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Factors affecting orthogonality in the deprotection of 2,4-di-protected aromatic ethers employing solid-supported acids

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ABSTRACT

Selective deprotection of aromatic ethers bearing two protecting groups on the same aromatic ring by solid-supported acids (Amberlyst-15 and PTS-Si) was systematically investigated. *ortho*-Directing protonation by the carbonyl group as well as carbocation stability and quenching are the important determining factors for the orthogonal deprotection process. Stablilized carbocations (e.g., those from the MOM and PMB groups) could be removed with high selectivity.

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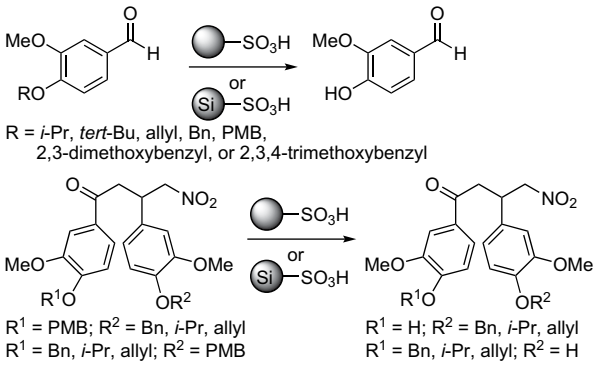
1. Introduction

Syntheses of complex natural products containing various functional groups inevitably involve the use of protecting groups. However, devising an appropriate strategy for protecting group manipulation is frequently challenging because the methods of introducing and removing such protecting groups must be compatible with other functional groups present in the molecules.[1,2] In addition, selective methods for removing a protecting group in the presence of other functional groups as well as other protecting groups are frequently required.[3–16] Thus, developing a general but selective method of deprotection can significantly reduce the number of steps in the protection/deprotection and render the overall syntheses less cumbersome and lengthy while more efficient and elegant.

Solid-supported reagents have been extensively used in organic synthesis and have drawn much attention from many research groups including ours because they are attractive alternatives to perform reactions more efficiently.[17–22] Immobilizing reagents on solid supports simplifies the experimental procedures by eliminating the necessity of aqueous workup. In addition, the use of solid-supported reagents provided better chemical selectivity for some transformations when compared with the solution-phase counterpart.[17,20] More importantly, conventional means such as TLC could be used to monitor the reaction progress.

Recently, our program has been involved with the use of solid-supported reagents in the synthesis of lamellarins and in the deprotection of aromatic ethers.[20–22] Our preliminary results of the deprotection of aromatic ethers employing solid-supported acids showed that the *p*-TsOH immobilized on either silica (PTS-Si) or polystyrene (PS)-divinyl benzene (DVB) polymer (Amberlyst-15) effectively cleaved various phenolic *O*-protecting groups (Scheme 1).[22] When two protecting groups were present simultaneously in the same molecule but on different aromatic rings, the group, which generated a more stabilized carbocation such as the *p*-methoxybenzyl (PMB) was removed orthogonally over the other (*i*-Pr, Bn, or allyl). Thus, carbocations were presumably the intermediates generated during the acid-mediated cleavage of these protecting groups. Carbocation stability is anticipated to play a critical role for the orthogonality. Herein, we wish to report our systematic investigation in the selective deprotection of aromatic



Scheme 1. Preliminary deprotection of aromatic ethers employing Amberlyst-15 and PTS-Si.

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ethers, which bear two protecting groups on the same aromatic rings, employing PTS-Si and Amberlyst-15 to determine the effects of *ortho*-directing protonation by the carbonyl group as well as the carbocation stability and quenching.

2. Results and discussion

The presence of two protecting groups on the same aromatic rings is arguably one of the most challenging systems to optimize for the orthogonal removal due to the susceptible nature of polyoxygenation on the aromatic ring towards the undesired Friedel–Crafts (FC)-type side reactions between the mono-deprotected product and the carbocations. We anticipated that the *ortho*-directing protonation by the carbonyl group may play an important role in the selective deprotection by directing the protonation to occur more readily on the oxygen of the protecting group *ortho* to a carbonyl-containing substituent (e.g., ester, aldehyde, or ketone). On the other hand, because the reaction mechanism implicated the intermediacy of carbocations during the deprotection, the carbocation stability and quenching was also an important consideration.

In addition to the *i*-Pr, Bn and PMB protecting groups, the methoxymethyl (MOM) group was also employed in this study. Among these four groups, the MOM group is the most easily cleaved because the resulting carbocation is stabilized by the nearby methoxy group. The benzyl-type carbocations from the Bn and PMB groups are resonance stabilized. However, the *i*-Pr cation is a localized secondary carbocation. Thus, on the basis of carbocation stability alone, the order of the C–O cleavage would follow MOM>PMB>Bn>*i*-Pr.

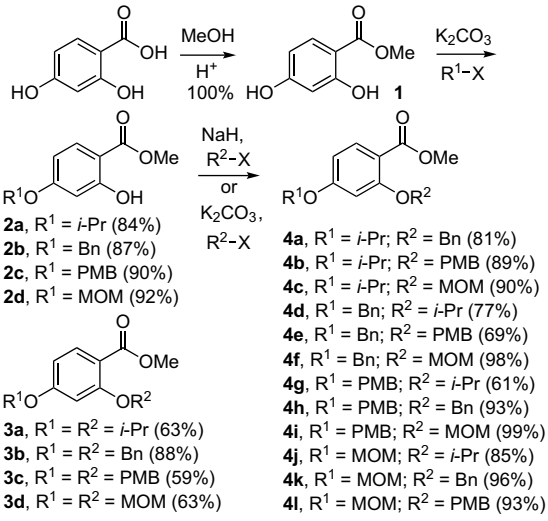
From the proposed mechanism of carbocation quenching, the *i*-Pr cation would form propene by losing a proton on the adjacent carbon. In contrast, due to the lack of such proton, the corresponding carbocations from the Bn, PMB and MOM groups are possibly quenched by nucleophile(s) such as toluene, which was used as solvent for these deprotection reactions, via the FC-type reactions. Thus, from this regard, it appears that the *i*-Pr cation may be quenched more effectively than others due to the thermodynamically favourable generation of propene.

The MOM as well as the *i*-Pr, Bn and PMB ethers of vanillin was used as models to establish the optimal reaction conditions for their removal without the contribution from the *ortho*-directing protonation by the carbonyl group. The optimal conditions for the *i*-Pr, Bn and PMB ethers of vanillin have been reported.[21,22] After some experimentation, the optimal conditions for the MOM ether of vanillin were found for Amberlyst-15 (40 °C for 72 h) and PTS-Si (40 °C for 5 h), which provided vanillin in 93% and 97% yields, respectively.[23]

To determine the effects of *ortho*-directing protonation by the carbonyl group as well as carbocation stability and quenching on the orthogonal deprotection of different protecting groups on the same aromatic ring, a number of similarly as well as differently di-protected 2,4-dihydroxy methylbenzoates were prepared (Scheme 2).

First, 2,4-dihydroxybenzoic acid was converted to its methyl ester **1** in quantitative yield. The *ortho*-hydroxy group of **1** was less acidic due to the intramolecular H-bonding with the carbonyl group, making it possible to selectively protect the more acidic *para*-hydroxy group first using weaker bases or lower temperatures. Under such reaction conditions, the mono-protected 2-hydroxy-4-alkyloxybenzoates **2a**–**d** were obtained in good to excellent yields (84–92%). The similarly di-protected products **3a**–**d** were obtained as by-products from this selective protection of the *para*-hydroxy group or directly as the products of the dialkylation of **1**. The *ortho*-hydroxy group could be protected subsequently using stronger bases such as NaH or at higher temperatures. The overall two-step sequential protection process furnished the desired differently di-protected compounds **4a**–**l** in good to excellent yields (61%–99%).

When the bis-protected benzoates **3a**–**d** were employed, all protecting groups at the position *ortho* to the ester carbonyl group



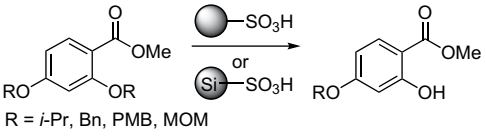
Scheme 2. Di-protected 2,4-dihydroxy benzoates (**3a**–**4l**).

were orthogonally removed in moderate to good yields (Table 1; 30%–98%). When the two protecting groups were identical, the *ortho*-directing protonation by the carbonyl group normally directed the selectivity of the deprotection. However, the PMB group exhibited only moderate selectivity (entries 5 and 6). The *para*-PMB could undergo competitive deprotection with the *ortho*-PMB.[24]

The benzyl carbocation could be effectively scavenged by MeOH, giving the mono-deprotected product in 89%–98% yields. However, the PMB cation was apparently too stabilized for effective quenching by MeOH. Methanol also competed for protons and thus slowed down the overall rate of deprotection reactions. For **3c** and **d**, adding MeOH to the reactions gave poorer yields of the desired products.[25]

After establishing that *ortho*-directing protonation by the carbonyl group could direct the orthogonal deprotection of the similarly di-protected benzoates **3a**–**d**, all other differently di-protected benzoates **4a**–**l** were studied and the results were summarized in Table 2. In general, contribution from the *ortho*-directing protonation by the carbonyl group was more pronounced than those from carbocation stability and quenching. Protecting groups at the *ortho* position were removed preferentially over the others at the *para* position.

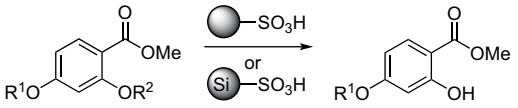
Table 1
Selective *ortho*-deprotection of similarly di-protected **3a**–**d**[a]



Entry	Comp	R	Acid[b]	Prod	Temp[c] (°C)	Time[d] (h)	Yield (%)
1	**3a**	*i*-Pr	A	**2a**	80	4.0	81
2	**3a**	*i*-Pr	B	**2a**	80	2.0	86
3[e]	**3b**	Bn	A	**2b**	80	4.0	89
4[e]	**3b**	Bn	B	**2b**	80	4.5	98
5[f]	**3c**	PMB	A	**2c**	rt	24	30
6[g]	**3c**	PMB	B	**2c**	65	0.5	68
7[h]	**3d**	MOM	A	**2d**	rt	1.0	60
8[i]	**3d**	MOM	B	**2d**	0	0.5	86

[a] The reactions were performed in toluene.
[b] A=Amberlyst-15; B=PTS-Si.
[c] Lowest temperatures for the best yields of the products.
[d] Shortest reaction times for the best yields of the products.
[e] MeOH (4–10 equiv) was added.
[f] Yield: 14% of **1** and 28% of **3c**.
[g] Yield: 16% of **1** and 5% of **3c**.
[h] Yield: 13% of **1** and 5% of **3d**.
[i] Yield: 4% of **1**.

Table 2
Orthogonal *ortho*-deprotection of differently di-protected benzoates **4a**–**f**, **4i** and **4l**[a]



4a-f, **4i** and **4l** — R^1 and R^2 = *i*-Pr, Bn, PMB, or MOM
2a-d — R^1 = *i*-Pr, Bn, PMB, or MOM

Entry	Compound	R^1	R^2	Deprotected group	Product	MeOH[b] (equiv)	Temp[c] (°C)	Time[d] (h)	Yield[e] (%)
1	**4a**	*i*-Pr	Bn	Bn	**2a**	10	80	4.5, 4.0	81, 99
2	**4b**	*i*-Pr	PMB	PMB	**2a**	10	65	0.5, 2.0	89, 87
3[f]	**4c**	*i*-Pr	MOM	MOM	**2a**	none	rt	0.83, 0.5	90, 95
4	**4d**	Bn	*i*-Pr	*i*-Pr	**2b**	none	80, 90	5.0, 1.0	83, 60
5	**4e**	Bn	PMB	PMB	**2b**	10	65	1.5, 1.5	82, 85
6	**4f**	Bn	MOM	MOM	**2b**	none	rt	1.5, 0.42	99, 99
7	**4i**	PMB	MOM	MOM	**2c**	none	0, rt	2, 0.67	99, 99
8[g]	**4l**	MOM	PMB	PMB	**2d**	2.5	40	3.0, 0.25	50, 65

[a] The reactions were performed in toluene, with 0.6 equiv of the acid.
[b] The amount of MeOH could not exceed 40 equiv (ca. 10% MeOH in toluene v/v). Greater amount of MeOH competed with the benzoates for protonation and the deprotection reactions would not proceed.
[c] Lowest temperatures required for the complete consumption of starting materials. The first numbers are the temperature for the reactions employing Amberlyst-15 while the second numbers for those employing PTS-Si. Single numbers in the temperature column mean identical temperatures for both acids.
[d] Shortest amount of times required for the complete consumption of starting materials. The first numbers are time for the reactions employing Amberlyst-15 while the second numbers for those employing PTS-Si.
[e] Isolated and optimized yields. The first numbers are the yields from reactions employing Amberlyst-15 while the second are those employing PTS-Si.
[f] By-products from *p*-QM were obtained in 10% from **4c** (Amberlyst-15).
[g] Other by-products were inseparable mixtures of the corresponding *o*- and *p*-PMBylated FC-type aromatic compounds.

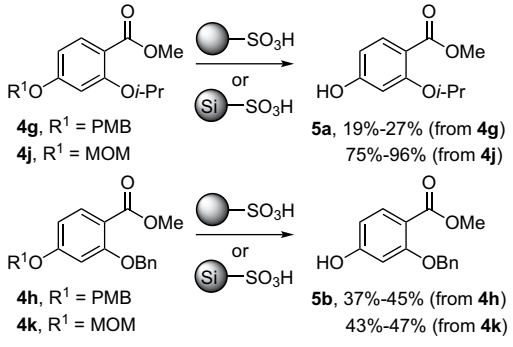
The deprotection reactions of compounds **4a**–**f**, with the *i*-Pr and Bn groups at the *para* position, occurred exclusively on the protecting groups at the *ortho* position. In fact, both *ortho*-directing protonation by the carbonyl group as well as carbocation stability and quenching would predict the observed selectivity in compounds **4a**–**c** and **4e**,**f** because the protecting groups at the *ortho* position gave more stabilized carbocations following their acid-mediated cleavage. In addition, the *ortho*-directing protonation by the carbonyl group was even more important than the carbocation stability and quenching as the *ortho* *i*-Pr group was removed preferentially over the *para* Bn group in compound **4d**.

Deprotection studies of the benzoates **4i** and **l** also supported the importance of the *ortho*-directing protonation by the carbonyl group. If considering the carbocation stability and nucleophilic quenching of the carbocations from the MOM and PMB groups alone, selective removal could be difficult due to the rather similar stability of the two carbocations generated from the cleavage of these groups. However, the results were unequivocal (entries 7 and 8). Selectivity for the deprotection between these two groups does not depend on the type of the protecting group but on the position. The group on the *ortho* position was removed preferentially.

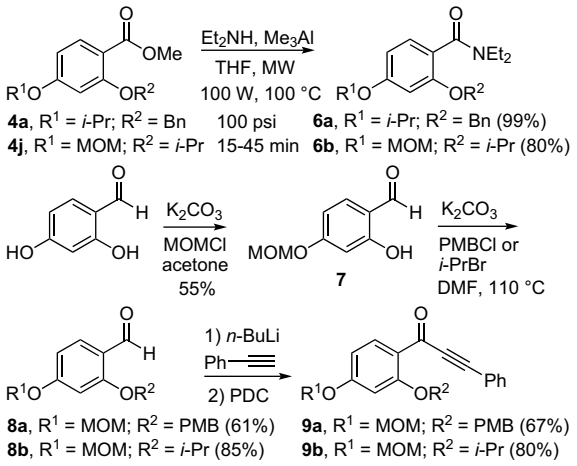
The importance of the combined carbocation stability and the nucleophilic quenching could compete with the *ortho*-directing protonation by the carbonyl group (Scheme 3). For example, the PMB and MOM groups at the position *para* to the ester carbonyl group in compounds **4g**,**h** and **4j**,**k** could be removed over the *ortho* *i*-Pr as well as Bn groups to provide the corresponding products **5a** and **b**.

Thus, when a stabilized carbocation with efficient quenching could be generated from a protecting group, the contribution from carbocation stability and quenching became significant. In most cases, the low yields of the reactions were the results of the FC-type C-alkylation side reactions between the desired mono-protected product and the carbocations generated. It can be implied that, in these cases, the rates of deprotecting the *para*-protecting groups, which generated more stable carbocations, were slower than the FC-type reactions. Thus, when the reactions proceeded until complete consumption of the starting materials, the FC-type reactions already occurred to large extent.[26] It is noteworthy that the di-deprotected by-products were not observed.

To demonstrate the scope and compatibility with other functional groups of the method, the following 2,4-di-protected compounds were prepared (Scheme 4). The methylbenzoates **4a** and **j** were converted directly to the corresponding *N*,*N*-diethyl benzamides **6a** and **b**. 2,4-Dihydroxybenzaldehyde was converted to the

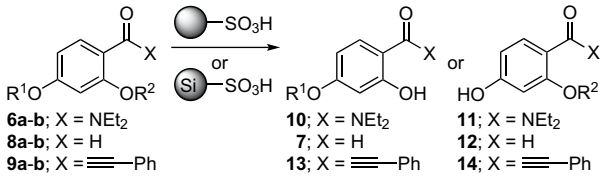


Scheme 3. Orthogonal *para*-deprotection of differently di-protected benzoates **4g**,**h** and **4j**,**k**.



Scheme 4. Synthesis of **6a**,**b**, **8a**,**b** and **9a**,**b**.

Table 3
Orthogonal deprotection of **6a**,**b**, **8a**,**b** and **9a**,**b**[a]



Entry	Compound	R^1	R^2	Deprotected group	Product	Acid[b]	MeOH (equiv)	Temp[c] (°C)	Time[d] (h)	Yield[e] (%)
1[f]	**6a**	*i*-Pr	Bn	Bn	**10**	B	25	80	50	40 (45)
2	**6b**	MOM	*i*-Pr	MOM	**11**	A	12	40	5.5	92
3[g]	**8a**	MOM	PMB	PMB	**7**	A,B	—	—	—	0
4	**8b**	MOM	*i*-Pr	MOM	**12**	A	10	40	54	74
5	**9a**	MOM	PMB	PMB	**13**	A	2.5	40	0.25	67
6	**9b**	MOM	*i*-Pr	MOM	**14**	B	1.0	50	72	54 (60)

[a] The reactions were performed in toluene, with 0.6 equiv of the acid.
[b] A=Amberlyst-15; B=PTS-Si.
[c] Lowest temperatures required for the complete consumption of starting materials.
[d] Shortest amount of times required for the complete consumption of starting materials.
[e] Isolated and optimized yields. The numbers in parentheses are those based on reacted starting materials.
[f] Other by-products included the benzylated mono-deprotected FC-type products (ca. 7% yield), benzylated di-deprotected FC-type products (ca. 21% yield) and the di-deprotected product (ca. 18% yield).
[g] The starting material was completely consumed but the reaction gave a complex mixture of PMBylated mono-deprotected products and PMBylated di-deprotected products without isolable amount of the desired product **7**.

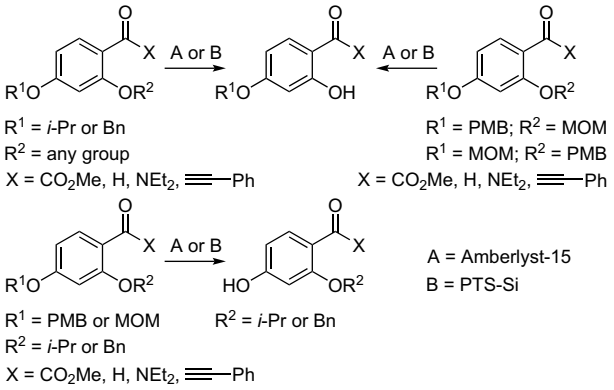
MOM ether **7**, which was subsequently protected to furnish the 2,4-di-protected benzaldehydes **8a**,**b**. The corresponding aryl phenylpropynones **9a**,**b** were synthesized from **8a**,**b** via phenyl acetylide addition followed by PDC oxidation.

The protecting groups (R^1 and R^2) were selected based on the good selectivity and yields of the product upon orthogonal removal shown in Table 2 and Scheme 3. As summarized in Table 3, the results were generally in accordance with those obtained from the benzoates (Table 2). It is interesting to note that the deprotection conditions are compatible with the benzamide, benzaldehyde and aryl phenylpropynone moieties. Thus, it is possible to remove the Bn and PMB groups in compounds **6a**, **8a**[27] and **9a**. These results supported the *ortho*-directing protonation for the selective deprotection of R^2. On the other hand, the MOM group at R^1 was consistently and selectively removed over the *i*-Pr group at R^2 (entries 2, 4 and 6), indicating the importance of the selective cleavage of the protecting group leading to the more stable carbocation.

The use of solid-supported acids (Amberlyst-15 or PTS-Si) for cleaving these aromatic ethers offers several advantages over the use of a conventional acid such as *p*-TsOH under similar reaction conditions. Due to the greater surface area of these solid-supported acids,[28] the reactions proceeded faster. While the deprotection of compound **4a** with Amberlyst-15 or PTS-Si took 4–4.5 h, a similar reaction using *p*-TsOH required 10 h. Yields of the products from the reactions using solid-supported acids are comparable to those using conventional acids.[29] For example, deprotection of compounds **4a** and **d** using *p*-TsOH gave **2a** and **b** in 70% and 75% yields, respectively. In addition, the reactions required virtually no aqueous workup and only simple filtration to remove the solid-supported materials was necessary.

3. Conclusion

In summary, a number of optimized reaction conditions[30] were found for orthogonal deprotection of compounds containing two different phenol-protecting groups on the same aromatic ring. In general, the *ortho*-directing protonation by the carbonyl group plays an important role as the group *ortho* to the carbonyl group is removed with high selectivity over the other at the *para* position. This is the case when *i*-Pr or Bn group is present at the 4-position. However, such preference could be partially or entirely reversed in case of the MOM or PMB group at the 4-position which could generate stabilized carbocations. Thus, in some of those cases, carbocation stability became a significant competing determinant. In addition, the deprotection conditions showed good compatibility with the benzamide, benzaldehyde and aryl phenyl propynone moieties.



Scheme 5. Schematic summary of selective deprotections.

A schematic summary of the selective deprotections is shown in Scheme 5. When the 4-position contains *i*-Pr or Bn, *ortho*-directing protonation by the carbonyl group governs the selective removal of any protecting group at the 2-position. For PMB and MOM groups at the 4-position, selective deprotection depends largely on the nature of the protecting group at the 2-position. If the 2-position contains *i*-Pr or Bn, the PMB or MOM group can be selectively removed. However, when the 2-position is PMB or MOM, the *ortho*-directing protonation directs the selective removal of the group at the 2-position.

4. Experimental

4.1. General experimental methods

Unless otherwise noted: reactions were run in oven-dried round-bottomed flasks. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl while dichloromethane (DCM) from

calcium hydride prior to use. All other compounds were used as received from the suppliers. PTS-Si (*p*-TsOH immobilized on silica) used in these experiments was purchased from Silicycle with the surface area of 500 m^2/g as indicated by the supplier. Other commercially available PTS-Si from other suppliers were not evaluated and thus other PTS-Si may or may not yield the results similar to those reported in this study. The crude reaction mixtures were concentrated under reduced pressure by removing organic solvents on rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06–0.2 mm; 70–230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminium sheets. Chemical shifts for ^1H nuclear magnetic resonance (NMR) spectra were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) and doublet of doublet (dd). Resonances for infrared (IR) spectra were reported in wavenumbers (cm^{-1}). Low resolution (LRMS) mass spectra were obtained either using electron ionization (EI) or time-of-flight (TOF) while high resolution (HRMS) mass spectra were obtained using time-of-flight (TOF). Melting points were uncorrected.

4.1.1. 3-Methoxy-4-methoxymethyloxybenzaldehyde

To a stirred suspension of vanillin (1.52 g, 10 mmol) in acetone (15 mL) was added anhydrous K_2CO_3 (2.07 g, 15 mmol) at rt and the reaction mixture was stirred at rt for 5 min. Chloromethyl methyl ether (1.14 mL, 15 mmol) was added dropwise into the reaction flask and the mixture was stirred at 10–15 °C for 1.5 h. Water (20 mL) and EtOAc (20 mL) were added and two phases were separated. The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (30% EtOAc/hexanes) to give the product as a white solid (1.87 g, 9.54 mmol, 95%). Mp (MeOH) 44–45 °C. IR (neat): ν_{max} 2940, 2831, 1682, 1587, 1507, 1261 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.53 (s, 3H), 3.96 (s, 3H), 5.34 (s, 2H), 7.23–7.33 (m, 1H), 7.39–7.49 (m, 2H), 9.88 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 56.0, 56.5, 94.9, 109.3, 114.5, 126.4, 131.0, 150.0, 151.9, 191.0. LRMS (EI) *m/z* (rel intensity) 197 ($M+H^+$, 21), 196 (M^+, 68), 166 (100), 165 (27), 77 (17), 45 (37). TOF-HRMS calcd for $C_{10}H_{13}O_4$ ($M+H^+$) 197.0808, found 197.0805.

4.1.2. Methyl 2,4-dihydroxybenzoate (**1**)

To a stirred solution of 2,4-dihydroxybenzoic acid (12.0 g, 77.9 mmol) in MeOH (60 mL) was added concd H_2SO_4 (5 mL) and the mixture was refluxed for 20 h. After cooling to rt, MeOH was removed under reduced pressure and the residue was poured into ice water (200 mL). The precipitates were collected and washed with water. The solid was recrystallized (MeOH/hexanes) to give the product (13.0 g, 77.3 mmol, 99%) as a white solid. Mp (EtOAc/hexanes) 112–114 °C (lit.[31] 118–121 °C; lit.[32] 116–117 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.33–6.39 (m, 2H), 7.68–7.73 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.9, 102.8, 105.1, 108.1, 131.7, 163.1, 163.3, 170.5. LRMS (EI) *m/z* (rel intensity) 169 ($M+H^+$, 20), 168 (M^+, 67), 137 (53), 136 (100), 108 (67), 80 (13), 52 (19). These spectroscopic data are identical to those reported previously.[33–36]

4.2. Preparation of mono-protected benzoates (2a–d)

4.2.1. Methyl 2-hydroxy-4-isopropoxybenzoate (**2a**)

A mixture of **1** (4.00 g, 23.8 mmol), isopropyl bromide (3.42 mL, 36 mmol), anhydrous K_2CO_3 (5.00 g, 36 mmol) in DMF (30 mL) was stirred at 70 °C for 4 h. After being cooled to rt, water (30 mL) and EtOAc (30 mL) were added. The two phases were separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layers were washed with water (4×20 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography on silica (30% EtOAc/hexanes) to give the desired product as a white solid (4.10 g, 19.5 mmol, 81%). Mp (EtOAc/hexanes) 46–48 °C (no previous literature values given). ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (d, *J*=5.8 Hz, 6H), 3.90 (s, 3H), 4.58 (sept, *J*=5.8 Hz, 1H), 6.37 (d, *J*=1.8 Hz, 1H), 6.42 (s, 1H), 7.71 (dd, *J*=9.6, 1.8 Hz, 1H), 10.9 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 51.9, 70.1, 101.8, 104.9, 108.6, 131.2, 163.2, 164.0, 170.4. LRMS (EI) *m/z* (rel intensity) 211 ($M+H^+$, 34), 210 (M^+, 100), 168 (4), 136 (12). These spectroscopic data were identical to those reported previously.[37]

4.2.2. Methyl 4-benzyloxy-2-hydroxybenzoate (**2b**)

A mixture of **1** (2.78 g, 16.5 mmol) and anhydrous K_2CO_3 (3.11 g, 22.5 mmol) in acetone (15 mL) was stirred at rt for 5 min. Benzyl bromide (1.96 mL, 16.5 mmol) was added dropwise into the reaction flask and the mixture was stirred at 10–15 °C for 3 h. Water (20 mL) and EtOAc (20 mL) were added and two phases were separated. The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (30% EtOAc/hexanes) to give the product as a white solid (3.20 g, 14.0 mmol, 85%). Mp (MeOH) 103–105 °C. IR (neat): ν_{max} 3100 (br), 3064, 3034, 2956, 1661, 1619, 1441, 1347, 1254, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 5.07 (s, 2H), 6.48–6.53 (m, 2H), 7.37–7.40 (m, 5H), 7.74 (d, *J*=9.4 Hz, 1H), 11.0 (s, 1H). The material is commercially available.[38,39]

4.2.3. Methyl 2-hydroxy-4-(4-methoxy)benzyloxybenzoate (**2c**)

A mixture of **1** (0.21 g, 1.20 mmol) and anhydrous K_2CO_3 (0.25 g, 1.80 mmol) in DMF (10 mL) was stirred at rt for 5 min. *para*-Methoxybenzyl chloride (0.28 g, 1.80 mmol) was added dropwise into the reaction flask and the mixture was stirred at 10–15 °C for 3 h. Water (10 mL) and EtOAc (10 mL) were added and the two phases were separated. The aqueous phase was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (30% EtOAc/hexanes) to give the product as a white solid (0.31 g, 1.08 mmol, 90%). Mp (EtOAc/hexanes) 89–90 °C. IR (neat): ν_{max} 3081, 1662, 1613, 1348, 1251 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.91 (s, 3H), 4.99 (s, 2H), 6.43–6.60 (m, 2H), 6.92 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.74 (d, *J*=8.0 Hz, 1H), 11.0 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.0, 55.3, 69.9, 101.5, 105.5, 108.1, 114.0, 128.0, 129.3, 131.2, 159.6, 163.6, 164.7, 170.4. LRMS (EI) *m/z* (rel intensity) 288 (M^+, 5), 121 (100). TOF-HRMS calcd for $C_{16}H_{17}O_5$ ($M+H^+$) 289.1071, found 289.1070.

4.2.4. Methyl 2-hydroxy-4-methoxymethyloxybenzoate (**2d**)

A mixture of **1** (3.00 g, 16.2 mmol) and anhydrous K_2CO_3 (3.36 g, 24.4 mmol) in acetone (40 mL) was stirred at rt for 5 min. Chloromethyl methyl ether (1.85 mL, 24.4 mmol) was added dropwise at 0 °C into the reaction flask. The reaction was heated to 60 °C for 2.5 h. After being cooled to rt, water (20 mL) and EtOAc (20 mL) were added and the two phases were separated. The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (30% EtOAc/hexanes) to furnish the product as a white solid (3.13 g, 14.9 mmol, 92%). Mp (EtOAc/hexanes) 35–36 °C. IR (neat): ν_{max} 3145, 2956, 1668, 1621, 1582, 1501, 1440, 1345, 1220, 1074 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.45 (s, 3H), 3.88 (s, 3H), 5.16 (s, 2H), 6.50 (dd, *J*=8.8, 2.2 Hz, 1H), 6.59 (d, *J*=2.2 Hz, 1H), 7.71 (d, *J*=8.8 Hz, 1H),

10.9 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.9, 56.1, 93.9, 103.4, 106.4, 108.2, 131.2, 163.0, 163.4, 172.2. LRMS (EI) *m*/*z* (rel intensity) 212 (M^+, 50), 182 (49), 150 (96), 122 (42), 45 (100). TOF-HRMS calcd for $C_{10}H_{13}O_5$ ($M+H^+$) 213.0757, found 213.0754.

4.3. General procedure for the preparation of similarly di-protected benzoates (3a–d)

A mixture of **1** (1.0 equiv) and anhydrous K_2CO_3 (3.0 equiv) in DMF (2 mL/mmol of **1**) was stirred at rt for 5 min. Alkyl or arylmethylene (benzyl-type) halide (3.0 equiv) was added dropwise and the reaction mixture was heated to 100 °C for 4.5 h. After being cooled to rt, water and EtOAc were added. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (20% EtOAc/hexanes) to furnish the products **3a–d**.

4.3.1. Methyl 2,4-diisopropoxybenzoate (*3a*)

IR (neat): ν_{max} 2982, 1760, 1697, 1241, 1200 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, *J*=7.2 Hz, 3H), 1.32 (t, *J*=7.0 Hz, 3H), 2.52 (s, 3H), 3.35 (s, 3H), 4.14 (q, *J*=7.2 Hz, 2H), 4.25 (q, *J*=7.0 Hz, 2H), 6.54 (s, 1H), 7.22–7.45 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.5, 14.0, 14.5, 31.5, 59.1, 64.7, 110.5, 111.8, 122.1, 126.0, 126.1, 127.5, 129.4, 132.2, 136.9, 149.5, 153.0, 165.5. LRMS (EI) *m*/*z* (rel intensity) 332 ($M+H^+$, 16), 331 (M^+, 100), 259 (25), 230 (43), 185 (31). TOF-HRMS calcd for $C_{18}H_{22}NO_5$ ($M+H^+$) 332.1492, found 332.1489. These spectroscopic data are identical to those reported previously.[22]

4.3.2. Methyl 2,4-dibenzyloxybenzoate (*3b*)

Mp (MeOH) 68–70 °C. IR (neat): ν_{max} 3032, 1721, 1606, 1253, 1143 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.87 (s, 3H), 5.07 (s, 2H), 5.14 (s, 2H), 6.52–6.66 (m, 2H), 7.22–7.58 (m, 10H), 7.89 (d, *J*=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.7, 70.2, 70.6, 101.5, 106.1, 113.3, 126.5, 127.5, 127.8, 128.2, 128.5, 128.7, 133.9, 136.2, 136.7, 160.2, 163.2, 166.2. LRMS (EI) *m*/*z* (rel intensity) 348 (M^+, 14), 316 (65), 181 (35), 91 (100). TOF-HRMS calcd for $C_{22}H_{21}O_4$ ($M+H^+$) 349.1434, found 349.1403.

4.3.3. Methyl 2,4-di-(4-methoxy)benzyloxybenzoate (*3c*)

Mp (MeOH) 67–68 °C. IR (neat): ν_{max} 2950, 1720, 1606, 1516, 1242, 1172, 1029 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 6H), 3.85 (s, 3H), 4.98 (s, 2H), 5.06 (s, 2H), 6.57 (d, *J*=6.6 Hz, 1H), 6.34 (s, 1H), 6.91 (d, *J*=8.6 Hz, 4H), 7.33 (d, *J*=8.6 Hz, 2H), 7.41 (d, *J*=8.6 Hz, 2H), 7.88 (d, *J*=8.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.6, 55.3, 70.0, 70.5, 101.6, 106.1, 113.2, 113.9, 114.1, 128.2, 128.4, 128.7, 129.3, 133.8, 159.3, 160.3, 163.2, 166.2. TOF-LRMS *m*/*z* (rel intensity) 431 ($M+Na^+$, 100). TOF-HRMS calcd for $C_{24}H_{24}NaO_6$ ($M+Na^+$) 431.1465, found 431.1465.

4.3.4. Methyl 2,4-dimethoxymethyloxybenzoate (*3d*)

IR (neat): ν_{max} 2952, 1723, 1606, 1249, 1135 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.42 (s, 3H), 3.48 (s, 3H), 3.81 (s, 3H), 5.15 (s, 2H), 5.20 (s, 2H), 6.66 (dd, *J*=8.8, 2.2 Hz, 1H), 6.68 (d, *J*=2.2 Hz, 1H), 7.77 (d, *J*=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.2, 55.7, 55.9, 93.7, 94.7, 104.0, 108.2, 113.9, 132.8, 158.3, 161.0, 165.4. LRMS (EI) *m*/*z* (rel intensity) 256 (M^+, 55), 225 (100). TOF-HRMS calcd for $C_{12}H_{17}O_6$ ($M+H^+$) 257.1020, found 257.1027.

4.4. General procedure for the preparation of differently di-protected benzoates (4a–l)

A mixture of mono-protected benzoates **2a–d** (1.0 equiv), base (K_2CO_3 or NaH; 1.5 equiv) in DMF (2.5 mL/mmol) was stirred at appropriate temperature (see Table 4 below) before the addition of the alkyl or arylmethylene (benzyl-type) halides (1.5 equiv). The resulting mixture was stirred at temperature and for the duration as indicated in Table 4. Water and EtOAc were added. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (25% EtOAc/hexanes) to furnish the desired products **4a–l**.

Table 4
Reaction conditions for the preparation of **4a–l**

Comp	Base	Temp[a] (°C)	Temp[b] (°C)	Time (h)	Prod	Yield (%)
2a	K_2CO_3	rt	110	4.5	**4a**	81
2a	K_2CO_3	rt	110	3.0	**4b**	89
2a	NaH	0	rt	1.5	**4c**	90
2b	K_2CO_3	rt	110	3.3	**4d**	77
2b	K_2CO_3	rt	110	3.0	**4e**	69
2b	NaH	0	rt	1.5	**4f**	98
2c	K_2CO_3	rt	110	2.0	**4g**	61
2c	K_2CO_3	rt	110	0.5	**4h**	93
2c	NaH	0	rt	1.0	**4i**	99
2d	K_2CO_3	rt	110	18	**4j**	85
2d	K_2CO_3	rt	110	0.5	**4k**	96
2d	K_2CO_3	rt	110	5.0	**4l**	93

[a] Temperature at which the base was added.
[b] Temperature of the reaction mixture.

4.4.1. Methyl 2-benzyloxy-4-isopropoxybenzoate (*4a*)

Mp (MeOH) 73.9–75.3 °C (no previous literature values given). IR (neat): ν_{max} 2978, 2924, 1722, 1604, 1572, 1502, 1437, 1249, 1184, 1132, 1085 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (d, *J*=5.8 Hz, 6H), 3.88 (s, 3H), 4.58 (sept, *J*=5.8 Hz, 1H), 5.16 (s, 2H), 6.45–6.49 (m, 2H), 7.28–7.42 (m, 3H), 7.49–7.52 (m, 2H), 7.85 (d, *J*=9.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 51.5, 70.1, 70.5, 102.1, 106.6, 126.7, 127.6, 128.4, 133.7, 136.7, 160.3, 162.5, 166.1. LRMS (EI) *m*/*z* (rel intensity) 301 ($M+H^+$, 5), 300 (M^+, 17), 268 (45), 226 (29), 168 (10), 136 (23), 92 (18), 91 (100), 81 (7), 41 (41). TOF-HRMS calcd for $C_{18}H_{21}O_4$ ($M+H^+$) 301.1434, found 301.1435. These spectroscopic data are identical to those reported previously.[22]

4.4.2. Methyl 4-isopropoxy-2-(4-methoxy)benzyloxybenzoate (*4b*)

IR (neat): ν_{max} 2978, 1721, 1604, 1572, 1514, 1439, 1244, 1174 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (d, *J*=6.0 Hz, 6H), 3.81 (s, 3H), 3.85 (s, 3H), 4.57 (sept, *J*=6.0 Hz, 1H), 5.08 (s, 2H), 6.48 (d, *J*=8.4 Hz, 1H), 6.50 (s, 1H), 6.92 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 7.85 (d, *J*=8.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 51.6, 55.3, 70.1, 70.5, 102.3, 106.7, 112.6, 113.9, 128.4, 128.8, 133.7, 159.3, 160.4, 162.5, 166.2. LRMS (EI) *m*/*z* (rel intensity) 330 (M^+, 8), 241 (17), 121 (100). TOF-HRMS calcd for $C_{19}H_{23}O_5$ ($M+H^+$) 331.1540, found 331.1541.

4.4.3. Methyl 4-isopropoxy-2-methoxymethyloxybenzoate (*4c*)

IR (neat): ν_{max} 2979, 1723, 1605, 1573, 1498, 1434, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, *J*=6.0 Hz, 6H), 3.52 (s, 3H), 3.85 (s, 3H), 4.59 (sept, *J*=6.0 Hz, 1H), 5.23 (s, 2H), 6.53 (dd, *J*=8.8, 2.4 Hz, 1H), 6.70 (d, *J*=2.4 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 51.6, 56.3, 70.1, 95.2, 104.1, 108.0, 112.9, 133.4, 159.0, 162.3, 166.0. LRMS (EI) *m*/*z* (rel intensity) 255 ($M+H^+$, 82), 254 (M^+, 100), 223 (94), 207 (45), 181 (30), 151 (38). TOF-HRMS calcd for $C_{13}H_{19}O_5$ ($M+H^+$) 255.1227, found 255.1219.

4.4.4. Methyl 4-benzyloxy-2-isopropoxybenzoate (*4d*)

IR (neat): ν_{max} 2978, 1724, 1604, 1572, 1242, 1188 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (d, *J*=6.0 Hz, 6H), 3.84 (s, 3H), 4.52 (sept, *J*=6.0 Hz, 1H), 5.08 (s, 2H), 6.48–6.63 (m, 2H), 7.28–7.49 (m, 5H), 7.82 (d, *J*=9.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0, 51.5, 70.2, 71.9, 103.0, 106.0, 114.2, 127.5, 128.2, 128.7, 133.7, 136.3, 159.8, 163.0, 166.3. LRMS (EI) *m*/*z* (rel intensity) 300 (M^+, 22), 226 (12), 91 (100). TOF-HRMS calcd for $C_{18}H_{21}O_4$ ($M+H^+$) 301.1434, found 301.1426.

*4.4.5. Methyl 4-benzyloxy-2-(4-methoxy)benzyloxybenzoate (**4e**)*

Mp (MeOH) 71–73 °C. IR (neat): ν_{max} 2949, 1721, 1606, 1514, 1244, 1174, 1027 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.87 (s, 3H), 5.07 (s, 4H), 6.57–6.63 (m, 2H), 6.93 (d, J=8.8 Hz, 2H), 7.37–7.45 (m, 6H), 7.88 (d, J=8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.6, 55.2, 70.1, 70.3, 101.4, 105.9, 113.0, 113.9, 127.5, 128.2, 128.4, 128.5, 128.7, 133.8, 136.1, 159.1, 160.2, 163.1, 166.1. LRMS (EI) m/z (rel intensity) 378 (M^+, 11), 287 (15), 121 (100), 91 (28). TOF-HRMS calcd for $C_{23}H_{23}O_5$ ($M+H^+$) 379.1540, found 379.1542.

*4.4.6. Methyl 4-benzyloxy-2-methoxymethyloxybenzoate (**4f**)*

Mp (MeOH) 61–62 °C. IR (neat): ν_{max} 2951, 1724, 1607, 1255, 1142 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.52 (s, 3H), 3.86 (s, 3H), 5.09 (s, 2H), 5.24 (s, 2H), 6.64 (dd, J=8.8, 2.2 Hz, 1H), 6.83 (d, J=2.2 Hz, 1H), 7.38–7.48 (m, 5H), 7.83 (d, J=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.7, 56.3, 70.9, 95.1, 103.4, 107.5, 113.4, 127.5, 128.2, 128.6, 133.4, 136.1, 158.9, 162.9, 165.9. LRMS (EI) m/z (rel intensity) 302 (M^+, 9), 238 (27), 91 (100). TOF-HRMS calcd for $C_{17}H_{19}O_5$ ($M+H^+$) 303.1227, found 303.1222.

*4.4.7. Methyl 2-isopropoxy-4-(4-methoxy)benzyloxybenzoate (**4g**)*

IR (neat): ν_{max} 2978, 1724, 1604, 1514, 1243, 1109 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (d, J=6.0 Hz, 6H), 3.81 (s, 3H), 3.84 (s, 3H), 4.52 (sept, J=6.0 Hz, 1H), 4.99 (s, 2H), 6.44–6.62 (m, 2H), 6.92 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.8 Hz, 2H), 7.82 (d, J=9.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 51.5, 55.2, 69.9, 71.7, 102.7, 105.7, 113.7, 114.0, 128.1, 129.3, 133.6, 159.5, 159.7, 163.0, 166.3. LRMS (EI) m/z (rel intensity) 330 (M^+, 2), 121 (100). TOF-HRMS calcd for $C_{19}H_{23}O_5$ ($M+H^+$) 331.1540, found 331.1536.

*4.4.8. Methyl 2-benzyloxy-4-(4-methoxy)benzyloxybenzoate (**4h**)*

Mp (MeOH) 66–67 °C. IR (neat): ν_{max} 2949, 1720, 1605, 1514, 1245, 1172 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 3.87 (s, 3H), 4.99 (s, 2H), 5.14 (s, 2H), 6.53–6.65 (m, 2H), 6.92 (d, J=8.0 Hz, 2H), 7.28–7.57 (m, 7H), 7.89 (d, J=9.4 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.6, 55.3, 70.0, 70.6, 101.5, 106.1, 113.1, 114.1, 126.8, 127.7, 128.2, 128.5, 129.3, 133.9, 136.7, 159.7, 160.2, 163.3, 166.2. LRMS (EI) m/z (rel intensity) 378 (M^+, 3), 211 (16), 121 (100), 91 (20). TOF-HRMS calcd for $C_{23}H_{23}O_5$ ($M+H^+$) 379.1540, found 379.1546.

*4.4.9. Methyl 2-methoxymethyloxy-4-(4-methoxy)benzyloxybenzoate (**4i**)*

Mp (MeOH) 50–52 °C. IR (neat): ν_{max} 2925, 1722, 1606, 1515, 1245, 1094 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.51 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 4.99 (s, 2H), 5.23 (s, 2H), 6.62 (dd, J=8.8, 2.2 Hz, 1H), 6.81 (d, J=2.2 Hz, 1H), 6.91 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.8 Hz, 2H), 7.83 (d, J=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.6, 55.2, 56.3, 69.9, 95.0, 103.3, 107.4, 113.3, 113.9, 128.0, 129.3, 133.3, 158.8, 159.5, 163.0, 165.9. LRMS (EI) m/z (rel intensity) 332 (M^+, 0.4), 121 (100). TOF-HRMS calcd for $C_{18}H_{21}O_6$ ($M+H^+$) 333.1333, found 333.1334.

*4.4.10. Methyl 2-isopropoxy-4-methoxymethyloxybenzoate (**4j**)*

IR (neat): ν_{max} 2977, 1727, 1605, 1576, 1499, 1436, 1245 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.38 (d, J=6.2 Hz, 6H), 3.48 (s, 3H), 3.84 (s, 3H), 4.55 (sept, J=6.2 Hz, 1H), 5.19 (s, 2H), 6.57–6.66 (m, 2H), 7.74–7.83 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0, 51.5, 56.2, 71.9, 94.2, 103.8, 107.5, 115.0, 133.4, 159.7, 161.5, 166.3. LRMS (EI) m/z (rel intensity) 255 ($M+H^+$, 52), 254 (M^+, 100), 223 (24). TOF-HRMS calcd for $C_{13}H_{19}O_5$ ($M+H^+$) 255.1227, found 255.1223.

*4.4.11. Methyl 2-benzyloxy-4-methoxymethyloxybenzoate (**4k**)*

IR (neat): ν_{max} 2951, 1722, 1605, 1436, 1247, 1139 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.46 (s, 3H), 3.87 (s, 3H), 5.16 (s, 2H), 5.17 (s, 2H), 6.66 (dd, J=10.2, 2.2 Hz, 1H), 6.69 (d, J=2.2 Hz, 1H), 7.20–7.58 (m, 5H), 7.86 (d, J=10.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.7, 56.2, 70.4, 94.1, 102.0, 107.5, 113.6, 126.8, 127.7, 128.4, 133.7, 136.5, 160.0, 161.6, 166.1. LRMS (EI) m/z (rel intensity) 302 (M^+, 15), 270 (54), 238 (32), 91 (100), 65 (13). TOF-HRMS calcd for $C_{17}H_{19}O_5$ ($M+H^+$) 303.1227, found 303.1228.

*4.4.12. Methyl 2-(4-methoxy)benzyloxy-4-methoxymethyloxybenzoate (**4l**)*

IR (neat): ν_{max} 2951, 1722, 1606, 1577, 1514, 1244 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.47 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 5.10 (s, 2H), 5.18 (s, 2H), 6.60–6.73 (m, 2H), 6.92 (d, J=8.8 Hz, 2H), 7.43 (d, J=8.8 Hz, 2H), 7.84 (d, J=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.7, 55.3, 56.2, 70.5, 94.3, 102.4, 107.7, 114.0, 128.6, 128.7, 133.6, 159.3, 160.2, 161.7, 166.2. LRMS (EI) m/z (rel intensity) 332 (M^+, 2), 122 (9), 121 (100), 91 (5), 77 (4). TOF-HRMS calcd for $C_{18}H_{21}O_6$ ($M+H^+$) 333.1333, found 333.1333.

4.5. General procedure for the deprotection

To a stirred solution of **3a–d** or **4a–l** (1.0 equiv) in toluene (20 mL/mmol of **3a–d** or **4a–l**) was added the solid-supported acid (either Amberlyst-15 (loading: 4.81 mmol/g) or PTS-Si (loading: 0.81 mmol/g); 0.6 equiv). The reaction mixture was kept at temperature and for the duration as indicated in Table 2. The reaction mixture was filtered and the solid-supported material was washed extensively with EtOAc. The filtrate was then concentrated under reduced pressure. The product was obtained by following column chromatography on silica (20% EtOAc/hexanes).

*4.5.1. Methyl 4-hydroxy-2-isopropoxybenzoate (**5a**)*

Mp (MeOH) 113–115 °C. IR (neat): ν_{max} 3323 (br), 2980, 1698, 1604, 1577, 1454, 1435, 1252, 1135 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (d, J=6.0 Hz, 6H), 3.83 (s, 3H), 4.42 (sept, J=6.0 Hz, 1H), 6.41–6.45 (m, 2H), 7.58 (apparent br s, 1H), 7.73 (d, J=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8, 51.8, 71.6, 102.3, 107.7, 112.0, 133.9, 160.2, 161.7, 167.3. LRMS (EI) m/z (rel intensity) 211 ($M+H^+$, 11), 210 (M^+, 99), 168 (83), 137 (50), 136 (100), 108 (43). TOF-HRMS calcd for $C_{11}H_{15}O_4$ ($M+H^+$) 211.0965, found 211.0961.

*4.5.2. Methyl 2-benzyloxy-4-hydroxybenzoate (**5b**)*

Mp (MeOH) 138–140 °C. IR (neat): ν_{max} 3311 (br), 1689, 1579, 1243, 1088 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 5.09 (s, 2H), 6.43 (d, J=8.8 Hz, 1H), 6.46 (s, 1H), 7.22–7.54 (m, 5H), 7.78 (d, J=8.8 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.7, 70.2, 101.1, 107.7, 111.2, 126.7, 127.7, 128.4, 134.0, 136.5, 160.6, 162.0, 166.8. LRMS (EI) m/z (rel intensity) 258 (M^+, 7), 226 (31), 91 (100). TOF-HRMS calcd for $C_{15}H_{15}O_4$ ($M+H^+$) 259.0965, found 259.0958.

4.6. Preparation of the benzamides 6a and b

*4.6.1. 2-Benzyloxy-N,N-diethyl-4-isopropoxybenzamide (**6a**)*

A 10 mL microwave vessel was charged with the methyl benzoate **4a** (0.60 g, 2.0 mmol), *N*,*N*-diethylamine (1.45 mL, 14.0 mmol), Me_3Al (2.0 M in toluene, 1.5 mL, 3.0 mmol) and THF (2 mL) at rt. The vessel was sealed and heated in the microwave reactor at 100 °C and 100 psi with the power set at 100 W for 45 min. At that time, the reaction was quenched with 2 N HCl and the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Further purification of the crude by column chromatography on silica (30% EtOAc/hexanes) furnished the desired product as a colourless oil (0.68 g, 2.0 mmol, 99%). IR (neat): ν_{max} 2975, 1630, 1429, 1276, 1175 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J=7.1 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.33 (d, J=6.0 Hz, 6H), 3.10–3.40 (br m, 3H), 3.79 (br s, 1H), 4.54 (sept, J=6.0 Hz, 1H), 5.05 (s, 2H), 6.49–6.53 (m, 2H), 7.13–7.17 (m, 1H), 7.29–7.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$):

δ 12.7, 14.0, 22.0, 38.7, 42.7, 70.0, 70.2, 101.6, 107.1, 120.0, 127.0, 127.8, 128.4, 136.7, 155.5, 159.4, 168.7. LRMS (EI) *m*/*z* (rel intensity) 342 ($M+H^+$, 25), 341 (M^+, 24), 269 (62), 227 (57), 179 (29), 91 (100). TOF-HRMS calcd for $C_{21}H_{28}NO_3$ ($M+H^+$) 342.2064, found 342.2058.

4.6.2. *N,N-Diethyl-2-isopropoxy-4-methoxymethyloxybenzamide (**6b**)*

A 10 mL microwave vessel was charged with the methyl benzoate **4j** (0.21 g, 0.84 mmol), *N,N*-diethylamine (0.61 mL, 5.85 mmol), Me_3Al (2.0 M in toluene, 0.63 mL, 1.26 mmol) and THF (0.85 mL) at rt. The vessel was sealed and heated in the microwave reactor at 100 °C and 100 psi with the power set at 100 W for 15 min. At that time, the reaction was quenched with 2 N HCl and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Further purification of the crude by column chromatography on silica (30% EtOAc/hexanes) furnished the desired product as a colourless oil (0.20 g, 0.68 mmol, 80%). IR (neat): ν_{max} 2975, 1629, 1431, 1274, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, *J*=7.1 Hz, 3H), 1.22 (t, *J*=7.1 Hz, 3H), 1.30 (d, *J*=6.0 Hz, 6H), 3.06–3.33 (br m, 3H), 3.48 (s, 3H), 3.76–3.92 (br m, 1H), 4.50 (sept, *J*=6.1 Hz, 1H), 5.16 (s, 2H), 6.57 (d, *J*=2.2 Hz, 1H), 6.63 (dd, *J*=8.3, 2.2 Hz, 1H), 7.12 (d, *J*=8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 14.0, 22.0, 38.5, 42.5, 56.0, 70.7, 94.5, 102.5, 107.8, 122.1, 128.4, 154.6, 158.6, 168.7. LRMS (EI) *m*/*z* (rel intensity) 296 ($M+H^+$, 46), 295 (M^+, 56), 294 ($M-H^+$, 100), 252 (85), 223 (68), 181 (35), 151 (39). TOF-HRMS calcd for $C_{16}H_{26}NO_4$ ($M+H^+$) 296.1856, found 296.1849.

4.7. Preparation of the aryl phenylpropynones 9a and b

4.7.1. *2-Hydroxy-4-methoxymethyloxybenzaldehyde (**7**)*

Using a procedure similar to that for the preparation of compound **2d**, compound **7** was prepared from 2,4-dihydroxybenzaldehyde (2.79 g, 20 mmol). Compound **7** (2.00 g, 11 mmol, 55%) was obtained as a white solid. Mp (EtOAc/hexanes) 53–54 °C. IR (neat): ν_{max} 2831, 1626, 1500, 1221, 1153 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.49 (s, 3H), 5.23 (s, 2H), 6.61 (d, *J*=2.2 Hz, 1H), 6.65 (dd, *J*=8.6, 2.2 Hz, 1H), 7.46 (d, *J*=8.6 Hz, 1H), 9.74 (s, 1H), 11.4 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.4, 94.0, 103.4, 109.0, 115.9, 135.4, 164.1, 164.3, 194.6. LRMS (EI) *m*/*z* (rel intensity) 183 ($M+H^+$, 100), 182 (M^+, 69), 167 (33). TOF-HRMS calcd for $C_9H_{11}O_4$ ($M+H^+$) 183.0652, found 183.0640.

4.7.2. *2-(4-Methoxy)benzyloxy-4-methoxymethyloxybenzaldehyde (**8a**)*

Using the procedure similar to that for the preparation of compound **4l**, compound **8a** was prepared from compound **7** (0.91 g, 5.00 mmol). Compound **8a** (0.92 g, 3.05 mmol, 61%) was obtained as a yellow oil. IR (neat): ν_{max} 2935, 1676, 1597, 1514, 1247 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.48 (s, 3H), 3.81 (s, 3H), 5.07 (s, 2H), 5.21 (s, 2H), 6.68 (dd, *J*=8.6, 2.2 Hz, 1H), 6.70 (s, 1H), 6.92 (d, *J*=8.7 Hz, 2H), 7.36 (d, *J*=8.7 Hz, 2H), 7.80 (d, *J*=8.6 Hz, 1H), 10.4 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.2, 56.3, 70.2, 94.1, 100.6, 108.4, 114.0, 119.8, 127.8, 129.1, 130.1, 159.6, 162.7, 163.6, 188.4. LRMS (EI) *m*/*z* (rel intensity) 302 (M^+, 5), 121 (100). TOF-HRMS calcd for $C_{17}H_{19}O_5$ ($M+H^+$) 303.1227, found 303.1230.

4.7.3. *2-Isopropoxy-4-methoxymethyloxybenzaldehyde (**8b**)*

Using the procedure similar to that for the preparation of compound **4j**, compound **8b** was prepared from compound **7** (0.22 g, 1.20 mmol). Compound **8b** (0.23 g, 1.02 mmol, 85%) was obtained as a yellow oil. IR (neat): ν_{max} 2978, 1678, 1597, 1256 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (d, *J*=6.1 Hz, 6H), 3.49 (s, 3H), 4.64 (sept, *J*=6.1 Hz, 1H), 5.22 (s, 2H), 6.60 (d, *J*=2.1 Hz, 1H), 6.65 (ddd, *J*=8.7, 2.1, 0.7 Hz, 1H), 7.79 (d, *J*=8.7 Hz, 1H), 10.3 (d, *J*=0.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 56.3, 71.1, 94.1, 101.4, 108.1, 120.4, 130.0, 162.2, 163.6, 188.8. LRMS (EI) *m*/*z* (rel intensity) 225 ($M+H^+$, 100), 224 (M^+, 47), 209 (35). TOF-HRMS calcd for $C_{12}H_{17}O_4$ ($M+H^+$) 225.1121, found 225.1112.

4.7.4. *1-(2-(4-Methoxy)benzyloxy-4-(methoxymethyloxy)phenyl)-3-phenylprop-2-yn-1-one (**9a**)*

To a stirred solution of phenyl acetylene (0.23 mL, 2.1 mmol) in anhydrous THF (19 mL) was added *n*-BuLi (3.47 M in hexanes, 0.62 mL, 2.15 mmol) at −78 °C and the resulting mixture was stirred at that temperature for 40 min. At that time, a solution of **8a** (0.60 g, 2.00 mmol) in THF (13 mL) was added via syringe. The reaction mixture was stirred at −78 °C for 15 min, slowly warmed up to rt at which the reaction was stirred for 16 h. The reaction was quenched by adding saturated solution of NH_4Cl. Water (20 mL) and EtOAc (20 mL) were added and the two phases were separated. The aqueous phase was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product (0.76 g), which was used in the next step without further purification.

To a stirred suspension of pyridinium dichromate (PDC; 1.06 g, 2.82 mmol) in DCM (10 mL) at 0 °C was added the crude solution (0.76 g) in DCM (8 mL) via pipette over 5 min. The reaction mixture was stirred at 0 °C and then warmed up to rt at which it was allowed to stir for 16 h. The mixture was filtered through a plug of Celite® and the resulting filtrate was concentrated under reduced pressure to give the crude mixture, which was further purified by column chromatography on silica (20% EtOAc/hexanes) to furnish the desired product as a yellow solid (0.54 g, 1.34 mmol, 67% over two steps). Mp (EtOAc/hexanes) 93–94 °C. IR (neat): ν_{max} 2934, 2197, 1610, 1587, 1514, 1248 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.49 (s, 3H), 3.76 (s, 3H), 5.14 (s, 2H), 5.23 (s, 2H), 6.70 (dd, *J*=9.7, 2.2 Hz, 1H), 6.73 (s, 1H), 6.81 (d, *J*=8.8 Hz, 2H), 7.22–7.40 (m, 5H), 7.43 (d, *J*=8.8 Hz, 2H), 8.07 (d, *J*=9.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.1, 56.3, 70.5, 89.6, 91.3, 94.1, 101.3, 107.8, 113.9, 120.8, 121.2, 127.9, 128.2, 129.1, 129.9, 132.7, 134.2, 159.3, 160.8, 162.9, 175.1. LRMS (EI) *m*/*z* (rel intensity) 403 ($M+H^+$, 27), 402 (M^+, 77), 357 (34), 181 (45), 121 (100). TOF-HRMS calcd for $C_{25}H_{23}O_5$ ($M+H^+$) 403.1540, found 403.1546.

4.7.5. *1-(2-Isopropoxy-4-(methoxymethyloxy)phenyl)-3-phenylprop-2-yn-1-one (**9b**)*

To a stirred solution of phenyl acetylene (0.26 mL, 2.4 mmol) in anhydrous THF (20 mL) was added *n*-BuLi (3.47 M in hexanes, 0.63 mL, 2.20 mmol) at −78 °C and the resulting mixture was stirred at that temperature for 40 min. At that time, a solution of **8b** (0.45 g, 2.00 mmol) in THF (13 mL) was added via syringe. The reaction mixture was stirred at −78 °C for 15 min, slowly warmed up to rt at which the reaction was stirred for 16 h. The reaction was quenched by adding saturated solution of NH_4Cl. Water (20 mL) and EtOAc (20 mL) were added and the two phases were separated. The aqueous phase was extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product (0.76 g), which was used in the next step without further purification.

To a stirred suspension of pyridinium dichromate (PDC; 1.13 g, 3.00 mmol) in DCM (12 mL) at 0 °C was added the crude solution (0.65 g) in DCM (8 mL) via pipette over 5 min. The reaction mixture was stirred at 0 °C and then warmed up to rt at which it was allowed to stir for 16 h. The mixture was filtered through a plug of Celite® and the resulting filtrate was concentrated under reduced pressure to give the crude mixture, which was further purified by column chromatography on silica (20% EtOAc/hexanes) to furnish

the desired product as a yellow solid (0.52 g, 1.60 mmol, 80% over two steps). Mp (EtOAc/hexanes) 68–69 °C. IR (neat): ν_{max} 2978, 2197, 1613, 1587, 1489, 1268 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (d, J=6.1 Hz, 6H), 3.50 (s, 3H), 4.66 (sept, J=6.1 Hz, 1H), 5.23 (s, 2H), 6.44 (d, J=2.2 Hz, 1H), 6.74 (dd, J=8.7, 2.2 Hz, 1H), 7.35–7.46 (m, 3H), 7.59–7.62 (m, 2H), 7.99 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 56.3, 71.4, 89.9, 90.9, 94.1, 102.2, 107.6, 121.2, 122.1, 128.5, 129.9, 132.5, 133.9, 160.2, 162.8, 175.5. LRMS (EI) m/z (rel intensity) 325 ($M+H^+$, 100), 309 (55), 281 (35), 251 (40). TOF-HRMS calcd for $C_{20}H_{21}O_4$ ($M+H^+$) 325.1434, found 325.1431.

4.8. Deprotection of 6a,b, 8a,b and 9a,b

Using the procedure similar to the general procedure for the deprotection (4.4) mentioned above, compounds **6a**,**b**, **8a**,**b** and **9a**,**b** were subjected to selective deprotection conditions as indicated in Table 3.

4.8.1. *N,N-Diethyl-2-hydroxy-4-isopropoxybenzamide (**10**)*

IR (neat): ν_{max} 3145 (br), 2976, 1613, 1580, 1428, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J=7.1 Hz, 6H), 1.27 (d, J=6.1 Hz, 6H), 3.34 (q, J=7.1 Hz, 4H), 4.49 (sept, J=6.1 Hz, 1H), 6.28 (dd, J=8.8, 2.5 Hz, 1H), 6.42 (d, J=2.5 Hz, 1H), 7.21 (d, J=8.8 Hz, 1H), 10.6 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 21.9, 42.2, 69.9, 103.2, 106.9, 109.6, 128.7, 161.3, 161.7, 171.9. LRMS (EI) m/z (rel intensity) 503 ($2M+H^+$, 85), 502 ($2M^+$, 100), 252 ($M+H^+$, 99), 137 (19), 72 (20). TOF-HRMS calcd for $C_{14}H_{22}NO_3$ ($M+H^+$) 252.1594, found 252.1586.

4.8.2. *N,N-Diethyl-4-hydroxy-2-isopropoxybenzamide (**11**)*

IR (neat): ν_{max} 3173 (br), 2976, 1582, 1434, 1290 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.00 (t, J=7.1 Hz, 3H), 1.08–1.29 (m, 9H), 2.97–3.40 (m, 3H), 3.66–4.00 (m, 1H), 4.21 (sept, J=6.0 Hz, 1H), 6.20 (dd, J=8.1, 2.2 Hz, 1H), 6.26 (d, J=2.2 Hz, 1H), 6.87 (d, J=8.1 Hz, 1H), 9.22 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.6, 13.9, 22.0, 39.1, 43.0, 70.3, 101.5, 107.9, 118.2, 128.1, 154.6, 159.3, 170.6. LRMS (EI) m/z (rel intensity) 252 ($M+H^+$, 59), 250 ($M-H^+$, 63), 208 (71), 137 (100). TOF-HRMS calcd for $C_{14}H_{22}NO_3$ ($M+H^+$) 252.1594, found 252.1595.

4.8.3. *4-Hydroxy-2-isopropoxybenzaldehyde (**12**)*

IR (neat): ν_{max} 3149 (br), 2978, 1658, 1572, 1460, 1264 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, J=6.1 Hz, 6H), 1.91 (br s, 1H), 4.62 (sept, J=6.1 Hz, 1H), 6.47 (d, J=2.0 Hz, 1H), 6.48–6.52 (m, 1H), 7.76 (d, J=8.5 Hz, 1H), 10.3 (d, J=0.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 71.1, 100.5, 108.6, 118.9, 130.7, 163.2, 164.1, 189.6. LRMS (EI) m/z (rel intensity) 181 ($M+H^+$, 100), 180 (M^+, 20), 138 (31). TOF-HRMS calcd for $C_{10}H_{13}O_3$ ($M+H^+$) 181.0859, found 181.0846.

4.8.4. *1-(2-Hydroxy-4-methoxymethyloxyphenyl)-3-phenylpropynone (**13**)*

Mp (EtOAc/hexanes) 73–74 °C. IR (neat): ν_{max} 2933, 2201, 1618, 1578, 1490, 1348 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.49 (s, 3H), 5.24 (s, 2H), 6.62 (d, J=2.3 Hz, 1H), 6.64 (dd, J=8.7, 2.3 Hz, 1H), 7.40–7.51 (m, 3H), 7.66–7.70 (m, 2H), 8.03 (d, J=8.7 Hz, 1H), 12.1 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.4, 93.6, 94.0, 95.2, 103.4, 109.0, 116.0, 119.9, 128.7, 130.9, 133.0, 134.8, 164.4, 165.2, 180.5. LRMS (EI) m/z (rel intensity) 282 (M^+, 92), 281 (100), 251 (35), 209 (46). TOF-HRMS calcd for $C_{17}H_{15}O_4$ ($M+H^+$) 283.0965, found 283.0971.

4.8.5. *1-(4-Hydroxy-2-isopropoxyphenyl)-3-phenylpropynone (**14**)*

Mp (EtOAc/hexanes) 107–108 °C. IR (neat): ν_{max} 3226 (br), 2979, 2196, 1603, 1552, 1292 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, J=6.1 Hz, 6H), 4.60 (sept, J=6.1 Hz, 1H), 6.54 (s, 1H), 6.59 (dd, J=8.7, 1.5 Hz, 1H), 7.33–7.44 (m, 3H), 7.53–7.57 (m, 2H), 8.01 (d, J=8.7 Hz, 1H), 8.37 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 71.4, 89.6, 92.6, 101.3, 108.5, 119.8, 120.8, 128.5, 130.2, 132.6, 135.2, 161.4, 164.0, 176.3. LRMS (EI) m/z (rel intensity) 281 ($M+H^+$, 16), 265 (21), 237 (100), 210 (33). TOF-HRMS calcd for $C_{18}H_{17}O_3$ ($M+H^+$) 281.1172, found 281.1170.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.089.

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24. Poor to moderate yields of the desired products (30% for Amberlyst-15 and 68% for PTS-Si) resulted from the PMBylated C-alkylation side reactions, which gave the corresponding FC-type by-products for the remaining mass accounts.
25. For **3c**, 52% and 35% yields of **2c** were obtained using PTS-Si with MeOH (10 and 25 equiv, respectively). For **3d**, 35% and 69% yields of **2d** were obtained using Amberlyst-15 and PTS-Si in the presence of MeOH (10 equiv), respectively.
26. Anisole was employed as a cation scavenger for the PMB cation but resulted in even more complicated reaction mixtures without any remarkable difference for the decrease of the by-products from the FC-type C-alkylation.
27. Despite 0% yield of the desired mono-PMB-deprotected product **10** (see Table 3), the product mixture obtained from the reaction contained the mono-deprotected product, which was further alkylated via the FC-type process. It seems that the rates of the subsequent FC-type reactions of both mono- and di-deprotected are faster than the initial deprotection reaction.
28. As listed by the suppliers, the surface areas of Amberlyst-15 and PTS-Si are 45 and 500 m^2/g, respectively.
29. For comparison of yields in other systems, see Refs. 21 and 22.
30. The reaction conditions were optimized for the lowest temperature and shortest time required for complete consumption of starting materials with minimal amount of the di-deprotected, the *C*-alkylated FC-type and/or other (e.g., *p*-QM) by-products.
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