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Domino "[3+3]-Cyclization-Homo-Michael" Reactions of 1,3-Bissilyl Enol Ethers with 1,1-Diacylcyclopropanes

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The Lewis acid mediated domino "[3+3]-cyclization-homo-Michael" reaction of 1,3-bissilyl enol ethers with 1,1-diacylcyclopropanes allows an efficient one-pot synthesis of functionalized salicylates containing a halogenated side chain. A great variety of substitution patterns could be realized by variation of the starting materials and of the Lewis acid. The mechanism of the domino process was studied.

1,3-Bissilyl enol ethers can be regarded as electroneutral 1,3-dicarbonyl dianion equivalents (masked dianions).[1,2] They represent useful synthetic building blocks in Lewis acid mediated transformations. In cyclization reactions, 1,3-bissilyl enol ethers can react as 1,3-dinucleophiles or, similar to the well-known Danishefsky diene,[3] as functionalized 1,4-butadienes. Chan and coworkers have reported $TiCl_4$-mediated [3+3] cyclizations of 1,3-bissilyl enol ethers with 3-silyloxyalk-2-en-1-ones and with ketals of β-keto aldehydes, β-ketoesters, and β-ketocarboxylic chlorides to give benzene derivatives.[2d,e] We have recently reported the $TiCl_4$-mediated domino "[3+3]-cyclization-homo-Michael" reaction of 1,3-bissilyl enol ethers with 1,1-diacetylcyclopropane.[4,5] This cyclization allows an efficient one-pot synthesis of functionalized salicylates containing a halogenated side chain. The strategic placement of the halide group in these products makes them versatile synthetic intermediates. With regard to our preliminary communication, we significantly extended the preparative scope and developed, for example, regioselective cyclizations of unsymmetrical 1,1-diacylcyclopropanes. In addition, we studied the mechanism of the domino process.

Results and Discussion

Mechanism. The $TiCl_4$-mediated reaction of 1,3-bissilyl enol ether **1a** with 1,1-diacetylcyclopropane (**2a**)[6] afforded the chlorinated salicylate **3a** in 82% yield. The best yields were obtained when 2 equiv of the Lewis acid were used. Two mechanisms can be discussed for the formation of **3a**. Path A: Titanium enolate **A** is formed by $TiCl_4$-mediated ring-opening of **2a**. The reaction of **A** with **1a** proceeds, in analogy to the known cyclization of 1,3-bissilyl enol ethers with 3-silyloxypent-3-en-2-one,[2e] by attack of **1a** onto the Michael position (intermediate **B**) and subsequent cyclization. Alternatively, the cyclization could proceed by formation of the spirocyclic intermediate **C** and subsequent $TiCl_4$-mediated ring cleavage (homo-Michael reaction) via intermediate **D**.

The mechanism of the cyclization was studied. Mechanism path A is supported by the following experiment: Treatment of **2a** with $TiCl_4$ and subsequent aqueous workup afforded 3-(2′-chloroethyl)pentane-2,4-dione (**4**) in 47% yield (Scheme 2). The formation of **4** can be explained by $TiCl_4$-mediated formation of titanium enolate **A** and subsequent hydrolysis. Although **4** fails to directly react with 1,3-bissilyl enol ethers, a cyclization of 1,3-bissilyl enol ethers with intermediate **A** cannot be ruled out. In fact, the related cyclization of 3-silyloxyalk-2-en-1-ones with 1,3-bissilyl enol ethers is known (vide supra).[2d,e]

However, we believe that the cyclization of the 1,3-bissilyl enol ether with 1,1-diacylcyclopropanes proceeds by mechanism type B, based on the following observa-

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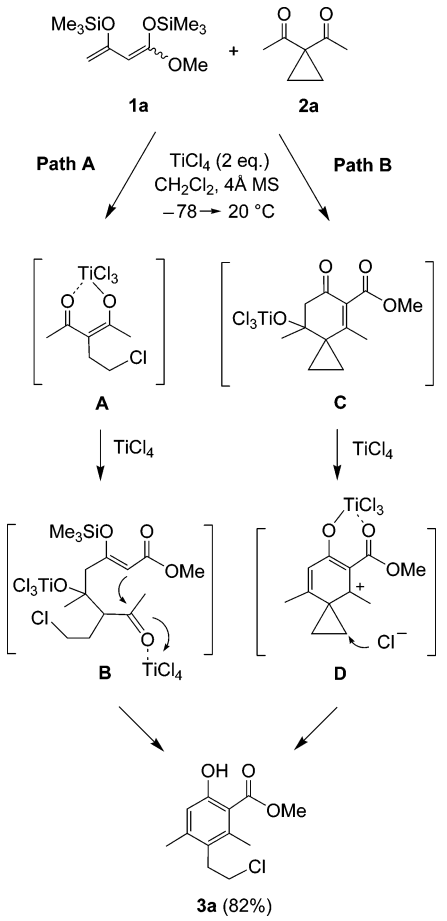
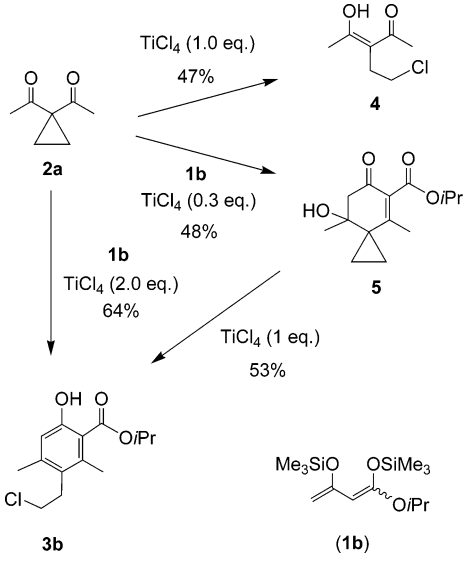
SCHEME 1. Possible Mechanisms of the Cyclization of 1,3-Bissilyl Enol Ether 1a with 1,1-Diacetylcyclopropane

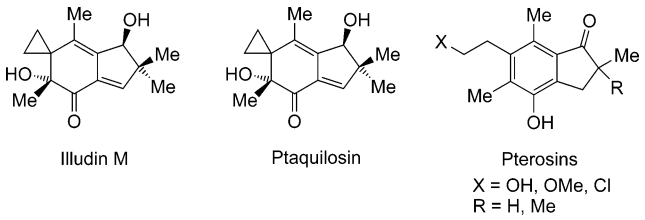


SCHEME 2. Mechanistic Studies



tions: The reaction of 1,3-bissilyl enol ether **1b** with **2a** in the presence of 0.3 rather than 2.0 equiv of $TiCl_4$ allowed the isolation of spirocyclopropane **5** in 48% yield.[7] The formation of **5** can be explained by $TiCl_4$-mediated cyclization, to give a spirocyclic titanium alkoxide (intermediate **C**, Scheme 1), and subsequent hydrolysis upon aqueous workup. Treatment of **5** with $TiCl_4$ afforded the salicylate **3b** in 53% yield. The yield was significantly improved when NBu_4Cl was employed. The use of more than 0.5 equiv of $TiCl_4$ in the reaction of **1b** with **2a** resulted in formation of significant amounts of **3b** at the expense of **5**. In fact, salicylate **3b** was isolated in 64% yield when the cyclization was carried out in the presence of 2.0 equiv of $TiCl_4$. The use of $BF_3{\cdot}OEt_2$, Me_3SiOTf, or TFA resulted in formation of complex mixtures.

CHART 1



Acceptor-substituted cyclopropanes represent important building blocks in homo-Michael reactions with various nucleophiles.[8] Reactions of acceptor-substituted cyclopropanes have been classified by Danishefsky in terms of "strictly nucleophilic ring openings", "electrophilically assisted ring openings", and "spiro-activations".[9] In the domino "[3+3]-cyclization-homo-Michael" reaction reported herein two effects are operating: (a) a "dynamic spiro-activation"[10] and (b) activation by an electrophile.

The second step of mechanism path B, the transformation of the spirocyclopropane into the salicylate, is related to the biosynthesis of the carcinogenic pterosins isolated from the bracken fern *Pteridium aquilinium*.[11] It was shown earlier that the pterosins are formed from their direct biogenetic precursor, the spirocyclopropane ptaquilosin, by treatment with acid. It was proposed that the pterosins, ptaquilosin, and illudin M (Chart 1) are all formed from farnesyl phosphate via a common biosynthetic intermediate.[12] The synthesis of analogues of these compounds is of considerable pharmacological relevance, due to their potential cytotoxic and cancerostatic activity.[13]

Preparative Scope. The $TiCl_4$-mediated reaction of 1,1-diacetylcyclopropane (**2a**) with a variety of 1,3-bissilyl enol ethers was studied. The reaction of **2a** with β-ketoester derived 1,3-bissilyl enol ethers **1a**−**d** afforded the

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SCHEME 3. Synthesis of Salicylates

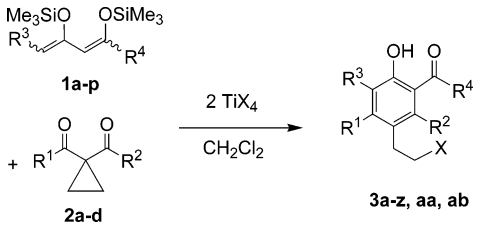

TABLE 1. Products and Yields

3	R^1	R^2	R^3	R^4	X	yield (%)[a]
a	Me	Me	H	OMe	Cl	82
b	Me	Me	H	O*i*Pr	Cl	64
c	Me	Me	H	OEt	Cl	72
d	Me	Me	H	$O(CH_2)_2OMe$	Cl	56
e	Me	Me	H	Me	Cl	82
f	Me	Me	Me	OMe	Cl	32
g	Me	Me	Et	OEt	Cl	38
h	Me	Me	*n*Pr	OEt	Cl	67
i	Me	Me	*n*Bu	OEt	Cl	44
j	Me	Me	*n*Hex	OEt	Cl	41
k	Me	Me	*n*Hept	OEt	Cl	51
l	Me	Me	*n*Oct	OEt	Cl	45
m	Me	Me	*n*Non	OEt	Cl	47
n	Me	Me	*n*Dec	OEt	Cl	55
o	Me	Me	OBn	OEt	Cl	45
p	Et	Et	H	OMe	Cl	47
q	Et	Et	H	OEt	Cl	42
r	Et	Et	H	O*i*Pr	Cl	37
s	Et	Et	H	$O(CH_2)_2OMe$	Cl	42
t	Me	Ph	H	OMe	Cl	73
u	Me	Ph	H	OEt	Cl	57
v	Me	Ph	H	O*i*Pr	Cl	34
w	Me	Ph	H	O*i*Bu	Cl	73
x	H	Me	H	OEt	Cl	42
y	H	Me	Et	OEt	Cl	33
z	Me	Me	H	OMe	Br	82
aa	Me	Me	*n*Bu	OEt	Br	43
ab	Me	Me	*n*Hex	OEt	Br	45

[a] Isolated yields.

functionalized salicyclates **3a**−**d** in good yields (Scheme 3, Table 1). Starting with **2a** and 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**1e**), the acetophenone **3e** was obtained. The reaction of **2a** with bissilyl enol ethers **1f**−**n** afforded the alkyl-substituted salicylates **3f**−**n**. The benzyloxy-substituted salicylate **3o** was prepared from **1o**. The 1,1-diacylcyclopropane was varied next. Cyclization of **1a**−**d** with 1,1-dipropionylcyclopropane (**2b**) afforded the ethyl-substituted salicylates **3p**−**s**. The reaction of β-ketoester derived 1,3-bissilyl enol ethers with (unsymmetrical) 1-acetyl-1-benzoylcyclopropane (**2c**) gave the methyl- and phenyl-substituted salicyclates **3t**−**w**. The products were formed with very good regioselectivity and the cyclizations proceeded by attack of the terminal carbon of the bissilyl enol ether onto the (more reactive) acetyl group rather than onto the benzoyl group. The cyclization of **1b** and **1g** with (unsymmetrical) 1-acetyl-1-formylcyclopropane (**2d**) afforded the salicylates **3x** and **3y**, respectively. The products were again formed with very good regioselctivity and the cyclizations proceeded by initial attack of the terminal carbon of the 1,3-bissilyl enol ethers onto the aldehyde and subsequent cyclization. The $TiBr_4$-mediated cyclization of **1a** with **2a** resulted in formation of salicylate **3z** containing a bromo-substituted side chain. Similarly, reaction of **1i** and **1j** with **2a** in the presence of $TiBr_4$ resulted in the formation of **3aa** and **3ab**.

The structure of all products was elucidated by spectroscopic methods. The structure of **3w** was independently confirmed by crystal structure analysis (see Supporting Information). As expected from the structure in solution, an intramolecular hydrogen bond O−H···O is observed. The two aryl moieties are orthogonally twisted.

In conclusion, we have reported the $TiCl_4$- or $TiBr_4$-mediated domino "[3+3]-cyclization-homo-Michael" reaction of 1,3-bissilyl enol ethers with 1,1-diacylcyclopropanes. These reactions allow a convenient one-pot synthesis of a great variety of functionalized salicylates containing a chlorinated or brominated side chain.

Experimental Section

General. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra (^1H NMR, 300, 600 MHz; ^{13}C NMR, 75, 150 MHz) the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained with the electron ionization (70 eV), the chemical ionization (CI, H_2O), or the electrospray ionization technique (ESI). For preparative scale chromatography silica gel (60−200 mesh) was used. Melting points are uncorrected

Typical Procedure for the Preparation of Salicylates 3. To a stirred CH_2Cl_2 solution (100 mL) of 1,1-diacetylcyclopropane (**2a**) (0.136 g, 1.1 mmol) and 1,3-bis(trimethylsilyloxy)-1,3-butadiene (**1a**) (0.421 g, 1.6 mmol) was added $TiCl_4$ (0.22 mL, 2.0 mmol in 2 mL of CH_2Cl_2) at −78 °C under argon atmosphere in the presence of molecular sieves (4 Å) (1.0 g). The temperature of the reaction mixture was allowed to rise to 20 °C over 6 h. The solution was stirred for an additional 6 h at 20 °C. The reaction mixture was filtered and the filtrate was poured into an aqueous solution of HCl (10%, 100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexane/ethyl acetate = 4:1) to give **3a** (0.251 g, 82%) as colorless crystals.

Methyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-2-benzoate (3a). Starting with **2a** (0.136 g, 1.08 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.420 g, 1.61 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3a** was isolated (0.215 g, 82%) as a colorless solid; mp 73−74 °C; R_f 0.53 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ = 2956 (m), 1722 (w), 1657 (s), 1601 (m), 1574 (m), 1437 (s), 1239 (s), 1072 (m), 804 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.68 (s, 1 H, OH), 6.70 (s, 1 H, ArH), 3.94 (s, 3 H, OCH_3), 3.51−3.46 (m, 2 H, CH_2), 3.12−3.06 (m, 2 H, CH_2), 2.48 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 160.3, 144.2, 139.0, 127.1, 117.2, 111.9, 52.1, 42.2, 32.9, 21.0, 18.5; MS (EI, 70 eV) *m/z* (%) 244.6 ($[M]^+$, 14), 242.5 ($[M]^+$, 42), 212.5 (37), 210.4 (85), 193.5 (21), 161.4 (100), 104.8 (14), 77.5 (13). Elemental analysis calcd for $C_{12}H_{15}O_3Cl$: C 59.39, H 6.22. Found: C 59.56, H 6.50.

Isopropyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-2-benzoate (3b). Starting with **2a** (0.126 g, 1.00 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.375 g, 1.30 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3b** was isolated (0.173 g, 64%) as a colorless solid; mp 51−52 °C; R_f 0.66 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2982 (m), 1731 (w), 1656 (s), 1601 (w), 1574 (m), 1467 (m), 1372 (s), 1238 (s), 1105 (m), 804 (w), 703 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1 H, OH), 6.70 (s, 1 H, ArH), 5.32 (sep, 1 H, J = 6.2 Hz, OCH), 3.53−3.46 (m, 2 H, CH_2), 3.12−3.06 (m, 2 H, CH_2), 2.50 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 1.46 (d, 6 H, J = 6.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 160.2, 143.9, 138.9,

127.0, 117.2, 112.3, 69.7, 42.2, 33.0, 21.9, 21.0, 18.6; MS (EI, 70 eV): *m/z* (%) 272.1 ([M]$^+$, 5), 270.1 ([M]$^+$, 15), 212.0 (26), 210.1 (74), 161.1 (100), 91.1 (8), 77.5 (7), 28.0 (35). Elemental analysis calcd for $C_{14}H_{19}O_3Cl$: C 62.10, H 7.07. Found: C 62.07, H 7.49.

Ethyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-2-benzoate (3c). Starting with **2a** (0.127 g, 1.00 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.355 g, 1.30 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3c** was isolated (0.186 g, 72%) as a colorless solid; mp 53−54 °C; R_f 0.57 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2978 (m), 1666 (s), 1606 (w), 1561 (m), 1467 (m), 1311 (s), 1072 (m), 699 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1 H, OH), 6.70 (s, 1 H, ArH), 4.43 (q, 2 H, J = 7.2 Hz, OCH_2), 3.52−3.47 (m, 2 H, CH_2), 3.13−3.07 (m, 2 H, CH_2), 2.51 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 1.42 (t, 3 H, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 160.2, 144.0, 139.0, 127.0, 117.2, 112.0, 61.6, 42.2, 32.9, 21.0, 18.5, 14.1; MS (EI, 70 eV) *m/z* (%) 258.4 ([M]$^+$, 12), 256.4 ([M]$^+$, 38), 212.2 (34), 210.2 (88), 161.2 (100), 91.1 (5), 77.5 (4). Elemental analysis calcd for $C_{13}H_{17}O_3Cl$: C 60.82, H 6.67. Found: C 60.81, H 7.09.

2-Methoxyethyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-2-benzoate (3d). Starting with **2a** (0.127 g, 1.00 mmol), 1-(2-methoxy)ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.395 g, 1.30 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3d** was isolated (0.162 g, 56%) as a colorless solid; mp. 41−42 °C; R_f 0.51 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2960 (m), 1727 (m), 1659 (s), 1610 (m), 1573 (m), 1467 (m), 1237 (s), 1072 (m), 802 (w), 703 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1 H, OH), 6.70 (s, 1 H, ArH), 4.50 (t, 2 H, J = 4.7 Hz, OCH_2), 3.72 (t, 2 H, J = 4.7 Hz, OCH_2), 3.52−3.46 (m, 2 H, CH_2), 3.42 (s, 3 H, OCH_3), 3.12−3.08 (m, 2 H, CH_2), 2.51 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 159.7, 144.1, 139.2, 127.0, 117.3, 112.4, 70.0, 64.1, 58.9, 42.2, 33.0, 21.0, 18.4; MS (EI, 70 eV) *m/z* (%) 288.1 ([M]$^+$, 6), 286.2 ([M]$^+$, 20), 212.0 (27), 210.0 (81), 161.0 (100), 91.1 (7), 77.5 (5), 28.1 (19). Elemental analysis calcd for $C_{14}H_{19}O_4Cl$: C 58.64, H 6.68. Found: C 58.54, H 6.97.

2-Acetyl-[4-(2-chloroethyl)]-1-hydroxy-3,5-dimethylbenzene (3e). Starting with **2a** (0.138 g, 1.09 mmol), 1-methyl-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.400 g, 1.64 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3e** (0.215 g, 82%) was obtained as a colorless oil; R_f 0.56 (hexane/ethyl acetate = 4:1); IR (neat) $\tilde{\nu}$ 3332 (br), 2956 (w), 1673 (s), 1600 (m), 1574 (m), 1446 (s), 1301 (s), 1239 (m), 723 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.72 (s, 1 H, OH), 6.67 (s, 1 H, ArH), 3.54−3.46 (m, 2 H, CH_2), 3.09−3.06 (m, 2 H, CH_2), 2.59 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 158.2, 143.9, 136.7, 127.2, 122.9, 117.4, 42.1, 32.8, 32.6, 20.7, 19.2; MS (EI, 70 eV) *m/z* (%) 228.3 ([M]$^+$, 20), 226.3 ([M]$^+$, 60), 213.2 (28), 211.2 (79), 177.3 (100), 159.3 (56), 91.1 (23), 77.5 (11). The exact molecular mass for $C_{12}H_{15}O_2Cl$ (*m/z* 226.0761 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Methyl 4-(2-Chloroethyl)-1-hydroxy-3,5,6-trimethyl-2-benzoate (3f). Starting with **2a** (0.128 g, 1.02 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)penta-1,3-diene (**2f**) (0.363 g, 1.32 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3f** was isolated (0.083 g, 32%) as a colorless solid; mp 95−96 °C; R_f 0.63 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2955 (m), 1649 (s), 1599 (m), 1564 (m), 1442 (s), 1211 (s), 1099 (m), 811 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.94 (s, 1 H, OH), 3.95 (s, 3 H, OCH_3), 3.51−3.45 (m, 2 H, CH_2), 3.17−3.12 (m, 2 H, CH_2), 2.46 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 158.2, 142.4, 135.4, 126.5, 122.9 111.3, 52.1, 42.3, 33.5, 18.6, 16.9, 12.2; MS (EI, 70 eV) *m/z* (%) 258.4 ([M]$^+$, 13), 256.4 ([M]$^+$, 37), 226.3 (39), 224.3 (90), 189.3 (569, 175.3 (100), 146.8 (16), 91.2 (9). Elemental analysis calcd for $C_{13}H_{17}O_3Cl$: C 60.82, H 6.68. Found: C 61.01, H 7.13.

Ethyl 4-(2-Chloroethyl)-6-ethyl-1-hydroxy-3,5-dimethyl-2-benzoate (**3g**): Starting with **2a** (0.139 g, 1.10 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)hexa-1,3-diene (**2g**) (0.500 g, 1.65 mmol), and $TiCl_4$ (0.24 mL, 2.20 mmol), **3g** was isolated (0.119 g, 38%) as a colorless solid; mp 38−39 °C; R_f 0.61 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2971 (m), 1652 (s), 1597 (w), 1565 (w), 1452 (m), 1275 (s), 1198 (s), 809 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.91 (s, 1 H, OH), 4.42 (q, 2 H, J = 7.2 Hz, OCH_2), 3.52−3.47 (m, 2 H, CH_2), 3.16−3.11 (m, 2 H, CH_2), 2.70 (q, 2 H, J = 7.5 Hz, CH_2), 2.48 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 1.09 (t, 3 H, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.0, 141.4, 135.6, 129.0, 126.7, 111.7, 61.6, 42.3, 33.6, 19.8, 18.6, 16.1, 14.2, 13.3; MS (EI, 70 eV) *m/z* (%) 286.2 ([M]$^+$, 9), 284.2 ([M]$^+$, 28), 240.2 (36), 238.2 (100), 212.1 (9), 210.1 (28), 203.1 (91), 189.2 (34), 91.1 (8), 29.1 (12). Elemental analysis calcd for $C_{15}H_{21}O_3Cl$: C 63.26, H 7.43. Found: C 63.12, H 7.43.

Ethyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-6-propyl-2-benzoate (3h). Starting with **2a** (0.190 g, 1.51 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)hepta-1,3-diene (0.711 g, 2.25 mmol), and $TiCl_4$ (0.33 mL, 3.00 mmol), **3h** was isolated (0.273 mg, 67%) as a colorless solid; mp 38−39 °C; R_f 0.66 (hexane/ethyl acetate = 7:3); IR (KBr) $\tilde{\nu}$ 2960 (m), 1653 (s), 1593 (w), 1449 (m), 1190 (s), 1041 (w), 769 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.90 (s, 1 H, OH), 4.44 (q, 2 H, J = 7.2 Hz, OCH_2), 3.50−3.46 (m, 2 H, CH_2), 3.15−3.08 (m, 2 H, CH_2), 2.48 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 1.38−1.46 (m, 4 H, CH_2), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 0.89 (t, 3 H, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.3, 141.7, 135.6, 127.7, 126.7, 111.7, 61.6, 42.2, 33.6, 28.7, 22.3, 18.6, 16.4, 14.4, 14.2; MS (EI, 70 eV) *m/z* (%) 300.0 ([M]$^+$, 11), 298.0 ([M]$^+$, 35), 254.0 (34), 252.0 (100), 239.0 (8), 237.0 (29), 217.0 (58), 91.0 (9), 28.0 (36). The exact molecular mass for $C_{16}H_{23}O_3Cl$ (*m/z* 298.1336 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 6-Butyl-4-(2-chloroethyl)-1-hydroxy-3,5-dimethyl-2-benzoate (3i). Starting with **2a** (0.190 g, 1.51 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)octa-1,3-diene (0.743 g, 2.25 mmol), and $TiCl_4$ (0.33 mL, 3.00 mmol), **3i** was isolated (0.206 g, 44%) as a colorless oil; R_f 0.69 (hexane/ethyl acetate = 7:3); IR (neat) $\tilde{\nu}$ =2929 (m), 1654 (s), 1597 (w), 1567 (w), 1450 (m), 1195 (s), 1039 (w), 806 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1 H, OH), 4.47 (q, 2 H, J = 7.2 Hz, OCH_2), 3.52−3.46 (m, 2 H, CH_2), 3.16−3.10 (m, 2 H, CH_2), 2.69−2.65 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 1.38−1.46 (m, 4 H, CH_2), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 0.89 (t, 3 H, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.4, 141.8, 135.8, 128.1, 126.9, 111.9, 61.8, 42.5, 33.9, 31.5, 26.6, 23.2, 18.8, 16.5, 14.3, 14.2; MS (EI, 70 eV) *m/z* (%) 314.0 ([M]$^+$, 17), 312.0 ([M]$^+$, 55), 268.0 (28), 266.0 (81), 253.0 (26), 251.0 (81), 223.9 (100), 188.9 (41), 91.0 (21), 28.0 (67). The exact molecular mass for $C_{17}H_{25}O_3Cl$ (*m/z* 312.1492 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-6-hexyl-1-hydroxy-3,5-dimethyl-2-benzoate (3j). Starting with **2a** (0.190 g, 1.51 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)deca-1,3-diene (0.806 g, 2.25 mmol), and $TiCl_4$ (0.33 mL, 3.00 mmol), **3j** was isolated (0.208 g, 41%) as a colorless oil; R_f 0.67 (hexane/ethyl acetate = 7:3); IR (neat) $\tilde{\nu}$ 2927 (s), 1725 (w), 1654 (s), 1597 (w), 1566 (w), 1452 (m), 1195 (s), 1041 (w), 808 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1 H, OH), 4.47 (q, 2 H, J = 7.2 Hz, OCH_2), 3.56−3.46 (m, 2 H, CH_2), 3.16−3.10 (m, 2 H, CH_2), 2.69−2.64 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 1.30−1.23 (br, 8 H, CH_2), 0.89 (t, 3 H, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.4, 141.8, 135.8, 128.2, 126.9, 111.9, 61. 8, 42.5, 33.8, 31.9, 29.9, 29.3, 26.9, 22.9, 18.8, 16.6, 14.4, 14.3; MS (EI, 70 eV) *m/z* (%) 342.0 ([M]$^+$, 17), 340.0 ([M]$^+$, 51), 296.0 (22), 294.0 (58), 281.0 (11), 279.0 (43), 225.0 (35), 223.0 (100), 189.0 (34), 91.0 (15), 28.0 (32). The exact molecular mass for $C_{19}H_{29}O_3Cl$ (*m/z* 340.1805 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-6-heptyl-1-hydroxy-3,5-dimethyl-2-benzoate (3k). Starting with **2a** (0.190 g, 1.51 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)undeca-1,3-diene (0.865 g, 2.25 mmol), and $TiCl_4$ (0.33 mL, 3.00 mmol), **3k** was isolated (0.269 g, 51%) as a colorless oil; R_f 0.67 (hexane/ethyl acetate = 7:3); IR (KBr) $\tilde{\nu}$ 2927 (s), 1727 (w), 1655 (s), 1597 (w), 1567

(w), 1452 (m), 1195 (s), 1039 (w), 853 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.90 (s, 1 H, OH), 4.42 (q, 2 H, J = 7.2 Hz, OCH_2), 3.46−3.52 (m, 2 H, CH_2), 3.16−3.10 (m, 2 H, CH_2), 2.69−2.64 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 1.37−1.25 (br, 10 H, CH_2), 0.91−0.89 (m, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.4, 141.8, 135.8, 128.2, 126.9, 111.9, 61. 8, 42.5, 33.9, 32.1, 30.2, 29.4, 29.4, 26.9, 22.9, 18.8, 16.6, 14.4, 14.3; MS (EI, 70 eV) *m/z* (%) 356.1 ($[M]^+$, 2), 354.1 ($[M]^+$, 7), 310.0 (2), 308.0 (6), 226.0 (4), 223.9 (15), 122.0 (24), 73.0 (36), 28.0 (100). The exact molecular mass for $C_{20}H_{31}O_3Cl$ (*m/z* 354.1962 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-6-octyl-2-benzoate (3*l*). Starting with **2a** (0.190 g, 1.51 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)dodeca-1,3-diene (0.869 g, 2.25 mmol), and $TiCl_4$ (0.33 mL, 3.00 mmol), ***3l*** was isolated (0.249 g, 45%) as a colorless oil; R_f 0.68 (hexane/ethyl acetate = 7:3); IR (neat) $\tilde{\nu}$ 2926 (s), 1697 (w), 1655 (s), 1597 (w), 1460 (m), 1195 (s), 1040 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1 H, OH), 4.42 (q, 2 H, J = 7.2 Hz, OCH_2), 3.52−3.46 (m, 2 H, CH_2), 3.16−3.10 (m, 2 H, CH_2), 2.69−2.64 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 1.37−1.23 (br, 12 H, CH_2), 0.90−0.80 (m, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.4, 141.8, 135.8, 128.2, 126.9, 111.9, 61.8, 42.5, 33.9, 32.1, 30.3, 29.7, 29.5, 29.4, 26.9, 22.9, 18.9, 16.6, 14.4, 14.3; MS (EI, 70 eV) *m/z* (%) 368.1 (M^+, 3), 296.1 (6), 281.0 (10), 240.0 (12), 196.9 (36), 122.1 (75), 73.1 (100), 28.0 (43). Elemental analysis calcd for $C_{21}H_{33}O_3Cl$: C 68.36, H 9.01. Found: C 68.37, H 8.40. The exact molecular mass for $C_{21}H_{33}O_3Cl$ (*m/z* 368.2118 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-1-hydroxy-3,5-dimethyl-6-nonyl-2-benzoate (3m). Starting with **2a** (0.190 g, 1.51 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)trideca-1,3-diene (0.901 g, 2.25 mmol), and $TiCl_4$ (0.33 mL, 3.00 mmol), **3m** was isolated (0.270 g, 47%) as a colorless oil; R_f 0.71 (hexane/ethyl acetate = 7:3); IR (neat) $\tilde{\nu}$ 2926 (s), 1698 (w), 1655 (s), 1597 (w), 1567 (w), 1461 (m), 1195 (s), 1040 (w), 847 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.93 (s, 1 H, OH), 4.47 (q, 2 H, J = 7.2 Hz, OCH_2), 3.56−3.51 (m, 2 H, CH_2), 3.21−3.15 (m, 2 H, CH_2), 2.69−2.63 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 1.42 (t, 3 H, J = 7.2 Hz, CH_3), 1.37−1.23 (br, 14 H, CH_2), 0.70 (t, 3 H, J = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 158.5, 141.8, 135.8, 128.2, 126.9, 111.9, 61.8, 42.5, 33.9, 32.1, 30.3, 29.8, 29.6, 29.4, 26.9, 22.9, 18.9, 16.6, 14.4, 14.3; MS (EI, 70 eV) *m/z* (%) 384.3 ($[M]^+$, 7), 382.3 ($[M]^+$, 24), 338.1 (4), 336.1 (14), 265.1 (21), 240.0 (34), 197.1 (37), 122.1 (75), 73.7 (100), 43.1 (42). The exact molecular mass for $C_{22}H_{35}O_3Cl$ (*m/z* 382.2275 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-6-decyl-1-hydroxy-3,5-dimethyl-2-benzoate (3n). Starting with **2a** (0.380 g, 3.02 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)tetradeca-1,3-diene (1.864 g, 4.5 mmol), and $TiCl_4$ (0.66 mL, 6.00 mmol), **3n** was isolated (0.512 g, 55%) as a colorless oil; R_f 0.68 (hexane/ethyl acetate = 7:3); IR (KBr) $\tilde{\nu}$ 2926 (s), 1697 (w), 1655 (s), 1620 (w), 1460 (m), 1195 (s), 1040 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.89 (s, 1 H, OH), 4.42 (q, 2 H, J = 7.2 Hz, OCH_2), 3.51−3.46 (m, 2 H, CH_2), 3.16−3.10 (m, 2 H, CH_2), 2.69−2.64 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 1.36−1.22 (br, 16 H, CH_2), 0.87 (t, 3 H, J = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 158.5, 141.8, 135.8, 128.2, 126.9, 111.8, 61.8, 42.5, 32.9, 32.1, 30.3, 30.2, 29.8, 29.8, 29.6, 29.4, 27.0, 22.9, 18.8, 16.6, 14.4, 14.2; MS (EI, 70 eV) *m/z* (%) 398.0 ($[M]^+$, 15), 396.0 ($[M]^+$, 47), 352.0 (11), 350.0 (30), 265.1 (53), 223.9 (70), 167.1 (86), 70.1 (100), 41.1 (95), 28.0 (73). The exact molecular mass for $C_{23}H_{37}O_3Cl$ (*m/z* 396.2431 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 1-Benzyloxy-5-(2-chloroethyl)-2-hydroxy-4,6-dimethyl-3-benzoate (3o). Starting with **2a** (0.380 g, 3.00 mmol), 1-ethoxy-4-benzyloxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (1.71 g, 4.5 mmol), and $TiCl_4$ (0.65 mL, 6.00 mmol), **3o** was isolated (0.492 g, 45%) as a colorless solid; mp 52−53 °C; R_f 0.58 (hexane/ethyl acetate = 7:3); IR (KBr) $\tilde{\nu}$ 3429 (br), 2929 (w), 1654 (s), 1594 (w), 1449 (m), 1276 (s), 1067 (m), 807 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.53 (s, 1 H, OH), 7.48−7.43 (m, 5 H, ArH), 4.97 (s, 2 H, OCH_2Ph), 4.45 (q, 2 H, J = 7.2 Hz, OCH_2), 3.49−3.43 (m, 2 H, CH_2), 3.11−3.06 (m, 2 H, CH_2), 2.46 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3), 1.43 (t, 3 H, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 153.5, 143.6, 137.7, 136.8, 133.4, 128.6, 128.3, 127.2, 113.7, 74.5, 61.9, 42. 33.5, 18.4, 14.4, 13.5; MS (EI, 70 eV) *m/z* (%) 363.4 ($[M]^+$, 5), 361.4 ($[M]^+$, 16), 291.1 (16), 276.5 (24), 197.5 (10), 90.7 (100), 28.0 (79). Elemental analysis calcd for $C_{20}H_{32}O_4Cl$: C 66.20, H 6.38. Found: C 65.84, H 6.97. The exact molecular mass for $C_{20}H_{32}O_4Cl$ (*m/z* 362.1285 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Methyl 4-(2-Chloroethyl)-3,5-diethyl-1-hydroxy-2-benzoate (3p). Starting with **2b** (0.152 g, 0.99 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.340 g, 1.30 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3p** was isolated (0.126 g, 47%) as a colorless oil; R_f 0.69 (hexane/ethyl acetate = 7:3); IR (KBr) $\tilde{\nu}$ 2966 (m), 1732 (w), 1663 (s), 1604 (m), 1570 (m), 1438 (s), 1335 (s), 1080 (m), 850 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.65 (s, 1 H, OH), 6.75 (s, 1 H, ArH), 3.96 (s, 3 H, OCH_3), 3.52−3.46 (m, 2 H, CH_2), 3.12−3.06 (m, 2 H, CH_2), 2.94 (q, 2 H, J = 7.5 Hz, CH_2), 2.65 (q, 2 H, J = 7.5 Hz, CH_2), 1.25 (t, 3 H, J = 7.5 Hz, CH_3), 1.19 (t, 3 H, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 160.6, 150.5, 145.2, 125.7, 115.7, 111.1, 52.1, 43.1, 31.9, 26.5, 24.3, 15.9, 14.7; MS (EI, 70 eV) *m/z* (%) 272.2 ($[M]^+$, 6), 270.2 ($[M]^+$, 19), 240.2 (23), 238.1 (70), 221.2 (11), 189.2 (100), 91.1 (12); the exact molecular mass for $C_{14}H_{19}O_3Cl$ (*m/z* 270.1023 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-3,5-diethyl-1-hydroxy-2-benzoate (3q). Starting with **2b** (0.155 g, 1.00 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.355 g, 1.30 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3q** was isolated (0.119 g, 42%) as a colorless solid; mp 62−63 °C; R_f 0.74 (hexane/ethyl acetate = 7:3); IR (KBr) $\tilde{\nu}$ 3432 (w), 2970 (m), 1725 (w), 1657 (s), 1602 (m), 1570 (m), 1235 (s), 1078 (m), 711 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1 H, OH), 6.74 (s, 1 H, ArH), 4.43 (q, 2 H, J = 7.1 Hz, OCH_2), 3.52−3.46 (m, 2 H, CH_2), 3.11−3.05 (m, 2 H, CH_2), 2.97 (q, 2 H, J = 7.4 Hz, CH_2), 2.64 (q, 2 H, J = 7.5 Hz, CH_2), 1.43 (t, 3 H, J = 7.2 Hz, CH_3), 1.24 (t, 3 H, J = 7.4 Hz, CH_3), 1.19 (t, 3 H, J = 7.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 160.8, 150.2, 145.3, 125.8, 115.8, 111.3, 61.7, 43.2, 32.0, 26.5, 24.3, 16.1, 14.8, 14.0; MS (EI, 70 eV) *m/z* (%) 286.2 ($[M]^+$, 6), 284.2 ($[M]^+$, 20), 240.2 (26), 238.2 (81), 189.2 (100), 91.1 (6). Elemental analysis calcd for $C_{15}H_{21}O_3Cl$: C 63.26, H 7.43. Found: C 63.32, H 7.69.

Isopropyl 4-(2-Chloroethyl)-3,5-diethyl-1-hydroxy-2-benzoate (3r). Starting with **2b** (0.156 g, 1.01 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.475 g, 1.65 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3r** was isolated (0.112 g, 37%) as a colorless oil; R_f 0.78 (hexane/ethyl acetate = 7:3); IR (neat) $\tilde{\nu}$ 2978 (m), 1725 (w), 1656 (s), 1601 (m), 1570 (m), 1457 (s), 1369 (s), 1104 (m), 838 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.81 (s, 1 H, OH), 6.73 (s, 1 H, ArH), 5.34 (sep, 1 H, J = 6.3 Hz, OCH), 3.51−3.46 (m, 2 H, CH_2), 3.11−3.05 (m, 2 H, CH_2), 2.94 (q, 2 H, J = 7.5 Hz, CH_2), 2.65 (q, 2 H, J = 7.5 Hz, CH_2), 1.41 (d, 6 H, J = 6.3 Hz, CH_3), 1.23 (t, 3 H, J = 7.2 Hz, CH_3), 1.21 (t, 3 H, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 161.3, 150.5, 145.7, 126.2, 116.2, 112.1, 70.3, 43.8, 32.5, 27.0, 24.8, 22.3, 16.8, 15.3; MS (EI, 70 eV) *m/z* (%) 300.0 ($[M]^+$, 6), 298.1 ($[M]^+$, 20), 240.0 (33), 238.1 (100), 189.0 (97), 91.0 (8), 28.0 (28). The exact molecular mass for $C_{16}H_{23}O_3Cl$ (*m/z* 298.1336 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

2-Methoxyethyl 4-(2-Chloroethyl)-3,5-diethyl-1-hydroxy-2-benzoate (3s). Starting with **2b** (0.152 g, 0.99 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.450 g, 1.48 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol), **3s** was isolated (0.130 g, 42%) as a colorless oil; R_f 0.58 (hexane/ethyl acetate = 7:3); IR (neat) $\tilde{\nu}$ 2966 (m), 1736 (w), 1665 (s), 1602 (m), 1588

(m), 1444 (s), 1335 (s), 1074 (m), 834 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.26 (s, 1 H, OH), 6.73 (s, 1 H, ArH), 4.50 (t, 2 H, $J = 4.8$ Hz, OCH_2), 3.72 (t, 2 H, $J = 4.8$ Hz, OCH_2), 3.51−3.46 (m, 2 H, CH_2), 3.41 (s, 3 H, OCH_3), 3.11−3.05 (m, 2 H, CH_2), 2.94 (q, 2 H, $J = 7.5$ Hz, CH_2), 2.65 (q, 2 H, $J = 7.5$ Hz, CH_2), 1.23 (t, 3 H, $J = 7.5$ Hz, CH_3), 1.21 (t, 3 H, $J = 7.5$ Hz, CH_3); MS (EI, 70 eV) *m/z* (%) 316.0 ($[M]^+$, 7), 314.0 ($[M]^+$, 24), 240.0 (32), 238.1 (100), 189.0 (99), 91.0 (8), 28.0 (18); the exact molecular mass for $C_{16}H_{23}O_4Cl$ (*m/z* 298.1336 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Methyl 4-(2-Chloroethyl)-1-hydroxy-5-methyl-3-phenyl-2-carboxylate (3t). Starting with **2c** (0.376 g, 2.00 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.780 g, 3.00 mmol), and $TiCl_4$ (0.44 mL, 4.00 mmol), **3t** was isolated (0.437 g, 73%) as a colorless solid; mp 95−96 °C; IR (KBr) $\tilde{\nu}$ 1663 (s), 1600 (m), 1572 (m), 1441 (s), 1347 (s), 1204 (s), 854 (m), 778 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.83 (s, 1 H, OH), 7.32−7.04 (m, 3 H, ArH), 7.09−7.06 (m, 2 H, ArH), 3.34 (s, 3 H, OCH_3), 3.30−3.24 (m, 2 H, CH_2), 2.79−2.56 (m, 2 H, CH_2), 2.04 (s, 3 H,CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 160.3, 144.8, 144.4, 141.3, 128.5, 127.8, 127.1, 119.1, 111.3 (C), 51.9, 42.8, 33.4, 20.9; MS (EI, 70 eV) *m/z* (%) 306.4 ($[M]^+$, 17), 304.3 ($[M]^+$, 50), 274.3 (36), 272.3 (88), 223.3 (100), 195.3 (17), 165.2 (36), 151.5 (28). Elemental analysis calcd for $C_{17}H_{17}O_3Cl$: C 66.99, H 5.62. Found: C 64.72, H 5.95. The exact molecular mass for $C_{17}H_{17}O_3Cl$ (*m/z* 304.0866 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Ethyl 4-(2-Chloroethyl)-1-hydroxy-5-methyl-3-phenyl-2-carboxylate (3u). Starting with **2c** (0.376 g, 2.00 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.822 g, 3.00 mmol), and $TiCl_4$ (0.44 mL, 4.00 mmol), **3u** was isolated (0.367 g, 57%) as a colorless solid; mp 104−105 °C; R_f 0.59 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2984 (m),1657 (s), 1597 (m), 1575 (m), 1462 (m), 1240 (s), 1015 (w), 776 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1 H, OH), 7.38−7.33 (m, 3 H, ArH), 7.11−7.07 (m, 2 H, ArH), 6.88 (s, 1 H, ArH), 3.86 (q, 2 H, $J = 7.2$ Hz, OCH_2), 3.29−3.24 (m, 2 H, CH_2), 2.78−2.72 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 0.66 (t, 3 H, $J = 7.2$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 160.6, 144.7, 144.4, 141.5, 128.6, 127.1, 119.2, 111.3, 61.0, 42.8, 33.4, 20.9, 13.1; MS (EI, 70 eV) *m/z* (%) 319.4 ($[M]^+$, 13), 317.4 ($[M]^+$, 39), 273.5 (16), 271.5 (77), 222.6 (100), 164.7 (19), 150.8 (15), 128.2 (24). Elemental analysis calcd for $C_{18}H_{19}O_3Cl$: C 67.81, H 6.00. Found: C 67.89, H 5.94.

Isopropyl 4-(2-Chloroethyl)-1-hydroxy-5-methyl-3-phenyl-2-carboxylate (3v). Starting with **2c** (0.376 g, 2.00 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.864 g, 3.00 mmol), and $TiCl_4$ (0.44 mL, 4.00 mmol), **3v** was isolated (0.229 g, 34%) as a colorless solid; R_f 0.62 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2981 (m), 1656 (s), 1599 (m), 1575 (m), 1458 (m), 1370 (s), 1240 (s), 1102 (m), 702 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.72 (s, 1 H, OH), 7.40−7.33 (m, 3 H, ArH), 7.10−7.06 (m, 2 H, ArH), 6.88 (s, 1 H, ArH), 4.87 (d, 1 H, $J =$ 6.3 Hz, OCH), 3.29−3.23 (m, 2 H, CH_2), 2.76−2.71 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 0.84 (d, 6 H, $J = 6.3$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 160.6, 144.5, 144.3, 141.6, 128.8, 127.9, 127.0, 119.0, 111.6, 68.8, 42.8, 33.4, 21.0, 20.9; MS (EI, 70 eV) *m/z* (%) 333.9 ($[M]^+$, 11), 331.9 ($[M]^+$, 34), 274.0 (33), 272.0 (100), 222.9 (99), 165.1 (17), 151.2 (13), 28.0 (25). Elemental analysis calcd for $C_{19}H_{21}O_3Cl$: C 68.56, H 6.36. Found: C 68.90, H 5.80.

Isobutyl 4-(2-Chloroethyl)-1-hydroxy-5-methyl-3-phenyl-2-carboxylate (3w). Starting with **2c** (0.376 g, 2.00 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (0.980 g, 3.00 mmol), and $TiCl_4$ (0.44 mL, 4.00 mmol), **3w** was isolated (0.509 g, 73%) as a colorless solid; mp 74−75 °C; R_f 0.63 (hexane/ethyl acetate = 4:1); IR (KBr) $\tilde{\nu}$ 2980 (m), 1651 (s), 1598 (m), 1465 (m), 1244 (s), 755 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.04 (s, 1 H, OH), 7.38−7.32 (m, 3 H, ArH), 7.19−7.08 (m, 2 H, ArH), 6.89 (s, 1 H, ArH), 3.62 (d, 2 H, $J = 6.9$ Hz, OCH_2), 3.28−3.22 (m, 2 H, CH_2), 2.75−2.69 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 1.24−1.17 (m, 1 H, CH), 0.60 (d, 6 H, $J =$ 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 160.6, 144.7, 144.2, 141.4, 128.5, 128.3, 128.0, 127.1, 119.1, 71.8, 42.8, 33.4, 20.9, 19.3, 19.0; MS (EI, 70 eV) *m/z* (%) 348.0 ($[M]^+$, 10), 346.1 ($[M]^+$, 34), 274.0 (34), 272.0 (100), 222.9 (93), 210.0 (78), 104.6 (34), 28.0 (78). Elemental analysis calcd for $C_{19}H_{21}O_3Cl$: C 69.25, H 6.68. Found: C 69.72, H 6.45.

Ethyl 4-(2-Chloroethyl)-1-hydroxy-3-methyl-2-benzoate (3x). Starting with **2d** (0.100 g, 0.89 mmol), 1-ethoxy-1,3-bis-(trimethylsilyloxy)buta-1,3-diene (0.366 g, 1.33 mmol), and $TiCl_4$ (0.20 mL, 1.80 mmol), **3x** was obtained (0.090 g, 42%) as a colorless solid; mp 43−44 °C; IR (KBr) $\tilde{\nu}$ 2963 (m), 1727 (w), 1661 (s), 1598 (m), 1471 (m), 1221 (s), 839 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.26 (s, 1H, OH), 7.22 (d, 1 H, $J =$ 8.7 Hz, ArH), 6.81 (d, 1 H, $J = 9$ Hz, ArH), 4.46 (q, 2 H, $J =$ 7.2 Hz, OCH_2), 3.60 (t, 2 H $J = 6.9$ Hz, CH_2 Cl), 3.06 (t, 2 H, $J = 7.8$ Hz, CH_2), 2.49 (s, 3 H, CH_3), 1.43 (t, 3 H, $J = 6.3$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 160.9, 138.6, 136.1, 128.2, 115.4, 114.0, 61.2, 43.8, 37.1, 18.4, 14.2; MS (EI, 70 eV) *m/z* (%) 244.1 ($[M]^+$, 6), 242.0 ($[M]^+$, 20), 198 (26), 196.0 (76), 146.5 (100), 91.0 (11), 43.1 (3.5), 28.0 (35.8). Elemental analysis calcd for $C_{12}H_{15}O_3Cl$: C 59.50, H 6.96. Found: C 58.90, H 7.39.

Ethyl 4-(2-Chloroethyl)-6-ethyl-1-hydroxy-3-methyl-2-benzoate (3y). Starting with **2d** (0.150 g, 1.33 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)hexa-1,3-diene (0.607 mg, 2.00 mmol), and $TiCl_4$ (0.290 mL, 2.66 mmol), **3y** was obtained (0.903 g, 33%) as a colorless oil; IR (neat) $\tilde{\nu}$ 2968 (m), 1728 (w), 1656 (s), 1614 (w), 1448 (m), 1283 (m), 1187 (s), 807 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.98 (s, 1 H, OH), 7.10 (s, 1 H, ArH), 4.43 (q, 2 H, $J = 7.2$ Hz, OCH_2), 3.59 (t, 2 H, $J =$ 7.2 Hz, CH_2Cl), 3.04 (t, 2 H, $J = 7.5$ Hz, CH_2), 2.64 (q, 2 H, J = 7.5 Hz, CH_2), 2.45 (s, 3 H, CH_3), 1.42 (t, 3 H, $J = 7.2$ Hz, CH_3), 1.20 (t, 3 H, $J = 7.5$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.9, 135.6, 135.5, 130.0, 127.4, 113.4, 61.7, 43.9, 37.2, 22.9, 18.2, 14.2, 13.8; MS (EI, 70 eV) *m/z* (%) 272.0 ($[M]^+$, 9), 270.0 ($[M]^+$, 26), 225.9 (33), 223.9 (100), 195.9 (82), 175.0 (40), 91(18), 77(8), 28.0 (35). Elemental analysis calcd for $C_{14}H_{19}O_3Cl$: C 62.22, H 7.00. Found: C 62.33, H 6.96.

Methyl 4-(2-Bromoethyl)-1-hydroxy-3,5-dimethyl-2-benzoate (3z). Starting with **2a** (0.136 g, 1.08 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**2b**) (0.420 g, 1.61 mmol), **3z** was obtained (0.215 g, 82%) as a colorless solid; mp 73−74 °C; IR (KBr) $\tilde{\nu}$ 2950 (m), 1721 (w), 1656 (s), 1599 (m), 1574 (m), 1436 (s), 1355 (s), 1237 (s), 1071 (m), 805 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.69 (s, 1 H, OH), 6.69 (s, 1 H, ArH), 3.95 (s, 3 H, OCH_3), 3.35−3.29 (m, 2 H, CH_2), 3.19−3.15 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 160.3, 144.0, 138.8, 128.2, 117.3, 111.8, 52.2, 33.3, 29.7, 20.9, 18.5; MS (EI, 70 eV) *m/z* (%) 288.0 ($[M]^+$, 24), 286.0 ($[M]^+$, 26), 256.0 (63), 254.0 (62), 207.0 (62), 193.0 (23), 175.0 (31), 161.0 (100), 77.0 (12). Elemental analysis calcd for $C_{12}H_{15}O_3Br$ (287.15): C 50.13, H 5.26. Found: C 50.29, H 5.43.

Ethyl 4-(2-Bromoethyl)-6-butyl-1-hydroxy-3,5-dimethyl-2-benzoate (3aa). Starting with **2a** (0.252 g, 2.00 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)octa-1,3-diene (0.990 g, 3.00 mmol), and $TiBr_4$ (1.500 g, 4.00 mmol), **3aa** was isolated (0.308 g, 43%) as a colorless oil; IR (neat) $\tilde{\nu}$ 2959 (s), 1715 (m), 1653 (s), 1598 (s), 1567 (m), 1451 (m), 1193 (s), 1031 (m), 850 (m); ^1H NMR (300 MHz, $CDCl_3$) δ 10.91 (s, 1 H, OH), 4.42 (q, 2 H, $J = 7.2$ Hz, OCH_2), 3.34−3.30 (m, 2 H, CH_2), 3.23−3.20 (m, 2 H, CH_2), 2.70−2.63 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 1.46−1.25 (m, 7 H, 1 × CH_3, 2 × CH_2), 0.96−0.87 (m, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 258.3, 141.5, 135.5, 128.0, 111.7, 61.6, 34.1, 31.3, 29.9, 26.4, 23.1, 18.6, 16.4, 14.2, 14.0; MS (EI, 70 eV) *m/z* (%) 358.5 ($M^+ + 2$, 21), 354.5 (M^+, 21), 312.3 (33), 310.3 (33), 270.3 (42), 268.3 (44), 231.3 (47), 189.2 (44), 91.1 (47), 73.7 (55), 41.2 (44), 29.1 (100); UV−vis λ_{max} (log ϵ) 222 (4.3), 255 (3.82), 320 (3.44); $C_{17}H_{25}O_3Br$.

Ethyl 4-(2-Bromoethyl)-6-hexyl-1-hydroxy-3,5-dimethyl-2-benzoate (3ab). Starting with **2a** (0.380 g, 3.00 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)deca-1,3-diene (1.730 g, 4.5 mmol), and $TiBr_4$ (2.210 g, 6.00 mmol), **3ab** was isolated (0.520

g, 45%) as a colorless oil; IR (neat) $\tilde{\nu}$ 2927 (s), 1715 (s), 1654 (s), 1597 (m), 1460 (m), 1193 (s), 1031 (m), 848 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.91 (s, 1 H, OH), 4.46 (q, 2 H, J = 7.2 Hz, OCH_2), 3.36−3.30 (m, 2 H, CH_2), 3.23−3.19 (m, 2 H, CH_2), 2.69−2.64 (m, 2 H, CH_2), 2.47 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 1.39 (t, 3 H, J = 7.2 Hz, CH_3), 1.34−1.21 (m, 8 H, CH_2), 0.91−0.88 (m, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 258.2, 141.4, 135.5, 128.0, 127.9, 111.7, 61.6, 34.1, 31.7, 29.9, 29.7, 29.1, 26.7, 22.6, 18.6, 16.3, 14.2, 14.1; MS (EI, 70 eV) *m/z* (%) 386.0 (M^+ + 2, 3), 384.0 (M^+, 3), 340.0 (4), 337.9 (4), 269.9 (10), 268 (10), 189.0 (10), 161.0 (10), 73.7 (10), 43.1 (14), 28.0 (100); UV−vis λ_{max} (log ϵ) 222 (4.3), 255 (3.73), 320 (3.29); $C_{19}H_{29}O_3Br$.

Crystal Structure Determination of 3w. The intensity data for the compound were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo Kα radiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects.[14,15] The structures were solved by direct methods (SHELXS)[16] and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97).[17] For the hydroxy group O1 the hydrogen atom was located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[17] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal Data for 3w: $C_{20}H_{23}ClO_3$, M_r = 346.83 g mol^{-1}, colorless prism, size 0.03 × 0.03 × 0.02 mm^3, monoclinic, space group $P2_1/n$, a = 8.8561(2) Å, b = 12.9712(3) Å, c = 15.8805(4) Å, β = 104.172(1)°, V = 1768.74(7) Å^3, T = −90 °C, Z = 4, $\rho_{calc.}$ = 1.302 g cm^{-3}, μ(Mo Kα) = 2.31 cm^{-1}, F(000) = 736, 6834 reflections in h (−11/11), k (−16/15), l (−20/20), measured in the range 2.42° ≤ Θ ≤ 27.48°, completeness Θ_{max} = 99.6%, 4050 independent reflections, R_{int} = 0.019, 3299 reflections with $F_o > 4\sigma(F_o)$, 221 parameters, 0 restraints, $R1_{obs}$ = 0.037, $wR2_{obs}$ = 0.090, $R1_{all}$ = 0.050, $wR2_{all}$ = 0.097, GOOF = 1.025, largest difference peak and hole 0.236/−0.268 e Å^{-3}.

Synthesis of 3-(2-Chloroethyl)pentane-2,4-dione (4). To a CH_2Cl_2 solution (100 mL) of **2a** (0.151 g, 1.2 mmol) was added dropwise $TiCl_4$ (0.13 mL, 1.2 mmol) at −78 °C under argon atmosphere. The reaction mixture was allowed to warm to 20 °C over 12 h and was stirred for an additional 6 h at 20 °C. The mixture was poured into an aqueous solution of HCl (1.0 M, 100 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1:4 → 1:1) to give **4** (0.086 g, 47%) as a colorless oil; IR (KBr) ν 3429 (br), 1725 (w), 1702 (m), 1605 (s), 1421 (s), 1284 (m), 985 (m), 688 (w) cm^{-1}; major isomer (enol from) ^{1}H NMR (300 MHz, $CDCl_3$) δ 16.88 (s, 1 H, OH), 3.49 (t, 2 H, J = 8.1 Hz, CH_2Cl), 2.73 (t, 2 H, J = 7.8 Hz, CH_2), 2.18 (s, 6 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 106.8, 43.3, 31.1, 23.1; minor isomer (keto form) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (t, 1 H, J = 7.2 Hz, CH), 3.53 (t, 2 H, J = 7.5 Hz, CH_2Cl), 2.28 (q, 2 H, J = 7.2 Hz, CH_2), 2.24 (s, 6 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 64.8, 42.6, 31.3, 29.6; MS (EI, 70 eV) *m/z* (%) 164.0 (M^+, 7), 162.0 (M^+, 21), 148.3 (5), 146.5 (15), 227.2 (16), 112.1 (99), 70.0 (20), 43.1 (100). The exact molecular mass for $C_7H_{11}O_2Cl$ (*m/z* 162.0448 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Synthesis of Isopropyl 8-Hydroxy-4,8-dimethyl-6-oxospiro[5.2]oct-4-ene-5-carboxylate (5). A CH_2Cl_2 solution (1 mL) of $TiCl_4$ (0.03 mL, 0.3 mmol) was added dropwise at −78 °C under argon atmosphere to a stirred CH_2Cl_2 solution (100 mL) of **2a** (0.131 g, 1.0 mmol) and **1b** (0.450 g, 1.6 mmol) in the presence of molecular sieves (4 Å, 1.0 g). The reaction mixture was allowed to warm to 20 °C over 6 h, stirred for an additional 6 h at 20 °C, and subsequently filtered. The filtrate was poured into an aqueous solution of HCl (1.0 M, 100 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 4:1→1:1) to give **5** (0.125 g, 48%) as a colorless oil; R_f 0.18 (hexane/EtOAc = 1:1); IR (neat) ν 3399 (br), 2983 (w), 1729 (s), 1659 (s), 1617 (m), 1380 (m), 1243 (s), 1024 (m), 745 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (sept, 1 H, J = 6.3 Hz, CH), 2.71 (d, 1 H, J = 15.6 Hz, CH_2), 2.59 (d, 1 H, J = 15.6 Hz, CH_2), 2.40 (br, 1 H, OH), 1.68 (s, 3 H, CH_3), 1.49−1.37 (m, 1 H, CH_2), 1.30 (d, 6 H, J = 6.3 Hz, CH_3), 1.26 (s, 3 H, CH_3), 1.15−1.04 (m, 2 H, CH_2), 0.88−0.81 (m, 1 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 166.8, 160.5, 133.2, 70.5, 69.0, 51.5, 32.1, 25.4, 21.7, 16.7, 10.8, 9.5; MS (EI, 70 eV) *m/z* (%) 252.2 (M^+, 40), 237.1 (13), 193.1 (65), 177.1 (41), 164.1 (47), 148.1 (100), 91.1 (17), 43.1 (78); the exact molecular mass for $C_{14}H_{20}O_4$ (*m/z* 252.1362 ± 2 mD) was confirmed by HRMS (EI, 70 eV).

Procedure for the Preparation of 3b from 5. A CH_2Cl_2 solution (1 mL) of $TiCl_4$ (0.06 mL, 0.5 mmol) was added dropwise at 0 °C to a CH_2Cl_2 solution (20 mL) of **5** (0.126 g, 0.5 mmol) and the solution was stirred for 1 h (TLC monitoring). The reaction mixture was extracted with an aqueous solution of HCl (1.0 M, 20 mL) and the aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica, hexane/EtOAc = 9:1→ 4:1) to give **3b** (0.072 g, 53%) as a colorless solid.

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Supporting Information Available: Details of the crystal structure analysis of **3w**. This material is available free of charge via the Internet at http://pubs.acs.org.

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