An Efficient Synthesis of 4-Oxoalkenoic Acids from 2-Alkylfurans

Suresh Palani Annangudi, Mingjiang Sun, Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, USA
Fax +1(216)3683006; E-mail: rgs@case.edu

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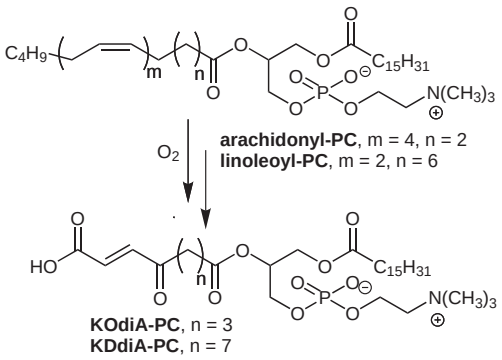
Abstract: An efficient synthesis of 4-oxo-2-alkenoic acids is achieved by the reaction of 2-alkylfurans with sodium chlorite in acidic aqueous solution. The method is applicable to the total synthesis of biologically active phospholipids containing this functional array. The oxidation procedure also converts 2,5-dialkyl furans to α,β-unsaturated-γ-diketones in good yields.

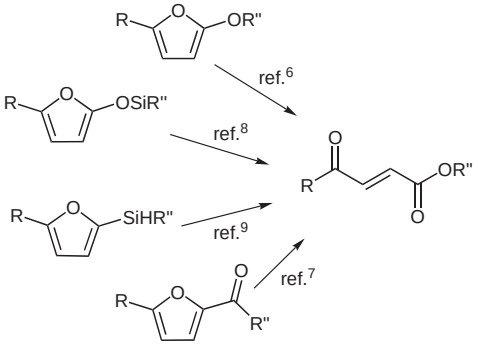
Key words: furan oxidation, sodium chlorite, ring opening, oxidized phospholipids, α,β-unsaturated acids

4-Oxo-2-alkenoic acids, and the closely related α,β-unsaturated-γ-diketones, are versatile intermediates for organic synthesis.[1,2] This functional array is present in many pharmaceutically important natural products, e.g., pyrenophorin, patulolide, grahamimycin and others,[3] that have antifungal, antibacterial, and anti-inflammatory properties.[4] Recently, we found that free radical-induced oxidative fragmentation of arachidonyl or linoleoyl phosphatidylcholine (PC) in vivo generates bioactive phospholipids, KOdiA-PC or KDdiA-PC (Scheme 1),[5] that incorporate 4-oxo-2-alkenoic acid functionality.



Scheme 1

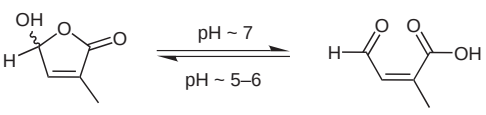
An efficient synthesis of 4-oxo-2-alkenoic acids from simple monosubstituted furan precursors is needed. An important shortcoming of previous methods for preparing 4-oxo-2-alkenoic acids has been the requirement for more elaborately functionalized furan intermediates such as 2-alkoxy-5-alkyl,[6] 2-acyl-5-alkyl,[7] 2-siloxy-5-alkyl[8] or 2-silyl-5-alkyl[9] as precursors (Scheme 2). A patent application reported a one-pot synthesis of 4-oxo-5-phthalimido-2-pentenoic acid from *N*-furfurylphthalimide through singlet oxygenation.[10] Generation of 4-oxo-2-alkenoic acids from 2-alkyl furans has also been accomplished previously through a variety of multi-step procedures involving treatment with reagents such as bromine[11] or NBS[12] followed by oxidation with sodium chlorite; PCC followed by Jones reagent;[13] or nitration followed by acidic oxidation.[14]



Scheme 2

Alkyl furans are easily accessible,[1] robust precursors that are compatible with a wide variety of reagents and reaction conditions making them highly desirable substrates. We now report efficient stereocontrolled methodology, that exploits sodium chlorite as an oxidizing agent, for the conversion of 2-alkyl furans into 4-oxo-2-alkenoic acids and for the conversion of 2,5-dialkylfurans into 1,4-enediones. The oxidation cleanly generates *cis*-isomers (butenolides) stereospecifically and in high yield. If desired, these can be cleanly and quantitatively converted to the corresponding *trans*-isomers by treatment with pyridine.[15]

Oxidation of 2-alkyl furans **1** in the presence of sodium chlorite in a slightly acidic aqueous solution (ca. pH 3.5) at room temperature generates 2-alkyl-2-hydroxy-butenolides **2**,[16] ring tautomers of 4-oxo-2(*Z*)-alkenoic acids (Scheme 3).[17] Owing to electron deficiency, 2-acetylfuran did not react under these conditions.



Scheme 3

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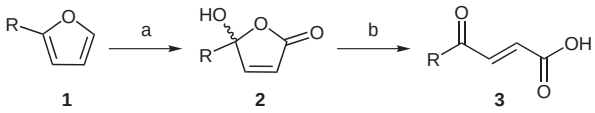
Table 1 Synthesis of 2-Alkyl-2-hydroxybutenolides from 2-Alkyl Furans



1 2 3

Entry	Alkyl furan **1** R	**1** → **2** Time (h)	Yield **2** (%)	**2** → **3** Time (h)	Yield **3** (%)
a	-$(CH_2)_3$-COO-PC [c]	1	66[d]	2	100
b	-$(CH_2)_7$-COO-PC [c]	1	64[d]	2	100
c	-CH_3	0.5	96[e]	2	100
d	-C_5H_{11}	1.5	95[e]	2	100
e	-$(CH_2)_4$-OTs	4	90[e]	2	96
f	-$(CH_2)_4$-OTHP	2	78[e]	2	90
g	-$(CH_2)_4$-OTBDMS	2	77[e]	2	95
h	-$(CH_2)_2$-(CH-O-TBDMS)-CH_3	2	75[e]	2	96

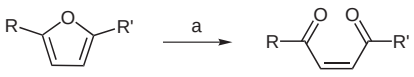
[a] $NaClO_2$ (3 equiv), NaH_2PO_4 (1.5 equiv), r.t.
[b] Pyridine (1 mol%), THF–acetone–H_2O (5:4:2, 0.2 mL/mmol of **2**), 2 h, r.t.
[c] PC = 2-lysophosphatidylcholine.
[d] Solvent: phosphate buffered saline (pH 3.5)–$CHCl_3$–H_2O, 2:1:1.
[e] Solvent: *t*-BuOH–H_2O (5:1, 1 mL/mmol of **1**).

The butenolides can be isolated, virtually pure (by NMR) by extraction into chloroform. This oxidative ring-opening methodology is compatible with a variety of functional groups used routinely in organic synthesis (Table 1). Stereoselective conversion of the alkyl butenolides **2** into 4-oxo-2(*E*)-alkenoic acids **3** is readily accomplished in excellent yield by treatment with a catalytic amount of pyridine (Table 1).[16]

The uptake of oxidized low-density lipoprotein by macrophage cells is an early event in the formation of atherosclerotic plaques. We recently identified the phospholipids KOdiA-PC (**3a**) and KDdiA-PC (**3b**) as potent ligands responsible for recognition and uptake of oxidized low-density lipoprotein.[5] Our previous synthesis of **3a** and **3b** from 2-substituted furan phospholipid precursors **1a** and **1b**, using oxidation with NBS followed by further oxidation with sodium chlorite, gave 46% and 36% yields, respectively.[18] Total syntheses involving phospholipids present special challenges owing to their unique solubility properties. We discovered that direct oxidation of **1a** or **1b** with sodium chlorite can be accomplished by employing a biphasic solvent system containing pH 3.5 phosphate buffer, chloroform and water in the ratio 2:1:1. For these phospholipids, the sodium chlorite oxidation method using *t*-BuOH–water (5:1) as solvent afforded poor yields, even after long reaction times. The biphasic aqueous sodium chlorite protocol decreased the reaction time, from nine hours to one hour and consistently gave 40–80% higher yields than the NBS–$NaClO_2$ procedure.

Oxidation of 2,5-dialkyl furans gave the corresponding 1,4-diketones (Table 2).[19] Substrates incorporating a vinyl substituent present a special challenge. For example, under the usual reaction conditions, **4j** did not give any of the corresponding enedione **5j**. However, in the presence of 2-methyl-2-butene, a chlorine scavenger, the sodium chlorite oxidation protocol gave enedione **5j** in good yield.

Table 2 Synthesis of 2-Ene 1,4-Diones from 2,5-Dialkyl Furans



4 5

Entry	R	R′	Product	Yield (%)
1	-CH_3	-CH_3	**5i**	93[b]
2	-$(CH_2)_7CHO$	-CH=CH(*E*)-C_4H_9	**5j**[d]	76[c]
3	-CH_3	-CH=CH(*E*)-C_4H_9	**5k**	78[c]

[a] $NaClO_2$ (3 equiv), NaH_2PO_4 (1.5 equiv), *t*-BuOH–H_2O (5:1).
[b] Reaction time 1 h.
[c] 2-Methyl-2-butene (0.1 mol equiv) added to the reaction, reaction time ca. 20 min, yield based on unrecovered starting material.
[d] The aldehyde is completely oxidized to the acid.

In summary, this new methodology provides ready access to either *cis*- or *trans*-isomers of 4-oxo-2-alkenoic acids from simple precursors in high yields, using readily available reagents. Compared to our previous total synthesis, the new procedure enables a major improvement in the overall yield and ease of preparing biologically active phospholipids that contain this functional array.

Acknowledgment

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(16) **Typical Procedure for Furan Oxidation.**
To a magnetically stirred solution of alkyl furan **1** (0.1 mmol) in *t*-BuOH–H_2O (5:1, v/v, 0.5 mL) was added NaH_2PO_4 (0.15 mmol), $NaClO_2$ (0.3 mmol). The resulting mixture was stirred at r.t. for 2 h or until the yellow color disappears. Then, the solvent was removed on a rotary evaporator. The residue was extracted with $CHCl_3$. The extract was washed with brine, dried on $MgSO_4$ and passed through a short plug of Celite. The resulting butenolides are at least 90% pure by NMR.
Typical Procedure for *cis*/*trans* Isomerization.
To a solution of **2** in 2 mL THF–acetone–H_2O (5:4:1) was added 10 μL of freshly distilled pyridine (1 mol%). The mixture was stirred for 2 h at r.t. Solvents were removed on a rotary evaporator and residual pyridine was removed in vacuo using a dry ice cooled trap. The residue was purified by flash chromatography on a silica gel column (30% EtOAc in hexanes) to afford the pure product **3**.
Toluene-4-sulfonic Acid 4-(Furan-2-yl)butyl Ester (1e).
^{1}H NMR (300 MHz, CD_3Cl): δ = 7.77 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.25 (dd, J_1 = 1.8 Hz, J_2 = 0.9 Hz, 1 H), 6.24 (dd, J_1 = 3.0 Hz, J_2 = 1.8 Hz, 1 H), 5.92 (dd, J_1 = 3.0 Hz, J_2 = 0.9 Hz, 1 H), 4.01 (t, *J* = 6.3 Hz, 2 H), 2.56 (t, *J* = 6.6 Hz, 2 H), 2.43 (s, 3 H), 1.63–1.64 (4 H). ^{13}C NMR (75 MHz, CD_3Cl): δ = 155.1, 144.6, 140.8, 132.9, 129.7, 127.8, 110.0, 105.0, 70.1, 28.1, 27.0, 23.8, 21.5. HRMS (FAB): *m/z* calcd for $C_{15}H_{18}O_4S^+$ [M^+]: 294.0926; found: 294.0924.
Toluene-4-sulfonic Acid 4-(2-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl Ester (2e).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 7.9 Hz, 2 H), 7.19 (d, *J* = 5.5 Hz, 1 H), 6.09 (d, *J* = 5.5 Hz, 1 H), 4.03 (m, 2 H), 2.43 (br s, 3 H), 1.40–1.80 (6 H).
4-Oxo-8-(toluene-4-sulphonyloxy)oct-2-enoic Acid (3e).
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 7.9 Hz, 2 H), 7.12 (d, *J* = 15.9 Hz, 1 H), 6.63 (d, *J* = 16.1 Hz, 1 H), 4.03 (m, 2 H), 2.62 (m, 2 H), 2.43 (br s, 3 H), 1.60–1.80 (4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.1, 168.1, 144.9, 144.8, 140.6, 132.9, 129.8, 127.8, 69.9, 40.5, 28.0, 21.6, 19.4. HRMS (FAB): *m/z* calcd for $C_{15}H_{19}O_6S^+$ [M + H^+]: 327.0902; found: 327.0903.
5-Hydroxy-5-pentyl-5*H*-furan-2-one (2d).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 5.7 Hz, 1 H), 6.11 (d, *J* = 5.7 Hz, 1 H), 1.98 (m, 2 H), 1.28–1.41 (7 H), 0.87 (t, *J* = 6.3 Hz, 3 H).
8-(*tert*-Butyldimethylsilanyloxy)-4-oxooct-2 (*Z*)-enoic Acid (3g).
TLC: 20% EtOAc in hexanes, R_f = 0.37; yield 77%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 5.5 Hz, 1 H), 6.10 (d, *J* = 5.5 Hz, 1 H), 3.64 (t, *J* = 5.9 Hz, 2 H), 2.10–1.90 (2 H), 1.70–1.40 (4 H), 0.88 (s, 9 H), 0.05 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 154.2, 123.1, 108.0, 62.9, 36.9, 31.8, 25.9, 20.2, 18.3, –5.3. HRMS (FAB): *m/z* calcd for $C_{14}H_{27}O_4Si^+$ [M + H^+]: 287.1673; found: 287.1679.
5-[3-(*tert*-Butyldimethylsilanyloxy)butyl]-5-hydroxy-5*H*-furan-2-one (2h).
TLC: 20% EtOAc in hexanes, R_f = 0.3. ^{1}H NMR (300 MHz, $CDCl_3$, diastereomeric mixture): δ = 7.19 (d, *J* = 6.0 Hz, 0.7 H), 7.15 (d, *J* = 6.0 Hz, 0.3 H), 6.05 (1 H), 4.01 (m, 0.7 H), 3.95 (m, 0.3 H), 1.60–2.20 (6 H), 1.10–1.20 (6 H), 0.80–0.90 (9 H), –0.01–0.16 (6 H).
1-Palmitoyl-2-[1-carboxy-4-(2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butanoyl]-*sn*-glycero-3-phosphatidylcholine (2a).
^{1}H NMR (300 MHz, CD_3OD): δ = 7.41 (br s, 1 H), 6.15 (d, *J* = 6.0 Hz, 1 H), 5.25 (m, 2 H), 4.39 (m, 1 H), 4.28 (m, 2 H), 4.21 (m, 1 H), 4.01 (m, 2 H), 3.66 (m, 2 H), 3.23 (s, 9 H), 2.30–2.40 (4 H), 1.50–2.10 (6 H), 1.20–1.30 (24 H), 0.88 (t, *J* = 6.0 Hz, 3 H). HRMS (MALDI-TOF): *m/z* calcd for $C_{32}H_{59}NO_{11}P^+$ [MH^+]: 664.3826; found: 664.3820.
1-Palmitoyl-2-[1-carboxy-8-(2-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)octanoyl]-*sn*-glycero-3-phosphatidylcholine (2b).
^{1}H NMR (300 MHz, CD_3OD): δ = 7.41 (br s, 1 H), 6.12 (d, *J* = 6.0 Hz, 1 H), 5.25 (m, 2 H), 4.40 (m, 1 H), 4.27 (m, 2 H), 4.16 (dd, J_1 = 12.6 Hz, J_2 = 6.3 Hz, 1 H), 4.01 (t, *J* = 5.1 Hz, 2 H), 3.66 (m, 2 H), 3.23 (s, 9 H), 2.30–2.40 (4 H), 1.50–2.10 (5 H), 1.20–1.30 (30 H), 0.88 (t, *J* = 6.0 Hz, 3 H). HRMS (MALDI-TOF): *m/z* calcd for $C_{36}H_{67}NO_{11}P^+$ [MH^+]: 720.4457; found: 720.4424.

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(19) **9,12-Dioxooctadeca-10(*Z*),13(*E*)-dienoic Acid (5j).**
To a magnetically stirred solution of aldehyde **4j** (39 mg, 0.14 mmol) in *t*-BuOH–H_2O (5:1, v/v, 0.3 mL) and 2-methyl-2-butene (1.44 mmol, 720 μL, 2 M in THF) were added NaH_2PO_4 (30 mg, 0.22 mmol) and $NaClO_2$ (40 mg, 0.4 mmol, 90%). The mixture was stirred at r.t. and monitored by TLC. The solvent was removed. The residue was purified by flash chromatography on a silica gel column (first eluted with 25% EtOAc in hexanes then EtOAc) affording yellowish crystals **5j**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.83 (dt, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 1 H), 6.48 (d, *J* = 12.0 Hz, 1 H), 6.38 (d, *J* = 12.0 Hz, 1 H), 6.18 (dt, J_1 = 16.0 Hz, J_2 = 1.5 Hz, 1 H), 2.52 (t, *J* = 7.2 Hz, 2 H), 2.10–2.40 (4 H), 1.10–1.80 (14 H), 0.91 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 192.6, 179.6, 150.8, 136.9, 134.2, 130.2, 42.6, 34.0, 32.5, 30.1, 29.0, 28.9, 24.6, 23.4, 22.3, 13.9. HRMS (EI): *m/z* calcd for $C_{18}H_{28}O_4^+$ [M^+]: 308.1988; found: 308.1978.