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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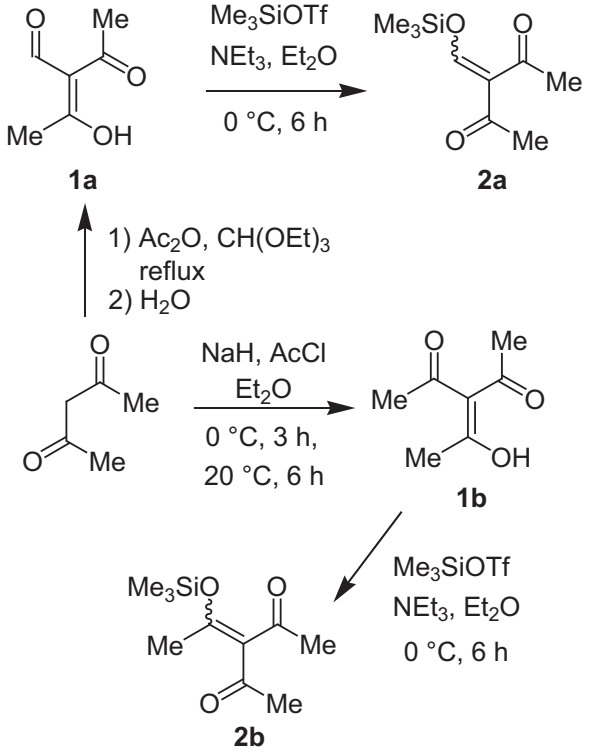
The $TiCl_4$-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 2-acetyl-1-silyloxybut-1-en-3-one and 3-acetyl-4-silyloxypent-3-en-2-one, readily available from 3-(formyl)acetylacetone and 3-(acetyl)acetylacetone (triacetylmethane), afforded a variety of functionalized acetophenones.

Key words: Cyclizations, Arenes, Regioselectivity, Acetophenones, Silyl Enol Ethers

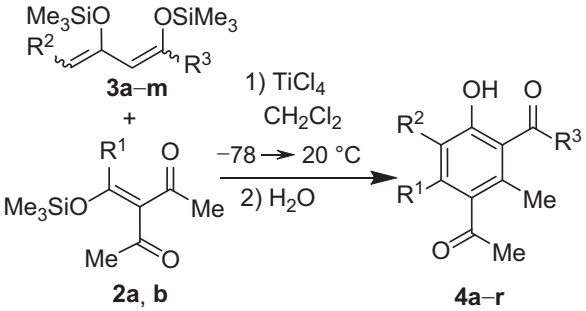
Introduction

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 dianions 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.



Scheme 1. Synthesis of **2a** and **2b**.



Scheme 2. Synthesis of **4a**–**r**.

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 Me_3SiOTf/NEt_3 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-buatdienes **3a**–**m** were prepared following literature procedures [30, 50 – 52].

The $TiCl_4$-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 $TiCl_4$.

The cyclization of dienes **3a**–**c**, **f**, **h** with **2b** afforded products **4n**–**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.

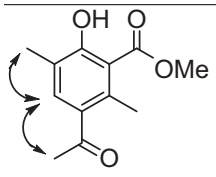
The structures of products **4a**–**e** ($R^1 = R^2 = H$) were elucidated simply by the neighborhood of two aromatic protons which was established by the presence of coupling constants in the range of $^3J = 8.7 – 8.8$ Hz. For

Table 1. Products and yields.

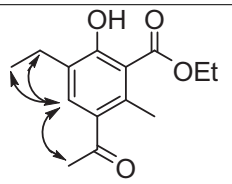
2	3	4	R^1	R^2	R^3	Yield (%) (**4**) [a]
a	**a**	**a**	H	H	Me	35
a	**b**	**b**	H	H	OMe	55
a	**c**	**c**	H	H	OEt	40
a	**d**	**d**	H	H	OBn	33
a	**e**	**e**	H	H	$O(CH_2)_2OMe$	14
a	**f**	**f**	H	Me	OMe	72
a	**g**	**g**	H	Et	OEt	59
a	**h**	**h**	H	*n*Bu	OMe	77
a	**i**	**i**	H	*n*Hex	OMe	38
a	**j**	**j**	H	Allyl	OEt	74
a	**k**	**k**	H	OMe	OMe	35
a	**l**	**l**	H	OEt	OEt	30
a	**m**	**m**	H	O(4-Tol)	OEt	35
b	**a**	**n**	Me	H	Me	30
b	**b**	**o**	Me	H	OMe	41
b	**c**	**p**	Me	H	OEt	33
b	**f**	**q**	Me	Me	OMe	24
b	**h**	**r**	Me	*n*Bu	OMe	21

[a] Yields of isolated products.

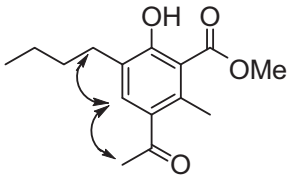
Table 2. Characteristic NOE effects.



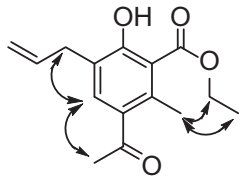
4f



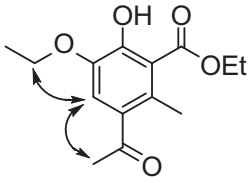
4g



4h



4i



4k

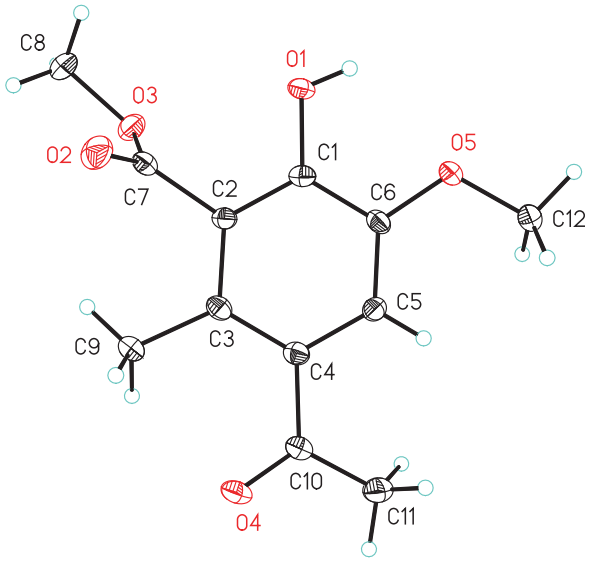


Fig. 1 (color online). Molecular structure of **4j** in the crystal (ellipsoids at the 50 % probability level).

4f–k, the structure elucidation was more difficult and had to rely on NOESY experiments (Table 2). In **4f** the aromatic hydrogen atom ($\delta = 7.47$) correlates with the aromatic methyl group ($\delta = 2.25$) and with the acetyl group ($\delta = 2.53$). In **4g** the aromatic hydrogen atom ($\delta = 7.46$) correlates with the ethyl group attached to the benzene moiety and with the acetyl group. In **4h** the aromatic hydrogen atom ($\delta = 7.45$) correlates with the acetyl group ($\delta = 2.53$) and with the CH_2 group attached to the benzene moiety. In **4i** the aromatic hydrogen atom ($\delta = 7.47$) correlates with the acetyl group ($\delta = 2.54$) and with the CH_2 group ($\delta = 3.42$). In addition, the methyl group ($\delta = 2.60$) was found to correlate with the ethoxy group. In **4k** the aromatic

hydrogen atom ($\delta = 7.15$) correlates with the acetyl group ($\delta = 2.53$) and with the ethoxy group ($\delta = 4.13$). 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 ^{1}H and ^{13}C 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 (0.063 – 0.200 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 acid 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 $CDCl_3$ at 25 °C); b. p. 57 °C (0.1 mbar). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3H, CH_3, minor), 2.54 (s, 6H, CH_3, major), 2.57 (s, 3H, CH_3, 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). – ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 25.0$ (CH_3, major), 28.4 (CH_3, 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}): $\tilde{\nu} = 3443$ (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 destilled 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 (Na_2SO_4), 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). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.24$ (s, 6H, CH_3), 2.44 (s, 3H, CH_3), 17.23 (s, 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 NEt_3 (2.82 g, 27.9 mmol). The reaction mixture was cooled to 0 °C, and Me_3SiOTf (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) NEt_3 (2.61 g, 25.7 mmol) was added. The reaction mixture was cooled to 0 °C, and Me_3SiOTf (5.49 g, 24.7 mmol) was added within 15 min. under vigorous stirring. The reaction mixture was stirred for 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 %). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.26$ (s, 9H, $Si(CH_3)_3$), 2.14 (s, 6H, CH_3), 2.32 (s, 3H, CH_3). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.6$ ($Si(CH_3)_3$), 21.4, 30.5 (CH_3), 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 CH_2Cl_2 solution of **2a** or **2b** was added $TiCl_4$ at −78 °C in the presence of molecular sieves (4 Å). The appropriate 1,3-bis(silyl enol 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**). CH_2Cl_2 was added, the molecular sieves were removed, and a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was repeatedly extracted with CH_2Cl_2 or

CH_2Cl_2 and ether. The aqueous layer was acidified by hydrochloric acid (10%) and again extracted. All organic extracts were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel) to give salicylates **4**.

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

Starting with **2a** (212 mg, 1.06 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (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 → 3 : 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, $CDCl_3$): $\delta = 2.56$ (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.87 (dd, $^3J = 8.8$ Hz, $^4J = 0.4$ Hz, 1H, Ar), 7.71 (d, $^3J = 8.8$ Hz, 1H, Ar), 10.75 (br, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 21.1$ ($ArCH_3$), 30.1, 33.1 ($COCH_3$), 115.3 (CH_{Ar}), 126.3, 131.7 (C_{Ar}), 134.7 (CH_{Ar}), 140.4 (C_{Ar}), 161.2 ($C_{Ar}OH$), 200.9, 207.2 (CO). – IR (KBr, cm^{-1}): $\tilde{\nu} = 3037$ (br, m), 2926 (m), 1695 (s), 1643 (m), 1557 (s), 1441 (m), 1364 (m), 1267 (m), 1215 (m), 818 (w). – MS (EI, 70 eV): m/z (%) = 192 (65) $[M]^+$, 177 (100), 159 (20), 103 (11), 77 (20). – Anal. for $C_{11}H_{12}O_3$ (192.21): calcd. C 68.74, H 6.29; found C 68.56, H 6.54.

*Methyl 3-acetyl-6-hydroxy-2-methylbenzoate (**4b**)*

Starting with **2a** (863 mg, 4.31 mmol), CH_2Cl_2 (20 mL), molecular sieves (4 Å, 2.0 g), $TiCl_4$ (0.47 mL, 4.3 mmol), and **3b** (1.56 g, 5.98 mmol), **4b** was isolated by column chromatography (silica gel; *n*-hexane-EtOAc = 3 : 1) as a yellow solid (495 mg, 55%). M. p. 112 – 113 °C; $R_f = 0.30$ (*n*-hexane-EtOAc = 3 : 1). Reaction time: 22 h. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.54$ (s, 3H, CCH_3), 2.61 (s, 3H, CCH_3), 3.99 (s, 3H, OCH_3), 6.88 (d, $^3J = 8.8$ Hz, 1H, Ar), 7.62 (d, $^3J = 8.8$ Hz, 1H, Ar), 11.06 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.9$ ($ArCH_3$), 30.2 ($COCH_3$), 52.4 ($COOCH_3$), 114.7 (CH_{Ar}), 114.9, 132.7 (C_{Ar}), 133.9 (CH_{Ar}), 141.2 (C_{Ar}), 162.9, 171.4 ($C_{Ar}OH$, $COOCH_3$), 201.6 ($COCH_3$). – IR (KBr, cm^{-1}): ν = 3068 (br, s), 2932 (s), 2852 (m), 2787 (m), 2712 (m), 1729 (s), 1643 (s), 1563 (s), 1437 (s), 1292 (s), 1235 (s), 1102 (s), 822 (m). – MS (EI, 70 eV): m/z (%) = 208 (38) $[M]^+$, 193 (19), 176 (36), 161 (100), 77 (13). – Anal. for $C_{11}H_{12}O_4$ (208.21): calcd. C 63.45, H 5.81; found C 63.32; H 5.87.

*Ethyl 3-acetyl-6-hydroxy-2-methylbenzoate (**4c**)*

Starting with **2a** (195 mg, 0.97 mmol), CH_2Cl_2 (5.0 mL), molecular sieves (4 Å, 0.6 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3c** (386 mg, 1.41 mmol), **4c** was isolated by column chromatography (silica gel; *n*-hexane-EtOAc = 5 : 1) as an orange solid (83 mg, 39%). M. p. 130 – 132 °C; $R_f = 0.63$ (*n*-hexane-EtOAc = 1 : 1). Reaction time: 23 h. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (t, $^3J = 7.2$ Hz, 3H, CH_2CH_3), 2.54 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.47 (q, $^3J = 7.2$ Hz, 2H, CH_2), 6.88 (dd, $^3J = 8.8$ Hz, $^4J = 0.3$ Hz, 1H, Ar), 7.61 (d, $^3J = 8.8$ Hz, 1H, Ar), 11.13 (s, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.2$ (CH_2CH_3), 20.3 ($ArCH_3$), 30.5 ($COCH_3$), 62.3 (CH_2), 115.1 (CH_{Ar}), 115.2, 133.1 (C_{Ar}), 134.1 (CH_{Ar}), 141.6 (C_{Ar}), 163.4, 171.3 ($C_{Ar}OH$, COOEt), 201.9 ($COCH_3$). – IR (KBr, cm^{-1}): $\tilde{\nu} = 3173$ (br, s), 2992 (s), 1731 (s), 1650 (s), 1568 (s), 1445 (m), 1359 (m), 1293 (s), 1232 (s), 1098 (s), 822 (m). – MS (EI, 70 eV): m/z (%) = 222 (33) $[M]^+$, 207 (12), 177 (18), 176 (46), 161 (100). – Anal. for $C_{12}H_{14}O_4$ (222.24): calcd. C 64.85; H, 6.35. Found: C, 64.91; H, 6.64.

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

Starting with **2a** (226 mg, 1.13 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (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, $CDCl_3$): $\delta = 2.45$ (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 6.81 (dd, $^3J = 8.7$ Hz, $^4J = 0.4$ Hz, 1H, Ar), 7.28 – 7.40 (m, 5H, Ph), 7.53 (d, $^3J = 8.7$ Hz, 1H, Ar), 10.96 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.4$ ($ArCH_3$), 30.4 ($COCH_3$), 67.9 (CH_2), 114.7 (C_{Ar}), 115.1, 128.6, 128.7, 128.7 (CH_{Ar}), 133.1 (C_{Ar}), 134.1 (CH_{Ar}), 134.6, 141.5 (C_{Ar}), 163.4, 171.0 ($C_{Ar}OH$, $COOCH_2$), 201.7 ($COCH_3$). – 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 (%) = 284 (9) $[M]^+$, 193 (19), 91 (100), 66 (7), 28 (6). – Anal. for $C_{17}H_{16}O_4$ (284.31): calcd. 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), CH_2Cl_2 (5.0 mL), molecular sieves (4 Å, 0.5 g), $TiCl_4$ (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, $CDCl_3$): $\delta = 2.54$ (s, 3H, CCH_3), 2.63 (s, 3H, CCH_3), 3.42 (s, 3H, OCH_3), 3.73 (m, 2H, CH_2OCH_3), 4.54 (m, 2H, $CH_2CH_2OCH_3$), 6.87 (dd, $^3J = 8.8$ Hz, $^4J = 0.3$ Hz, 1H, Ar), 7.62 (d, $^3J = 8.8$ Hz, 1H, Ar), 10.57 (br, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 20.0$ ($ArCH_3$), 30.6 ($COCH_3$), 59.1 (OCH_3), 64.7, 70.0 (CH_2), 115.2 (CH_{Ar}), 115.7, 133.1 (C_{Ar}), 134.2 (CH_{Ar}), 141.7 (C_{Ar}), 162.8, 170.5 ($C_{Ar}OH$, $COOCH_2$), 201.8 ($COCH_3$). – IR (KBr, cm^{-1}): $\tilde{\nu} = 3101$ (br, s), 2934

(s), 1733 (s), 1645 (s), 1562 (s), 1356 (m), 1296 (s), 1243 (s), 1100 (m), 814 (m). – MS (EI, 70 eV): m/z (%) = 252 (42) $[M]^+$, 193 (12), 177 (31), 176 (70), 161 (100). – Anal. for $C_{13}H_{16}O_5$ (252.26): calcd. C 61.90, H 6.39; found C 61.86, H 6.21.

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

Starting with **2a** (206 mg, 1.03 mmol), CH_2Cl_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 (164 mg, 72 %). M. p. 65 – 66 °C; $R_f = 0.56$ (*n*-hexane-EtOAc = 3 : 1). Reaction time: 24 h. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.25$ (s, 3H, $ArCH_3$), 2.53 (s, 3H, CCH_3), 2.57 (s, 3H, $ArCH_3$), 3.98 (s, 3H, OCH_3), 7.47 (s, 1H, Ar), 11.31 (s, 1H, OH). – ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.7$, 19.8 ($ArCH_3$), 30.4 ($COCH_3$), 52.4 (OCH_3), 113.9, 123.8, 132.3 (C_{Ar}), 134.6 (CH_{Ar}), 138.4 (C_{Ar}), 161.7, 172.1 ($C_{Ar}OH$, *C*$OOCH_3$), 201.9 (*C*OCH_3). – IR (KBr, cm^{-1}): $\tilde{\nu} = 3222$ (br, s), 2951 (m), 1733 (s), 1647 (s), 1561 (s), 1439 (m), 1362 (m), 1303 (s), 1211 (s), 1149 (s), 1065 (m). – MS (EI, 70 eV): m/z (%) = 222 (49) $[M]^+$, 191 (23), 190 (84), 175 (100), 162 (24), 91 (23). – Anal. for $C_{12}H_{14}O_4$ (222.24): calcd. C 64.85, H 6.35; found: C 64.94, H 6.28.

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

Starting with **2a** (113 mg, 0.56 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.2 g), $TiCl_4$ (0.07 mL, 0.6 mmol), and 3 g (229 mg, 0.76 mmol), dissolved in CH_2Cl_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, $^3J = 7.5$ Hz, 3H, $ArCH_2CH_3$), 1.43 (t, $^3J = 7.1$ Hz, 3H, OCH_2CH_3), 2.53 (s, 3H, $COCH_3$), 2.58 (s, 3H, $ArCH_3$), 2.67 (q, $^3J = 7.5$ Hz, 2H, $ArCH_2CH_3$), 4.45 (q, $^3J = 7.1$ Hz, 2H, OCH_2CH_3), 7.46 (s, 1H, Ar), 11.35 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.8$, 14.3 (CH_2CH_3), 20.2 ($ArCH_3$), 23.2 ($ArCH_2$), 30.7 ($COCH_3$), 62.2 (OCH_2), 114.3, 129.9, 132.8 (C_{Ar}), 133.2 (CH_{Ar}), 138.5 (C_{Ar}), 161.7, 172.0 ($C_{Ar}OH$, COOEt), 202.5 (*C*OCH_3). – IR (KBr, cm^{-1}): $\nu = 3168$ (br, s), 2978 (s), 2937 (s), 1717 (s), 1652 (s), 1558 (s), 1458 (m), 1365 (m), 1298 (s), 1204 (s), 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 $C_{14}H_{18}O_4$ (250.29): calcd. C 67.18, H 7.25; found C 67.18, H 7.21.

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

Starting with **2a** (198 mg, 0.99 mmol), CH_2Cl_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 colorless solid (200 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, $^3J = 7.3$ Hz, 3H, CH_2CH_3), 1.31 – 1.44 (m, 2H, CH_2), 1.53 – 1.64 (m, 2H, CH_2), 2.53 (s, 3H, CCH_3), 2.56 (s, 3H, $ArCH_3$), 2.64 (t, $^3J = 7.7$ 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_2CH_3), 20.2 ($ArCH_3$), 22.8, 29.8 (CH_2), 30.8 ($COCH_3$), 31.7 (CH_2), 52.7 (OCH_3), 114.3, 128.7, 132.8 (C_{Ar}), 134.2 (CH_{Ar}), 138.6 (C_{Ar}), 161.8, 172.5 ($C_{Ar}OH$, *C*$OOCH_3$), 202.5 (*C*OCH_3). – IR (nujol, cm^{-1}): $\tilde{\nu} = 3193$ (br, s), 1721 (s), 1648 (s), 1563 (s), 1298 (s), 1254 (s), 1220 (s), 1145 (m), 1066 (m), 959 (m). – MS (GC-EI, 70 eV): m/z (%) = 264 (61) $[M]^+$, 217 (51), 204 (100), 190 (81), 189 (61), 175 (20), 162 (36). Anal. for $C_{15}H_{20}O_4$ (264.32): calcd. C 68.16, H 7.63; found: C 68.17, H 7.72.

*Methyl 3-acetyl-5-hexyl-6-hydroxy-2-methylbenzoate (**4i**)*

Starting with **2a** (0.400 g, 2.0 mmol), **3i** (0.751 g, 2.18 mmol) and $TiCl_4$ (0.238 mL, 2.18 mmol), **4i** was isolated as a colorless oil (0.221 g, 38 %). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.81$ (t, $^3J = 7.4$ Hz, 3 H, $CH_2(CH_2)_4CH_3$), 1.18−1.27 (m, 8 H, $CH_2(CH_2)_4CH_3$), 2.45 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 2.55 (t, $^3J = 7.2$ Hz, 2 H, $CH_2(CH_2)_4CH_3$), 3.92 (s, 3 H, OCH_3), 7.39 (s, 1 H, CH_{Ar}), 11.19 (s(br), 1 H, OH). – ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 14.1$, 19.9 (CH_3), 22.5, 28.9, 29.1, 29.2 (CH_2), 29.8 (CH_3), 31.6 (CH_2), 52.4 (OCH_3), 114.0, 128.4, 132.4 (C), 133.9 (CH_{Ar}), 138.3 (C), 161.5 (COH), 172.2, 194.1 (CO). – GC-MS (EI, 70 eV): m/z (%) = 292 (49) $[M]^+$, 277 (12), 261 (11), 245 (37), 232 (100), 217 (26), 203 (18), 190 (74), 175 (18). – HRMS (EI): m/z = 292.16754 (calcd. 292.16691 for $C_{17}H_{24}O_4$, $[M]^+$).

*Ethyl 3-acetyl-5-allyl-6-hydroxy-2-methylbenzoate (**4j**)*

Starting with **2a** (218 mg, 1.09 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.14 mL, 1.3 mmol), and **3j** (495 mg, 1.57 mmol), **4j** was isolated by column chromatography (silica gel; *n*-hexane-EtOAc = 1 : 0 → 20 : 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, $^3J = 7.1$ Hz, 3H, OCH_2CH_3), 2.54 (s, 3H, $COCH_3$), 2.60 (s, 3H, $ArCH_3$), 3.42 (d, $^3J = 6.5$ Hz, 2H, $ArCH_2$), 4.47 (q, $^3J = 7.1$ Hz, 2H, OCH_2CH_3), 5.06 – 5.11 (m, 1H, $CHCH_AH_B$), 5.12 – 5.15 (m, 1H, $CHCH_AH_B$), 5.93 – 6.07 (m, 1H, $CHCH_AH_B$), 7.47 (s, 1H, Ar), 11.39 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9$ (CH_2CH_3), 19.9 ($ArCH_3$), 30.3 ($COCH_3$), 33.6 ($ArCH_2$), 62.0 (CH_2CH_3), 114.2 (C_{Ar}), 116.1 ($CH_{2\ Allyl}$), 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 (*C*OCH_3). – IR (neat, cm^{-1}): $\nu = 3334$ (br, w), 3079 (w), 2982 (m), 2939 (w), 1682 (s), 1658 (s), 1446

(m), 1323 (s), 1230 (s), 1199 (s), 1150 (m), 1018 (m). – MS (GC-EI, 70 eV): m/z (%) = 262 (70) $[M]^+$, 216 (49), 201 (67), 188 (89), 173 (100), 115 (30). – HRMS (EI, 70 eV): m/z = 262.12000 (calcd. 262.11996 for $C_{15}H_{18}O_4$, $[M]^+$).

*Methyl 3-acetyl-6-hydroxy-5-methoxy-2-methylbenzoate (**4k**)*

Starting with **2a** (231 mg, 1.15 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (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 °C; R_f = 0.12 (*n*-hexane-EtOAc = 3 : 1). Reaction time: 26 h. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.13 (s, 1H, Ar), 9.77 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 ($ArCH_3$), 30.4 ($COCH_3$), 52.5, 56.3 (OCH_3), 114.1 (CH_{Ar}), 117.3, 130.7, 131.9 (C_{Ar}), 145.4, 151.4 (C_{Ar}, $C_{Ar}OH$), 170.4 ($COOCH_3$), 201.5 ($COCH_3$). – IR (nujol, cm^{-1}): $\tilde{\nu}$ = 3301 (br, m), 1732 (s), 1667 (s), 1573 (m), 1499 (m), 1291 (s), 1217 (s), 1196 (s), 1077 (s), 887 (w). – MS (GC-EI, 70 eV): m/z (%) = 238 (52) $[M]^+$, 207 (46), 206 (100), 191 (51), 178 (64), 177 (46), 163 (24). – HRMS (EI, 70 eV): m/z = 238.08392 (calcd. 238.08358 for $C_{12}H_{14}O_5$, $[M]^+$).

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

Starting with **2a** (207 mg, 1.03 mmol), CH_2Cl_2 (5.0 mL), molecular sieves (4 Å, 0.5 g), $TiCl_4$ (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; R_f = 0.19 (*n*-hexane-EtOAc = 3 : 1). Reaction time: 24 h. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, ^3J = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.47 (t, ^3J = 7.0 Hz, 3H, $ArOCH_2CH_3$), 2.49 (s, 3H, $ArCH_3$), 2.53 (s, 3H, $COCH_3$), 4.13 (q, ^3J = 7.0 Hz, 2H, $ArOCH_2CH_3$), 4.45 (q, ^3J = 7.1 Hz, 2H, $COOCH_2CH_3$), 7.15 (s, 1H, Ar), 9.53 (s, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 14.9 (CH_2CH_3), 19.0 ($ArCH_3$), 30.6 ($COCH_3$), 62.2, 65.3 (CH_2), 115.6 (CH_{Ar}), 118.2, 131.0, 132.0 (C_{Ar}), 144.8, 151.5 (C_{Ar}, $C_{Ar}OH$), 170.1 (COOEt), 201.7 ($COCH_3$). – IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3223 (br, w), 2983 (w), 1726 (s), 1658 (m), 1574 (s), 1295 (s), 1201 (s), 1161 (m), 1077 (m). – MS (EI, 70 eV): m/z (%) = 266 (69) $[M]^+$, 221 (37), 220 (92), 205 (89), 192 (92), 177 (100), 148 (27). – Anal. for $C_{14}H_{18}O_5$ (266.29): calcd. C 63.15, H 6.81; found C 63.07, H 7.04.

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

Starting with **2a** (0.400 g, 2.0 mmol), **5b** (0.829 g, 2.18 mmol) and $TiCl_4$ (0.238 mL, 2.18 mmol), **4m** was isolated as a colorless oil (0.229 g, 35 %). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3), 2.18 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 2.44 (s, 3 H, OCH_3), 4.34 (q, ^3J = 7.3 Hz, 2 H, OCH_2CH_3), 6.72 (d, ^3J = 8.4 Hz, 2 H, CH_{Ar}), 6.98 (d, ^3J = 8.3 Hz, 2 H, CH_{Ar}), 7.18 (s, 1 H, CH_{Ar}), 10.23 (s(br), 1 H, OH). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 19.3, 20.6, 30.2 (CH_3), 62.2 (OCH_2CH_3), 117.1 ($2CH_{Ar}$), 118.1 (C), 123.7 (CH_{Ar}), 130.2 ($2CH_{Ar}$), 132.1, 132.8, 135.4, 141.9, 154.0 (C), 154.0 (C), 154.8 (COH), 170.2, 200.9 (CO). – IR (neat, cm^{-1}): $\tilde{\nu}$ = 3423 (w), 1654 (s), 1569 (m), 1442 (m), 1329 (m), 1271 (s), 1045 (w), 914 (w), 858 (w), 744 (m). – GC-MS (EI, 70 eV): m/z (%) = 328 (51) $[M]^+$, 282 (100), 267 (32), 239 (30), 211 (29), 119 (80), 91 (18), 65 (17), 43 (21). – HRMS (EI): m/z = 328.13039 (calcd. 328.13053 for $C_{19}H_{20}O_5$, $[M]^+$).

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

Starting with **2b** (203 mg, 0.95 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (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 %); R_f = 0.23 (*n*-hexane-EtOAc = 3 : 1). Reaction time: 3 d. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.18 (d, ^4J = 0.7 Hz, 3H, $ArCH_3$), 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.66 (s, 1H, Ar), 11.56 (br, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.8, 19.9 ($ArCH_3$), 32.9, 33.3 ($COCH_3$), 117.8 (CH_{Ar}), 121.5, 133.4, 136.3, 139.9 (C_{Ar}), 160.9 ($C_{Ar}OH$), 205.8, 207.9 (CO). – IR (neat, cm^{-1}): $\tilde{\nu}$ = 3293 (br, s), 2991 (m), 2927 (m), 1696 (s), 1597 (s), 1356 (s), 1307 (s), 1218 (s), 1188 (s), 1070 (m), 854 (m). – MS (EI, 70 eV): m/z (%) = 206 (39) $[M]^+$, 192 (11), 191 (100), 173 (22). – HRMS (EI, 70 eV): m/z = 206.09367 (calcd. 206.09375 for $C_{12}H_{14}O_3$, $[M]^+$). It has been claimed that this compound was prepared before, but no spectroscopic data were given [53].

*Methyl 3-acetyl-6-hydroxy-2,4-dimethylbenzoate (**4o**)*

Starting with **2b** (208 mg, 0.97 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.12 mL, 1.1 mmol), and **3b** (411 mg, 1.58 mmol), **4o** was isolated by column chromatography (silica gel; *n*-hexane-EtOAc = 10 : 1) as a slightly yellow solid (88 mg, 41 %). M. p. 103 – 105 °C; R_f = 0.31 (*n*-hexane-EtOAc = 5 : 1). Reaction time: 1 week. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (d, ^4J = 0.7 Hz, 3H, $ArCH_3$), 2.39 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.69 (s, 1H, Ar), 11.17 (s, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.8, 20.0 ($ArCH_3$), 33.0 ($COCH_3$), 52.4 (OCH_3), 110.7 (C_{Ar}), 117.4 (CH_{Ar}), 135.6, 136.4, 140.0 (C_{Ar}), 162.4, 171.8 ($C_{Ar}OH$, $COOCH_3$), 207.9 ($COCH_3$). – IR (nujol, cm^{-1}): $\tilde{\nu}$ = 1703 (s), 1662 (s), 1602

(m), 1586 (m), 1320 (s), 1252 (s), 1233 (s), 1178 (m), 1105 (m), 811 (m). – MS (GC-EI, 70 eV): m/z (%) = 222 (20) $[M]^+$, 207 (18), 190 (21), 175 (100). – Anal. for $C_{12}H_{14}O_4$ (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), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (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; $R_f = 0.35$ (*n*-hexane-EtOAc = 5 : 1). Reaction time: 3 d. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (t, $^3J = 7.1$ Hz, 3H, OCH_2CH_3), 2.20 (d, $^4J = 0.6$ Hz, $ArCH_3$), 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.44 (q, $^3J = 7.1$ Hz, 2H, OCH_2CH_3), 6.71 (s, 1H, Ar), 11.30 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (CH_2CH_3), 19.5, 19.8 ($ArCH_3$), 32.7 ($COCH_3$), 61.7 (CH_2), 110.6 (C_{Ar}), 117.1 (CH_{Ar}), 135.4, 136.1, 139.6 (C_{Ar}), 162.2, 171.2 ($C_{Ar}OH$, COOEt), 207.7 ($COCH_3$). – IR (Nujol, cm^{-1}): $\tilde{\nu} = 1703$ (s), 1655 (s), 1602 (m), 1586 (m), 1355 (s), 1318 (s), 1234 (s), 1186 (s), 809 (m). – MS (GC-EI, 70 eV): m/z (%) = 236 (20) $[M]^+$, 221 (16), 191 (13), 190 (28), 175 (100). – Anal. for $C_{13}H_{16}O_4$ (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), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.14 mL, 1.3 mmol), and **3f** (406 mg, 1.48 mmol), **4q** was isolated by column chromatography (silica gel; *n*-hexane-EtOAc = 20 : 1) as a colorless oil (63 mg, 24 %); $R_f = 0.25$ (*n*-hexane-EtOAc = 10 : 1). Reaction time: 5 d ($T_{max} = 13$ °C). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.15$ (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 11.57 (s, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 11.6$, 17.3, 19.8 ($ArCH_3$), 33.4 ($COCH_3$), 52.4 (OCH_3), 110.2, 123.7, 131.8, 136.3, 137.8 (C_{Ar}), 160.5, 172.5 ($C_{Ar}OH$, $COOCH_3$), 208.8 $COCH_3$). – IR (nujol, cm^{-1}): $\tilde{\nu} =$ 1700 (m), 1663 (s), 1595 (w), 1325 (m), 1263 (m), 1213 (s), 1149 (m), 1099 (w), 806 (w). – MS (GC-EI, 70 eV): m/z (%) = 236 (35) $[M]^+$, 221 (9), 204 (52), 189 (100), 176 (35), 161 (11). – Anal. for $C_{13}H_{16}O_4$ (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), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (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 %); $R_f = 0.25$ (*n*-hexane-EtOAc = 10 : 1). Reaction time: 4 d. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (t, $^3J = 7.1$ Hz, 3H, CH_2CH_3), 1.33 – 1.52 (m, 4H, $CH_2CH_2CH_3$), 2.17 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.66 (t, $^3J = 7.6$ Hz, 2H, $ArCH_2$), 3.95 (s, 3H, OCH_3), 11.49 (s, 1H, OH). – ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.0$, 16.5 (CH_2CH_3, $ArCH_3$), 19.7 ($ArCH_3$), 23.1, 25.8, 31.0 (CH_2), 33.2 ($COCH_3$), 52.2 (OCH_3), 110.2, 128.4, 131.7, 136.3, 137.1 (C_{Ar}), 160.4, 172.4 ($C_{Ar}OH$, $COOCH_3$), 208.9 ($COCH_3$). – IR (Nujol, cm^{-1}): $\tilde{\nu} = 1705$ (m), 1662 (s), 1598 (w), 1263 (w), 1215 (s), 1152 (m). – MS (GC-EI, 70 eV): m/z (%) = 278 (48) $[M]^+$, 263 (16), 231 (99), 218 (100), 204 (35), 203 (47), 176 (27). – Anal. for $C_{16}H_{22}O_4$ (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 MoK_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption [54, 55]. The structure was solved by Direct Methods (SHELXS-97) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97). The hydrogen atoms were located by difference Fourier synthesis and refined isotropically [56]. All non-hydrogen atoms were refined anisotropically [56]. XP [57] was used for structure representations. *Crystal Data for **4j***: $C_{12}H_{14}O_5$, $M_r = 238.23$ g mol^{-1}, colorless prism, size $0.05 \times 0.05 \times 0.04$ mm^3, monoclinic, space group $P2_1/n$, $a = 8.7850(7)$, $b = 7.3091(10)$, $c = 18.1530(18)$ Å, $\beta = 94.624(6)°$, $V = 1161.8(2)$ Å^3, $T = -90$ °C, $Z = 4$, $\rho_{calcd.} = 1.36$ g cm^{-3}, μ(MoK_α) = 1.1 cm^{-1}, $F(000) =$ 504 e, 7822 reflections in *hkl* ($-11 \rightarrow 11$; $-9 \rightarrow 8$; $-22 \rightarrow 23$), measured in the range $3.58° \leq \theta \leq 27.48°$, completeness $\theta_{max} = 99.5$ %, 2648 independent reflections, $R_{int} = 0.1095$, 1234 reflections with $F_o > 4\sigma(F_o)$, 210 parameters, 0 restraints, $R1_{obs} = 0.0586$, $wR2_{obs} = 0.1064$, $R1_{all} = 0.1668$, $wR2_{all} = 0.1409$, GOOF = 0.961, largest difference peak / hole: 0.248 / -0.288 e Å^{-3}.

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