Synthons for Polyketides: An Improved Synthesis of Methyl 3,3-Dialkoxy-2-methylpropanoates

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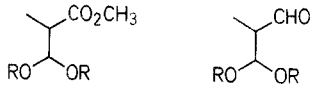
A versatile conversion of methyl methacrylate to methyl 3,3-dialkoxy-2-methylpropanoates proceeds *via* bromination, then treatment with excess sodium methoxide to yield methyl 3,3-dimethoxy-2-methylpropanoate, which can be transacetalized by treatment with alcohols under acid catalysis to yield the title compounds. Stereoselective chain-extension reactions of these compounds by aldol additions to the aldehydes derived from the ester group (C-1), or by titanium(IV)-mediated allylsilane additions to the acetal carbon (C-3), are examples of the potential utility of methyl 3,3-dialkoxy-2-methylpropanoates to natural products syntheses.

Our involvement in the total syntheses of the polyacetate tumor promotors has led us to the realization that methyl 3,3-dialkoxy-2-methylpropanoates (**1**) may be useful starting materials for the syntheses of such polyketide (polyacetate/polypropanoate) natural products, because the different functional groups at C-1 and C-3 in **1** invite selective chain-extension reactions to form acyclic polyhydroxy carbon chains typical for these natural products. The esters **1** have been used for the syntheses of coumarins,[1] and the related aldehydes **2** have been found to undergo stereoselective reactions with Grignard[2] and allylchromium[3] reagents.

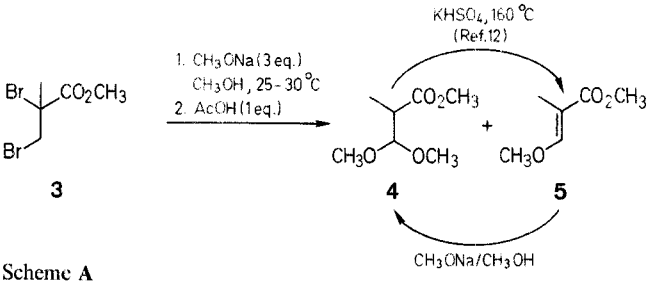


1 **2**

To our knowledge, no other applications of compounds **1** and **2** to natural products syntheses have been reported.[4] This may be due to the as-yet limited accessibility of synthons **1** and **2**, and a paucity of knowledge about their reactivities toward nucleophiles and other reagents. In this paper we discuss a practical general synthesis of methyl 3,3-dialkoxy-2-methylpropanoates (**1**) from methyl methacrylate and results which demonstrate the feasibility of using chain-extension reactions to elaborate C-1 or C-3 of **1** with moderate stereoselectivity.

Esters of 3,3-dialkoxy-2-methylpropanoic acid have been synthesized in the past by a zinc-mediated reaction between alkyl 2-bromopropanoates and triethyl orthoformate,[5] by an oxypalladation/reductive elimination/1,4-addition reaction between diols and methacrylates,[6] and by an electrochemical oxidation of 3-amido-2-methylpropanoates.[7,8] Only one direct synthesis of a 3,3-dialkoxy-2-methylpropanal (**2**) [a 5-step sequence starting with methacrolein] has been reported.[9,10,11]

We decided that the reported[12] conversion of methyl 2,3-dibromo-2-methylpropanoate (**3**) to methyl 3,3-dimethoxy-2-methylpropanoate (**4**) by reaction with excess sodium methoxide (Scheme **A**) deserved reinvestigation as a general method for synthesizing esters **1** because of the simplicity of the procedure and the low cost of the required reagents. Until now, a detailed procedure for the conversion **3** → **4** has not been reported. We have found, after much experimentation, that an optimized yield of the water soluble ester **4** can be obtained by adding a 4 molar solution of 3 equivalents of sodium methoxide in methanol to 1 equivalent of the dibromoester **3** (obtained by neat bromination of methyl methacrylate) followed by a non-aqueous work-up consisting of the careful addition of 1 equivalent of glacial acetic acid, concentration, dilution with ether, filtration, and distillation. The distilled product, obtained in 75–80% yield, consists of 11–12% (molar) of methyl 3-methoxy-2-methylpropenoate (**5**).

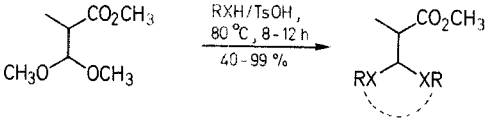


3 **4** **5**

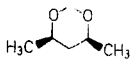
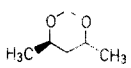
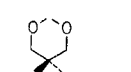
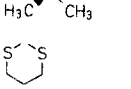
Scheme **A**

Attempts to diminish the amount of **5** co-occurring with **4** by varying the number of equivalents of sodium methoxide used, the reaction temperature, the alkali metal counterion, or the solvent were all fruitless. The dimethoxy ester **4** could be converted to **5** by treatment with catalytic potassium hydrogen sulfate at 160 °C,[12] and treatment of **5** with excess methanolic sodium methoxide yielded **4** contaminated with less than 5% (molar) of **5** (Scheme **A**). Thus, the relatively pure ester **4** can be obtained. However, the distilled **4**/**5** mixture initially obtained according to Lit.[12] was routinely used as discussed below without further enrichment in **4**.

Attempts to form a series of methyl 3,3-dialkoxy-2-methylpropanoates (**1**) by reacting the dibromoester **3** with various alkoxide salts gave low yields of the dialkoxyesters. However, when the neat ester **4** was stirred overnight with an alcohol or a diol at 80 °C in the presence of *p*-toluenesulfonic acid, methyl 3,3-dialkoxy-2-methylpropanoates were formed in high yields, as shown in Scheme **B**.[11,14]

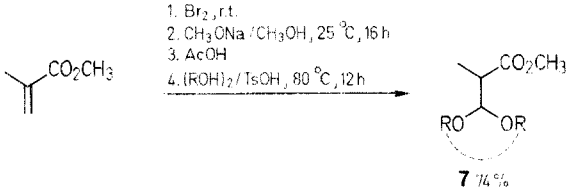


4 **6-12**

Product	$(RX)_2$	Product	RX or $(RX)_2$
6		10	
7		11	
8		12	
9			

Scheme **B**

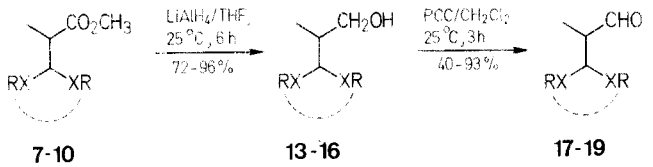
We have found that these esters can be effectively synthesized as the sole products from a "one-pot" sequential treatment of methyl methacrylate with bromine, sodium methoxide, glacial acetic acid, and an alcohol. Scheme **C** lists some representative results.

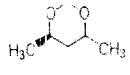
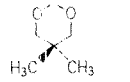
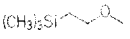


Scheme **C**

This streamlined procedure for converting methyl methacrylate to methyl 3,3-dialkoxy-2-methylpropanoates is general with respect to any alcohols used to form the 3,3-dialkoxy moiety. Other α-substituted acrylic acid derivatives (e.g., methacrylonitrile) appear to undergo this reaction as readily as methyl methacrylate.

With the exception of the dithioacetals **9** and **11**,[15] the esters **1** can undergo a facile reduction using lithium tetrahydridoaluminate to form 3,3-dialkoxy-2-methylpropanols which can then undergo oxidation with pyridinium chlorochromate to yield 3,3-dialkoxy-2-methylpropanals (**2**) in good yields.[16] Scheme **D** indicates some representative examples.[11] Thus, our one-pot synthesis of esters **1** provides a readily available source of aldehydes **2** for use in organic syntheses.



	(RX)$_2$		RX or (RX)$_2$
7, 13, 17		9, 15	
8, 14, 18		10, 16, 19	

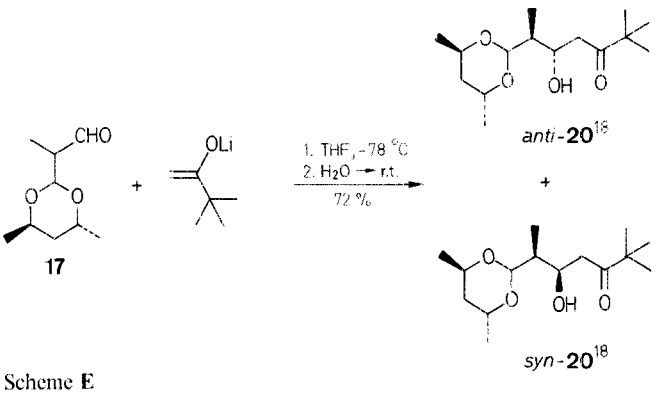
PCC = pyridinium chlorochromate

Scheme **D**

To demonstrate the potential utility of methyl 3,3-dialkoxy-2-methylpropanoates in organic syntheses, the aldehyde **17** derived from the ester **7** was reacted with the lithium enolate of pinacolone as shown in Scheme **E**.[17] Aqueous work-up gave the aldol **20** in 72% yield as a 72:28 mixture of diastereoisomers according to ^{1}H-NMR analysis.[18]

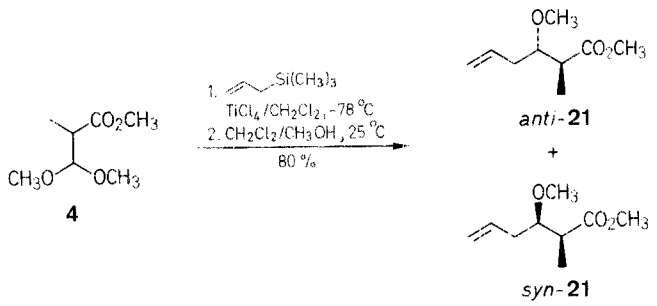
Based on previous observations of selectivity for the *anti* diastereoisomer in the additions of lithium enolates to β-alkoxyaldehydes,[19] we have assumed that the major diastereoisomer of **20** from our aldol addition has the *anti* configuration. The aldehydes **18** and **19** were also observed to undergo aldol addition reactions with comparable diastereoselectivity.

To demonstrate chain-extension reactions of the esters **1** at C-3, the ester **4** was allowed to react with allyltrimethylsilane in the



Scheme **E**

presence of titanium(IV) chloride,[20] as shown in Scheme **F**, to afford the β-methoxyester **21** in 80% yield as a 60:40 *anti*/*syn* mixture, according to the ^{1}H-NMR spectrum of the product mixture.[21] This reaction apparently proceeds *via* a direct displacement of one of the acetal methoxy groups and not via an allylation of the acrylate **5** (which could be conceived to be an intermediate formed by an initial elimination step) because the acrylate **5**, when subjected to these allylation conditions, did not react to form any of the ester **21** (instead, **5** decomposed during the protic work-up of the reaction mixture).



Scheme **F**

The stereochemical outcome of the allylation of the dimethyl acetal **4** can be explained by a chelation-controlled addition of the allyl moiety to the acetal center. That is, one of the ester *O*-atoms and one of the acetal *O*-atoms coordinate to the titanium to form a cyclic complex which then undergoes an electrophilic addition to allyltrimethylsilane in a manner similar to what has been implied for the Lewis acid-mediated allylations of β-alkoxyaldehydes.[22] However, we have observed a selectivity for the *syn* diastereomer from the allylations of other methyl 3,3-dialkoxy-2-methylpropanoates (70:30 *syn*/*anti* from **6**; 73:27 *syn*/*anti* from **10**[23]), and this suggests that esters **1** having relatively bulky alkoxy groups at the acetal center may have a tendency to undergo allylation via a non-chelation controlled ("Cram's rule") mechanism. A "Cram's rule" selectivity (*syn*) has been observed for the allylations of α-methyl acetals derived from 2,4-pentanediol (cf. **7**).[24] However, when the ester **7** was subjected to the Ti(IV)-mediated allylation, a 65:35 *anti*/*syn*[23] mixture of allylated products was obtained, possibly because the two diastereoisomers of **7** [which are epimeric at C-2 (see Table 1, footnotes h and i) and thus different in their steric environments around C-3] react with different diastereoselectivities.

Studies aimed at better defining explanations for our observations concerning the Lewis acid-mediated allylations of methyl 3,3-dialkoxy-2-methylpropanoates and utilizations of these synthons in natural products syntheses are currently underway.

Table 1. Transacetalization of Methyl 3,3-Dimethoxy-2-methylpropanoate (**4**) to Methyl 3,3-Dialkoxy-2-methylpropanoates (**6–12**)

Product	Yield[a] (%)	b.p. (°C)/torr[b]	Molecular Formula[c]	MS (70 eV)[f] *m/e* (%)	IR (NaCl)[d] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ (ppm)
6	99	–	$C_{10}H_{18}O_4$ (202.2)	202 (M^+, 1); 171 (3); 142 (4); 115 (100)	1740	4.70 (d, 1H, J = 7 Hz); 4.10 (m, 2H); 3.70 (s, 3H); 2.69 (quin, 1H, J = 7 Hz); 1.45 (m, 2H); 1.20 (d, 9H, J = 7 Hz)
7[g]	99	74–77/2.5	$C_{10}H_{18}O_4$[h] (202.2)	identical to mass spectrum of **6**	1740	5.00, 4.90 (d, 1H, J = 7 Hz)[i]; 4.10 (m, 2H); 3.70 (s, 3H); 2.69 (quin, 1H, J = 7 Hz); 1.45 (m, 2H); 1.20 (d, 9H, J = 7 Hz)
8	63	67–69/1.0	$C_{10}H_{18}O_4$ (202.2)	202 (M^+, 0.5); 187 (22); 171 (1); 142 (4); 115 (100)	1748	4.62 (d, 1H, J = 7 Hz); 3.72 (s, 3H); 3.58 (d, 2H, J = 7 Hz); 3.42 (d, 2H, J = 4 Hz); 2.82 (quin, 1H, J = 7 Hz); 1.20 (s, 3H); 1.18 (d, 3H, J = 7 Hz); 0.80 (s, 3H)
9	83	–	$C_8H_{14}O_2S_2$[j] (206.2)	208/206 [M^+ + 2(1)/M^+ (13)]; 175 (1); 147 (3); 121 (9); 119 (100)	1737	4.20 (d, 1H, J = 7 Hz); 3.83 (s, 3H); 3.22 (quin, 1H, J = 7 Hz); 2.95 (m, 4H); 2.10 (m, 2H); 1.41 (d, 3H, J = 7 Hz)
10	40	–	$C_{15}H_{34}O_4Si_2$[j] (334.6)	291 (1); 247 (0.3); 217 (1); 191 (59); 145 (33); 133 (40); 101 (60); 73 (100)	1736	4.60 (d, 1H, J = 7 Hz); 3.60 (s, 3H); 3.58 (t, 2H, J = 7 Hz); 2.71 (quin, 1H, J = 7 Hz); 1.15 (d, 3H, J = 7 Hz); 0.86 (t, 2H, J = 7 Hz); 0.12 (s, 9H)
11	68	–	$C_7H_{12}O_2S_2$ (192.1)	194/192 [M^+ + 2(2)/M^+ (16)]; 177 (1); 161 (2); 105 (100)	1732	4.78 (d, 1H, J = 7 Hz); 3.80 (s, 3H); 3.72 (s, 4H); 2.69 (quin, 1H, J = 7 Hz); 1.38 (d, 3H, J = 7 Hz)
12	57	60–64/1.0	$C_7H_{12}O_4$ (160.2)	159 (M^+ – 1, 1); 145 (1); 129 (4); 73 (100)	1737	5.08 (d, 1H, J = 6 Hz); 3.90 (br. s, 4H); 3.70 (s, 3H); 2.70 (quin, 1H, J = 6 Hz); 1.20 (d, 3H, J = 6 Hz)

[a] Yield of purified products.
[b] Determined during distillation.
[c] Unless otherwise indicated, satisfactory microanalyses were obtained: C ±0.25, H ±0.25.
[d] Recorded on a Nicolet MX-S spectrophotometer.
[e] Obtained on a Varian EM-360 or a Varian XL-100 spectrometer.
[f] Recorded on a Hewlett-Packard 5995 spectrometer.
[g] See reference 11.
[h] Obtained from *dl*-2,4-pentanediol. Capillary GLC indicates a 50 : 50 mixture of two diastereoisomers, presumably epimeric at C-2.
[i] These two signals correspond to the two diastereoisomers of **7** which are epimeric at C-2. No other signals in the NMR spectrum of **7** indicate this stereoisomerism.
[j] A satisfactory analysis could not be obtained for this ester; see Table 2 for a satisfactory analysis of the alcohol derivative.

Table 2. Reduction of Methyl 3,3-Dialkoxy-2-methylpropanoates (**7–10**) to 3,3-Dialkoxy-2-methylpropanols (**13–16**)

Product	Yield[a] (%)	Molecular Formula	MS (70 eV)[d] *m/e* (%)	IR (NaCl)[b] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[c] δ (ppm)
13	96	$C_9H_{18}O_3$[e] (174.2)	174 (M^+, 1); 141 (1); 115 (99); 45 (100)	3464, 1462	4.83 (d, 1H, J = 6 Hz); 4.25 (sext, 1H, J = 6 Hz); 4.00 (br. m, 1H); 3.60 (br. t, 2H, J = 6 Hz); 3.15 (br. s, 1H, D_2O-exchangeable); 1.86 (m, 3H); 1.36 (d, 3H, J = 7 Hz); 1.20 (d, 3H, J = 7 Hz); 0.90 (d, 3H, J = 7 Hz)
14	72	$C_9H_{18}O_3$ (174.2)	174 (M^+, 1); 157 (1); 141 (3); 115 (100); 56 (100)	3412, 1470	4.45 (d, 1H, J = 4 Hz); 1.60 (m, 6H); 3.08 (br. s, 1H, D_2O-exchangeable); 1.98 (m, 1H); 1.22 (s, 3H); 1.98 (d, 3H, J = 7 Hz); 1.78 (s, 3H)
15	94	$C_7H_{14}OS_2$[f] (178.2)	178 (M^+, 45); 160 (1); 147 (8); 119 (100)	3400, 1418	4.32 (d, 1H, J = 5 Hz); 3.65 (d, 2H, J = 6 Hz); 2.85 (m, 5H, includes D_2O-exchangeable signal); 2.05 (m, 3H); 1.08 (d, 3H, J = 7 Hz)
16	82	$C_{14}H_{34}O_3Si_2$[g] (306.4)	193 (6); 191 (64); 161 (18); 147 (42); 115 (59); 73 (100)	3440, 1421	4.38 (d, 1H, J = 6 Hz); 3.60 (m, 6H); 2.00 (septet, 1H, J = 6 Hz); 0.95 (m, 4H); 0.90 (d, 3H, J = 6 Hz); 0.05 (s, 18H)

[a] Yield of products purified by chromatography; in each case the alcohol was a viscous high-boiling oil.
[b] Recorded on a Nicolet MX-S spectrophotometer.
[c] Obtained using a Varian EM-360 spectrometer.
[d] Recorded on a Hewlett-Packard 5995 spectrometer.
[e] The two diastereoisomers of this alcohol derivative of **7** (see Table 1, footnotes h and i) could not be distinguished by capillary GLC nor by 60 MHz NMR spectroscopy.
[f] Satisfactory analysis was obtained for this alcohol derivative of the ester **9**: C ±0.21, H ±0.23.
[g] Satisfactory analysis was obtained for this alcohol derivative of the ester **10**: C ±0.30, H +0.25.

Methyl 3,3-Dimethoxy-2-methylpropanoate (4):
Sodium metal (7.2 g, 0.32 mol) is added piecewise to absolute methanol (80 ml) which is stirred under a calcium chloride-filled drying tube. The resulting solution of sodium methoxide is then transferred to an addition funnel and added dropwise to methyl 2,3-dibromo-2-methylpropanoate[25] (**3**; 27.3 g, 0.105 mol). The temperature of the mixture is maintained at 25–30 °C during this addition by cooling the reaction vessel in an ice-water bath. The resulting white suspension is stirred at 25 °C under the drying tube for 16 h, then glacial acetic acid (6.5 ml, 0.114 mol) is added dropwise. The mixture is concentrated using a rotary evaporator to a volume of ~ 25 ml, the milky suspension is diluted with anhydrous diethyl ether (50 ml) and filtered through a 2 cm pad of Celite 545, and the filter pad is washed with ether (100 ml). The combined filtrates are concentrated using a rotary evaporator to a clear liquid which is distilled in vacuum to give an 89:11 (molar) mixture of the ester **4** and the ester **5**; b.p. 45–46 °C (3.0 torr) (b.p. of **4** not given in the literature; Lit.[12], b.p. of **5**: 180 °C/760 torr).

MS (70 eV) of **4**: m/e = 131 (M^+-OCH_3, 8%), 75 (100).

^{1}H-NMR ($CDCl_3$) of **4**: δ = 4.48 (d, 1 H, J = 7 Hz); 3.71 (s, 3 H); 3.40 (s, 6 H); 2.75 (quin, 1 H, J = 7 Hz); 1.12 ppm (d, 3 H, J = 7 Hz).

IR (NaCl) of **5**: ν = 2957, 1740 cm^{-1}.

^{1}H-NMR of **5**: δ = 7.25 (m, 1 H); 3.80 (s, 3 H); 1.68 ppm (br.s, 3 H).

Methyl 3,3-Dialkoxy-2-methylpropanoates (6–12) by Transacetalization of the Ester 4; General Procedure:
Methyl 3,3-dimethoxy-2-methylpropanoate (**4**) and the alcohol (1–2 molecular equivalents) or the diol (0.5–1.0 molecular equivalent) are stirred with *p*-toluenesulfonic acid monohydrate (~ 0.01 mol equiv) in a single-necked round-bottomed flask equipped with a Dean-Stark trap, a reflux condenser, and a calcium chloride-filled drying tube. The reaction vessel is warmed to 80 °C,[26] and the evolved methanol condenses into the trap over a 12 h period. The mixture is then cooled to 25 °C and distilled under vacuum or chromatographed on 230–400 mesh silica gel[27] using 5–30% (by volume) ethyl acetate in hexane containing 1% (by volume) of triethylamine (to neutralize the silica gel and thus prevent decomposition of the esters during chromatography) to yield the pure esters **6**–**12** (Table 1).

"One-Pot" Conversion of Methyl Methacrylate to Methyl 3,3-Dialkoxy-2-methylpropanoates (7, 8, 12); General Procedure:
Methyl methacrylate (6 g, 0.06 mol) is stirred at 0 °C while bromine (9.6 g, 0.06 mol) is added at a rate which maintains the reaction temperature at 20 °C. The resulting dibromoester **3** is stirred under a calcium chloride-filled drying tube for 2 h. A 4 molar solution of sodium methoxide in methanol (45 ml, 0.18 mol) is then added dropwise and the resulting mixture is stirred under the drying tube at 25 °C for 16 h. Glacial acetic acid (3.6 ml, 0.06 mol) is then added dropwise, the solution is concentrated to a 15 ml volume, and the residue is diluted with anhydrous ether (100 ml), filtered through celite, and concentrated again. *p*-Toluenesulfonic acid monohydrate (0.1 g, 0.5 mmol) and the appropriate diol (0.03–0.06 mol) are added and the solution is stirred under a reflux condenser, a Dean-Stark trap, and a drying tube at 80 °C for 12 h. The product ester is then distilled under vacuum directly from the product mixture.

3,3-Dialkoxy-2-methylpropanols (13–16); General Procedure:
A solution of a methyl 3,3-dialkoxy-2-methylpropanoate in dry tetrahydrofuran (1.0 mmol ester/ml) is added dropwise under a dry nitrogen atmosphere to a stirring suspension of lithium tetrahydridoaluminate (0.7 mol equiv) in dry tetrahydrofuran (0.1 mmol/ml) cooled in an ice-water bath and the suspension is stirred at room temperature for 6 h. Water (0.7 mol equiv) is then carefully added, followed by 1 normal sodium hydroxide (0.7 mol equiv) and water (1.4 mol equiv), and the resulting mixture is diluted with diethyl ether and filtered through a 2 cm pad of Celite 545. Concentration of the filtrate followed by column chromatography on 230–400 mesh silica gel (70:30 hexane/ethyl acetate as eluent)[27] yields the pure alcohols **13**–**16** (Table 2).

3,3-Dialkoxy-2-methylpropanals (17–19); General Procedure:
A solution of a 3,3-dialkoxy-2-methylpropanol in dry dichloromethane (0.5 mmol/ml) is added dropwise to a stirring suspension of pyridinium chlorochromate (1.3 mol equivalents), sodium acetate (1 mol equiv), and anhydrous magnesium sulfate powder (10 mol equiv) in dry dichloromethane (20 ml/mmol of alcohol added). (The magnesium sulfate is used to adsorb the reduced chromium by-products formed during the reaction, thus easing recovery of the product). The mixture is stirred under a calcium chloride-filled drying tube at 25 °C for 6–12 h, then diluted with 3 volumes of dry diethyl ether, and filtered through a 2 cm pad of florisil. Concentration of the filtrate and chromatography on 230–400 mesh silica gel (80:20 hexane/ethyl acetate as eluent)[27] yields the pure aldehydes (Table 3). These aldehydes are unstable, and decompose upon standing even in the refrigerator to intractable polymeric material and autooxidized products.

Table 3. Oxidation of 3,3-Dialkoxy-2-methylpropanols (**13, 14, 16**) to 3,3-Dialkoxy-2-methylpropanals (**17–19**)

Product	Yield[a] (%)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ (ppm)
17	93	$C_9H_{16}O_3$[d]	9.87 (d, 1 H, J = 2 Hz); 5.08 (d, 1 H, J = 4 Hz); 4.27 (sext, 1 H, J = 6 Hz); 4.00 (m, 1 H); 2.50 (m, 1 H); 1.75 (m, 2 H); 1.35 (d, 3 H, J = 7 Hz); 1.19 (d, 3 H, J = 6 Hz); 1.10 (d, 3 H, J = 7 Hz)
18[e]	50	$C_9H_{16}O_3$	9.88 (d, 1 H, J = 2 Hz); 4.70 (d, 1 H, J = 4 Hz); 3.65 (d, 2 H, J = 14 Hz); 3.48 (d, 2 H, J = 14 Hz); 2.62 (m, 1 H); 1.20 (s, 3 H); 1.17 (d, 3 H, J = 7 Hz); 0.72 (s, 3 H)
19	40	$C_{14}H_{32}O_3Si_2$	9.80 (d, 1 H, J = 2 Hz); 4.60 (d, 1 H, J = 5 Hz); 3.60 (m, 4 H); 2.58 (m, 1 H); 1.18 (d, 3 H, J = 7 Hz); 0.90 (m, 4 H); 0.05 (s, 18 H)

[a] Yield of purified products (see note b).
[b] Due to the instability of these aldehydes, losses occurred during purification, and satisfactory analytical data could not be obtained.
[c] Obtained using a Varian EM-360 spectrometer.
[d] The two diastereomers of this derivative of the ester **7** (see Table 1, footnotes h and i) could not be distinguished by capillary GLC nor by 60 MHz NMR spectroscopy.
[e] See reference 11.

6-(4,6-Dimethyl-1,3-dioxan-2-yl)-5-hydroxy-2,2-dimethyl-3-heptanone (20):
A solution of freshly-distilled diisopropylamine (0.06 ml, 0.43 mmol) in dry tetrahydrofuran (5 ml) is stirred under a nitrogen atmosphere at −78 °C, and a 1.6 molar solution of butyllithium in hexane (0.26 ml, 0.42 mmol) is added dropwise. A solution of pinacolone (0.05 ml, 0.40 mmol) in dry tetrahydrofuran (0.5 ml) is then added dropwise, and the solution is stirred at −78 °C for 10 min. A solution of the aldehyde **17** (0.047 g, 0.27 mmol) in dry tetrahydrofuran (2 ml) is added dropwise, and the solution is stirred at −78 °C for 30 min. Water (10 ml) is then added, the mixture is allowed to warm to room temperature, and the phases are separated. The aqueous phase is extracted with ether (3 × 20 ml), and the combined organic phases are washed with saturated sodium chloride solution (20 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuum*. The resulting crude product is chromatographed on 230–400 mesh silica gel (80:20 hexane/ethyl acetate as eluent)[27] to give the pure product **20** as a mixture of diastereoisomers discernable by ^{1}H-NMR spectroscopy;[18] yield: 0.053 g (72%).

$C_{15}H_{28}O_4$	calc.	C 66.14	H 10.36
(272.4)	found	65.94	10.61

MS (70 eV): Major *(anti)* diastereomer: m/e = 197 (M^+-*t*-C_4H_9-H_2O, 1%), 157 (loss of dioxanyl radical, 4), 129 (2), 115 (49), 85 (13), 57 (98), 41 (100); Minor *(syn)* diastereomer: m/e = 157 (2%), 129 (1), 115 (43), 85 (11), 57 (76), 41 (100).

IR (NaCl): ν = 3520, 1709 cm^{-1}.

^{1}H-NMR ($CDCl_3$): Major *(anti)* diastereomer: δ = 4.94 (d, 1 H, J = 4 Hz); 4.20 (m, 3 H); 2.70 (d of d, 2 H); 1.70 (m, 2 H); 1.36 (d, 3 H, J = 7 Hz); 1.19 (d, 3 H, J = 7 Hz); 1.15 (s, 9 H); 0.92 (d, 3 H, J = 7 Hz); 0.90 (m, 1 H); Minor *(syn)* diastereomer: δ = 4.90 (d, 1 H, J = 4 Hz); 4.20 (m, 3 H); 2.61 (d of d, 2 H); 1.70 (m, 2 H); 1.36 (d, 3 H, J = 7 Hz); 1.19 (d, 3 H, J = 7 Hz); 1.15 (s, 9 H); 0.97 (d, 3 H, J = 7 Hz); 0.90 ppm (m, 1 H):

Methyl 3-Methoxy-2-methyl-5-hexenoate (21):
Titanium(IV) chloride (0.19 ml, 1.7 mmol) is added dropwise to a solution of the ester **4** (0.155 g, 0.96 mmol) and allyltrimethylsilane (0.437 g, 3.86 mmol) in dichloromethane (15 ml) which has been cooled to −78 °C and is stirring under a dry nitrogen atmosphere. The resulting reddish-orange solution is stirred at −78 °C for 20 min, then a 1:1 (by volume) methanol/dichloromethane solution (1 ml) is added and the mixture warmed to 25 °C, then partitioned between 5% aqueous hydrochloric acid (25 ml) and dichloromethane (2 × 25 ml). The combined dichloromethane extracts are dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude product is chromatographed on 230–400 mesh silica gel (80:20 hexane/ethyl acetate as eluent) to yield the pure methoxy ester **21**, which could be discerned as a mixture of diastereomers by ^{1}H-NMR spectrometry.

$C_9H_{16}O_3$ calc. C 62.77 H 9.36
(172.2) found 62.73 9.67

MS (70eV): *m/e* = 141 (M^+-OCH_3, 3%), 131 (loss of allyl radical, 40); 85 (56); 75 (100).

IR (NaCl): ν = 1734, 1637 cm^{-1}.

^{1}H-NMR ($CDCl_3$): Major *(anti)* diastereoisomer: δ = 5.75 (m, 1 H); 5.15 (m, 1 H); 5.02 (m, 1 H); 3.69 (s, 3 H); 3.57 (d of d, 1 H); 3.36 (s, 3 H); 2.63 (quin, 1 H; irradiation of doublet at 1.18 ppm changes this to doublet, J = 8 Hz); 2.29 (m, 2 H); 1.18 (d, 3 H, J = 7 Hz); Minor *(syn)* diastereoisomer: δ = 5.75 (m, 1 H); 5.02 (m, 1 H); 3.71 (s, 3 H); 3.57 (d of d, 1 H); 3.36 (s, 3 H); 2.59 (quin, 1 H; irradiation of doublet at 1.11 ppm changes this to doublet, J = 3 Hz); 2.29 (m, 2 H); 1.11 ppm (d, 3 H, J = 7 Hz).

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