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Graphical Abstract

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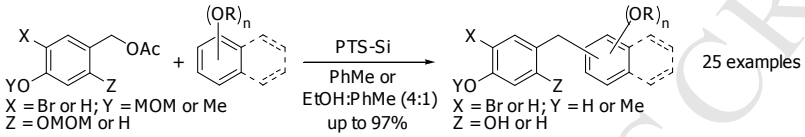

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Facile synthesis of diarylmethanes via quinone methides

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ABSTRACT

A novel acid-mediated generation of quinone methides followed by nucleophilic addition of electron-rich aromatic compounds to furnish diarylmethanes has been developed. A wide range of electron-rich aromatic compounds including some heterocycles can be employed for this reaction to provide the corresponding diarylmethanes in good yields and regioselectivities.

1. Introduction

Diarylmethane constitutes an important core of some natural products and synthetic compounds (**1**–**5**; Figure 1) with interesting biological activities. Recent studies have been directed to profile some diarylmethane derivatives as thyroid hormone analogs (**1**),[1–3] macrocyclic receptors for some amino acids,[4,5] anti-implantation agents (**2**),[6] as well as inhibitors of matrix metalloproteinase (**3**),[7] phosphodiesterase-4 (PDE-4; **4**),[8] and C-C chemokine receptor type 5 (CCR5; **5**).[9]

Figure 1. Some natural and synthetic biologically active diarylmethanes

A number of different strategies have been developed for the synthesis of the diarylmethane core.[10] Benzylation via tandem Grignard reaction-iodotrimethylsilane (TMSI) mediated reduction,[11] Cu- and Pd-catalyzed reactions,[5,12–16] benzotriazole-mediated reaction,[17] *L*-proline-catalyzed multicomponent Mannich-type Friedel-Crafts reaction,[18] organocatalyzed Friedel-Crafts arylation,[19] and TfOH/HNTf$_2$-catalyzed electrophilic aromatic substitution[20] have been reported as the effective means.

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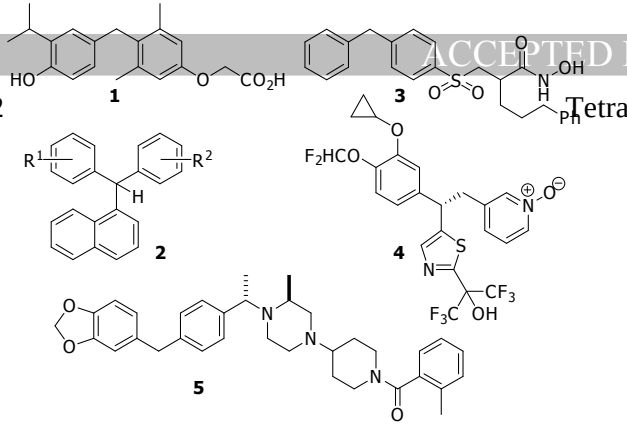
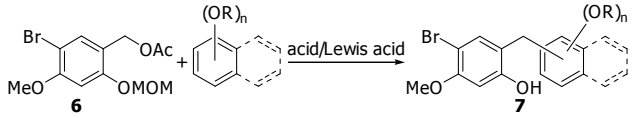


During the past few years, our research group has reported the use of solid-supported reagents, especially *p*-TsOH on silica (PTS-Si), in organic synthesis including the total synthesis of



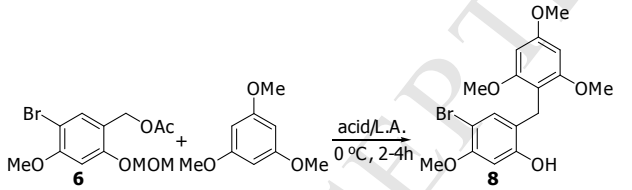
lamellarins,[21] the facile deprotection of aromatic ethers,[22] and the generation of *ortho*-quinone methides (*o*-QMs) as well as their formal intermolecular/intramolecular [4+2]-cycloaddition reactions to form chromans.[23] As shown in Scheme 1, we now envisioned that the reactions between electron-rich aromatic compounds[24] and quinone methides derived from the precursors such as **6**[23] may furnish the diarylmethane core **7**. Herein, we wish to report our investigation in the use of PTS-Si as well as other transition metal Lewis acids to generate quinone methides (QMs) and their subsequent reactions with aromatic compounds to provide the corresponding diarylmethanes.

Scheme 1. General schematic representation of the diarylmethane synthesis

2. Results and Discussion

We first investigated the reaction between the QM precursor **6** with 1,3,5-trimethoxybenzene under various conditions. The results are summarized in Table 1.

Table 1
Screening of the acid/Lewis acid-mediated reactions for diarylmethane **8**.[a]



Entry	Acid/Lewis Acid	mol (%)	Yield (%)[b]
1[c]	$ZnCl_2$	100	32
2[c]	$ZrCl_4$	100	64
3	$InCl_3$	10	36
4[c]	$PtCl_2$	100	46
5	$PtCl_4$	10	52
6[c,d]	PTS-Si	110	71

[a] Unless otherwise noted, the reactions were performed in CH_2Cl_2. Five equivalents of 1,3,5-trimethoxybenzene were employed.

[b] Isolated yields.

[c] Catalytic amount (10 mol%) of these acids/Lewis acids led to incomplete consumption of starting material.

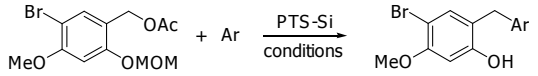
[d] Toluene was used as solvent.

From Table 1, the best condition (PTS-Si) gave the corresponding diarylmethane **8** in 71% yield (entry 6) while other acid/Lewis acids gave lower yields. While CH_2Cl_2 was used for the conditions using metal salts as Lewis acids (entries 1–5), toluene was employed for the reaction using PTS-Si as previously reported.[22,23] In the case of $InCl_3$ (entry 3) and $PtCl_4$ (entry 5), a stoichiometric amount of these Lewis acids gave complex mixtures.

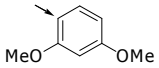
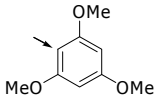
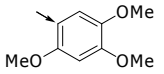
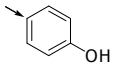
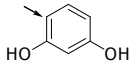
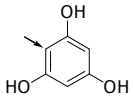
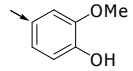
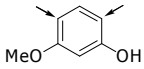
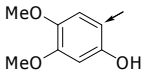
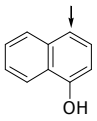
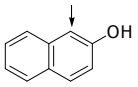
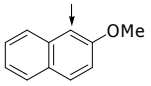
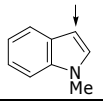
The scope of aromatic compounds containing different electron-donating groups (EDGs) was investigated using the optimized conditions from Table 1 (PTS-Si in toluene) and the results are summarized in Table 2. In most cases, the reactions proceeded with high regioselectivity, providing the corresponding products **8** and **9a-m** up to 96% yield (entries 3 and 11). As expected, the regiochemistry of the products was determined by the position of the EDGs (hydroxyl or methoxy). When unsubstituted, the position *para* to the hydroxyl group was attacked by the electrophilic quinone methide generated from the precursor **6**. 3-Methoxyphenol (entry 8), on the other hand, gave the product **9g** as a 1:1 inseparable mixture of regioisomers arising from the reaction at the position *para* to either the methoxy or the hydroxyl group. Interestingly, when the position *para* to the hydroxyl or methoxy group was not available (entries 9, 11 and 12), the reactions proceeded to furnish the products from the exclusive attack on the position *ortho* to these EDGs instead. In addition, heterocyclic aromatic compounds such as benzofuran and *N*-methylindole (entries 13 and 14) also gave the corresponding diarylmethanes **9l** and **9m** arising from the reactions at position 3 on both heterocycles in 32% and 84% yields, respectively. However, furan, *N*-protected pyrroles, thiophene, or thianaphthene gave no desired products.

It should be noted that all the reactions were first performed using condition A and other conditions (B or C) were employed when condition A gave either low yields of the expected products or complex mixtures. For condition A, toluene, a non-polar solvent was used (Table 1) in order to suppress other side reactions when the aromatic compounds, especially those

Table 2
Scope of oxygenated aromatic compounds in the synthesis of diarylmethanes **8** and **9a**-**n**.



6 **8** and **9a-n**

Entry	Ar[a]	Condition[b]	Product	Yield (%)[c]
1		A	**9a**	78
2		A	**8**	71
3		C	**9b**	96
4		B	**9c**	54
5[d]		C	**9d**	70
6		C	**9e**	72
7[e]		C	**9f**	59
8[f]		C	**9g**	95
9		C	**9h**	60
10[g]		C	**9i**	61
11		A	**9j**	96
12[h]		C	**9k**	49
13[i]		C	**9l**	32
14[j]		C	**9m**	84

[a] The arrows on the structures of the aromatic compounds indicate the position whereby the attack from the electrophilic quinone methide occurred. Five equivalents of each aromatic compound were employed in each reaction.

[b] A = toluene at 0 °C to rt; B = EtOH : toluene (4 : 1 v/v) at 0 °C to rt; C = EtOH : toluene (4 : 1 v/v) at 60 °C. The reactions were monitored by tlc and normally took 1.5–5 h for completion.

[c] Isolated yields.

[d] Condition A gave **9d** in 52% yield.

[e] Conditions A and B gave **9f** in 15% and 32% yields, respectively.

[f] A 1 : 1 mixture of inseparable regioisomers was obtained.

[g] Condition A gave a complex mixture while condition B gave **9i** in 55% yield.

[h] Condition A gave **9k** in 29% yield.

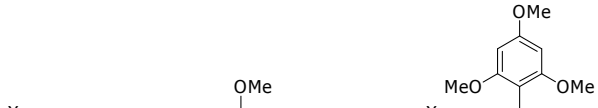
[i] Condition A gave **9l** in 24% yield.

[j] Condition A gave **9m** in 9% yield while the starting compound **6** was recovered in 79% yield.

containing free phenolic group(s), were employed (entries 4–12). Ethanol (conditions B or C) was anticipated to help improve solubility of some of the aromatic compounds as well as to prevent their polymerization under the reaction conditions. After some experimentation, the optimal ratio between ethanol and toluene was found to be 4:1 (v/v). However, the presence of ethanol in the reaction conditions B or C rendered them more ionic in character than condition A.

We also investigated the extent and contribution of the *ortho*- and *para*-quinone methides toward this PTS-Si-mediated preparation of diarylmethanes. As summarized in Table 3, it is evident that the *p*-quinone methide derived from the precursors **6** and **10c**–**h** contributed significantly toward the formation of the corresponding diarylmethanes **8**, **11c**–**e**. Better yield (76%) of the product **11c** was obtained from the *p*-OMOM containing precursor **10c** while the corresponding precursor **10b**[22a] containing only the *o*-OMOM gave the corresponding product **11b** in much lower yield (38%). Other protecting groups (Me, *i*-Pr and Ac) were investigated; compounds **10d** and **10f**[25] gave **11d** and **11e**[25] in 95% and 81% yields, respectively, whose *i*-Pr and methyl groups were not cleaved. On the other hand, compound **10e** gave **11c** in 75% yield. Thus, it appears that the cleavage of the protecting groups occurred after the nucleophilic addition to the QMs. Without any electron-donating group either at the *ortho*- or *para*-position (**10a**), there was no reaction. In addition, compounds **10g** and **10h**[23a], with the difference only in their positions of the OMe and OMOM as the substituents either at Y or Z, did not provide the corresponding products **11f**–**g**; compound **12** was obtained instead in 56% and 23% yields, respectively, as shown in Scheme 2.[26]

Table 3
Extent of *ortho*- and *para*-quinone methides[a]



6, **10a-h** **8**, **11a-g**

Comp	X	Y	Z	Prod	A	B	Yield (%)[b]
10a	H	H	H	**11a**	H	H	0
10b	H	H	OMOM	**11b**	OH	H	38
10c	H	OMOM	H	**11c**	H	OH	76
10d	H	O*i*-Pr	H	**11d**	H	O*i*-Pr	95[c]
10e	H	OAc	H	**11c**	H	OH	75
10f	H	OMe	H	**11e**	H	OMe	81
10g	H	OMOM	OMe	**11f**	OMe	OH	0
10h	H	OMe	OMOM	**11g**	OH	OMe	0
6	Br	OMe	OMOM	**8**	OH	OMe	71

[a] Unless otherwise noted, the reactions were performed in toluene at 0 °C to rt until completion (2 h).

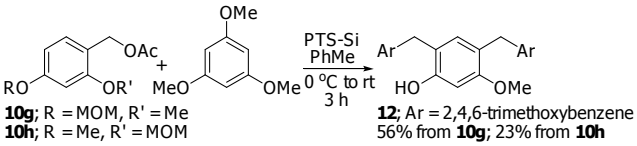
[b] Isolated yields.

[c] Toluene at 60 °C.

Compound **10c** was employed for the reactions with a number of aromatic compounds as summarized in Table 4. In general,

the reactions using **10c** furnished the corresponding products **13a**–**g** in better yields (25–97%) than those using **6** with similar regiocontrol. It was found that one of the two hydroxy groups in the product **13b** was methylated under reaction condition, presumably from the methyl group of the MOM ether.[26] From the nOe experiment, methylation was tentatively assigned to occur on the phenol group of the aromatic ring originally from the starting material **10c** (See Supplementary Material). The reaction using 1,3,5-trimethylbenzene (entry 7), a much less activated aromatic compound, furnished the product **13g** albeit in low yield (25%).

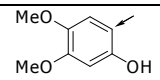
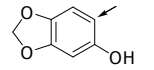
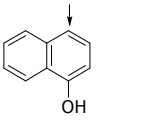
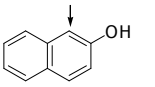
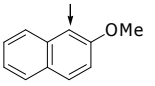
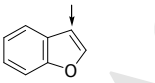
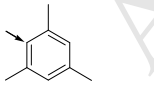
Scheme 2. Reactions of **10g** and **10h** to **12**



An advantage of using PTS-Si for these reactions is its recyclability. Following filtration, the recovered PTS-Si could be subjected to methanol washing and then used directly (the zeroth to the third times of recycling; Scheme 3), yielding **13d** in 75–97% from **10c**. The lower yields in the third and fourth cycle could be improved after the same batch of PTS-Si was subjected to acid washing, which gave **13d** in 82% yield.

Table 4

Reactions of **10c** with various aromatic compounds[a]

Entry	Ar[b]	Product	Yield (%)[c]
	MOMO, OAc (**10c**) + Ar → PTS-Si, conditions → HO, Ar (**13a-g**)		
1		**13a**	83
2[d]		**13b**	86
3		**13c**	78
4[e]		**13d**	97
5		**13e**	73
6		**13f**	77
7[f]		**13g**	25

[a] Unless otherwise noted, the reactions were performed in EtOH : toluene (4 : 1 v/v) at 60 °C until completion (1–3 h).

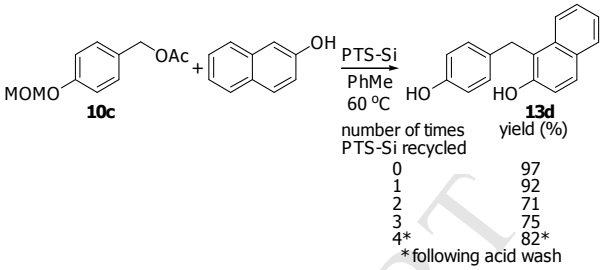
[b] The arrows on the structures of the aromatic compounds indicate the position whereby the attack from the electrophilic quinone methide occurred. Five equivalents of each aromatic compound were employed in each reaction.

[c] Isolated yields.

[d] Under the reaction condition, methylation of one of the hydroxy groups in the product occurred concomitantly.

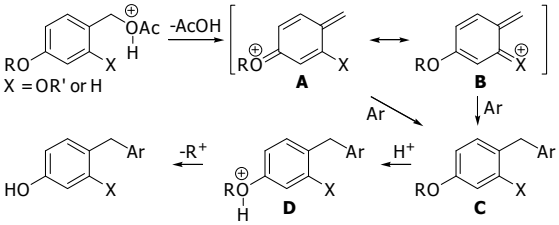
[e] The reaction was performed in toluene at 60 °C.

[f] No desired product was formed when **6** was used.



Scheme 3. Yields of **13d** from **10c** and the number of times PTS-Si recycled

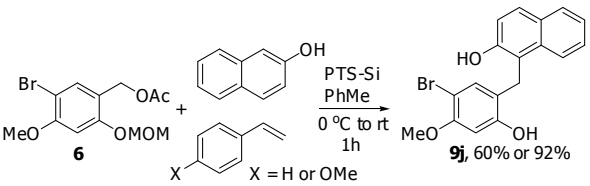
A plausible reaction mechanism appears to involve a stepwise process featuring the departure of the protonated acetate via the assistance from the oxygen atom *para* to the benzyl acetate to generate the corresponding *p*-QMs (intermediate **A**) which is a resonance structure of the *o*-QMs (intermediate **B**). Ensuing nucleophilic addition of aromatic compounds and cleavage of the protecting group then led to the formation of the products (Scheme 4). In case of the isopropyl group (compound **10c**; Table 3), nucleophilic addition apparently occurred without the cleavage of the protecting group under the reaction condition. This observation is consistent with our previous findings that the cleavage of the isopropyl group using PTS-Si required higher temperature.[22] In addition, the proposed mechanism also signifies the importance of the contributions from either the *p*- or *o*-QMs to the observed chemistry. Simple nucleophilic substitution reaction mechanism (S_N1 or S_N2) can be clearly ruled out since the substrate **10a** (simple benzyl acetate), capable of undergoing such reaction, did not proceed to give the corresponding product when reacted with 1,3,5-trimethoxybenzene under similar reaction conditions (Table 3, entry 1).



Scheme 4. A plausible mechanism

Our previous studies on the formal [4+2]-cycloaddition of the *o*-QMs and styrene derivatives[23] also prompted us to carry out a competitive reaction between the cycloaddition and nucleophilic addition of the QMs using PTS-Si. As shown in Scheme 5, the nucleophilic addition is the more preferential mode of reaction, giving the diarylmethane **9j** in 60% yield without any detectable amount of the product from the cycloaddition reaction. Even when *p*-methoxystyrene, a more electron-rich styrene derivative, was employed, no product from cycloaddition reaction could be detected while **9j** was obtained in 92% yield.

Scheme 5. Competitive reactions of **6** with 2-naphthol and styrenes



3. Conclusion

In summary, we have shown that quinone methides generated under acidic conditions by PTS-Si can react with a number of aromatic compounds with electron-donating groups to furnish the corresponding diarylmethanes in good yields and excellent regiocontrol. In addition, our mechanistic studies revealed a significant contribution from the corresponding *p*-QMs and the nucleophilic addition reaction to the QMs occurred more preferentially over the corresponding cycloaddition reaction with styrene.

4. Experimental Section

General Procedure for the nucleophilic addition to QMs: The corresponding benzyl acetate (0.16 mmol) was dissolved in toluene or 4:1 EtOH/toluene (see details in each reaction) (1 mL) and then aromatic compound (0.80–1.6 mmol) and PTS-Si (0.17 mmol) were sequentially added at 0 °C. The stirring was continued (for time and temperature noted in each Table) and then the mixture was filtered through a short pad cotton wool. Removal of the solvent afforded the crude product, which was purified by preparative thin-layer chromatography (PTLC).

4-Bromo-5-methoxy-2-(2,4,6-trimethoxybenzyl)phenol (8). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.042 g, 0.11 mmol, 71%). R_f 0.50 (20% EtOAc/hexanes). Mp 110.5–112.5 °C. FTIR (UATR): ν_{max} 3370, 2940, 2839, 1594, 1488, 1455, 1196, 1137, 1104, 1051 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 3.93 (s, 6H), 6.18 (s, 2H), 6.45 (s, 1H), 7.55 (s, 1H), 7.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.6, 55.4, 55.9 (2C), 56.2, 91.2 (2C), 100.7, 100.8, 108.8, 120.2, 135.1, 154.95, 155.04, 157.7 (2C), 159.9. LRMS (EI) *m/z* (rel intensity) 384 (4) $[C_{17}H_{19}{}^{81}BrO_5]^+$, 382 (4) $[C_{17}H_{19}{}^{79}BrO_5]^+$, 168 (100), 139 (25). TOF-HRMS calcd for $C_{17}H_{20}{}^{81}BrO_5$ $(M+H)^+$, 385.0470, found 385.0477, for $C_{17}H_{20}{}^{79}BrO_5$ $(M+H)^+$, 383.0489, found 383.0489.

4-Bromo-2-(2,4-dimethoxybenzyl)-5-methoxyphenol (9a). Following the general procedure and purification by PTLC, the product was obtained as colorless oil (0.043 g, 0.12 mmol, 78%). R_f 0.38 (30% EtOAc/hexanes). FTIR (UATR): ν_{max} 3373, 2938, 2836, 1610, 1587, 1505, 1489, 1464, 1289, 1206, 1153, 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.73 (s, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 6.45 (s, 1H), 6.49 (dd, *J* = 6.2, 2.3 Hz, 1H), 7.14 (d, *J* = 6.2 Hz, 1H), 7.16 (d, *J* = 2.3 Hz, 1H), 7.34 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.3, 55.5, 55.8, 56.2, 98.8, 101.3, 101.4, 105.7, 120.5, 120.8, 130.9, 133.8, 154.4, 155.4, 156.0, 159.8. LRMS (EI) *m/z* (rel intensity) 354 (4) $[C_{16}H_{17}{}^{81}BrO_4]^+$, 352 (4) $[C_{16}H_{17}{}^{79}BrO_4]^+$, 138 (100). TOF-HRMS calcd for $C_{16}H_{18}{}^{81}BrO_4$ $(M+H)^+$, 355.0364, found 355.0349, for $C_{16}H_{18}{}^{79}BrO_4$ $(M+H)^+$, 353.0383, found 353.0368.

4-Bromo-5-methoxy-2-(2,4,5-trimethoxybenzyl)phenol (9b). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.059 g, 0.15 mmol, 96%). R_f 0.38 (20% EtOAc/hexanes, developed three times). Mp 115.0–116.5 °C**.** FTIR (UATR): ν_{max} 3394, 2993, 2937, 2835, 1610, 1508, 1442, 1398, 1202, 1166, 1028 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.74 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 6.46 (s, 1H), 6.55 (s, 1H), 6.76 (s, 1H), 7.36 (s, 1H), 7.38 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.9, 56.5, 56.6, 57.0, 57.2, 98.3, 101.8, 101.9, 114.7, 120.2, 121.3, 134.5, 145.1, 149.5, 149.9, 155.6, 156.4. LRMS (EI) *m/z* (rel intensity) 384 (6) $[C_{17}H_{19}{}^{81}BrO_5]^+$, 382 (6) $[C_{17}H_{19}{}^{79}BrO_5]^+$, 168 (100), 153 (31). TOF-HRMS calcd for $C_{17}H_{20}{}^{81}BrO_5$ $(M+H)^+$, 385.0471, found 385.0470, for $C_{17}H_{20}{}^{79}BrO_5$ $(M+H)^+$, 353.0383, found 383.0489.

4-Bromo-2-(4-hydroxybenzyl)-5-methoxyphenol (9c). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.026 g, 0.084 mmol, 54%). R_f 0.22 (20% EtOAc/hexanes). Mp 124.5–126.5 °C. FTIR (UATR): ν_{max} 3388, 1611, 1509, 1444, 1400, 1205, 1130, 1049 cm^{-1}. ^1H NMR (MeOH-d_4, 300 MHz): δ 3.79 (s, 3H), 3.81 (s, 2H), 6.63 (s, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.16 (s, 1H), 8.20 (br s, 1H), 8.68 (br s, 1H). ^{13}C NMR (MeOH-d_4, 75 MHz): δ 33.6, 55.5, 99.9, 100.5, 115.1 (2C), 122.4, 129.7 (2C), 131.7, 133.7, 154.8, 155.2, 155.6. LRMS (EI) *m/z* (rel intensity) 310 (44) $[C_{14}H_{13}{}^{81}BrO_3]^+$, 308 (46) $[C_{14}H_{13}{}^{79}BrO_3]^+$, 217 (95), 215 (100), 115 (56), 107 (68), 94 (53), 69 (45). TOF-HRMS calcd for $C_{14}H_{12}{}^{81}BrO_3$ $(M-H)^+$, 308.9945, found 308.9957, for $C_{14}H_{12}{}^{79}BrO_3$ $(M-H)^+$, 306.9964, found 306.9957.

4-Bromo-2-(2,4-dihydroxybenzyl)-5-methoxyphenol (9d). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.036 g, 0.11 mmol, 70%). R_f 0.33 (10% MeOH/CH_2Cl_2). Mp 168.5–169.5 °C. FTIR (UATR): ν_{max} 3311, 2935, 1614, 1506, 1490, 1443, 1292, 1201, 1163, 1130, 1049 cm^{-1}. ^1H NMR (MeOH-d_4, 300 MHz): δ 3.78 (s, 2H), 3.79 (s, 3H), 6.32 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 6.60 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H). ^{13}C NMR (MeOH-d_4, 75 MHz): δ 28.2, 55.5, 56.6, 100.1, 100.6, 102.6, 107.1, 117.9, 122.0, 131.0, 133.6, 155.0, 155.2, 156.9. LRMS (EI) *m/z* (rel intensity) 326 (16) $[C_{14}H_{13}{}^{81}BrO_4]^+$, 324 (16) $[C_{14}H_{13}{}^{79}BrO_4]^+$, 217 (54), 215 (58), 123 (100), 71 (63), 69 (63). TOF-HRMS calcd for $C_{14}H_{18}{}^{81}BrO_5$ $(M+H)^+$, 327.0070, found 327.0051, for $C_{14}H_{14}{}^{79}BrO_5$ $(M+H)^+$, 325.0070, found 325.0056.

4-Bromo-2-(2,4,6-trihydroxybenzyl)-5-methoxyphenol (9e). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.038 g, 0.12 mmol, 72%). R_f 0.33 (10% MeOH/CH_2Cl_2). Mp 199.0–200.0 °C. FTIR (UATR): ν_{max} 3326, 1614, 1489, 1467, 1199, 1142, 1035 cm^{-1}. ^1H NMR (MeOH-d_4, 300 MHz): δ 3.60 (s, 2H), 3.62 (s, 3H), 5.87 (s, 2H), 6.37 (s, 1H), 7.29 (s, 1H), 8.58 (s, 2H). ^{13}C NMR (MeOH-d_4, 75 MHz): δ 22.0, 55.5, 94.9 (2C), 100.1, 100.7, 105.2, 121.7, 134.2, 154.8, 155.0, 155.9 (2C), 157.0. TOF-HRMS calcd for $C_{14}H_{14}{}^{81}BrO_4$ $(M+H)^+$, 343.0000, found 343.000, for $C_{14}H_{14}{}^{79}BrO_4$ $(M+H)^+$, 341.0019, found 341.0003.

4-Bromo-2-(4-hydroxy-3-methoxybenzyl)-5-methoxyphenol (9f). Following the general procedure and purification by PTLC, the product was obtained as a pale yellow solid (0.032 g, 0.09 mmol, 59%). R_f 0.49 (60% EtOAc/hexanes). Mp 110.3–112.4 °C. FTIR (UATR): ν_{max} 3430, 2937, 1059, 1205 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.81 (s, 3H), 3.82 (s, 5H), 5.18 (brs, 1H), 5.57 (brs 1H), 6.42 (s, 1H), 6.62–6.73 (m, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.5, 55.9, 56.2, 101.0, 101.7, 110.9, 114.5, 120.5, 121.1, 130.9, 134.2, 144.3 146.8, 154.2, 155.3. LRMS (EI) *m/z* (rel intensity) 340 (17) $[C_{15}H_{15}{}^{81}BrO_4]^+$, 338 (17) $[C_{15}H_{15}{}^{79}BrO_4]^+$, 217 (39), 215 (43), 124 (100). TOF-HRMS calcd for $C_{15}H_{14}{}^{81}BrO_4$ $(M-H)^+$, 339.0062, found 339.0055, for $C_{15}H_{14}{}^{79}BrO_4$ $(M-H)^+$, 337.0081, found 337.0074.

4-Bromo-2-(4-hydroxy-2-methoxybenzyl)-5-methoxyphenol and 4-bromo-2-(2-hydroxy-4-methoxybenzyl)-5-methoxyphenol (9g). Following the general procedure and purification by PTLC, the product was obtained as red brown oil (0.052 g, 0.15 mmol, 95%). R_f 0.49 (60% EtOAc/hexanes). FTIR (UATR): ν_{max} 3363, 2939, 1613, 1196 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.66 (s, 3H), 3.67 (s, 3H),

3.70 (s, 2H), 3.73 (s, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 6.31–6.41 (m, 4H), 6.42–6.49 (m 2H), 7.04 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.34 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.2, 29.3, 55.3, 55.7, 56.1, 56.2, 99.2, 100.9, 101.2, 101.5, 101.9, 102.1, 106.9, 108.4, 119.2, 120.1, 120.8, 120.9, 131.0, 131.1, 133.8, 133.9, 152.8, 153.0, 154.1, 155.1, 155.2, 155.6, 156.0, 159.3. LRMS (EI) *m/z* (rel intensity) 340 (25) $[C_{15}H_{15}{}^{81}BrO_4]^+$, 338 (27) $[C_{15}H_{15}{}^{79}BrO_4]^+$, 217 (59), 215 (65), 137 (80), 124 (100). TOF-HRMS calcd for $C_{15}H_{14}{}^{81}BrO_4$ $(M-H)^+$, 339.0062, found 339.0065, for $C_{15}H_{14}{}^{79}BrO_4$ $(M-H)^+$, 337.0081, found 337.0083.

4-Bromo-2-(2-hydroxy-4,5-dimethoxybenzyl)-5-methoxyphenol (9h). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.036 g, 0.10 mmol, 60%). R_f 0.34 (60% EtOAc/hexanes, developed twice). Mp 188.3–190.0 °C. FTIR (UATR): ν_{max} 3355, 2936, 1200 cm^{-1}. ^{1}H NMR (10:1 $CDCl_3$:MeOH-d_4, 300 MHz): δ 3.75 (s, 2H), 3.81 (s, 9H), 6.48 (s, 2H), 6.72 (s, 1H), 7.30 (s, 1H). ^{13}C NMR (10:1 $CDCl_3$:MeOH-d_4, 75 MHz): δ 29.3, 55.5, 55.8, 56.4, 100.6, 100.7, 100.8, 114.0, 117.8, 121.2, 133.4, 142.5, 147.1, 148.1, 153.9, 154.7. LRMS (EI) *m/z* (rel intensity) 370 (10) $[C_{16}H_{17}{}^{81}BrO_5]^+$, 368 (10) $[C_{16}H_{17}{}^{79}BrO_5]^+$, 167 (100), 154 (90). TOF-HRMS calcd for $C_{16}H_{16}{}^{81}BrO_5$ $(M-H)^+$, 369.0157, found 339.0184, for $C_{16}H_{16}{}^{79}BrO_5$ $(M-H)^+$, 367.0176, found 367.0174.

4-(5-Bromo-2-hydroxy-4-methoxybenzyl)naphthalen-1-ol (9i). Following the general procedure and purification by PTLC, the product was obtained as a brown solid (0.035 g, 0.10 mmol, 61%). R_f 0.51 (60% EtOAc/hexanes). Mp 124.1–125.8 °C. FTIR (UATR): ν_{max} 3404, 2925, 1587, 1204 cm^{-1}. ^{1}H NMR (20:1 $CDCl_3$:MeOH-d_4, 300 MHz): δ 3.82 (s, 3H), 4.22 (s, 2H), 6.50 (s, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.40–7.52 (m, 2H), 7.85–7.98 (m, 1H), 8.20–8.33 (m, 1H). ^{13}C NMR (20:1 $CDCl_3$:MeOH-d_4, 75 MHz): δ 31.3, 56.1, 100.3, 100.8, 107.6, 121.0, 122.5, 123.9, 124.5, 125.2, 126.2, 126.75, 126.81, 132.9, 133.7, 151.6, 154.4, 154.6. LRMS (EI) *m/z* (rel intensity) 360 (8) $[C_{18}H_{15}{}^{81}BrO_3]^+$, 358 (9) $[C_{18}H_{15}{}^{79}BrO_3]^+$, 217 (36), 215 (37), 144 (100). TOF-HRMS calcd for $C_{18}H_{14}{}^{81}BrO_3$ $(M-H)^+$, 359.0102, found 359.0123, for $C_{18}H_{14}{}^{79}BrO_3$ $(M-H)^+$, 357.0121, found 357.0126.

1-(5-Bromo-2-hydroxy-4-methoxybenzyl)naphthalen-2-ol (9j). Following the general procedure and purification by PTLC, the product was obtained as a red brown solid (0.055 g, 0.15 mmol, 96%). R_f 0.49 (60% EtOAc/hexanes). Mp 111.3–114.4 °C. FTIR (UATR): ν_{max} 3287, 2938, 1199 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.52 (s, 1H), 3.59 (s, 3H), 4.26 (s, 2H), 6.31 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.47–7.60 (m, 3H), 7.73 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.6, 56.0, 100.8, 101.8, 117.2, 118.0, 119.7, 122.9, 123.5, 127.0, 128.8 (2C), 129.8, 133.1, 134.3, 149.6, 153.8, 155.1. LRMS (EI) *m/z* (rel intensity) 360 (11) $[C_{18}H_{15}{}^{81}BrO_3]^+$, 358 (11) $[C_{18}H_{15}{}^{79}BrO_3]^+$, 217 (31), 215 (31), 204 (31), 202 (35), 144 (100). TOF-HRMS calcd for $C_{18}H_{14}{}^{81}BrO_3$ $(M-H)^+$, 359.0102, found 359.0118, for $C_{18}H_{14}{}^{79}BrO_3$ $(M-H)^+$, 357.0121, found 357.0119.

4-Bromo-5-methoxy-2-((2-methoxynaphthalen-1-yl)methyl)phenol (9k). Following the general procedure and purification by PTLC, the product was obtained as brown oil (0.029 g, 0.08 mmol, 49%). R_f 0.62 (60% EtOAc/hexanes). FTIR (UATR): ν_{max} 3354, 2937, 1249 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.76 (s, 3H), 4.09 (s, 3H), 4.28 (s, 2H), 6.41 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 7.54 (s, 1H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.61 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 8.17 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 56.1, 57.0, 100.9, 101.1, 112.8, 119.2, 120.4, 123.4, 124.0, 127.1, 128.8, 129.1, 130.0, 132.9, 134.3, 152.4, 155.2 (2C). LRMS (EI) *m/z* (rel intensity) 374 (5) $[C_{19}H_{18}{}^{81}BrO_3]^+$, 372 (5) $[C_{19}H_{18}{}^{79}BrO_3]^+$, 158 (100). TOF-HRMS calcd for $C_{19}H_{19}{}^{81}BrO_3$ $(M+H)^+$, 375.0416, found 375.0401, for $C_{19}H_{19}{}^{79}BrO_3$ $(M+H)^+$, 373.0434, found 373.0418.

2-(Benzofuran-3-ylmethyl)-4-bromo-5-methoxyphenol (9l). Following the general procedure and purification by PTLC, the product was obtained as brown oil (0.017 g, 0.05 mmol, 32%). R_f 0.24 (30% EtOAc/hexanes). FTIR (UATR): ν_{max} 3502, 2925, 2853, 1454, 1205 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84, (s, 3H), 4.02 (s, 2H), 5.46 (s, 1H), 6.42 (s, 1H), 6.47 (s, 1H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.36 (s, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.9, 56.3, 101.3 102.2, 103.3, 110.9, 116.9, 120.6, 122.8, 123.8, 128.5, 134.4, 154.1, 154.8, 155.7, 156.2. LRMS (EI) *m/z* (rel int, ensity) 334 (8) $[C_{16}H_{13}{}^{81}BrO_3]^+$, 332 (8) $[C_{16}H_{13}{}^{79}BrO_3]^+$, 178 (100), 57 (70). TOF-HRMS calcd for $C_{16}H_{13}{}^{81}BrO_3$ $(M)^+$, 334.0023, found 334.0031, for $C_{16}H_{13}{}^{79}BrO_3$ $(M)^+$, 332.0043, found 332.0037.

4-Bromo-5-methoxy-2-((1-methyl-1*H*-indol-3-yl)methyl)phenol (9m). Following the general procedure and purification by PTLC, the product was obtained as brown oil (0.047 g, 0.14 mmol, 84%). R_f 0.24 (30% EtOAc/hexanes). FTIR (UATR): ν_{max} 3463, 2920, 1049, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (s, 3H), 3.80 (s, 3H), 4.00 (s, 2H), 6.44 (s, 1H), 6.79 (s, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.16–7.33 (m, 2H), 7.37 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.0, 32.7, 56.2, 101.1, 101.5, 109.3, 111.3, 119.1, 119.2, 119.9, 122.1, 127.0, 127.3, 133.9, 137.4, 154.7, 155.2. LRMS (EI) *m/z* (rel intensity) 347 (10) $[C_{17}H_{16}{}^{81}BrNO_3]^+$, 345 (10) $[C_{17}H_{16}{}^{79}BrNO_3]^+$, 131 (100). TOF-HRMS calcd for $C_{17}H_{17}{}^{81}BrNO_3$ $(M+H)^+$, 348.0418, found 348.0419, for $C_{17}H_{17}{}^{79}BrNO_3$ $(M+H)^+$, 346.0437, found 346.0439. Note that this compound is not stable and decomposes upon storage even at low temperature (−20 °C).

4-(Methoxylmethoxy)benzyl acetate (10c). To a solution of 4-hydroxybenzaldehyde (2.50 g, 20 mmol) in DMF (30 mL) was sequentially added NaH (1.30 g, 30 mmol), and MOMCl (2.30 mL, 30 mmol) at 0 °C. The reaction mixture was stirred for 4 h at rt and then quenched with water (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (7 x 50 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude product, which was purified by column chromatography (0–30% EtOAc/hexane) to furnish the product as colorless oil (2.60 g, 16 mmol, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.50 (s, 3H), 5.26 (s, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H), 9.91 (s, 1H).

A mixture of 4-(methoxylmethoxy)benzaldehyde (1.10 g, 6.80 mmol) in EtOH (10 mL) was added $NaBH_4$ (0.88 g, 17.0 mmol) and stirred for 1 h at rt. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (15 mL). The organic layer was washed with water (3 x 10mL), brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 4-(methoxylmethoxy)benzyl alcohol which was used for the next step without purification.

To a solution of 4-(methoxylmethoxy)benzyl alcohol in DCM (20 mL) was sequentially added *N*,*N*-dimethylaminopyridine (DMAP; 1.20 g, 10.2 mmol), Et_3N (1.40 mL, 10.2 mmol) and acetic anhydride (1.00 mL. 10.2 mmol) at 0 °C. The reaction mixture was stirred for 3 h at rt and then quenched with water (15 mL). The aqueous layer was extracted with DCM (3 x 20 mL).

The combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude product, which was purified by column chromatography (0–30% EtOAc/hexane) to give the desired benzyl acetate as colorless oil (1.10 g, 5.10 mmol, 75%). R_f 0.45 (25% EtOAc/hexanes). FTIR (UATR): ν_{max} 2956, 1736, 1514, 1226 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.08 (s, 3H), 3.47 (s, 3H), 5.04 (s, 2H), 5.18 (s, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.0, 56.0, 66.0, 94.3, 116.2 (2C), 129.3, 130.0 (2C), 157.2, 170.9. LRMS (EI) *m/z* (rel intensity) 210 (M^+, 100), 121 (93). TOF-HRMS calcd for $C_{11}H_{14}NaO_4$ ($M+Na^+$) 233.0784, found 233.0786.

4-Isopropoxybenzyl acetate (10d). To a solution of 4-hydroxybenzaldehyde (1.20 g, 9.80 mmol) in DMF (20 ml) was sequentially added NaH (0.65 g, 14.7 mmol), and *i*-PrBr (1.4 mL. 14.7 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt and then quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (7 x 50 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 4-isopropoxybenzaldehyde which was used for the next step without purification.

A mixture of 4-isopropoxybenzaldehyde in EtOH (20 mL) was added $NaBH_4$ (1.30 g, 24.5 mmol) and stirred for 1 h at rt. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (20 mL). The organic layer was washed with water (3 x 20mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 4-isopropoxybenzyl alcohol which was used for the next step without purification.

To a solution of 4-isopropoxybenzyl alcohol in DCM (20 mL) was sequentially added *N*,*N*-dimethylaminopyridine (DMAP; 1.80 g, 14.7 mmol), Et_3N (2.1 mL, 14.7 mmol) and acetic anhydride (1.40 mL. 14.7 mmol) at 0 °C. The reaction mixture was stirred for 3 h at rt and then quenched with water (15 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried over Na_2SO_4) and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude product, which was purified by column chromatography (0–30% EtOAc/hexane) to give the desired benzyl acetate as colorless oil (1.4 g, 6.7 mmol, 70%). R_f 0.30 (25% EtOAc/hexanes). FTIR (UATR): ν_{max} 2978, 1736, 1510, 1223 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (d, *J* = 5.9 Hz, 6H), 2.07 (s, 3H), 4.54 (sep, *J* = 5.9 Hz, 1H), 5.03 (s, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 22.0 (2C), 66.1, 69.8, 115.8 (2C), 127.7, 130.1 (2C), 158.0, 171.0. LRMS (EI) *m/z* (rel intensity) 208 (M^+, 20), 166 (27), 124 (64), 107 (100). TOF-HRMS calcd for $C_{12}H_{16}NaO_3$ ($M+Na^+$) 231.0992, found 231.0988.

4-(Acetyloxy)benzyl acetate (10e). To a mixture of 4-hydroxybenzaldehyde (1.20 g, 10 mmol) in EtOH (20 mL) was added $NaBH_4$ (1.3 g, 25 mmol) and the reaction was stirred for 1 h at rt. The solvent was removed under reduced pressure and the residue dissolved in water (20 mL). The aqueous layer was acidified with 6 M HCl to pH 2 and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 4-hydroxybenzyl alcohol which was used directly in the next step without purification.

To a solution of 4-hydroxybenzyl alcohol in DCM (50 mL) was sequentially added *N*,*N*-dimethylaminopyridine (DMAP; 3.70 g, 30 mmol), Et_3N (4.2 mL, 30 mmol) and acetic anhydride (2.80 mL. 30 mmol) at 0°C. The reaction mixture was stirred for 3 h at rt and then quenched with water (20 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude product, which was purified by column chromatography (0–40% EtOAc/hexane) to furnish the desired product as colorless oil (1.10 g, 5.50 mmol, 55%). R_f 0.33 (25% EtOAc/hexanes). FTIR (UATR): ν_{max} 2956, 1736, 1509, 1188 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.10 (s, 3H), 2.30 (s, 3H), 5.09 (s, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1 (2C), 65.6, 121.7 (2C), 129.5 (2C), 133.5, 150.5, 169.4, 170.8. LRMS (EI) *m/z* (rel intensity) 208 (M^+, 10), 166 (64), 124 (59), 107 (100). TOF-HRMS calcd for $C_{11}H_{12}NaO_4$ ($M+Na^+$) 231.0628, found 231.0621.

2-Methoxy-4-(methoxylmethoxy)benzyl acetate (10g). To a solution of 2,4-dihydroxybenzaldehyde (2.10 g, 15.0 mmol) in DMF (30 mL) was sequentially added K_2CO_3 (2.50 g, 18.0 mmol), and MOMCl (1.40 mL, 18.0 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt and then quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (7 x 50 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 2-hydroxy-4-(methoxylmethoxy)benzaldehyde which was used in the next step without purification.

A crude 2-hydroxy-4-(methoxylmethoxy)benzaldehyde was dissolved in DMF (20 mL) and then NaH (1.00 g, 22.5 mmol) and iodomethane (1.4 mL, 22.5 mmol) were sequentially added at rt. The stirring was continued for 1 h at the same temperature and the reaction was then quenched with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (7 x 50 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 2-methoxy-4-(methoxylmethoxy)benzaldehyde which was used in the next step without purification.

To a mixture of the crude 2-methoxy-4-(methoxylmethoxy)benzaldehyde in EtOH (30 mL) was added $NaBH_4$ (2.00 g, 37.5 mmol) and the mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (20 mL). The organic layer was washed with water (3 x 20mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude 2-methoxy-4-(methoxylmethoxy)benzyl alcohol which was used for the next step without purification.

To a solution of 2-methoxy-4-(methoxylmethoxy)benzyl alcohol in DCM (30 mL) was sequentially added *N*,*N*-dimethylaminopyridine (DMAP; 2.80 g, 22.5 mmol), Et_3N (3.1 mL, 22.5 mmol) and acetic anhydride (2.10 mL. 22.5 mmol) at 0 °C. The reaction mixture was stirred for 3 h at rt and then quenched with water (15 mL). The aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with water (3 x 20 mL), brine (20 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated (aspirator then vacuo) to give a crude product, which was purified by column chromatography (0–30% EtOAc/hexane) to give the desired benzyl acetate as colorless oil (1.30 g, 5.20 mmol, 35%). R_f 0.33 (25% EtOAc/hexanes). FTIR (UATR): ν_{max} 2957, 1733, 1226, 1004 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.07 (s, 3H), 3.48 (s, 3H), 3.82 (s, 3H), 5.09 (s, 2H), 5.18 (s, 2H), 6.60 (s, 1H), 6.62 (d, *J* = 9.6 Hz, 1H), 7.23 (d, *J* = 9.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75

MHz): δ 21.1, 55.5, 56.0, 61.6, 94.4, 100.0, 107.0, 117.7, 131.3, 158.8 (2C), 171.1. LRMS (EI) *m/z* (rel intensity) 240 (M^+, 37), 181 (42), 151 (47), 136 (86), 108 (100). TOF-HRMS calcd for $C_{12}H_{16}O_5Na$ ($M+Na^+$) 263.0890, found 263.0876.

2-(2,4,6-Trimethoxybenzyl)phenol (11b). Following the general procedure and purification by PTLC, the product was obtained as colorless oil (0.016 g, 0.068 mmol, 38%). R_f 0.40 (20% EtOAc/hexanes). FTIR (UATR): ν_{max} 3392, 2940, 2838, 1593, 1488, 1455, 1204, 1145, 1114 cm^{-1}. ^1H NMR ($CDCl_3$, 300MHz): δ 3.77 (s, 3H), 3.84 (s, 2H), 3.89 (s, 6H), 6.15 (s, 2H), 6.77-6.83 (m, 2H), 7.06 (td, *J* = 7.5, 1.6 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.5, 55.4, 55.9 (2C), 91.1 (2C), 109.0, 116.0, 119.8, 126.5, 127.6, 131.8, 154.6, 157.8 (2C), 159.8. LRMS (EI) *m/z* (rel intensity) 275 ($M+H^+$, 4), 274 (M^+, 23), 168 (100), 139 (32). TOF-HRMS calcd for $C_{16}H_{19}O_4$ ($M+H^+$) 275.1278, found 275.1279.

4-(2,4,6-Trimethoxybenzyl)phenol (11c). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.033 g, 0.12 mmol, 76% from 10b, 0.033 g, 0.12 mmol, 75% from 10c). R_f 0.20 (20% EtOAc/hexanes). Mp 142.0–143.8 °C. FTIR (UATR): ν_{max} 3415, 2939, 2837, 1594, 1456, 1203, 1186, 1146, 1117 cm^{-1}. ^1H NMR ($CDCl_3$, 300MHz): δ 3.77 (s, 6H), 3.79 (s, 3H), 3.83 (s, 2H), 6.14 (s, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.3, 55.3, 55.7 (2C), 90.7 (2C), 110.8, 114.8 (2C), 129.4 (2C), 133.9, 153.7, 158.8 (2C), 159.5. LRMS (EI) *m/z* (rel intensity) 275 ($M+H^+$, 13), 274 (M^+, 75), 181 (40), 168 (100), 137 (27), 121 (29), 107 (36). TOF-HRMS calcd for $C_{16}H_{19}O_4$ ($M+H^+$) 275.1278, found 275.1279.

2-(4-Isopropoxybenzyl)-1,3,5-trimethoxybenzene (11d). Following the general procedure and purification by PTLC, the product was obtained as colorless oil (0.049 g, 0.15 mmol, 95%). R_f 0.48 (10% EtOAc/hexanes, developed twice). FTIR (UATR): ν_{max} 2974, 2936, 1595, 1116 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (d, *J* = 6.0 Hz, 6H), 3.77 (s, 6H), 3.79 (s, 3H), 3.85 (s, 2H), 4.44 (sep, *J* = 6.0 Hz, 1H), 6.14 (s, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.1 (2C), 27.3, 55.3, 55.7 (2C), 69.7, 90.6 (2C), 110.7, 115.4 (2C), 129.2 (2C), 134.2, 155.6, 158.7 (2C), 159.5. LRMS (EI) *m/z* (rel intensity) 316 (M^+, 31), 274 (19), 181 (36), 168 (100), 107 (46). ESITOF-HRMS calcd for $C_{19}H_{24}NaO_4$ ($M+Na^+$) 339.1566, found 339.1563.

2-(4-Methoxybenzyl)-1,3,5-trimethoxybenzene (11e). Following the general procedure and purification by PTLC, the product was obtained as colorless oil (0.038 g, 0.13 mmol, 81%). R_f 0.50 (10% EtOAc/hexanes, developed three times). FTIR (UATR): ν_{max} 2937, 2836, 1595, 1116 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.74 (s, 3H), 3.78 (s, 9H), 3.86 (s, 2H), 6.14 (s, 2H), 6.75 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.3, 55.1, 55.3, 55.7 (2C), 90.6 (2C), 110.7, 113.3 (2C), 129.2 (2C), 134.4, 157.3, 158.7 (2C), 159.5. LRMS (EI) *m/z* (rel intensity) 288 (M^+, 36), 257 (15), 181 (27), 121 (100), 91 (23). ESITOF-HRMS calcd for $C_{17}H_{20}NaO_4$ ($M+Na^+$) 311.1253, found 311.1252.

5-Methoxy-2,4-bis(2,4,6-trimethoxybenzyl)phenol (12). Following the general procedure and purification by PTLC, the product was obtained as orange solid (0.044 g, 0.09 mmol, 56% from **10e**, 0.018 g, 0.04 mmol, 23% from **10f**). R_f 0.43 (80:18:2 CH_2Cl_2/hexanes/MeOH). Mp 184.4–186.8 °C. FTIR (UATR): ν_{max} 3407, 2940, 1594, 1204 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.61 (s, 2H), 3.69 (s, 6H), 3.71 (s, 6H), 3.74 (s, 3H), 3.79 (s, 5H), 3.85 (s, 3H), 6.06 (s, 2H), 6.21 (s, 2H), 6.37 (s, 1H), 6.66 (s, 1H), 7.29 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 22.6, 55.4 (2C), 55.45, 55.53 (2C), 55.8 (2C), 90.8 (2C), 91.0 (2C), 98.9, 109.7, 110.0, 117.4, 120.7, 130.4, 152.9, 156.7, 157.6 (2C), 159.5 (4C). LRMS (EI) *m/z* (rel intensity) 484 (M^+, 33), 316 (82), 181 (100), 168 (90). TOF-HRMS calcd for $C_{27}H_{32}NaO_8$ ($M+Na^+$) 507.1989, found 507.1984.

2-(4-Hydroxybenzyl)-4,5-dimethoxyphenol (13a). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.034 g, 0.13 mmol, 83%). R_f 0.34 (60% EtOAc/hexanes). Mp 165.7–167.0 °C. FTIR (UATR): ν_{max} 3393, 1513, 1203 cm^{-1}. ^1H NMR (5:1 $CDCl_3$:MeOH-d_4, 300 MHz): δ 3.74 (s, 3H), 3.79 (s, 3H), 3.83 (s, 2H), 6.47 (s, 1H), 6.57 (s, 1H), 6.74 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (5:1 $CDCl_3$:MeOH-d_4, 75 MHz): δ 34.2, 55.6, 56.4, 100.7, 114.4, 114.9 (2C), 118.9, 129.4 (2C), 132.0, 142.1, 147.6, 148.1, 154.4. LRMS (EI) *m/z* (rel intensity) 260 (M^+, 75), 166 (100). TOF-HRMS calcd for $C_{15}H_{16}O_4$ (M^+) 260.1043, found 260.1039.

4-((6-Methoxybenzo[d][1,3]dioxol-5-yl)methyl)phenol (13b). Following the general procedure and purification by PTLC, the product was obtained as a white solid (0.036 g, 0.14 mmol, 86%). R_f 0.33 (80:18:2 CH_2Cl_2/hexanes/MeOH). Mp 107.8–109.2 °C. FTIR (UATR): ν_{max} 3417, 1508, 1175, 1037 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.77 (s, 3H), 3.81 (s, 2H), 4.60 (s, 1H), 5.86 (s, 2H), 6.38 (s, 1H), 6.57 (s, 1H), 6.82 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.3, 55.3, 98.6, 100.9, 109.9, 114.1 (2C), 119.1, 129.5 (2C), 131.8, 141.4, 146.5, 148.1, 158.2. LRMS (EI) *m/z* (rel intensity) 258 (M^+, 24), 150 (50), 108 (100). TOF-HRMS calcd for $C_{15}H_{14}O_4$ (M^+) 258.0887, found 258.0875.

4-(4-Hydroxybenzyl)naphthalen-1-ol (13c). Following the general procedure and purification by PTLC, the product was obtained as a pale orange solid (0.031 g, 0.12 mmol, 78%). R_f 0.54 (60% EtOAc/hexanes). Mp 182.1–184.5 °C. FTIR (UATR): ν_{max} 3337, 1511, 1223 cm^{-1}. ^1H NMR (4:1 $CDCl_3$:MeOH-d_4, 300 MHz): δ 4.25 (s, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 6.1, 3.1 Hz, 2H), 7.90 (dd, *J* = 6.1, 3.1 Hz, 1H), 8.26 (dd, *J* = 6.1, 3.1 Hz, 1H). ^{13}C NMR (4:1 $CDCl_3$:MeOH-d_4, 75 MHz): δ 37.3, 107.1, 114.7 (2C), 122.2, 123.8, 123.9, 125.1, 125.6, 126.9, 127.8, 129.1 (2C), 132.0, 132.7, 151.4, 154.3. LRMS (EI) *m/z* (rel intensity) 250 (M^+, 100), 144 (60), 107 (52). TOF-HRMS calcd for $C_{17}H_{14}O_2$ (M^+) 250.0988, found 250.0992.

1-(4-Hydroxybenzyl)naphthalen-2-ol (13d). Following the general procedure and purification by PTLC, the product was obtained as a pale orange solid (0.039 g, 0.15 mmol, 97%). R_f 0.51 (60% EtOAc/hexanes). Mp 203.0–205.4 °C. FTIR (UATR): ν_{max} 3345, 1510, 1219 cm^{-1}. ^1H NMR (4:1 $CDCl_3$:MeOH-d_4, 300 MHz): δ 4.36 (s, 2H), 6.67 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (4:1 $CDCl_3$:MeOH-d_4, 75 MHz): δ 29.3, 114.7 (2C), 117.6, 118.6, 122.2, 123.2, 125.8, 127.6, 128.0, 128.7, 128.9 (2C), 132.0, 133.6, 151.9, 154.1. LRMS (EI) *m/z* (rel intensity) 250 (M^+, 56), 157 (100), 128 (36). TOF-HRMS calcd for $C_{17}H_{14}O_2$ (M^+) 250.0988, found 250.0997.

4-((2-Methoxynaphthalen-1-yl)methyl)phenol (13e). Following the general procedure and purification by PTLC, the product was obtained as brown oil (0.031 g, 0.12 mmol, 73%). R_f 0.63 (60% EtOAc/hexanes). FTIR (UATR): ν_{max} 3368, 2929, 1509, 1249 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H), 4.37 (s, 2H), 5.19 (brs, 1H), 6.62 (d, *J* = 7.9 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 2H), 7.22–7.34 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.76 (d,

J = 8.8 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.6, 56.6, 133.6, 115.1 (2C), 122.0, 123.2, 123.7, 126.4, 128.2, 128.4, 129.2 (3C), 133.2, 133.3, 153.4, 154.6. LRMS (EI) *m/z* (rel intensity) 264 (M^+, 100), 233 (43), 158 (46). TOF-HRMS calcd for $C_{18}H_{16}O_2$ (M^+) 264.1145, found 264.1152.

4-(Benzofuran-3-ylmethyl)phenol (13f). Following the general procedure and purification by PTLC, the product was obtained as yellow oil (0.028 g, 0.12 mmol, 77%). R_f 0.47 (60% EtOAc/hexanes). FTIR (UATR): ν_{max} 3374, 2924, 1515, 1252, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.01 (s, 2H), 5.07 (brs, 1H), 6.33 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.16–7.25 (m, 2H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.1, 103.1, 110.9, 115.4 (2C), 120.3, 122.5, 123.3, 128.8, 129.4, 130.1 (2C), 130.8, 154.3, 158.2. LRMS (EI) *m/z* (rel intensity) 224 (M^+, 93), 223 (100), 131 (38). TOF-HRMS calcd for $C_{15}H_{12}O_2$ (M^+) 224.0832, found 224.0841.

4-(2,4,6-Trimethylbenzyl)phenol (13g). Following the general procedure and purification by PTLC, the product was obtained as white solid (0.009 g, 0.04 mmol, 25%). R_f 0.49 (30% EtOAc/hexanes). Mp 91.8–93.2 °C. FTIR (UATR): ν_{max} 3337, 2922, 1613, 1509, 1227 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.20 (s, 6H), 2.28 (s, 3H), 3.92 (s, 2H), 4.71 (brs, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.88 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.1 (2C), 20.9, 33.8, 115.2 (2C), 128.86 (2C), 128.89 (2C), 132.2, 134.1, 135.7, 136.9 (2C), 153.5. LRMS (EI) *m/z* (rel intensity) 226 (M^+, 17), 211 (48), 149 (33), 132 (100). TOF-HRMS calcd for $C_{16}H_{18}O$ (M^+) 226.1352, found 226.1344.

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24. It has been anticipated that generation of QM under acidic conditions may not be compatible with electron-rich aromatic systems and would lead to increased dimerization of QM or side reactions between QMs and nucleophiles. While nucleophilic addition to quinone methides has been studied before, the use of electron-rich aromatic compounds as nucleophiles for such reaction has been scarcely described before. For some examples, see: (a) Lau, C. K.; Williams, H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Belanger, P. C. *Can. J. Chem.* **1989**, *67*, 1384–1387. (b) Chambers, J. D.; Crawford, J.; Williams, H. W. R.; Dufresne, C.; Scheigetz, J.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1992**, *70*, 1717–1732. (c) Biljic, O.; Young, D. W. *J. Chem. Soc,. Perkin Trans. 1* **1980**, 1233–1239. (d) Asherson, J. L.; Bilgic, O.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3041–3047.
25. A similar reaction using *p*-methoxybenzyl alcohol as a starting material gave **11e** in 86% yield but as an inseparable mixture with a dimer, resulting from dehydration of *p*-methoxybenzyl alcohol under the reaction condition. For characterization of **10f**, please see: (a) Prashad, M.; Jigajinni, V. B. *Indian J. Chem.* **1980**, *19B*, 822-823. (b) Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani *Tetrahedron* **2003**, *59*, 7661-7668.
26. It appears that the [$^+$CH$_2$–OMe] from the cleavage of the MOM group participated in these reactions differently. For compound **10g** and **10h**, [$^+$CH$_2$–OMe] was attacked by the resulting monoalkylated products. Subsequently, the methoxy group was cleaved and another molecule of 1,3,5-trimethoxybenzene was incorporated. For compound **13b**, [$^+$CH$_2$–OMe] served as a methylating agent, which methylated the hydroxy group, generating formaldehyde as a by-product.

Supplementary Material

Supplementary data related to this article can be found online. These data include MOL files and InChiKeys of the most important compounds described in this article.