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An efficient regioselective synthesis of functionalized biphenyls via sequential reactions of aromatic aldehydes and β-keto esters or ketones

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ABSTRACT

Knoevenagel/Michael/Aldol reactions of aromatic aldehydes and β-keto esters/ketones in a sequential manner yielded intermediate cyclohexanones in good yields. The latter, on oxidative aromatization with iodine, afforded functionalized biphenyls with at least one phenolic hydroxyl in moderate to good yields.
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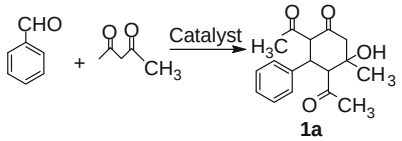
The phenyl group and polysubstituted benzenes are key structures of great utility in synthetic and natural product chemistry, medicinal chemistry and material sciences. Hydroxylated biphenyl derivatives occur in a large number of naturally occurring compounds, such as vancomycin, biphenomycin and ellagitannins.[1] Therefore, the preparation of polysubstituted aromatics in general and biphenyls in particular has been a fascinating area in organic syntheses.[2] Classical approaches are based on aromatic substitution, which introduces a substituent to the benzene ring. Synthetic methodologies based on this route have been developed including electrophilic[3] or nucleophilic substitutions[4], coupling reactions[5] catalyzed by transition metals and metallation–functionalization reactions.[6] However, these approaches have some drawbacks from the viewpoint of atom economy[7] or environmental concern. The methods that construct the aromatic backbone from acyclic precursors have received growing interest recently due to their short synthetic steps and selective nature.[8] These general features are common in the most useful benzannulation reactions involving different inter- and intramolecular cyclizations, cycloadditions and benzannulation reactions,[9–16] synthesis of acetophenones and methyl benzoates via the reaction of 1,3-dinitroalkanes with 2-ene-1,4-dione or 2-ene-4-oxo ester derivatives[17] and [4+2] annulation strategy from the Baylis–Hillman reaction.[18] Within a short span of time four different approaches were reported for the synthesis of biphenyls starting from Baylis–Hillman adducts.[19] Keeping in view the above points, we were prompted to synthesize functionalized biphenyls, starting from β-keto carbonyl compounds and aromatic aldehydes. These may serve as starting material for the synthesis of antitubercular agents in our ongoing programme. Our method of preparation is simple and economical as no special apparatus or chemical is required and is also devoid of any toxic byproducts during the reaction.

The reaction of a mixture of benzaldehyde and pentane-2,4-dione in the presence of piperidine (20 mol %) resulted in an intermediate cyclohexanone derivative **1a** in good yields (Scheme 1).

Compound **1a** was a diastereoisomeric mixture as evident from its spectral data (^{1}H and ^{13}C NMR) and used altogether in the next step. In order to screen the suitability of the base used for cyclohexanone preparation, we have carried out the above-mentioned



1a

Scheme 1.

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Table 1
Synthesis of intermediate cyclohexanone derivative **1a** under the influence of various catalysts

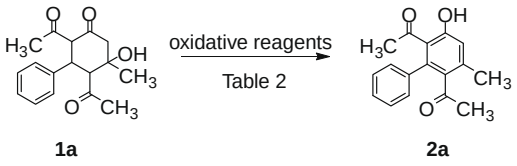
Base	Mol (%)	Reaction time (h)	Yield (%)
Piperidine	20	10	80
DABCO	20	12	70
DBU	20	12	63
Et_3N	20	15	62
K_2CO_3	20	15	40
Pyrrolidine	20	16	56

reaction with different organic and inorganic bases and the results are shown in Table 1.

Using the above reaction conditions (Table 1, entry 1), other compounds of the series viz. **1b–k** were similarly prepared from respective aldehydes and β-keto compounds as diastereoisomeric mixtures and were used as such for the next step of oxidative aromatization. It is important to mention here that the reaction of β-keto carbonyl compounds and aromatic aldehydes which results in most of these intermediate cyclohexanone derivatives has also been reported[21] earlier, and the compounds were fully characterized by spectroscopic techniques.[20]

The cyclohexanone derivative (**1a**) thus obtained was subjected to oxidative aromatization with iodine in methanol to give the biphenyl derivative (**2a**) in moderate yields (55%) (Scheme 2). A number of other reagents were also explored to carry out oxidative aromatization to the respective biphenyl derivative **2a** (Table 2). However, only iodine/methanol and DABCO/DMF gave the desired results. While a combination of I_2 in methanol afforded the maximum yield (55%), DABCO in DMF gave only a 50% yield of the compound in either the presence or the absence of oxygen. Therefore, only the iodine/ methanol combination was used for oxidative aromatization with other substrates.

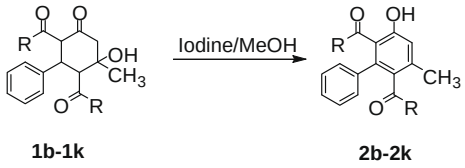
To see the scope of this method, different aromatic aldehydes and β-keto compounds were successfully used to get the intermediate cyclohexanone derivatives (**1b–k**) as diastereoisomeric mixtures which in turn were oxidized with iodine separately to give their respective biphenyl derivatives (**2b–k**) (Scheme 3). The results are depicted in Table 3.



Scheme 2.

Table 2
Optimization of the reaction condition for the conversion of **1a** to **2a**

Entry	Conditions	% Yield
1	DDQ(1.0 equiv), benzene, 80–120 °C, 24 h	No reaction
2	DDQ(5.0 equiv), toluene, 120–140 °C, 24 h	No reaction
3	DBU(10 mol %), THF, 80–100 °C, 72 h	No reaction
4	DBU(3.0 equiv), DMF, 120–140 °C, 12 h	20%
5	DABCO(5.0 equiv), DMF, 120–140 °C, 12 h	50%
6	I_2, toluene, 120–140 °C, 16 h	20%
7	I_2, isopropanol, 80–120 °C, 16 h	No reaction
8	I_2, propanol, 80–120 °C, 14 h	30%
9	I_2, ethanol, 80–120 °C, 14 h	20% and *trans*-esterification product
10	I_2, methanol, 80–120 °C, 12 h	55%



Scheme 3.

Structural elucidation of all the biphenyls so obtained was carried out by their detailed spectroscopic analysis.[22] The position of different substituents in the biphenyls (**2b–k**) was further confirmed by the NOESY experiment with one such compound (Fig. 2, **2c**), which shows the interaction of the C-5 proton of the penta-substituted benzene ring with the adjacent methyl protons of the same ring and no interaction with protons of the other aromatic ring. This clearly indicates the closeness of the C-5 proton to the methyl group at C-6 of the penta-substituted benzene ring.

A plausible mechanism for the formation of cyclohexanone derivatives during the reaction of aldehyde and β-keto ester or ketone has already been reported by Enders et al.[21] It involves the Knoevenagel condensation of an aldehyde with β-keto ester or ketone to give a Knoevenagel product (**A**), which undergoes

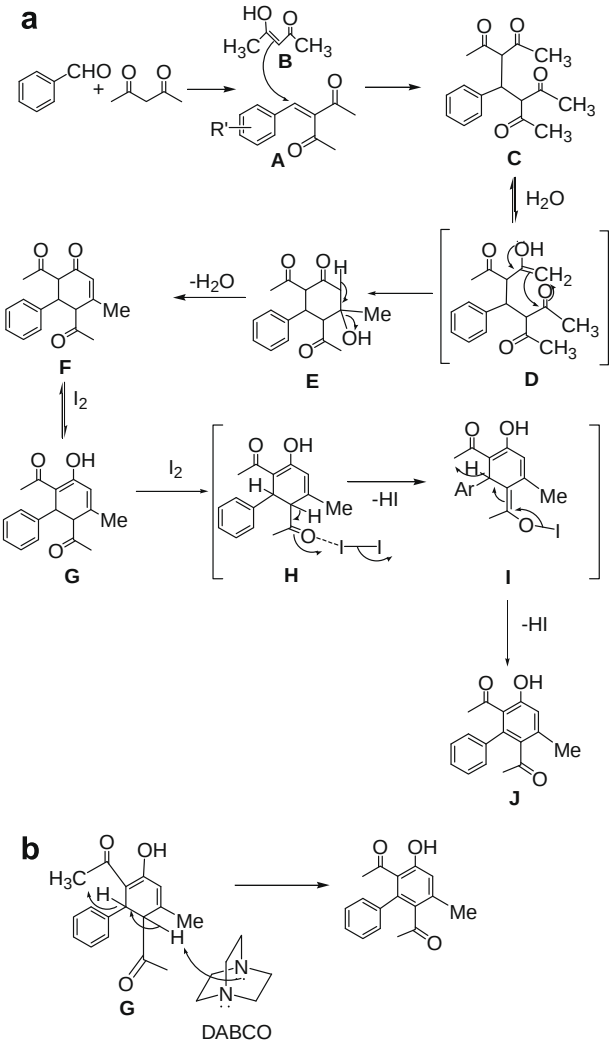
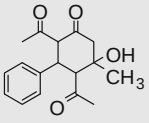
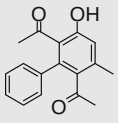
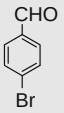
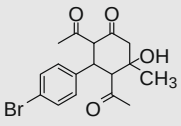
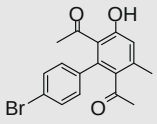
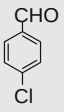
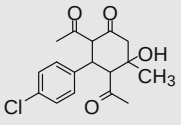
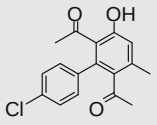
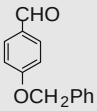
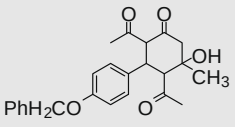
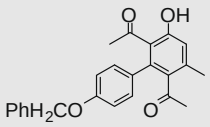
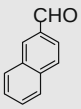
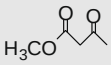
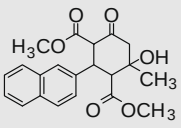
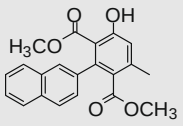
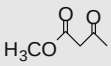
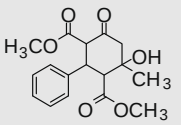
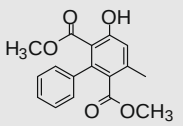
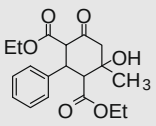
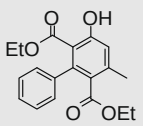
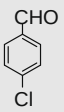
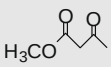
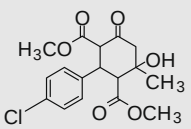
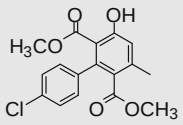
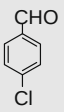
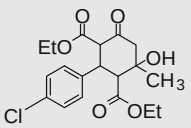
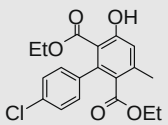
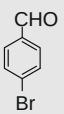
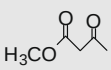
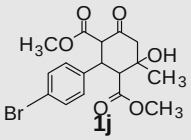
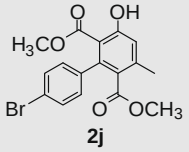


Figure 1.

Table 3
Synthesis of biphenyls via sequential reactions of different aromatic aldehydes and β-keto esters or ketones

Entry	Aromatic aldehyde	β-Keto compound	Cyclohexanone	% Yield	Biphenyl derivatives	Reaction time (h)	% Yield
1			 **1a**	82	 **2a**	12	55
2			 **1b**	61	 **2b**	12	55
3			 **1c**	75	 **2c**	11	55
4			 **1d**	72	 **2d**	12	55
5			 **1e**	69	 **2e**	14	40
6			 **1f**	75	 **2f**	14	45
7			 **1g**	66	 **2g**	14	45
8			 **1h**	65	 **2h**	14	45
9			 **1i**	69	 **2i**	14	50
10			 **1j**	70	 **2j**	14	40
11			**1k**	75	**2k**	12	60

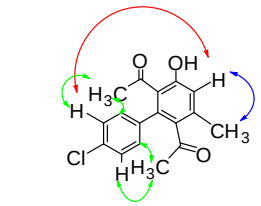


Figure 2.

a Michael addition of an active methylene compound via its enol form (**B**) to give an intermediate (**C**). The latter undergoes intramolecular aldol condensation in the presence of a base via enol (**D**) to give an intermediate cyclized aldol product (**E**), which, on dehydration, results in a cyclohexenone derivative (**F**), which exists as a tautomeric mixture with a predominance of the enol form (**G**) in the presence of iodine. Dehydration and enolization are facilitated by iodine as it acts as a Lewis acid. Dehydration in such compounds with iodine in methanol or other solvents is well known.[23,24] Finally, the removal of hydroiodic acid from intermediate (I) mediated by iodine results in the desired biphenyl derivatives (Fig. 1a). The final site of aromatization is also possible in the presence of the base, which may abstract a proton from carbon adjacent to the carbonyl carbon in intermediate G followed by rearrangement to more stable biphenyl derivatives (Fig. 1b).

In summary, we have developed a simple method for the preparation of functionalized biphenyls via domino Knoevenagel, Michael and Aldol reactions, followed by the oxidation of the intermediate cyclohexanone with iodine. The compounds are obtained in moderate yields. The application of these compounds in the designing of new biologically important molecules is underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.001.

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22. *Typical procedure for the synthesis of biphenyls and their physical data*: To a magnetically stirred solution of β keto compound (6.07 ml, 59.0 mmol) and benzaldehyde (3.0 ml, 29.5 mmol) in ethanol (5.0 mL), piperidine (0.583 ml, 5.9 mmol) was added, and the reaction mixture was stirred at ambient temperature. The stirring continued till the disappearance of aldehyde; the reaction mixture was filtered and the solid so obtained was washed with ethanol followed by water and *n*-hexane sequentially to get cyclized product **1a** as a colourless powder which was dried under a vacuum. The latter (**1a**, 1.0 g, 3.70 mmol) was undergoing oxidation with I_2 (1.88 g, 7.40 mmol) in MeOH under refluxing conditions. After refluxing at 70 °C for the given time (Table 3), the reaction mixture was evaporated under reduced pressure. The residue was extracted with ethylacetate and water followed by washing with a saturated sol. of sodium thiosulfate. The ethyl acetate layer was dried over sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography over SiO_2 (60–120 mesh) using EtOAc/*n*-hexane (2:8) as eluent to give the desired biphenyl (**2a**) as a light yellow solid. Mp 90–91 °C. IR (KBr): ν_{max} = 3436, 3019, 2363, 1693, 1631. ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.73 (s, 1H, OH), 7.45–7.42 (m, 3H, ArH), 7.30–7.26 (m, 2H, ArH), 6.85 (s, 1H, ArH), 2.26 (s, 3H, CH_3), 1.71 and 1.70 (two s, 6H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 206.5, 206.1 (2CO), 161.6, 141.2, 139.9, 139.5, 135.9 (5ArC), 130.6, 129.3, 129.2 (5ArCH), 119.8 (ArC), 119.4 (ArCH), 32.1 and 31.7 ($2COCH_3$), 20.5 (CH_3). MS (ESMS): *m/z*: 269 $[M+H]^+$. Elemental Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.08; H, 6.00. Compound **2b**: Light yellow solid. Mp 131–132 °C. IR (KBr): ν_{max} = 3779, 3345, 2922, 2143, 1592. ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.72 (s, 1H, OH), 7.61 (d, 2H, *J* = 8.4 Hz, ArH), 7.18 (d, 2H, *J* = 8.4 Hz, ArH), 6.87 (s, 1H, ArH), 2.25 (s, 3H, CH_3), 1.78 and 1.75 (two s, 6H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4,): δ 205.9, 205.8 (2CO), 161.7, 141.2, 138.3, 135.9 (5ArC), 132.5, 132.2 (4ArCH), 123.9 (ArC), 119.8 (ArCH), 119.6 (ArC), 32.3 and 32.0 ($2COCH_3$), 20.4 (CH_3). MS (ESI^+): *m/z*: 348 $[M+H]^+$. Elemental Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.35. Found: C, 58.79; H, 4.37. Compound **2c**: Light yellow solid. Mp 140–142 °C. IR (KBr): ν_{max} = 3852, 3430, 3020, 2924, 2361, 1685, 1634, 1596 ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.72 (s, 1H, OH), 7.45 (d, 2H, *J* = 8.4 Hz, ArH), 7.25 (d, 2H, *J* = 8.4 Hz, ArH), 6.86 (s, 1H, ArH), 2.25 (s, 3H, CH_3), 1.78 and 1.74 (two s, 6H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 206.1, 206.0 (2CO), 161.7, 141.3, 138.4, 137.8, 136.0, 135.8 (6ArC), 131.9, 129.5, 119.8 (5ArCH), 109.9 (ArC), 32.3, 32.0 ($2COCH_3$), 20.4 (CH_3).. MS (ESI^+): *m/z*: 303.5 $[M+H]^+$; Elemental Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99. Found: C, 67.42; H, 5.00. Compound **2d**: White solid. Mp 134–136 °C. IR (KBr): ν_{max} = 3427, 3021, 2923, 2363, 1632. ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.69 (s, 1H, OH), 7.45–7.33 (m, 5H, ArH), 7.20 (d, 2H, *J* = 8.6 Hz, ArH,), 7.04 (d, 2H, *J* = 8.6 Hz, ArH), 6.83 (s, 1H, ArH), 5.10 (s, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.74 (s, 6H, $2COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 206.7, 206.5 (2CO), 161.6, 159.8, 141.3, 139.8, 136.6, 136.0, 131.7, 120.1 (6ArC), 131.8, 129.0, 128.6, 127.9 (7ArCH), 120.1 (ArC),

119.1, 115.7 (3ArCH), 32.1, 31.8 ($2COCH_3$), 20.5 (CH_3). MS (ESI^+): *m/z*: 375 $[M+H]^+$. Elemental Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.97; H, 5.93. Compound **2e**: Light yellow solid. Mp 135–136 °C. IR (KBr): ν_{max} = 3781, 3697, 3410, 3021, 2929, 2359, 1725, 1666, 1595. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.03 (s, 1H, OH), 7.85–7.75 (m, 3H, ArH), 7.60 (s, 1H, ArH), 7.49–7.47 (m, 2H, ArH), 7.46–7.29 (m, 2H, ArH), 6.91 (s, 1H, ArH), 3.32 and 3.23 (two s, 3H, OCH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 171.2, 169.1 (2CO), 162.7, 142.4, 142.3, 138.2, 133.1, 132.6, 128.4 (7ArC), 128.3, 127.9, 127.8, 126.9, 126.7, 126.4, 126.3, 118.8 (8ArCH), 110.4 (ArC), 52.0, 51.8 ($2OCH_3$), 20.6 (CH_3). MS (ESI^+): *m/z*: 351 $[M+H]^+$. Elemental Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 71.96; H, 5.19. Compound **2f**: Light yellow oil. IR (neat): ν_{max} = 3692, 3389, 3021, 2360, 1724, 1667, 1578. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 10.97 (s, 1H, OH), 7.31–7.26 (m, 3H, ArH), 7.15–7.11 (m, 2H, ArH), 6.86 (s, 1H, ArH), 3.40 and 3.37 (two s, 6H, OCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 171.2, 169.2 (2CO), 162.4, 142.6, 142.2, 140.5 (5ArC), 128.7, 127.6, 127.3, 118.6 (6ArCH), 110.4 (ArC), 52.0, 51.9 ($2OCH_3$), 20.5 (CH_3). MS (ESI^+): *m/z*: 301 $[M+H]^+$. Elemental Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.97; H, 5.39. Compound **2g**: Light yellow solid. Mp 101–102 °C. IR (KBr): ν_{max} = 3782, 3021, 2360, 1723, 1664, 1596. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.11 (s, 1H, OH), 7.30–7.27 (m, 3H, ArH), 7.18–7.13 (m, 2H, ArH), 6.86 (s, 1H, ArH), 3.96–3.80 (m, 4H, OCH_2), 2.34 (s, 3H, CH_3), 0.90 and 0.71 (two t, *J* = 7.2 Hz, 3H, CH_3,). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 170.8, 168.7 (2CO), 162.5, 142.3, 142.0, 140.8 (4ArC), 129.0 (2ArCH), 128.6 (ArC), 127.5, 127.2, 118.6 (4ArCH), 110.5 (ArC), 61.2, 61.0 ($2OCH_2$), 20.5 (CH_3), 14.0, 13.3 ($2CH_3$). MS (ESI^+): *m/z*: 329 $[M+H]^+$. Elemental Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.47; H, 6.15. Compound **2h**: Light yellow oil. IR (neat): ν_{max} = 3781, 3425, 3020, 2360, 1724, 1607. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.02 (s, 1H, OH), 7.32 (d, 2H, *J* = 10.0 Hz, ArH), 7.11 (d, 2H, *J* = 10.0 Hz, ArH), 6.87 (s, 1H, ArH), 3.45 and 3.42 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 171.0, 168.9 (2CO), 162.6, 142.4, 141.1, 138.9, 133.5 (5ArC), 130.1(2ArCH), 128.5 (ArC), 127.8, 119.0 (3ArCH), 110.2 (ArC), 52.2, 52.0 ($2OCH_3$), 20.5 (CH_3). MS (ESI^+): *m/z*: 335.5 $[M+H]^+$. Elemental Anal. Calcd for $C_{17}H_{15}ClO_5$: C, 61.00; H, 4.52. Found: C, 59.98; H, 4.54. Compound **2i**: Light yellow oil. IR (neat): ν_{max} = 3781, 3410, 3021, 2360, 1721, 1663, 1599. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 11.17 (s, 1H, OH), 7.31 (d, 2H, *J* = 10.0 Hz, ArH), 7.14 (d, 2H, *J* = 10.0 Hz, ArH), 6.87 (s, 1H, ArH), 4.00–3.85 (m, 4H, OCH_2), 2.33 (s, 3H, CH_3), 0.94 (t, 3H, *J* = 7.2 Hz, CH_3), 0.76 (t, 3H, *J* = 7.2 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 170.2, 168.1 (2CO), 162.3, 141.9, 140.5, 138.7, 133.1 (6ArC), 130.0 (2ArCH), 128.1(ArC), 127.3, 118.6 (3ArCH), 109.8 (ArC), 61.1, 60.8, ($2OCH_2$), 20.0, 13.7, 12.9, ($3CH_3$). MS (ESMS): *m/z*: 363.5 $[M+H]^+$. Elemental Anal. Calcd for $C_{19}H_{19}ClO_5$: C, 62.90; H, 5.28. Found: C, 62.88; H, 5.29. Compound **2j**: Light yellow solid. Mp 95–96 °C. IR (KBr): ν_{max} = 3781, 3407, 3021, 2361, 1726 1599. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 10.97 (s, 1H, OH), 7.46 (d, 2H, *J* = 8.4 Hz, ArH), 7.03 (d, 2H, *J* = 8.4 Hz, ArH), 6.85 (s, 1H, ArH), 3.45 and 3.40 (two s, 3H, OCH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 170.9, 168.7 (2CO), 162.7, 142.4, 141.0, 139.5, (4ArC), 130.7, 130.5, (4ArCH), 128.3, 121.5(2ArC), 119.0 (ArCH), 110.1 (ArC), 52.1, 51.9 ($2OCH_3$), 20.5(CH_3). MS (ESI^+): *m/z*: 380 $[M+H]^+$. Elemental Anal. Calcd for $C_{17}H_{15}BrO_5$: C, 53.85; H, 3.99. Found: C, 53.84; H, 4.00. Compound **2k**: Light yellow solid. Mp 104–106 °C. IR (KBr): ν_{max} = 3450, 3020, 2924, 2359, 1631, 1523. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 12.50 (s, 1H, OH), 7.46–7.26 (m, 4H, ArH), 6.88 (s, 1H, ArH), 2.25 (s, 3H, CH_3), 1.84 and 1.78 (two s, 6H, $COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 205.3, 205.2 (2CO), 162.9, 141.8, 138.3, 136.6, 135.9, 134.6 (6ArC), 133.0, 130.9, 130.4, 127.7, 120.8 (5ArCH), 118.7 (ArC), 31.6, 31.2 ($2COCH_3$), 20.6 (CH_3). MS (ESI^+): *m/z*: 303.5 $[M+H]^+$; Elemental Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99. Found: C, 67.42; H, 5.00.*Intermediate* **G**: (Fig. 1a): Light yellow solid. Mp 75–80 °C. IR (KBr): ν_{max} = 3626, 3020, 2925, 2361, 1521, 1425. ^1H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 16.2 (s, 1H, OH), 7.42–7.09 (m, 4H, ArH), 6.14 (s, 1H, H-5), 4.76 (s, 1H, H-2), 3.22 (s, 1H, H-1), 2.36 (s, 3H, CH_3), 1.84 and 1.83 (two s, 6H, $COCH_3$). MS (ESI^+): *m/z*: 305 $[M+H]^+$; Elemental Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.00; H, 5.62. Found: C, 67.42; H, 5.00.

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