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Lipase-Catalysed Regio- and Enantioselective Deacetylation of 2,4-Diacetoxyphenyl Alkyl Ketones

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Abstract—Porcine pancreatic lipase in tetrahydrofuran catalyses the deacetylation of 2,4-diacetoxyphenyl alkyl ketones in a highly regioselective fashion. The strategy of regioselective deacetylation of diacetoxyphenyl alkyl ketones has also resulted in the enantiomeric resolution of a racemic diacetoxyphenyl alkyl ketone, i.e. (±)-2,4-diacetoxyphenyl (1-ethyl)pentyl ketone, a precursor for the synthesis of an antifungal coumarin, 7-acetoxy-4-(1-ethyl)pentyl-3-phenyl-2*H*-1-benzopyran-2-one.

Introduction

Polyphenolics occur widely in nature and being the secondary metabolites of plants possess a variety of biological activities.[1–5] Polyhydroxyaryl alkyl ketones are versatile starting materials for the synthesis of different classes of natural polyphenolics, e.g. coumarins,[6] chalcones,[7] flavones,[8] flavanones,[9] chromones,[10] etc. Synthesis of these natural products requires selective protection/deprotection of the starting compounds leading to multistep synthetic protocols and hence overall low yields. Lipases are the most frequently used enzymes in organic synthesis[11,12] to carry out regioselective and/or enantioselective acylation of polyols[13] and synthesis of chiral intermediates and target molecules.[14] Recently, we have demonstrated that the lipases from porcine pancreas (PPL) and *Aspergillus* species[15] can be used for the regioselective de-esterification of peracetates of different classes of polyphenolics, e.g. acetophenones,[16,17] chalcones,[17] desoxybenzoins,[18] coumarins,[19] flavones,[19] and esters and amides of aromatic carboxylic acids.[20,21] Earlier studies had revealed that PPL in tetrahydrofuran (THF) is the best combination to carry out efficient, regioselective deacetylation on different polyphenolic peracetates. We wish to report herein the regioselective deacetylation of 2,4-diacetoxyphenyl alkyl ketones mediated by PPL in THF. This system also exhibited enantioselectivity while catalysing the selective deacetylation of one of two acetoxy functions of a racemic diacetoxyphenyl alkyl ketone, this perhaps is the first report of the recognition of phenolic acetoxy function by lipase as a remote handle for chiral discrimination.

Results and Discussion

The starting aryl alkyl ketones, i.e. 2,4-dihydroxyphenyl undecyl ketone (**1**), 2,4-dihydroxyphenyl pentadecyl ketone (**2**), 2,4-dihydroxyphenyl *iso*propyl ketone (**3**), 2,4-dihydroxyphenyl *iso*butyl ketone (**4**) and 2,4-dihydroxyphenyl (1-ethyl)pentyl ketone (**5**) were prepared by Friedel–Crafts acylation of resorcinol with the corresponding acids in the presence of fused $ZnCl_2$ at 150°C. The dihydroxy ketones **1**–**5** were characterised on the basis of their spectral analysis and comparison of their physical data with those reported in the literature.[22–24] The diacetates of compounds **1**–**5**, i.e. 2,4-diacetoxyphenyl undecyl ketone (**6**), 2,4-diacetoxyphenyl pentadecyl ketone (**7**), 2,4-diacetoxyphenyl *iso*propyl ketone (**8**), 2,4-diacetoxyphenyl *iso*butyl ketone (**9**) and 2,4-diacetoxyphenyl (1-ethyl)pentyl ketone (**10**) were prepared by the acetic anhydride/pyridine method in more than 80% yields. The new diacetoxy compounds **6** and **8**–**10** were identified from their spectral data (^{1}H NMR, ^{13}C NMR, IR, UV and MS, cf. Experimental), whereas the known diacetate **7** was characterised on the basis of its spectral data and comparison of physical data with those reported in literature.[25,26]

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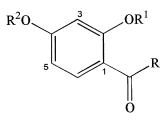
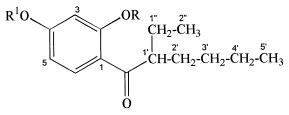
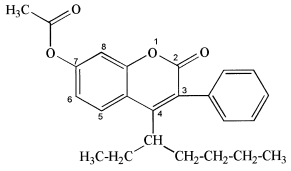




1. R = CH_3-$(CH_2)_{10}$; $R^1 = R^2 = H$
2. R = CH_3-$(CH_2)_{14}$; $R^1 = R^2 = H$
3. R = $(CH_3)_2CH$; $R^1 = R^2 = H$
4. R = $(CH_3)_2CH$-CH_2; $R^1 = R^2 = H$
6. R = CH_3-$(CH_2)_{10}$; $R^1 = R^2 = COCH_3$
7. R = CH_3-$(CH_2)_{14}$; $R^1 = R^2 = COCH_3$
8. R = $(CH_3)_2CH$; $R^1 = R^2 = COCH_3$
9. R = $(CH_3)_2CH$-CH_2; $R^1 = R^2 = COCH_3$
11. R = CH_3-$(CH_2)_{10}$; $R^1 = COCH_3$; $R^2 = H$
12. R = CH_3-$(CH_2)_{14}$; $R^1 = COCH_3$; $R^2 = H$
13. R = $(CH_3)_2CH$; $R^1 = COCH_3$; $R^2 = H$
14. R = $(CH_3)_2CH$-CH_2; $R^1 = COCH_3$; $R^2 = H$

5. $R = R^1 = H$
10. $R = R^1 = COCH_3$
15. R = $COCH_3$; $R^1 = H$



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The enzymatic deacetylation of 2,4-diacetoxyphenyl undecyl ketone (**6**) and 2,4-diacetoxyphenyl pentadecyl ketone (**7**) with PPL in THF gave exclusively the 2-acetoxy-4-hydroxyphenyl undecyl ketone (**11**) and 2-acetoxy-4-hydroxyphenyl pentadecyl ketone (**12**) in 45 and 60% yields, respectively (Table 1). In both cases the enzyme selectively deacetylates the acetoxy group *para* to the nuclear carbonyl group. The result that the *ortho* acetoxy function is inert to PPL-catalysed deacetylation is in conformity with our earlier findings.[16–19] Further, the results indicate that the increase in the lipophilicity of the substrate due to increase in chain length of the alkyl moiety does not affect the regioselectivity of PPL in THF. This is the first example of enzymatic de-esterification of long-chain alkyl (C_{11}-C_{15}) aryl ketones.

In addition to the selective deacetylation study on ketones **6** and **7** with straight chain alkyl groups, 2,4-diacetoxyphenyl *iso*propyl ketone (**8**) and 2,4-diacetoxyphenyl *iso*butyl ketone (**9**) were also incubated with PPL in THF to investigate the effect of branching in the alkyl chain on the regioselectivity of the enzymatic reaction. It was observed that the enzyme deacetylates the *para* acetoxy group of compounds **8** and **9** exclusively over the *ortho* acetoxy group in the same fashion leading to the formation of 2-acetoxy-4-hydroxyphenyl *iso*propyl ketone (**13**) and 2-acetoxy-4-hydroxyphenyl *iso*butyl ketone (**14**), respectively (Table 1). This result indicates that the different array of carbon atoms of the alkyl group does not affect the selectivity of the enzymatic reaction, i.e. the enzyme and alkyl group interaction does not play any crucial role in the de-esterification of phenolic acetoxy function. These results are in accordance with our earlier proposed hypothesis on the mechanism of action of PPL in THF involving a dynamic Schiff's base complex formation between the ε-amino group of the lysine residue in the active site of the PPL and the keto group directly attached to the benzenoid ring.[27] The formation of this complex causes the *ortho* acetoxy function to be embedded under the hydrophobic bulk of the active site of the enzyme and the serine-OH takes part in deacetylation of other more suitably placed acetoxy function(s) (*para* acetoxy function in the present study) in the same molecule.

In order to investigate the possibility of enantiomeric resolution through the de-esterification of the acetoxy function in the phenyl ring of racemic aryl alkyl ketones, 2,4-diacetoxyphenyl (1-ethyl)pentyl ketone (**10**) was incubated with PPL in THF and the reaction was stopped by filtering off the enzyme after about 45% conversion of the diacetate to monoacetate. It was observed that the enzyme selectively deacetylates the *para* acetoxy function over the *ortho* acetoxy function of the chiral ketone **10** as in the case of achiral ketones **6**–**9**. In addition to the regioselectivity in deacetylation of compound **10**, the lipase also showed enantioselectivity and deacetylated the *para* acetoxy function of one enantiomer leading to optically active (−)-2-acetoxy-4-hydroxyphenyl alkyl ketone **15** (Table 1). The detailed study of enantioselectivity of the enzymatic deacetylation is in progress. The products of all enzymatic deacetylation reactions, i.e. 2-acetoxy-4-hydroxyphenyl alkyl ketones **11**–**15** are new compounds and have been fully characterised on the basis of their spectral (^{1}H NMR, ^{13}C NMR, IR, UV and MS) analysis (cf. Experimental). The presence of hydroxyl function at the *para* position with respect to the nuclear carbonyl group in the compounds **11**–**15** was further supported by the observance of bathochromic shifts in their UV absorption maxima in the presence of NaOAc and no change in their λ_{max} values on the addition of $AlCl_3$ and HCl.[28] No deacetylation reaction was observed on any of the above substrates by carrying out the reactions under identical conditions but without addition of the lipase.

The enzymatic method developed for the selective deacetylation of polyacetoxyphenyl alkyl ketones may offer a significant advantage over the chemical method for selectively protecting the chelated hydroxyl function en route to the synthesis of bioactive polyphenolic compounds. This strategy of selective de-esterification has been applied fruitfully in the enantiomeric separation of a chiral ketone. This is the first example of resolution of a polyphenolic compound involving the phenolic acetoxy

Table 1. Regioselective deacetylation of diacetoxyphenyl alkyl ketones mediated by PPL in THF at 42–45°C in the presence of *n*-butanol[a]

Substrate	Time (h)	Product (% yield)
2,4-Diacetoxyphenyl undecyl ketone (**6**)	24	2-Acetoxy-4-hydroxyphenyl undecyl ketone (**11**)[29] (45)
2,4-Diacetoxyphenyl pentadecyl ketone (**7**)	24	2-Acetoxy-4-hydroxyphenyl pentadecyl ketone (**12**) (60)
2,4-Diacetoxyphenyl *iso*propyl ketone (**8**)	48	2-Acetoxy-4-hydroxyphenyl *iso*propyl ketone (**13**)[29] (55)
2,4-Diacetoxyphenyl *iso*butyl ketone (**9**)	48	2-Acetoxy-4-hydroxyphenyl *iso*butyl ketone (**14**)[29] (45)
2,4-Diacetoxyphenyl (1-ethyl)pentyl ketone (**10**)	48	(−)-2-Acetoxy-4-hydroxyphenyl (1-ethyl)pentyl ketone (**15**)[29] (45)

[a] All these reactions, when performed under identical conditions but without adding the lipase, did not yield any product.

function situated far away from the asymmetric centre as remote site for chiral recognition by the lipase. Further work in this direction is in progress in our laboratory. The chiral ketone (**10**) resolved herein is a precursor for the synthesis of a highly potent antifungal coumarin, 7-acetoxy-4-(1-ethyl)pentyl-3-phenyl-2*H*-1-benzopyran-2-one (**16**).[6] Since it is well established that the biological activities of two enantiomers are not the same, the strategy of enantiomeric separation via enzymatic deacetylation of an acetoxy function can be used to synthesise (*R*)- and (*S*)-forms of the active coumarin to study their comparative antifungal activity. Further, in the course of this enzymatic de-esterification study nine new compounds, i.e. **6** and **8**–**15**, have been obtained.

Experimental

Melting points were determined in a bath and are uncorrected. The UV and IR spectra were recorded on a Beckman DU-2 spectrophotometer and Shimadzu model 435 spectrophotometer, respectively. The ^{1}H NMR and the ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 and 62.9 MHz, respectively using TMS as an internal standard. The chemical shift values are on δ scale and the coupling constants (*J*) are in Hz. The EI mass spectra were recorded on a Jeol AX 505 W instrument at 70 eV. The enzyme, porcine pancreatic lipase (PPL) (Type-II), was purchased from Sigma Chemical Co. (USA) and used after keeping in vacuo over P_2O_5 for 12 h. The organic solvents used were redistilled and dried over molecular sieves (4 Å). Analytical thin layer chromatography (TLC) was performed on silica gel coated on 5×20 cm glass plates and/or Merck silica gel 60 F_{254} plates. Solvent systems used were A (benzene:ethyl acetate, 17:3) and B (benzene:ethyl acetate, 9:1). The developing agents were alcoholic $FeCl_3$ solution (3%) or iodine vapour. The diacetates **6**–**10** of dihydroxy ketones **1**–**5** were prepared in high yields by the acetic anhydride–pyridine method either at room temperature or by heating to 80°C.

General procedure of enzymatic deacetylation of 2,4-diacetoxyphenyl alkyl ketones 6–10

To a solution of 2,4-diacetoxyphenyl alkyl ketone (1–2 mmol) in dry THF (20–25 mL) containing *n*-butanol (5 molar equivalent), PPL (200–300 mg) was added and the suspension was stirred at 42–45°C. The progress of the reaction was monitored by TLC. The reaction was quenched on completion (in the case of chiral ketone **10** the reaction was quenched after about 45% conversion of the diacetate to a product) by filtering off the enzyme, solvent was removed under reduced pressure and the crude product was purified by column or preparative TLC and/or by crystallisation affording pure monoacetoxyphenyl alkyl ketones **11**–**15**. All diacetoxyphenyl alkyl ketones and their enzymatic reaction products were characterised on the basis of their spectroscopic data.

2,4-Diacetoxyphenyl undecyl ketone (6). Obtained as a white solid, mp 50–51°C; R_f 0.5 (solvent B); IR (nujol) cm^{-1}: 2990, 1780, 1700, 1615, 1190, 1010 and 900; UV (MeOH) nM: 259 and 273; ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, J=6.7 Hz, CH_3), 1.26 (16H, brs, $(CH_2)_8$), 1.66 (2H, m, CO−CH_2−CH_2), 2.28 and 2.31 (6H, 2s, 3H each, 2×OCOCH_3), 2.84 (2H, t, J=7.0 Hz, COCH_2), 6.94 (1H, d, J=2.2 Hz, C−3H), 7.07 (1H, dd, J=8.6 and 2.2 Hz, C−5H) and 7.78 (1H, d, J=8.6 Hz, C−6H); ^{13}C NMR ($CDCl_3$): δ 13.97 (CH_3), 20.92 (CH_3-CH_2), 22.55 and 23.98 (2×OCOCH_3), 28.72, 29.13, 29.20, 29.32, 29.37 and 29.49 (7×CH_2), 31.78 (COCH_2CH_2), 41.27 (COCH_2), 117.24 and 118.92 (C-3 and C-5), 128.34 (C-1), 130.58 (C-6), 149.76 (C-2), 153.54 (C-4), 168.20 and 168.87 (2×COCH$_3$) and 199.08 (CO); EIMS, *m*/*z* (% rel. int.): 376 [M$^+$] (22), 334 (20), 315 (60), 273 (90), 235 (85), 220 (40), 206 (25), 193 (90), 178 (85), 165 (65), 152 (95), 137 (100), 123 (22), 81 (10), 69 (10) and 55 (14).

2,4-Diacetoxyphenyl *iso*propyl ketone (8). Obtained as an oil; R_f 0.4 (solvent A); IR (film) cm^{-1}: 3000, 1780, 1690, 1620, 1250, 1190, 1140, 1110, 1010, 990, 910 and 820; UV (MeOH) nM: 259 and 276; ^{1}H NMR ($CDCl_3$): δ 1.13 (6H, d, J=6.8 Hz, CH(CH_3)$_2$), 2.27 and 2.29 (6H, 2s, 3H each, 2×OCOCH_3), 3.33 (1H, m, CH(CH$_3$)$_2$), 6.96 (1H, d, J=2.1 Hz, C−3H), 7.09 (1H, dd, J=8.5 and 2.1 Hz, C-5H) and 7.73 (1H, d, J=8.5 Hz, C-6H); ^{13}C NMR ($CDCl_3$): δ 18.47 (2×CH_3), 20.73 and 20.82 (2×OCOCH_3), 38.03 (CH), 117.28 and 118.86 (C-3 and C-5), 127.81 (C-1), 130.25 (C-6), 149.78 (C-2),153.27 (C-4), 168.23 and 168.86 (2×COCH$_3$) and 203.44 (CO); EIMS, *m*/*z* (% rel. int.): 264 [M$^+$] (7), 222 (80), 221 (90), 180 (95), 137 (100), 108 (15), 81 (25), 69 (10) and 53 (8).

2,4-Diacetoxyphenyl *iso*butyl ketone (9). Obtained as an oil; R_f 0.5 (solvent B); IR (film) cm^{-1}: 3000, 2930, 1780, 1690, 1610, 1590, 1500, 1420, 1300, 1250, 1120, 1010, 970, 910, 815 and 670; UV (MeOH) nM: 259 and 276; ^{1}H NMR ($CDCl_3$): δ 0.95 (6H, d, J=6.7 Hz, CH(CH_3)$_2$), 2.27 (1H, m, CH(CH$_3$)$_2$), 2.29 and 2.32 (6H, 2s, 3H each, 2×OCOCH_3) 2.72 (2H, d, J=6.8 Hz, CH_2), 6.94 (1H, d, J=2.2 Hz, C-3H), 7.08 (1H, dd, J=8.6 and 2.2 Hz, C-5H) and 7.77 (1H, d, J=8.6 Hz, C-6H); ^{13}C NMR ($CDCl_3$): δ 20.97 and 22.50 (2×CH_3 and 2×OCOCH_3), 24.68 (CH), 50.18 (COCH_2), 117.28 and 118.95 (C-3 and C-5), 128.64 (C-1), 130.59 (C-6), 149.69 (C-2), 153.49 (C4), 168.27 and 168.94 (2×COCH$_3$) and 198.89 (CO); EIMS, *m*/*z* (% rel. int.): 278 [M$^+$] (3), 236 (28), 221 (14). 194 (52), 179 (43), 152 (33), 137 (100) and 43 (21).

2,4-Diacetoxyphenyl (1-ethyl)pentyl ketone (10). Obtained as a viscous oil; R_f 0.45 (solvent B); IR (film) cm^{-1}: 3000, 2950, 1780, 1690, 1620, 1490, 1420, 1250, 1200, 1140, 1110, 1010, 905 and 820; UV (MeOH) nM: 259 and 275; ^{1}H NMR ($CDCl_3$): δ 0.87 (6H, m, 2×CH_3), 1.26 (4H, m, C-3′H and C-4′H), 1.53 (2H, m, C-2′H), 1.70 (2H, m, C-1″H), 2.29 and 2.31 (6H, 2s, 3H each, 2×OCOCH_3), 3.14 (1H, m, C-1′H), 6.95 (1H, d, J=2.2 Hz, C-3H), 7.08 (1H, dd, J=8.6 and 2.2 Hz, C-5H) and 7.73 (1H, d, J=8.6 Hz, C-6H); ^{13}C NMR ($CDCl_3$): δ 11.55 and 13.78 (C-5′ and C-2″), 20.82 and 20.96 (C-3′ and C-4′), 22.75 and 24.55 (2×OCOCH_3), 29.47 (C-2′), 30.78 (C-1″), 50.41 (C-1′), 117.55 and

118.89 (C-3 and C-5), 129.11 (C-1), 130.32(C-6), 149.86 (C-2), 153.29 (C-4), 168.26 and 168.93 (2×*C*OCH$_3$) and 203.13 (CO); EIMS, *m*/*z* (% rel. int.): 320 [M$^+$] (10), 278 (15), 263 (85), 236 (5), 234 (10), 221 (95), 178 (85), 137 (100), 108 (10), 81 (15), 69 (8) and 57 (25).

2-Acetoxy-4-hydroxyphenly undecyl ketone (11). Obtained as a light yellow solid, mp 104°C; R_f 0.5 (solvent A); IR (nujol) cm^{-1}: 3320, 2960, 1740, 1685, 1615, 1510, 1320, 1250, 1230, 1150, 1115, 1020, 955 and 910; UV (MeOH) nM: 313 and 326; + NaOAc: 322 and 353; ^{1}H NMR (CDCl$_3$): δ 0.87 (3H, t, *J* = 7.6 Hz, CH$_3$), 1.25 (16H, s, (CH$_2$)$_8$), 1.64 (2H, m, CO-CH$_2$-C*H*$_2$), 2.35 (3H, s, OCOCH$_3$), 2.81 (2H, t, *J* = 7.6 Hz, COCH$_2$), 6.48 (1H, d, *J* = 1.9 Hz, C-3H), 6.64 (1H, dd, *J* = 8.0 and 1.9 Hz, C-5H) and 7.70 (1H, d, *J* = 8.0 Hz, C-6H), ^{13}C NMR (CDCl$_3$): δ 14.08 (CH$_3$), 21.22 (CH$_3$*C*H$_2$) 22.65 (OCO*C*H$_3$), 24.44, 24.95, 26.04, 28.90, 29.23, 29.59 and 31.87 (8×CH$_2$), 40.78 (CO*C*H$_2$), 111.17 and 113.24 (C-3 and C-5), 122.49 (C-1), 132.24 (C-6), 151.02 (C-2), 160.74 (C-4), 170.44 (*C*OCH$_3$) and 199.27 (CO); EIMS, *m*/*z* (% rel. int.): 334 [M$^+$] (6), 316 (7), 292 (8), 274 (30), 194 (20), 165 (25), 152 (78), 137 (100), 123 (5) and 43 (13).

2-Acetoxy-4-hydroxyphenyl pentadecyl ketone (12). Obtained as a white solid, mp 105°C; R_f 0.5 (solvent A); IR (nujol) cm^{-1}: 3330, 2960, 1740, 1690, 1250, 1230, 1115 and 960; UV (MeOH) nM: 296; + NaOAc: 323 and 332; ^{1}H NMR (CDCl$_3$): δ 0.87 (3H, t, *J* = 7.6 Hz, CH$_3$), 1.26 (24H, s, (CH$_2$)$_{12}$), 1.63 (2H, m, CO−CH$_2$ −C*H*$_2$), 2.35 (3H, s, OCOCH$_3$), 2.81 (2H, t, *J* = 7.6 Hz, COCH$_2$), 6.49 (1H, d, *J* = 2.4 Hz, C-3H), 6.70 (1H, dd, *J* = 8.6 and 2.4 Hz, C-5H) and 7.72 (1H, d, *J* = 8.6 Hz, C-6H); ^{13}C NMR (CDCl$_3$): δ 14.09 (CH$_3$), 21.22 (CH$_3$-*C*H$_2$), 22.68(OCO*C*H$_3$), 24.42, 24.68, 29.22, 29.34, 29.42, 29.44, 29.58, 29.67, 31.91 and 33.95 (12×CH$_2$), 40.82 (CO*C*H$_2$), 111.18 and 113.20 (C-3 and C-5), 122.67 (C-1), 132.22 (C-6), 151.06 (C-2), 160.57 (C-4), 170.27 (*C*OCH$_3$) and 199.06 (CO); EIMS, *m*/*z* (% rel. int.): 392 (1), 390 [M$^+$] (missing), 279 (4), 256 (100), 227 (10), 214 (12), 213 (34), 199 (10), 185 (22), 171 (15), 157 (20), 149 (18), 129 (45), 115 (20), 97 (22), 85 (27), 73 (80), 60 (65), 57 (63), 43 (55) and 41 (37).

2-Acetoxy-4-hydroxyphenyl *iso*propyl ketone (13). Obtained as a semi solid; R_f 0.4 (solvent B); IR (nujol) cm^{-1}: 3400, 3000, 1750, 1680, 1615, 1585, 1525, 1320, 1220, 1125, 1110, 980, 960 and 810; UV (MeOH) nM: 323 and 334; + NaOAc: 323 and 346; ^{1}H NMR (CDCl$_3$): δ 1.15 (6H, d, *J* = 6.9 Hz, CH(C*H*$_3$)$_2$) 234 (3H, s, OCOCH$_3$), 3.37 (1H, m, C*H*(CH$_3$)$_2$) 6.50 (1H, d, *J* = 2.4 Hz, C-3H), 6.67 (1H, dd, *J* = 8.7 and 2.4 Hz, C-5H) and 7.67 (1H, d, *J* = 8.7 Hz, C-6H); ^{13}C NMR (CDCl$_3$): δ 18.97 (2×CH$_3$), 21.17 (OCO*C*H$_3$), 37.29 (CH), 111.37 and 113.28 (C-3 and C-5), 121.82 (C-1), 131.96 (C-6), 151.22 (C-2), 160.66 (C-4), 170.63 (*C*OCH$_3$) and 203.71 (CO); EIMS, *m*/*z* (% rel. int.): 222 [M$^+$] (5), 180 (17), 179 (20), 137 (100), 81 (8), 69 (5) and 43 (7).

2-Acetoxy-4-hydroxyphenyl *iso*butyl ketone (14). Obtained as an oil; R_f 0.4 (solvent B); IR (film) cm^{-1}: 3400, 3000, 1780, 1740, 1620, 1515, 1320, 1300, 1250, 1160, 1110, 1010, 970, 890, 850 and 810; UV (MeOH) nM: 320 and 325; + NaOAc: 323 and 345; ^{1}H NMR (CDCl$_3$): δ 0.95 (6H, d, *J* = 6.7 Hz, CH(C*H*$_3$)$_2$) 2.20 (1H, m, CH), 2.34 (3H, s, OCOCH$_3$), 2.70 (2H, d, *J* = 6.9 Hz, COCH$_2$), 6.50 (1H, d, *J* = 2.4 Hz, C-3H), 6.66 (1H, dd, *J* = 8.7 and 2.4 Hz, C-5H) and 7.67 (1H, d, *J* = 8.7 Hz, C-6H); ^{13}C NMR (CDCl$_3$): δ 21.21 and 22.62 (2×CH$_3$ and OCO*C*H$_3$), 25.29 (CH), 49.68 (CO*C*H$_2$), 111.20 and 113.28 (C-3 and C-5), 122.70 (C-1), 132.32 (C-6), 150.98 (C-2), 160.93 (C-4), 170.57 (*C*OCH$_3$) and 199.38 (CO); EIMS, *m*/*z* (% rel. int.): 236 [M$^+$] (17), 194 (25), 179 (26), 152 (21), 137 (100), 108 (3), 81 (5) and 43 (12).

2-Acetoxy-4-hydroxyphenyl (1-ethyl)pentyl ketone (15). Obtained as a viscous oil; R_f 0.4 (solvent A); $[\alpha]_D^{23}$ −6.6° (*c* 0.66, CHCl$_3$); IR (nujol) cm^{-1}: 3350, 3000, 1780, 1740, 1670, 1610, 1510, 1320, 1250, 1150, 1110, 1010, 900 and 820; UV (MeOH) nM: 259 and 296; + NaOAc: 323 and 337; ^{1}H NMR (CDCl$_3$): δ 0.83 (6H, m, 2×CH$_3$), 1.25 (4H, m, C-3′H and C-4′H), 1.50 (2H, m, C-2′H), 1.70 (2H, m, C-1″H), 2.34 (3H, s, OCOCH$_3$), 3.17 (1H, m, C-1′H), 6.47 (1H, d, *J* = 2.4 Hz, C-3H), 6.65 (1H, dd, *J* = 8.7 and 2.4 Hz, C-5H) and 7.65 (1H, d, *J* = 8.7 Hz, C-6H); ^{13}C NMR (CDCl$_3$): δ 11.70 and 13.80 (C-5′ and C-2″), 21.75, 22.75 and 25.11 (OCO*C*H$_3$, C-3′ and C-4′), 31.39 and 32.01 (C-2′ and C-1″), 49.45 (C-1′), 107.81 and 113.21 (C-3 and C-5), 123.07 (C-1), 131.89 (C-6), 150.93 (C-2), 160.79 (C-4), 170.72 (*C*OCH$_3$) and 203.79 (CO); EIMS, *m*/*z* (% rel. int.): 279 [M$^+$ + 1] (25), 278 [M$^+$] (6), 264 (5), 237 (85), 234 (10), 222 (95), 180 (98), 138 (95), 137 (100), 109 (30), 97 (45), 81 (65), 71 (70), 57 (90) and 43 (8).

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29. The ^{1}H NMR spectra of compounds **11**, **13**, **14** and **15** also revealed the presence of chelated hydroxyl group (between δ 12.50 and 13.00) together with expected sets of resonances due to corresponding 2-hydroxy-4-acetoxy ketones in 5–10% amounts of the 2-acetoxy ketones. This may be due to the migration of acetoxy function from *ortho* to *para* position between the time of isolation/purification and NMR spectral recording giving rise to thermodynamically stable *o*-hydroxy ketones. The possibility of formation of *o*-hydroxy products during the reaction is remote as no ferric positive products were observed on TLC while monitoring the progress of the reaction in all the above cases.