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Direct Oxidative Cleavage of α- and β-Dicarbonyls and α-Hydroxyketones to Diesters with $KHSO_5$

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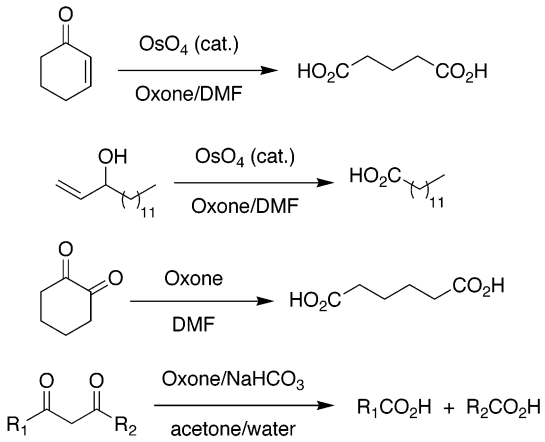
Abstract: Presented is a methodology to oxidatively cleave α-hydroxyketones and α- or β-diones using the environmentally benign reagent $KHSO_5$, prepared easily from Oxone, to diesters in one simple transformation. In addition, we undertook a mechanistic study to provide a plausible mechanistic interpretation. These reactions may prove to be valuable alternatives to other related metal-mediated processes.

Oxone is a triple salt containing two parts $KHSO_5$, one part $KHSO_4$, and one part K_2SO_4. Owing to its nontoxic "green" nature, affordability, and safety profile, Oxone has become an increasingly popular reagent for oxidative transformations such as the oxidation of aldehydes to acids or esters, oxidative removal of aryl boronic acids to phenols, and most commonly generation of DMDO for epoxidations.[1−5] Work in our laboratory has previously focused on the use of Oxone as a co-oxidant for the oxidative cleavage of olefins and the oxidation of aldehydes to acids and esters.[1,6−9] Continuing studies with the Oxone-mediated oxidative cleavage of olefins with a variety of reactants showed that neither α,β-unsaturated carbonyls nor α-hydroxyolefins provided the expected α-ketoacids or α-hydroxyacids, but instead the one-carbon-deleted carboxylic acid products were isolated. This also led to the investigation of α-diones, which cleaved under similar conditions to provide the desired diacid. Interestingly, a related study by Ashford and Grega[10] reported that β-diones could be oxidatively cleaved to the corresponding one-carbon-deleted carboxylic acid using Oxone/$NaHCO_3$/acetone/water (Scheme 1).

Oxidative cleavage of α-hydroxyketones, α-diones, and β-diones to their corresponding dicarboxylic acids is well precedented with reagents such as calcium hypochlorite, sodium percarbonate, copper perchlorate, basic peroxide, bismuth, and rhenium.[11−16] In addition, vanadium-based systems have been reported to convert α-hydroxyketones or α-diones into the corresponding methyl or ethyl esters in the presence of the appropriate alcohol.[17,18] Herein, we report a mild and efficient method that utilizes Oxone as the sole oxidant for the direct transformation of the aforementioned functional groups to yield diesters in high yields.

SCHEME 1



Oxidation of various α- or β-diones and α-hydroxyketones were performed in methanol at rt for 18 h with the purified (>95%) $KHSO_5$ (see Table 1). It should be noted that even though $KHSO_5$ was used in all the studies cited in this report, similar reactivity and yields were obtained if Oxone (triple salt containing $KHSO_5$) was utilized. As can be seen from Table 1, oxidation of α-hydroxyketones and α- and β-diones in methanol provided good to excellent yields of the desired dimethyl esters. For instance, α-hydroxyketones (entries 1 and 2) provided products in 98% and 69% yield, respectively, and cyclic α-diones (entries 3 and 4) were converted efficiently to their corresponding dimethyl esters. Cyclic and acyclic β-diones (entries 5, 8, 9, and 11) afforded the desired dimethyl esters in 78−99% yield. α-Branching did not affect the reaction (entries 6 and 10); however, the bis α-branching in the 1,3-dione **7**[19] did hinder the reaction significantly providing the tertiary hydroxyketone **7a** in a modest 65% yield. Interestingly, **7a** does not undergo further oxidation without heating, presumably due to

(1) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031−1034.
(2) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117−5118.
(3) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; Depue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391−1407.
(4) Baumstark, A. L.; Beeson, M.; Vasquez, P. C. *Tetrahedron Lett.* **1989**, *30*, 5567−5570.
(5) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311−3314.
(6) Schomaker, J. M.; Travis, B. R.; Borhan, B. *Org. Lett.* **2003**, *5*, 3089−3092.
(7) Travis, B.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 7741−7745.
(8) Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem.* **2002**, 3429−3434.
(9) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824−3825.
(10) Ashford, S. W.; Grega, K. C. *J. Org. Chem.* **2001**, *66*, 1523−1524.
(11) AbuOmar, M. M.; Espenson, J. H. *Organometallics* **1996**, *15*, 3543−3549.
(12) Coin, C.; Le Boisselier, V.; Favier, I.; Postel, M.; Dunach, E. *Eur. J. Org. Chem.* **2001**, 735−740.
(13) Yang, D. T. C.; Evans, T. T.; Yamazaki, F.; Narayanna, C.; Kabalka, G. W. *Synth. Commun.* **1993**, *23*, 1183−1187.
(14) Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 3135−3138.
(15) Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061−4066.
(16) Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089−6092.
(17) El Aakel, L.; Launay, F.; Atlamsani, A.; Bregeault, J. M. *Chem. Commun.* **2001**, 2218−2219.
(18) Kirihara, M.; Takizawa, S.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 7−8.
(19) Crispin, D. J.; Vanstone, A. E.; Whitehurst, J. S. *J. Chem. Soc.* **1970**, 10−18.

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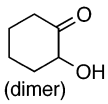
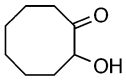
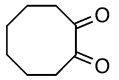
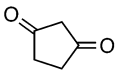
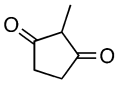
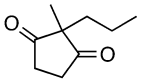
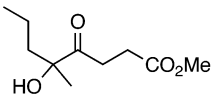
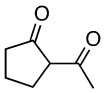
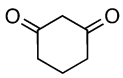
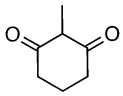
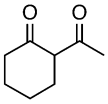
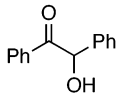
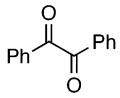
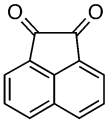
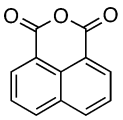
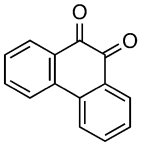
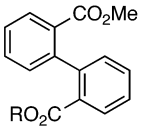
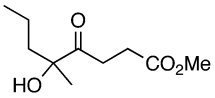
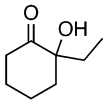
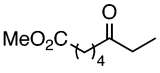
TABLE 1. Oxidative Cleavage in MeOH[a]

Entry	Substrate		Product	Yield (%)[b]
1	 (dimer)	**1**	$MeO_2C(CH_2)_4CO_2Me$	**1a** 98
2		**2**	$MeO_2C(CH_2)_6CO_2Me$	**2a** 69
3		**3**	$MeO_2C(CH_2)_4CO_2Me$	**1a** 90
4		**4**	$MeO_2C(CH_2)_6CO_2Me$	**2a** 79
5		**5**	$MeO_2C(CH_2)_2CO_2Me$	**5a** 85
6		**6**	$MeO_2C(CH_2)_2CO_2Me$	**5a** 80
7		**7**		**7a** 65
8		**8**	$MeO_2C(CH_2)_3CO_2Me$	**8a** 86
9		**9**	$MeO_2C(CH_2)_3CO_2Me$	**8a** 99
10		**10**	$MeO_2C(CH_2)_3CO_2Me$	**8a** 86
11		**11**	$MeO_2C(CH_2)_4CO_2Me$	**1a** 78
12[c]		**12**	$PhCO_2Me$	**12a** 73
13[c]		**13**	$PhCO_2Me$	**12a** 77
14		**14**		**14a** 98
15		**15**		**15a** R=Me 19 **16** R=H 64
16[c]		**7a**	$MeO_2C(CH_2)_2CO_2Me$	**5a** 54 **7a** 22
17		**17**		**18** 10 **1a** 40

[a] Substrate (1 equiv), $KHSO_5$ (4 equiv), rt, 18 h. [b] Isolated yields. [c] Reactions performed at 50 °C.

steric constraints that hinder nucleophilic attack of the oxidant at the carbonyl carbon. Heating the reaction to 50 °C, however, did initiate the oxidative cleavage, but with poor conversion leading to only 54% of the desired diester with 22% of the starting material being recovered (entry 16). The structurally related cyclic tertiary hydroxyketone **17**[20] reacted at room temperature providing an inseparable 4:1 mixture of the dimethyl ester and the keto ester in a modest 50% yield. Benzil and benzoin were also notable because they required heating to 50 °C for a facile reaction (entries 12 and 13). Additionally, the α-dione **14** did not yield the expected diester but provided anhydride **14a** (98%). Ketone **15** did not provide the diester exclusively, affording both the dimethyl and monomethyl esters in 19% and 64% yield, respectively. Conversion of **14** to the cyclic anhydride **14a** and not the diester (and conversely the oxidation of **15** to **15a** and **16**) is probably related to the observations made by Blanc in acetylation of 1,5- and 1,6-dicarboxylic acids and, in particular, the differences in the reaction of the latter two compounds.[21,22]

Reactions in EtOH and ^{i}PrOH (Table 2) proved to be quite reluctant to yield diesters exclusively, and instead, a reproducible mixture of mono- and diesters was obtained. Notably, the overall yield of these products remains high (51−86%). Benzil and benzoin again proved to be more difficult substrates requiring heating to 50 °C. Generally, yields of diethyl esters were higher than the corresponding diisopropyl esters; however, significant amounts of monoesters were isolated in all reactions. Reactions with ^{t}BuOH provided the diacid exclusively. This is in agreement with our previous observations, which demonstrated that oxidation of aldehydes in ^{t}BuOH with Oxone provided carboxylic acids without any trace of the desired ester.[1]

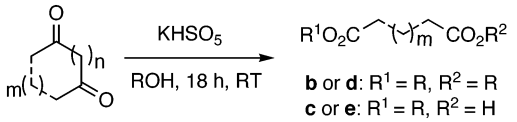
The mixed products observed during the oxidation in ethanol and 2-propanol prompted a mechanistic study for their origins. It was of interest to ascertain whether diesters are generated via Fisher esterification of monoesters, i.e., monoesters or dicarboxylic acids are the products of the oxidation, or different and competing

(20) Tamura, Y.; Annoura, H.; Kondo, H.; Fuji, M.; Yoshida, T.; Fujioka, H. *Chem. Pharm. Bull.* **1987**, *35*, 2305−2313.

(21) Kwart, H.; King, K. In *The Chemistry of Carboxylic Acids and Esters*; Patai, J., Ed.; Interscience: London, 1969; p 362.

(22) Blanc, H. G. *Compt. Rend.* **1907**, *144*, 1356−1358.

TABLE 2. Oxidative Cleavage in EtOH and ^{i}PrOH[a]



entry	substrate	solvent	product	yield[b] (%)
1	**1**	EtOH	**1b/1c**	49:25
2	**3**	EtOH	**1b/1c**	44:28
3	**5**	EtOH	**5b/5c**	61:25
4	**6**	EtOH	**5b/5c**	42:38
5	**10**	EtOH	**8b/8c**	62:14
6	**11**	EtOH	**1b/1c**	35:48
7[c]	**12**	EtOH	**12b/12c**	25:37
8[c]	**13**	EtOH	**12b/12c**	44:37
9	**14**	EtOH	**14a**	98
10	**1**	^{i}PrOH	**1d/1e**	34:45
11	**3**	^{i}PrOH	**1d/1e**	33:18
12	**5**	^{i}PrOH	**5d/5e**	31:31
13	**6**	^{i}PrOH	**5d/5e**	30:38
14	**10**	^{i}PrOH	**8d/8e**	24:45
15	**11**	^{i}PrOH	**1d/1e**	40:43
16[c]	**12**	^{i}PrOH	**12d/12c**	15:51
17[c]	**13**	^{i}PrOH	**12d/12c**	38:43
18	**14**	^{i}PrOH	**14a**	90

[a] Substrate (1 equiv), $KHSO_5$ (4 equiv), rt, 18 h. [b] Isolated yields. [c] Reactions performed at 50 °C.

mechanisms lead to mono- and diesters. To address these two differing mechanistic interpretations, adipic acid was treated with $KHSO_5$ or $KHSO_4$ in both MeOH and ^{i}PrOH. $KHSO_4$, the byproduct of the oxidative reaction, can be utilized in general acidic Fisher esterifications, but generally under heated or microwave-assisted conditions.[23−25] Incubation of adipic acid for 18 h in ^{i}PrOH with either $KHSO_5$ or $KHSO_4$ did not lead to any detectable amounts of esterified product as analyzed by GC. Alternatively, adipic acid in MeOH and $KHSO_4$ led to the generation of dimethyl adipate in 1 h. However, the same reaction with $KHSO_5$ did not yield any esterified product within 5 h. Conversion to the diester was observed after 9 h, presumably due to the auto-decomposition of $KHSO_5$ to $KHSO_4$ in the wet alcoholic solvent. The presumed auto-decomposition was verified by iodometric titration[8] indicating that simply stirring MeOH and $KHSO_5$ for 9 h led to a 1% loss in oxidative activity, thus slowly generating the more acidic $KHSO_4$ that could be responsible for catalyzing the esterification. Moreover, addition of adipic acid (0.25 equiv) led to increased decomposition of $KHSO_5$ (4%) during the 9 h span.

Considering the fact that the oxidation of cyclohexanedione **3** to dimethyl adipate is nearly complete in 3 h, it seems unlikely that **3** is converted to adipic acid, which in turn is esterified under the reaction conditions. More evidence of the latter is realized with experiments that demonstrate neither $KHSO_5$ nor $KHSO_4$ can convert simple carboxylic acids to isopropyl esters, but yet mono- and diisopropyl esters are isolated upon oxidation of α- or β-diones and α-hydroxyketones. Although it is not possible to present a detailed mechanistic picture from these experiments, it seems likely that the oxidative cleavage of the functional groups presented here is faster than Fischer esterification of their corresponding carboxylic acids, and that the formation of the isolated mono and diesters most probably occurs via different mechanisms. In other words, one can imagine diesters can originate without the intermediacy of monoesters, although it cannot be ruled out (at least for generation of dimethyl esters) that some supplementary Fischer esterification of monoesters to diesters is occurring.

Scheme 2 depicts possible routes to both monoesters and diesters from α-diones, α-hydroxyketones, and β-diones. The route to monoesters would most probably involve the intermediacy of a peroxyhemiacetal, which upon Baeyer−Villiger-like rearrangement would lead to the carboxylic acid functionality of the monoesters. This is shown for α-diones and α-hydroxyketones (intermediates **20** and **29**), which upon oxidative rearrangement lead to the monoester **22** or the aldehyde **31**, respectively. Further oxidation of aldehyde **31** with Oxone in the alcoholic solvent would lead to the monoester **22**. Conversely, the intermediacy of a peroxyacetal, such as **24** or **33,** could lead to the isolation of the diesters **27** without the need for esterification of monoesters to the diesters. In a similar manner, β-diones could also lead to either mono- or diesters. Presumably, α-hydroxyketone **41** is produced as an intermediate to the final product, although we have not observed this via NMR spectroscopy. Finally, it was shown that a minimum of 1 equiv of $KHSO_5$ for α-dione **3** and 2 equiv of $KHSO_5$ for α-hydroxyketone **1** in EtOH was necessary for their oxidation to yield the ratios of products listed in Table 2 (entries 1 and 2). Increasing the amount of oxidant did not change the ratio of the mono- and diester products isolated. However, β-dione **10** required a minimum of 3 equiv of $KHSO_5$ to yield consistent product ratios listed in Table 2 (entry 5). These observations are in line with the postulated mechanism depicted in Scheme 2.

In conclusion, the oxidative cleavage of α- or β-diones and α-hydroxyketones to esters with $KHSO_5$ is a valuable addition to the oxidative arsenal of Oxone chemistry. These results demonstrate a new methodology aimed at the direct synthesis of esters from α- or β-diones and α-hydroxyketones and also without the need for the use of transition metal oxides.

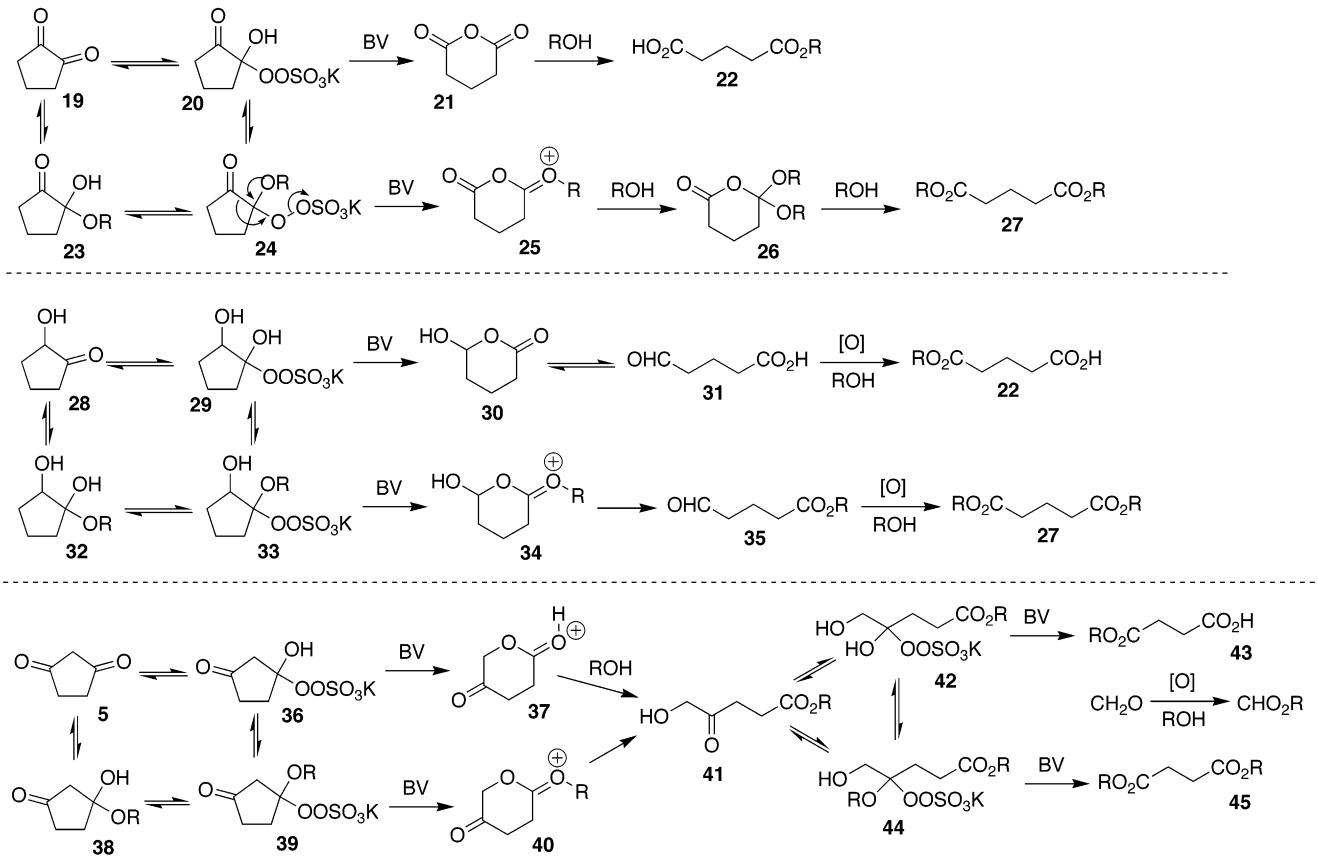
Experimental Section

General Procedure for Oxidation of α- or β-Diones and α-Hydroxyketones with Oxone. The substrate (1 equiv) was dissolved in either methanol, ethanol, or 2-propanol (0.2 M). Dry $KHSO_5$ (95% pure, 4 equiv) was added to the solution in one portion and stirred at room temperature for 18 h. The reactions were monitored by TLC, GC, or NMR analysis. After the substrate had been consumed the reaction was diluted with Et_2O and filtered through a pad of Celite. The filtrate was concentrated, and the crude products were purified by silica gel column chromatography.

Preparation of 7a. $KHSO_5$ (547 mg, 3.6 mmol) was added in one portion to a solution of diketone **7** (145 mg, 0.9 mmol) in methanol (8 mL) at rt (the salt is not completely soluble). The reaction was stirred at rt for 18 h, after which it was diluted with Et_2O (8 mL) and the precipitate (presumably unreacted $KHSO_5$ and $KHSO_4$ generated during the reaction) was filtered through a pad of Celite. The filtrate was concentrated, and the crude products were purified by silica gel column chromatography (20% EtOAc/hexanes) to furnish ester **7a** as a colorless oil (58 mg, 65% yield). **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H), 2.87−2.72 (m, 2H), 2.61−2.56 (m, 2H), 1.66−1.60 (m, 2H),

(23) Li, Y.-Q. *Synth. Commun.* **1999**, *29*, 3901−3903.
(24) Ling, S.; Lu, D. *Guangdong Chemical Industry* **2003**, *30*, 12−14.(25) Newman, M. S. *J. Am. Chem. Soc.* **1941**, *63*, 2431−2435.

SCHEME 2. Probable Mechanistic Routes for the Oxidative Cleavage of α- and *β*-Diones and α-Hydroxyketones



1.32 (s, 3H), 1.09−0.97 (m, 2H), 0.85 (t, 3H, J = 7.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 212.8, 172.9, 78.7, 51.8, 41.8, 30.8, 27.6, 25.5, 16.5, 14.2; IR (thin film) 3400, 2961, 1741, 1713, 1441, 1373, 1242, 1173, 1047 cm^{-1}; LRMS (70 eV, EI) *m/z* 202 $[M]^+$, 184 $[M - H_2O]^+$, 171 $[M - CH_3O]^+$; HRMS (CI) calcd for $C_{10}H_{19}O_4$ 203.1283 *m/z* $[M + H]^+$, obsd 203.1283 *m/z*.

Preparation of 1e. $KHSO_5$ (608 mg, 4 mmol) was added in one portion to a solution of diketone **3** (112 mg, 1 mmol) in 2-propanol (10 mL) at rt. The reaction was stirred at rt for 18 h, after which it was diluted with Et_2O (8 mL) and the precipitate (presumably unreacted $KHSO_5$ and $KHSO_4$ generated during the reaction) was filtered through a pad of Celite. All of the filtrate was concentrated, and the crude products were purified by silica gel column chromatography (20% EtOAc/hexanes) to furnish esters **1d** (70 mg, 33%) and **1e** (32 mg, 18%) as colorless oils. **1e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.05 (br, 1H), 4.95 (sept, 1H, J = 6.32 Hz), 2.32 (t, 2H, J = 6.87 Hz), 2.25 (t, 2H, J = 7.14 Hz), 1.67−1.57 (m, 4H), 1.17 (d, 6H, J = 6.04 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 179.6, 172.9, 67.6, 34.2, 33.6, 24.3, 23.9, 21.7; IR (thin film) 3210, 2982, 2939, 1730, 1729, 1375, 1242, 1182, 1109, 1047, 939, 822 cm^{-1}; LRMS (70 eV, EI) *m/z* 170 $[M - H_2O]^+$, 129 $[M - OCH(CH_3)_2]^+$; HRMS (CI) calcd for $C_9H_{17}O_4$ 189.1127 *m/z* $[M + H]^+$, obsd 189.1128 *m/z*.

Preparation of 8d. $KHSO_5$ (608 mg, 4 mmol) was added in one portion to a solution of diketone **10** (126 mg, 1 mmol) in 2-propanol (10 mL) at rt. The reaction was stirred at rt for 18 h, after which it was diluted with Et_2O (8 mL) and the precipitate (presumably unreacted $KHSO_5$ and $KHSO_4$ generated during the reaction) was filtered through a pad of Celite. The crude product was purified by silica gel column chromatography (20% EtOAc/hexanes) to furnish esters **8d** (51 mg, 24%) and **8e** (77 mg, 45%) as colorless oils. **8d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (sept, 2H, J = 6.32 Hz), 2.27 (t, 4H, J = 7.14 Hz), 1.88 (p, 2H, J = 7.14 Hz), 1.18 (d, 12H, J = 6.32 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.5, 67.6, 33.6, 21.8, 20.2; IR (thin film) 2982, 2934, 1732, 1375, 1256, 1202, 1181, 1109, 1057, 1011, 970, 933 cm^{-1}; LRMS (70 eV, EI) *m/z* 216 $[M]^+$, 157 $[M - OCH(CH_3)_2]^+$; HRMS (CI) calcd for $C_{11}H_{21}O_4$ 217.1440 *m/z* $[M + H]^+$, obsd 217.1440 *m/z*.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds described in the Experimental Section are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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