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Proton-exchanged montmorillonite-mediated reactions of methoxybenzyl esters and ethers

Dongyin Chen [a], Chang Xu [a], Jie Deng [a], Chunhuan Jiang [a], Xiaoan Wen [a], Lingyi Kong [a], Ji Zhang [b,*], Hongbin Sun [a,b,*]

[a] State Key Laboratory of Natural Medicines and Center of Drug Discovery, China Pharmaceutical University, 24 Tongjia Xiang, Nanjing 210009, China
[b] Department of Physical Chemistry, China Pharmaceutical University, Nanjing 210009, China

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ABSTRACT

Proton-exchanged montmorillonite (H-mont) was found to be an eco-friendly and cost-effective catalyst for the generation of *O*-methylated quinone methides (QM) from the corresponding *p* or *o*-methoxybenzyl esters and ethers. Nucleophilic trapping of the *O*-methylated QM with arenes, alcohols, 1,3-dicarbonyl compounds, silyl enol ethers, and allylsilanes has been carried out, respectively, leading to eco-friendly benzylation reactions. Using this protocol, H-mont-mediated deprotection of PMB-protected esters and ethers have been realized for the first time. This work would pave the way for further exploration in *O*-alkylated QM that are of chemical and biological significance.

1. Introduction

The *p*- and *o*-quinone methides (QM) (e.g., **1** and **2**, Fig. 1) have been of great interest to the chemical and biological community due to their distinctive properties as Michael acceptors.[1] By contrast, surprisingly few studies[2] have addressed the existence, generation, and reactions of *O*-methylated QM (e.g., **3a** and **4a**) that should be more reactive than the corresponding QM (e.g., **3b** and **4b**). That is probably in part due to the extreme difficulties in formation, detection, and characterization of these highly reactive and unstable species.[1,3,4] We envisioned that *O*-alkylated QM could not only act as highly reactive intermediates in organic synthesis,[2e] but also might play a key role in metabolic activation of some therapeutic agents, especially anticancer agents such as combretastatin A-4 (**5**),[5] podophyllotoxin (**6**),[6] trabectedin (**7**),[7] etc. Therefore, extensive exploration in *O*-alkylated QM is highly desirable.

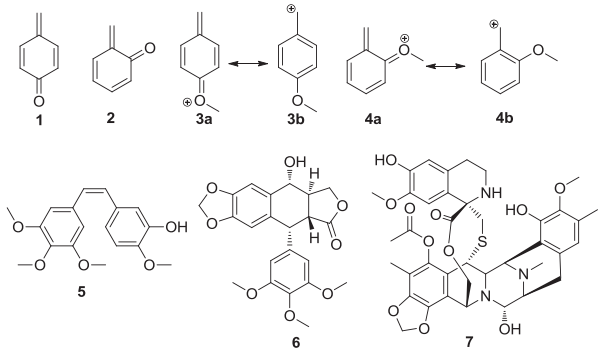

Fig. 1. Structures of quinone methides and related drugs.

On the other hand, heterogeneous Brønsted and Lewis acid catalysts based on montmorillonite clays have recently received much attention since they enable a variety of highly selective organic reactions.[8] For example, proton-exchanged montmorillonite (H-mont) has been successfully used as the catalyst in carbosilylation,[8d] C–N bond formation,[8e] addition reactions,[8f] polymerization reactions,[8g] and nucleophilic substitution reactions of alcohols.[8i] We report here that *O*-methylated QM could be generated via H-mont-mediated transformations of the corresponding methoxybenzyl esters and ethers. Synthetic applications of this protocol are also presented.

2. Results and discussion

p-Methoxybenzyl carbocation **3b** was thought to be generated from *p*-methoxybenzyl derivatives by solvolysis,[4a,b] Lewis acid-

* Corresponding authors. Tel./fax: +86 25 83271198; e-mail addresses: jzhangcpu@126.com (J. Zhang), hbsun2000@yahoo.com (H. Sun).

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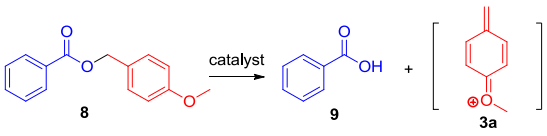
catalyzed cleavage,[4c] Brönsted acid-catalyzed cleavage,[4d] and photolysis.[4e] We reasoned that the *p*-methoxy function should play a key role as the secondary driving force through electron delocalization during the above transformations. If that was true, the first in situ generated species should be *O*-methylated QM **3a** instead of **3b**. In any cases, the existence of **3a** should be of significance, or even more favored than that of **3b**.

To establish an efficient approach to generation of *O*-methylated QM **3a**, acid-catalyzed transformation of *p*-methoxybenzyl benzoate **8** was examined, with using the release of benzoic acid **9** as an indicator (Table 1). After screening of a variety of acidic catalysts, H-mont was found to be the best choice in terms of high yields, eco-friendly conditions, quick reactions, and work-up convenience (Table 1, entries 1 and 2). Proper aprotic solvents (e.g., CH_2Cl_2 or toluene) were also critical for the successful reactions.

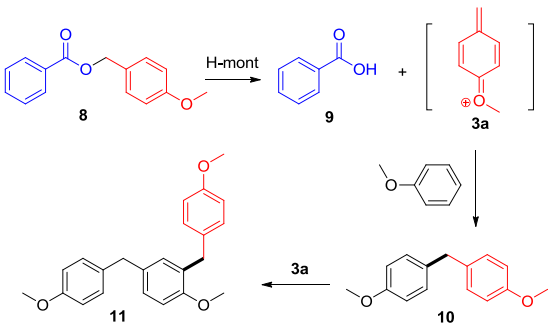
Table 1
Acid-catalyzed transformation of *p*-methoxybenzyl benzoate **8**[a]



Entry	Catalyst	Solvent	Time (h)	Conversion[b] (%)
1	H-mont	CH_2Cl_2	3.5	95
2	H-mont	toluene	4.5	97
3	H-mont	acetone	24	Trace
4	H-mont	EtOAc	36	11
5	Mont K10	CH_2Cl_2	12	95
6	Mont KSF	CH_2Cl_2	28	97
7	Na-bentonite	CH_2Cl_2	24	NR[c]
8	Kaolin 1250	CH_2Cl_2	48	20
9	H_2SO_4/SiO_2	CH_2Cl_2	24	NR
10	AcOH	AcOH	24	NR
11	TFA	CH_2Cl_2	5	97
12	aq HCl	H_2O	48	NR
13	aq H_2SO_4	H_2O	48	NR

[a] Reaction conditions: *p*-methoxybenzyl benzoate (0.366 mmol), solvent (3 mL), rt; for solid catalysts: 260 mg; for AcOH: 52.5 mmol; for TFA, aq HCL, or aq H_2SO_4: 1.5 mmol.
[b] The conversion yields of benzoic acid were determined by HPLC using *p*-methoxybenzyl benzoate as the internal standard.
[c] NR means no reaction.

To further demonstrate the occurrence of **3a** during H-mont-mediated transformation of **8**, nucleophilic trapping with anisole was examined (Scheme 1). When adding 1.5 equiv of anisole into the reaction system, as expected, bis(4-methoxyphenyl)methane **10** was obtained in 80% yield, along with benzoic acid **9** and 4,4′-(4-methoxy-1,3-phenylene)bis(methylene)bis(methoxybenzene) **11** in yields of 84% and 33%, respectively. Notably, with the protonation of the carboxyl O atom of the benzoate acting as the first driving force, the *p*-methoxy function plays a key synergistic role via electron resonance, leading to the formation of **3a**. When using anisole as the solvent, **9** and **10** were obtained in yields of 85% and 90%, respectively, without the formation of **11**. This should be due to that the large excess of anisole left no chance for the further trapping of **3a** by **10**.

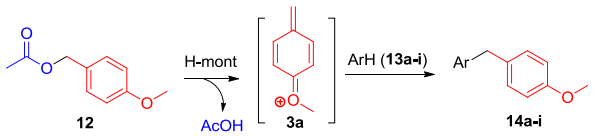


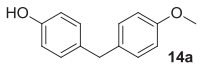
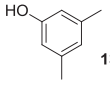
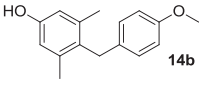
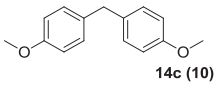
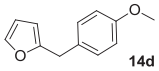
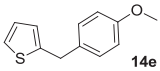
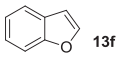
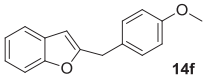
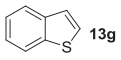
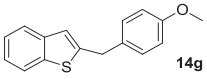
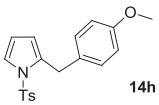
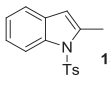
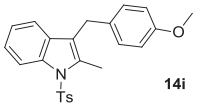
Scheme 1. Nucleophilic trapping of **3a** by anisole.

To explore this protocol, nucleophilic trapping of **3a**, which could be readily produced via H-mont-mediated transformation of *p*-methoxybenzyl acetate **12**, with arenes and heteroarenes was examined. As expected, H-mont was found to efficiently catalyze *p*-methoxybenzylation of aromatic compounds **13a**–**i** with **12**, leading to diarylmethanes **14a**–**i** in moderate to good yields (Table 2). Transition-metal or Brönsted acid-catalyzed synthesis of diarylmethanes with non-genotoxic benzyl acetates has attracted attention due to the drawbacks of the traditional Friedel–Crafts alkylation conditions.[2f,4d,9] In contrast to the reported procedures, the present approach is more eco-friendly without using heavy metals and the generation acidic wastes.

Mitsudome et al. reported titanium cation-exchanged montmorillonite-catalyzed etherification between different alcohols.[8h]

Table 2
H-mont-mediated Friedel–Crafts-like alkylation of arenes and heteroarenes **13a**–**i** by **12**[a]



Entry	ArH	Product	Yield[b] (%)
1	 13a	 14a	68
2	 13b	 14b	82
3[c]	 13c	 14c (10)	95
4[c]	 13d	 14d	48
5[c]	 13e	 14e	84
6[c]	 13f	 14f	53
7[c]	 13g	 14g	95
8[d]	 13h	 14h	48
9[d]	 13i	 14i	49

[a] Reaction conditions: *p*-methoxybenzyl acetate (0.366 mmol), arene (0.549 mmol), CH_2Cl_2 (3 mL), H-mont (260 mg), rt.
[b] Isolated yields.
[c] Anisole and heteroarenes were used as the solvents, respectively.
[d] Under reflux temperature.

In this context, H-mont-mediated etherification of a variety alcohols with **12** was achieved to afford the corresponding unsymmetrical ethers in moderate to high yields (Table 3). The reaction mechanism is thought to be nucleophilic trapping of the resulting *O*-methylated QM **3a** by alcohols. Besides primary and secondary alcohols, tertiary alcohols proved to be good nucleophiles as well (Table 3, entry 5). In most cases, the alcohols could be used as the solvents. To our knowledge, this is the first example for etherification of alcohols with benzyl acetates under eco-friendly conditions.

Table 3
H-mont-mediated etherification of alcohols **15a**–**g** by **12**[a]

Entry	Alcohol	Product	Yield[b] (%)
1	MeOH **15a**	**16a**	48
2	OH **15b**	**16b**	54
3	OH **15c**	**16c**	90
4	OH **15d**	**16d**	70
5	OH **15e**	**16e**	52
6[c]	OH **15f**	**16f**	94
7[c]	Cl, F_3C, OH **15g**	Cl, F_3C **16g**	68

[a] Reaction conditions: *p*-methoxybenzyl acetate **12** (0.366 mmol), alcohols **15a**–**e** were used as the reactants as well as the solvents, H-mont (260 mg), reflux.
[b] Isolated yields.
[c] *n*-Octane was used as the solvent, alcohols **15f**,**g**: each 0.549 mmol, rt.

Recently, Mendoza et al. reported triflimide-catalyzed benzylation of silyl enol ethers or allylsilanes with benzyl acetates.[10] Moreover, Motokura et al. reported H-mont-catalyzed benzylation of 1,3-dicarbonyl compounds with benzyl alcohols.[8i] These studies inspired us to examine H-mont-mediated *p*-methoxybenzylation of 1,3-dicarbonyl compounds, allylsilanes, and silyl enol ethers (Table 4). When used as the reactants as well as the solvents, 1,3-dicarbonyl compounds **17a** and **17b** underwent H-mont-catalyzed *p*-methoxybenzylation by **12** in quantitative yield, respectively (Table 4, entries 1 and 2). Reaction of allyltrimethylsilane **17c** with **12** in the presence of H-mont afforded olefin **18c** in 83% yield (Table 4, entry 3). In contrast to the reported procedures involving *p*-methoxybenzylation of **17c** with **12** catalyzed by $\{[Rh(cod)Cl]_2\}$[11a] or $Fe(OTf)_3$,[11b] this protocol is more eco-friendly and cost-effective. In addition, reaction of trimethylsilyl enol ether **17d** with **12** proceeded smoothly at room temperature to give ketone **18d** in 66% yield (Table 4, entry 4).

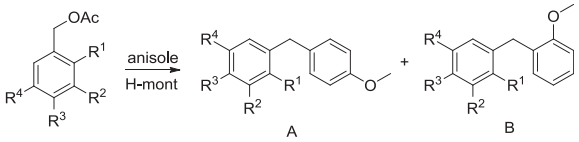
To explore the generality of the benzylation reagents, a variety of benzyl acetates were examined for H-mont-catalyzed benzylation of anisole (Table 5). As mentioned above with benzoate **8**, *p*-methoxybenzyl acetate **12** quickly and regioselectively reacted with anisole at room temperature, affording *para*-substitution product in 95% yield (Table 5, entry 4). By contrast, when using

Table 4
H-mont-mediated *p*-methoxybenzylation of 1,3-dicarbonyl compounds **17a**,**b** and silyl nucleophiles **17c**,**d** by **12**[a]

Entry	Nucleophile	Product	Yield[b] (%)
1	**17a**	**18a**	98
2	**17b**	**18b**	98
3	$SiMe_3$ **17c**	**18c**	83
4	$SiMe_3$ **17d**	**18d**	66

[a] Reaction conditions: **12** (0.366 mmol), nucleophile acting as the solvent, H-mont (260 mg), 100 °C or rt.
[b] Isolated yields based on **12**.

Table 5
H-mont-mediated benzylation of anisole with a variety of benzyl acetates[a]



Entry	R^1	R^2	R^3	R^4	Yield[b] (%) (A/B)
1	H	H	H	H	98 (49:51)
2	OMe	H	H	H	96 (67:33)[c]
3	H	OMe	H	H	93 (57:43)[c]
4	H	H	OMe	H	95 (>99:1)
5	OMe	H	OMe	H	Mixture
6	H	OMe	OMe	H	73 (90:10)[c]
7	H	OMe	H	OMe	85 (59:41)[c]
8	H	OMe	OMe	OMe	12 (>99:1)

[a] Reaction conditions: benzyl acetate (0.366 mmol), H-mont (260 mg), anisole (3 ml), reaction temperature: 100 °C for entries 1, 3, 7, and 8; 50 °C for entry 2; room temperature for entries 4, 5, and 6.
[b] Isolated yield.
[c] Estimated regioselectivity determined by the ^1H NMR analysis of the crude product.

o-methoxybenzyl acetate as the benzylating reagent, the reaction did not occur at room temperature, implying that the generation of *O*-methylated *o*-QM was not as easy as that of *O*-methylated *p*-QM. When the reaction temperature was raised to 50 °C, the reaction proceeded smoothly to give a separable mixture of *para* and *ortho* substitution products in 96% total yield (Table 5, entry 2). When using 2,4-dimethoxybenzyl acetate as the benzylating reagent, the starting material quickly disappeared at room temperature to result in a very complexed product mixture (Table 5, entry 5), indicating the formation of oligomeric compounds.[4f] For 3,4-dimethoxy benzyl acetate, the reaction took longer time to completion at room temperature, affording an inseparable product mixture of *para* and *ortho* isomers (Table 5, entry 6), together with some unidentified side-products. The high reactivity of benzyl acetates with *p*-methoxy function (Table 5, entries 4–6) should be attributed to the ease in generation of the corresponding *O*-methylated *p*-QM **19**. Surprisingly, the reaction of 3,4,5-trimethoxybenzyl acetate did not occur at room temperature, and when the reaction temperature was raised to 100 °C, the starting material quickly disappeared to afford the desired product in only 12% yield, together with some unidentified side-products (Table 5, entry 8). For benzyl acetate, 3-

methoxybenzyl acetate, and 3,5-dimethoxybenzyl acetate, the reactions took place at 100 °C to give the corresponding products in moderate to good yields, with loss of regioselectivity (Table 5, entries 1, 3, 7). This low reactivity might be owing to the difficulty in generation of the corresponding benzylic carbocations **20** in comparison with the easier formation of **19** (Fig. 2).

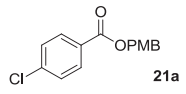
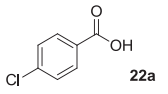
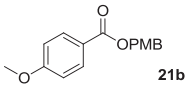
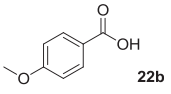
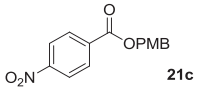
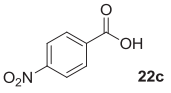
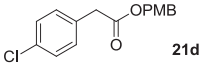
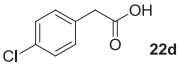
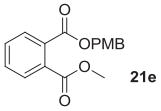
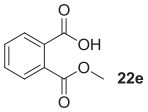
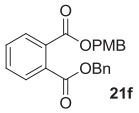
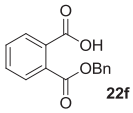
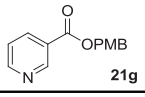
Fig. 2. Structures of benzylic carbocations **19** and **20**.

p-Methoxybenzyl (PMB) group is one of the most common protecting groups in organic synthesis.[12] Deprotecting agents for PMB ethers and esters include DDQ,[13a] CAN,[13b] hydrogen/palladium carbon,[13c] $AlCl_3$,[13d,e] $SnCl_2$/EtSH,[13d] $BF_3\cdot Et_2O/NaBH_3CN$,[13f] $MgBr_2$/Me_2S,[13g] BCl_3/Me_2S,[13h] $AgSbF_6$,[13i] trifluoroacetic acid,[13j,k] and triflic acid.[13l] However, these deprotection methods suffer from the use of expensive and toxic reagents, harsh conditions, and complexity in side-product profile. Based on the above experimentation, we reasoned that H-mont should be an efficient deprotecting agent for PMB group. To test this, deprotection of a variety of PMB-protected esters and ethers by H-mont was examined.

As expected, treatment of PMB-protected esters **21a**–**g** with H-mont in dichloromethane at room temperature afforded the corresponding carboxylic acids in high yields (Table 6, entries 1–6). Under this condition, methyl and benzyl esters were well tolerated while the PMB ester was selectively deprotected (Table 6, entries 5 and 6). It seemed that basic nitrogen atom had deleterious effect on the deprotection reaction, probably due to the preferred protonation taking place at nitrogen atom instead of the ester group (Table 6, entry 7).

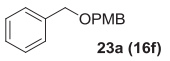
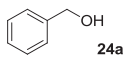
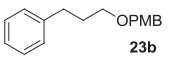
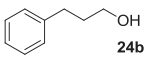
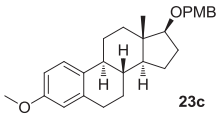
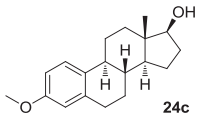
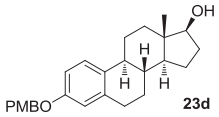
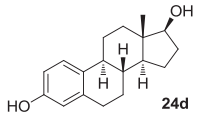
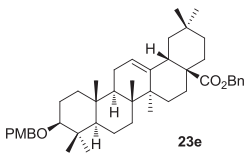
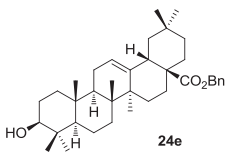
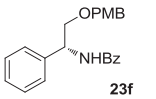
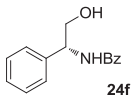
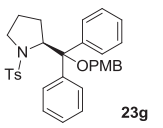
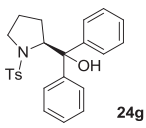
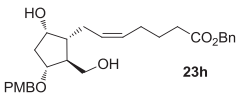
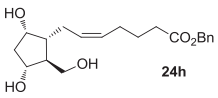
To check the efficiency of this protocol on deprotection of ethers, PMB-protected ethers **23a**–**h** were examined (Table 7). As shown in Table 7, treatment of a variety of PMB ethers with H-mont in dichloromethane at room temperature afforded the corresponding hydroxyl compounds **24a**–**h** in moderate to good yields. The reactions were generally quick at room temperature except for the deprotection of ether **23f** (Table 7, entry 6), which took much longer time for the reaction to complete. The tolerance of this reaction condition toward other functional groups, including hydroxyl, olefinic, and benzyl ester groups, is well illustrated by the deprotection of ether **23h** (Table 7, entry 8).

Table 6
H-mont-mediated deprotection of PMB-protected esters **21a**–**g**[a]

Entry	Ester	Product	Yield[b] (%)
1	 **21a**	 **22a**	90
2	 **21b**	 **22b**	99
3	 **21c**	 **22c**	87
4	 **21d**	 **22d**	95
5	 **21e**	 **22e**	99
6	 **21f**	 **22f**	92
7[c]	 **21g**	NR	NR

[a] Reaction conditions: ester (0.366 mmol), H-mont (260 mg), CH_2Cl_2 (3 mL), rt.
[b] Determined by HPLC using the PMB ester as the internal standard.
[c] No reaction.

Table 7
H-mont-mediated deprotection of PMB-protected ethers **23a**–**h**[a]

Entry	Ether	Product	Yield[b] (%)
1	 **23a (16f)**	 **24a**	90
2	 **23b**	 **24b**	60
3	 **23c**	 **24c**	83
4	 **23d**	 **24d**	78
5	 **23e**	 **24e**	60
6	 **23f**	 **24f**	72
7	 **23g**	 **24g**	85
8	 **23h**	 **24h**	83

[a] Reaction conditions: ester (0.366 mmol), H-mont (260 mg), CH_2Cl_2 (3 mL), rt.
[b] Isolated yield.

3. Conclusion

In conclusion, generation of *O*-methylated quinone methides could be readily achieved via H-mont-mediated transformations of the corresponding *p* or *o*-methoxybenzyl esters and ethers. Using this protocol, H-mont-mediated deprotection of PMB-protected esters and ethers have been developed for the first time. This PMB-deprotecting agent is more advantageous over the reported

ones in terms of eco-friendly conditions, cost-effectiveness, and work-up convenience. Moreover, nucleophilic trapping of the *O*-methylated quinone methides with arenes, alcohols, 1,3-dicarbonyl compounds, silyl enol ethers, and allylsilanes have been realized, respectively, leading to eco-friendly benzylation reactions. Further utilizations of this protocol are underway to construct more complex molecules.

4. Experimental section

4.1. General information

Low- and high-resolution mass spectra (LRMS and HRMS) were recorded in electron impact mode. The mass analyzer type used for the HRMS measurements was TOF. Reactions were monitored by TLC on silica gel 60 F_{254} plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Ocean Chemical Company, China).

4.2. Preparation of proton-exchanged montmorillonite (H-mont)

A mixture of Montmorillonite K 10 (9.0 g) and aqueous HCl (1.1 wt %, 600 mL) was stirred under reflux for 24 h. The obtained slurry was filtered and washed with distilled water (3 L) to ensure the removal of chloride, followed by drying at 110 °C in air to afford H-mont as a white gray powder.[8e]

4.3. H-mont-mediated Friedel–Crafts-like alkylation of anisole by *p*-methoxybenzyl benzoate (8)

To a mixture of **8** (89 mg, 0.366 mmol) and anisole (59 mg, 0.549 mmol) in anhydrous CH_2Cl_2 (3 mL) was added H-mont (260 mg). The reaction mixture was stirred at room temperature until the TLC indicated the consumption of **8**. The mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 100:1) to give benzoic acid **9** (37 mg, 84% yield), **10** (67 mg, 80% yield), and **11** (21 mg, 33% yield). On the other hand, to a mixture of **8** (89 mg, 0.366 mmol) and anisole (3 mL) was added H-mont (260 mg). The reaction mixture was stirred at room temperature until the TLC indicated the consumption of **8**. The mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 100:1) to give **9** (38 mg, 85% yield) and **10** (75 mg, 90% yield).

*4.3.1. 4,4′-((4-Methoxy-1,3-phenylene)bis(methylene))bis(methoxybenzene) (**11**).*[14] Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.11 (m, 2H), 7.10–7.07 (m, 2H), 6.98 (dd, J=8.2, 2.2 Hz, 1H), 6.94 (d, J=2.1 Hz, 1H), 6.86–6.78 (m, 5H), 3.90 (s, 2H), 3.84 (s, 2H), 3.80 (s, 9H).

4.4. General procedure for H-mont-mediated Friedel–Crafts-like alkylation of arenes and heteroarenes 13a–i by 12

To a mixture of arene or heteroarene (0.549 mmol) and **12** (66 mg, 0.366 mmol) in anhydrous CH_2Cl_2 (3 mL) was added H-mont (260 mg). The reaction mixture was stirred at room temperature or under reflux temperature until the TLC indicated the consumption of the starting material. The mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 200:1 to 10:1) to give the product. Following the procedure, **14a**,**b** and **14h**,**i** were prepared.

*4.4.1. 4-(4-Methoxybenzyl)phenol (**14a**).*[4d] White amorphous solid, 53 mg (68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J=8.5 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 6.75 (d, J=8.4 Hz, 2H), 4.91 (brs, 1H), 3.87 (s, 2H), 3.80 (s, 3H).

*4.4.2. 4-(4-Methoxybenzyl)-3,5-dimethylphenol (**14b**).*[15] Yellow solid, 73 mg (82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, J=8.6 Hz, 2H), 6.77 (d, J=8.6 Hz, 2H), 6.55 (s, 2H), 3.90 (s, 2H), 3.76 (s, 3H), 2.18 (s, 6H).

*4.4.3. 2-(4-Methoxybenzyl)-1-tosyl-1H-pyrrole (**14h**).* White solid, 60 mg (48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J=8.3 Hz, 2H), 7.31 (d, J=1.7 Hz, 1H), 7.19 (d, J=8.1 Hz, 2H), 6.94 (d, J=8.5 Hz, 2H), 6.73 (d, J=8.5 Hz, 2H), 6.17 (t, J=3.3 Hz, 1H), 5.75 (s, 1H), 4.00 (s, 2H), 3.77 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 144.4, 136.2, 134.7, 130.3, 129.9, 129.7, 126.7, 122.5, 114.0, 113.6, 111.1, 55.1, 32.5, 21.5. ESI-MS m/z 364.1 $[M+Na]^+$. HRMS calcd for $C_{19}H_{19}NO_3SNa$ $[M+Na]^+$ 364.0983, found 364.0986.

*4.4.4. 3-(4-Methoxybenzyl)-2-methyl-1-tosyl-1H-indole (**14i**).* White solid, 73 mg (49% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J=8.0 Hz, 1H), 7.61 (d, J=8.3 Hz, 2H), 7.27–7.13 (m, 5H), 6.94 (d, J=8.5 Hz, 2H), 6.73 (d, J=8.6 Hz, 2H), 3.90 (s, 2H), 3.75 (s, 3H), 2.56 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 144.4, 136.6, 136.2, 133.5, 131.4, 130.6, 129.7, 128.8, 126.2, 123.9, 123.3, 119.4, 118.7, 114.7, 113.7, 55.1, 28.9, 21.4, 12.8. ESI-MS m/z 428.1 $[M+Na]^+$. HRMS calcd for $C_{24}H_{23}NO_3SNa$ $[M+Na]^+$ 428.1296, found 428.1300.

To a mixture of **12** (66 mg, 0.366 mmol) and arenes or heteroarenes (1 mL) was added H-mont (260 mg). The reaction mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. The mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 200:1 to 10:1) to give the product. Following the procedure, **14c**–**g** were prepared.

*4.4.5. Bis(4-methoxyphenyl)methane (**14c** or **10**).*[4d] White solid, 79 mg (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J=8.5 Hz, 4H), 6.84 (d, J=8.6 Hz, 4H), 3.89 (s, 2H), 3.80 (s, 6H).

*4.4.6. 2-(4-Methoxybenzyl)furan (**14d**).*[4d] Colorless oil, 33 mg (48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.15 (d, J=8.4 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 6.28–6.27 (m, 1H), 5.97 (d, J=3.0 Hz, 1H), 3.91 (s, 2H), 3.78 (s, 3H).

*4.4.7. 2-(4-Methoxybenzyl)thiophene (**14e**).*[4d] Colorless oil, 63 mg (84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.14 (m, 2H), 7.13–7.10 (m, 1H), 6.91–6.89 (m, 1H), 6.85–6.82 (m, 2H), 6.78–6.77 (m, 1H), 4.09 (s, 2H), 3.78 (s, 3H).

*4.4.8. 2-(4-Methoxybenzyl)benzofuran (**14f**)..*[16] White solid, 46 mg (53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J=7.0 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.23–7.19 (m, 2H), 7.17–7.14 (m, 2H), 6.86 (d, J=8.5 Hz, 2H), 6.33 (s, 1H), 4.04 (s, 2H), 3.78 (s, 3H).

*4.4.9. 2-(4-Methoxybenzyl)benzo[b]thiophene (**14g**).*[16] White solid, 88 mg (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.85 (m, 1H), 7.72–7.70 (m, 1H), 7.36–7.33 (m, 2H), 7.24–7.17 (m, 2H), 7.00 (s, 1H), 6.87–6.84 (m, 2H), 4.14 (s, 2H), 3.80 (s, 3H).

4.5. General procedure for H-mont-mediated etherification of alcohols 15a–g by 12

To a mixture of **12** (66 mg, 0.366 mmol) and the alcohol (3 mL) was added H-mont (260 mg). The reaction mixture was stirred

under reflux until the TLC indicated the consumption of the starting material. The reaction mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 300:1 to 200:1) to give the product. Following the procedure, **16a**–**e** were prepared.

*4.5.1. 1-Methoxy-4-(methoxymethyl)benzene (**16a**).*[17] Colorless oil, 27 mg (48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.35 (s, 3H).

*4.5.2. 1-(Ethoxymethyl)-4-methoxybenzene (**16b**).*[17] Colorless oil, 33 mg (54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J=8.9 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.51 (q, J=7.0 Hz, 2H), 1.23 (t, J=7.0 Hz, 3H).

*4.5.3. 1-(Isopropoxymethyl)-4-methoxybenzene (**16c**).*[17] Colorless oil, 59 mg (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J=8.3 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.67 (dt, J=12.2, 6.1 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 3H).

*4.5.4. 1-(Butoxymethyl)-4-methoxybenzene (**16d**).*[17] Colorless oil, 50 mg (70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.23 (m, 2H), 6.88–6.86 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, J=6.6 Hz, 2H), 1.58 (dt, J=14.5, 6.7 Hz, 2H), 1.42–1.35 (m, 2H), 0.91 (t, J=7.4 Hz, 3H).

*4.5.5. 1-(tert-Butoxymethyl)-4-methoxybenzene (**16e**).*[17] Colorless oil, 37 mg (52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 4.37 (s, 2H), 3.79 (s, 3H), 1.28 (s, 9H).

To a mixture of **12** (66 mg, 0.366 mmol) and the alcohol (0.549 mmol) in *n*-octane (3 mL) was added H-mont (260 mg), and then the mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. The reaction mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 300:1 to 200:1) to give the product. Following the procedure, **16f**,**g** were prepared.

*4.5.6. 1-((Benzyloxy)methyl)-4-methoxybenzene (**16f** or **23a**).*[18] Colorless oil, 79 mg (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 7.30 (d, J=8.7 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 4.54 (s, 2H), 4.50 (s, 2H), 3.82 (s, 3H).

*4.5.7. 1-Chloro-2-(((4-methoxybenzyl)oxy)methyl)-4-(trifluoromethyl)benzene (**16g**).* Colorless oil, 82 mg (68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.48–7.44 (m, 2H), 7.32 (d, J=8.5 Hz, 1H), 6.91 (d, J=8.5 Hz, 1H), 4.63 (s, 2H), 4.60 (s, 2H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 137.4, 136.1, 132.8, 129.6, 129.5, 129.4, 129.0, 125.6, 125.1, 113.9, 72.8, 68.2, 55.1. ESI-MS m/z 353.1 $[M+Na]^+$. HRMS calcd for $C_{16}H_{14}ClF_3O_2Na$ $[M+Na]^+$ 353.0532, found 353.0535.

4.6. General procedure for H-mont-mediated *p*-methoxybenzylation of 1,3-dicarbonyl compounds 17a,b and silyl nucleophiles 17c,d by 12

To a mixture of **12** (66 mg, 0.366 mmol) and 1,3-dicarbonyl compounds (3 mL) or silyl nucleophiles (1 mL) was added H-mont (260 mg). The reaction mixture was stirred at 100 °C or room temperature until the TLC indicated the consumption of the starting material. The mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 400:1 to 10:1) to give the product. Following the procedure, **18a**–**d** were prepared.

*4.6.1. 3-(4-Methoxybenzyl)pentane-2,4-dione (**18a**) (existing in both keto and enol forms).*[19] Colorless oil, 79 mg (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.79 (s, 1H), 7.07 (d, J=8.7 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.09 (s, 6H).

*4.6.2. Ethyl 2-(4-methoxybenzyl)-3-oxobutanoate (**18b**).*[20] Colorless oil, 90 mg (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 4.19–4.12 (m, 2H), 3.78 (s, 3H), 3.74 (t, J=7.6 Hz, 1H), 3.11 (d, J=7.6 Hz, 2H), 2.18 (s, 3H), 1.22 (t, J=7.2 Hz, 3H).

*4.6.3. 1-(But-3-en-1-yl)-4-methoxybenzene (**18c**).*[11a] Colorless oil, 49 mg (83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.96–5.82 (m, 1H), 5.10–4.99 (m, 2H), 3.82 (s, 3H), 2.72–2.66 (m, 2H), 2.38 (dd, J=15.0, 7.0 Hz, 2H).

*4.6.4. 2-(4-Methoxybenzyl)cyclohexanone (**18d**).*[10] Colorless oil, 53 mg (66% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J=8.5 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 3.78 (s, 3H), 3.15 (dd, J=13.8, 4.7 Hz, 1H), 2.56–2.25 (m, 4H), 2.09–1.99 (m, 2H), 1.85–1.80 (m, 1H), 1.69–1.50 (m, 2H), 1.41–1.26 (m, 1H).

4.7. General procedure for H-mont-mediated benzylation of anisole with a variety of benzyl acetates (for Table 5)

To a mixture of anisole (3 mL) and an acetate (0.366 mmol) was added H-mont (260 mg). The reaction mixture was stirred at the temperature indicated in Table 5 until the TLC indicated the consumption of the acetate. The mixture was filtered to remove H-mont, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 300:1 to 10:1) to give the product. The results are summarized in Table 5.

4.8. General procedure for the preparation of 8, 21a–d and 21g

To a solution of the corresponding carboxylic acid (3.6 mmol) in anhydrous CH_2Cl_2 (20 mL) was added thionyl chloride (2.6 mL, 36 mmol). The reaction mixture was stirred at 40 °C for 2 h, and then concentrated in vacuo to dryness. The residue was dissolved in anhydrous CH_2Cl_2 (20 mL), then *p*-methoxybenzyl alcohol (497 mg, 3.6 mmol) and excess triethylamine were added. The reaction mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. An aqueous solution of 10% HCl was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 200:1 to 20:1) to give the product.

*4.8.1. 4-Methoxybenzyl benzoate (**8**).*[21] Colorless oil, 0.70 g (80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J=7.5 Hz, 2H), 7.57–7.50 (m, 1H), 7.47–7.37 (m, 4H), 6.91 (d, J=8.5 Hz, 2H), 5.30 (s, 2H), 3.81 (s, 3H).

*4.8.2. 4-Methoxybenzyl 4-chlorobenzoate (**21a**).*[22] White solid, 0.98 g (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J=8.6 Hz, 2H), 7.53–7.34 (m, 4H), 6.95 (d, J=8.6 Hz, 2H), 5.33 (s, 2H), 3.85 (s, 3H).

*4.8.3. 4-Methoxybenzyl 4-methoxybenzoate (**21b**).*[23] Colorless oil, 0.66 g (67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03–7.98 (m, 2H), 7.39–7.36 (m, 2H), 6.93–6.87 (m, 4H), 5.27 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H).

*4.8.4. 4-Methoxybenzyl 4-nitrobenzoate (**21c**).*[24] Light yellow solid, 1.01 g (98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (q, J=8.9 Hz,

4H), 7.43 (d, *J*=8.7 Hz, 2H), 6.96 (d, *J*=8.4 Hz, 2H), 5.37 (s, 2H), 3.86 (s, 3H).

*4.8.5. 4-Methoxybenzyl 2-(4-chlorophenyl)acetate (**21d**).* White solid, 0.80 g (76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 4H), 7.19 (d, *J*=8.0 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 3.60 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 159.7, 133.0, 132.4, 130.6, 130.1, 128.7, 127.8, 114.0, 66.6, 55.3, 40.6. ESI-MS *m*/*z* 313.1 $[M+Na]^+$. HRMS calcd for $C_{16}H_{15}ClO_3Na$ $[M+Na]^+$ 313.0607, found 313.0613.

*4.8.6. 4-Methoxybenzyl nicotinate (**21g**).*[25] Colorless oil, 0.83 g (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25–9.24 (m, 1H), 8.76 (dd, *J*=4.9, 1.7 Hz, 1H), 8.31 (dt, *J*=7.9, 2.0 Hz, 1H), 7.39 (d, *J*=8.7 Hz, 2H), 7.39–7.35 (m, 1H), 6.92 (d, *J*=8.6 Hz, 2H), 5.34 (s, 2H), 3.83 (s, 3H).

4.9. General procedure for the preparation of 21e and 21f

To a solution of phthalic anhydride (250 mg, 1.69 mmol) in pyridine (3 mL) was added *p*-methoxybenzyl alcohol (280 mg, 2.03 mmol) and catalytic amount of 4-dimethylaminopyridine. The reaction mixture was stirred overnight at room temperature, and then concentrated in vacuo to dryness. An aqueous solution of 10% HCl (25 mL) was added to the reaction mixture. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in acetone (5 mL), then methyl iodide or benzyl bromide (2.53 mmol) and K_2CO_3 (467 mg, 3.38 mmol) were added. The reaction mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. Then the mixture was filtered to remove K_2CO_3, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 20:1 to 15:1) to give the product.

*4.9.1. 4-Methoxybenzyl methyl phthalate (**21e**).* Colorless oil, 213 mg (42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.73 (m, 1H), 7.70–7.68 (m, 1H), 7.53–7.51 (m, 2H), 7.37–7.35 (m, 2H), 6.91–6.89 (m, 2H), 5.28 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H).

*4.9.2. Benzyl 4-methoxybenzyl phthalate (**21f**).* Colorless oil, 509 mg (80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.72 (m, 2H), 7.52–7.50 (m, 2H), 7.37–7.33 (m, 5H), 7.31–7.29 (m, 2H), 6.88–6.86 (m, 2H), 5.23 (s, 2H), 5.17 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 159.8, 135.5, 132.1, 132.0, 131.1, 131.1, 130.3, 129.0, 129.0, 128.6, 128.4, 128.3, 127.6, 114.0, 67.4, 67.3, 55.3. ESI-MS *m*/*z* 399.2 $[M+Na]^+$. HRMS calcd for $C_{23}H_{20}O_5Na$ $[M+Na]^+$ 399.1208, found 399.1212.

4.10. General procedure for the preparation of 23a–h

To a solution of the corresponding alcohol (3.6 mmol) in anhydrous DMF (5 mL) was added sodium hydride (60% in mineral oil, 216 mg, 5.4 mmol) in several portions at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then *p*-methoxybenzyl chloride (564 mg, 3.6 mmol) was added. The mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. An aqueous solution of ammonium chloride was added to the reaction mixture. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 200:1 to 20:1) to give the product. Following the procedure, **23a**–**g** were prepared.

*4.10.1. 1-((Benzyloxy)methyl)-4-methoxybenzene (**23a** or **16f**).*[18] Colorless oil, 0.69 g (84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.40 (m, 4H), 7.36–7.33 (m, 3H), 6.96–6.93 (m, 2H), 4.59 (s, 2H), 4.55 (s, 2H), 3.86 (s, 3H).

*4.10.2. 1-Methoxy-4-((3-phenylpropoxy)methyl)benzene (**23b**).*[13i] Colorless oil, 0.55 g (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.24 (m, 5H), 7.19–7.16 (m, 2H), 6.90–6.86 (m, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.46 (t, *J*=6.4 Hz, 2H), 2.70 (t, *J*=7.5 Hz, 2H), 1.97–1.87 (m, 2H).

*4.10.3. 3-O-Methyl-17-(4-methoxybenzyl)-β-estradiol (**23c**).*[26] White solid, 0.88 g (60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.5 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 1H), 6.87 (d, *J*=8.1 Hz, 2H), 6.70 (dd, *J*=8.5, 2.5 Hz, 1H), 6.62 (d, *J*=2.2 Hz, 1H), 4.50 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.48 (t, *J*=8.4 Hz, 1H), 2.86–2.79 (m, 2H), 2.29–2.26 (m, 1H), 2.20–2.14 (m, 1H), 2.09–1.99 (m, 2H), 1.88–1.85 (m, 1H), 1.69–1.15 (m, 8H), 0.85 (s, 3H).

*4.10.4. 3-O-(4-Methoxybenzyl)-β-estradiol (**23d**).* White solid, 0.57 g (40% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.33 (m, 2H), 7.19 (d, *J*=8.4 Hz, 1H), 6.93–6.88 (m, 2H), 6.77 (dd, *J*=8.5, 2.7 Hz, 1H), 6.70 (d, *J*=2.6 Hz, 1H), 4.95 (s, 2H), 3.81(s, 3H), 3.73 (t, *J*=8.7 Hz, 1H), 2.87–2.79 (m, 2H), 2.33–2.28 (m, 1H), 2.23–2.04 (m, 2H), 1.97–1.84 (m, 2H), 1.74–1.64 (m, 1H), 1.56–1.14 (m, 8H), 0.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 156.8, 138.0, 132.9, 129.4, 129.2, 126.3, 114.9, 114.0, 112.3, 81.9, 69.8, 55.3, 50.1, 44.0, 43.3, 38.9, 36.7, 30.6, 29.8, 27.3, 26.3, 23.1, 11.1. ESI-MS *m*/*z* 415.2 $[M+Na]^+$. HRMS calcd for $C_{26}H_{32}O_3Na$ $[M+Na]^+$ 415.2249, found 415.2253.

*4.10.5. Benzyl-3β-(4-methoxybenzyl)olean-12-en-28-oic acid (**23e**).* White solid, 2.09 g (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.29 (m, 7H), 6.89–6.85 (m, 2H), 5.29 (t, *J*=3.4 Hz, 1H), 5.13–5.00 (m, 2H), 4.59 (d, *J*=11.5 Hz, 1H), 4.36 (d, *J*=11.5 Hz, 1H), 3.80 (s, 3H), 2.92–2.86 (m, 2H), 2.02–0.68 (m, 22H), 1.16 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 158.8, 143.6, 136.4, 131.5, 128.9, 128.3, 127.9, 127.8, 122.5, 113.5, 86.0, 70.9, 65.8, 55.7, 55.1, 47.5, 46.7, 45.8, 41.6, 41.3, 39.3, 38.8, 38.3, 36.9, 33.8, 33.1, 32.7, 32.3, 30.6, 28.2, 27.5, 25.8, 23.6, 23.4, 23.0, 22.7, 18.2, 16.8, 16.6, 15.2. HRMS calcd for $C_{45}H_{62}O_4Na$ $[M+Na]^+$ 689.4540, found 689.4541.

*4.10.6. (R)-N-(2-((4-Methoxybenzyl)oxy)-1-phenylethyl)benzamide (**23f**).* White solid, 1.18 g (91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.53–7.27 (m, 8H), 7.21–7.20 (m, 2H), 6.87–6.85 (m, 2H), 5.40–5.37 (m, 1H), 4.53–4.47 (m, 2H), 3.87–3.79 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 159.4, 139.9, 134.5, 131.5, 129.4, 128.5, 128.4, 127.5, 127.1, 126.9, 113.9, 72.8, 72.0, 55.3, 53.1. ESI-MS *m*/*z* 384.2 $[M+Na]^+$. HRMS calcd for $C_{23}H_{23}NO_3Na$ $[M+Na]^+$ 384.1576, found 384.1580.

*4.10.7. (S)-2-(((4-Methoxybenzyl)oxy)diphenylmethyl)-1-tosylpyrrolidine (**23g**).* White solid, 1.25 g (66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.1 Hz, 2H), 7.48 (m, 2H), 7.42 (m, 2H), 7.36–7.27 (m, 6H), 7.22 (d, *J*=8.5 Hz, 2H), 7.16 (d, *J*=8.0 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 4.22 (d, *J*=11.1 Hz, 1H), 3.83 (d, *J*=11.1 Hz, 1H), 3.79 (s, 3H), 3.35–3.30 (m, 1H), 2.39 (s, 3H), 1.97–1.92 (m, 2H), 1.86–1.80 (m, 2H), 1.25–1.21 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 142.7, 139.9, 139.3, 137.4, 131.3, 130.0, 130.0, 129.7, 129.2, 128.5, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 113.4, 86.3, 65.8, 65.2, 55.2, 49.3, 28.1, 24.2, 21.4. ESI-MS *m*/*z* 550.2 $[M+Na]^+$. HRMS calcd for $C_{32}H_{33}NO_4SNa$ $[M+Na]^+$ 550.2028, found 550.2034.

4.10.8. (Z)-Benzyl 7-((1R,2S,3R,5S)-5-hydroxy-2-(hydroxymethyl)-3-((4-methoxybenzyl)oxy)cyclopentyl)hept-5-enoate

(**23h**).[27] Following the method described in Ref. 27, **23h** was obtained as a colorless oil, 130 mg (60% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40–7.29 (m, 5H), 7.25–7.20 (m, 2H), 6.90–6.85 (m, 2H), 5.50–5.28 (m, 2H), 5.08 (d, J=1.7 Hz, 2H), 4.45 (dt, J=10.2, 5.1 Hz, 1H), 4.41–4.30 (m, 2H), 4.09 (dd, J=18.8, 5.1 Hz, 1H), 3.98–3.94 (m, 1H), 3.80–3.76 (m, 1H), 3.73 (s, 3H), 3.50–3.47 (m, 1H), 3.38–3.33 (m, 1H), 2.35–2.32 (m, 2H), 2.24–2.16 (m, 1H), 2.13–1.90 (m, 4H), 1.84–1.80 (m, 1H), 1.67–1.57 (m, 3H), 1.55–1.49 (m, 1H). ESI-MS m/z 491.2 $[M+Na]^+$.

4.11. General procedure for H-mont-mediated deprotection of PMB-protected esters 21a–g

To a solution of *p*-methoxybenzyl ester (0.366 mmol) in anhydrous CH_2Cl_2 (3 mL) was added H-mont (260 mg), and then the mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. The mixture was filtered to remove H-mont, and the filtrate was diluted with CH_2Cl_2 for HPLC analysis. The results are summarized in Table 6.

4.12. General procedure for H-mont-mediated deprotection of PMB-protected ethers 23a–h

To a solution of *p*-methoxybenzyl ether (0.366 mmol) in anhydrous CH_2Cl_2 (3 mL) was added H-mont (260 mg). The reaction mixture was stirred at room temperature until the TLC indicated the consumption of the starting material. The mixture was filtered to remove H-mont. The filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 20:1 to 1:1) to give the product. Following the procedure, **24a–h** were prepared.

*4.12.1. Phenylmethanol (**24a**).*[28] Colorless oil, 36 mg (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 4.62 (d, J=5.6 Hz, 2H), 2.82 (t, J=5.7 Hz, 1H).

*4.12.2. 3-Phenylpropan-1-ol (**24b**).*[29] Colorless oil, 30 mg (60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.22–7.19 (m, 3H), 3.70 (t, J=6.4 Hz, 2H), 2.73 (t, J=7.5 Hz, 2H), 1.95–1.89 (m, 2H).

*4.12.3. 3-O-Methyl-β-estradiol (**24c**).*[30] White solid, 87 mg (83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J=8.6 Hz, 1H), 6.73 (dd, J=8.6, 2.8 Hz, 1H), 6.65 (d, J=2.7 Hz, 1H), 3.80 (s, 3H), 3.75 (t, J=8.5 Hz, 1H), 2.90–2.84 (m, 2H), 2.36–2.31 (m, 1H), 2.24–2.10 (m, 2H), 1.99–1.95 (m, 1H), 1.93–1.88 (m, 1H), 1.76–1.69 (m, 1H), 1.56–1.28 (m, 7H), 1.25–1.19 (m, 1H), 0.80 (s, 3H).

*4.12.4. β-Estradiol (**24d**).*[31] White solid, 78 mg (78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J=8.4 Hz, 1H), 6.62 (dd, J=8.3, 2.8 Hz, 1H), 6.56 (d, J=2.7 Hz, 1H), 3.78–3.69 (m, 1H), 2.87–2.77 (m, 2H), 2.34–2.26 (m, 1H), 2.22–2.06 (m, 2H), 1.99–1.82 (m, 2H), 1.75–1.64 (m, 1H), 1.58–1.12 (m, 7H), 0.78 (s, 3H).

*4.12.5. Benzyl-olean-12-en-28-oic acid (**24e**).*[32] White solid, 120 mg (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H), 5.30 (t, J=3.3 Hz, 1H), 5.14–5.04 (m, 2H), 3.22 (dd, J=10.5, 4.8 Hz, 1H), 2.92 (dd, J=13.8, 3.9 Hz, 1H), 2.07–1.93 (m, 1H), 1.87 (dd, J=8.7, 3.4 Hz, 2H), 1.79–0.71 (m, 20H), 1.14 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.79 (s, 3H), 0.63 (s, 3H).

*4.12.6. (R)-N-(2-Hydroxy-1-phenylethyl)benzamide (**24f**).*[33] White solid, 64 mg (72% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (d, J=8.0 Hz, 1H), 7.92–7.89 (m, 2H), 7.54–7.44 (m, 3H), 7.41–7.38 (m, 2H), 7.34–7.29 (m, 2H), 7.25–7.20 (m, 1H), 5.07 (td, J=7.9, 5.8 Hz, 1H), 4.91 (t, J=5.9 Hz, 1H), 3.76–3.61 (m, 2H).

*4.12.7. (S)-Diphenyl(1-tosylpyrrolidin-2-yl)methanol (**24g**).*[34] White solid, 127 mg (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J=8.2 Hz, 2H), 7.47–7.39 (m, 4H), 7.38–7.25 (m, 8H), 4.86 (dd, J=8.9, 3.5 Hz, 1H), 4.52 (brs, 1H), 3.30 (m, 1H), 2.81 (m, 1H), 2.47 (s, 3H), 1.90–1.79 (m, 2H), 1.26–1.19 (m, 1H), 0.85–0.76 (m, 1H).

*4.12.8. (Z)-Benzyl 7-((1R,2S,3R,5S)-3,5-dihydroxy-2-(hydroxymethyl) cyclopentyl)hept-5-enoate (**24h**).* Colorless oil, 106 mg (83% yield). $[\alpha]_D^{25}$ +26.3 (c 0.1, CH_3OH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.48–5.43 (m, 1H), 5.41–5.36 (m, 1H), 5.12 (s, 2H), 4.18 (s, 2H), 3.78 (dd, J=10.6, 4.6 Hz, 1H), 3.48 (dd, J=10.5, 7.7 Hz, 1H), 2.38 (t, J=7.2 Hz, 2H), 2.34–2.30 (m, 1H), 2.25 (brs, 3H), 2.23–2.17 (m, 1H), 2.13 (q, J=7.3 Hz, 2H), 1.96–1.91 (m, 2H), 1.86 (d, J=14.3 Hz, 1H), 1.72 (p, J=7.3 Hz, 2H), 1.56–1.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.8, 135.8, 130.3, 129.8, 129.4, 129.2, 128.5, 128.1, 128.1, 76.2, 74.1, 66.2, 63.9, 54.7, 47.1, 42.3, 33.6, 26.6, 26.5, 24.7. ESI-MS m/z 371.2 $[M+Na]^+$. HRMS calcd for $C_{20}H_{28}O_5Na$ $[M+Na]^+$ 371.1834, found 371.

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Supplementary data

^{1}H NMR and ^{13}C NMR copies of all synthesized compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.01.064.

References and notes

1. For a comprehensive review on QM see: (a) Rokita, S. E. *Quinone Methides*. Wiley Series of Reactive Intermediates in Chemistry and Biology; John Wiley & Sons: Hoboken, NJ, 2009; Vol. 1; (b) Toteva, M. M.; Richard, J. P. *Adv. Phys. Org. Chem.* **2011**, *45*, 39–91.
2. (a) Kim, C. K.; Han, I. S.; Ryu, W. S.; Lee, H. W.; Lee, B. S.; Kim, C. K. *J. Phys. Chem. A* **2006**, *110*, 2500–2504; (b) Toteva, M. M.; Moran, M.; Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8814–8819; (c) Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990**, *112*, 9513–9519; (d) Tsuji, Y.; Hara, D.; Hagimoto, R.; Richard, J. P. *J. Org. Chem.* **2011**, *76*, 9568–9571; (e) Dehn, R.; Katsuyama, Y.; Weber, A.; Gerth, K.; Jansen, R.; Steinmetz, H.; Hoefle, G.; Mueller, R.; Kirschning, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3882–3887; (f) Tangdenpaisal, K.; Phakhodee, W.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* **2013**, *69*, 933–941.
3. Poverenov, E.; Leitus, G.; Milstein, D. *J. Am. Chem. Soc.* **2006**, *128*, 16450–16451.
4. (a) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 9507–9512; (b) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9798–9805; (c) Gansauer, A.; Fielenbach, D.; Stock, C.; Geich-Gimbel, D. *Adv. Synth. Catal.* **2003**, *345*, 1017–1030; (d) Mendoza, O.; Rossey, G.; Ghosez, L. *Tetrahedron Lett.* **2011**, *52*, 2235–2239; (e) McClelland, R. A.; Chan, C.; Cozens, F.; Modro, A.; Steenken, S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1337–1339; (f) Salmón, M.; Miranda, R.; Nicolás-Vázquez, I.; Vargas-Rodriguez, Y. M.; Cruz-Borbolla, J.; Medrano, M. I.; Morales-Serna, J. A. *Molecules* **2011**, *16*, 1761–1775.
5. (a) Hori, K. *Cancer Metastasis Rev.* **2012**, *31*, 109–122; (b) Lin, C. M.; Ho, H. H.; Pettit, G. R.; Hamel, E. *Biochemistry* **1989**, *28*, 6984–6991.
6. Wang, S. L.; Yao, S. D.; Mei, W.; Zhang, Y. L.; Zhang, M. W.; Zhang, Z. C. *Radiat. Phys. Chem.* **1998**, *53*, 623–628.
7. D'Incalci, M.; Galmarini, C. M. *Mol. Cancer Ther.* **2010**, *9*, 2157–2163.
8. (a) Motokura, K.; Tada, M.; Iwasawa, Y. *J. Am. Chem. Soc.* **2009**, *131*, 7944–7945; (b) Mitsudome, T.; Nose, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3288–3290; (c) Kaneda, K. *Synlett* **2007**, 999–1015; (d) Motokura, K.; Baba, T. *Green Chem.* **2012**, *14*, 565–579; (e) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617–4620; (f) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem.* **2006**, *118*, 2667–2671; (g) Harrane, A.; Meghabar, R.; Belbachir, M. *React. Funct. Polym.* **2006**, *66*, 1696–1702; (h) Mitsudome, T.; Matsuno, T.; Sueoka, S.; Mizugaki, T.; Jitsukawa,

K.; Kaneda, K. *Green Chem.* **2012**, *14*, 610–613; (i) Motokura, K.; Nakagiri, N.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **2007**, *72*, 6006–6015.
9. (a) Mertins, K.; Jovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238–242; (b) Jovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913–3917.
10. Mendoza, O.; Rossey, G.; Ghosez, L. *Tetrahedron Lett.* **2010**, *51*, 2571–2575.
11. (a) Onodera, G.; Yamamoto, E.; Tonegawa, S.; Iezumi, M.; Takeuchi, R. *Adv. Synth. Catal.* **2011**, *353*, 2013–2021; (b) Chan, L. Y.; Kim, S.; Chung, W. T.; Long, C.; Kim, S. *Synlett* **2011**, 415–419.
12. Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833–7863.
13. (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524–2536; (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371–2374; (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7–9; (d) Bouzide, A.; Sauvé, G. *Synlett* **1997**, 1153–1154; (e) Ohtani, M.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1984**, *49*, 5271–5272; (f) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Vijaykumar, D. *J. Org. Chem.* **1995**, *60*, 5961–5962; (g) Onoda, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1997**, *38*, 1443–1446; (h) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663–664; (i) Kern, N.; Dombray, T.; Blanc, A.; Weibel, J. M.; Pale, P. *J. Org. Chem.* **2012**, *77*, 9227–9235; (j) Tanaka, H.; Taniguchi, M.; Kameyama, Y.; Torii, S.; Sasaoka, M.; Shiroi, T.; Kikuchi, R.; Kawahara, I.; Shimabayashi, A.; Nagao, S. *Tetrahedron Lett.* **1990**, *31*, 6661–6662; (k) Yan, L.; Kahne, D. *Synlett* **1995**, 523–524; (l) Jung, M. E.; Koch, P. *Tetrahedron Lett.* **2011**, *52*, 6051–6054.
14. Srimani, D.; Bej, A.; Sarkar, A. *J. Org. Chem.* **2010**, *75*, 4296–4299.
15. Boyer, S. H.; Erion, M. D.; Ito, B.; Jacintho, J. WO 2011038207 A1.
16. Duez, S.; Steib, A. K.; Knochel, P. *Org. Lett.* **2012**, *14*, 1951–1953.
17. Chavan, S. P.; Harale, K. R. *Tetrahedron Lett.* **2012**, *53*, 4683–4686.
18. Sirkecioglu, O.; Karliga, B.; Talinli, N. *Tetrahedron Lett.* **2003**, *44*, 8483–8485.
19. Tsai, C. Y.; Sung, R.; Zhuang, B. R.; Sung, K. S. *Tetrahedron* **2010**, *66*, 6869–6872.
20. Kischel, J.; Mertins, K.; Michalik, D.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2007**, *349*, 865–870.
21. Ohno, O.; Ye, M.; Koyama, T.; Uemura, D. *Bioorg. Med. Chem.* **2008**, *16*, 7843–7852.
22. Zhang, W.; Lu, Y. M. *J. Comb. Chem.* **2007**, *9*, 836–843.
23. Rolfe, A.; Loh, J. K.; Maity, P. K.; Hanson, P. R. *Org. Lett.* **2011**, *13*, 4–7.
24. Massah, A. R.; Kalbasi, R. J.; Toghiani, M.; Hojati, B.; Adibnejad, M. *E-J. Chem.* **2012**, *9*, 2501–2508.
25. Bald, E. *Chem. Scr.* **1979**, *13*, 47.
26. Sharma, G. V. M.; Mahalingam, A. K. *J. Org. Chem.* **1999**, *64*, 8943–8944.
27. Alberico, D.; Clayton, J.; Gorin, B. I.; Oudenes, J. US 7,928,252 B2.
28. Kathrin, J.; Bianca, W.; Shaolin, Z.; Matthias, B. *Eur. J. Org. Chem.* **2013**, *11*, 2061–2065.
29. Gallois, P.; Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1946–1950.
30. Muddana, S. S.; Price, A. M.; MacBride, M. M.; Peterson, B. R. *J. Med. Chem.* **2004**, *47*, 4985–4988.
31. Cui, X. X.; Li, B.; Liu, T. Z.; Li, C. B. *Green Chem.* **2012**, *14*, 668–672.
32. Wen, X. A.; Sun, H. B.; Liu, J.; Cheng, K. G. *J. Med. Chem.* **2008**, *51*, 3540–3554.
33. Matsui, T.; Kondo, T.; Nishita, Y.; Itadani, S. *Bioorg. Med. Chem.* **2002**, *10*, 3757–3786.
34. Selvakumar, S.; Baktharaman, S.; Singh, V. K. *J. Org. Chem.* **2007**, *72*, 10141–10146.