Regioselective Cyclodehydration of *ortho*-Hydroxy Acetyl Aryloxyketones to Benzofuran

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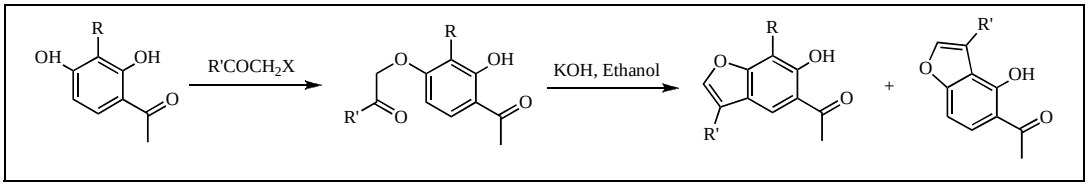

ortho-Hydroxy acetyl benzofuran derivatives have been synthesized in a regioselective cyclodehydration of aryloxyketones obtained from β-resacetophenone and α-halo ketones.

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INTRODUCTION

o-Hydroxy acetophenone are versatile building blocks serving a variety of applications such as pharmaceuticals, fine chemicals and specialty polymers. They are important starting materials in the synthesis of chalcones [1], flavonoids [2], psoralens and angelicins [3], 4-hydroxy coumarins [4], which are well known naturally occurring compounds having diverse pharmacological properties along with benzofurans [5]. Naturally occurring Pongaglabol (8-hydroxy-5-phenyl-furo[2,3-*h*]benzo[*b*]-pyran-7-one) have been synthesized from Phloroacetophenone [6]. Some bioactive compounds have been synthesized from Visnaginone (5-acetyl-6-hydroxy-4-methoxybenzo[*b*]furan) [7]. Hydroxylated benzofurans such as Euparin [8], Coumestrol [9], dehydrotremetone [10] or Cicerfuran [11] plays important role in natural defense mechanism of their plants. One pot synthesis of similar homologues has also been studied [12].

Synthesis of benzofuran based on MacLeod's work is well documented [13-16]. The synthetic pathway followed by MacLeod *et al.* has been employed to prepare the title compounds [17]; where the cyclodehydration of aryloxyketone to benzofuran has been carried out in alkaline medium instead of the generally used sulfuric acid, polyphosphoric acid, phosphorus (III) oxychloride and zinc chloride. The disadvantage with the acid catalyst is the mixture of 2- and 3-substituted benzofuran in the product by rearrangement [18]. Many instances of rearrangement leading to 2-aryl benzofuran have been observed depending on the condition (structure of ketone, medium, temperature) [19].

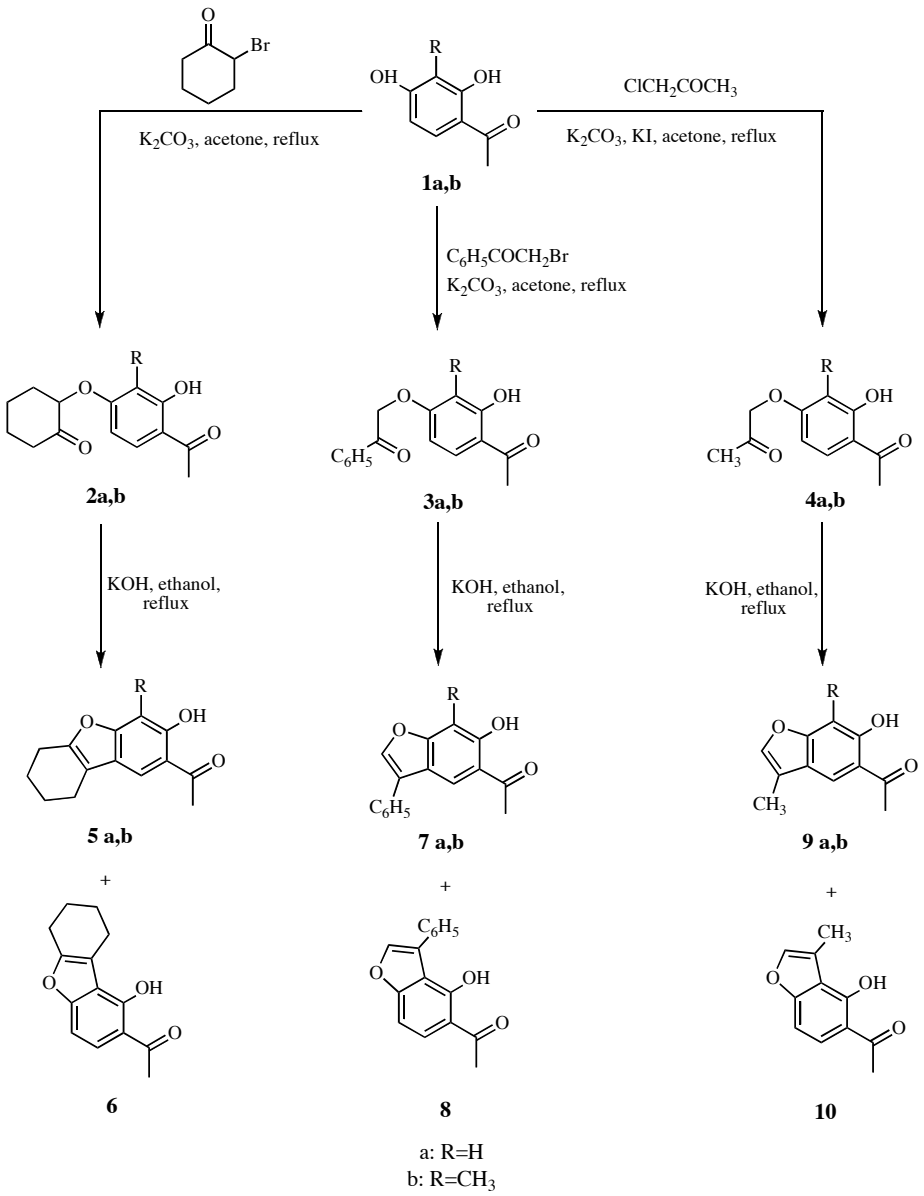
Most of the study done hitherto has been on coumarin nucleus which shows the formation of linear furocoumarin as the exclusive product with no emphasis on the formation of angular furocoumarin except as reported by A. Guiotto *et al.* using the said procedure [20]. Even K. N. Trivedi *et al.* did not report the formation of angular isomer in their synthesis of 1-(3-hydroxy-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone (linear isomer) [3], which now has been reported here.

In the present communication we report the regioselective cyclodehydration of aryloxyketones in an intramolecular Aldol type condensation to benzofuran derivatives. The reaction sequence for different title compounds is outlined in Scheme 1.

RESULTS AND DISCUSSION

1-(2,4-Dihydroxyphenyl)-ethanone **1a** [21], on condensation with different α-halo ketones, *e.g.* α-bromo cyclohexanone, phenacyl bromide and mono chloroacetone, in presence of anhydrous potassium carbonate/dry acetone gave 2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a**, 2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a** and 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a** respectively. Further, 2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a** when subjected to cyclization in 0.1 *N* ethanolic potassium hydroxide showed two products on tlc with very little difference in r_f values, which were then separated on column chromatography with silica gel (60-120 mesh) and petroleum ether 60-80 °C. The two products were characterized as 1-(6-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **7a-linear isomer** and 1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **8-angular isomer** by nmr spectra. The ^{1}H nmr showed singlets at δ 7.05 (1H, C7-H) and δ 8.13 (1H, C4-H) corresponding to the aromatic protons for linear isomer **7a** and doublets (*ortho* coupling) at δ 6.95-6.98 (1H, J = 8.8 Hz, C7-H) and δ 7.58-7.61 (1H, J = 8.8 Hz, C6-H) again corresponding to the aromatic protons for angular isomer **8**. Further, ^{13}C nmr values δ 129.179 (C-4) and δ 161.214 (C-6) for linear isomer and δ 129.306 (C-6) and δ 160.694 (C-4) for angular isomer corroborated the cyclic structure. The mechanism as established by MacLeod *et al.* is an intramolecular Aldol condensation in which the

Scheme 1



phenoxide ion formed promotes attack at the exocyclic carbonyl function through the resonance stabilized carbanion generated at the position *para* relative to the phenoxide ion. The irreversibility of the process is established by abstraction of the proton from the newly formed ring junction. On acidification water is spontaneously eliminated from the labile β-hydroxy dihydrofuran ring system to give the unsaturated benzofuran. Although the carbanion generated *para* to the phenoxide ion is resonance stabilized, the formation of the carbanion generated *ortho* to the phenoxide ion cannot be ruled out as it is the basis for the formation of two isomers. The low yield of angular isomer compared to the linear isomer, which is approximately in the ratio of 1:3, is in accordance with the theory postulated above. To confirm the cyclization products and to get the higher yield of the linear isomer, we started with 1-(2,4-dihydroxy-3-methylphenyl)-ethanone **1b**, which gave the expected results.

Similar observations were recorded for the cyclization of 2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a** and 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a**. Potassium carbonate and triethylamine in place of potassium hydroxide failed to improve the overall yield of the cyclization reaction. Cyclization, especially in case of phenacyl bromide took more time comparatively, because of the stabilization of exocyclic carbonyl function by the phenyl ring. The structures of the compounds have been established on the basis of their elemental analyses and spectral (ir and nmr) data as shown in Table 1. The long range coupling between C3 – CH_3 and C2 – H in compounds **9a**, **9b** and **10** have been confirmed by ^{1}H – COSY spectra.

Table 1
Characterization Data

Compound	Mp	Yield %	Anal. Calcd.	ir (KBr): ν_{max}, cm^{-1}	nmr (ppm)
2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a**	136°C lit. [3] 136°C	45.3%	$C_{14}H_{16}O_4$ (248.27): %C 67.72, %H 6.49; Found %C 68.02, %H 6.34	3468, 3128, 1788, 1699, 1605, 1211, 1256, 1177	^{1}H nmr (90 MHz, CDCl3): δ 2.51 (s, 3H, C4-$COCH_3$), 1.72-2.7 (m, 8H, -CH_2-cyclohexanone), 4.77 (t, 1H, -OC*H*(CH_2)CO-), 6.23 (d, 1H, J = 9 Hz, C6-H), 7.39 (d, 1H, J = 9 Hz, C5-H), 12.61 (s, 1H, C3-OH chelated)
2-(4-acetyl-3-hydroxy-2-methyl-phenoxy)-cyclohexanone **2b**	125°C lit. [3] 125°C	60%	$C_{15}H_{18}O_4$ (262.30): %C 68.68, %H 6.91; Found %C 68.44, %H 6.79	3379, 3098, 1734, 1632, 1611, 1259, 1223, 1149	^{1}H nmr (90 MHz, $CDCl_3$): δ 2.2 (s, 3H, C2-CH_3), 2.55 (s, 3H, C4-$COCH_3$), 1.7-2.6 (m, 8H, -CH_2-cyclohexanone), 4.7 (t, 1H, -OC*H*(CH_2)CO-), 6.2 (d, 1H, J = 9 Hz, C6-H), 7.45 (d, 1H, J = 9 Hz, C5-H), 12.72 (s, 1H, C3-OH chelated)
2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a**	132-133°C	52.9%	$C_{13}H_{15}O_4$ (270.28): %C 71.10, %H 5.22; Found %C 70.86, %H 5.09	3630, 3209, 2923, 1701, 1685, 1654, 1610, 1543, 1353, 1222, 726	^{1}H nmr ($CDCl_3$): δ 2.53 (s, 3H, C4-$COCH_3$-), 5.33 (s, 2H, -OCH_2CO-), 6.4 (d, 1H, J = 2.4 Hz, C2-H), 6.5-6.6 (dd, 1H, J_{meta} = 2.42 Hz, J_{ortho} = 8.9 Hz, C6-H), 7.45-7.57 (m, 2H, C3'-H and C5'-H), 7.52-7.56 (d, 1H, J = 8.89 Hz, C5-H), 7.62-7.68 (m, 1H, C4'-H), 7.9-8 (m, 2H, C2'-H and C6'-H), 12.68 (s, 1H, C3-OH chelated)
2-(4-acetyl-3-hydroxy-2-methyl-phenoxy)-1-phenyl-ethanone **3b**	124-125°C	56%	$C_{14}H_{17}O_4$ (284.30): %C 71.81, %H 5.67; Found %C 71.86, %H 5.36	3397, 3065, 2923, 1708, 1636, 1604, 1501, 1449, 1436, 1373, 1274, 1225, 1139, 764	^{1}H nmr ($CDCl_3$): δ 2.17 (s, 3H, C2-CH3), 2.53 (s, 3H, C4-$COCH_3$), 5.35 (s, 2H, -OCH_2CO-), 6.28-6.31 (d, 1H, J = 8.9 Hz, C6-H), 7.48-7.53 (m, 2H, J_{ortho} = 7.43 Hz, C3'-H and C5'-H), 7.51-7.54 (d, 1H, J = 8.93 Hz, C5-H), 7.60-7.65 (m, 1H, J_{ortho} = 7.39 Hz, J_{meta} = 2.05 Hz, C4'-H), 7.97-8.01 (m, 2H, J_{ortho} = 7.48 Hz, J_{meta} = 1.41Hz, C2'-H and C6'-H), 12.76 (s, 1H, C3-OH chelated)
1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a**	102-103°C	74.53%	$C_{11}H_{12}O_4$ (208.21): %C 63.45, %H 5.80; Found %C 63.19, %H 5.61	3438, 3081, 2913, 1730, 1686, 1611, 1508, 1431, 1371, 1258	^{1}H nmr ($CDCl_3$): δ 2.27 (s, 3H, -$COCH_3$), 2.56 (s, 3H, C4-$COCH_3$), 4.59 (s, 2H, -OCH_2CO-), 6.34 (d, 1H, J = 2.44 Hz, C2-H), 6.47 (dd, 1H, J_{meta} = 2.49 Hz, J_{ortho} = 8.92 Hz, C6-H), 7.66 (d, 1H, J = 8.92 Hz, C5-H), 12.69 (s, 1H, C3-OH chelated)
1-(4-acetyl-3-hydroxy-2-methyl-phenoxy)-propan-2-one **4b**	126-128°C	79%	$C_{12}H_{14}O_4$ (222.23): %C 64.85, %H 6.34; Found %C 65.20, %H 6.31	3417, 2928, 2902, 1718, 1626, 1498, 1417, 1360, 1282, 1227, 1135, 1112	^{1}H nmr ($CDCl_3$): δ 2.18 (s, 3H, C2-CH_3), 2.31 (s, 3H, -$COCH_3$), 2.56 (s, 3H, C4-$COCH_3$), 4.60 (s, 2H, -OCH_2CO-), 6.25 (d, 1H, J = 8.97 Hz, C6-H), 7.57 (d, 1H, J = 8.94 Hz, C5-H), 12.77 (s, 1H, C3-OH chelated)
1-(3-hydroxy-6,7,8,9-tetrahydro-dibenzofuran-2-yl)-ethanone **5a-linear isomer**	186-188°C lit. [3] 182°C	64.43%	$C_{14}H_{14}O_3$ (230.26): %C 73.02, %H 6.12; Found %C 73.26, %H 6.45	3448, 2930, 1638, 1616, 1458, 1143	^{1}H nmr (90 MHz, $CDCl_3$): δ 1.6-2.0 (m, 4H, C7-CH_2- and C8-CH_2-), 2.6 (s, 3H, C2-$COCH_3$), 2.4-2.8 (m, 4H, C6-CH_2- and C9-CH_2-), 6.9 (s, 1H, C4-H), 7.7 (s, 1H, C1-H), 12.0 (s, 1H, C3-OH chelated)
1-(3-hydroxy-4-methyl-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone **5b**	148°C lit. [3] 148°C	49.02%	$C_{15}H_{16}O_3$ (244.28): %C 73.75, %H 6.60; Found %C 73.56, %H 6.39	3458, 2923, 1649, 1613, 1467, 1136	^{1}H nmr (90 MHz, $CDCl_3$): δ 1.7-2.0 (m, 4H, C7-CH_2- and C8-CH_2-), 2.45 (s, 3H, C4-CH_3), 2.7 (s, 3H, C2-$COCH_3$), 2.5-2.8 (m, 4H, C6-CH_2- and C9-CH_2-), 7.5 (s, 1H, C1-H), 12.60 (s, 1H, C3-OH chelated)
1-(1-hydroxy-6,7,8,9-tetrahydro-dibenzofuran-2-yl)-ethanone **6-angular isomer**	107-108°C	26.84%	$C_{14}H_{14}O_3$ (230.26): %C 73.02, %H 6.12; Found %C 73.26, %H 6.45	3568, 2938, 1635, 1616, 1560, 1462, 1438, 1317, 1065, 781	^{1}H nmr ($CDCl_3$): δ 1.77-1.94 (m, 4H, C7-CH_2- and C8-CH_2-), 2.61 (s, 3H, C2-$COCH_3$), 2.66-2.88 (m, 4H, C6-CH_2- and C9-CH_2-), 6.87-6.90 (d, 1H, J = 8.76 Hz, C4-H), 7.49-7.52 (d, 1H, J = 8.79 Hz, C3-H), 13.04 (s, 1H, C1-OH chelated)
1-(6-hydroxy-3-phenylbenzo-furan-5-yl)-ethanone **7a-linear isomer**	111-113°C	23.57%	$C_{16}H_{12}O_3$ (252.26): %C 76.17, %H 4.79; Found %C 75.86, %H 4.67	3506, 3105, 1637, 1615, 1584, 1461, 1371, 1329, 1252, 1165, 766	^{1}H nmr ($CDCl_3$): δ 2.69 (s, 3H, C5-$COCH_3$), 7.05 (s, 1H, C7-H), 7.39-7.43 (m, 1H, C4'-H), 7.48-7.52 (m, 2H, C3'-H and C5'-H), 7.57-7.60 (m, 2H, C2'-H and C6'-H), 7.68(s, 1H, C2-H), 8.13 (s, 1H, C4-H), 12.48 (s, 1H, C6-OH chelated); ^{13}C nmr ($CDCl_3$): δ 26.785 (-CO*C*H_3), 100.074 (C-3), 117.098 (C-7), 119.482 (C-3a), 122.302 (C-5), 123.160 (C-4'), 127.395 (C-3', C-5'), 127.938 (C-2', C-6'), 129.179 (C-4), 131.161 (C-1'), 141.737 (C-2), 160.292 (C-7a), 161.214 (C-6), 204.040 (>C=O)
1-(6-hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-ethanone **7b**	150-151°C	65.7%	$C_{17}H_{14}O_3$ (266.29): %C 76.67, %H 5.29; Found %C 76.58, %H 5.09	3448, 3107, 3056, 2925, 1632, 1585, 1423, 1374, 1329, 1261, 1104, 770	^{1}H nmr ($CDCl_3$): δ 2.38 (s, 3H, C7-CH_3), 2.65 (s, 3H, C5-$COCH_3$), 7.36-7.41 (m, 1H, C4'-H), 7.45-7.50 (m, 2H, C3'-H and C5'-H), 7.55-7.59 (m, 2H, C2'-H and C6'-H), 7.68 (s, 1H, C2-H), 7.97 (s, 1H, C4-H), 12.68 (s, 1H, C6-OH chelated)
1-(4-hydroxy-3-phenylbenzo-furan-5-yl)-ethanone **8-angular isomer**	102-104°C	9.21%	$C_{16}H_{12}O_3$ (252.26): %C 76.17, %H 4.79; Found %C 75.86, %H 4.67	3568, 3128, 3099, 1615, 1490, 1475, 1370, 1268, 1050, 760	^{1}H nmr ($CDCl_3$): δ 2.57 (s, 3H, C5-$COCH_3$), 6.95-6.98 (d, 1H, J = 8.85 Hz, C7-H), 7.33-7.37 (m, 1H, C4'-H), 7.40-7.42 (m, 2H, C3'-H and C5'-H), 7.53 (s, 1H, C2-H), 7.58-7.61(d, 1H, J = 8.88 Hz, C6-H), 7.64-7.66 (m, 2H, C2'-H and C6'-H), 13.60 (s, 1H, C4-OH chelated); ^{13}C nmr ($CDCl_3$): δ 26.922 (-CO*C*H_3), 103.787 (C-3), 114.363 (C-7), 115.521 (C-3a), 124.013 (C-5), 127.465 (C-4'), 127.647 (C-3', C-5'), 128.089 (C-2', C-6'), 129.306 (C-6), 131.024 (C-1'), 141.495 (C-2), 160.106 (C-7a), 160.694 (C-4), 204.188 (>C=O)

Table 1 (continued

Compound	Mp	Yield %	Anal. Calcd.	ir (KBr): ν_{max}, cm^{-1}	nmr (ppm)
1-(6-hydroxy-3-methylbenzo-furan-5-yl)-ethanone **9a-linear isomer**	132-133°C	29%	$C_{11}H_{10}O_3$ (190.19): %C 69.46, %H 5.29; Found %C 69.78, %H 5.37	3630, 3122, 2951, 1644, 1622, 1454, 1372, 1253, 1142, 1057, 792	^{1}H nmr ($CDCl_3$): δ 2.23 (d, 3H, J = 1.1 Hz long range coupling, C3-CH_3), 2.71 (s, 3H, C5-$COCH_3$), 6.96 (s, 1H, C7-H), 7.33 (d, 1H, J = 1.1 Hz long range coupling, C2-H), 7.84 (s, 1H, C4-H), 12.46 (s, 1H, C6-OH chelated)
1-(6-hydroxy-3,7-dimethyl-benzofuran-5-yl)-ethanone **9b**	99-100°C	55.07%	$C_{12}H_{12}O_3$ (204.22); %C 70.57, %H 5.92; Found %C 70.78, %H 5.87	3630, 3124, 2921, 1636, 1420, 1367, 1274, 1096, 793	^{1}H nmr ($CDCl_3$): δ 2.22 (d, 3H, J = 1.35 Hz long range coupling, C3-CH_3), 2.35 (s, 3H, C7-CH_3), 2.70 (s, 3H, C5-$COCH_3$), 7.35 (d, 1H,J = 1.35 Hz long range coupling, C2-H), 7.71 (s, 1H, C4-H), 12.67 (s, 1H, C6-OH chelated)
1-(4-hydroxy-3-methylbenzo-furan-5-yl)-ethanone **10-angular isomer**	64-65°C	10.94%	$C_{11}H_{10}O_3$ (190.19): %C 69.46, %H 5.29; Found %C 69.78, %H 5.37	3630, 3110, 2934, 1616, 1597, 1478, 1426, 1373, 1299, 1234, 1048, 786	^{1}H nmr (400MHz,$CDCl_3$): δ 2.41 (d, 3H, J = 1.24 Hz long range coupling, C3-CH_3), 2.64 (s, 3H, C5-$COCH_3$), 6.94 (d, 1H, J = 8.96 Hz, C7-H), 7.29 (d, 1H, J = 1.24 Hz long range coupling, C2-H), 7.59 (d, 1H, J = 8.84 Hz, C6-H), 13.28 (s, 1H, C4-OH chelated)

EXPERIMENTAL

Melting points (uncorrected) were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by tlc on Acme's silica gel G plates using UV/Iodine vapour as visualizing agent and Acme's silica gel (60-120 mesh) was used for column chromatographic purification. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400). Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (spectrum RX1) using potassium bromide optics. Nmr spectra were recorded on Brucker 300 MHz spectrophotometer except where mentioned. Chemical shifts are relative to tetramethylsilane on δ-scale with deuteriochloroform as solvent. Coupling constants are given in Hz and relative peak areas are in agreement with all assignments.

General procedure for the preparation of 2a, 2b, 3a, 3b, 4a and 4b. To a stirred solution of 1-(2,4-dihydroxyphenyl)-ethanone **1a** (5 g, 0.033 moles) and anhydrous potassium carbonate (5.68 g, 0.041 moles) in (30 ml) dry acetone was added drop wise a solution of phenacyl bromide (6.54 g, 0.033 moles) in (20 ml) dry acetone at reflux temperature. Reflux was continued for 12 hours. The reaction mixture was concentrated to dryness and then poured into ice water and the solid collected by filtration. The crude product was purified by column chromatography using petroleum ether (60-80°C): ethyl acetate mixture and crystallized therein to give white crystals (4.7 g, 52.9%) of 2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a.**

Potassium iodide was added in catalytic amount in the preparation of compounds **4a** and **4b** by the said procedure.

General procedure for the preparation of 5a, 5b, 6, 7a, 7b, 8, 9a, 9b and 10. 2-(4-Acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a** (1 g, 0.0037 moles) was dissolved in 0.1 *N* ethanolic potassium hydroxide (100 ml) and refluxed for 30 hours. The excess ethanol was then removed by distillation *in vacuo* and the reaction mixture was poured into ice-hydrochloric acid and the solid collected by filtration. The crude product showed two products on tlc developing with petroleum ether (60-80°C) and visualizing in iodine. Both the products were separated by column chromatography using petroleum ether (60-80°C) as eluent. The first product (non polar) to come out of the column was characterized as 1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **8-angular isomer** and obtained as light greenish yellow crystals (0.086 g, 9.21%).

The second product from the column was characterized as 1-(6-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **7a-linear isomer** and obtained as light greenish yellow crystals (0.22 g, 23.57%).

Cyclization for compounds **5a**, **5b**, **6**, **9a**, **9b** and **10** took 18 hours for completion of reaction.

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