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Domino [Pd]-Catalysis: One-pot Synthesis of Isobenzofuran-1(*3H*)-ones

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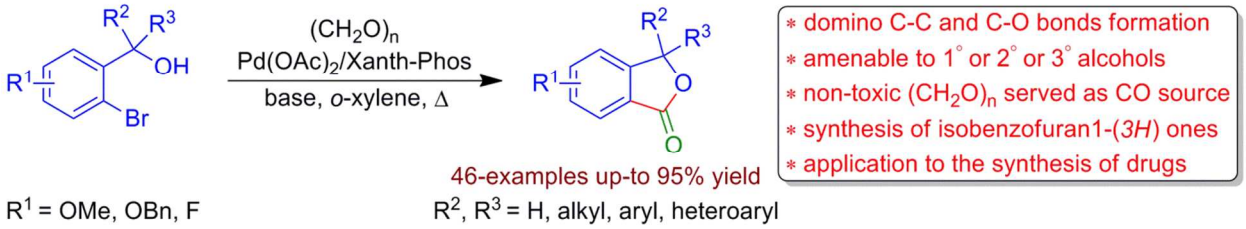
Abstract:

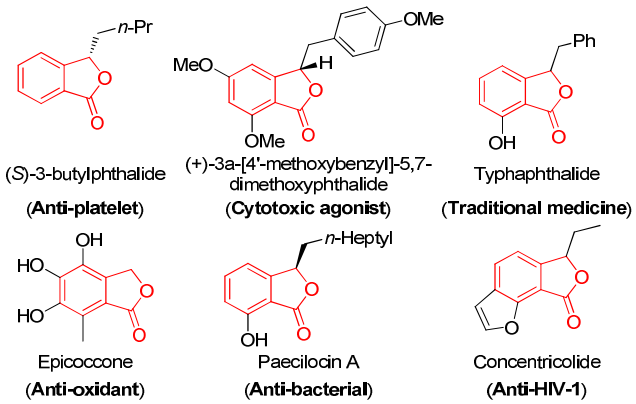


An efficient domino [Pd]-catalysis for the synthesis of isobenzofuran-1(*3H*)-ones, is presented. The strategy showed broad substrate scope and amenable to *ortho*-bromobenzyl tertiary/secondary/primary alcohols. Significantly, the method was applied to the synthesis of anti-platelet drug *n*-butyl phthalide and cytotoxic agonist 3a-[4'-methoxylbenzyl]-5,7-dimethoxyphthalide.

Introduction

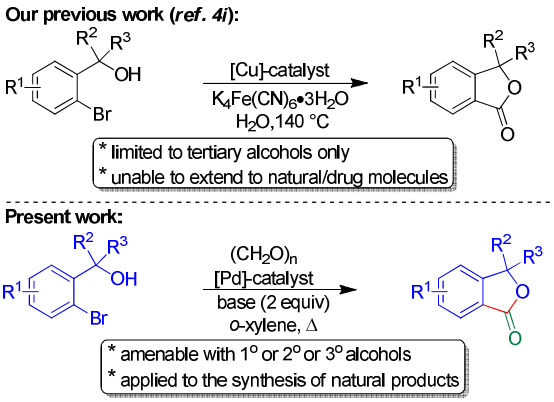
Isobenzofuranones (phthalides) are emerging class of compounds in medicinal chemistry. Phthalides are found in many naturally occurring compounds that exhibit interesting biological activities (Figure 1).[1] They are proven to be useful in the treatment of circulatory and heart diseases.[1a] Phthalides also act as key structural units in organic synthesis, particularly, in the synthesis of functionalized anthracenes, naphthalenes, and naphthacene based natural products.[2] As a result, their synthesis has attracted much attention from organic as well as pharmaceutical chemists.[3] In this context, reasonable attempts have been made on the synthesis of isobenzofuran-1(*3H*)-ones.[4] Nevertheless, some of reported methods are still lacking the simplicity and generality.[5]

Figure 1: Biologically active natural isobenzofuranones.



Domino processes are extremely useful in organic synthesis as they can be performed under simple one-step conditions, thus eliminating tedious isolation and purification of intermediate products(s). Therefore, such processes are ultimately useful in saving energy and minimizing the waste formation.[6] Transition metal catalysis has been proven to be an efficient tool for the development of new synthetic methods, especially in the creation of new C-C and C-X heteroatom bonds with increasing molecular complexity.[7] In continuation of our on-going research interests in domino processes using transition metal-catalysis,[8] we have reported an efficient [Cu]-catalyzed domino one-pot method for the synthesis of isobenzofuran-1(*3H*)-ones using nontoxic $K_4[Fe(CN)_6]$ as the source of CO, under environmentally benign conditions (Scheme 1).[4i] However, this process was limited to the *ortho*-bromobenzyl tertiary alcohols. Though carbon monoxide (CO)[9] is an inexpensive and readily available carbonylation source, its toxicity and the requirement of high pressure operations limits its synthetic applications. CO remains significant to the advancement of carbonylation reactions.[10] On these grounds, Skrydstrup et al. reported CO-free carbonylations using in-situ generated carbon monoxide.[11] Also, the research group of Beller et al. developed new methods using CO surrogates, such as, aryl formates and $[Mo(CO)_6]$.[12] However, compared to all CO surrogates used in previous reports, paraformaldehyde was found superior, because it is cheap, stable and also ease of use. As a result, the research group of Beller disclosed an elegant approach demonstrating the palladium-catalyzed reductive carbonylations and alkoxycarbonylations using

paraformaldehyde as an external CO source.[13a] Subsequently, Xiao-Feng Wu et al. disclosed paraformaldehyde mediated carbonylations for the synthesis of benzoxazinones.[13b] Paraformaldehyde had also been used in Rh-catalyzed CO-free carbonylations of alkynes.[14] However, paraformaldehyde has not been properly explored for the [Pd]-catalyzed carbonylation.[13,15] In continuation of our research interests on domino transition metal-catalysis, herein, we report an efficient [Pd]-catalyzed concise approach for the syntheses of phthalides, using paraformaldehyde as the source of CO (Scheme 1). Significantly, the strategy was extended to the synthesis of isobenzofuranone based natural products, from simple *ortho*-bromobenzyl alcohols. Remarkably, unlike our previous report,[4i] the present strategy was proved to be much versatile, as it was amenable to primary/secondary/tertiary *ortho*-bromobenzyl alcohols and also applied to the synthesis of natural/drug products. To the best of our knowledge, there are no reports on the synthesis of isobenzofuran-1(*3H*)-ones using paraformaldehyde as carbonylating agent.



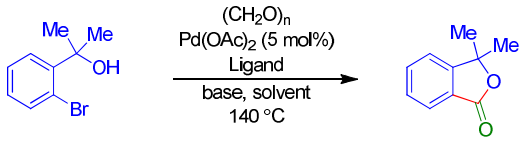
Scheme 1: Present study and our previous approach for the synthesis of isobenzofuranones.

Result and Discussions

To initiate the synthetic study, we have chosen *ortho*-bromobenzyl tertiary alcohol **1aa** as a model. Thus the reaction was carried out with paraformaldehyde as CO source in the presence of $Pd(OAc)_2$, base KOAc in H_2O, and with PPh_3 and Xanth-Phos, respectively. The desired product **2aa** was formed, albeit in poor to moderate yields (Table 1, entries 1 to 2). The reaction was then conducted under different

solvents using Xanth-Phos as the ligand (Table 1, entries 3 to 10). Gratifyingly, *ortho*-xylene was found as the best solvent, afforded the product **2aa** in excellent yield (Table 1, entry 6). Other varying conditions, such as with different bases in *ortho*-xylene were found inferior to the conditions of entry 6 (Table 1, entries 11-18).

Table 1: Screening conditions for the synthesis of **2aa**.



1aa **2aa**

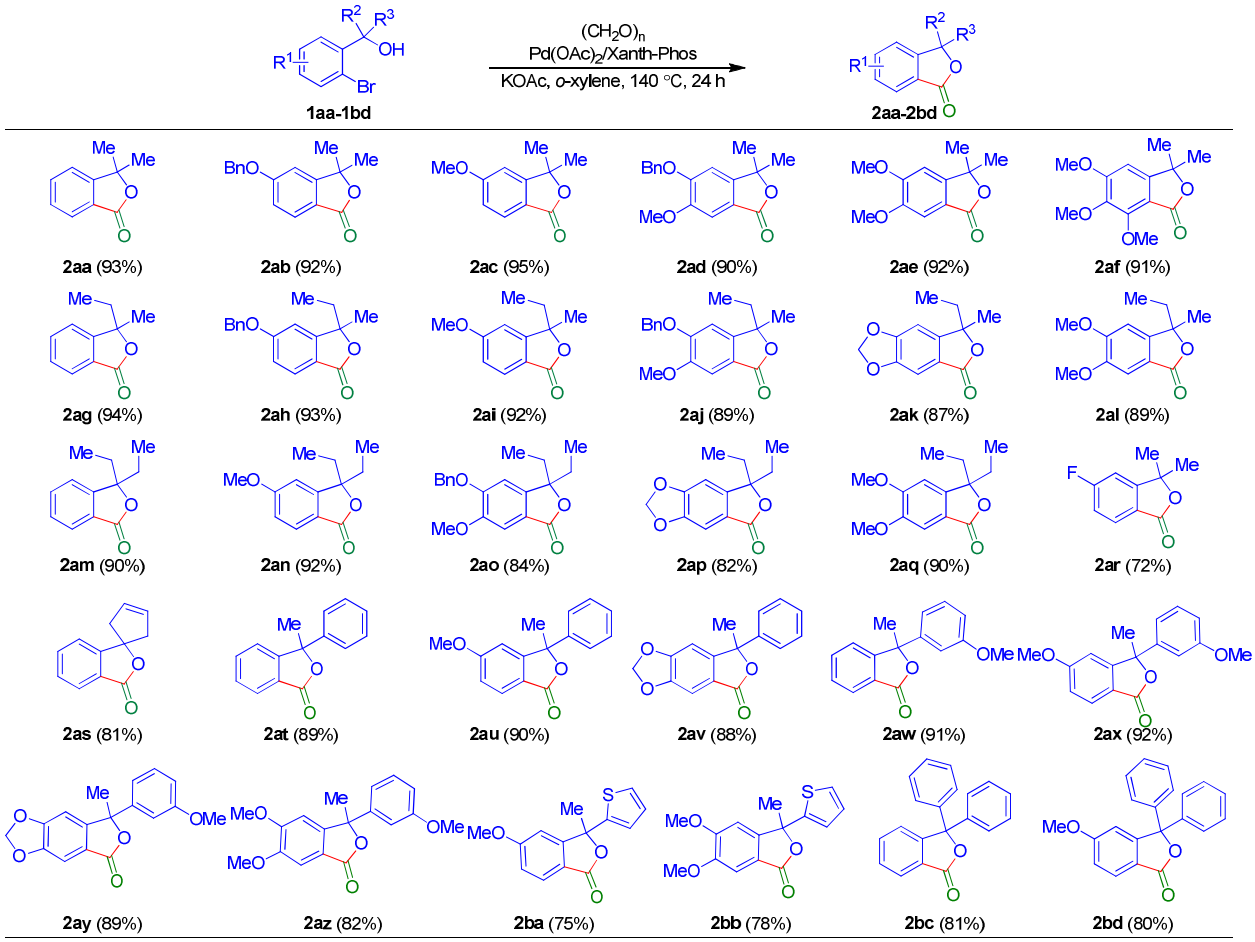
Entry[a]	Ligand (10 mol %)	Solvent	Base (2 equiv)	**2aa** (%)[b]
3	PPh_3	H_2O	KOAc	36[d]
2	Xant-Phos	H_2O	KOAc	51[d]
3	Xant-Phos	DMA	KOAc	–[c]
4	Xant-Phos	DMSO	KOAc	45[d]
5	Xant-Phos	DMF	KOAc	41[d]
6	**Xant-Phos**	***o*-xylene**	**KOAc**	**93**
7	Xant-Phos	dioxane	KOAc	42[d]
8	Xant-Phos	CH_3CN	KOAc	60
9	Xant-Phos	*p*-xylene	KOAc	87
10	Xant-Phos	DCE	KOAc	–[c]
11	Xant-Phos	*o*-xylene	K_3PO_4	71
12	Xant-Phos	*o*-xylene	K_2CO_3	61
13	Xant-Phos	*o*-xylene	Na_2CO_3	–[c]
14	Xant-Phos	*o*-xylene	NaOAc	66
15	Xant-Phos	*o*-xylene	Cs_2CO_3	48[d]
16	Xant-Phos	*o*-xylene	NEt_3	46[d]
17	Xant-Phos	*o*-xylene	$HNEt_2$	48[d]
18	Xant-Phos	*o*-xylene	DMED	26[d]

[a] All reactions were carried out on (0.5 mol) scale of **1aa** and (2.5 mol) of $(CH_2O)_n$ and solvent (0.5 mL). [b] Isolated yields of chromatographically pure products. [c] Starting material was recovered. [d] Starting material **1aa** was recovered along with the product **2aa**.

With the optimized conditions in hand (Table 1, entry 6), to check the scope and generality of the method, the reaction was explored with other *ortho*-bromobenzyl tertiary alcohols **1aa**–**1bd**. To our delight, the reaction showed broad substrate scope and furnished the benzofuranones **2aa–2bd**, in very good to excellent yields (Table 2). Interestingly, the reaction was successful with di-alkyl substituents (entries **2aa**-**2ar**), cyclic tertiary alcohol **1as** (entry **2as**), alkyl-aryl groups (entries **2at**-**2az**), alkyl-heteroaryl groups (entries **2ba** & **2ab**) as well as diaryl substituents (entries **2bc** & **2bd**). Remarkably, the reaction

showed broad functional group tolerance, such as, donating groups on the *ortho*-bromoarene moiety (compare entries **2ae** vs **2ar**).

Table 2: Syntheses of isobenzofuranones **2aa-2bd** from *ortho*-bromobenzyl tertiary alcohols **1aa-1bd**.[a,b]

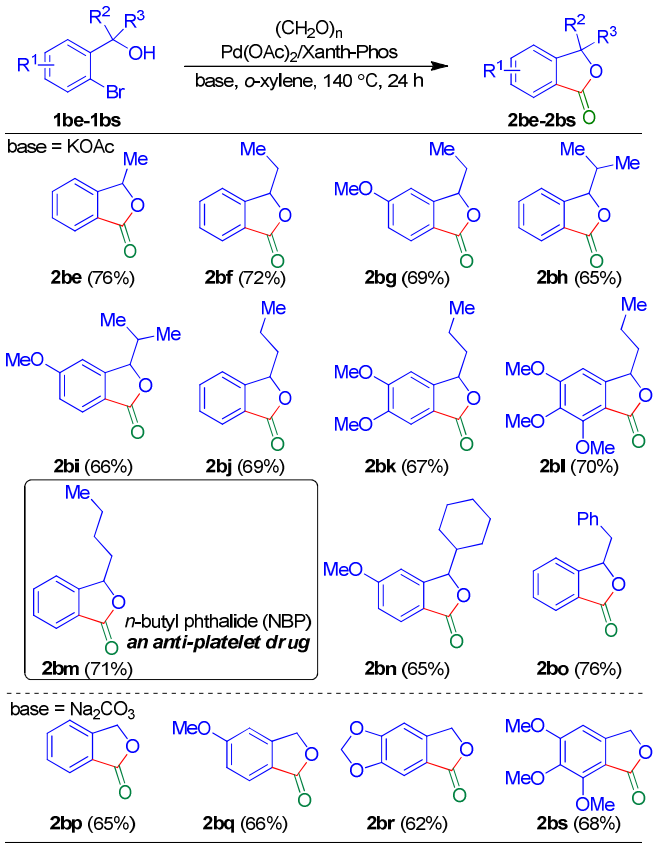


[a]Reaction conditions: **1aa**−**1bd** (0.50 mmol), $(CH_2O)_n$ (2.5 mmol), $Pd(OAc)_2$ (5 mol%), Xanth-Phos (10 mol%), KOAc (2 equiv) in 0.5 mL *ortho*-xylene, at 140 °C for 24 h. [b]Isolated yields of chromatographically pure products.

After successful synthesis of benzofuranones **2aa–2bd** (Table 2) with a quaternary carbon atom, to demonstrate the scope and generality of the method, we planned to explore the reaction with *ortho*-bromobenzyl secondary alcohols. Thus, the reaction was performed with *ortho*-bromobenzyl secondary alcohols **1be–1bo**, under standard conditions. Gratifyingly, the reaction was quite successful and furnished the desired lactones **2be–2bo**, in fair to good yields (Table 3). Notably, the reaction proceeded smoothly with different alkyl substituents on the carbinol center (Table 3, entries **2be–2bo**). Significantly,

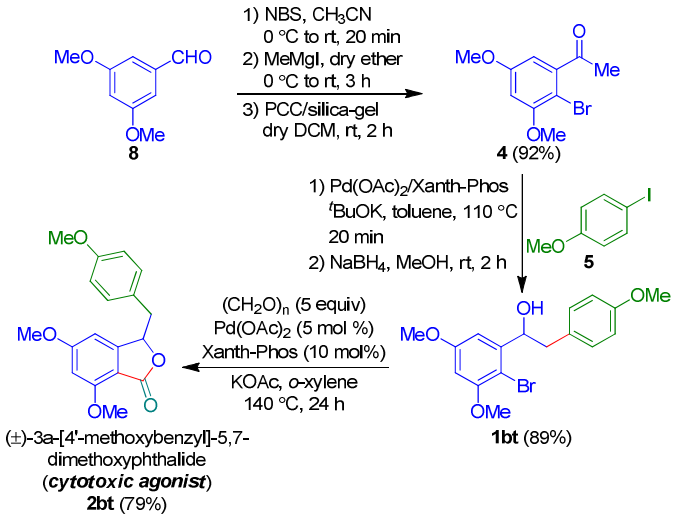
this strategy was successfully applied to the synthesis of an anti-platelet drug *n*-butylphthalide (NBP)[16] **2bm**. Notably, the reaction was also amenable with cyclic alkyl as well as benzyl groups (entries **2bn** & **2bo**). Most significantly, demonstrating the utility of the current method over previous reported methods, primary alcohols **1bp**–**1bs** were successfully cyclized to give the desired lactones **2bp**–**2bs** (Table 3). It is worth noting that the reaction with primary alcohols **1bp**–**1bs** was not successful with the base KOAc. However, to our delight, changing the base from KOAc to Na_2CO_3, gave the desired lactones in good yields (Table 3). It is worth noting that in contrast to our previous report,[4i] which was limited to *ortho*-bromobenzyl tertiary alcohols, the present protocol amenable to the *ortho*-bromobenzyl secondary/primary alcohols.

Table 3: Syntheses of isobenzofuranones **2be-2bs** from **1be-1bs**.[a,b,c,d]



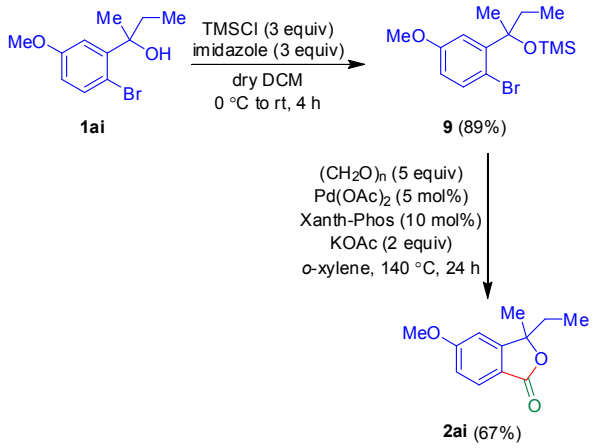
[a]Reaction conditions: **1be−1bo/1bp−1bs** (0.50 mmol), $(CH_2O)_n$ (2.5 mmol), $Pd(OAc)_2$ (5 mol%), Xanth-Phos (10 mol%), base (2 equiv) in 0.5 mL *ortho*-xylene, at 140 °C for 24 h. [b]For **1be−1bo**; KOAc was used as the base. [c]In case of **1bp−1bs**; Na_2CO_3 was used as the base. [d]Isolated yields of chromatographically pure products.

To demonstrate the utility of the domino [Pd]-catalysis process, we applied the strategy to the synthesis of a cytotoxic antagonist, 3a-[4'-methoxybenzyl]5,7-dimethoxypthalide **2bt**[17] (Scheme 2). Therefore, the required secondary alcohol **1bt** was synthesized using established conditions as depicted in Scheme 2. Thus, NBS promoted bromination, methylmagnesium iodide addition followed by oxidation protocol, afforded the acetophenone **4** (Scheme 2). The [Pd]-catalyzed α-arylation of acetophenone **4** and reduction of the resultant ketone **3** with $NaBH_4$, furnished the alcohol **1bt** (Scheme 2). Finally, the key [Pd]-catalyzed lactonization of **1bt** was amenable and furnished the cytotoxic agonist 3a-[4'-methoxybenzyl]-5,7-dimethoxyphthalide **2bt** in its racemic form, in good yield (Scheme 2).



Scheme 2: Synthesis of cytotoxic agonist 3a-[4'-methoxybenzyl]-5,7-dimethoxyphthalide **2bt**.

Interestingly, when we attempted the reaction of silyl ether **9**, the benzofuranone **2ai** was obtained in 67% yield (Scheme 3). This may be probably due to in-situ deprotection of TMS-group which might feasible under basic reaction conditions and then usual [Pd]-catalyzed lactonization process.



Scheme 3: Formation of isobenzofuranone **2ai** from TMS ether **9**.

Further the chemical structure of **2** was confirmed by single crystal X-ray diffraction analysis of **2bq** and **2br** as shown in Figure 2 (see; SI for X-ray data of **2bq** & **2br**).

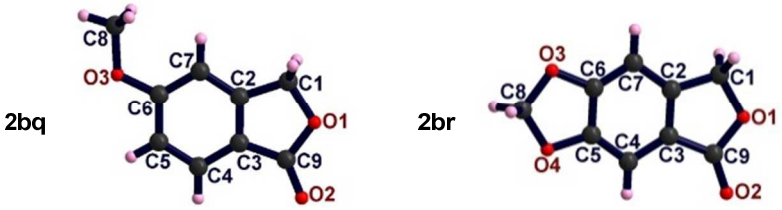
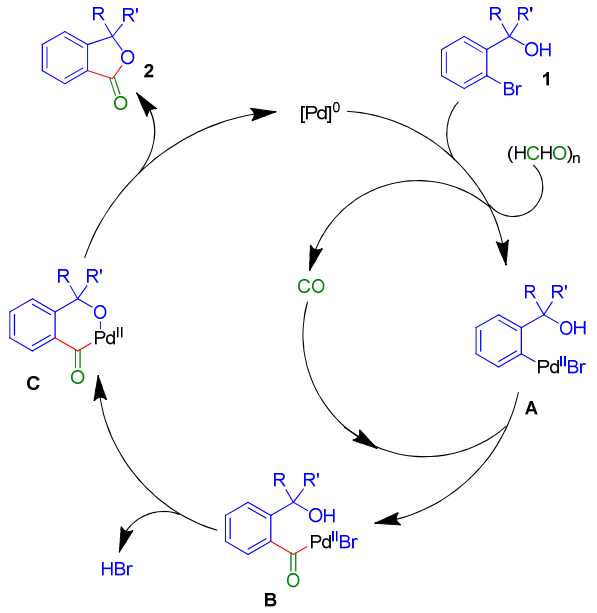


Figure 2: X-ray crystal structures for products **2bq** and **2br**.

On the basis of established reports using paraformaldehyde as CO-free carbonylating agent and their experimental studies probed to understand the mechanistic path,[13] the plausible reaction mechanism for the formation of isobenzofuranones **2** is shown in Scheme 4. Thus, the initial oxidative insertion of Pd^0-catalyst into the C-Br bond of **1** generates the aryl-Pd^{II} species **A**. Then the migratory insertion of CO on **A** furnishes new Pd^{II}-species **B**. Subsequent intramolecular nucleophilic chelation of the OH group and concomitant elimination of HBr leads to the six membered Pd^{II}-intermediate **C**. Finally, reductive elimination of **C** through the formation of Pd^0- catalyst, gives isobenzofuranones **2**, thus completes the catalytic cycle. Presumably, CO might be formed via an independent path by the reaction of paraformdaldehyde with the [Pd]-catalyst.



Scheme 4: Plausible reaction path for the formation of **2**.

Conclusions

In conclusion, we have described an efficient domino [Pd]-catalysis for one-pot synthesis of isobenzofuran-1(3*H*)-ones. Unlike our previous report, the present strategy showed broad substrate scope and amenable to *ortho*-bromobenzyl tertiary/secondary/primary alcohols. Significantly, the method was also successfully applied to the synthesis of anti-platelet drug *n*-butyl phthalide and cytotoxic agonist 3a-[4'-methoxylbenzyl]-5,7-dimethoxyphthalide.

Experimental Section

General Considerations

IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H=0.00 ppm) or $CHCl_3$ (δ_H=7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C=77.00 ppm (central line of triplet)]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra

and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^1H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui =quintet, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by ^1H, ^{13}C CPD (carbon proton decoupled), and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Benzaldehydes, immidazole, aryl halides, methyl iodide, bromoethane, Mg metal and Na_2SO_4 were commercially available (local made) used without further purification, $Pd(OAc)_2$, PPh_3, Xanth-Phos, $(HCHO)_n$, Cs_2CO_3, KOAc, K_3PO_4, K_2CO_3, Na_2CO_3, NaOAc, NEt_3, $NHEt_2$ and DMED (dimethyl ethelene diamine) purchased from commercial source. All dry solvents were used, diethyl ether, toluene, Dioxane and THF were dried over sodium metal, DCM, DMA, CH_3CN, DCE and DMF were dried over calcium hydride.

All the solvents (diethyl ether, THF, DCM, DMF, *para*-xylene, DMSO and *ortho*-xylene) are commercially available (LR Grade). All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 °C was used. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

General Procedure (For the synthesis of lactones) (**2aa-2bt**):

In an oven-dried Schlenk tube 2-bromobenzyl alcohols **1** (0.50 mmol), paraformaldehyde (2.50 mmol), $Pd(OAc)_2$ (0.02 mmol), Xanth-Phos (0.05 mmol), base [(1.00 mmol) for primary alcohols Na_2CO_3 for tertiary and secondary alcohols KOAc] and solvent (*otho*-xylene) (0.5 mL) were added. The resulting reaction mixture was stirred at 140 °C for 24 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool to room temperature, then diluted with (10 mL) ethyl acetate and saturated NH_4Cl was added fallowed by extraction with ethyl acetate. The

organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent furnished the lactone **2**.

1-(2-bromo-3,5-dimethoxyphenyl)ethanol (**1bu**):

To a cold (0 °C), magnetically stirred solution of a bromobenzaldehyde **7f** (1.29 mmol) in dry dry ether (2 mL) was added methylmagnesium iodide (2.59 mmol) [prepared from magnesium (2.59 mmol) and methyl iodide (2.59 mmol) in 10 mL of dry ether]. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then poured into saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude secondary alcohol **1bu** was purified by column chromatography on silica using petroleum ether/ethyl acetate (85:15) as eluent and isolated as white colored solid 89% yield (339 mg): mp 76–78 °C; [TLC (petroleum ether/ethyl acetate 8:2, R_f(**7f**)=0.40, R_f(**1bu**)=0.30, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=6.79 (d, *J*=2.9 Hz, 1H), 6.40 (d, *J*=2.4 Hz, 1H), 5.27 (q, *J*=6.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.00 (br. s, 1H), 1.45 (d, *J*=6.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=160.1 (C_q), 156.4 (C_q), 146.8 (C_q), 102.4 (CH), 101.8 (C_q), 98.8 (C_q), 69.4 (CH), 56.3 (CH_3), 55.6 (CH_3), 23.4 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3320, 2932, 1490, 1345, 1286, 1181, 1050, 962, 758, 689 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{10}H_{14}BrO_3]^+$=$[M+H]^+$: 261.0121; found: 261.0125.

1-(2-bromophenyl)butan-1-ol (**1bj**):

To a cold (0 °C), magnetically stirred solution of a bromobenzaldehyde **7a** (2.70 mmol) in dry THF (2 mL) was added propylmagnesium bromide (5.40 mmol), [prepared from magnesium (5.40 mmol) and 1-bromopropane (5.40 mmol) and a catalytic amount of iodine in 10 mL of dry THF]. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then poured into saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude secondary alcohol **1bj** was purified by column chromatography on

silica using petroleum ether/ethyl acetate (92:08) as eluent and isolated as colorless liquid 78% yield (486 mg); [TLC (petroleum ether/ethyl acetate 9:1, R_f(**7a**)=0.50, R_f(**1bj**)=0.40, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.58-7.40 (m, 2H), 7.31 (dd, *J*=7.3 and 7.3 Hz, 1H), 7.10 (dd, *J*=7.8 and 7.3 Hz, 1H), 5.10-5.00 (m, 1H), 2.23 (br. s, 1H), 1.80-1.60 (m, 2H), 1.58-1.35 (m, 2H), 0.95 (t, *J*=7.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=143.9 (C_q), 132.5 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 121.9 (C_q), 72.6 (CH), 39.8 (CH_2), 18.9 (CH_2), 13.8 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3320, 2930, 1496, 1341, 1286, 1181, 1050, 962, 750, 687 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{10}H_{13}OBrNa]^+$=$[M+Na]^+$: 251.0042; found: 251.0046.

1-(2-bromo-3,4,5-trimethoxyphenyl)butan-1-ol (**1bl**):

To a cold (0 °C), magnetically stirred solution of a bromobenzaldehyde **7d** (2.0 mmol) in dry THF (2 mL) was added propylmagnesium bromide (4.0 mmol) [prepared from magnesium (4.0 mmol) and 1-bromopropane (4.0 mmol) and a catalytic amount of iodine in 10 mL of dry THF]. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then poured into saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude secondary alcohol **1bl** was purified by column chromatography on silica using petroleum ether/ethyl acetate (75:25) as eluent and isolated as brown colored viscous liquid 85% yield (549 mg); [TLC (petroleum ether/ethyl acetate 7:3, R_f(**7d**)=0.60, R_f(**1bl**)=0.50, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=6.91 (s, 1H), 5.08-5.00 (m, 1H), 3.84 (s, 3H), 3.83 (s, 2 x 3H), 2.28 (br. s, 1H), 1.80-1.30 (m, 4H), 0.93 (t, *J*=7.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=152.9 (C_q), 150.2 (C_q), 141.9 (C_q), 139.8 (C_q), 107.9 (C_q), 105.7 (CH), 72.5 (CH), 61.0 (CH_3), 60.9 (CH_3), 56.0 (CH_3), 39.8 (CH_2), 19.0 (CH_2), 13.8 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3349, 2930, 1493, 1355, 1276, 1181, 1052, 962, 759, 679 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{13}H_{19}O_4BrNa]^+$=$[M+Na]^+$: 341.0359; found: 341.0350.

1-(2-bromo-3,5-dimethoxyphenyl)ethanone (**4**):

To a magnetically stirred solution of the secondary alcohol **1bu** (1.21 mmol) in dry CH_2Cl_2 (10 mL) was added a homogeneous mixture (1:1) of PCC (3.64 mmol) and silica gel. The resulting reaction mixture was stirred at room temperature for 2 h. Filtration of the reaction mixture through a short silica column with excess CH_2Cl_2 furnished the pure ketone **4** and isolated as pale yellow colored oil 94% yield (281 mg); [TLC (petroleum ether/ethyl acetate 8:2, R_f(**1bu**)=0.40, R_f(**4**)=0.50, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=6.51 (d, *J*=2.9 Hz, 1H), 6.46 (d, *J*=2.4 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=202.4 (C_q), 160.0 (C_q), 156.9 (C_q), 144.3 (C_q), 103.8 (CH), 101.1 (CH), 98.9 (C_q), 56.5 (CH_3), 55.7 (CH_3), 30.6 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2939, 1689, 1546, 1460, 1355, 1280, 1171, 1055, 962, 758, 680 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{10}H_{11}BrO_3Na]^+$=$[M+Na]^+$: 280.9784; found: 280.9789.

1-(2-bromo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (**3**):

In an oven -dried Schlenk tube under nitrogen atmosphere were added p-iodoanisole **5** (1.34 mmol), *ortho*-bromoacetophenone **4** (1.22 mmol), $Pd(OAc)_2$ (2 mol%), xantphos (4 mol%) and ^{t}BuOK (2.44 mmol) followed by addition of dry toluene (4 mL). The resulting reaction mixture was stirred at 80 °C for 20 min. Progress of the reaction was monitored by TLC until the reaction is completed. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude ketone **3** was purified by column chromatography on silica using petroleum ether/ethyl acetate (85:15) as eluent and isolated as pale yellow colored liquid 66% yield (296 mg); [TLC (petroleum ether/ethyl acetate 8:2, R_f(**4**)=0.60, R_f(**3**)=0.50, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.15 (d,

J=8.8 Hz, 2H), 6.84 (d, *J*=8.8 Hz, 2H), 6.49 (d, *J*=2.9 Hz, 1H), 6.27 (d, *J*=2.9 Hz, 1H), 4.13 (s, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=202.7 (C_q), 159.9 (C_q), 158.7 (C_q), 156.7 (C_q), 144.0 (C_q), 130.8 (CH), 125.4 (C_q), 114.0 (CH), 103.9 (CH), 100.8 (CH), 98.6 (C_q), 56.4 (CH_3), 55.7 (CH_3), 55.2 (CH_3), 48.8 (CH_2) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2938, 1679, 1550, 1453, 1340, 1280, 1176, 1050, 962, 756, 680 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{17}H_{18}BrO_4]^+$=$[M+H]^+$: 365.0383; found: 365.0378.

1-(2-bromo-3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol (**1bt**):

To a magnetically stirred solution of the aryl ketone **3** (0.54 mmol) in dry MeOH (10 mL) was added a $NaBH_4$ (1.08 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. It was then poured into saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude secondary alcohol **1** was purified by column chromatography on silica using petroleum ether/ethyl acetate (85:15) as eluent and isolated as colorless oil 92% yield (186 mg); [TLC (petroleum ether/ethyl acetate 8:2, R_f(**3**)=0.50, R_f(**1bt**)=0.30, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.24 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 6.79 (d, *J*=2.9 Hz, 1H), 6.43 (d, *J*=2.9 Hz, 1H), 5.28-5.20 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.20-3.10 (m, 1H), 2.65-2.55 (m, 1H), 2.11 (br. s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=160.0 (C_q), 158.4 (C_q), 158.3 (C_q), 145.0 (C_q), 130.4 (CH), 130.3 (C_q), 113.9 (CH), 102.8 (CH), 101.9 (C_q) 98.9 (C_q), 74.3 (CH), 56.3 (CH_3), 55.5 (CH_3), 55.2 (CH_3), 43.1 (CH_2) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3329, 2930, 1530, 1443, 1350, 1240, 1178, 1050, 945, 750, 676 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{17}H_{19}BrO_4Na]^+$=$[M+Na]^+$: 389.0359; found: 389.0364.

[(2-(2-bromo-5-methoxyphenyl)butan-2-yl)oxy]trimethylsilane (**9**)

To a magnetically stirred solution of the tertiary alcohol **1ai** (0.39 mmol) and imidazole (3 mmol) in dry CH_2Cl_2 (6 mL) trimethylsilyl chloride (3 mmol) was added at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction mixture was quenched and extracted with CH_2Cl_2 (3 × 15 mL). The collected organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:03) as eluent furnished trimethyl silylether **9** in 89% yield (114 mg) as colorless viscous liquid: [TLC (petroleum ether/ethyl acetate 9:1, R_f(**1ai**)=0.40, R_f(**9**)=0.60, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz) δ=7.42 (d, 1H, *J*=8.3 Hz), 7.33 (d, 1H, *J*=3.4 Hz), 6.61 (dd, 1H, *J*=8.3 and 3.4 Hz), 3.78 (s, 3H), 2.55-2.40 (m, 1H), 1.85-1.71 (m, 1H), 1.76 (s, 3H), 0.64 (t, 3H, *J*=7.3 Hz), 0.18 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ=158.5 (C_q), 147.1 (C_q), 135.5 (CH), 115.5 (CH), 113.1 (CH), 110.1 (C_q), 79.4 (C_q), 55.2 (CH_3), 33.5 (CH_2), 28.0 (CH_3), 8.5 (CH_3), 2.4 (3 × CH_3) ppm; IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max}=2958, 1568, 1460, 1372, 1249, 1170, 1056, 835, 752, 673 cm^{-1}; HR-MS (ESI+) m/z calculated for $[C_{14}H_{23}{}^{81}BrNaSiO_2]^+$=$[M+Na]^+$ 353.0543, found 353.0540.

3-ethyl-5-methoxyisobenzofuran-1(*3H*)-one (**2bg**):

This compound was prepared according to the GP and using petroleum ether/ethyl acetate (85:15) as eluent isolated as brown colored viscous liquid 72% yield (75 mg): [TLC (petroleum ether/ethyl acetate 8:2, R_f(**1bg**)=0.50, R_f(**2bg**)=0.40, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.76 (d, *J*=8.3 Hz, 1H), 6.99 (dd, *J*=1.9 and 8.3 Hz, 1H), 6.93 (d, *J*=1.9 Hz, 1H), 5.33 (dd, *J*=4.4 and 7.3 Hz, 1H), 3.87 (s, 3H), 2.00-2.15 (m, 1H), 1.85-1.70 (m, 1H), 0.96 (t, *J*=7.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.4 (C_q), 164.6 (C_q), 152.4 (C_q), 127.1 (CH), 118.5 (C_q), 116.2 (CH), 105.8 (CH), 81.5 (C_q), 55.8 (CH_3), 27.6 (CH_2), 8.7 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2947, 1750, 1598,

1465, 1338, 1282, 1190, 1054, 965, 741, 692 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{11}H_{13}O_3]^+=[M+H]^+$: 193.0859; found: 193.0853.

3-isopropyl-5-methoxyisobenzofuran-1(*3H*)-one (**2bi**):

This compound was prepared according to the GP and using petroleum ether/ethyl acetate (85:15) as eluent isolated as colorless oil 66% yield (68 mg): [TLC (petroleum ether/ethyl acetate 8:2, R_f(**1bi**)=0.50, R_f(**2bi**)=0.40, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.88 (d, *J*=7.8 Hz, 1H), 7.65 (dd, *J*=1.5 and 7.8 Hz, 1H), 7.51 (dd, *J*=7.3 and 7.3 Hz, 1H), 7.43 (d, *J*=7.8 Hz, 1H), 5.36 (d, *J*=3.9 Hz, 1H), 2.35-2.20 (m, 1H), 1.11 (d, *J*=7.3 Hz, 3H), 0.79 (d, *J*=6.8 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.8 (C_q), 148.8 (C_q), 133.8 (CH), 129.0 (CH), 126.7 (C_q), 125.6 (CH), 122.1 (CH), 85.6 (C_q), 32.3 (2C, 2 × CH), 18.6 (CH_3), 15.6 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2941, 1752, 1588, 1460, 1348, 1280, 1191, 1052, 966, 740, 690 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{12}H_{14}O_3Na]^+=[M+Na]^+$: 229.0835; found: 229.0830.

5,6-dimethoxy-3-propylisobenzofuran-1(*3H*)-one (**2bk**):

This compound was prepared according to the GP and using petroleum ether/ethyl acetate (80:20) as eluent isolated as white colored solid 69% yield (82 mg): mp 82–84 °C; [TLC (petroleum ether/ethyl acetate 7:3, R_f(**1bk**)=0.40, R_f(**2bk**)=0.30, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.26 (s, 1H), 6.80 (s, 1H), 5.30-5.43 (m, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 1.90-2.07 (m, 1H), 1.60-1.76 (m, 1H), 1.40-1.58 (m, 2H), 0.96 (t, *J*=7.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=171.0 (C_q), 154.7 (C_q), 150.3 (C_q), 144.7 (C_q), 118.0 (C_q), 106.1 (CH), 103.0 (CH), 80.6 (C_q), 56.4 (CH_3), 56.3 (CH_3), 36.9 (CH_2), 18.2 (CH_2), 13.8 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2939, 1749, 1582, 1463, 1345,

1286, 1181, 1050, 962, 758, 689 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{13}H_{17}O_4]^+$=$[M+H]^+$: 237.1121; found: 237.1115.

5,6,7-trimethoxy-3-propylisobenzofuran-1(*3H*)-one (**2bl**):

This compound was prepared according to the GP and using petroleum ether/ethyl acetate (75:25) as eluent isolated as colorless oil 67% yield (89 mg): [TLC (petroleum ether/ethyl acetate 6:4, R_f(**1bl**)=0.50, R_f(**2bl**)=0.40, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=6.56 (s, 1H), 5.20-5.30 (m, 1H), 4.11 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 1.88-2.00 (m 1H), 1.60-1.75 (m 1H), 1.40-1.55 (m 2H), 0.95 (t, *J*=7.3 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=168.2 (C_q), 159.5 (C_q), 152.3 (C_q), 148.0 (C_q), 141.6 (C_q), 110.6 (C_q), 99.1 (CH), 79.8 (CH), 62.3 (CH_3), 61.4 (CH_3), 56.4 (CH_3), 37.0 (CH_2), 18.2 (CH_2), 13.8 (CH_3) ppm. IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2943, 1742, 1578, 1462, 1341, 1282, 1187, 1054, 960, 757, 687 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{14}H_{18}O_5Na]^+$=$[M+Na]^+$: 289.1046; found: 289.1038.

3-cyclohexyl-5-methoxyisobenzofuran-1(*3H*)-one (**2bn**):

This compound was prepared according to the GP and using petroleum ether/ethyl acetate (85:15) as eluent isolated as white colored solid 66% yield (81 mg): mp 200–202 °C; [TLC (petroleum ether/ethyl acetate 8:2, R_f(**1bn**)=0.50, R_f(**2bn**)=0.40, UV detection]. ^{1}H NMR ($CDCl_3$ 400 MHz): δ=7.76 (d, *J*=8.3 Hz, 1H), 6.99 (dd, *J*=2.0 and 8.3 Hz, 1H), 6.84 (d, *J*=2.0 Hz, 1H), 5.24 (d, *J*=3.4 Hz, 1H), 3.89 (s, 3H), 1.55-1.95 (m, 5H), 1.00-1.40 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=170.6 (C_q), 164.5 (C_q), 151.5 (C_q), 127.1 (CH), 119.0 (C_q), 115.9 (CH), 106.4 (CH), 84.6 (CH), 55.8 (CH_3), 42.0 (CH), 29.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.6 (CH_2) ppm. IR

(MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2940, 1739, 1568, 1469, 1340, 1282, 1187, 1054, 964, 752, 686 cm^{-1}. HR-MS (ESI+) m/z calculated for $[C_{15}H_{18}O_3K]^+$=$[M+K]^+$: 285.0888; found: 285.0882.

Associated Content:

Supporting Information

The X-ray crystallographic data (CIF files) for **2bq** and **2br** and copies of NMR spectra reported. This material is available free of charge via the Internet at **http://pubs.acs.org**.

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