An Efficient Butenolide Annulation via α′-Chloroacetoxylation of Enones Using Manganese(III) Acetate and Chloroacetic Acid

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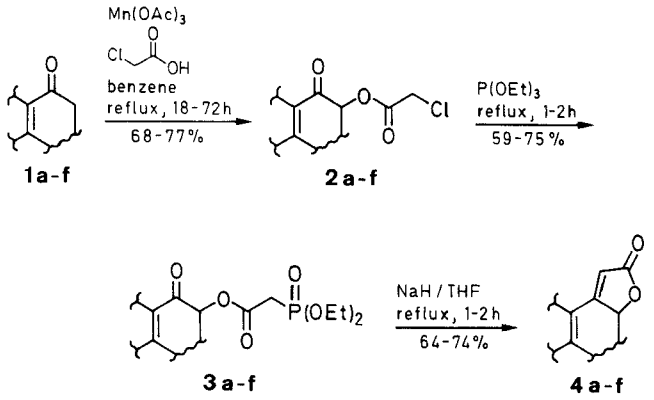
The α′-chloroacetoxylation of α,β-unsaturated ketones using manganese(III) acetate and chloroacetic acid followed by Arbuzov reaction and intramolecular Horner–Emmons olefination provided a convenient synthesis of annulated 2-buten-4-olides.

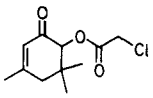
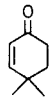
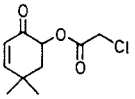
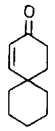
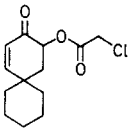
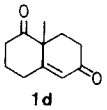
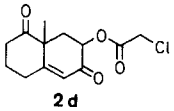
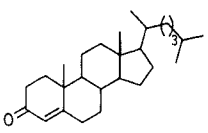
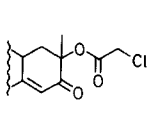
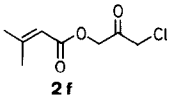
We have described a synthesis of α′-acyloxy-α,β-unsaturated ketones from the corresponding α,β-unsaturated ketones using manganese(III) acetate in combination with carboxylic acids using various cyclic and acyclic α,β-unsaturated ketones.[1] We now report the extension of this method to the synthesis of annulated 2-buten-4-olides. These products occur frequently as structural units of natural products[2], and they have functionalities suitable for a wide range of chemical manipulations.

As shown in the Scheme, the use of 6 equivalents of manganese(III) acetate in combination with 12 equivalents of chloroacetic acid led to the desired α′-chloroacetoxy-α,β-unsaturated ketones **2** from the ketones **1** in good yield (Table 1). The anhydrous manganese(III) acetate, which is used for the oxidation was prepared from manganese(II) nitrate and acetic anhydride and dried over phosphorus(V) oxide prior to use. A negligible ammount of α′-acetylated α,β-unsaturated ketones were



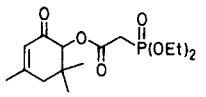
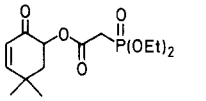
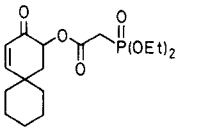
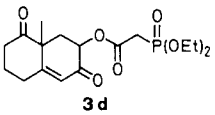
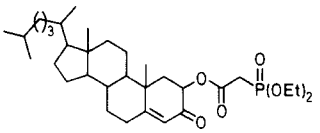
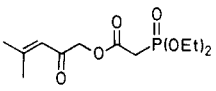
Scheme

Table 1. α′-Chloroacetoxy α,β-Unsaturated Ketones **2** Prepared

Substrate	Reflux Time (h)	Product	Yield (%)	Molecular Formula[a]	IR (film) ν (cm⁻¹)	¹H-NMR ($CDCl_3$/TMS) δ, J (Hz)
 **1a**	18	 **2a**	75	$C_{11}H_{15}ClO_3$ (230.7)	1740, 1670, 1600	1.00 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.25 (s, 2H, CH_2), 4.26 (s, 2H, CH_2Cl), 5.26 (s, 1H, α′-CH), 5.92 (s, 1H, H_{olef})
 **1b**	36	 **2b**	74	$C_{10}H_{13}ClO_3$ (216.65)	1735, 1665, 1605	0.98 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.10–2.25 (m, 2H, CH_2), 4.35 (s, 2H, CH_2Cl), 5.50 (dd, 1H, J = 5.2, 12.3, α′-CH), 5.85 (d, 1H, J = 10.3, H_{olef}), 6.70 (d, 1H, J = 10.5, α-CH_{olef})
 **1c**	18	 **2c**	74	$C_{13}H_{17}ClO_3$ (256.7)	1750, 1680, 1600	1.30–1.90 (m, 12H, CH_2), 4.20 (s, 2H, CH_2Cl), 5.50 (dd, 1H, J = 5.5, 12.5, α′-CH), 5.90 (d, 1H, J = 10.5, H_{olef}), 6.80 (d, 1H, J = 10.5, α-CH_{olef})
 **1d**	72	 **2d**	72	$C_{13}H_{15}ClO_4$ (270.7)	1770, 1740, 1675, 1600	1.45 (s, 3H, CH_3), 2.25–2.56 (m, 8H, CH_2), 4.10 (s, 2H, CH_2Cl), 5.25 (dd, 1H, J = 5.1, 12, α′-CH), 5.85 (s, 1H, H_{olef})
 **1e**	36	 **2e**	68	$C_{29}H_{45}ClO_3$ (477.1)	1730, 1660, 1600	0.50–2.50 (m, 41H, CH_3, CH_2, CH-ring), 4.20 (s, 2H, CH_2Cl), 5.40 (dd, 1H, J = 5.0, 11.5, α′-CH), 5.75 (s, 1H, H_{olef})
 **1f**	30	 **2f**	77	$C_8H_{11}ClO_3$ (190.6)	1720, 1680, 1600	1.90 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.20 (s, 2H, CH_2Cl), 4.75 (s, 2H, CH_2), 6.00 (m, 1H, H_{olef})

[a] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.3.

Table 2. Phosphonates **3** Prepared

Substrate	Time (h)	Product	Yield (%)	Molecular Formula[a]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	1	 **3a**	75	$C_{15}H_{25}O_6P$ (332.3)	1730, 1660, 1600, 1210	0.90 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.20–1.40 (m, 6H, CH_3CH_2), 1.80 (s, 3H, β-C CH_3), 2.20 (s, 2H, CH_2), 2.45 (s, 2H, CH_2P), 3.95–4.35 (m, 4H, CH_3CH_2), 5.20 (s, 1H, α'-CH), 5.85 (s, 1H, H_{olef})
2b	2	 **3b**	62	$C_{14}H_{23}O_6P$ (318.3)	1720, 1650, 1600, 1200	0.98 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.11–1.39 (m, 6H, CH_3CH_2), 2.10–2.25 (m, 2H, CH_2), 2.55 (s, 2H, CH_2P), 3.85–4.30 (m, 4H, CH_3CH_2), 5.35 (dd, 1H, J = 5, 12.1, α'-CH), 5.90 (d, 1H, J = 10.3, H_{olef}), 6.70 (d, 1H, J = 10.3, α-CH_{olef})
2c	1	 **3c**	69	$C_{17}H_{27}O_6P$ (358.4)	1740, 1680, 1590	1.12–1.41 (m, 6H, CH_3CH_2), 1.42–1.90 (m, 12H, CH_2-ring), 2.41 (s, 2H, CH_2P), 3.76–4.22 (m, 4H, CH_3CH_2), 5.51 (dd, 1H, J = 5.5, 12.5, α'-CH), 5.92 (d, 1H, J = 10.5, H_{olef}), 6.78 (d, 1H, J = 10.5, α-CH_{olef})
2d	2	 **3d**	61	$C_{17}H_{25}O_7P$ (372.3)	1770, 1740, 1680, 1600, 1220	1.15–1.35 (m, 6H, CH_3CH_2), 1.40 (s, 3H, CH_3), 2.25–2.56 (m, 10H, CH_2-ring, CH_2P), 3.80–4.25 (m, 4H, CH_3CH_2), 5.40 (dd, 1H, J = 5.2, 12.1, α'-CH), 5.85 (s, 1H, H_{olef})
2e	2	 **3e**	59	$C_{33}H_{55}O_6P$ (578.7)	1725, 1670, 1600, 1225	0.50–2.50 (m, 51H, CH, CH_2, CH_3-ring, CH_3CH_2, CH_2P), 3.90–4.35 (m, 4H, CH_3CH_2), 5.30 (dd, 1H, J = 5, 12.2, α'-CH), 5.75 (s, 1H, H_{olef})
2f	2	 **3f**	63	$C_{12}H_{21}O_6P$ (292.3)	1710, 1680, 1600, 1210	1.15–1.5 (m, 6H, CH_3CH_2), 1.75 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.48 (s, 2H, CH_2P), 3.9–4.4 (m, 4H, CH_3CH_2), 4.95 (s, 2H, CH_2), 5.60 (s, 1H, H_{olef})

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.3.

obtained from this reaction (3–5% GLPC). These could easily be separated by column chromatography. The Arbuzov reaction of α'-chloroacetoxy compounds **2** with excess triethyl phosphite proceeds in good yield to give the corresponding phosphonates **3** (Table 2). The formation of the phosphonates **3** could be monitored by ^{1}H-NMR analysis based on the disappearance of the RCH_2Cl signal as well as on the formation of a signal for the RCH_2P group.

The intramolecular Horner–Emmons cyclization reaction of the phosphonates **3** with sodium hydride in tetrahydrofuran under reflux gave the butenolides **4** summarized in Table 3. Cyclization of the phosphonates **3** under Evans conditions[3] (33 equivalents lithium chloride, 30 equivalents triethylamine/acetonitrile, 25 °C, 36 h) afforded the butenolides **4a** and **4d** in 58–64% yield.

The mechanism of these oxidations remains uncertain. The initial reaction takes place between the manganese(III) acetate and chloroacetic acid, that results in a mixed manganese(III) complex having both acetate and chloroacetate ligands. The interaction of the α,β-unsaturated ketones with this complex should result in chloroacetate transfer via metal enolate formation (analogous to the enol-lead triacetate intermediate proposed by Corey and Schaefer for acetoxylation reaction of ketones[4,5]).

All reagents were of commercial quality, and reagent quality solvents were used without further purification. IR spectra were determined on a Philips model PU9700 spectrophotometer. ^{1}H-NMR spectra were determined on a Bruker AC 80 MHz FT spectrometer. GC analyses were determined on a HP 5890 gas chromatograph. Elemental analysis were performed at the Middle East Technical University Analysis Center.

8a-Methyl-2,8-dioxo-2,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-*b*]furan (4d); Typical Procedure:

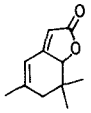
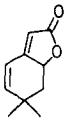
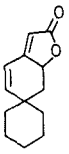
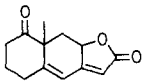
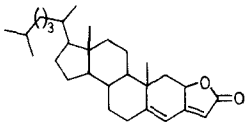
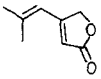
7-(Chloroacetoxy)-8a-methyl-1,6-dioxo-1,2,3,4,6,7,8,8a-Octahydronaphthalene **(2d)**: A mixture of $Mn(OAc)_3$ (2.12 g, 10 mmol) and chloroacetic acid (2.83 g, 30 mmol) in benzene (40 mL) is refluxed for 1 h under a Dean-Stark trap. The mixture is cooled to 25 °C, and **1d** (0.445 g, 2.5 mmol) is added. The mixture is refluxed for 48 h and is then cooled to 25 °C, diluted with EtOAc, washed with 1 M aq HCl, sat. aq $NaHCO_3$ and brine, and dried ($MgSO_4$). The crude product is chromatographed on PTLC plates (silica gel F-254 in 1:3 EtOAc/hexane) to afford 0.487 g (72%) of **2d** as an oil.

7-[(Diethoxyphosphoryl)acetoxy]-8a-methyl-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydronaphthalene **(3d)**:

A mixture of **2d** (0.676, 2.5 mmol) and $P(OEt)_3$ (1.3 g, 8 mmol) is refluxed under Ar for 2 h (the reaction is monitored by TLC on silica gel with EtOAc/hexane, 1:1, as eluent). During this time $P(OEt)_3$ (1.3 g, 8 mmol) is added at 1 h intervals. The excess of $P(OEt)_3$ is distilled under vacuum and the residue is chromatographed on PTLC plates (silica gel F-254 in EtOAc/hexane, 1:1) to afford 0.567 g (61%) of **3d**.

8a-Methyl-2,8-dioxo-2,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-b]furan **(4d)**: Compound **3d** (0.93 g, 2.5 mmol) is dissolved in anhydrous THF (25 mL) and added dropwise under Ar into a suspension of NaH (0.096 g, 4 mmol) (washed from oil with pentane) in the

Table 3. Butenolides **4** Prepared

Substrate	Time (h)	Product	Yield (%)	Molecular Formula[a]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ
3a	2	 **4a**	68	$C_{11}H_{14}O_2$ (178.2)	1770, 1740, 1600	1.10 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.20 (s, 2H, CH_2), 5.95 (s, 1H, CH–O), 6.25 (s, 1H, α-CH_{olef}), 6.60 (s, 1H, H_{olef})
3b	1	 **4b**	72	$C_{10}H_{12}O_2$ (164.2)	1765, 1740, 1610	0.95 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.0–2.5 (m, 2H, CH_2), 5.60 (dd, 1H, J = 5.6, 12.5, CH–O), 5.90 (d, 1H, J = 10.2, H_{olef}), 6.10 (s, 1H, α-CH_{olef}), 6.70 (d, 1H, J = 10.2, H_{olef})
3c	1.5	 **4c**	74	$C_{13}H_{16}O_2$ (204.3)	1775, 1740, 1665	1.31–1.98 (m, 12H, CH_2-ring), 5.58 (dd, 1H, J = 5.6, 12.5, CH), 5.92 (d, 1H, J = 10.5, H_{olef}), 6.12 (s, 1H, α-CH_{olef}), 6.78 (d, 1H, J = 10.5, H_{olef})
3d	1	 **4d**	66	$C_{13}H_{14}O_3$ (218.2)	1770, 1735, 1650	1.39 (s, 3H, CH_3), 1.82–2.76 (m, 8H, CH_2-ring), 5.20 (dd, 1H, J = 5.2, 12.0, CH), 5.75 (s, 1H, α-CH_{olef}), 6.45 (s, 1H, H_{olef})
3e	1	 **4e**	64	$C_{29}H_{10}O_2$ (424.6)	1740, 1690, 1600	0.80–2.50 (m, 41H, CH_3, CH_2, CH-ring), 5.30 (dd, 1H, J = 5.2, 11.9, CH–O), 5.95 (s, 1H, α-CH_{olef}), 6.50 (s, 1H, H_{olef})
3f	1.5	 **4f**	73	$C_8H_{10}O_2$ (138.2)	1720, 1680, 1600	1.50 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 5.80 (s, 1H, H_{olef}), 5.95 (s, 1H, α-CH_{olef})

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.2.

same solvent. The mixture is refluxed for 2 h. The cooled mixture is quenched with H_2O and extracted with EtOAc. The organic layer is washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue is chromatographed on PTLC plates to afford 0.36 g (66%) of **4d**.

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