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Preparation of tetrahydro-1*H*-xanthen-1-one and chromen-1-one derivatives *via* a Morita-Baylis-Hillman/oxa-Michael/elimination cascade

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We dedicate this work to Professor José Manuel Riveros for his outstanding contributions to Brazilian chemistry

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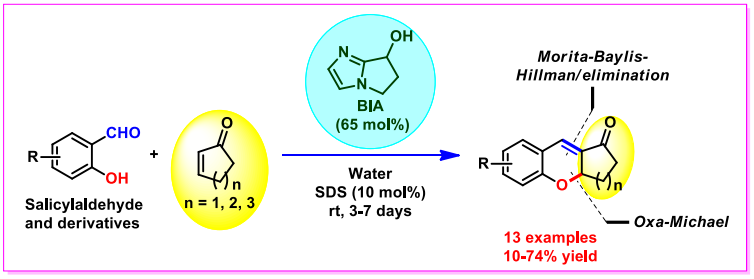
Abstract

The Morita-Baylis-Hillman (MBH) reaction is a carbon-carbon bond forming transformation between an electrophile, typically an aldehyde, and an activated olefin. MBH adducts obtained from 2-hydroxy-benzaldehydes and cyclic enones are potential substrates for the synthesis of xanthenone and chromenone derivatives. In this work, we investigated conditions to obtain tetrahydro-1*H*-xanthen-1-ones and chromen-1-ones directly *via* a Morita-Baylis-Hillman/oxa-Michael/elimination cascade catalyzed by a bifunctional, bicyclic imidazolyl alcohol (BIA), which proved to be an effective catalyst for this transformation. The reactions were performed at room temperature in water to give the products in 10-74 % yield.



Keywords: Morita-Baylis-Hillman, imidazole, reactions in water, xanthenone, chromenone, organocatalysis

Introduction

The Morita-Baylis-Hillman (MBH) reaction is a carbon-carbon bond forming transformation between an electrophile and an activated olefin, typically catalysed by a Lewis base, to form most commonly α-methylene-β-hydroxycarbonyl species.[1–3] Due to the high functionalization degree of the adducts obtained from MBH reactions, they have been employed in the synthesis of a variety of heterocycles.[4–9]

Among the examples of oxygenated heterocycles, a class that has not been particularly explored is the tetrahydroxanthenones and chromenones and the possibility of obtaining them from the reaction of 2-hydroxybenzaldehydes and cyclic enones. These compounds are important heterocycles with a wide range of biological activities such as antimicrobial, antifungal and anticancer.[10–13] Tricyclic chromenones also figure in the structure of some natural products, as shown in Figure 1.[14–16]

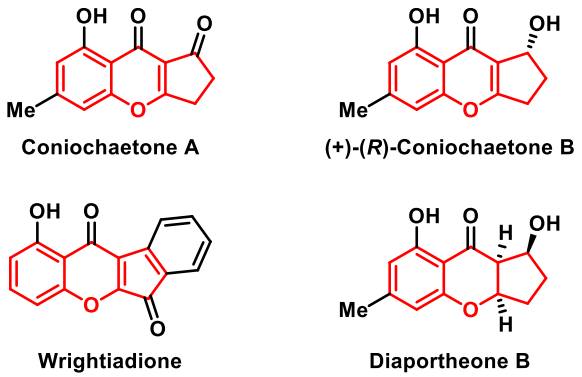
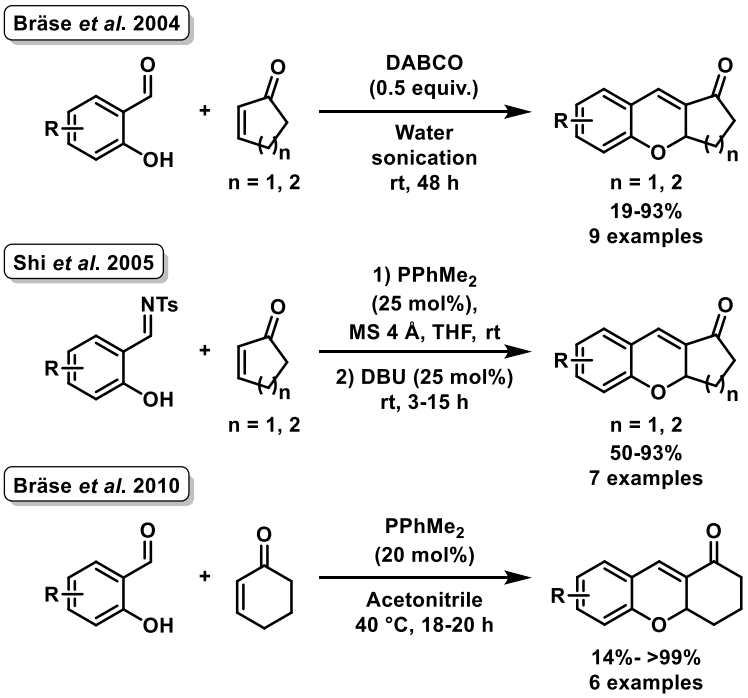


Figure 1. Some examples of naturally occurring polycyclic derivatives of chromen-1-ones.



Scheme 1. Previously reported[17-19] syntheses of racemic tetrahydroxanthenone and chromen-1-one derivatives from 2-hydroxybenzaldehydes and cyclic enones.

The methodologies described so far for obtaining these moieties from 2-hydroxybenzaldehydes and activated olefins in a single step are summarized in Scheme 1.[17–19]

In the first description of this transformation, Bräse *et al.* found that DABCO in water was able to provide in a single step tetrahydroxanthenone derivatives in yields ranging from poor to excellent.[17] In this work, the authors were not able to intercept the MBH adduct, and thus proposed a mechanism in which the first step was the oxa-Michael addition followed by an aldol condensation step. In 2005 Shi *et al.* prepared tetrahydroxanthenones and chromenone derivatives by reacting salicyl *N*-tosylimines with cyclic enones using a phosphine as the catalyst.[18] Contrasting with Bräse's results, the authors intercepted the aza-MBH adducts, indicating that the overall transformation might also proceed firstly by a MBH step. In their protocol, an additional step with DBU was necessary to promote elimination and the overall yields ranged from moderate to excellent. In 2010,[19] Bräse *et al.* employed the same catalytic system developed by Shi *et al.* with salicylaldehydes, obtaining the corresponding tetrahydroxanthenones in poor to quantitative yields (most examples in less than 65 % yield). The authors concluded that the MBH pathway could be an alternative with less basic catalysts such as phosphines.

In the present work we describe the use of a bicyclic imidazolyl alcohol (BIA) as a new bifunctional organocatalyst for the synthesis of tetrahydroxanthenones and tricyclic chromenones from the direct reaction of 2-hydroxybenzaldehydes and cyclic enones in water using sodium dodecyl sulfate (SDS) as an additive.

Results and Discussion

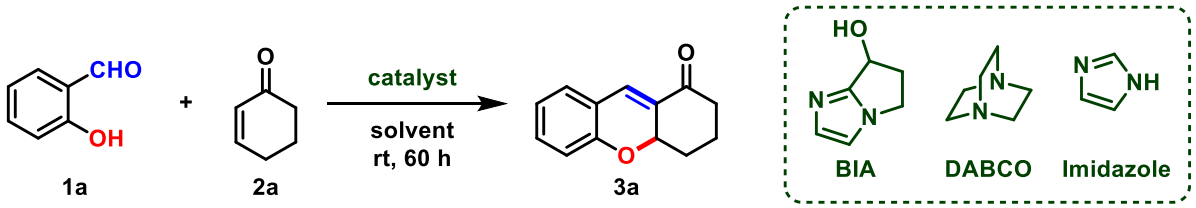
We began our investigation with the reaction of salicylaldehyde (**1a**) and 2-cyclohexen-1-one (**2a**) as model reaction, and screened a series of parameters. Our group has previously shown that BIA is an excellent catalyst for the aqueous MBH reaction in which cyclic enones are the nucleophilic partners.[20–22] Given the evidence that the reaction might be proceeding through the MBH adduct,[19] we decided to test this catalytic system in the synthesis of the tetrahydroxanthenone **3a** and to compare it with catalysts already known to perform this transformation (Table 1).

We first tested the use of equimolar quantities of salicylaldehyde and 2-cyclohexen-1-one, 50 mol% of BIA and 10 mol% of sodium dodecyl sulfate (SDS) in water, and, after 60 hours, the tetrahydroxanthenone **3a** was obtained in 58 % yield (entry 1). In order to check if we could improve this yield, knowing that BIA provides best results in aqueous conditions, we tested different solvent combinations with water (entries 2-5). However, no improvement was observed and, in fact, all results were inferior to those in pure water. We also evaluated the neat transformation, but the yield was also low (entry 6). Thus, water was established as the optimal solvent for the reaction.

We also evaluated the impact of catalyst loading of BIA to the yield of **3a**. The use of only 20 mol% of BIA led to an unsatisfactory yield of 30 % (entry 7). When 65 mol% of BIA was used, however, a slightly enhanced yield was observed (entry 8). A further increase in the catalyst loading to 100 mol% did not improve the isolated yield (entry 9). Having fixed 65 mol% of BIA as an optimal catalyst charge, we then evaluated the number of 2-cyclohexen-1-one equivalents in relation to salicylaldehyde (entries 10-12). The reaction performed better when excess of **2a** was employed, and the use of 2.0 equivalents of the 2-cycloenone led to a 68 % isolated yield of **3a** (77 % yield considering the recovery of unreacted salicylaldehyde). Increasing the temperature of the reaction did not improve the yields (entries 13 and 14).

Thus, the optimal conditions were defined as 0.65 equiv. of BIA, 2.0 equiv. of 2-cycloenone and water as the solvent at room temperature (entry 11). In order to compare our protocol with the one reported in the literature by Bräse *et al.*, we performed the reaction of **1a** in the same conditions as reported by the authors (entry 15).[17] Unfortunately, we were not able to reproduce the yield described by Bräse. We also tested the use of imidazole as catalyst, which is a structurally simple catalyst compared to BIA (entry 16). However, the isolated yield was lower (60 %), confirming the importance of the bifunctional nature of the BIA catalyst to furnish **3a** in higher yields.

Table 1. Optimization of the reaction conditions



Entry	Aldehyde **1a** (mmol)	Cycloenone **2a** (mmol)	Lewis base (mmol)	Solvent(s)	Additive[a] (mol%)	Yield[b] (%)
1	1.0	1.0	BIA, 0.50	H_2O (1 mL)	10	58[c]
2	1.0	1.0	BIA, 0.50	H_2O (0.65 mL) : Dioxane (0.35 mL)	10	23[c]
3	1.0	1.0	BIA, 0.50	H_2O (0.65 mL) : Dioxane (0.35 mL)	-	25[c]
4	1.0	1.0	BIA, 0.50	Glycerol (1 mL)	-	18[c]
5	1.0	1.0	BIA, 0.50	Dioxane (1 mL)	-	10[c]
6	1.0	1.0	BIA, 0.50	-	-	13[c]
7	1.0	1.0	BIA, 0.20	H_2O (1 mL)	10	30[c]
8	1.0	1.0	BIA, 0.65	H_2O (1 mL)	10	61[c]
9	1.0	1.0	BIA, 1.00	H_2O (1 mL)	10	60[c]
10	1.0	1.5	BIA, 0.65	H_2O (1 mL)	10	63[c]
11	1.0	2.0	BIA, 0.65	H_2O (1 mL)	10	68[c,d]
12	2.0	1.0	BIA, 0.65	H_2O (1 mL)	10	52[c]
13	1.0	2.0	BIA, 0.65	H_2O (1 mL)	10	53[c,e]
14	1.0	2.0	BIA, 0.65	H_2O (1 mL)	10	38[f]
15	1.0	1.0	DABCO, 0.50	H_2O (0.65 mL) : Dioxane (0.35 mL)	-	58[c,g]
16	1.0	2.0	Imidazole, 0.65	H_2O (1 mL)	10	60[c]

[a] Sodium dodecyl sulfate (SDS) was used as additive; [b] isolated yields; [c] recovery of the limiting starting material; [d] 77 % yield, based on recovery of salicylaldehyde (**1a**); [e] run at 75 °C; [f] run at 100 °C; [g] reaction time: 48 h

With the optimized conditions, we moved on to evaluate the scope of the reaction by applying seven different salicylaldehydes and six different 2-cycloenones (Scheme 2). The yields reported are all isolated yields after complete consumption of the starting materials or stagnation of the reaction (as confirmed by ^{1}H NMR of a crude sample). Electron-rich salicylaldehydes gave generally better yields than electron-deficient

ones with 2-cyclohexen-1-one. The lowest yield of the 2-cyclohexen-1-one series was when 2-formyl-β-naphthol was the coupling partner.

When 4-bromo-2-hydroxybenzaldehyde was employed, besides the expected product (**3f**), we also noticed significant formation of **4a**, a product from the aldol condensation of **3f** with a second molecule of aldehyde. When 2-cyclopenten-1-one was used as reactant, the obtained yields were generally lower and, with electron rich aldehydes, we also observed the formation of the aldol-condensation products (**4b** and **4c**). With electron poor aldehydes, we did not observe aldol-condensation products, nevertheless, we were able to isolate the intermediates MBH adducts (**5a** and **5b**). To the best of our knowledge, this is the first time these MBH adducts are isolated. In addition, in presence of BIA catalyst and in aqueous medium, MBH adduct **5a** slowly converts to dihydrocyclopenta[*b*]chromen-1(2*H*)-one **3j** (35 % yield of **3j** after 5 days of reaction). These empirical observations are a strong evidence that the reaction proceeds *via* an MBH reaction followed by oxa-Michael/elimination steps under our conditions, and not the opposite way. With 2-cyclohepten-1-one as the coupling partner, a low yield (13 %) of the expected product was observed. An extensive degradation of compound **3m** was observed by thin-layer chromatography during the reaction, which might explain the reduced yield. *Gem*-disubstituted 2-cyclohexen-1-ones at position 4 or 5 did not give the desired products **3n**, **3o** and **3p** after 7 days of reaction time. This is probably due to a combination of stereoelectronic and steric factors, which might hinder the 1,4-addition of the BIA catalyst to the cycloenone.[23]

To demonstrate the feasibility of this reaction, we ran an essay on a gram scale. The reaction between salicylaldehyde (**1a**, 8.46 mmol) and cyclohexenone (2 equiv.) provided the xanthenone **3a** in 63 % yield (1.07 g), after 5 days at room temperature.

A single crystal of **4c** could be obtained and analyzed by X-ray diffraction and its ORTEP diagram is shown in Figure 2 (CCDC 1980794). This compound co-crystallized with chloroform and is a definitive proof of the structure of the aldol condensation product and the geometry of the double bond.

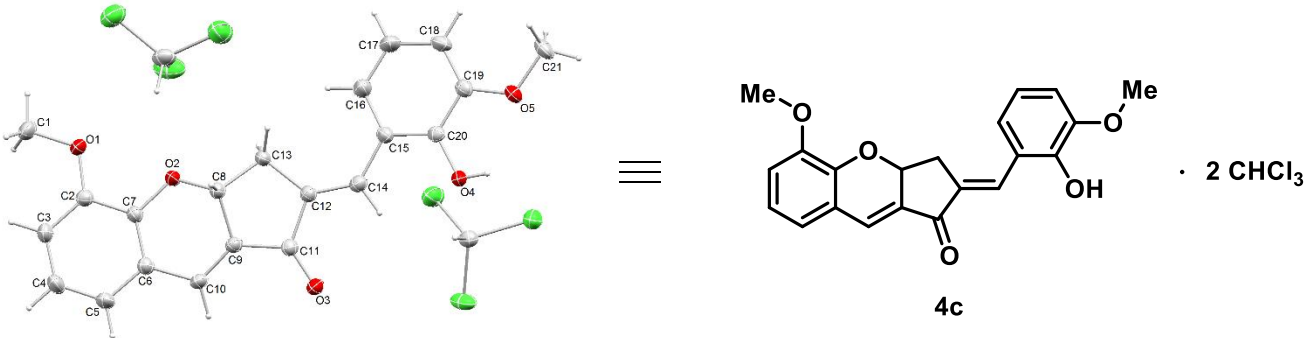
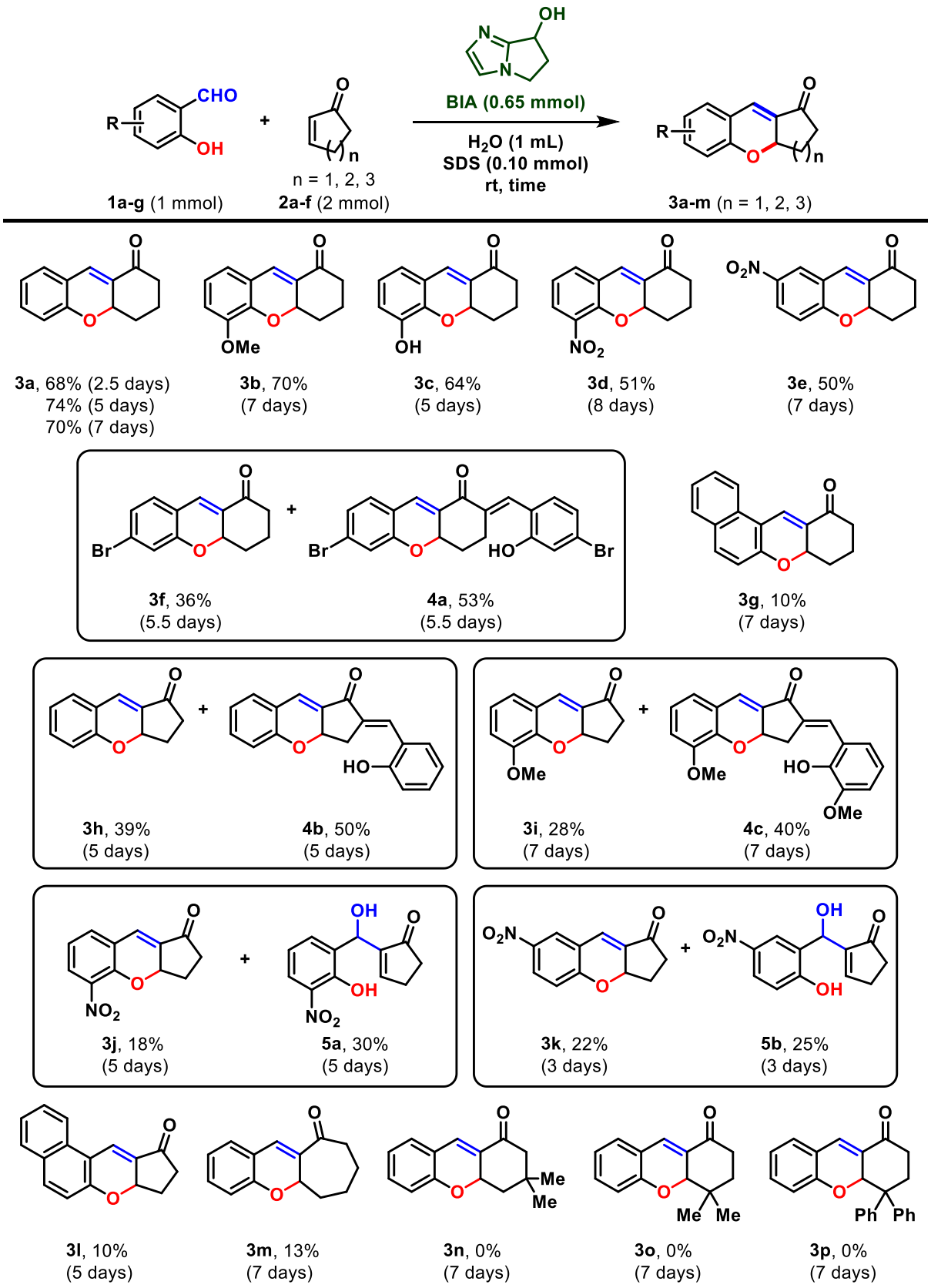


Figure 2. ORTEP diagram of compound **4c** co-crystallized with chloroform, with 50 % probability displacement ellipsoids. The crystallographic details are available in the Supplementary Material.



Scheme 2. Scope of the reaction.

Conclusions

In this work, we developed a new catalytic system to obtain tetrahydro-1*H*-xanthen-1-ones and fused chromen-1-ones derivatives directly from the corresponding 2-hydroxybenzaldehydes and 2-cycloenones. The reaction proceeds under catalysis of a bifunctional, bicyclic imidazole alcohol (BIA) using water as solvent, and several examples were synthetized in low to good yields. We believe that under our optimized conditions this transformation involves a Morita-Baylis-Hillman step followed by cyclization (oxa-Michael/elimination steps), which is in contrast to what has previously been published in the literature. Strong evidence for this proposition is the isolation of the MBH adducts **5a** and **5b**. The synthesized products will be screened for potential biological applications and we are currently exploring the possibility of an asymmetric version of this transformation by employing enantioenriched bifunctional catalysts.

Experimental Section

General. All reagents were used from commercial suppliers without further purification. BIA catalyst was readily prepared according to a previously reported procedure.[24] The reaction progress was monitored by thin layer chromatography on silica gel-coated aluminium foils. The products were revealed under UV light (254 nm), followed by staining with 25 % phosphomolybdic acid solution in ethanol or with sulfuric vanillin and heating with a heat gun. Reaction products were purified by flash column chromatography using silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker Avance 250 (250 MHz for ^{1}H NMR and 63 MHz for ^{13}C NMR); Bruker Avance 400 (400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) or Bruker Avance 500 (500 MHz for ^{1}H and 126 MHz for ^{13}C NMR). Chemical shifts (δ) were reported in ppm and the coupling constants (*J*) in Hertz (Hz). Signal multiplicity was assigned as singlet (s), broad singlet (brs), doublet (d), double doublet (dd), double triplet (dt), double double doublet (ddd), double double triplet (ddt), triplet (t), triple doublet (td), quartet (q). High resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) on a Waters Synapt mass spectrometer. Melting points were obtained using a Gehaka equipment model PF 1500 FARMA and were corrected. The compounds were named according to IUPAC rules using the software MarvinSketch version 16.11.21.

General procedure for the preparation of tetrahydro-1*H*-xanthen-1-ones (3a-3g) and chromen-1-ones (3h-3m/4a-4c). To a 5 mL round bottomed flask containing a stir-bar, the corresponding 2-hydroxybenzaldehyde (1.00 equiv.), the BIA catalyst (0.65 equiv.), prepared according to the procedure described by Zhang *et al.*,[24] sodium dodecyl sulfate (SDS, 0.10 equiv.) and the 2-cycloenone (2.00 equiv.) were added. Distilled water (1.0 mL) was then added and the reaction mixture was magnetically stirred at room temperature until complete consumption of the starting aldehyde or stagnation of the reaction. After that, the volatiles were evaporated under reduced pressure and the remaining residue was directly subjected to flash column chromatography purification to furnish the desired products, the structures of which are collected in Scheme 2.

2,3,4,4a-Tetrahydro-1*H*-xanthen-1-one (**3a**).[17] Purified by column chromatography (hexane/EtOAc 98:2 → 80:20) to give **3a** (148 mg, 0.74 mmol, 74 %) as a yellow solid. When the reaction was performed on a larger scale (8.46 mmol of salicylaldehyde), compound **3a** was obtained after 120 h in 63 % yield (1.071 g, 5.35 mmol). R_f = 0.54 (4:1 hexane/EtOAc). Mp 136-138 °C (lit.[17] Mp 137-139 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37

(d, *J* 2.4 Hz, 1H), 7.27 – 7.10 (m, 2H), 7.01 – 6.78 (m, 2H), 4.94 (ddd, *J* 10.6, 6.0, 2.4 Hz, 1H), 2.69 – 2.21 (m, 3H), 2.13 – 1.86 (m, 2H), 1.84 – 1.51 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.3, 155.9, 132.0, 131.4, 130.4, 129.8, 122.2, 122.1, 116.0, 74.6, 38.8, 29.7, 18.0. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{13}O_2^+$ $[M + H]^+$ 201.0910, found 201.0936.

2,3,4,4a-Tetrahydro-5-methoxy-1*H*-xanthen-1-one (**3b**).[17] Purified by column chromatography (hexane/EtOAc 9:1) to give **3b** (162 mg, 0.70 mmol, 70 %) as a yellow solid. R_f = 0.18 (4:1 hexane/EtOAc). Mp 121-122 °C (lit.[17] Mp 124-130 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 (d, *J* 2.4 Hz, 1H), 6.73 (q, *J* 4.9 Hz, 3H), 4.85 (ddd, *J* 10.6, 6.0, 2.4 Hz, 1H), 3.72 (s, 3H), 2.71 – 2.38 (m, 2H), 2.24 (ddd, *J* 18.3, 12.9, 5.8 Hz, 1H), 2.06 – 1.81 (m, 2H), 1.50-1.63 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.4, 147.8, 144.9, 131.5, 130.5, 122.9, 121.8, 121.8, 114.6, 74.9, 56.1, 38.8, 29.7, 18.0. HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{15}O_3^+$ $[M + H]^+$ 231.1016, found 231.0998.

2,3,4,4a-Tetrahydro-5-hydroxy-1*H*-xanthen-1-one (**3c**).[17] Purified by column chromatography (hexane/EtOAc 95:5 → 60:40) to give **3c** (158 mg, 0.73 mmol, 64 %) as a bright yellow solid. Mp 143-145 °C (lit.[25] Mp 146-147 °C). R_f 0.32 (2:1 hexane/EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, *J* 2.4 Hz, 1H), 6.93 (dd, *J* 7.6, 2.1 Hz, 1H), 6.85 (t, *J* 7.6 Hz, 1H), 6.80 (dd, *J* 7.6, 2.1 Hz, 1H), 5.55 (s, 1H), 5.02 (ddd, *J* 10.6, 6.0, 2.4 Hz, 1H), 2.70 – 2.54 (m, 1H), 2.54 – 2.31 (m, 2H), 2.19 – 1.94 (m, 2H), 1.82 – 1.59 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.4, 144.1, 142.4, 131.8, 130.6, 122.4, 122.4, 121.3, 118.3, 75.5, 38.9, 29.7, 18.0. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{13}O_3^+$ $[M + H]^+$ 217.0859, found 217.0865.

5-Nitro-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (3d). Purified by column chromatography (hexane/EtOAc 8:2) to give **3d** (125 mg, 0.51 mmol, 51 %) as a yellow solid. R_f = 0.18 (4:1 hexane/EtOAc). Mp 139-140 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80 (dd, *J* 8.3, 1.6 Hz, 1H), 7.41 (dd, *J* 7.6, 1.7 Hz, 1H), 7.34 (d, *J* 2.5 Hz, 1H), 7.01 (dd, *J* 8.3, 7.5 Hz, 1H), 5.12 (ddd, *J* 10.7, 5.9, 2.5 Hz, 1H), 2.83 – 2.52 (m, 2H), 2.40 (ddd, *J* 18.3, 13.0, 6.0 Hz, 1H), 2.00-2.19 (m, 2H), 1.94 – 1.56 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.9, 149.4, 138.5, 134.1, 132.0, 129.2, 127.2, 124.7, 121.4, 75.9, 38.9, 29.5, 17.8. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{12}NO_4^+$ $[M + H]^+$ 246.0761, found 246.0743.

7-Nitro-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (**3e**).[17] Purified by column chromatography (hexane/EtOAc 8:2) to give **3e** (122 mg, 0.50 mmol, 50 %) as a yellow solid. R_f = 0.10 (4:1 hexane/EtOAc). Mp 197-198 °C, decomp. (lit.[17] Mp 195-198 °C, decomp.). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.20 – 8.08 (m, 1H), 7.38 (d, *J* 2.5 Hz, 1H), 6.96 (d, *J* 8.5 Hz, 1H), 5.18 (dd, *J* 11.0, 2.5 Hz, 1H), 2.74 – 2.35 (m, 1H), 2.25 – 1.95 (m, 1H), 1.87 – 1.63 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.9, 160.7, 142.5, 132.2, 129.1, 127.5, 125.3, 122.0, 116.8, 76.0, 39.0, 29.9, 18.0. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{12}NO_4^+$ $[M + H]^+$ 246.0761, found 246.0771.

6-Bromo-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (**3f**).[25] Purified by column chromatography (hexane/EtOAc 95:5 → 60:40) to give **3f** (99 mg, 0.36 mmol, 36 %) as a pale yellow solid. Mp 107-108 °C (lit.[25] Mp 119 °C). R_f 0.53 (4:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* 2.2 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.06 – 7.02 (m, 2H), 4.98 (ddd, *J* 10.9, 6.1, 2.2 Hz, 1H), 2.58 (ddt, *J* 18.0, 4.4, 2.3 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.37 (ddd, *J* 18.1, 13.3, 6.1 Hz, 1H), 2.14 – 2.05 (m, 1H), 2.04 – 1.93 (m, 1H), 1.69 (qdd, *J* 13.5, 4.6, 2.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 156.4, 130.7, 130.7, 130.6, 125.5, 125.4, 121.2, 119.6, 75.1, 38.9, 29.7, 18.0. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{12}BrO_2^+$ $[M + H]^+$ 279.0015, found 279.0031.

(2*E*)-6-Bromo-2-[(4-bromo-2-hydroxyphenyl)methylidene]-2,3,4,4a-tetrahydro-1*H*-xanthen-1-one (**4a**). Purified by column chromatography (hexane/EtOAc 95:5 → 60:40) to give **4a** (122 mg, 0.26 mmol, 53 %) as a viscous yellow oil. R_f 0.41 (4:1 hexane/EtOAc). ^{1}H NMR (250 MHz, DMSO-d_6) δ ^{1}H NMR (250 MHz, DMSO) δ 7.74 (d, *J* 2.5 Hz, 1H), 7.56 (d, *J* 2.3 Hz, 1H), 7.40 (d, *J* 8.2 Hz, 1H), 7.26 (d, *J* 8.2 Hz, 1H), 7.20 (dd, *J* 8.2, 1.9 Hz, 1H), 7.14 (d, *J* 1.9 Hz, 1H), 7.09 (d, *J* 1.9 Hz, 1H), 7.05 (dd, *J* 8.2, 1.9 Hz, 1H), 5.26 (ddd, *J* 11.6, 5.1, 2.3 Hz, 1H),

2.93 (dt, *J* 7.6, 3.3 Hz, 1H), 2.74 – 2.55 (m, 1H), 2.46 – 2.33 (m, 1H), 2.00 – 1.79 (m, 2H). ^{13}C NMR (63 MHz, DMSO-d_6) δ 184.8, 157.9, 155.9, 134.0, 131.7, 131.7, 131.3, 131.2, 130.1, 125.2, 124.5, 123.1, 121.7, 121.6, 121.5, 118.7, 118.3, 74.2, 28.4, 22.8. HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{15}Br_2O_3^+$ $[M + H]^+$ 460.9382, found 460.9370.

7a,8,9,10-Tetrahydro-11*H*-benzo[*a*]xanthen-11-one (**3g**).[17] Purified by column chromatography (hexane / EtOAc 9:1) to give **3g** (27 mg, 0.10 mmol, 10 %) as a white solid. R*f* = 0.30 (4:1 hexane/EtOAc). Mp 141-143 °C (lit.[17] Mp 142-146 °C). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.21 (d, *J* 2.2 Hz, 1H), 8.10 (dd, *J* 8.5, 1.1 Hz, 1H), 7.88 – 7.74 (m, 2H), 7.58 (ddd, *J* 8.4, 6.9, 1.4 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.14 (dd, *J* 8.9, 0.8 Hz, 1H), 5.09 (ddd, *J* 10.1, 6.2, 2.2 Hz, 1H), 2.74 – 2.37 (m, 3H), 2.26 – 2.04 (m, 2H), 1.91 – 1.72 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.4, 155.7, 133.3, 131.6, 129.7, 128.9, 128.7, 128.0, 127.6, 124.8, 122.2, 117.5, 116.0, 74.9, 38.9, 29.6, 18.2. HRMS (ESI-TOF) *m/z* calcd for $C_{17}H_{14}NaO_2^+$ $[M + Na]^+$ 273.0886, found 273.0895.

3,3a-Dihydrocyclopenta[*b*]chromen-1(2*H*)-one (**3h**).[17] Purified by column chromatography (hexane/EtOAc 9:1 → 7:3) to give **3h** (73 mg, 0.70 mmol, 39 %) as a yellow solid. R_f = 0.33 (4:1 hexane/EtOAc). Mp 114-116 °C (lit.[17] Mp 107-110 °C).^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 1H), 7.09 – 6.80 (m, 1H), 5.30 (td, *J* 8.2, 7.6, 2.5 Hz, 1H), 2.89 – 2.54 (m, 1H), 2.45 – 1.99 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 201.6, 155.5, 132.6, 131.9, 130.6, 127.8, 122.5, 122.1, 116.7, 75.9, 37.2, 28.3. HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{11}O_2^+$ $[M + H]^+$ 187.0754, found 187.0758.

(2*E*)-3,3a-Dihydro-2-[(2-Hydroxyphenyl)methylidene]cyclopenta[*b*]chromen-1(2*H*)-one (**4b**).[26] Purified by column chromatography (hexane/EtOAc 9:1 → 7:3) to give **4b** (72 mg, 0.25 mmol, 50 %) as an orange solid. R_f 0.21 (7:3 hexane/EtOAc). Mp 160-164 °C, decomp. ^{1}H NMR (250 MHz, $CDCl_3$/MeOH-d_4 6:1) δ 8.03 (t, *J* 2.7 Hz, 1H), 7.62 – 7.37 (m, 1H), 7.38 – 7.13 (m, 4H), 7.13 – 6.78 (m, 4H), 5.60 – 5.13 (m, 1H), 3.59 (ddd, *J* 16.7, 8.2, 2.1 Hz, 1H), 3.09 (ddd, *J* 16.8, 6.9, 3.5 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$/MeOH-d_4 6:1) δ 192.2, 158.2, 156.0, 135.5, 134.1, 132.9, 132.2, 131.7, 130.9, 130.3, 129.2, 123.0, 122.9, 120.0, 117.1, 116.3, 74.5, 35.5. HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{15}O_3^+$ $[M + H]^+$ 291.1016, found 291.1021.

3,3a-Dihydro-5-methoxycyclopenta[*b*]chromen-1(2*H*)-one (**3i**). Purified by column chromatography (hexane/EtOAc 9:1) to give **3i** (61 mg, 0.28 mmol, 28 %) as a yellow solid. R_f = 0.16 (4:1 hexane/EtOAc). Mp 143-146 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.13 (d, *J* 2.5 Hz, 1H), 6.92 – 6.75 (m, 3H), 5.35 – 5.20 (m, 1H), 3.84 (s, 3H), 2.89 – 2.66 (m, 1H), 2.71 – 2.44 (m, 1H), 2.37 – 2.07 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 201.5, 148.4, 144.4, 131.9, 127.8, 122.8, 122.4, 122.1, 115.1, 76.2, 56.3, 37.2, 28.4. HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{13}O_3^+$ $[M + H]^+$ 217.0859, found 263.1189.

(2*E*)-2-[(2-Hydroxy-3-methoxyphenyl)methylidene]-5-methoxycyclopenta[*b*]chromen-1(2*H*)-one (**4c**). Purified by column chromatography (hexane/EtOAc 9:1) to give **4c** (70 mg, 0.20 mmol, 40 %) as a yellow solid. R_f = 0.15 (7:3 hexane/EtOAc). Mp 171-175 °C, decomp. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* 3.6, 2.0 Hz, 1H), 7.38 (d, *J* 2.5 Hz, 1H), 7.11 (dd, *J* 6.3, 3.1 Hz, 1H), 7.04 – 6.86 (m, 5H), 6.15 (s, 1H), 5.33 (ddd, *J* 8.2, 6.7, 2.9 Hz, 1H), 3.94 (d, *J* 3.3 Hz, 6H), 3.73 (ddd, *J* 16.9, 8.2, 2.0 Hz, 1H), 3.28 (ddd, *J* 16.9, 6.8, 3.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 148.5, 146.9, 146.3, 144.6, 136.3, 134.0, 129.4, 128.3, 123.5, 122.4, 122.2, 121.9, 121.8, 119.7, 114.9, 112.0, 74.5, 56.4, 35.6. HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{19}O_5^+$ 351.1227 $[M + H]^+$, found 351.1232. CCDC 1980794 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.

3,3a-Dihydro-5-nitrocyclopenta[*b*]chromen-1(2*H*]-one (**3j**)**.** Purified by column chromatography (hexane/EtOAc 8:2) to give **3j** (36 mg, 0.18 mmol, 18 %) as a yellow solid. R_f 0.15 (4:1 hexane/EtOAc). Mp 195-197 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85 (dd, *J* 8.2, 1.6 Hz, 1H), 7.70 – 7.42 (m, 1H), 7.22 (d, *J* 2.6 Hz, 1H),

7.07 (t, *J* 7.9 Hz, 1H), 5.61 – 5.30 (m, 1H), 2.95 – 2.58 (m, 2H), 2.54 – 2.17 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.7, 149.0, 139.3, 134.7, 133.4, 127.7, 125.8, 124.7, 121.7, 76.8, 37.2, 28.1. HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{10}NO_4^+$ $[M + H]^+$ 232.0604, found 232.0657.

2-[Hydroxy(2-hydroxy-3-nitrophenyl)methyl]cyclopent-2-en-1-one (**5a**). Purified by column chromatography (hexane/EtOAc 9:1) to give **5a** (75 mg, 0.30 mmol, 30 %) as a viscous yellow oil. R_f 0.21 (1:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.04 (dd, *J* 8.5, 1.7 Hz, 1H), 7.83 (dd, *J* 7.5, 1.7 Hz, 1H), 7.38 (td, *J* 2.7, 1.1 Hz, 1H), 7.02 (dd, *J* 8.5, 7.5 Hz, 1H), 5.91 (s, 1H), 4.17 (brs, 1H), 2.70 – 2.55 (m, 2H), 2.52 – 2.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 160.2, 152.0, 145.2, 135.4, 133.6, 132.4, 124.4, 120.0, 64.8, 35.3, 26.8. HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{11}NNaO_5^+$ 272.0529 $[M + Na]^+$, found 272.0525.

3,3a-Dihydro-7-nitrocyclopenta[*b*]chromen-1(2*H*]-one (**3k**).[27] Purified by column chromatography (hexane / EtOAc 8:2) to give **3k** (50 mg, 0.22 mmol, 22 %) as a yellow solid. R_f 0.18 (4:1 hexane/EtOAc). Mp 175-177 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.14 (dd, *J* 4.7, 2.3 Hz, 1H), 7.19 (d, *J* 2.6 Hz, 1H), 7.00 (d, *J* 9.7 Hz, 1H), 5.42 (ddd, *J* 9.6, 8.0, 2.6 Hz, 1H), 3.03 – 2.58 (m, 1H), 2.52 – 2.13 (m, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.4, 160.2, 142.6, 133.4, 127.8, 125.9, 125.5, 121.9, 117.3, 76.8, 37.0, 28.2. HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_9NNaO_4^+$ $[M + Na]^+$ 254.0424, found 254.0452.

2-[Hydroxy-(2-hydroxy-5-nitrophenyl)methyl]cyclopent-2-en-1-one (**5b**). Purified by column chromatography (hexane/EtOAc 6:4) to give **5b** (62 mg, 0.25 mmol, 25 %) as a viscous yellow oil. R_f = 0.16 (1:1 hexane/EtOAc). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.26 (brs, 1H), 8.24 – 7.94 (m, 2H), 7.39 (s, 1H), 7.00 (d, *J* 8.8 Hz, 1H), 5.87 (s, 1H), 2.70 (dt, *J* 4.3, 2.1 Hz, 2H), 2.66 – 2.44 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 211.3, 161.7, 145.3, 141.1, 125.8, 123.8, 118.7, 69.2, 35.5, 27.3. HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{11}NNaO_5^+$ 272.0529 $[M + Na]^+$, found 272.0561.

8,9-Dihydrobenzo[*f*]cyclopenta[*b*]chromen-10(7a*H*]-one (**3l**).[28] Purified by column chromatography (hexane/EtOAc 8:2) to give **3l** (24 mg, 0.10 mmol, 10 %) as a yellow solid. R_f = 0.32 (4:1 hexane/EtOAc). Mp 138-139 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 1H), 7.95 (d, *J* 2.4 Hz, 1H), 7.91 – 7.79 (m, 2H), 7.59 (ddd, *J* 8.4, 6.9, 1.3 Hz, 1H), 7.44 (ddd, *J* 8.0, 6.8, 1.1 Hz, 1H), 7.16 (d, *J* 8.8 Hz, 1H), 5.43 (td, *J* 8.0, 2.4 Hz, 1H), 2.88 – 2.76 (m, 1H), 2.73 – 2.63 (m, 1H), 2.45 (ddd, *J* 18.3, 12.3, 8.7 Hz, 1H), 2.35 – 2.21 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4, 154.7, 133.4, 131.7, 129.6, 129.1, 128.8, 128.0, 124.7, 124.5, 121.9, 117.6, 115.7, 76.1, 37.3, 28.0. HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{13}O_2^+$ 237.0910 $[M + H]^+$, found 237.0932.

6,7,8,9-Tetrahydrocyclohepta[*b*]chromen-10(5a*H*]-one (**3m**)**.** Purified by column chromatography (hexane / EtOAc 8:2) to give **3m** (28 mg, 0.13 mmol, 13 %) as an orange solid. R_f = 0.37 (4:1 hexane/EtOAc). Mp 51-57 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 – 7.09 (m, 2H), 6.90 (td, *J* 7.4, 1.1 Hz, 1H), 6.80 (d, *J* 8.1 Hz, 1H), 5.26 (dd, *J* 10.8, 2.7 Hz, 1H), 2.80 – 2.58 (m, 1H), 2.49 (ddd, *J* 14.2, 12.1, 2.1 Hz, 1H), 2.31 – 1.90 (m, 4H), 1.82 – 1.50 (m, 2H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 199.4, 154.1, 134.7, 132.2, 129.8, 129.4, 121.7, 120.3, 116.2, 77.6, 43.5, 37.7, 27.7, 25.0. HRMS (ESI-TOF) *m/z* calcd for $C_{14}H_{15}O_2^+$ 215.1067 $[M + H]^+$, found 215.1075.

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Supplementary Material

Copies of the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra and X-ray crystallographic data for compound **4c** are provided in the Supplementary Material.

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