H); ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 185.9, 171.5, 150.6, 133.5, 127.9, 126.7, 124.3, 121.2, 108.4, 74.5, 46.7, 31.7, 28.0. HRMS ESI (70 eV) for $C_{16}H_{17}O_4$ $[M+H]^+$ calcd: 273.1127, found: 273.1141.

5.1.4. 3-(2-Acetoxy-4,4-dimethyl-6-oxo-cyclohexen-1-yl)-3*H*-isobenzofuran-1-one (14). Ac_2O (1 mL) was added to a solution of **13** (100 mg, 0.37 mmol) in pyridine (1 mL). The mixture was stirred for 18–20 h at room temperature. After completion of the reaction as checked by TLC, it was quenched by addition of saturated $CuSO_4$ solution (5 mL) and extracted with ethyl acetate (2×30 mL). The combined organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (1:1 ethyl acetate/petroleum ether) to produce **14** (86 mg) as a waxy solid. Yield: 67%; R_f: 0.5 (1:1 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 2962, 1768, 1722, 1677, 1467, 1369, 1286, 1232; ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, 1H, J=7.4 Hz), 7.60 (t, 1H, J=7.4 Hz), 7.51 (t, 1H, J=7.4 Hz), 7.25 (d, 1H, J=7.4 Hz), 6.54 (s, 1H), 2.48 (s, 2H), 2.37 (s, 2H), 1.82 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.8, 170.9, 168.3, 166.7, 148.9, 133.7, 128.2, 125.8, 125.1, 122.0, 121.9, 73.4, 50.7, 43.0, 31.9, 27.9, 27.4, 20.2; HRMS ESI (70 eV) for $C_{18}H_{19}O_5$ $[M+H]^+$ calcd: 315.1232, found: 315.1289. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.92; H, 5.71.

5.1.5. 3-(1,3-Dihydro-3-oxo-1-isobenzofuranyl)-2,4-pentanedione (16).[22] This compound was obtained as an inseparable mixture with tautomer **17**. To a stirred solution of acetylacetone (**15**) (675 mg, 6.75 mmol) in $CHCl_3$ (5 mL), DBU (1.01 mL, 6.75 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid (**11**) (1.01 g, 6.75 mmol) was added to it and the mixture was allowed to stir for 5 h at room temperature. The reaction was quenched with 10% HCl (3 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated and washed with H_2O (2×20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from ethyl acetate to give **16** (1.27 g) as a white solid. Yield: 81%; R_f: 0.5 (1:1 ethyl acetate/petroleum ether); mp: 104–105 °C; ^1H NMR (200 MHz, $CDCl_3$) for the keto isomer: δ 7.83 (d, 1H, J=7.4 Hz), 7.70–7.40 (m, 2H), 7.33 (d, 1H, J=7.4 Hz), 6.11 (d, 1H, J=9.1 Hz), 4.00 (d, 1H, J=9.1 Hz), 2.34 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.7, 199.6, 169.3, 147.3, 134.6, 130.0, 126.0, 125.7, 123.2, 78.6, 72.0, 31.0, 29.9.

5.1.6. Methyl 2-(2-acetyl-3-oxo-but-1-enyl)benzoate (18). A stirred solution of **16** and **17** (200 mg, 0.86 mmol), PTSA (5 mg) in EtOH (5 mL), and C_6H_6 (10 mL) was heated at reflux with constant removal of water by means of Dean–Stark apparatus for 48 h. It was then diluted with ethyl acetate (70 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (10 mL), H_2O (2×15 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:3 ethyl acetate/petroleum ether) to give **18** (120 mg) as a semi solid. Yield: 53%; R_f: 0.5 (1:3 ethyl acetate/petroleum ether); mp: 93–94 °C; ν_{max} (KBr, cm^{-1}): 1714, 1666, 1619, 1596, 1479, 1367, 1268, 1079, 763, 715; ^1H NMR (200 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.15–8.02 (m, 1H), 7.58–7.40 (m, 2H), 7.28 (d, 1H, J=8.4 Hz), 4.38 (q, 2H, J=7.2 Hz), 2.46 (s, 3H), 2.04 (s, 3H), 1.40 (t, 3H, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 203.7, 196.4, 165.8, 142.6, 141.6, 135.4, 132.4, 130.8, 129.7, 129.3, 128.7, 61.2, 31.5, 26.5, 14.0; HRMS ESI (70 eV) for $C_{15}H_{17}O_4$ $[M+H]^+$ calcd: 261.1127, found: 261.1120.

5.1.7. Ethyl 1-acetyl-1-(1,3-dihydro-3-oxoisobenzofuranyl)acetate (20).[23] This compound was obtained as an inseparable mixture, other component being its tautomer **21**. To a stirred solution of ethyl acetoacetate (**19**) (600 mg, 4.61 mmol) in $CHCl_3$ (5 mL), DBU (0.69 mL, 4.61 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid (**11**) (692 mg, 4.61 mmol) was added to it and the mixture was allowed to stir for 5 h at room temperature. The reaction was quenched with 10% HCl (3 mL) and diluted with ethyl acetate (60 mL). The organic layer

was washed with H_2O (2×20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from ethyl acetate to give **20** (665 mg) as a white solid. Yield: 55%; R_f: 0.5 (1:3 ethyl acetate/petroleum ether); mp: 78–79 °C; ^{1}H NMR (200 MHz, $CDCl_3$) for the keto isomer: δ 7.87 (d, 1H, J=7.3 Hz), 7.80–7.35 (m, 3H), 6.08 (d, 1H, J=7.9 Hz), 4.30–4.05 (m, 2H), 3.90–3.81 (m, 1H), 2.36 (s, 3H), 1.27–1.11 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.5, 178.5, 165.9, 147.1, 134.4, 129.8, 125.5, 123.1, 121.5, 77.9, 62.5, 62.1, 30.4, 13.8.

5.1.8. 3-(2-Oxopropyl)-3*H*-isobenzofuran-1-one (22).[23] Ac_2O (2 mL) was added to a solution of **20** and **21** (200 mg, 0.76 mmol) in pyridine (2 mL). The mixture was stirred for 18–20 h at room temperature and then heated at reflux for 3–4 h. The reaction mixture was quenched by addition of saturated $CuSO_4$ solution (5 mL) and diluted with ethyl acetate (50 mL). The organic layer was separated and washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to give **22** (86 mg, 0.58 mmol) as a white solid. Yield: 74%; R_f: 0.3 (1:1 ethyl acetate/petroleum ether); mp: 191–192 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87 (d, 1H, J=7.3 Hz), 7.65 (t, 1H, J=7.3 Hz), 7.52 (t, 1H, J=7.3 Hz), 7.46 (d, 1H, J=7.3 Hz), 5.91 (t, 1H, J=6.7 Hz), 3.12 (dd, 1H, J=17.5, 6.7 Hz), 2.91 (dd, 1H, J=17.5, 6.7 Hz), 2.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 204.3, 169.9, 149.2, 134.2, 129.3, 125.5, 122.2, 76.6, 47.9, 30.5 (one quaternary carbon was absent).

5.1.9. 2-(1,3-Dihydro-3-oxo-1-isobenzofuranyl)-1*H*-indene-1,3(2*H*)-dione (24).[6] To a stirred solution of indane-1,3-dione (**23**) (220 mg, 1.51 mmol) in $CHCl_3$ (5 mL), DBU (0.22 mL, 1.51 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid (**11**) (226 mg, 1.51 mmol) was added to it and the mixture was allowed to stir for 5 h at room temperature. The reaction was quenched with 10% HCl (3 mL) and diluted with ethyl acetate (40 mL). The organic phase was separated and washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from ethyl acetate to give **24** (360 mg) as a light brown solid. Yield: 86%; R_f: 0.7 (1:1 ethyl acetate/petroleum ether); mp: 216–217 °C; IR and NMR data are provided in Ref. 6.

5.1.10. 3-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-3*H*-isobenzofuran-1-one (26). To a stirred solution of cyclohexane-1,3-dione (**25**) (800 mg, 7.1 mmol) in CH_3CN (10 mL), DBU (1.06 mL, 7.1 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid (**11**) (1.07 g, 7.1 mmol) was added and the mixture heated at reflux for 6–7 h. Then the reaction was quenched with 10% HCl (10 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated and washed with H_2O (2×20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by recrystallization from ethyl acetate to give **26** (1.22 g) as a white solid. Yield: 70%; R_f: 0.2 (ethyl acetate); mp: 219–220 °C; ν_{max} (KBr, cm^{-1}): 3433 (br), 2947, 1753, 1568, 1385, 1065, 761; ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.74 (d, 1H, J=7.7 Hz), 7.48 (dd, 1H, J=7.4, 7.2 Hz), 7.37 (dd, 1H, J=7.7, 7.2 Hz), 7.20 (d, 1H, J=7.4 Hz), 6.67 (s, 1H), 2.42–2.30 (m, 4H), 1.93–1.83 (m, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 186.6, 170.9, 150.8, 133.8, 128.2, 126.6, 124.3, 121.5, 109.3, 74.4, 32.8, 20.2; HRMS ESI (70 eV) for $C_{14}H_{12}O_4Na$ $[M+Na]^+$ calcd: 267.0633, found: 267.0626.

5.1.11. 3-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-3*H*-isobenzofuran-1-one (27). A stirred solution of **26** (100 mg, 0.41 mmol), PTSA (5 mg) in EtOH (5 mL), and C_6H_6 (10 mL) was heated at reflux with constant removal of water by means of Dean–Stark apparatus for 48 h. It was then diluted with ethyl acetate (30 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (5 mL), H_2O (2×5 mL), and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:3 ethyl acetate/petroleum ether) to give **27** (80 mg) as a white solid. Yield: 73%; R_f: 0.5 (1:1 ethyl acetate/petroleum ether); mp: 143–144 °C; ν_{max} (KBr, cm^{-1}): 2989, 1758, 1633, 1590, 1386, 1058, 734; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, 1H, J=7.3 Hz), 7.57 (dd, 1H, J=7.5, 6.4 Hz), 7.44 (dd, 1H, J=7.5, 7.3 Hz), 7.24 (d, 1H, J=6.4 Hz), 6.79 (s, 1H), 3.99–3.65 (m, 2H), 2.62–2.40 (m, 4H), 2.10–1.94 (m, 2H), 0.86 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.9, 177.3, 171.2, 150.4, 133.2, 127.7, 126.6, 124.2, 121.0, 112.8, 73.8, 64.2, 35.6, 25.4, 20.0, 13.7; HRMS ESI (70 eV) for $C_{16}H_{17}O_4$ $[M+H]^+$ calcd: 273.1127, found: 273.1140.

5.1.12. 3-(2,6-Dimethoxyphenyl)-3*H*-isobenzofuran-1-one (28). I_2 (125 mg, 0.50 mmol) was added to a stirred solution of **26** (60 mg, 0.24 mmol) in MeOH (10 mL). The mixture was heated at reflux for 0.5 h and then quenched by addition of saturated sodium thiosulfate solution (10 mL) after removal of methanol in vacuum. Then it was diluted with ethyl acetate (50 mL). The organic layer was separated and washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to give **28** (50 mg) as a white solid compound. Yield: 77%; R_f: 0.4 (1:1 ethyl acetate/petroleum ether); mp: 151–152 °C; ν_{max} (KBr, cm^{-1}): 2213, 1762, 1596, 1473, 1253, 1106, 744; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.91(d, 1H, J=7.0 Hz), 7.55 (dd, 1H, J=7.4, 7.2 Hz), 7.46 (dd, 1H, J=7.2, 7.0 Hz), 7.32–7.19 (m, 2H), 6.54 (s, 1H), 6.52 (d, 2H, J=8.4 Hz), 3.64 (br s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.7, 159.3, 150.8, 133.3, 130.9, 128.1, 127.1, 124.7, 121.5, 111.8, 104.4, 75.0, 55.8; MS ESI (70 eV): 271.2050. Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 69.83; H, 5.12.

5.1.13. 3-(2,6-Dihydroxyphenyl)-3*H*-isobenzofuran-1-one (29). To a stirred solution of **26** (240 mg, 0.98 mmol) in AcOH (5 mL), $Hg(OAc)_2$ (940 mg, 2.95 mmol) and anhydrous NaOAc (242 mg, 2.95 mmol) were added. The mixture was heated at reflux for 3 h when initially formed precipitates were dissolved. After cooling, 6 N HCl (5 mL) was added to it and stirred for another 15 min. The mixture was filtered through a pad of Celite and the filtrate was diluted by addition of ethyl acetate (60 mL). The organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum

ether) to give **29** (225 mg) as a white solid. Yield: 95%; R_f: 0.8 (2:1 ethyl acetate/petroleum ether); mp: 239–240 °C; ν_{max} (KBr, cm^{-1}): 3469 (br), 2612, 1722, 1612, 1470, 1017, 720; ^1H NMR (200 MHz, DMSO-d_6+$CDCl_3$): δ 8.78 (br s, 2H, OH), 7.65 (d, 1H, J=7.4 Hz), 7.34 (dd, 1H, J=8.1, 7.3 Hz), 7.29 (dd, 1H, J=8.1, 7.4 Hz), 7.13 (d, 1H, J=7.3 Hz), 6.88 (s, 1H), 6.75 (t, 1H, J=8.1 Hz), 6.13 (d, 2H, J=8.1 Hz); ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): δ 172.0, 157.3, 151.2, 133.3, 130.2, 127.8, 127.2, 124.3, 121.9, 108.6, 107.1, 75.9; MS ESI (70 eV): 242 (M^+), 225, 197, 168. Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.74; H, 4.30.

5.1.14. 3-(3-Chloro-2,6-dihydroxyphenyl)-3*H*-isobenzofuran-1-one (30). This compound was obtained as a side product along with the expected phenol **29**. A mixture of compound **26** (410 mg, 1.68 mmol), $CuCl_2\cdot 2H_2O$ (571 mg, 3.36 mmol), and LiCl (142.8, 3.36 mmol) in 8 mL DMF was heated at reflux for 1 h. After dilution with ethyl acetate (50 mL), the organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The resulting crude product was purified through column chromatography (1:1 ethyl acetate/petroleum ether) to give **30** (140 mg, 0.51 mmol) as a white solid along with **29** (205 mg). Yield: 30%; R_f: 0.5 (2:1 ethyl acetate/petroleum ether); mp: 196–197 °C; ν_{max} (KBr, cm^{-1}): 3480 (br), 2364, 1729, 1600, 1463, 1311, 973; ^1H NMR (400 MHz, MeOH-d_4): δ 7.77 (d, 1H, J=7.6 Hz), 7.58 (dd, 1H, J=7.6, 7.2 Hz), 7.45 (dd, 1H, J=7.6, 7.2 Hz), 7.23 (d, 1H, J=7.6 Hz), 7.03 (d, 1H, J=8.8 Hz), 7.01 (s, 1H), 6.26 (d, 1H, J=8.8 Hz); ^{13}C NMR (100 MHz, MeOH-d_4): δ 174.2, 157.8, 154.0, 152.1, 135.1, 131.3, 129.6, 128.3, 125.6, 122.9, 112.6, 112.1, 108.9, 77.6; HRMS ESI (70 eV) for $C_{14}H_{10}{}^{35}ClO_4$ $[M+H]^+$ calcd: 277.0268, found: 277.0260.

5.1.15. 3-(2,6-Diacetoxyphenyl)-3*H*-isobenzofuran-1-one (31). To a stirred solution of phenol **29** (100 mg, 0.70 mmol) in Ac_2O (3 mL), one drop of concd H_2SO_4 was added and the resulting solution was heated at reflux for 30 min. The reaction was quenched by the addition of saturated $NaHCO_3$ solution (5 mL) and diluted with ethyl acetate (40 mL). The organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), concentrated, and the resulting crude product was purified by column chromatography (1:5 ethyl acetate/petroleum ether) to furnish **31** (100 mg, 0.30 mmol) as solid crystals. Yield: 76%; R_f: 0.3 (1:3 ethyl acetate/petroleum ether); mp: 172–173 °C; ν_{max} (KBr, cm^{-1}): 1768, 1612, 1467, 1293, 1181, 750; ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, 1H, J=7.4 Hz), 7.64 (dd, 1H, J=7.5, 7.3 Hz), 7.55 (dd, 1H, J=7.4, 7.3 Hz), 7.43 (t, 1H, J=8.3 Hz), 7.35 (d, 1H, J=7.5 Hz), 7.02 (d, 2H, J=8.3 Hz), 6.55 (s, 1H), 2.05 (br s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 168.5, 150.0, 148.6, 134.4, 130.4, 129.2, 126.1, 125.0, 122.9, 120.9, 120.1, 74.5, 20.4. Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.10; H, 4.25.

5.1.16. 3,7-Dihydroxy-1(3*H*)isobenzofuranone (32b). This compound was prepared by $AlCl_3$ mediated demethylation of **32a** following the procedure described for the preparation of **9** from **37**. Yield: 67%; R_f: 0.5 (2:1 ethyl acetate/petroleum ether); mp: 120–121 °C; ν_{max} (KBr, cm^{-1}): 3473 (br), 1722, 1608, 1475, 1303, 1141; ^1H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 7.37 (dd, 1H, J=7.9, 7.2 Hz), 6.91 (d, 1H, J=7.2 Hz), 6.84 (d, 1H, J=7.2 Hz), 6.41 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6): δ 168.9, 156.6, 148.0, 136.2, 117.7, 114.5, 112.3. Anal. Calcd for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.98; H, 3.58.

5.1.17. 3-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-7-methoxy-3*H*-isobenzofuran-1-one (33a). To a stirred solution of cyclohexane-1,3-dione (**25**) (68 mg, 0.61 mmol) in CH_3CN (5 mL), DBU (0.09 mL, 0.61 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid **32a** (110 mg, 0.61 mmol) was added and the mixture heated at reflux for 6–7 h. Then the reaction was quenched with 10% HCl (3 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated and washed with H_2O (2×5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by recrystallization from ethyl acetate to give **33a** (115 mg) as a white solid. Yield: 68%; R_f: 0.1 (ethyl acetate); mp: 245–246 °C; ν_{max} (KBr, cm^{-1}): 3480 (br), 2927, 1751, 1662, 1639, 1373, 1182; ^1H NMR (400 MHz, MeOH-d_4): δ 7.49 (t, 1H, J=8.0 Hz), 6.91 (d, 1H, J=8.2 Hz), 6.72 (d, 1H, J=7.6 Hz), 6.50 (s, 1H), 3.85 (s, 3H), 2.40–2.30 (m, 3H), 1.95–1.82 (m, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 170.9, 158.1, 153.6, 136.0, 113.7, 112.7, 109.8, 109.7, 74.0, 54.7, 32.6, 20.1, due to very poor solubility in common deuteriated solvents including deuteriated MeOH, the carbonyl peak is absent; HRMS ESI (70 eV) for $C_{15}H_{15}O_5$ $[M+H]^+$ calcd: 275.0920, found: 275.0909.

5.1.18. 3-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-7-hydroxy-3*H*-isobenzofuran-1-one (33b).[6] This compound was prepared as a mixture of tautomeric keto and enol forms. To a stirred solution of cyclohexane-1,3-dione (**25**) (20 mg, 0.18 mmol) in $CHCl_3$ (5 mL), DBU (0.05 mL, 0.18 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid **32b** (30 mg, 0.18 mmol) was added to it and the mixture was allowed to stir for 5 h at room temperature. The reaction was quenched with 10% HCl (3 mL) and diluted with ethyl acetate (30 mL). The organic layer was separated and washed with H_2O (2×5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from ethyl acetate to give **33b** (35 mg) as a white solid. Yield: 74%; R_f: 0.1 (ethyl acetate); mp: 250–251 °C; IR and NMR data are given in Ref. 6.

5.1.19. 3-(2,6-Dihydroxyphenyl)-7-methoxy-3*H*-isobenzofuran-1-one (34). To a stirred solution of **33a** (70 mg, 0.25 mmol) in AcOH (3 mL), $Hg(OAc)_2$ (244 mg, 0.75 mmol) and anhydrous NaOAc (63 mg, 0.75 mmol) were added. The mixture was heated at reflux for 3 h, when initially formed precipitates were dissolved. After cooling, 6 N HCl (2 mL) was added to it and stirred for another 15 min. The mixture was filtered through a pad of Celite and the filtrate was diluted by addition of ethyl acetate (30 mL). The organic layer was washed with H_2O (2×5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to give **34** (60 mg) as a white solid. Yield: 86%; R_f: 0.4 (1:1 ethyl acetate/petroleum ether); mp: 269–270 °C; ν_{max} (KBr, cm^{-1}): 3470 (br), 1714, 1610, 1469, 1303, 1068, 790; ^1H NMR (400 MHz, MeOH-d_4): δ 7.49 (t, 1H, J=8.0 Hz), 6.93 (d,

1H, J=8.4 Hz), 6.88 (s, 1H), 6.87 (dd, 1H, J=8.4, 7.2 Hz), 6.72 (d, 1H, J=7.2 Hz), 6.19 (d, 2H, J=8.0 Hz), 3.89 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.8, 159.4, 159.0, 155.6, 137.4, 131.6, 115.4, 114.7, 111.2, 109.8, 107.7, 76.8, 56.2. Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.37; H, 4.35.

5.1.20. 3-(2-Hydroxy-6-oxo-1-cyclohexen-1-yl)-7-methoxy-5-methyl-3*H*-isobenzofuran-1-one (37). This compound was prepared as a white solid from phthalaldehydic acid **36** and cyclohexane-1,3-dione (**25**), following the same procedure adopted for the preparation of **26**. Yield: 60%; R_f: 0.1 (ethyl acetate); mp: 267–268 °C; ν_{max} (KBr, cm^{-1}): 3430 (br), 2592, 1757, 1577, 1480, 1375, 1294, 1057, 995; ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.82 (s, 1H), 6.58 (s, 1H), 6.37 (s, 1H), 3.85 (s, 3H), 2.50–2.30 (m, 4H), 2.34 (s, 3H), 1.89–1.80 (m, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 186.4, 168.3, 157.2, 153.8, 146.9, 113.4, 111.4, 111.2, 109.7, 72.6, 55.5, 32.8, 21.8, 20.2; MS ESI (70 eV): 288 (M^+), 259, 243, 232, 149. Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.40; H, 5.50.

5.1.21. 3-(2,6-Dihydroxyphenyl)-7-methoxy-5-methyl-3*H*-isobenzofuran-1-one (38).[6] To a stirred solution of **37** (90 mg, 0.31 mmol) in AcOH (3 mL), $Hg(OAc)_2$ (298 mg, 0.93 mmol) and anhydrous NaOAc (77 mg, 0.93 mmol) were added. The mixture was heated at reflux for 3 h when initially formed precipitates were dissolved. After cooling, 6 N HCl (2 mL) was added to it and stirred for another 15 min. The mixture was filtered through a pad of Celite and the filtrate was diluted by addition of ethyl acetate (30 mL). The organic layer was washed with H_2O (2×5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to give **38** (85 mg) as a white solid. Yield: 93%; R_f: 0.3 (1:1 ethyl acetate/petroleum ether); mp: 305–306 °C; IR and NMR data are provided in Ref. 6.

5.1.22. 3-(2-Hydroxy-4-methyl-6-oxo-1-cyclohexen-1-yl)-3*H*-isobenzofuran-1-one (40). This compound was prepared as a white solid from phthalaldehydic acid **11** and cyclohexane-1,3-dione **39**, following the same procedure adopted for the preparation of **26**. Yield: 73%; R_f: 0.5 (ethyl acetate); mp: 119–120 °C; ν_{max} (KBr, cm^{-1}): 3490 (br), 1762, 1571, 1386, 1317, 1027, 757; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.71 (d, 1H, J=7.6 Hz), 7.55 (dd, 1H, J=7.6, 7.2 Hz), 7.40 (dd, 1H, J=7.6, 7.2 Hz), 7.21 (d, 1H, J=7.6 Hz), 6.59 (s, 1H), 2.45–2.30 (m, 2H), 2.20–2.00 (m, 3H), 0.98 (d, 3H, J=5.2 Hz); ^{13}C NMR (100 MHz, MeOH-d_4): δ 189.6, 174.1, 152.3, 135.1, 129.4, 128.1, 125.9, 122.9, 110.6, 76.4, 42.1, 29.4, 21.0. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.91; H, 5.53.

5.1.23. 3-(2,6-Dihydroxy-4-methylphenyl)-3*H*-isobenzofuran-1-one (41). This compound was prepared as a white solid by aromatization of **40**, following the same procedure described for the preparation of **29** from **26**. Yield: 89%; R_f: 0.6 (1:1 ethyl acetate/petroleum ether); mp: 238–239 °C; ν_{max} (KBr, cm^{-1}): 3212 (br), 1725, 1621, 1598, 1465, 1049, 738; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.72 (d, 1H, J=7.6 Hz), 7.53 (t, 1H, J=7.2 Hz), 7.40 (dd, 1H, J=7.6, 7.2 Hz), 7.19 (d, 1H, J=7.2 Hz), 6.92 (s, 1H), 6.01 (s, 2H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 174.6, 158.7, 153.0, 142.2, 134.9, 129.2, 128.3, 125.4, 122.9, 108.5, 106.8, 78.0, 21.6; HRMS ESI (70 eV) for $C_{15}H_{13}O_4$ $[M+H]^+$ calcd: 257.0814, found: 257.0825.

5.1.24. 3-(2,6-Dimethoxy-4-methylphenyl)-3*H*-isobenzofuran-1-one (42). This compound was prepared as a white solid by the I_2/MeOH mediated aromatization of **40**, following the procedure described for the preparation of **28** from **26**. Yield: 65%; R_f: 0.4 (1:3 ethyl acetate/petroleum ether); mp: 189–190 °C; ν_{max} (KBr, cm^{-1}): 1754, 1610, 1463, 1122, 744; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1H, J=7.6 Hz), 7.54 (dd, 1H, J=8.0, 7.6 Hz), 7.45 (dd, 1H, J=7.6, 7.2 Hz), 7.22 (d, 1H, J=7.6 Hz), 7.02 (s, 1H), 6.33 (br s, 2H), 3.63 (br s, 6H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 159.0, 151.0, 141.4, 133.2, 127.9, 127.0, 124.6, 121.5, 108.6, 105.1, 75.1, 55.7, 22.1. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.01; H, 5.62.

5.1.25. 3-(4-Carboxy-2-hydroxy-6-oxo-1-cyclohexen-1-yl)-3*H*-isobenzofuran-1-one (44). To a stirred solution of **43** (170 mg, 1.09 mmol) in CH_3CN (5 mL), DBU (0.32 mL, 2.18 mmol) was added dropwise at room temperature. After 5 min, phthalaldehydic acid (**11**) (164 mg, 1.09 mmol) was added and the mixture was heated at reflux for 10–12 h. The reaction was quenched by the addition of 10% HCl (5 mL) and diluted with ethyl acetate (70 mL). The organic layer was separated and washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/methanol) to get **44** (230 mg, 0.80 mmol) as a white solid. Yield: 73%; R_f: 0.4 (1:1 ethyl acetate/methanol); mp: 252–254 °C; ν_{max} (KBr, cm^{-1}): 3310 (br), 1718, 1675, 1639, 1396, 1110, 939, 730; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.74 (d, 1H, J=7.6 Hz), 7.57 (t, 1H, J=7.2 Hz), 7.43 (dd, 1H, J=7.6, 7.2 Hz), 7.22 (d, 1H, J=7.2), 6.61 (s, 1H), 3.20–3.01 (m, 1H), 2.99–2.90 (m, 1H), 2.74–2.50 (m, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 195.3, 174.5, 172.6, 150.7, 133.8, 128.2, 126.6, 124.2, 121.2, 109.6, 74.8, 37.3, 34.7; HRMS ESI (70 eV) for $C_{15}H_{13}O_6$ $[M+H]^+$ calcd: 289.0712, found: 289.0695.

5.1.26. 4-(1,3-Dihydro-3-oxo-1-isobenzofuranyl)-3,5-dihydroxybenzoic acid (45). To a stirred solution of **44** (130 mg, 0.45 mmol) in AcOH (3 mL), $Hg(OAc)_2$ (431 mg, 1.35 mmol) and anhydrous NaOAc (111 mg, 1.35 mmol) were added. The mixture was heated at reflux for 3 h when initially formed precipitates were dissolved. After cooling, 6 N HCl (3 mL) was added to it and stirred for another 15 min. The mixture was filtered through a pad of Celite and the filtrate was diluted by addition of ethyl acetate (30 mL). The organic layer was washed with H_2O (2×5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (2:1 ethyl acetate/petroleum ether) to give **45** (120 mg) as a white solid. Yield: 93%; R_f: 0.9 (ethyl acetate); mp: partially melted at 158–160 °C, charred at 290–291 °C; ν_{max} (KBr, cm^{-1}): 3615 (br), 1710, 1604, 1436, 1251, 1052, 738; ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.77 (d, 1H, J=7.6 Hz), 7.58 (t, 1H, J=7.6 Hz), 7.45 (dd, 1H, J=7.6, 7.2 Hz), 7.24 (d, 1H, J=7.6 Hz), 7.01 (s, 1H), 6.89 (s, 2H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.9, 168.0, 157.3,

150.5, 133.7, 132.5, 128.1, 126.7, 124.1, 121.4, 112.8, 107.4, 75.7; HRMS ESI (70 eV) for $C_{15}H_{11}O_6$ $[M+H]^+$ calcd: 287.0556, found: 287.0562.

5.1.27. Methyl 4-(1,3-dihydro-3-oxo-1-isobenzofuranyl)-3,5-dihydroxybenzoate (46). To a stirred solution of **45** (50 mg, 0.17 mmol) in methanol (4 mL), $SOCl_2$ (0.01 mL, 0.17 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 3–4 h. After completion of the reaction as checked by TLC, it was concentrated in vacuum and saturated $NaHCO_3$ solution (5 mL) was added to it. The mixture was extracted with ethyl acetate (2×20 mL) and the combined organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to give **46** (40 mg) as a white solid. Yield: 77%; R_f: 0.7 (1:1 ethyl acetate/petroleum ether); mp: 286–287 °C; ν_{max} (KBr, cm^{-1}): 3410 (br), 1727, 1600, 1432, 1261, 1052, 771; ^1H NMR (400 MHz, MeOH-d_4): δ 7.75 (d, 1H, J=7.6 Hz), 7.55 (dd, 1H, J=7.6, 7.2 Hz), 7.43 (dd, 1H, J=7.6, 7.2 Hz), 7.21 (d, 1H, J=7.6 Hz), 6.98 (s, 1H), 6.84 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.8, 166.7, 157.5, 150.5, 133.7, 131.8, 128.2, 126.8, 124.2, 121.5, 113.2, 107.2, 75.7, 51.3. Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found: C, 64.22; H, 4.11.

5.1.28. 3-Hydroxy-4-carbomethoxy-5-methylcyclohexenone (47). Methyl acetoacetate (14 g, 120.6 mmol) was added to a solution of NaOMe, prepared by the addition of Na (4 g, 17.04 mmol) in MeOH (50 mL) at 0 °C and the mixture was heated at reflux for 30 min. Methyl crotonate (12.06 g, 120.6 mmol) was then added to it dropwise and the mixture heated at reflux for another 22 h. Excess methanol was removed and the solid mass was dissolved in water (20 mL). It was extracted with ethyl acetate (50 mL). The organic layer was discarded and the water layer acidified with concd HCl (5 mL). The aqueous layer was extracted with ethyl acetate (2×100 mL) and the combined organic layer was washed with H_2O (2×30 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by recrystallization from ethyl acetate to provide compound **47** (15.5 g) as a colorless solid. Yield: 70%; R_f: 0.3 (ethyl acetate); mp: 127–128 °C; ν_{max} (KBr, cm^{-1}): 3450 (br), 1739, 1614, 1240, 1157, 759; ^1H NMR (400 MHz, $CDCl_3$): δ 12.17 (s, 1H), 5.65 (s, 1H), 3.85 (s, 3H), 3.84–2.10 (m, 4H), 1.20–0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 185.4, 171.1, 103.7, 58.2, 52.4, 37.2, 31.7, 19.7. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.40; H, 6.67.

5.1.29. Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (48). To a solution of **47** (10.5 g, 57.06 mmol) in methanol (30 mL) was added iodine (29 g, 114.1 mmol) and the mixture was heated at reflux for 3 h. Excess methanol was removed and saturated $Na_2S_2O_3$ solution (40 mL) was added to the residue. The resulting mixture was extracted with ethyl acetate (2×70 mL) and the combined organic layer was washed with H_2O (2×30 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:10 ethyl acetate/petroleum ether) to give **48** (6.3 g) as a low melting solid. Yield: 56%; R_f: 0.8 (1:10 ethyl acetate/petroleum ether); mp: 70–71 °C; ν_{max} (KBr, cm^{-1}): 1648, 1617, 1328, 1268, 1155, 815; ^1H NMR (400 MHz, $CDCl_3$): δ 11.80 (s, 1H), 6.33 (s, 1H), 6.28 (s, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 165.5, 163.8, 143.0, 111.1, 105.1, 98.6, 55.2, 51.8, 24.3. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.52; H, 6.03.

5.1.30. Methyl 2-acetoxy-4-methoxy-6-methylbenzoate (49). Et_3N (9.0 mL, 65 mmol) was added to a solution of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**48**) (6.3 g, 32.1 mmol) in 30 mL dichloromethane and stirred for 10 min. Acetyl chloride (3.4 mL, 48.1 mmol) was then added to this mixture dropwise at 0 °C and allowed to stir for 4–5 h at room temperature. Reaction was quenched by the addition of water and extracted with dichloromethane (2×50 mL). The combined organic layer was washed with H_2O (2×30 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:5 ethyl acetate/petroleum ether) to give **49** (5.2 g) as a colorless liquid. Yield: 68%; R_f: 0.2 (1:5 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 1772, 1722, 1614, 1272, 1153, 773; ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (s, 1H), 6.47 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.41 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 166.5, 161.2, 150.6, 140.7, 117.9, 114.3, 106.2, 55.4, 51.9, 21.1, 20.8. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.28; H, 5.85.

5.1.31. 3,7-Dihydroxy-5-methoxy-1(3*H*)-isobenzofuranone (51). A mixture of methyl 2-acetoxy-4-methoxy-6-methylbenzoate (**49**) (3.6 g, 15.1 mmol) and NBS (5.87 g, 33.2 mmol) in CCl_4 (40 mL) containing AIBN (5 mg) was heated at reflux for 10 h while irradiated by a 100 W electric bulb. At the end of the reaction, the reaction mixture was chilled (ice bath) and filtered. Removal of solvent from the filtrate furnished the crude dibromo compound **50** (4.5 g, 11.3 mmol). It was, without further purification, mixed with concd HCl (3 mL), AcOH (3 mL), and H_2O (10 mL) and heated at reflux for 5 h. The solution was diluted with ethyl acetate (30 mL) and extracted with saturated sodium bicarbonate solution (2×30 mL). The organic part was discarded and the water layer was acidified with concd HCl (10 mL). It was again extracted with ethyl acetate (2×100 mL) and the combined organic layer was washed with H_2O (2×30 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by recrystallization from ethyl acetate to furnish **51** (1.12 g) as a white solid. Yield: 38%; R_f: 0.4 (2:1 ethyl acetate/petroleum ether); mp: 159–160 °C; ν_{max} (KBr, cm^{-1}): 3399 (br), 1747, 1617, 1224, 1166, 1031; ^1H NMR (400 MHz, MeOH-d_4): δ 6.61 (s, 1H), 6.43 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 169.7, 168.8, 159.4, 150.4, 106.6, 104.2, 103.9, 101.8, 56.6. Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 55.40; H, 4.20.

5.1.32. Methyl 2-formyl-4,6-dimethoxybenzoate (52).[21] To a stirred solution of **51** (300 mg, 1.53 mmol) in acetone (5 mL) was added K_2CO_3 (633 mg, 4.59 mmol). After stirring for 10 min, MeI (0.38 mL, 6.0 mmol) was added to it and the mixture was allowed to stir for 12–15 h. After completion of the reaction as checked by TLC, acetone was removed and the mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with H_2O (2×10 mL) and brine (10 mL), dried (Na_2SO_4), and

concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to furnish compound **52** (250 mg) as a white solid. Yield: 73%; R_f: 0.6 (1:1 ethyl acetate/petroleum ether); mp: 85–86 °C (lit.[21] 85–87 °C); ν_{max} (KBr, cm^{-1}): 1724, 1698, 1606, 1265, 960; ^1H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 6.91 (s, 1H), 6.65 (s, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 166.9, 161.9, 158.3, 135.7, 117.4, 104.9, 104.2, 56.2, 55.7, 52.6.

5.1.33. 3-Hydroxy-5,7-dimethoxy-1(3*H*)-isobenzofuranone (53).[18] To a stirred solution of **52** (90 mg, 0.40 mmol) in methanol (4 mL) was added a solution of NaOH (320 mg, 8.0 mmol) in 3 mL H_2O. The reaction mixture was stirred for 2–3 h and quenched by addition of concd HCl (2 mL). The mixture was extracted with ethyl acetate (2×30 mL) and the combined organic layer was washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by recrystallization from ethyl acetate to furnish **53** (70 mg) as a white solid. Yield: 83%; R_f: 0.6 (ethyl acetate); mp: 185–186 °C (lit.[21] 186–189 °C); ν_{max} (KBr, cm^{-1}): 3280 (br), 1735, 1616, 1465, 1216, 1060; ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (d, 1H, J=1.6 Hz), 6.56 (d, 1H, J=1.6 Hz), 6.34 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H).

5.1.34. 3-(4-Carboxy-2-hydroxy-6-oxo-1-cyclohexen-1-yl)-5,7-dimethoxy-3*H*-isobenzofuran-1-one (54). It was prepared as a white solid from phthalaldehydic acid **53** and cyclohexane-1,3-dione **43**, following the procedure adopted for the preparation of **44**. Yield: 30% (50% based on recovered phthalaldehydic acid **53**). R_f: 0.3 (methanol); mp: 299–300 °C; ν_{max} (KBr, cm^{-1}): 3230 (br), 1729, 1702, 1614, 1394, 1078, 838; ^1H NMR (400 MHz, MeOH-d_4): δ 7.83 (s, 1H, –OH), 6.51 (s, 1H), 6.35 (s, 1H), 6.26 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.90–2.75 (m, 1H), 2.60–2.45 (m, 4H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 193.7, 173.3, 168.3, 160.4, 159.9, 108.8, 108.2, 108.0, 101.7, 101.3, 78.3, 56.1, 55.9, 41.6, 39.9; HRMS ESI (70 eV) for $C_{17}H_{17}O_8$ $[M+H]^+$ calcd: 349.0923, found: 349.0915.

5.1.35. 4-(1,3-Dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-3,5-dihydroxybenzoic acid (55). This compound was obtained as a white solid along with an unidentified compound by the $Hg(OAc)_2$/NaOAc mediated aromatization of **54** as described for the preparation of **29** from **26**. Yield: 60%; R_f: 0.2 (ethyl acetate); mp: 311–312 °C; ν_{max} (KBr, cm^{-1}): 1725, 1709, 1602, 1436, 1047; ^1H NMR (400 MHz, MeOH-d_4): δ 6.87 (s, 2H), 6.80 (s, 1H), 6.43 (s, 1H), 6.23 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.5, 169.5, 168.6, 160.6, 158.8, 157.2, 133.9, 114.6, 108.9, 108.5, 99.4, 98.7, 75.9, 56.5, 56.3. Anal. Calcd for $C_{17}H_{14}O_8$: C, 58.96; H, 4.07. Found: C, 59.19; H, 4.15.

5.1.36. Methyl 4-(1,3-dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-3,5-dihydroxybenzoate (56). This compound was prepared as a white solid from **55** by the $SOCl_2$/MeOH mediated esterification as described for the preparation of **46** from **45**. Yield: 73%; R_f: 0.2 (1:1 ethyl acetate/petroleum ether); mp: 284–285 °C; ν_{max} (KBr, cm^{-1}): 3392 (br), 1741, 1725, 1610, 1438, 1078; ^1H NMR (400 MHz, MeOH-d_4): δ 6.86 (s, 2H), 6.80 (s, 1H), 6.44 (s, 1H), 6.23 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.4, 168.7, 168.1, 160.6, 158.9, 157.1, 133.2, 114.8, 108.6, 99.4, 98.6, 75.9, 56.5, 56.3, 52.7. Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48. Found: C, 60.11; H, 4.57.

5.1.37. Methyl 4-(1,3-dihydro-4,6-dimethoxy-3-oxo-1-isobenzofuranyl)-3,5-dimethoxybenzoate (57).[2j] To a stirred solution of **56** (30 mg, 0.083 mmol) in acetone (5 mL) was added K_2CO_3 (35 mg, 0.25 mmol) and stirred for 10 min. MeI (0.03 mL, 0.41 mmol) was added to it dropwise and stirred at room temperature for 15–20 h. After completion of the reaction as judged by TLC, inorganic salts were filtered, acetone was removed, and the residue was diluted with ethyl acetate (40 mL) and H_2O (10 mL). The organic layer was separated, washed with H_2O (2×10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to furnish **57** (25 mg) as a white solid. Yield: 77%; R_f: 0.5 (1:1 ethyl acetate/petroleum ether); mp: 175–176 °C (lit.[2j] 170–175 °C); ν_{max} (KBr, cm^{-1}): 3350 (br), 1752, 1720, 1612, 1459, 1328, 1218, 773; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (br s, 2H), 6.88 (s, 1H), 6.39 (s, 1H), 6.18 (s, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.59 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 166.4, 166.3, 159.2 (br), 159.0, 155.1, 132.2, 116.7, 107.7, 105.9 (br), 98.4, 97.1, 73.2, 56.2, 55.9, 55.8, 52.4.

5.1.38. Methyl 4-(1,3-dihydro-4,6-dihydroxy-3-oxo-1-isobenzofuranyl)-3,5-dihydroxybenzoate (58).[2j] Compound **55** (50 mg, 0.14 mmol) was added to a mixture of HBr (1 mL) and AcOH (1 mL) and the mixture was heated at reflux for 15–16 h. The solution was concentrated and diluted with ethyl acetate (50 mL). The layers were separated and the organic phase was washed with water (2×10 mL) and brine (5 mL). After drying (Na_2SO_4) and concentration, the crude product was dissolved in methanol (2 mL) and $SOCl_2$ (0.1 mL) was added to it dropwise at 0 °C. The mixture was again stirred at room temperature for 5 h and quenched by addition of H_2O (5 mL). It was diluted with ethyl acetate (50 mL) and the layers were separated. The organic layer was washed with water (2×10 mL) and brine (5 mL). Drying (Na_2SO_4) and solvent removal produced a residue, which was purified by column chromatography (1:1 ethyl acetate/petroleum ether) to get **58** (20 mg) as a white solid. Yield: 42%; R_f: 0.5 (1:1 ethyl acetate/petroleum ether); mp: 165–166 °C; ν_{max} (KBr, cm^{-1}): 3585 (br), 1727, 1712, 1614, 1434, 1051, 773; ^1H NMR (400 MHz, acetone-d_6): δ 9.34 (s, 1H, –OH), 9.11 (s, 2H, –OH), 8.44 (s, 1H, –OH), 7.08 (s, 2H), 6.91 (s, 1H), 6.34 (s, 1H), 6.24 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4): δ 173.6, 168.3, 166.7, 159.3, 159.0, 156.2, 133.1, 115.4, 108.7, 106.2, 103.1, 101.2, 76.2, 52.8.

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Supplementary data

Crystallographic data of compound **31**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.048.

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