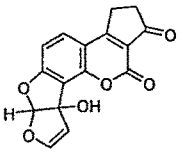
Chapter 2: Regioselective Cyclodehydration of Aryloxyketones to Benzofuran

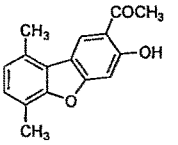
2.1 Introduction

o-Hydroxy acetophenone are versatile building blocks serving variety of applications such as pharmaceuticals, fine chemicals and speciality polymers. They are important starting materials in the synthesis of chalcones,[1] flavanoids,[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) has 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]

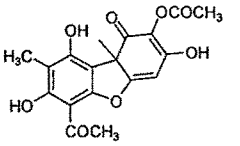
Benzofurans are versatile building blocks serving variety of applications such as pharmaceuticals and fine chemicals.



Aflatoxins



Ruscodibenzofuran

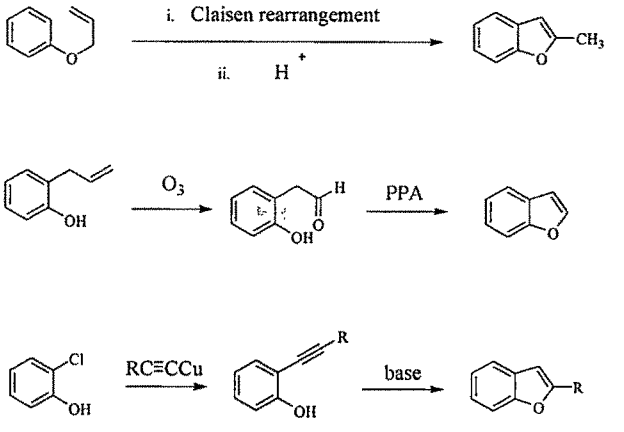


Usnic acid

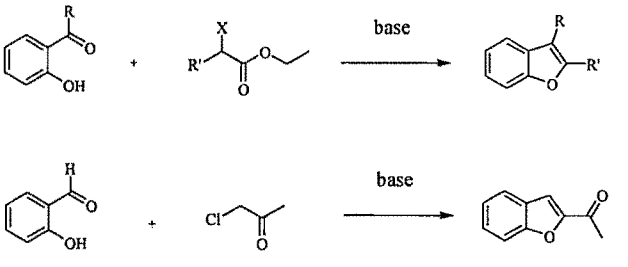
Aflatoxins, Psoralens, Usnic acid, 5-Cinnamoylbenzofurans, 2-aminomethyl-2,3-dihydrobenzofurans, 5-acyl-2,3-dihydrobenzofuran-2-carboxyclic acids, 5-benzofuranyl carbamates, Ruscodibenzofuran are pharmacologically active benzofurans.

Several methods have been known for the synthesis of benzo[*b*]furans. This includes:

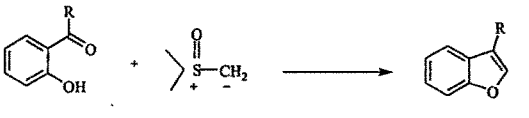
- Intramolecular cyclization of *ortho*-substituted phenols.



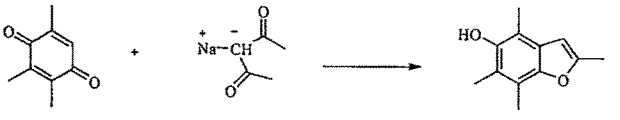
- Reaction of *ortho*-acylphenols with α-halo ketones and esters.



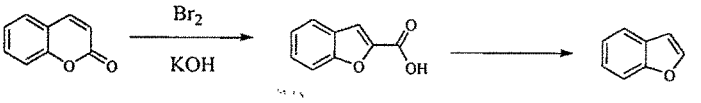
- Reaction of *ortho*-acylphenols with dimethylsulfoxonium methylide.



- From *para*-benzoquinones.

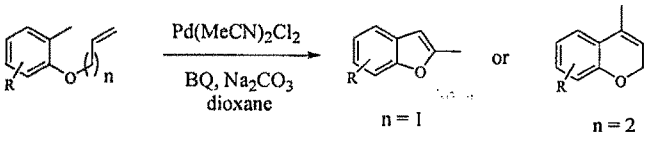


- Ring contraction of Coumarins.

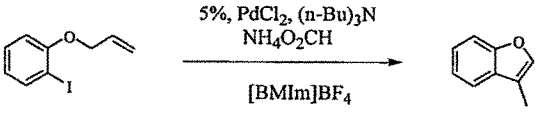


Recent advances in the synthesis of benzofurans:

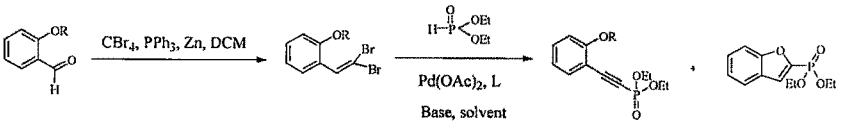
- "Facile construction of the Benzofuran and Chromene ring systems via Pd III – catalyzed oxidative cyclization"; Youn, So Won; Eom, Jeong Im. *Org. Lett.*, **2005**, 7(15), 3355-3358.



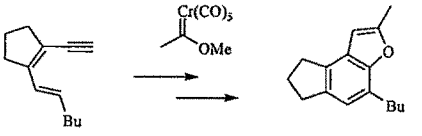
- "Syntheis of benzofurans in ionic liquid by a $PdCl_2$ – catalyzed intramolecular Heck reaction"; Xie, X.; Chen, B.; Lu, J.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.*, **2004**, 45, 6235.



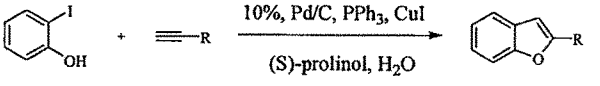
➢ "New synthesis of benzo[*b*]furan and indole derivatives from 1,1-dibromo-1-alkene using a tandem Pd – assisted cyclization – coupling reaction"; Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.*, **2004**, 45, 907.



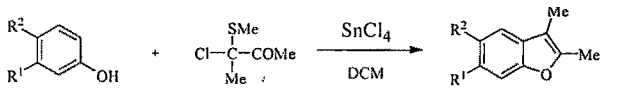
➢ "Synthesis of benzofurans through coupling of dienylacetylenes with carbene complexes: total synthesis of egonol"; Zhang, J; Zhang, Y.; Zhang, Y.; Herndon, J. W. *Tetrahedron*, **2003**, 59, 5609.



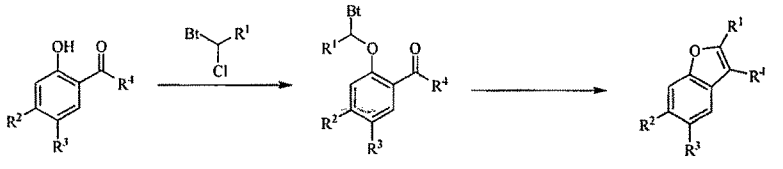
➢ "Pd/C mediated synthesis of 2-substituted benzo[*b*]furans/nitrobenzo[*b*]furans in water"; Pal, M.; Subramanian, V.; Yeleswarapu, K. *Tetrahedron Lett.*, **2003**, 44, 8221.



➢ "Synthesis of 2,3-disubstituted benzofuran derivatives from substituted phenols"; Choi, H. D.; Seo, P. J.; Son, B. W. *J. Korean Chem. Soc.*, **2001**, 45(5), 500.



➢ "Novel synthesis of 2,3-disubstituted benzofurans"; Katritzky, A. R.; Yu Ji; Fang, Y.; Prakash, I. *J. Org. Chem.*, **2001**, 66(16), 5613.



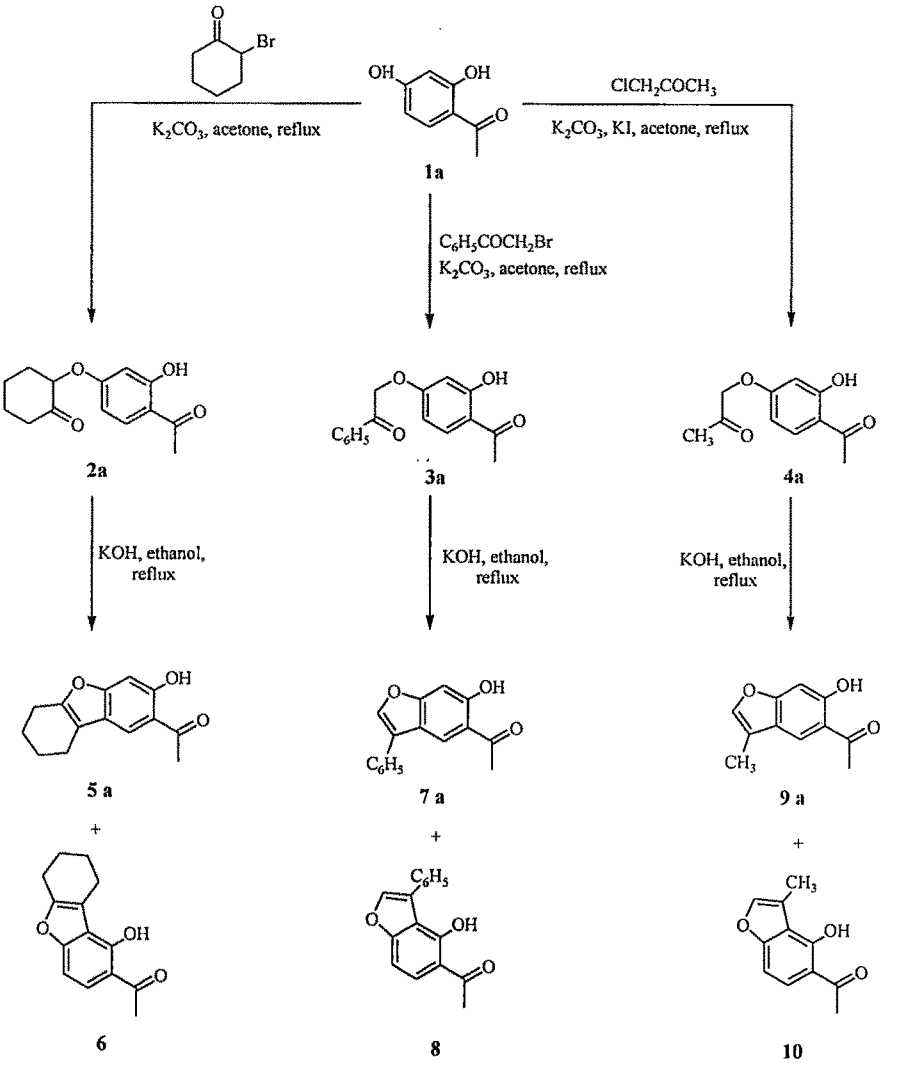
Bt = benzotriazol-1-yl

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 in the cyclodehydration of aryloxyketone to benzofuran has been carried out in alkaline medium instead of 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 work 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.**


K2CO3, acetone, reflux
ClCH2COCH3
K2CO3, KI, acetone, reflux
1a
C6H5COCH2Br
K2CO3, acetone, reflux
2a
3a
4a
KOH, ethanol, reflux
KOH, ethanol, reflux
KOH, ethanol, reflux
5 a
7 a
9 a
6
8
10

Scheme 1

2.2 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. The ^{1}H NMR of **3a** showed signals at δ 2.53 (s, 3H, C4-$COCH_3$-), 5.33 (s, 2H, -OCH_2CO-), 6.4 (d, 1H, J_{meta} = 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_{ortho} = 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). Further, 2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a** when subjected to cyclization in 0.1 *N* ethanolic potassium hydroxide solution 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 (Figure 1)** 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 (Figure 2)**. Further, ^{13}C NMR values δ 129.179 (C-4) and δ 161.214 (C-6) for linear isomer **(Figure 3)** and δ 129.306 (C-6) and δ 160.694 (C-4) for angular isomer **(Figure 4)** corroborated the cyclic structure.

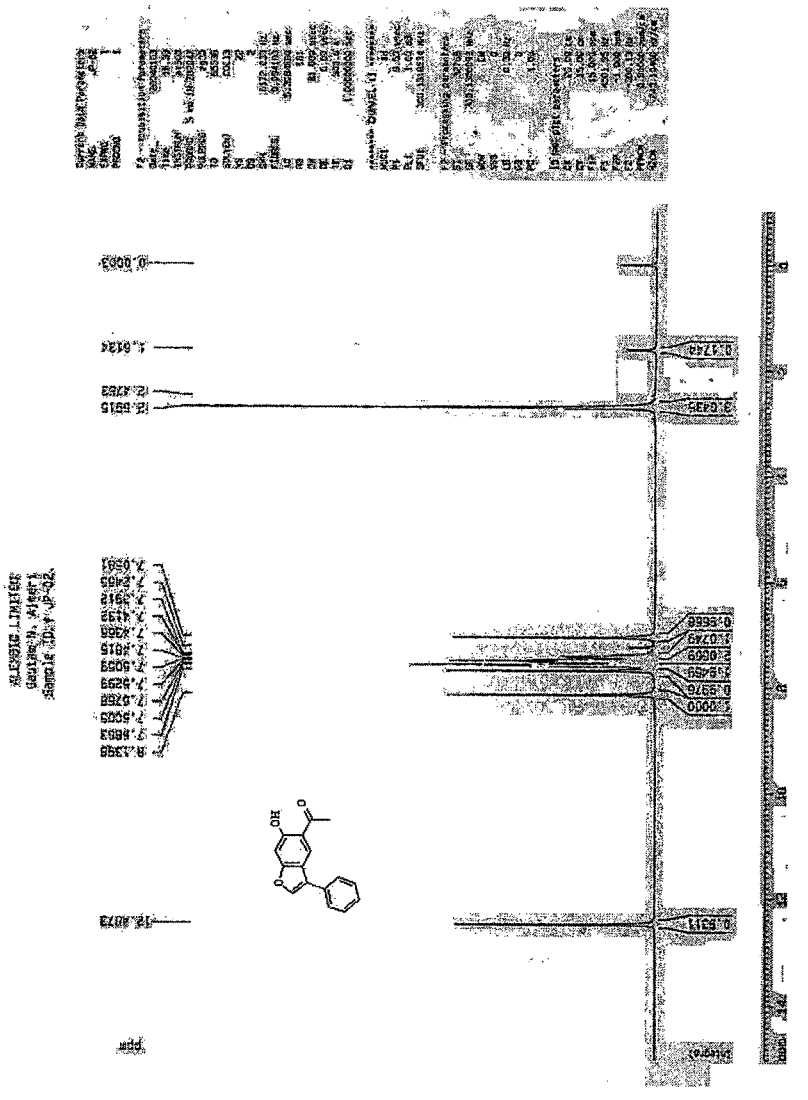


Figure 1: ^{1}H NMR of 1-(6-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **7a**-linear isomer.

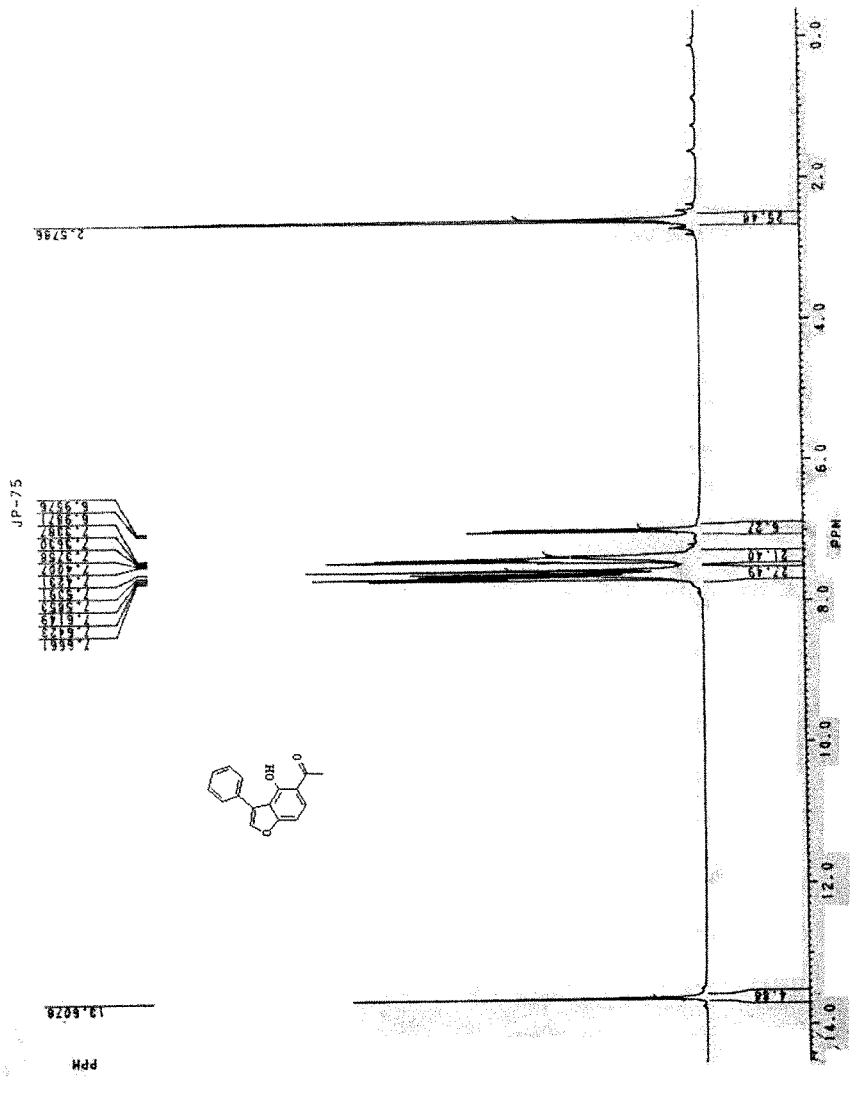


Figure 2: ^{1}H NMR of 1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **8**-angular isomer.

Figure 3: ^{13}C NMR of 1-(6-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **7a**-linear isomer.

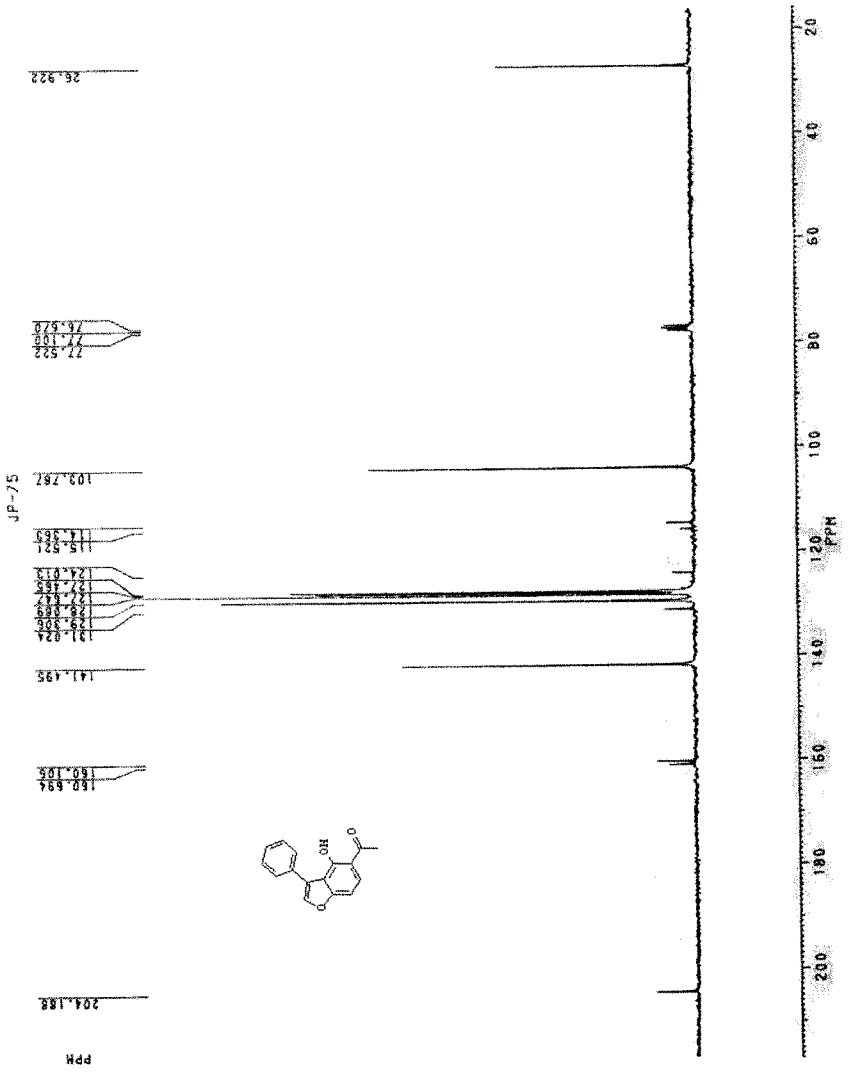
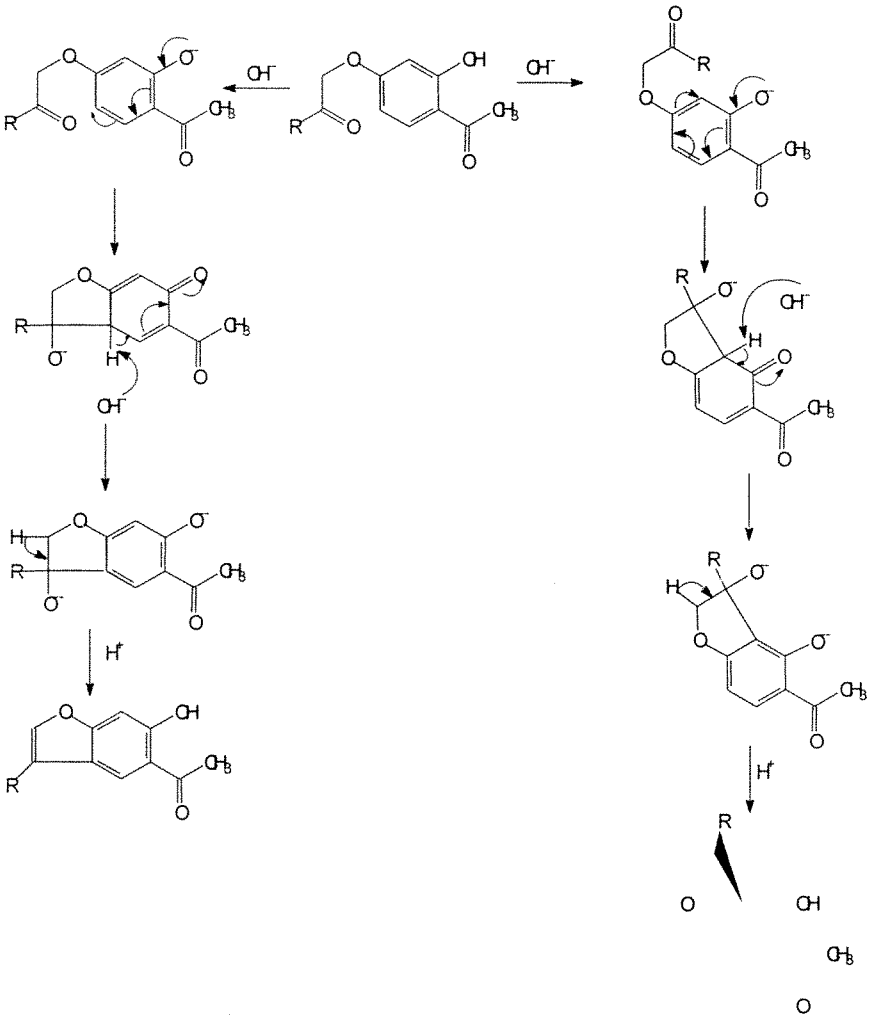


Figure 4: ^{13}C NMR of 1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **8**-angular isomer.

The mechanism as established by MacLeod *et al.*[17] is an intramolecular aldol condensation in which the phenoxide ion formed promotes attack at the exocyclic carbonyl function through the resonance stabilized carbanion generated at the position para 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 carbanion generated *ortho* to the phenoxide ion cannot be ruled out and which forms the basis of formation of two isomers as shown in **Scheme 2**. 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.

Similar results were obtained for the synthesis of 1-(3-hydroxy-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone **5a-linear isomer** and 1-(1-hydroxy-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone **6-angular isomer** by cyclization of 2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a**. ^{1}H NMR of **6** is shown in **Figure 8**.

Synthesis of 1-(6-hydroxy-3-methylbenzofuran-5-yl)-ethanone **9a-linear isomer** and 1-(4-hydroxy-3-methylbenzofuran-5-yl)-ethanone **10-angular isomer** was carried out similarly by cyclization of 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a** in 0.1 *N* ethanolic potassium hydroxide solution **(Scheme 1)**. ^{1}H NMR of **9a** is shown in **Figure 6** and that of **10** is shown in **Figure 7** and its IR is shown in **Figure 9** and **Figure 10** respectively.



Scheme 2: Probable mechanism for the formation of linear and angular isomers.

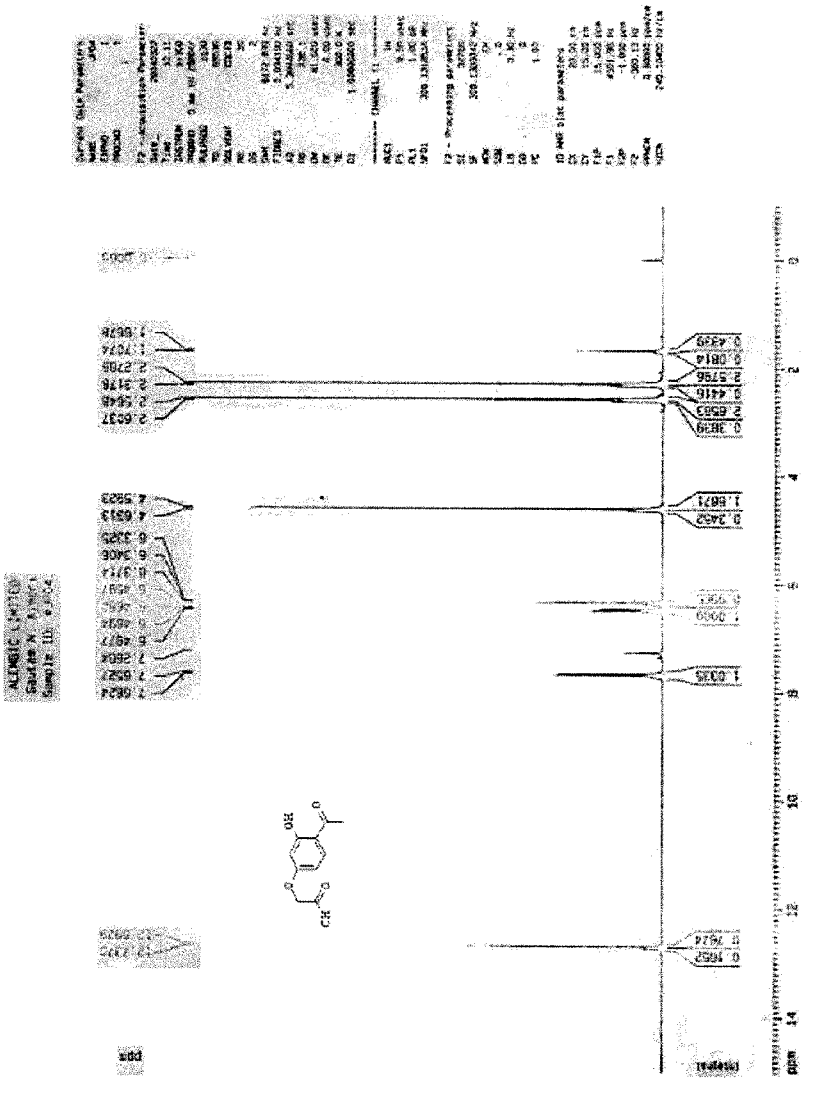


Figure 5: ^{1}H NMR of 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a**.

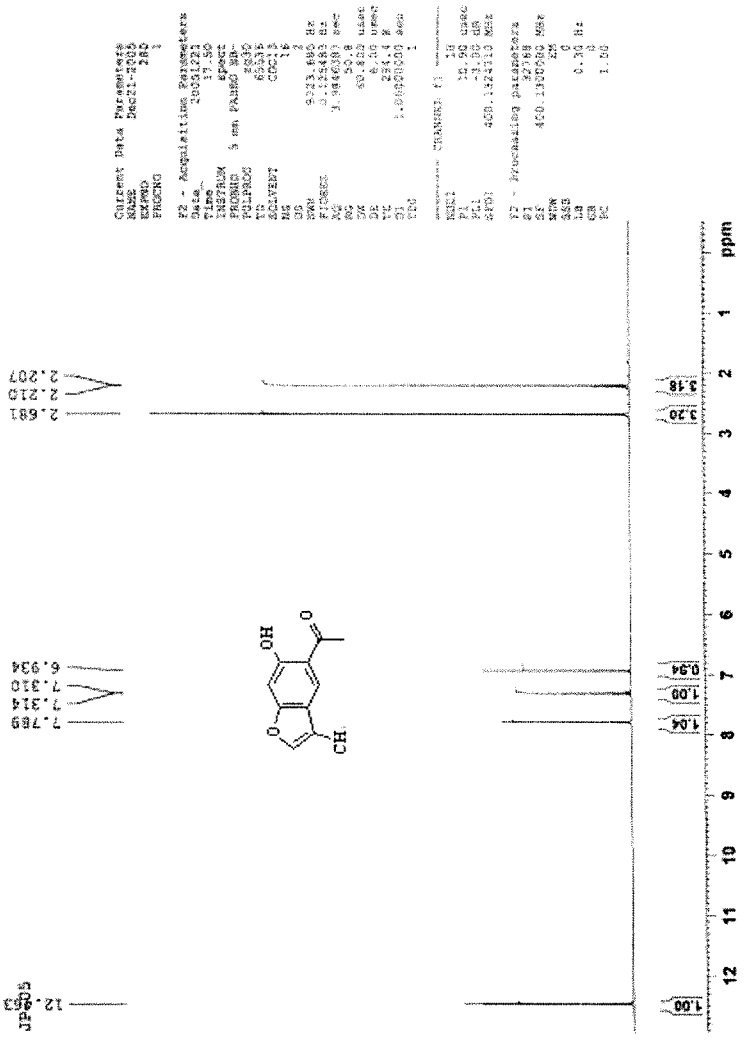


Figure 6: ^{1}H NMR of 1-(6-hydroxy-3-methylbenzofuran-5-yl)-ethanone **9a**.

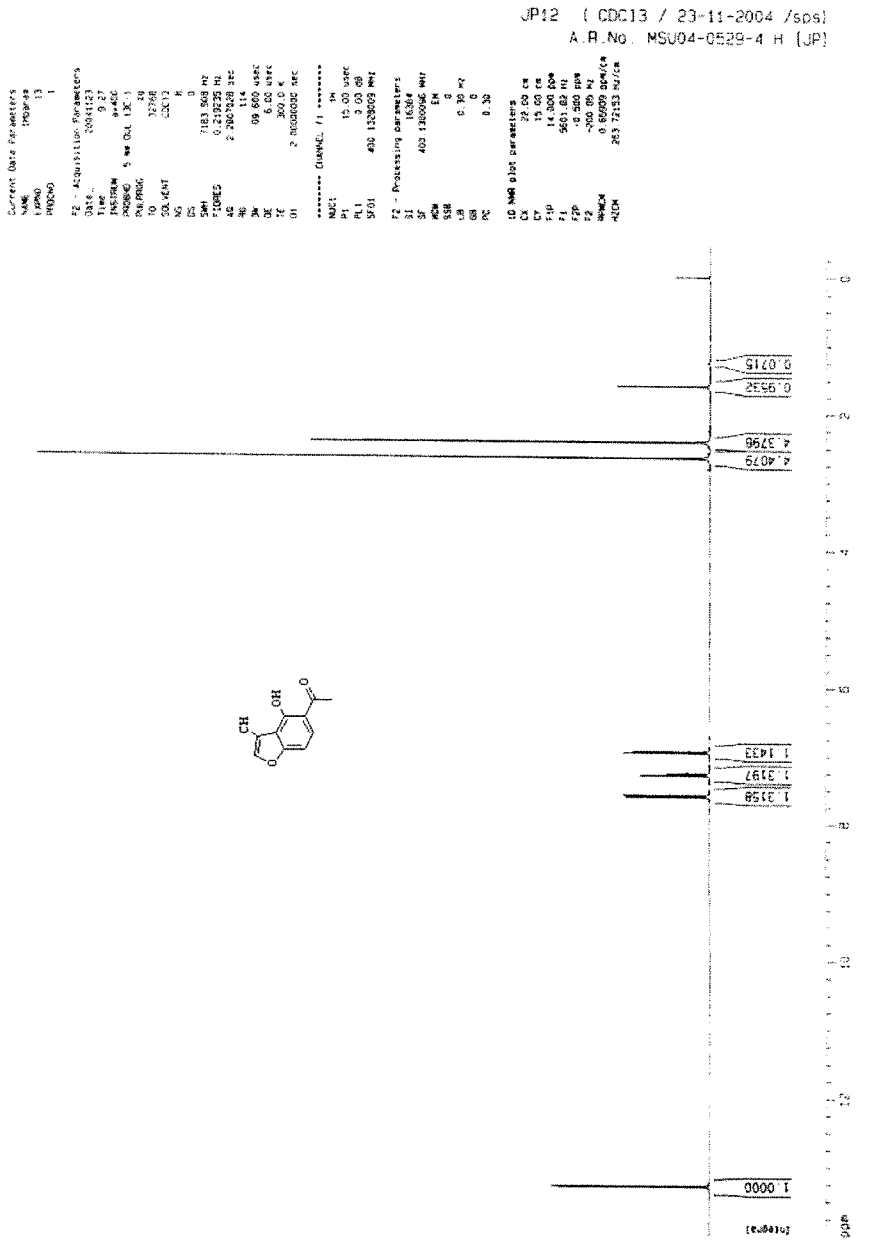


Figure 7: ^{1}H NMR of 1-(4-hydroxy-3-methylbenzofuran-5-yl)-ethanone **10**.

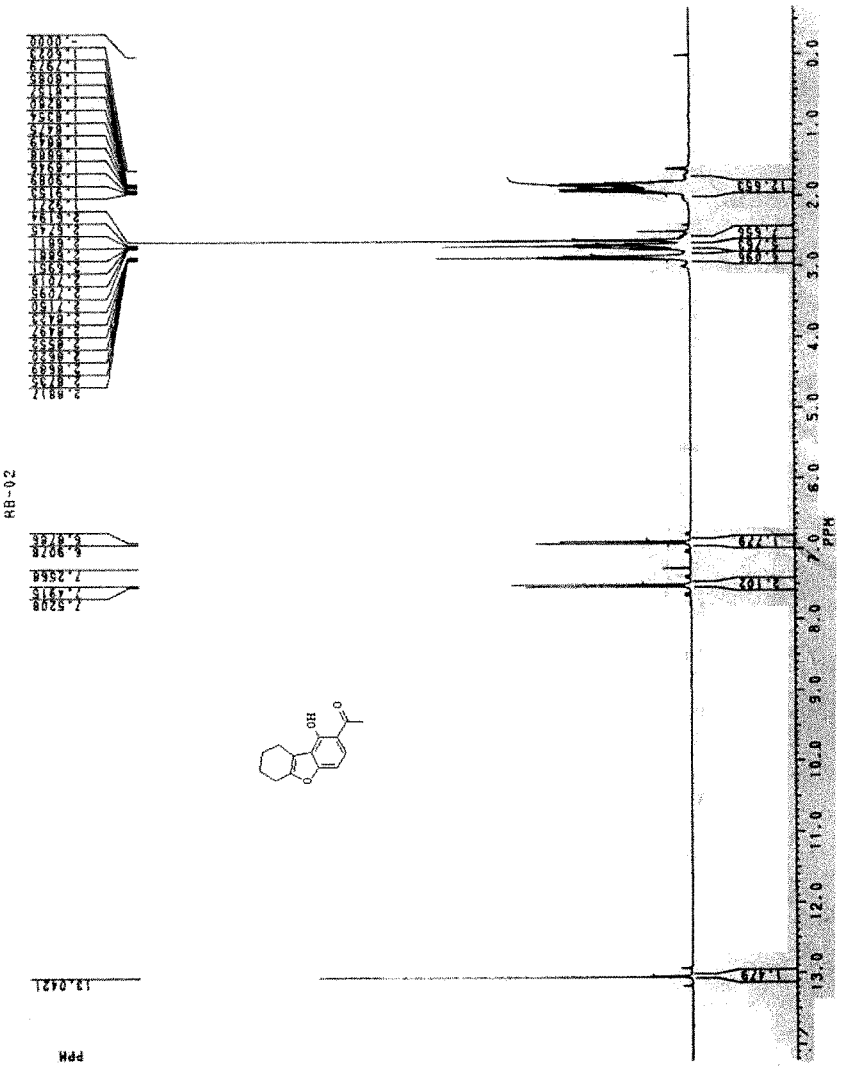
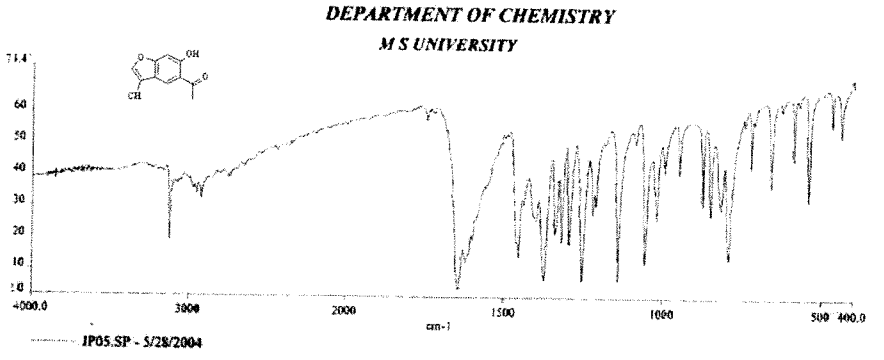


Figure 8: ^{1}H NMR of 1-(1-hydroxy-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone **6**.



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1220.32 28.32 1210.52 31.22 1142.09 7.32 1087.94 50.69 1057.33 13.00
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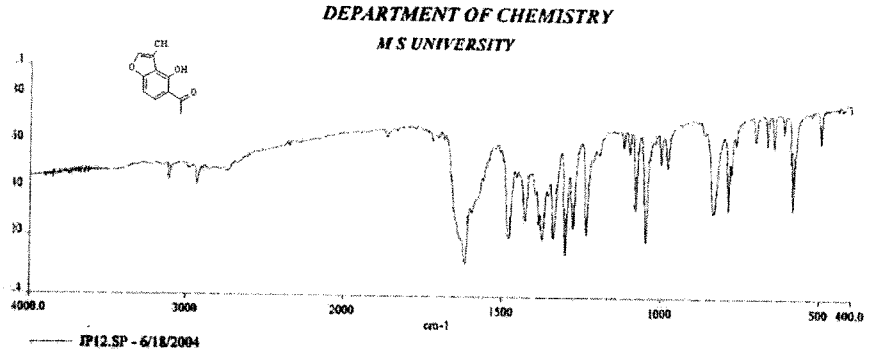
815.97 30.23 792.88 14.46 743.83 56.68 723.91 43.24 666.18 37.23
626.85 61.61 588.66 46.02 540.94 33.09 468.00 56.58 439.88 52.95

Figure 9: IR of 1-(6-hydroxy-3-methylbenzofuran-5-yl)-ethanone **9a**.



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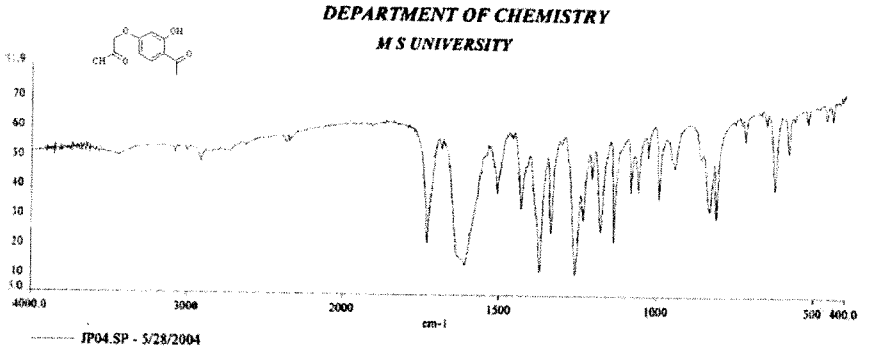
2345.82 58.61 1861.94 62.94 1717.87 67.22 1616.57 8.65 1597.33 30.70
1478.94 19.76 1455.65 46.45 1426.75 27.41 1384.08 25.84 1373.05 19.00
1354.06 38.34 1337.67 19.88 1299.89 12.81 1275.94 24.54 1234.81 21.16
1119.52 59.34 1108.04 56.69 1079.99 32.13 1048.06 18.58 990.95 52.06
878.71 50.55 832.86 31.14 786.54 32.37 778.04 48.37 764.03 60.35
702.34 62.10 665.99 60.64 644.30 59.92 613.70 65.39 584.24 32.69
496.48 61.40 430.14 75.20

Figure 10: IR of 1-(4-hydroxy-3-methylbenzofuran-5-yl)-ethanone **10**.



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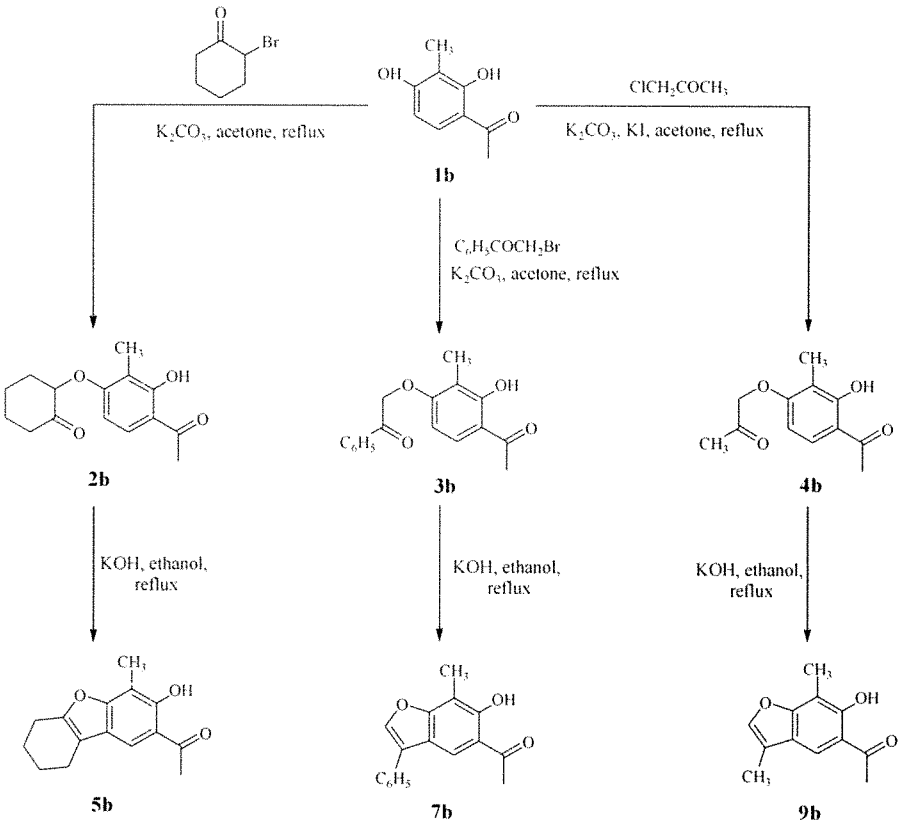
3081.23 52.21 2913.95 49.32 2360.04 55.94 2345.55 56.48 1730.80 22.50
1686.01 54.32 1611.28 13.33 1508.11 39.19 1458.49 58.17 1431.93 34.12
1371.90 13.04 1335.97 26.57 1258.28 12.35 1234.48 30.65 1208.10 44.95
1179.51 26.63 1137.67 23.36 1083.67 40.11 1060.66 40.38 1029.97 51.84
993.71 37.72 944.43 48.56 860.92 51.34 832.60 54.05 810.25 31.26
719.96 57.66 652.28 63.08 625.05 41.23 581.08 53.68 519.74 64.05
460.47 65.44 441.47 64.89

Figure 11: IR of 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a**.



Scheme 3

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**,[21] which gave the expected results **(Scheme 3)**. 1-(2,4-dihydroxy-3-methylphenyl)-ethanone **1b** 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-hydroxy-2-methylphenoxy)-cyclohexanone **2b**, 2-(4-acetyl-3-hydroxy-2-methylphenoxy)-1-phenyl-ethanone **3b** and 1-(4-acetyl-3-hydroxy-2-methylphenoxy)-propan-2-one **4b** respectively; which when subjected to cyclization in 0.1 *N* ethanolic potassium

hydroxide solution gave only the desired linear isomers 1-(3-hydroxy-4-methyl-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone **5b**, 1-(6-hydroxy-7-methyl-3-phenylbenzofuran-5-yl)-ethanone **7b** and 1-(6-hydroxy-3,7-dimethylbenzofuran-5-yl)-ethanone **9b (Figure 12)** respectively. The ^{1}H NMR of 1-(6-hydroxy-7-methyl-3-phenylbenzofuran-5-yl)-ethanone **7b (Figure 13)** showed signals at 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). The mass spectrum **(lcms – Figure 14)** was obtained as m/z (relative intensity, 100%): 289.1 (9.52) M+23 (from Na^{+}), 267.2 (100) M+1 and 247.3 (9.52) using mobile phase Acetonitrile: Ammonium acetate 1mM (90:10 % v/v) which further confirmed the structure.

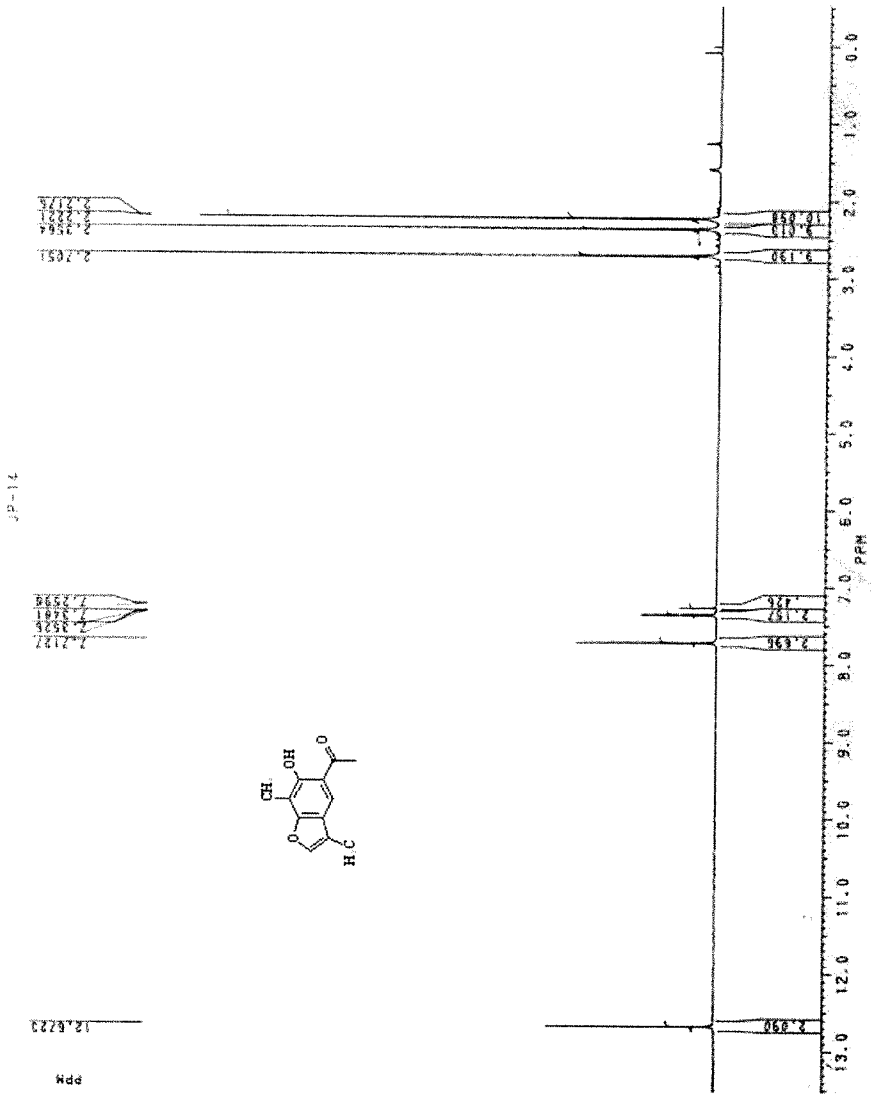


Figure 12: ^{1}H NMR of 1-(6-hydroxy-3,7-dimethylbenzofuran-5-yl)-ethanone **9b**.

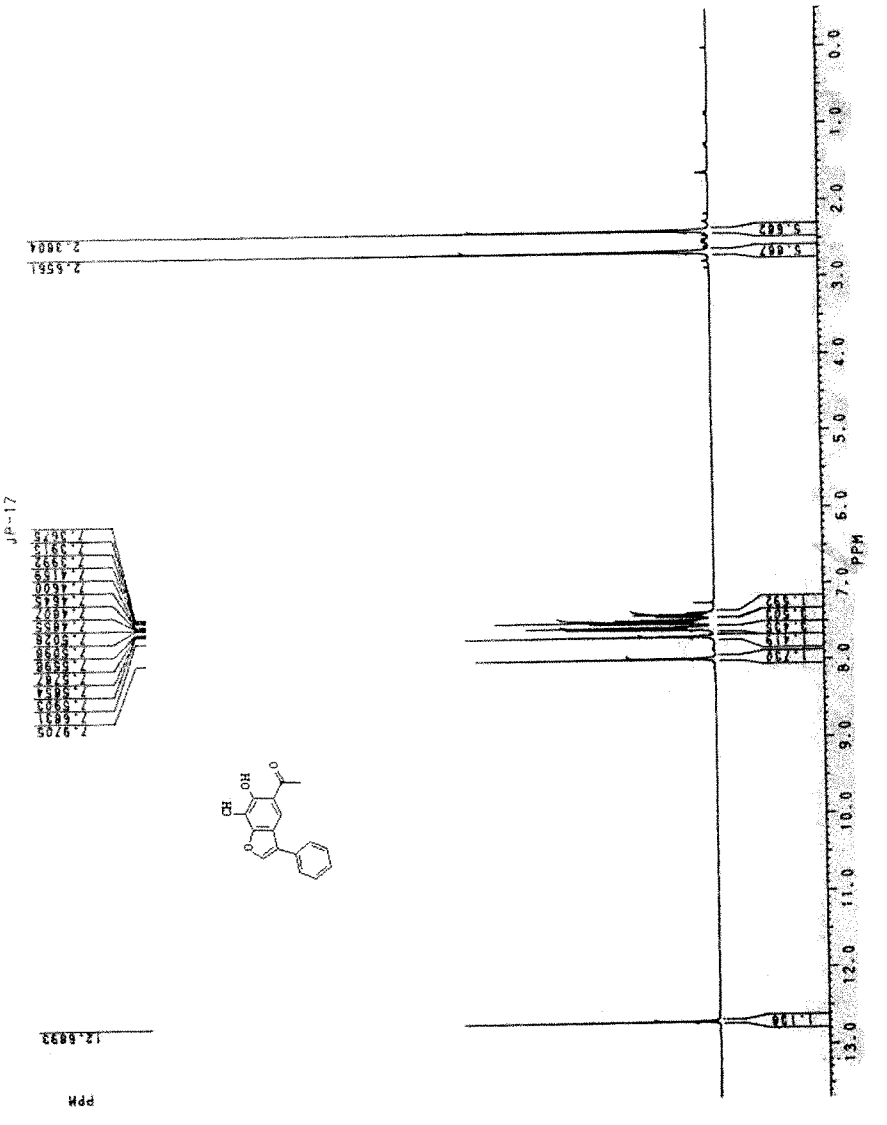


Figure 13: ^{1}H NMR of 1-(6-hydroxy-7-methyl-3-phenylbenzofuran-5-yl)-ethanone **7b**.

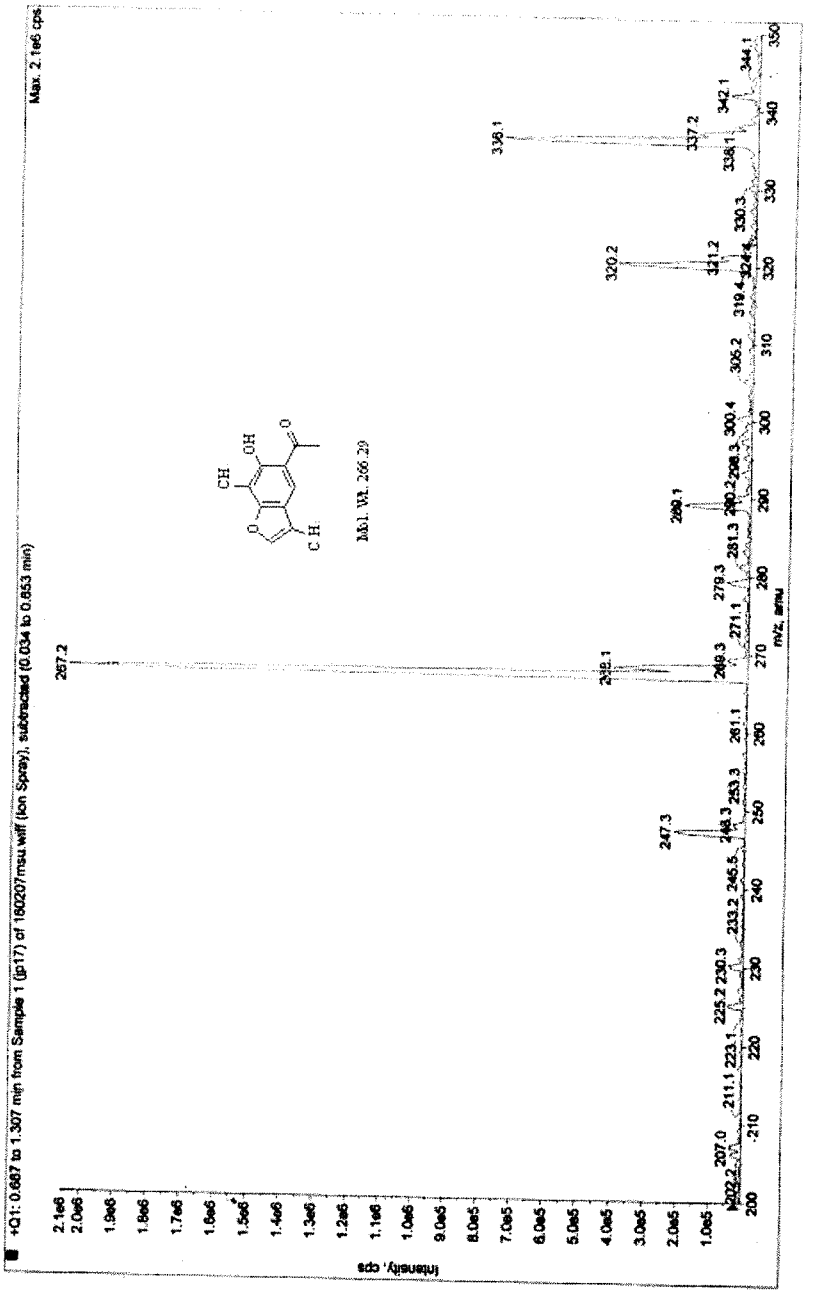
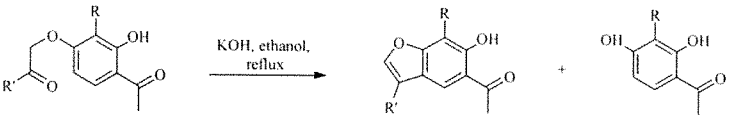


Figure 14: LCMS of 1-(6-hydroxy-7-methyl-3-phenylbenzofuran-5-yl)-ethanone **7b**.

It was also observed that the over yield of the cyclization reaction is lowered by the hydrolysis of ether linkage of aryloxyketones back to β-resacetophenone.



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. The long range coupling between C3 – CH_3 and C2 – H in compounds **9a**, **9b** and **10** has been confirmed by ^1H – COSY spectra **(Figure 15)**.

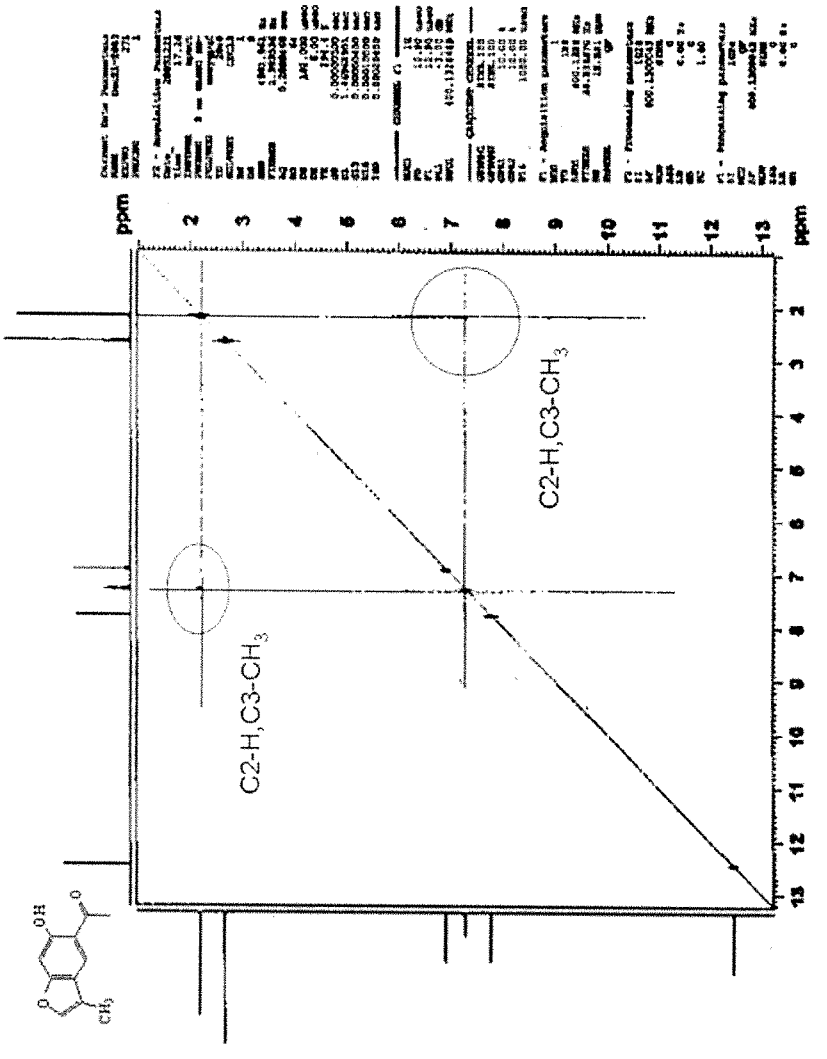


Figure 15: ^{1}H – COSY spectra of 1-(6-hydroxy-3-methylbenzofuran-5-yl)-ethanone **9a**.

2.3 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. The mass spectrum was obtained on Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS Mass Spectrometer (Model-016932) using Ion Spray source. NMR spectra were recorded on Bruker 300 MHz. spectrophotometer except where mentioned. Chemical shifts are given in ppm relative to tetramethylsilane on δ-scale with deuteriochloroform as solvent. Coupling constants are given in Hz. and relative peak areas were in agreement with all assignments.

General procedure for 2a, 2b, 3a, 3b, 4a and 4b.

2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone 3a.

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 and then poured in to ice water and solid obtained was collected by filteration. 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.

2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone 2a

This compound was obtained as white crystals, mp 136 °C (lit. [3] 136 °C); 45.3 %; Anal. Calcd.: $C_{14}H_{16}O_4$ (248.27): %C 67.72, %H 6.49; Found %C 68.02, %H 6.34; IR (KBr): ν_{max}, cm^{-1}: 3468, 3128, 1788, 1699, 1605, 1211, 1256, 1177; ^1H NMR (90 MHz, $CDCl_3$): 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). δ 1Cd, 1H, J=2.4 H_2 (C2-H)

2-(4-acetyl-3-hydroxy-2-methylphenoxy)-cyclohexanone 2b

This compound was obtained as white crystals, mp 125 °C (lit. [3] 125 °C); 60 %; Anal. Calcd.:$C_{15}H_{18}O_4$ (262.30): %C 68.68, %H 6.91; Found %C 68.44, %H 6.79; IR (KBr): ν_{max}, cm^{-1}: 3379, 3098, 1734, 1632, 1611, 1259, 1223, 1149; ^1H 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

This compound was obtained as white crystals, mp 132-133 °C; 52.9 %; Anal. Calcd.: $C_{13}H_{15}O_4$ (270.28): %C 71.10, %H 5.22; Found %C 70.86, %H 5.09; IR (KBr): ν_{max}, cm^{-1}: 3630, 3209, 2923, 1701, 1685, 1654, 1610, 1543, 1353, 1222, 726; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H, C4-$COCH_3$-), 5.33 (s, 2H, -OCH_2CO-), 6.4 (d, 1H, J_{meta} = 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_{ortho} = 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-methylphenoxy)-1-phenyl-ethanone 3b

This compound was obtained as white crystals, mp 124-125 °C; 56 %; Anal. Calcd.: $C_{14}H_{17}O_4$ (284.30): %C 71.81, %H 5.67; Found %C 71.86, %H 5.36; IR (KBr): ν_{max}, cm^{-1}: 3397, 3065, 2923, 1708, 1636, 1604, 1501, 1449, 1436, 1373, 1274, 1225, 1139, 764; ^1H 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} = 1.41 Hz, C2'-H and C6'-H), 12.76 (s, 1H, C3-OH chelated).

1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one 4a

This compound was obtained as white crystals, mp 102-103 °C; 74.53 %; Anal. Calcd.: $C_{11}H_{12}O_4$ (208.21): %C 63.45, %H 5.80; Found %C 63.19, %H 5.61; IR (KBr): ν_{max}, cm^{-1}: 3438, 3081, 2913, 1730, 1686, 1611, 1508, 1431, 1371, 1258; ^1H 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-methylphenoxy)-propan-2-one 4b

This compound was obtained as white crystals, mp 126-128 °C; 79 %; Anal. Calcd.: $C_{12}H_{14}O_4$ (222.23): %C 64.85, %H 6.34; Found %C 65.20, %H 6.31; IR (KBr): ν_{max}, cm^{-1}: 3417, 2928, 2902, 1718, 1626, 1498, 1417, 1360, 1282, 1227, 1135, 1112; ^1H 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).

General procedure for 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 distilled off *in vacuo* and the reaction mixture was poured into ice-hydrochloric acid and 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) that came out of the column was obtained as light greenish yellow crystals (0.086 g, 9.21 %) and characterized as 1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **8-angular isomer**.

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

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

1-(3-hydroxy-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone 5a-linear isomer

This compound was obtained as light greenish yellow crystals, mp 186-188 °C (lit. [3] 182 °C); 64.43 %; Anal. Calcd.: $C_{14}H_{14}O_3$ (230.26): %C 73.02, %H 6.12; Found %C 73.26, %H 6.45; IR (KBr): ν_{max}, cm^{-1}: 3448, 2930, 1638, 1616, 1458, 1143; ^1H 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

This compound was obtained as light greenish yellow crystals, mp 148 °C (lit. [3] 148 °C); 49.02 %; Anal. Calcd.: $C_{15}H_{16}O_3$ (244.28): %C 73.75, %H 6.60; Found %C 73.56, %H 6.39; IR (KBr): ν_{max}, cm^{-1}: 3458, 2923, 1649, 1613, 1467, 1136; ^1H 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-tetrahydrodibenzofuran-2-yl)-ethanone 6-angular isomer

This compound was obtained as light greenish yellow crystals, mp 107-108 °C; 26.84 %; Anal. Calcd.: $C_{14}H_{14}O_3$ (230.26): %C 73.02, %H 6.12; Found %C 73.26, %H 6.45; IR (KBr): ν_{max}, cm^{-1}: 3568, 2938, 1635, 1616, 1560, 1462, 1438, 1317, 1065, 781; ^1H 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-phenylbenzofuran-5-yl)-ethanone 7a-linear isomer

This compound was obtained as light greenish yellow crystals, mp 111-113 °C; 23.57 %; Anal. Calcd.: $C_{16}H_{12}O_3$ (252.26): %C 76.17, %H 4.79; Found %C 75.86, %H 4.67; IR (KBr): ν_{max}, cm^{-1}: 3506, 3105, 1637, 1615, 1584, 1461, 1371, 1329, 1252, 1165, 766; ^1H 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 26.78 (-$COCH_3$), 100.07 (C-3), 117.09 (C-7), 119.48 (C-3a), 122.30 (C-5), 123.16 (C-4'), 127.39 (C-3', C-5'), 127.93 (C-2', C-6'), 129.17 (C-4), 131.16 (C-1'), 141.73 (C-2), 160.29 (C-7a), 161.21 (C-6), 204.04 (>C=O).

1-(6-hydroxy-7-methyl-3-phenylbenzofuran-5-yl)-ethanone 7b

This compound was obtained as light greenish yellow crystals, mp 150-151 °C; 65.7 %; Anal. Calcd.: $C_{17}H_{14}O_3$ (266.29): %C 76.67, %H 5.29; Found %C 76.58, %H 5.09; IR (KBr): ν_{max}, cm^{-1}: 3448, 3107, 3056, 2925, 1632, 1585, 1423, 1374, 1329, 1261, 1104, 770; ^1H 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); lcms: m/z (relative intensity, 100%): 289.1 (9.52) M+23 (from Na^+), 267.2 (100) M+1 and 247.3 (9.52).

1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone 8-angular isomer

This compound was obtained as light greenish yellow crystals, mp 102-104 °C; 9.21 %; Anal. Calcd.: $C_{16}H_{12}O_3$ (252.26): %C 76.17, %H 4.79; Found %C 75.86, %H 4.67; IR (KBr): ν_{max}, cm^{-1}: 3568, 3128, 3099, 1615, 1490, 1475, 1370, 1268, 1050, 760; ^1H 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 26.92 (-$COCH_3$), 103.78 (C-3), 114.36 (C-7), 115.52 (C-3a), 124.01 (C-5), 127.46 (C-4'), 127.64 (C-3', C-5'), 128.08 (C-2', C-6'), 129.30 (C-6), 131.02 (C-1'), 141.49 (C-2), 160.10 (C-7a), 160.69 (C-4), 204.18 (>C=O).

1-(6-hydroxy-3-methylbenzofuran-5-yl)-ethanone 9a-linear isomer

This compound was obtained as light greenish yellow crystals, mp 132-133 °C; 29 %; Anal. Calcd.: $C_{11}H_{10}O_3$ (190.19): %C 69.46, %H 5.29; Found %C 69.78, %H 5.37; IR (KBr): ν_{max}, cm^{-1}: 3630, 3122, 2951, 1644, 1622, 1454, 1372, 1253, 1142, 1057, 792; ^1H 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 (q, 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-dimethylbenzofuran-5-yl)-ethanone 9b

This compound was obtained as light greenish yellow crystals, mp 99-100 °C; 55.07 %; Anal. Calcd.: $C_{12}H_{12}O_3$ (204.22): %C 70.57, %H 5.92; Found %C 70.78, %H 5.87; IR (KBr): $\nu_{max.}$ cm^{-1}: 3630, 3124, 2921, 1636, 1420, 1367, 1274, 1096, 793; ^1H 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-methylbenzofuran-5-yl)-ethanone 10-angular isomer

This compound was obtained as light greenish yellow crystals, mp 64-65 °C; 10.94 %; Anal. Calcd.: $C_{11}H_{10}O_3$ (190.19): %C 69.46, %H 5.29; Found %C 69.78, %H 5.37; IR (KBr): $\nu_{max.}$ cm^{-1}: 3630, 3110, 2934, 1616, 1597, 1478, 1426, 1373, 1299, 1234, 1048, 786; ^1H NMR (400 MHz, $CDCl_3$): 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).

2.4 Conclusions

- Although the carbanion generated *para* to the phenoxide ion is resonance stabilized, the formation of carbanion generated *ortho* to the phenoxide ion cannot be ruled out, which forms the basis of 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.

- The over all yield of the cyclization reaction is lowered by the hydrolysis of ether linkage of aryloxyketones back to β-resacetophenone.

- These *ortho*-hydroxy acetyl benzofurans,[22] have been used as starting material for the synthesis of various heterocyclic compounds in subsequent chapters.

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