Stereoselective and Regioselective Reaction of Cyclic Ortho Esters with Phenols

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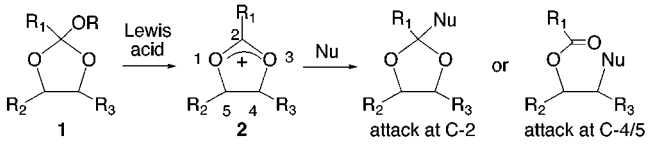
Cyclic ortho esters undergo stereoselective and regioselective reaction with phenols when treated with $BF_3{\cdot}OEt_2$ at low temperatures. Attack of the phenol on the ortho ester occurs at an open carbon *para* to electron-donating groups on the phenol ("C-addition") or at the phenolic hydroxyl group ("O-addition") depending on the nature of the cation formed from reaction of the ortho ester and $BF_3{\cdot}OEt_2$. Products resulting from O-addition undergo reversion to a mixture of starting phenol, C-addition product, and O-addition product if treated with $BF_3{\cdot}OEt_2$ at room temperature, but C-addition products are stable under the same conditions. X-ray structural analysis of the C-addition compound indicates that its stereochemistry is opposite to that observed in reaction of similar ortho esters with chloride from TMSCl. However, the stereochemistry of the reaction can be rationalized by the ability of the ortho ester to isomerize via an intermediate benzylic cation and examination of the preferred trajectory of attack of the nucleophile on the intermediate oxonium ion.

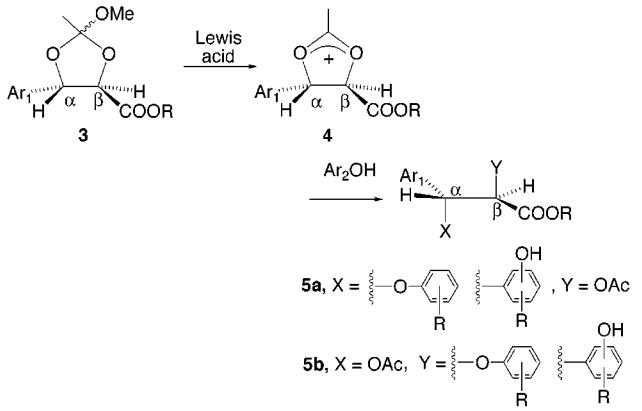
Introduction

Cyclic ortho esters such as **1** are valuable intermediates for a variety of synthetic transformations.[2] Upon treatment with a Lewis acid they are converted into highly stabilized ambident oxonium ions **2** (Scheme 1).[3] The oxonium ions undergo reaction with nucleophiles at either C-2 or C-4/5 depending on the nature of the nucleophile.[4] Hard nucleophiles, such as silyl enol ethers,[5] cuprates[6] and titanium enolates,[7] add at C-2 in a kinetically controlled process, whereas soft nucleophiles, such as alcohols and phenols[8] or $Co(CO)_4^-$ anion, [9] add at C-4/5 in a thermodynamic process. Silylated nucleotides react at either site depending on reaction conditions.[10]

Scheme 1



Scheme 2



As part of our program to develop renewable biomass as a raw material for chemical production,[11] we required a stereospecific synthesis of compounds **5** for the preparation of materials that model lignin, a highly underused source of renewable carbon (Scheme 2).[12]

Conventional synthesis of compounds such as **5** commonly gives mixtures of diastereomers.[13] Stereoselective syntheses of these compounds have been reported, but only for dimeric and a few trimeric examples.[14] Synthesis of higher oligomers, more representative of the actual

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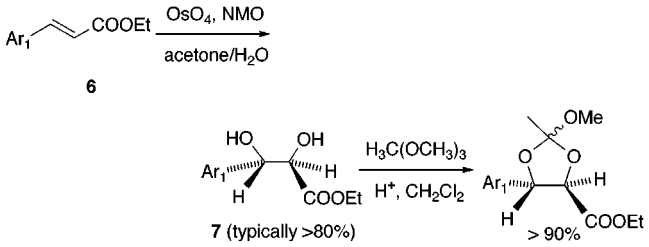
Scheme 3



lignin structure, results in complex mixtures of isomers as the number of chiral centers in the molecule increases.[15] We felt that setting the stereochemistry of the α and *β* carbons early in the synthesis via ortho ester **3** could avoid these problems and lead to a stereoselective preparation of models **5a** or **5b** upon reaction of **3** with a Lewis acid and a phenol. Formation of oxonium ion **4** would be expected to exert a significant influence on the direction of attack of the incoming phenol. We wish to report a new stereoselective and regioselective arylation of cyclic ortho esters that should be useful for the preparation of a variety of novel compounds.

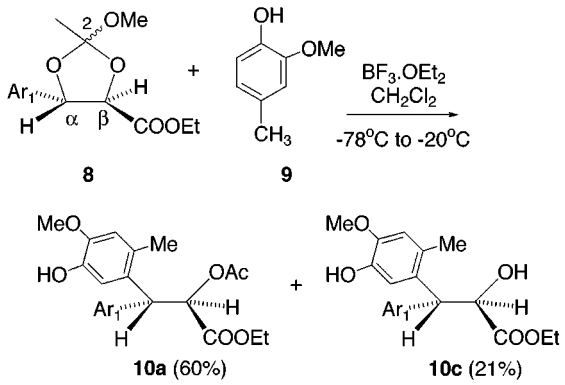
Results and Discussion

Ortho Ester Synthesis. The starting ortho esters were prepared as shown in Scheme 3. Starting cinnamates **6** were commercially available or prepared in >90% yield by Knoevenagel reaction of monoethylmalonate with substituted benzaldehydes.[16] High yield *cis*-dihydroxylation of *trans*-cinnamate esters **6** gave racemic diols **7**.[17] The conversion of **7** to cyclic 1,3-dioxolane ortho esters was achieved in yields generally >90% by treatment of the diols with trimethyl orthoacetate and catalytic *p*-TsOH. The ortho esters are obtained as a mixture of epimers at C-2 of the dioxolane ring (normally in about a 45/55 ratio by NMR integration) but with retention of the relative stereochemistry at the α and *β* carbons set by the *cis*-dihydroxylation of **6**.

Arylation of Ortho Esters. Scheme 4 shows a typical arylation sequence. Ortho ester **8** (Ar_1 = *p*-methoxyphenyl) was treated with methyl guaiacol (**9**) and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 solvent between −78 and −20 °C. Reaction occurred at the carbon *para* to the CH_3O group of **9** to give α-aryl-*β*-acetoxy adduct **10a** and the deacetylated derivative **10c** in 81% overall yield. The reaction occurred regioselectively at the less electron rich α-carbon of **8**.[18] No evidence for reaction of **9** at either the *β*-carbon or C-2 of **8** was seen.

Previous reports on Lewis acid promoted arylation of ortho esters are scarce, but indicate that simple noncyclic ortho esters serve as acylation reagents for arenes, forming benzaldehydes rather than the more structurally

Scheme 4



elaborated **10a** and **10c**.[19] Deacylation to give product **10c** appears to be Lewis acid induced because replacement of $BF_3{\cdot}OEt_2$ with stronger Lewis acids ($SnCl_4$, $TiCl_4$) leads to higher relative amounts of **10c**, although overall reaction yields are much lower. Product **10c** also appears at longer reaction times in the presence of $BF_3{\cdot}OEt_2$. Compound **10a** was analyzed by X-ray diffraction to indicate that reaction of **8** and **9** occurred to give the relative stereochemistry shown in Scheme 4. The $H-C_\alpha-C_\beta-H$ dihedral angle for **10a** is estimated from the X-ray data to be 169°, meaning that the observed H_α/H_β coupling constant of 5−7.5 Hz is somewhat smaller than expected from the Karplus equation. However, the presence of electron-withdrawing substituents at C_β could affect the observed *J*-value.[20,21] Several other combinations of ortho ester and substituted phenols were investigated under these conditions. The results are summarized in Table 1.

The chemoselectivity of the reaction displays a dependence on the nature of the aryl group on the ortho ester. The added phenol reacts with the ortho ester through a carbon atom ("C-addition") *para* to an electron-donating group on the phenol when the arene on the starting ortho ester is substituted with electron-donating groups (**10**−**13**). If an open site exists *para* to both a hydroxy and methoxy group, attack occurs *para* to the OMe (**15**). C-addition correlates well with the expected amount of cationic character present at the benzylic position of intermediate **4** (Scheme 2). Electron-releasing groups on the Ar_1 substituent stabilize the partial positive charge at the benzylic position, making it more susceptible to reaction with the soft aromatic ring rather than the harder oxygen of the phenol. Lower electron density on the aryl group of the ortho ester leads to reaction primarily through the oxygen of the added phenol ("O-addition", **14**−**18**). Introduction of a nitro substituent on the aryl group of the ortho ester decreased the reactivity significantly to give a very slow reaction and low product yield (**18**). No deacylation was observed in reactions with ortho esters bearing less electron rich Ar_1 substituents. HPLC analysis of the reaction between ortho ester **8** (Ar_1 = phenyl) and phenol **9**, which forms both C- and O-addition products (Table 1), indicates that at −78 °C small amounts of both appear almost immediately upon addition of $BF_3{\cdot}OEt_2$. The amounts do not change sig-

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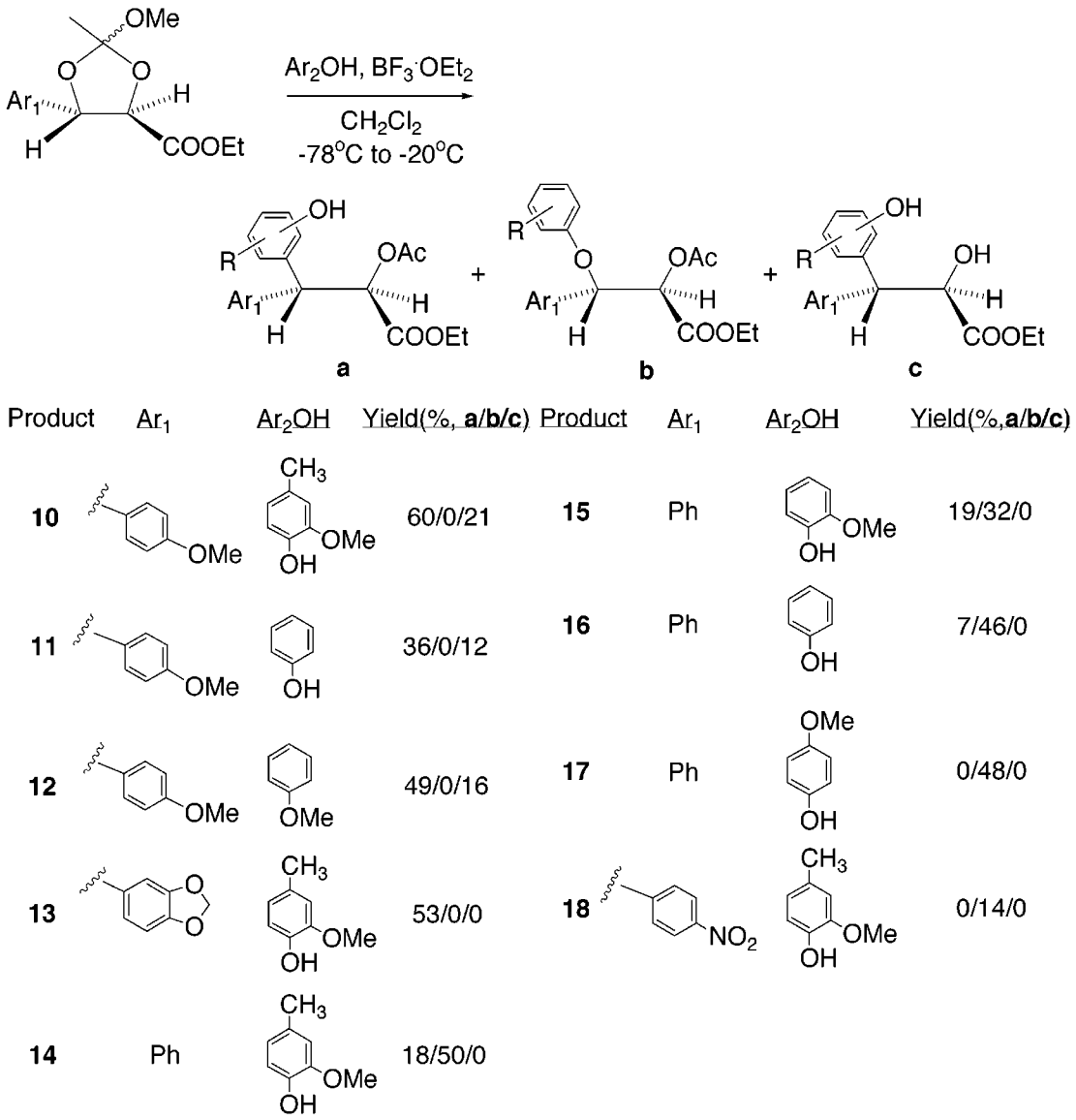
Table 1. Arylation of Ortho Esters



Product	Ar_1	Ar_2OH	Yield(%, **a**/**b**/**c**)	Product	Ar_1	Ar_2OH	Yield(%,**a**/**b**/**c**)
10			60/0/21	**15**	Ph		19/32/0
11			36/0/12	**16**	Ph		7/46/0
12			49/0/16	**17**	Ph		0/48/0
13			53/0/0	**18**			0/14/0
14	Ph		18/50/0				

nificantly at this temperature over 2 h. On warming to −20 °C, the reaction proceeds more rapidly, and the amounts of both C- and O-addition increase.

Using HPLC, we investigated the stability of the individual C- and O-addition products described in Table 1 under a variety of reaction conditions. Isolated O-addition product **14b** exhibits interesting reactivity as a function of temperature. Upon treatment with $BF_3{\cdot}OEt_2$ at −78 °C, **14b** remains unchanged for 3 h. Warming to the normal reaction temperature (−20 °C) also failed to cause any reaction, even after 72 h. However, warming to ambient temperature induced a reversion of **14b** to a mixture of phenol **9**, **14a** (C-addition), and residual **14b**. Interestingly, this reversion appears to be inhibited by excess **9**. Performing the same reaction in the presence of **9** gave significantly smaller amounts of products other than **14b** after 20 h at room temperature. In contrast, **14a** was stable to the reaction conditions. No conversion to other products was observed at any of the temperatures studied. These results indicate that a C-addition product can arise from the initially formed O-addition product at sufficiently high temperatures. However, the C-addition products described in Table 1 are probably not formed by O-addition reversion, since the O-addition product is stable at reaction temperatures normally employed (−20 °C). Moreover, reaction under normal conditions always uses a slight excess of **9**, which could further inhibit reversion. In some reactions NMR reveals small amounts (e.g., **13a**, ca. 1−5%) of other diastereomers that appear to be additional C-addition products. It is possible that these materials are formed via reversion during reaction workup at room temperature.

Stereochemistry of the Reaction. Treatment of ortho esters with TMSCl has been used to study the stereochemistry of the nucleophilic attack.[22] As expected, nucleophilic attack of chloride occurs stereoselectively from the backside of the oxonium ion (i.e., **2**, Scheme 1). However, this earlier work predicts a product stereochemistry opposite to that revealed by our X-ray analysis. While we have not carried out detailed mechanistic studies, a rationalization for the source of the stereoselectivity consistent with the results observed is shown in Figure 1.

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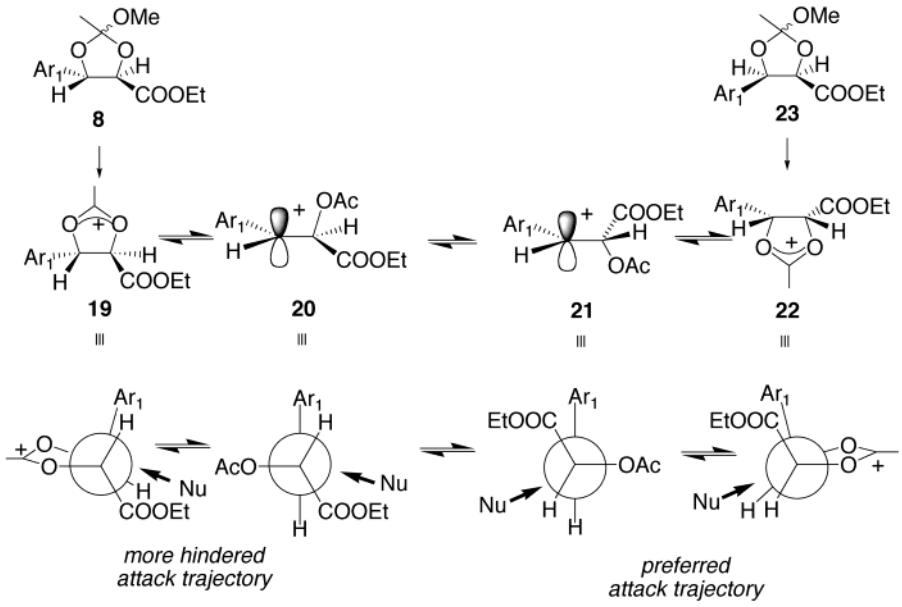

Figure 1. Reaction paths for intermediate carbocations.

The primary reactive intermediate in Lewis acid promoted reaction of ortho ester **8** (Ar_1 = *p*-methoxyphenyl) with nucleophiles is oxonium ion **19** bearing Ar_1 and COOEt groups in a *trans* orientation.[23] The preferred trajectory for attack of the added nucleophile on **19** is hindered by the presence of the COOEt group and, in any case, would result in a product stereochemistry opposite to that observed by X-ray.[24]

The presence of an aromatic ring at the α-carbon of **19** suggests that it may exist in equilibrium with the stabilized benzylic carbonium ion **20**. Such equilbria are known in other systems, for example, carbohydrates.[25] Rotation around the $C_\alpha-C_\beta$ bond affords intermediate **21** and access to oxonium ion **22**. These intermediates offer a less hindered trajectory for the nucleophile to give the product stereochemistry seen in the X-ray analysis. This hypothesis is analogous to the Felkin−Ahn explanation for the stereochemistry of nucleophilic attack on carbonyl groups adjacent to chiral centers.[26] In our case, the ability of an acetate group to interact with the adjacent cationic center allows it to adopt the role of the "large" group in this analysis. Moreover, the much larger size of the phenolic nucleophile in comparison to the chloride nucleophile used in earlier studies renders it more sensitive to steric effects.

This hypothesis also suggests that *cis*-ortho ester **23** should give rise to the same stereochemistry, since **23** could undergo reaction with $BF_3{\cdot}OEt_2$ to form intermediate **22** directly. We prepared **23**[27] and treated it under standard conditions with phenol **9**. The only product observed was **10a** (48%), identical to that obtained from the corresponding *trans*-ortho ester **8**. Reaction of **23** with phenol gave **11a** identical to that starting from the corresponding *trans*-cinnamate, albeit in only 8% yield.

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(27) Ando, K, *J. Org. Chem.* **1997**, *62*, 1934. NMR indicated retention of the *cis* orientation of the aryl and carbethoxy groups upon formation of ortho ester **23**.

Conclusions

These results indicate that aryl substituted ortho esters will undergo reaction with added phenols to give good yields of compounds **4**. Attack of the phenol (C- vs O-) can be controlled by the electron density of the aryl substituent on the ortho ester. Moreover, the observed stereochemistry of the reaction can be rationalized by a simple Felkin−Ahn analysis. More recently, we have found that this process can be carried out asymmetrically to give optically active products in both good yield and enantiomeric excess. The process also works in an intramolecular fashion, affording an efficient synthesis of benzopyrans. Detailed results of these new transformations will be reported in future publications.

Experimental Section

General. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution using a Varian Unity 300 instrument at 300 and 75 MHz, respectively. Chemical shifts are reported relative to tetramethylsilane (^1H) or solvent resonance (^{13}C) and are reported in δ. Infrared spectra were measured on KBr pellets for solids (0.5 wt %, 1.5 mg sample per 300 mg KBr) or neat for oils using a Nicolet 5SXC instrument equipped with a deuterated triglycine sulfate detector and are reported in cm^{-1}. HPLC was performed on a Waters 2690 instrument with a model 996 photodiode array detector. Analysis was carried out on a 0.5 × 150 mm Novapak C18 reverse-phase column. Typical elution conditions used a sample injection volume of 3 μL, a flow rate of 0.5 mL/min, and a H_2O/MeCN solvent gradient progressing from 50/50 to 5/95 over 15 min, followed by an additional 30−60 min of run time. Routine column chromatography was performed using Aldrich 200−400 mesh silica gel. Thin-layer chromatography (TLC) was carried out on Baker-Flex 1BF 2.5 × 7.5 cm silica gel plates with a variety of solvent systems. "Degassed" refers to the procedure of alternately evacuating a flask on the vacuum line followed by refilling with argon. Degassing was repeated three times. X-ray analyses were carried out by Dr. Joyce Waters of Massey University, Auckland, NZ. High-resolution mass spectra were obtained from the University of Colorado-Boulder. Elemental analyses were performed by Huffman Laboratories, Golden, CO. Melting points are uncorrected.

Materials. THF and Et_2O were distilled from Na/benzophenone prior to use. Hexane for chromatography was distilled

before use. Other solvents were reagent grade and used without further purification unless otherwise noted. Noncommercial cinnamates and all diols were prepared according to literature methods.[16,17] $BF_3{\cdot}OEt_2$ was distilled under an inert atmosphere and stored under argon. All other materials were commercially available and used as received.

General Procedure for the Preparation of Ortho Esters. A mixture of the diol (1 mmol) and trimethylorthoacetate (1.5 mmol) was dissolved in THF (10 mL). The solution was degassed and taken to −20 °C. It was treated with a solution (2 mg/mL) of *p*-TsOH in THF to give a catalyst level of 0.2−0.5 mol %. The reaction was stirred at −20 °C until complete as indicated by TLC (usually 30−60 min). The reaction was quenched by the addition of saturated $NaHCO_3$ (50−75 μL). The solvent was removed on the rotary evaporator. The residue was purified by rapid filtration through a 2.5 × 5 cm bed of silica gel using 1:1 hexane/Et_2O as the eluent. Solvent removal gave the ortho ester as a clear oil. The ortho esters were normally used immediately after preparation. The ^{1}H NMR spectrum for ortho ester **8b** is typical for the diastereomeric mixture obtained: 1.3 (overlapping t, 3H), 1.70 (s, 3H), 1.75 (s, 3H), 3.40 (s, 3H), 3.43 (s, 3H), 4.25 (overlapping m, 2H), 4.40 and 5.35 (dd, 2H), 4.44 and 5.10 (dd, 2H), 7.28−7.47 (m, 5H).

General Procedure for Ortho Ester Arylation. The ortho ester and phenol (1:1 molar ratio) were dissolved in freshly distilled THF (10−15 mL/mmol). The solution was cooled to −78 °C and stirred for 5 min. It was treated with $BF_3{\cdot}OEt_2$ (3 mmol) and stirred for 60 min at −78 °C. The reaction was warmed to −20 °C and stirred for 72 h. It was quenched by the addition of saturated $NaHCO_3$ (1 mL). The solvent was removed on the rotary evaporator, and the residue was purified by column chromatography on silica gel using a variety of solvent systems. When necessary, samples for analysis were further purified by recrystallization at −20 °C from mixtures of Et_2O/hexane.

C-Addition Products. Ethyl-2-acetoxy-3-(4-methoxyphenyl)-3-(3-hydroxy-4-methoxy-6-methylphenyl)propionate (10a). Ortho ester **8a** (710 mg, 2.4 mmol) was treated with methyl guaiacol (**9**) (331 mg, 2.4 mmol, 303 μL, ρ = 1.092) and $BF_3{\cdot}OEt_2$ (886 μL, 7.2 mmol) according to the general procedure. Normal workup and purification on silica gel (5:1 hexane/EtOAc to 2:1 EtOAc/hexane) gave 570 mg (60%) of **10a** as a white solid, mp 147.5−148.5 °C. Also isolated was 200 mg (21%) of the corresponding deacylated product **10c**, mp 113.5−114.5 °C. ^{1}H NMR (**10a**): 0.93 (t, J = 7.0 Hz, 3H), 2.02 (s, 3H), 2.12 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 3.92 (m, 2H), 4.58 (d, J = 8.2 Hz, 1H), 5.49 (s, 1H), 5.53 (d, J = 8.2 Hz, 1H), 6.59 (s, 1H), 6.75 (m, 2H), 7.06−7.12 (m, 3H). ^{13}C NMR: 13.6, 19.3, 20.6, 47.1, 55.1, 55.8, 61.1, 75.2, 113.2, 113.4, 113.7, 128.2, 129.8, 130.5, 130.7, 143.4, 144.8, 158.4, 169.5, 170.4; IR: 3441, 2979, 2848, 1738, 1614, 1517, 1469, 1250, 1055, 832. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; O, 27.83. Found: C, 65.79; H, 6.55; O, 27.66. ^{1}H NMR (**10c**): 1.04 (t, J = 7.2 Hz, 3H), 2.16 (s, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 4.02 (m, 2H), 4.44 (d, J = 6.2 Hz, 1H), 4.76 (br m, 1H), 5.48 (br s, 1H), 6.59 (s, 1H), 6.75−6.81 (m, 2H), 7.15−7.20 (m, 3H). ^{13}C NMR: 13.8, 19.3, 49.1, 55.2, 55.8, 61.4, 74.1, 113.1, 113.7, 114.4, 128.1, 129.6, 130.7, 132.5, 143.4, 144.9, 158.2, 173.7; IR: 3518, 3473, 2953, 2842, 1729, 1617, 1513, 1461, 1250, 1093, 781. Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71; O, 26.64. Found: C, 66.67; H, 6.71; O, 26.62.

Ethyl-2-acetoxy-3-(4-methoxyphenyl)-3-(4-hydroxyphenyl)propionate (11a). Ortho ester **8a** (585 mg, 1.97 mmol) was treated with phenol (187 mg, 1.97 mmol) and $BF_3{\cdot}OEt_2$ according to the general procedure. Normal workup and purification on silica gel (3:2 hexane/Et_2O) gave 254 mg (36%) of **11a** as a white solid, mp 109.5−110.5 °C. Also isolated was 84 mg (12%) of the corresponding deacylated product **11c** as a clear oil. ^{1}H NMR (**11a**): 0.99 (t, J = 7.0 Hz, 3H), 2.02 (s, 3H), 3.75 (s, 3H), 3.98 (m, 2H), 4.45 (d, J = 6.5 Hz, 1H), 5.62 (m, 1H), 6.60−6.80 (m, 4H), 7.05−7.24 (m, 4H). ^{13}C NMR: 13.8, 20.6, 50.8, 55.2, 61.4, 74.9, 113.8, 115.3, 129.4, 129.6, 129.9, 131.4, 132.0, 154.8, 158.5, 169.5, 170.6; IR: 3405, 2927, 2833, 1761, 1250, 1030. MS *m*/*z* calcd 358.1416, found 358.1403. ^{1}H NMR (**11c**): 1.16 (t, J = 7.2 Hz, 3H), 3.74 (br s, 1H), 3.76 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 4.34 (d, J = 4.1 Hz, 1H), 4.82 (br t, J = 4.1 Hz, 1H), 5.48 (br s, 1H), 6.59 (s, 1H), 6.75−6.81 (m, 2H), 7.15−7.20 (m, 3H). ^{13}C NMR 14.0, 52.7, 55.1, 61.8, 73.7, 113.7, 115.2, 129.4, 130.2, 131.1, 133.6, 154.7, 158.1, 173.9; IR: 3450, 2968, 2861, 1734, 1609, 1050, 1116. MS *m*/*z* calcd 316.1311, found 316.1296.

Ethyl-2-acetoxy-3,3-di-(4-methoxyphenyl)propionate (12a). Ortho ester **8a** (701 mg, 2.37 mmol) was treated with anisole (256 mg, 2.37 mmol, 257 μL, ρ = 0.995) and $BF_3{\cdot}OEt_2$ (874 μL, 7.1 mmol) according to the general procedure. Normal workup and purification on silica gel (5:1 hexane/EtOAc) gave 429 mg (49%) of **12a** as a white solid, mp 83.5−84.5 °C. Also isolated was 141 mg (16%) of the corresponding deacylated product **12c** as a clear oil. ^{1}H NMR (**12a**): 1.00 (t, J = 7.1 Hz, 3H), 2.04 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 3.98 (br q, J = 7.1 Hz, 2H), 4.49 (d, J = 7.1 Hz, 1H), 5.64 (d, J = 7.1 Hz, 1H), 6.82 (m, 4H), 7.19 (m, 4H). ^{13}C NMR: 13.8, 20.6, 50.8, 55.1, 61.2, 74.9, 113.8, 129.4, 129.7, 131.7, 132.0, 158.4, 169.2, 170.3. IR: 2975, 2834, 1758, 1610, 1521, 1461, 1380, 1250, 1031, 828. Anal. Calcd for $C_{22}H_{26}O_7$: C, 67.73; H, 6.50; O, 25.78. Found: C, 67.66; H, 6.72; O, 25.62. ^{1}H NMR (**12c**): 1.30 (t, J = 7.0 Hz, 3H), 2.98 (br s, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.25 (q, J = 7.0 Hz, 2H), 4.50 (d, J = 3.9 Hz, 1H), 4.95 (br d, J = 3.9 Hz, 1H), 6.90−6.97 (m, 4H), 7.27−7.32 (m, 4H), 7.40−7.45 (m, 4H). ^{13}C NMR: 14.0, 52.6, 55.1, 61.6, 73.6, 113.6, 129.4, 130.2, 133.7, 158.4, 158.8, 173.7. IR: 3489, 2965, 2839, 1745, 1619, 1516, 1464, 1250, 1031, 734. MS *m*/*z* calcd 330.1467, found 330.1458.

Ethyl-2-acetoxy-3-(3,4-methylenedioxyphenyl)-3-(3-hydroxy-4-methoxy-6-methylphenyl)propionate (13a). Ortho ester **8c** (607 mg, 1.96 mmol) was treated with methyl guaiacol (**9**) (405 mg, 2.94 mmol, 303 μL, ρ = 1.092) and $BF_3{\cdot}OEt_2$ according to the general procedure. Normal workup and purification on silica gel (4:1 hexane/EtOAc) gave 433 mg (53%) of **13a** as a white solid, mp 48.5−49.5 °C. ^{1}H NMR: 1.10 (t, J = 7.5 Hz, 3H), 2.15 (s, 3H), 2.25 (s, 3H), 3.94 (s, 3H), 4.08 (m, 2H), 4.68 (d, J = 7.7 Hz, 1H), 5.58 (br s, 1H), 5.63 (d, J = 7.8 Hz, 1H), 5.99 (dd, J = 7.6, 1.9 Hz, 2H), 6.59−6.82 (m, 5H). ^{13}C NMR: 13.7, 19.4, 20.6, 47.5, 55.8, 61.1, 75.2, 100.9, 108.0, 109.3, 113.2, 113.4, 122.2, 128.3, 130.3, 132.5, 143.4, 145.0, 146.4, 147.6, 169.4, 170.3. IR: 3460, 2934, 1743, 1591, 1515, 1438, 1376, 1234. Anal. Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81; O, 30.74. Found: C, 63.57; H, 5.66; O, 30.77.

Ethyl-2-acetoxy-3-phenyl-3-(3-hydroxy-4-methoxy-6-methylphenyl)propionate (14a). Ortho ester **8b** (601 mg, 2.26 mmol) was treated with methyl guaiacol (**9**) (312 mg, 2.26 mmol, 286 μL, ρ = 1.092) and $BF_3{\cdot}OEt_2$ (833 μL, 6.77 mmol) according to the general procedure. Normal workup and purification on silica gel (3:2 Et_2O/hexane) gave 152 mg (18%) of **14a** as a white solid, mp 103−104 °C. ^{1}H NMR: 0.98 (t, J = 7.0 Hz, 3H), 2.01 (s, 3H), 2.28 (s, 3H), 3.80 (s, 3H), 3.99 (m, 2H), 4.72 (d, J = 7.6 Hz, 1H), 5.36 (s, 1H), 5.60 (d, J = 7.6 Hz, 1H), 6.58 (s, 1H), 6.82 (s, 1H), 7.13−7.29 (m, 5H). ^{13}C NMR: 13.7, 19.5, 20.6, 47.5, 55.8, 61.2, 74.3, 112.8, 115.0, 126.7, 127.3, 128.3, 128.6, 130.5, 139.6, 143.4, 145.1, 169.4, 170.2. IR: 3531, 3447, 2978, 1751, 1519, 1378, 1264, 1205, 1037. Anal. Calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50; O, 25.78. Found: C, 67.68; H, 6.44; O, 25.88.

Ethyl-2-acetoxy-3-phenyl-3-(3-hydroxy-4-methoxyphenyl)propionate (15a). Ortho ester **8b** (601 mg, 2.26 mmol) was treated with guaiacol (336 mg, 2.7 mmol, 297 μL, ρ = 1.129) and $BF_3{\cdot}OEt_2$ (833 μL, 6.77 mmol) according to the general procedure. Normal workup and purification on silica gel (3:2 Et_2O/hexane) gave 156 mg (19%) of **15a** as a clear oil. ^{1}H NMR: 0.98 (t, 3H), 2.2 (s, 3H), 3.78 (s, 3H), 3.92−4.0 (m, 2H), 4.47−4.51 (d, J = 8.3 Hz, 1H), 5.59 (s, 1H), 5.64−5.68 (d, J = 10.4 Hz, 1H), 6.68−6.8 (m, 3H), 7.19−7.34 (m, 5H). ^{13}C NMR: 13.7, 20.5, 52.1, 55.8, 61.2, 74.7, 111.1, 114.2, 121.4, 126.9, 128.4, 128.5, 131.3, 139.6, 144.7, 146.3, 169.2, 170.3. IR: 3451, 2977, 2839, 1742, 1598, 1511, 1442, 1374. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19; O, 26.79. Found: C, 67.12; H, 6.32; O, 26.56.

O-Addition Products. Ethyl-2-acetoxy-3-phenyl-3-(2-methoxy-4-methylphenoxy)propionate (14b). Ortho ester

8b (597 mg, 2.24 mmol) was treated with methyl guaiacol (**9**) (309 mg, 2.24 mmol, 283 μL, ρ = 1.092) and BF_3·OEt_2 (829 μL, 6.73 mmol) according to the general procedure. Normal workup and purification on silica gel (5:1 hexane/Et_2O) gave 308 mg (50%, based on recovered starting material) of **14b** as a clear oil. ^{1}H NMR: 1.3 (t, J = 7.0 Hz, 2H), 2.18 (s, 3H), 2.35 (s, 3H), 3.89 (s, 3H), 4.30 (q, J = 7.0 Hz, 2H), 5.62 (d, J = 5.4 Hz, 1H), 5.68 (d, J = 5.4 Hz, 1H), 6.6 (d, 1H), 6.8 (s, 2H), 7.4 (m, 3H), 7.6 (m, 2H). ^{13}C NMR: 13.8, 20.2, 20.7, 55.5, 61.2, 74.2, 80.5, 113.4, 118.3, 120.7, 127.4, 127.9, 128.2, 132.6, 136.4, 144.0, 150.3, 167.6, 169.6. IR: 2983, 2867, 1749, 1593, 1519, 1464, 1376, 1218, 1031, 703. MS *m*/*z* calcd 372.1573, found 372.1557.

Ethyl-2-acetoxy-3-phenyl-3-(2-methoxyphenoxy)propionate (15b). Ortho ester **8b** (601 mg, 2.26 mmol) was treated with guaiacol (336 mg, 2.7 mmol, 297 μL, ρ = 1.129) and BF_3·OEt_2 (833 μL, 6.77 mmol) according to the general procedure. Normal workup and purification on silica gel (4:1 hexane/EtOAc) gave 259 mg (32%) of **15b** as a clear oil. ^{1}H NMR: 1.22 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 3.81 (s, 3H), 4.19 (m, 2H), 5.51 (s, 2H), 6.75 (m, 2H), 6.88 (m, 2H), 7.3 (m, 3H), 7.44 (m, 2H). ^{13}C NMR: 13.9, 20.5, 55.8, 61.5, 74.4, 80.4, 112.6, 118.2, 120.7, 123.0, 127.5, 128.2, 128.4, 136.4, 146.5, 150.7, 167.9, 169.8. IR: 2979, 1753, 1590, 1501, 1457, 1376, 1218, 1031, 750. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19; O, 26.79. Found: C, 66.85; H, 6.13; O, 27.02.

Ethyl-2-acetoxy-3-phenyl-3-phenoxypropionate (16b). Ortho ester **8b** (522 mg, 1.96 mmol) was treated with phenol (184 mg, 1.96 mmol) and BF_3·OEt_2 (724 μL, 5.88 mmol) according to the general procedure. Normal workup and purification on silica gel (4:1 hexane/EtOAc) gave 283 mg (46%) of **16b** as a clear oil. ^{1}H NMR: 1.38 (t, J = 7.5 Hz, 3H), 2.20 (s, 3H), 4.37 (m, 2H), 5.59 (dd, J = 5.3, 1.8 Hz, 1H), 5.69 (br dd, J = 5.3, 1.8 Hz, 1H), 6.92−7.06 (m, 3H), 7.28−7.58 (m, 7H). ^{13}C NMR: 14.0, 20.4, 61.6, 74.9, 78.7, 115.2, 115.9, 121.5, 127.1, 128.4, 129.3, 136.2, 157.1, 167.7, 169.8. IR: 3641, 3471, 3051, 2983, 1756, 1593, 1491, 1458, 1376, 1219, 1047, 750, 711. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; O, 24.36. Found: C, 69.34; H, 6.34; O, 24.32.

Ethyl-2-acetoxy-3-phenyl-3-(4-methoxyphenoxy)propionate (17b). Ortho ester **8b** (323 mg, 1.21 mmol) was treated with 4-methoxyphenol (150 mg, 1.21 mmol)) and BF_3·OEt_2 (447 μL, 3.63 mmol) according to the general procedure. Normal workup and purification on silica gel (5:1 hexane/EtOAc) gave 208 mg (48%) of **17b** as a clear oil. ^{1}H NMR: 1.22 (t, J = 7.1 Hz, 3H), 2.18 (s, 3H), 3.68 (s, 3H), 4.19 (m, 2H), 5.40 (s, 2H), 6.75 (m, 4H), 7.26−7.42 (m, 5H). ^{13}C NMR: 14.1, 20.5, 55.5, 61.6, 74.8, 79.9, 114.5, 117.5, 127.3, 128.4, 128.5, 136.5, 151.3, 154.5, 167.8, 169.9. IR: 3049, 2958, 2832, 1756, 1504, 1455, 1372, 1218, 1039, 828, 703. MS *m*/*z* calcd 358.1416, found 358.1414.

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Supporting Information Available: ORTEP diagram and parameter for compound **10a** and ^{1}H NMR spectra of compounds **11a**, **11c**, **12c**, **14b**, and **17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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