Convenient Synthesis of Volatile *Streptomyces* Lactones

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Dedicated to Prof. Ian Blair on the occasion of his 60th birthday

Abstract: A convenient three-step synthetic approach towards 3-alkyl-5-methyl-2[5H]furanones is described. The steps involved in the synthesis are domino primary alcohol oxidation–Wittig reaction, acid-catalysed lactonisation and isomerisation. This synthetic approach has been exploited to synthesise four *Streptomyces* lactones.

Key words: domino reaction, Wittig reaction, isomerisation, lactone, oxidation

Butenolide (3-alkyl-5-methyl-2[5H]furanone), a five-membered unsaturated lactone, is widely encountered in many natural products.1 Butenolides are of interest2 due to their broad range of biological activities e.g. butenolide 1a is a component of mushroom flavour,3 1b has fungicidal activity,4 1c–g are metabolites from *Streptomyces griseus*,1b,5 while 2 and 3 isolated from leaves of *Hortonia* exhibited mosquito larvicidal activities (Figure 1).6 Substituted-5-methyl-2[5H]furanone is believed to be one of the essential subunits responsible for the cytotoxicity of acetogenins.6g

![Figure 1](image_url)

Figure 1: Domino reactions have attracted considerable attention7 as they result in the reduction in the amount of by-products, solvents, eluents, time and energy used. In continuation of our research work dealing with the use of domino primary alcohol oxidation–Wittig reactions,8 we were interested in testing functionalised Wittig reagent 5 for its own and its products’ stability towards the domino reaction conditions (Scheme 1). Thus, butanol was subjected to the domino primary alcohol oxidation–Wittig reaction, after three hours the alcohol was found to be consumed (TLC). On usual work-up, only one product was obtained. As the product could be E or Z, it was necessary to know the geometry of the product. As the product was a trisubstituted olefin it was necessary to compare the 1H NMR chemical shift values with syn and anti protons attached at the \( \beta \)-carbon of the unsaturated system. To do this, stable phosphorane \( \text{5} \) was condensed with formaldehyde to give \( \text{6a} \) (Figure 2). The protons at the \( \beta \)-carbon appeared at 5.77 and 6.20 ppm. The signal at 5.77 ppm was due to the anti proton and the signal at 6.20 ppm was due to the syn proton with respect to carboethoxy group and thus 6c was confirmed to be the E-isomer. Prolonging the reaction time (> 4 h) resulted in a decrease in yield showing just how sensitive the product was to reaction conditions. The E-ester 6e was then subjected to acid-catalysed lactonisation followed by isomerisation using \( \text{RhCl}_3 \cdot 3\text{H}_2\text{O} \) as depicted (Scheme 1), to yield racemic 3-butyl-5-methyl-2[5H]furanone (1e), a naturally occurring butenolide. Optically active compound 1e is a precursor9 to (+)-blastmycinone and (−)-3-epi-blastmycinone. Similarly, hexanol and 3-methyl butanol were subjected to the above protocol to obtain (±)-butenolides 1d,e. For volatile aldehydes direct condensation of phosphorane 5 with 37% formalin and 20% aqueous acetaldehyde was necessary to obtain 6a,b. In our hands, pure butenolide 1a was not obtained by the isomerisation of 7a. Incidentally all the (±)-\( \gamma \)-methyl-\( \alpha \)-alkylidene-\( \gamma \)-lactones (7b–e) have exclusive E-geometry.10

In conclusion, we have demonstrated that functionalised Wittig reagent 5 can also be used for the domino primary alcohol oxidation–Wittig reaction. Using this protocol, four volatile *Streptomyces* lactones were synthesized as racemates in just three steps in a convenient manner. Synthesis of two of them (1d and 1e) is reported for the first time.

![Figure 2](image_url)
Column chromatography was performed on silica gel (60–120 mesh) and TLC on silica gel (13% CaSO₄ as binder). IR spectra were recorded on Shimadzu FT-IR spectrophotometer (KBr pellet or neat sample). ¹H NMR and ¹³C NMR were recorded on a Bruker-300 MHz instrument. The multiplicities of carbon signals were obtained from DEPT experiments. Low resolution mass spectra were recorded on triple quadrupole MS/MS instrument (Applied Biosystems Inc.) and high resolution mass spectra (HRMS) were recorded on a MicroMass ES-QTOF Mass spectrometer.

**Phosphorane 5**

A mixture of carboethoxymethylenetriphenylphosphorane (10 g, 2.87 mmol) and allyl bromide (4.16 g, 3.44 mmol) was refluxed in CHCl₃ (25 mL) for 5 h. The solvent was evaporated under vacuum. To a solution of phosphorane (1 mmol) in MeOH (10 mL) was added an aq solution of aldehyde (2 mL, 5 mmol) and the reaction mixture was shaken vigorously. Benzene (2 × 20 mL). Benzene (50 mL) and phenolphthalein (2 drops) were added to the aqueous layer and 2 N NaOH was added dropwise with vigorous shaking till a pink colour persisted. The benzene layer was separated, washed with H₂O (20 mL), brine (10 mL), dried over Na₂SO₄ and concentrated to get a thick syrupy liquid which on scratching after addition of anhyd hexane (15 mL) resulted in a solid product. The solid, on recrystallisation (benzene–hexane), yielded phosphorane 5 (7.8 g, 70%); mp 122 °C.¹²

**Esters 6a,b; General Procedure**

To a solution of phosphorane (1 mmol) in MeOH (10 mL) was added an ag solution of aldehyde (2 mL, 5 mmol) and the reaction mixture was refluxed for 2 h. After the completion of reaction, hexanes (20 mL) was added and the reaction mixture was shaken vigorously. The upper layer was separated, evaporated and the resulting crude product was purified by silica gel column chromatography (hexanes) to afford a pleasant-smelling volatile liquid.

**Ethinyl-2-methylidenepent-4-enoate (6a)**

Yield: 50%.

**IR (neat):** 1722 (C=O), 1660 (C=C), 1643 (C=C) cm⁻¹.

**¹H NMR (300 MHz, CDCl₃):** δ = 7.1 Hz, 2 H, OCH₃(CH₂), 5.11 (m, 2 H, CH₂CH=CH₂), 5.57 (br s, 1 H, HCH=C, 5.84 (m, 1 H, CH₂CH=CH₂), 6.20 (br s, 1 H, HCH=C).

**¹³C NMR (75 MHz, CDCl₃):** δ = 14.10 (CH₃), 35.82 (CH), 60.60 (OCH₃), 116.65 (CH=CH₂), 125.08 (=CH₂), 135.10 (=CH=), 139.18 (C), 166.86 (C=O).

**MS:** m/z (%) = 141 (28, M⁺ + 1), 113 (100), 112 (12), 95 (48), 67(36).

**E-(Ethyl-2-ethylidenepent-4-enoate (6b)**

Yield: 50%.

**IR (neat):** 1722 (C=O), 1660 (C=C), 1643 (C=C) cm⁻¹.

**¹H NMR (300 MHz, CDCl₃):** δ = 1.28 (t, J = 7.2 Hz, 3 H, OCH₃(CH₂), 1.79 (d, J = 6.9 Hz, 3 H, CH₃), 3.08 (d, J = 6.0 Hz, 2 H, CH₂CH=CH₂), 4.19 (q, J = 7.2 Hz, 2 H, OCH₂CH₂), 5.00 (m, 2 H, CH₂CH=CH₂), 5.81 (m, 1 H, CH₂CH=CH₂), 6.95 (q, J = 6.9 Hz, 1 H, =CHCH₃).

**¹³C NMR (75 MHz, CDCl₃):** δ = 14.12 (CH₃), 14.21 (CH₂), 30.45 (CH₃), 60.36 (OCH₃), 114.91 (CH=CH₂), 130.96 (C), 135.19 (CH=CH₂), 138.28 (=CH₂), 167.45 (C=O).

**MS:** m/z (%) = 155 (22, M⁺ + 1), 127 (100), 109 (54), 99 (48), 81 (39), 79 (11).

**Esters 6c–e; General Procedure**

To a magnetically stirred suspension of PCC (1.5 mmol) and NaOAc (1.5 mmol) in anhyd CH₂Cl₂ (5 mL) was added followed by phosphorane (1 mmol) in one portion. After 3 h, Et₂O (5 mL) was added and the supernatant solution was decanted from the black granular solid. The residue obtained after evaporation of the solvent was further purified by column chromatography using hexanes as the eluent to afford a pleasant-smelling liquid.

**Ethyl-2-(prop-2-enyl)hex-2-enoate (6c)**

Yield: 57%.

**IR (neat):** 1716 (C=O), 1654 (C=C), 1643 (C=C) cm⁻¹.

**¹H NMR (300 MHz, CDCl₃):** δ = 3.9 (t, J = 7.2 Hz, 3 H, OCH₃(CH₂), 1.29 (t, J = 7.2 Hz, 3 H, OCH₃(CH₂), 1.49 (q, J = 7.5 Hz, 2 H, CH₃CH=CH₂), 2.17 (q, J = 7.5 Hz, 2 H, CH₃CH=CH₂), 3.07 (d, J = 6.0 Hz, 2 H, CH₂CH=CH₂), 4.19 (q, J = 7.2 Hz, 2 H, OCH₂CH₂), 4.99 (m, 2 H, CH₂CH=CH₂), 5.80 (m, 1 H, CH₂CH=CH₂), 6.84 (t, J = 7.5 Hz, 1 H, =CH).

**¹³C NMR (75 MHz, CDCl₃):** δ = 13.80 (CH₃), 14.15 (CH₂), 21.89 (CH₂), 30.46 (CH₃), 30.75 (CH₃), 60.30 (CH₂), 114.00 (CH=CH₂), 130.02 (C), 135.55 (=CH=), 143.45 (CH), 167.52 (C=O).

**MS:** m/z (%) = 183 (6, M⁺ + 1), 155 (3), 137 (73), 109 (100), 67 (45).

**Ethyl-2-(prop-2-enyl)oct-2-enoate (6d)**

Yield: 60%.

**IR (neat):** 1716 (C=O), 1653 (C=C), 1643 (C=C) cm⁻¹.

**¹H NMR (300 MHz, CDCl₃):** δ = 0.82 (t, J = 7.5 Hz, 3 H, CH₃CH₂), 1.11–1.35 (m, 9 H, OCH₂CH₂ and 3 × CH₂), 2.11 (m, 2 H, =CHCH₂), 3.00 (d, J = 6 Hz, 2 H, CH₂CH=CH₂), 4.12 (q, J = 7.2 Hz, 2 H, =CHCH₂).
5-Methyl-3-(methylidene)dihydrofuran-2(5H)-one (7d)  
Yield: 85%.  
IR (neat): 1753 (C=O), 1685 (C=C) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.90 (d, J = 6.6 Hz, 6 H, CH(CH₃)₂), 1.41 (q, J = 7.2 Hz, 2 H, CH₂), 4.91 (m, 1 H, =CHCH₃), 7.30 (m, 1 H, =CH).  
13C NMR (75 MHz, CDCl₃): δ = 14.21 (CH₃), 29.08 (CH), 31.58 (CH₂), 37.58 (CH₂), 60.38 (OCH₂), 114.98 (CH=CH₂), 130.48 (C), 135.56 (CH₂=CH₂), 148.13 (=CH), 167.58 (C=O).  
HRMS: m/z calc for C₇H₁₀O₂ + Na (M + Na⁺): 219.1361; found: 219.1361.

7a-e; General Procedure  
To a flask containing ice-cold ester 6 (1 mmol) was added ice-cold concd H₂SO₄ (2 mL) and the reaction mixture was stirred in an ice bath for 1 h. After the completion of reaction sufficient crushed ice (10 mL) was added to the reaction mixture and the reaction mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried over anhyd Na₂SO₄ and the crude product was purified by silica gel column chromatography (EtOAc–hexanes, 1:9) to yield liquid lactone.

5-Methyl-3-(methylene)dihydrofuran-2(5H)-one (7a)  
Yield: 87%.  
IR (neat): 1765 (C=O), 1665 (C=C) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.43 (d, J = 6.3 Hz, 3 H, CHCH₃), 2.56 (ddt, J = 16.8, 5.7, 2.7 Hz, 1 H, HCHCH), 3.10 (ddt, J = 16.8, 7.2, 2.7 Hz, 1 H, HCHCH), 4.66 (m, 1 H, CHCH₃), 5.63 (t, J = 2.7 Hz, 1 H, HCH=CH₂), 6.23 (t, J = 2.7 Hz, 1 H, HCH=CH₂).  
13C NMR (75 MHz, CDCl₃): δ = 21.88 (CH₃), 35.10 (CH₂), 73.82 (CH₁), 121.94 (CH₃), 134.80 (C), 176.20 (C=O).  
MS: m/z (%) = 113 (8, M⁺ + 1), 95 (17), 67 (100), 65 (20), 43 (13).  
5-Methyl-3-[(E)-ethylidene]dihydrofuran-2(5H)-one (7b)  
Yield: 85%.  
IR (neat): 1756 (C=O), 1680 (C=C) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.35 (d, J = 6.3 Hz, 3 H, CHCH₃), 1.84 (dt, J = 6.9, 2.1, 1.8 Hz, 3 H, CHCH₂), 2.35 (ddt, J = 16.8, 5.2, 1.8 Hz, 1 H, HCH CH₃), 3.01 (ddt, J = 16.8, 7.8, 2.1 Hz, 1 H, HCHCH), 4.61 (ddq, J = 7.8, 6.5, 5.2 Hz, 1 H, CHCH₃), 6.78 (m, 1 H, =CH).  
13C NMR (75 MHz, CDCl₃): δ = 15.55 (CH₃), 22.20 (CH₃), 32.65 (CH₃), 73.85 (CH), 127.55 (C), 135.38 (CH), 170.64 (C=O).  
MS: m/z (%) = 127 (7, M⁺ + 1), 109 (29), 81 (100), 79 (37), 77 (6), 43 (5).  
5-Methyl-3-[(E)-butylidene]dihydrofuran-2(5H)-one (7c)  
Yield: 92%.  
IR (neat): 1753 (C=O), 1690 (C=C) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.87 (t, J = 7.5 Hz, 3 H, CH₂CH₃), 1.19–1.53 (m, 4 H, 2 × CH₂), 1.34 (d, J = 6.0 Hz, 3 H, CH₂CH₂), 2.22
\[ t, J = 7.5 \text{ Hz}, 2 \text{ H}, \text{=CHCH}_2 \text{CH}_3; 4.95 \text{ (q, } J = 7.5 \text{ Hz, 1 H, CH)}, 6.90 \text{ (m, 1 H, } \text{=CH}) \text{.} \]

\[ ^{1}C \text{ NMR (75 MHz, CDCl}_3\text{): } \delta = 13.68 \text{ (CH}_3\text{), 19.13 \text{ (CH}_3\text{), 22.18 \text{ (CH}_2\text{), 24.78 \text{ (CH}_3\text{), 29.43 \text{ (CH}_2\text{), 75.45 \text{ (CH)}}, 134.24 \text{ (C, 134.59 (C, 148.65 (CH)\text{, 170.01 (C=O)})}}. \]

MS: \text{m/z (\%) = 155 (32, M}^+ + 1\text{), 137 (47), 109 (100), 67 (20).} \]

**3-Hexyl-5-methyl-2[5H]furanone (1d)**

Yield: 93%.

IR (neat): 1750 (C=O), 1650 (C=C) cm\(^{-1}\).

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