Synthesis of Functionalized Acetophenones by Formal [3 + 3] Cyclocondensations of 1,3-Bis(silyloxy)-1,3-butadienes with 3-Alkoxy- and 3-Silyloxy-2-acetyl-2-en-1-ones

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The TiCl\textsubscript{4}-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 2-acetyl-1-(trimethylsilyloxy)but-1-en-3-one and 3-acetyl-4-silyloxypent-3-en-2-one, readily available from 3-(formyl)acetylacetone and 3-(acetyl)acetylacetone (triacetylmethane), afforded a variety of functionalized acetophenones.

\textbf{Key words:} Cyclizations, Arenes, Regioselectivity, Acetophenones, Silyl Enol Ethers

Introduction

Highly functionalized benzene derivatives, such as hydroxylated benzoates, benzodioates and acetophenones, are of considerable interest as lead structures and synthetic building blocks in medicinal and agricultural chemistry [1 – 14]. Classical syntheses of such compounds are based on electrophilic substitution and oxidation reactions. Despite their great utility, electrophilic substitutions have several drawbacks (e. g., low regioselectivity and low reactivity of electron-poor substrates). Oxidations of toluene to benzoic acid derivatives often require drastic conditions. Transition metal-catalyzed functionalizations of functionalized benzene derivatives proceed under relatively mild conditions [15 – 20]. However, the synthesis of the required starting materials, highly functionalized or sterically encumbered benzene derivatives, can be a difficult task.

Functionalized benzene derivatives have been prepared also by application of a ‘building block’ strategy. Examples include base-mediated cyclizations of acetone-1,3-dicarboxylates [21, 22]. Harris et al. reported reactions of 1,3-dicarbonyl di-anions with carboxylic acid derivatives and subsequent intramolecular cyclocondensations [23 – 27]. In addition, [4 + 2] cycloadditions have been reported [28, 29]. Salicylates are available [30] by formal [3 + 3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes [31] with 1,3-dielectrophiles. This strategy has been widely applied in recent years [32, 33]. We have reported preliminary results related to the synthesis of acetophenones by formal [3 + 3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 2-acetyl-1-(trimethylsilyloxy)but-1-en-3-one which is derived from 3-formylacetylacetone [34]. Herein, we report full details of this study and an extension of the scope. In this context, we report the synthesis of related functionalized benzene derivatives based on cyclizations of 1,3-bis(silyloxy)-1,3-butadienes with a triacetylmethane derivative.
Results and Discussion

3-Formylacetylacetone (1a) is available by reaction of acetylacetone with triethyl orthoformate and acetic anhydride [35–37]. Its reactivity towards various nucleophiles has been previously reported [38–47]. Although the molecule is known for a long time, its detailed structure in solution was not studied until recently [48].

The reaction of an ether solution of 1a with Me3SiOTf/NET3 afforded 2-acetyl-1-silyloxybut-1-en-3-one 2a in 85% yield (Scheme 1). The formyl rather than the acetyl group was regioselectively silylated. Likewise, 2b [48] was prepared by silylation of 3-(acetyl)acetylacetone (1b) which is available by reaction of acetylacetone with acetyl chloride. The known 1,3-bis(trimethylsilyloxy)-1,3-butadienes 3a–m were prepared following literature procedures [30, 50–52].

The TiCl4-mediated formal [3 + 3] cyclization of 2a with 1,3-bis(silyloxy)-1,3-butadiene 3a afforded acetophenone 4a with very good regioselectivity (Scheme 2). The reaction proceeded by regioselective attack of the more nucleophilic terminal carbon atom of the diene onto the sterically less hindered carbon atom of 2a attached to the silyloxy group and the hydrogen atom. Subsequently, the cyclization proceeded by attack of the central carbon atom of the diene onto the acetyl group. The cyclization of 2a with other 1,3-bis(silyloxy)-1,3-butadienes 3a–m followed the same pattern of selectivity and afforded acetophenones 4a–m (Scheme 2, Table 1). The cyclization of dienes containing an alkyl group located at the terminal carbon atom of the diene (3f–h and 3j, but not 3i) tends to proceed in higher yields as compared to unsubstituted dienes. The yield of product 4a, prepared from the acetylacetone-derived diene 3a, was, in many (but not all) cases, lower as compared to the yields of products derived from β-ketoesters, due to its lower nucleophilicity. Rather low yields were obtained for products 4d and 4e derived from dienes containing a benzyloxy and 2-methoxethoxy group. This might be explained by the low stability of these groups in the presence of TiCl4.

The cyclization of dienes 3a–c, f, h with 2b afforded products 4a–r. The yields of the reactions of diene 3a were lower than those of the other dienes. This can again be explained by the higher reactivity of β-ketoester-derived dienes as compared to 1,3-diketone-derived dienes. In contrast to the situation for substrate 2a, the best yields were obtained for those products which are derived from dienes which contain no substituent located at carbon C-4 of the diene, presumably due to steric reasons.

The structures of products 4a–e (R1 = R2 = H) were elucidated simply by the neighborhood of two aromatic protons which was established by the presence of coupling constants in the range of $^3J = 8.7–8.8$ Hz. For
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<sup>a</sup> Yields of isolated products.

Table 2. Characteristic NOE effects.

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4f–k, the structure elucidation was more difficult and had to rely on NOESY experiments (Table 2). In 4f the aromatic hydrogen atom (δ = 7.47) correlates with the aromatic methyl group (δ = 2.25) and with the acetyl group (δ = 2.53). In 4g the aromatic hydrogen atom (δ = 7.46) correlates with the ethyl group attached to the benzene moiety and with the acetyl group. In 4h the aromatic hydrogen atom (δ = 7.45) correlates with the acetyl group (δ = 2.53) and with the CH₂ group attached to the benzene moiety. In 4i the aromatic hydrogen atom (δ = 7.47) correlates with the acetyl group (δ = 2.54) and with the CH₂ group (δ = 3.42). In addition, the methyl group (δ = 2.60) was found to correlate with the ethoxy group. In 4k the aromatic...
hydrogen atom (δ = 7.15) correlates with the acetyl group (δ = 2.53) and with the ethoxy group (δ = 4.13). For products 4l–p, no regioisomers are expected. The structure of 4j was confirmed by X-ray crystal structure analysis (Fig. 1) [53].

In conclusion, we have reported the synthesis of various functionalized acetophenones by formal [3 + 3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes.

**Experimental Section**

**General comments:** All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For ¹H and ¹³C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.20–0.25 mm, 70–230 mesh) was used. 1,3-Bis(silyloxy)-1,3-butadienes 3a–m were prepared according to the literature from the corresponding β-ketoesters in two steps [30, 50–52].

### 3-Formyl-4-hydroxypent-3-en-2-one (1a)

A mixture of acetylacetone (25.2 g, 252 mmol), triethyl orthoformate (37.8 g, 255 mmol), and acetic anhydride (43.2 g, 423 mmol) was refluxed for 3 h and then cooled to 0 °C. Water (10 mL) was added, and the reaction mixture was refluxed for 10 min. Volatile compounds were removed in vacuo, and the residue was distilled to yield 1a as a colorless solid quickly developing an oily surface (17.8 g, 55%), ratio of tautomers = 4 : 1 in CDCl₃ at 25 °C; b. p. 57 °C (0.1 mbar). – ¹H NMR (300 MHz, CDCl₃): δ = 2.34 (s, 3H, CH₃, minor), 2.54 (s, 6H, CH₂, major), 2.57 (s, 3H, CH₃, minor), 8.98 (d, ³J = 7.0 Hz, 1H, CH, minor), 10.03 (s, 1H, CHO, major), 17.20 (d, ³J = 7.0 Hz, 1H, OH, minor), 18.36 (s, 1H, OH, major), – ¹³C NMR (150 MHz, CDCl₃): δ = 25.0 (CH₃, major), 28.4 (CH₂, minor), 114.8 (C, major), 117.2 (C, minor), 184.5 (CHOH, minor), 187.2 (CO, COH, major), 194.3 (CO, minor), 200.3 (CHO, major), 202.7 (CO, minor), – IR (neat, cm⁻¹): ν = 3443 (br, w), 1787 (m), 1771 (m), 1723 (m), 1674 (s), 1614 (s), 1568 (s), 1411 (s), 1363 (m), 1029 (m). MS (EI, 70 eV); m/z (%) = 128 (20) [M⁺], 100 (41), 72 (35), 68 (32), 43 (100). The spectroscopic data (IR) are in accordance with those reported in the literature [35].

### Triacetylmethane (1b)

NaH (8.11 g, 338 mmol) was suspended in dry ether (300 mL), and the suspension was cooled to 0 °C. Acetylacetone (33.7 g, 337 mmol) was added dropwise. Freshly distilled acetyl chloride (26.4 g, 336 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to 20 °C within 3 h. After stirring for further 12 h the reaction mixture was filtered and the solid washed with ether. The precipitate was dissolved in water (100 mL) and extracted with ether (3 × 75 mL). The filtrate and organic extracts were combined, dried (Na₂SO₄), and filtered. The filtrate was concentrated in vacuo. A small amount of sodium tritylate was added for stabilization and distillation yielded 1b as a clear yellow liquid (25.6 g, 53%); b. p. 60 °C (0.1 mbar), – ¹H NMR (300 MHz, CDCl₃): δ = 2.24 (s, 6H, CH₂), 2.44 (s, 3H, CH₃), 17.23 (2H, 1H, OH). The spectroscopic data are in accordance with those presented in the literature [49].

### 3-(Trimethylsilyloxy-methylidene)-pentane-2,4-dione (2a)

To an ether solution (50 mL) of 1a (3.49 g, 27.2 mmol) was added NEt₃ (2.82 g, 27.9 mmol). The reaction mixture was cooled to 0 °C, and Me₃SiOTf (5.93 g, 26.7 mmol) was added within 20 min. under vigorous stirring. The reaction was stirred for 6 h at 0 °C. The ether phase was isolated, and the residue was washed with ether (20 mL). The ether phases were combined and concentrated in vacuo to yield 2a as a clear orange liquid (4.82 g, 88%). A detailed NMR spectroscopic study has been reported [47].

### 3-(1-Trimethylsilyloxy-ethylidene)-pentane-2,4-dione (2b)

To an ether solution (50 mL) of triacetylmethane 1b (3.58 g, 25.2 mmol) NEt₃ (2.61 g, 25.7 mmol) was added. The reaction mixture was cooled to 0 °C, and Me₃SiOTf (5.49 g, 24.7 mmol) was added within 15 min. under vigorous stirring. The reaction mixture warmed to 4.5 h at 0 °C. The ether phase was isolated, and the residue was washed with ether (20 mL). The ether phases were combined and concentrated in vacuo to yield 2b as a clear yellow liquid (4.52 g, 84%). – ¹H NMR (300 MHz, CDCl₃): δ = 0.26 (s, 9H, Si(CH₃)₃), 2.14 (s, 6H, CH₂), 2.32 (s, 3H, CH₃), – ¹³C NMR (75 MHz, CDCl₃): δ = 10.6 (Si(CH₃)₃), 21.4, 30.5 (CH₃), 127.2, 165.4 (C), 199.1 (CO). Due to the unstable nature of this molecule, no further spectroscopic data were obtained. The spectroscopic data are in accordance with those reported in the literature [49].

**General procedure for the preparation of acetophenones**

To a CH₂Cl₂ solution of 2a or 2b was added TiCl₄ at −78 °C in the presence of molecular sieves (4 Å). The appropriate 1,3-bis(silyl end ether) 3 was subsequently added. The reaction mixture was allowed to warm to 20 °C in about 20 h and was stirred for another 4 h (in case of 2a) or for 2–7 d (in case of 2b). CH₂Cl₂ was added, the molecular sieves were removed, and a saturated aqueous solution of NaHCO₃ was added. The organic layer was separated, and the aqueous layer was repeatedly extracted with CH₂Cl₂ or
CH₂Cl₂ and ether. The aqueous layer was acidified by hydrochloric acid (10%) and again extracted. All organic extracts were combined, dried (Na₂SO₄), and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel) to give salicylates for analysis.

1-(3-Acetyl-4-hydroxy-2-methylphenyl)ethanone (4a)

Starting with 2a (212 mg, 1.06 mmol), CH₂Cl₂ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl₄ (0.13 mL, 1.2 mmol), and 3a (385 mg, 1.57 mmol), 4a was isolated by column chromatography (silica gel; n-hexane-EtOAc = 10 : 1) as an orange solid (71 mg, 35%). M. p. 152 – 153 °C. \( R_f = 0.14 \) (n-hexane-EtOAc = 3 : 1). Reaction time: 25 h. \(-^1\)H NMR (300 MHz, CDCl₃): \( \delta = 2.56 \) (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 6.87 (dd, \( J = 8.8 \) Hz, 1H, Ar), 7.28 – 7.40 (m, 5H, Ph), 7.53 (d, \( J = 8.8 \) Hz, 1H, Ar), 7.62 (d, \( J = 8.8 \) Hz, 1H, Ar). – IR (KBr, cm⁻¹): ν = 3037 (br, s), 2934 (br, s), 1573 (m), 1450 (m), 1288 (s), 1229 (s), 1102 (m), 820 (m). – MS (EI, 70 eV): \( m/z (%): 317 (33) [M]^{+}, 207 (12), 178 (17), 166 (46), 161 (100). \) – Anal. for C₁₃H₁₄O₂: calc. C 64.85; H, 4.97; O, 29.18; found C 64.91; H, 5.64.

Benzyl 3-acetyl-6-hydroxy-2-methylbenzoate (4d)

Starting with 2a (226 mg, 1.13 mmol), CH₂Cl₂ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl₄ (0.12 mL, 1.1 mmol), and 3d (532 mg, 1.58 mmol), 4d was isolated by column chromatography (silica gel; n-hexane-EtOAc = 8 : 1) as a colorless solid (105 mg, 33%). M. p. 99 – 100 °C. \( R_f = 0.35 \) (n-hexane-EtOAc = 3 : 1). Reaction time: 23 h. \(-^1\)H NMR (300 MHz, CDCl₃): \( \delta = 2.45 \) (s, 3H, CH₃), 2.52 (s, 3H, CH₃), 5.36 (s, 2H, CH₂), 6.81 (dd, \( J = 8.7 \) Hz, \( J = 0.4 \) Hz, 1H, Ar), 7.28 – 7.40 (m, 5H, Ph), 7.53 (d, \( J = 8.7 \) Hz, 1H, Ar), 10.96 (s, 1H, OH). – 13C NMR (75 MHz, CDCl₃): \( \delta = 20.4 \) (ArCH₃), 30.4 (COCH₃), 67.9 (CH₂), 114.7 (C₆Ar), 115.1, 128.6, 128.7 (CH₂Ar), 131.3 (C₆Ar), 134.1 (CH₃Ar), 134.6, 141.5 (C₆Ar), 163.4, 171.0 (C₆Ar, COOH, COOH), 201.7 (COOH). – IR (KBr, cm⁻¹): ν = 3065 (s), 3036 (s), 2929 (s), 2707 (m), 1732 (s), 1641 (m), 1559 (s), 1450 (m), 1288 (s), 1229 (s), 1102 (m), 820 (m). – MS (EI, 70 eV): \( m/z (%): 222 (33) [M]^{+}, 207 (12), 178 (17), 166 (46), 161 (100). \) – Anal. for C₁₃H₁₂O₄ (284.31): calcld. C 71.82, H 5.67; found C 71.64, H 5.86.

2-Methoxy-ethyl 3-acetyl-6-hydroxy-2-methylbenzoate (4e)

Starting with 2a (205 mg, 1.02 mmol), CH₂Cl₂ (5.0 mL), molecular sieves (4 Å, 0.5 g), TiCl₄ (0.11 mL, 1.0 mmol), and 3e (432 mg, 1.42 mmol), 4e was isolated by column chromatography (silica gel; n-hexane-EtOAc = 5 : 1) as a slightly yellow solid (36 mg, 14%). M. p. 113 – 115 °C. \( R_f = 0.20 \) (n-hexane-EtOAc = 3 : 1). Reaction time: 22 h. \(-^1\)H NMR (300 MHz, CDCl₃): \( \delta = 2.54 \) (s, 3H, CH₂OCH₃), 2.63 (s, 3H, CH₃), 3.42 (s, 3H, OCH₃), 3.73 (m, 2H, CH₂OCH₃), 4.54 (m, 2H, CH₂OCH₃), 6.87 (dd, \( J = 8.8 \) Hz, \( J = 0.3 \) Hz, 1H, Ar), 7.62 (d, \( J = 8.8 \) Hz, 1H, Ar), 10.57 (br, 1H, OH). – 13C NMR (150 MHz, CDCl₃): \( \delta = 20.0 \) (ArCH₃), 30.6 (COCH₃), 59.1 (OCH₃), 64.7, 70.0 (CH₂), 115.2 (C₆Ar), 115.7, 133.1 (C₆Ar), 134.2 (CH₃Ar), 141.7 (C₆Ar), 162.8, 170.5 (C₆Ar, COOH, COOCH₃), 201.8 (COOH). – IR (KBr, cm⁻¹): ν = 3101 (br, s), 2934 (br, s).
Methyl 3-acetyl-6-hydroxy-2,5-dimethylbenzoate (4f)

Starting with 2a (206 mg, 1.03 mmol), CH$_2$Cl$_2$ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl$_4$ (0.13 mL, 1.2 mmol), and 3f (418 mg, 1.52 mmol), 4f was isolated by column chromatography (silica gel; n-hexane-EtOAc = 10 : 1) as a colorless solid (202 mg, 77%). M. p. 54 – 55 °C; R$_f$ = 0.42 (n-hexane-EtOAc = 5 : 1). Reaction time: 25 h. – $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.94 (t, $J$ = 7.3 Hz, 3H, CH$_3$CH$_2$), 1.31 – 1.44 (m, 2H, CH$_2$), 1.53 – 1.64 (m, 2H, CH$_2$), 2.53 (s, 3H, OCH$_3$), 2.56 (s, 3H, ArCH$_3$), 2.64 (t, $J$ = 7.7 Hz, 2H, ArCH$_2$), 3.98 (s, 3H, OCH$_3$), 7.45 (s, 1H, Ar), 11.27 (s, 1H, OH). – $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 14.2 (CH$_2$CH$_3$), 20.2 (ArCH$_3$), 22.8, 29.8 (CH$_2$), 30.8 (COCH$_3$), 31.7 (CH$_3$), 52.7 (OCH$_3$), 114.3, 124.7, 132.8 (C$_{Ar}$), 134.2 (CH$_2$), 138.6 (C$_{Ar}$), 161.8, 172.5 (C$_{Ar}$OH, COOCH$_3$), 202.5 (COCH$_3$). – IR (nujol, cm$^{-1}$): $\tilde{\nu}$ = 3193 (br, s), 1721 (s), 1648 (s), 1563 (s), 1298 (s), 1254 (s), 1120 (s), 1066 (m), 959 (m). – MS (GC-FT-ICR, 70 eV): $m$/z (%) = 264 (61) [M$^+$], 217 (51), 204 (100), 190 (81), 189 (61), 175 (20), 162 (36). Anal. for C$_8$H$_8$O$_2$ (264.32): calcd. C 68.16, H 7.63; found: C 68.17, H 7.72.

Ethyl 3-acetyl-5-ethyl-6-hydroxy-2-methylbenzoate (4g)

Starting with 2a (113 mg, 0.56 mmol), CH$_2$Cl$_2$ (3.0 mL), molecular sieves (4 Å, 0.2 g), TiCl$_4$ (0.07 mL, 0.66 mmol), and 3g (229 mg, 0.76 mmol), dissolved in CH$_2$Cl$_2$ (0.5 mL) 4g was isolated by column chromatography (silica gel; n-hexane-EtOAc = 10 : 1) as a colorless solid (83 mg, 59%). M. p. 39 – 40 °C; R$_f$ = 0.40 (n-hexane-EtOAc = 10 : 1). Reaction time: 27 h. – $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.22 (t, $J$ = 7.5 Hz, 3H, ArCH$_2$CH$_2$), 1.43 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_2$), 2.53 (s, 3H, ArCO), 2.58 (s, 3H, ArCH$_3$), 2.67 (q, $J$ = 7.5 Hz, 2H, ArCH$_2$CH$_2$), 4.45 (q, $J$ = 7.1 Hz, 2H, OCH$_2$CH$_2$), 7.46 (s, 1H, Ar), 11.35 (s, 1H, OH). – $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 13.8, 14.3 (CH$_2$CH$_3$), 20.2 (ArCH$_3$), 23.2 (ArCH$_2$), 30.7 (COCH$_3$), 62.2 (OCH$_2$CH$_3$), 114.3, 129.9, 132.8 (C$_{Ar}$), 133.2 (CH$_3$), 138.5 (C$_{Ar}$), 161.7, 172.0 (C$_{Ar}$OH, COOEt), 202.5 (COCH$_3$). – IR (KBr, cm$^{-1}$): $\tilde{\nu}$ = 3168 (br, s), 2978 (s), 2937 (s), 1717 (s), 1652 (s), 1558 (s), 1545 (m), 1365 (m), 1298 (s), 1204 (m), 1066 (m), 1027 (m). – MS (EI, 70 eV): $m$/z (%) = 250 (53) [M$^+$], 205 (23), 204 (100), 189 (43), 176 (99), 28 (71). – Anal. for C$_8$H$_8$O$_2$ (250.29): calcd. C 67.18, H 7.25; found C 67.18, H 7.21.

Ethyl 3-acetyl-5-butyl-6-hydroxy-2-methylbenzoate (4h)

Starting with 2a (198 mg, 0.99 mmol), CH$_2$Cl$_2$ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl$_4$ (0.12 mL, 1.1 mmol), and 3h (469 mg, 1.48 mmol), 4h was isolated by column chromatography (silica gel; n-hexane-EtOAc = 10 : 1) as a yellow oil (209 mg, 74%); R$_f$ = 0.38 (n-hexane-EtOAc = 10 : 1). Reaction time: 25 h. – $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.44 (t, $J$ = 7.1 Hz, 3H, OCH$_2$CH$_2$), 2.54 (s, 3H, COCH$_3$), 2.60 (s, 3H, ArCH$_3$), 3.42 (d, $J$ = 6.5 Hz, 2H, ArCH$_2$), 4.47 (q, $J$ = 7.1 Hz, 2H, OCH$_2$CH$_2$), 5.06 – 5.11 (m, 1H, CH$_2$CH$_2$H$_2$), 5.12 – 5.15 (m, 1H, CH$_2$CH$_2$H$_2$), 5.93 – 6.07 (m, 1H, CH$_2$CH$_2$H$_2$), 7.47 (s, 1H, Ar), 11.39 (s, 1H, OH). – $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 13.9 (CH$_2$CH$_3$), 19.9 (ArCH$_3$), 30.3 (COCH$_3$), 33.6 (ArCH$_2$), 62.0 (CH$_2$CH$_2$), 114.2 (C$_{Ar}$), 116.1 (CH$_2$Alk), 125.7, 132.5 (C$_{Ar}$), 133.7, 135.6 (CH), 138.8 (C$_{Ar}$), 161.2, 171.5 (C$_{Ar}$OH, COOEt), 201.8 (COCH$_3$). – IR (neat, cm$^{-1}$): $\tilde{\nu}$ = 3334 (br, w), 3079 (w), 2982 (m), 2939 (w), 1682 (s), 1658 (s), 1446
Methyl 3-acetyl-6-hydroxy-5-methoxy-2-methylbenzoate (4k)

Starting with 2a (231 mg, 1.15 mmol), CH₂Cl₂ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl₄ (0.14 mL, 1.3 mmol), and 3k (468 mg, 1.61 mmol). 4k was isolated by column chromatography (silica gel: n-hexane-EtOAc = 10 : 1 – 3 : 1) as a slightly yellow solid (96 mg, 35%). M. p. 143 – 144 (EtOAc).

η 2a (203 mg, 0.95 mmol), CH₂Cl₂ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl₄ (0.12 mL, 1.1 mmol), and 3a (323 mg, 1.32 mmol). 4n was isolated by column chromatography (silica gel: n-hexane-EtOAc = 3 : 1) as an orange-brown oil (56 mg, 29%).

Ethyl 3-acetyl-5-ethoxy-6-hydroxy-2-methylbenzoate (4l)

Starting with 2a (207 mg, 1.03 mmol), CH₂Cl₂ (5.0 mL), molecular sieves (4 Å, 0.5 g), TiCl₄ (0.11 mL, 1.0 mmol), and 3l (454 mg, 1.43 mmol). 4l was isolated by column chromatography (silica gel: n-hexane-EtOAc = 5 : 1) as a yellow solid (80 mg, 29%). M. p. 82 – 83 °C; δ = 0.19 (n-hexane-EtOAc = 3 : 1). Reaction time: 24 h.

Ethyl 3-acetyl-6-hydroxy-2,4-dimethyl-5-(p-tolytolyl)benzoate (4m)

Starting with 2a (0.400 g, 2.0 mmol), 5b (0.829 g, 2.18 mmol) and TiCl₄ (0.238 mL, 2.18 mmol). 4m was isolated as a colorless oil (0.229 g, 35%).

1-(3-Acetyl-4-hydroxy-2,6-dimethyl)-ethanone (4n)

Starting with 2b (203 mg, 0.95 mmol), CH₂Cl₂ (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl₄ (0.12 mL, 1.1 mmol), and 3a (323 mg, 1.32 mmol).
(m), 1586 (m), 1320 (s), 1252 (s), 1233 (s), 1178 (m), 1105 (m), 811 (m). MS (GC-El, 70 eV): m/z (%) = 222 (20) [M]+, 207 (18), 190 (21), 175 (100). Anal. for C12H14O4 (222.24): calcd. C 64.85, H 6.35; found C 64.72, H 6.53.

**Ethyl 3-acetyl-6-hydroxy-2,4-dimethylbenzoate (4p)**

Starting with 2b (240 mg, 1.12 mmol), CH3Cl2 (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl4 (0.14 mL, 1.3 mmol), and 3c (369 mg, 1.34 mmol), 4p was isolated by column chromatography (silica gel; n-hexane-EtOAc = 15 : 2) as a yellow solid (85 mg, 33%). M. p. 108 – 109 °C. Rf = 0.35 (n-hexane-EtOAc = 5 : 1). Reaction time: 3 d. – 1H NMR (300 MHz, CDCl3): δ = 1.43 (t, J = 7.1 Hz, 3H, OCH2CH3), 2.20 (d, J = 0.6 Hz, ArCH3), 2.42 (s, 3H, CH3), 2.45 (s, 3H, CH3), 2.44 (q, J = 7.1 Hz, 2H, OCH2CH3), 6.71 (s, 3H, Ar), 11.30 (s, 1H, OH), – 13C NMR (75 MHz, CDCl3): δ = 14.1 (CH2CH3), 19.5, 19.8 (ArCH3), 32.7 (COCH3), 61.7 (CH2), 110.6 (CAr), 117.1 (CHAr), 135.4, 136.1, 139.6 (CAr), 162.2, 171.2 (CArOH, COOEt), 207.7 (COCH3) – IR (Nujol, cm⁻¹): ˜ν = 1705 (s), 1655 (s), 1602 (m), 1586 (m), 1355 (s), 1234 (s), 1186 (s), 809 (m). – MS (GC-El, 70 eV): m/z (%) = 236 (20) [M]+, 221 (16), 191 (13), 190 (28), 175 (100). Anal. for: C13H12O4 (236.26): calcd. C 66.09, H 6.83; found C 65.94, H 6.87.

**Methyl 3-acetyl-6-hydroxy-2,4,5-trimethylbenzoate (4q)**

Starting with 2b (234 mg, 1.09 mmol), CH3Cl2 (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl4 (0.14 mL, 1.3 mmol), and 3f (406 mg, 1.48 mmol), 4q was isolated by column chromatography (silica gel; n-hexane-EtOAc = 10 : 1). Reaction time: 5 d (Tmax = 13 °C). – 1H NMR (300 MHz, CDCl3): δ = 2.15 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3), 2.16 (s, 3H, CH3). 3.96 (s, 3H, OCH3), 11.57 (s, 1H, OH). – 13C NMR (150 MHz, CDCl3): δ = 11.6, 17.3, 19.8 (ArCH3), 33.4 (COCH3), 52.4 (OCH3), 110.2, 123.7, 131.8, 136.3, 137.8 (CAr), 160.5, 172.5 (CArOH, COOCH3), 208.8 COCH3. – IR (Nujol, cm⁻¹): ˜ν = 1700 (m), 1663 (s), 1595 (w), 1325 (m), 1263 (m), 1213 (s), 1149 (m), 1099 (w), 806 (w). MS (GC-El, 70 eV): m/z (%) = 236 (35) [M]+. 221 (9), 204 (52), 189 (100), 176 (35), 161 (11). – Anal. for C12H14O4 (236.26): calcd. C 66.09, H 6.83; found C 66.05, H 6.95.

**Methyl 3-acetyl-5-butyl-6-hydroxy-2,4-dimethylbenzoate (4r)**

Starting with 2b (174 mg, 0.81 mmol), CH3Cl2 (4.5 mL), molecular sieves (4 Å, 0.4 g), TiCl4 (0.10 mL, 0.9 mmol), and 3h (360 mg, 1.14 mmol), 4r was isolated by column chromatography (silica gel; n-hexane-EtOAc = 10 : 1) as a slightly yellow oil (47 mg, 21%); Rf = 0.25 (n-hexane-EtOAc = 10 : 1). Reaction time: 4 d. – 1H NMR (300 MHz, CDCl3): δ = 0.94 (t, J = 7.1 Hz, 3H, CH3CH3), 1.33 – 1.52 (m, 4H, CH2CH2CH2CH3), 2.17 (s, 3H, CH3), 2.36 (s, 3H, CH3), 2.45 (s, 3H, CH3), 2.66 (t, J = 7.6 Hz, 2H, ArCH2), 3.95 (s, 3H, OCH3), 11.49 (s, 1H, OH). – 13C NMR (150 MHz, CDCl3): δ = 14.0, 16.5 (CH2CH3, ArCH3), 19.7 (ArCH3), 23.1, 25.8, 31.0 (CH2), 33.2 (COCH3), 52.2 (OCH3), 110.2, 128.4, 131.7, 136.3, 137.1 (CAr), 160.4, 172.4 (CArOH, COOCH3), 208.9 (COCH3). – IR (Nujol, cm⁻¹): ˜ν = 1705 (m), 1662 (s), 1598 (w), 1263 (w), 1215 (s), 1152 (m). MS (GC-El, 70 eV): m/z (%) = 278 (48) [M]+, 263 (16), 231 (99), 218 (100), 204 (35), 203 (47), 176 (27). – Anal. for: C16H22O4 (278.34): calcd. C 69.04, H 7.97; found: C 69.01, H 8.05.

**Crystal structure determination**

The intensity data were collected on a Nonius KappaCCD diffractometer, using graphite-monochromatized MoKα radiation. Data were corrected for Lorentz and polarization effects, but not for absorption [54, 55].

The structure was solved by Direct Methods (SHELXTL-97) and refined by full-matrix least-squares techniques against F2 (SHELXL-97). The hydrogen atoms were located by difference Fourier synthesis and refined isotropically [56]. All non-hydrogen atoms were refined anisotropically [56].

**Crystal data for 4q:** C12H14O5, M = 238.23 g mol⁻¹, colorless prism, size 0.05 × 0.05 × 0.04 mm³, monoclinic, space group P21/n, a = 8.7850(7), b = 7.3091(10), c = 18.1530(18) Å, β = 94.624(6)°, V = 1160.8(2) Å³, T = –90 °C. Z = 4, rcalcd = 1.36 g cm⁻³, μ(MoKα) = 1.1 cm⁻¹, F(000) = 504 e, 7822 reflections in hkl (–11–1; –9–8; –22–23), measured in the range 3.58° ≤ θ ≤ 27.48°, completeness θmax = 99.5 %, 2648 independent reflections, Rint = 0.1095, 1234 reflections with F0 > 4σ(F0), 210 parameters, 0 restraints, R1 = 0.0856, wR2 = 0.1064, R1(all) = 0.1668, wR2(all) = 0.1409, GOOF = 0.961, largest difference peak / hole: 0.248 / –0.288 e Å⁻³.


