

RESEARCH ARTICLE

Synthesis of 7-functionalized γ -lactones from furfural

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Abstract: Condensation of the methyl ketones, 2-propanone, 2-butanone, 2-pentanone, 2-hexanone and 2-heptanone with furfural under alkaline conditions yielded the corresponding furfurylidene ketones arising from condensation at the methyl group. Hydrolytic ring cleavage of the furfurylidene ketones under acidic conditions yielded the corresponding 4,7-dioxocarboxylic acids. Borohydride reduction of these acids followed by acidification yielded the corresponding 7-hydroxy- γ -lactones. The 7-hydroxy group could be oxidized to a keto group or acetylated easily. The 7-hydroxy-, 7-oxo- and 7-acetoxy- γ -lactones synthesized are not natural compounds, and are being reported for the first time. Their structures were established by Infra Red (IR), ¹H and ¹³C Nuclear Magnetic Resonance (NMR), 2D NMR (COSY and HETCOR) spectroscopy and Gas Chromatography-Mass Spectrometry (GC-MS).

Keywords: Dioxocarboxylic acids, furfural, furfurylidene ketones, gamma lactones

INTRODUCTION

Furfural is a readily available, versatile and cheap material which can be generated from a variety of waste agricultural biomass such as rice hull and bagasse¹.

Gamma lactones are widely distributed in nature. They are an important class of compounds found in both natural and synthetic flavours and fragrances^{2,3}. They have been also reported to exhibit biological activities such as cytotoxicity, pheromone activity and anti-feedant activity. The biological activity, as well as the flavour and fragrance of the individual gamma lactones vary with the structural features associated with side chain attached to the 4-position of the butyrolactone nucleus, such as chain length, chain branching, unsaturation, substitution and stereochemistry⁴. Thus, synthetic methods for functionalizing the side chain and for further manipulation

of the functionality will be useful in generating new potentially bioactive compounds.

We report here a convenient synthesis of 7-functionalized γ -lactones, using furfural as a common precursor. These compounds have been neither reported from nature, nor synthesized earlier.

METHODS AND MATERIALS

¹H Nuclear Magnetic Resonance (NMR) (300 and 200 MHz) : Varian Mercury- 300 and Bruker AC-F 200 with 2D programme¹³. C NMR (75 and 50 MHz) : Varian Mercury- 300 and Bruker AC-F 200 with DEPT programme. Varian II Column J & Gas chromatography-mass spectrometry (GC-MS) W DB5, 0.25 μ m 30 m, carrier gas He. Infra Red (IR) : Unicam SP 1025. Melting Point: Reichert Thermovar hot plate microscope. Preparative Thin Layer Chromatography (PTLC):60 PF254 (Merck no. 7747). Thin Layer Chromatography (TLC): 60 GF254 (Merck no. 7730). Column chromatography : Merck Art 7734 (30-70 mesh).

Preparation of furfurylidene ketones: A mixture of furfural (1.27 mol), water (1 L) and the methyl ketone **1a**, **1b**, **1c**, **1d** or **1e** (2.87 mol) was cooled to 10 °C. A solution of 33% aqueous sodium hydroxide (25 mL) was added slowly while stirring. Stirring was continued for 4 h without external cooling and the reaction mixture was acidified with 20% sulphuric acid. The liquid separated out into two layers on standing. The organic layer was purified by column (silica) chromatography, using a gradient elution with hexane-dichloromethane-methanol.

4-(2-Furyl)but-3-ene-2-one (2a), Yellow needles (87.3%); m.p. 37.0- 37.2 °C (lit.⁵ 37-39 °C); ¹H NMR

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(200 MHz, CDCl_3) δ : 7.51 (1H, d, $J = 2.0$ Hz, furan), 7.28 (1H, d, $J = 16.0$ Hz), 6.67 (1H, d, $J = 4.0$ Hz, furan), 6.61 (1H, d, $J = 16.0$ Hz), 6.49 (1H, dd, furan) 2.32 (3H, s); ^{13}C NMR (50 MHz, CDCl_3) δ : 197.7 (C-7), 150.8 (C-4), 144.9 (C-1), 129.3 (C-5), 124.2 (C-6), 115.5 (C-2), 112.5 (C-3), 27.8 (C-8).

1-(2-Furyl)pent-1-en-3-one (2b), Yellow, transparent oily liquid (71%); ^1H NMR (300 MHz, CDCl_3) δ : 7.51 (1H, d, $J = 1.9$ Hz, furan), 7.32 (1H, d, $J = 16.0$ Hz), 6.70 (1H, d, $J = 3.7$ Hz, furan), 6.61 (1H, d, $J = 16.0$ Hz), 6.47 (1H, dd, furan), 2.63 (2H, q, $J = 5.0$ Hz), 1.11 (3H, t, $J = 5.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 199.5 (C-7), 151.9 (C-4), 145.3 (C-1), 128.9 (C-5), 123.5 (C-6), 116.0 (C-3), 112.9 (C-2), 34.7 (C-8), 25.9 (C-9).

1-(2-Furyl)hex-1-en-3-one (2c), Yellow, transparent oily liquid (72.5%); ^1H NMR (300 MHz, CDCl_3) δ : 7.55 (1H, broad singlet, furan), 7.34 (1H, d, $J = 16.5$ Hz), 6.65 (1H, d, $J = 3.1$ Hz, furan), 6.55 (1H, d, $J = 16.5$ Hz), 6.48 (1H, dd, furan), 2.58 (2H, t, $J = 7.2$ Hz); 1.76 (2H, m), 0.97 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 199.8 (C-7), 144.6 (C-4), 130.8 (C-1), 128.4 (C-5), 123.4 (C-6), 115.4 (C-2), 112.4 (C-3), 43.4 (C-8), 22.8 (C-9), 13.9 (C-10).

1-(2-Furyl)hept-1-en-3-one (2d), Yellow needles (76%); m.p. 42.4-44.1 °C (lit.⁵ 45-46 °C); ^1H NMR (300 MHz, CDCl_3) δ : 7.48 (1H, broad singlet, furan), 7.32 (1H, d, $J = 15.5$ Hz), 6.66 (1H, d, $J = 3.1$ Hz, furan), 6.63 (1H, d, $J = 15.0$ Hz), 6.47 (1H, dd, furan), 2.59 (2H, t, $J = 6.9$ Hz), 1.64 (2H, m), 1.34 (2H, m), 0.92 (3H, T, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 199.7 (C-7), 150.9 (C-4), 144.5 (C-1), 128.3 (C-5), 123.2 (C-6), 115.3 (C-2), 112.3 (C-3), 41.0 (C-8), 26.5 (C-9), 22.4 (C-10), 13.9 (C-11).

1-(2-Furyl)oct-1-en-3-one(2e), Yellow needles (76%); m.p. 39.1-40.8 °C (lit.⁵ 44 °C); ^1H NMR (300 MHz, CDCl_3) δ : 7.46 (1H, broad singlet, furan), 7.29 (1H, d, $J = 16.5$ Hz), 6.66 (1H, d, $J = 3.0$ Hz, furan), 6.61 (1H, d, $J = 16.5$ Hz), 6.44 (1H, dd, furan), 2.56 (2H, t, $J = 7.2$ Hz), 1.66-1.27 (6H, m), 0.87 (3H, t, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 195.4 (C-7), 146.6 (C-4), 140.2 (C-1), 123.8 (C-5), 118.8 (C-6), 110.9 (C-2), 107.9 (C-3), 36.9 (C-8), 27.1 (C-9), 19.7 (C-10), 18.1 (C-11), 9.6 (C-12).

Preparation of 4,7-dioxocarboxylic acids: Compound **2a** (0.022 mol) was dissolved in cyclohexane (50 mL) and was added to a mixture of acetic acid (20 mL), hydrochloric acid (15 mL), ethanol (15 mL) and water (20 mL). The reaction mixture was heated on an oil bath under reflux, while stirring mechanically for 24 hrs. After the reaction was completed, the solvents and acids were removed under reduced pressure. The resultant dark brown product was treated with saturated aqueous

sodium hydrogen carbonate until there was no further evolution of carbon dioxide, and then extracted with diethyl ether to remove unreacted **2a**. The aqueous layer was acidified with 20% sulphuric acid and extracted into ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain a pale creamy solid. Crystallization from hexane-ethyl acetate gave **3a**.

4,7-Dioxooctanoic acid (3a), Off white triangular plate type crystals (15.3%); m.p. 76.5-76.9 °C (lit.⁶ 75-76 °C); ^1H NMR (200 MHz, CDCl_3) δ : 8.2 (OH, broad singlet), 2.83-2.40 (8H, m), 2.11 (3H, s); ^{13}C NMR (50 MHz, CDCl_3) δ : 207.5 (C-4), 207.3 (C-7), 178.1 (C-1), 36.8, 36.7, 35.8, 29.7 (C-2, C-3, C-5, C-6), 27.6 (C-8).

Compounds **2b**, **2c**, **2d** or **2e**, (30 g) in methanol (50 mL) was added drop-wise during 30 h to a solution of concentrated hydrochloric acid (150 mL) and methanol (250 mL), heated to 80-90 °C under reflux on an oil bath. After a further 30 h under reflux, the organic solvent was removed under reduced pressure and the residue was treated with aqueous sodium hydrogen carbonate until there was no further evolution of carbon dioxide and then extracted with dichloromethane to remove unreacted enone. The aqueous layer left after the dichloromethane extraction was acidified with 20% sulphuric acid and extracted into ethyl acetate. After drying the solution with anhydrous sodium sulphate, the ethyl acetate extracts were concentrated under reduced pressure to obtain the products as a pale creamy solid. Crystallization from hexane-ethyl acetate gave the corresponding 4,7-dioxocarboxylic acid.

4,7-Dioxononanoic acid (3b), Off white triangular plates (10.3%); m.p. 87.6-87.7 °C (lit.⁷ 85-86 °C); ^1H NMR (200 MHz, CDCl_3) δ : 2.85-2.57 (8H, m), 2.49 (2H, q, $J = 7.3$ Hz), 0.95 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (50 MHz, CDCl_3) δ : 210.1 (C-4), 207.4 (C-7), 178.2 (C-1), 36.9, 35.9, 35.8, 35.6 (C-2, C-3, C-5, C-6), 27.7 (C-8), 7.7 (C-9).

4,7-Dioxodecanoic acid (3c), Off white triangular plates (2.2%); m.p. 83.2-83.4 °C (lit.⁷ 83-84 °C); ^1H NMR (300 MHz, CDCl_3) δ : 9.10 (1H, br. s), 2.81-2.56 (8H, m), 2.40 (2H, t, $J = 7.2$ Hz), 1.58 (2H, hex., $J = 7.2$ Hz), 0.93 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ : 209.4 (C-4), 207.1 (C-7), 178.1 (C-1), 44.7 (C-2), 36.9, 36.1, 35.9 (C-3, C-5, C-6), 27.8 (C-8), 17.4 (C-9), 13.7 (C-10).

4,7-Dioxoundecanoic acid (3d), Off white triangular plates (17.5%); m.p. 83.6-84.2 °C (lit.⁷ 84-85 °C); ^1H NMR (300 MHz, CDCl_3) δ : 2.80-2.51 (8H, m), 2.42 (2H, t, $J = 7.5$ Hz), 1.61 (2H, pen., $J = 7.5$ Hz), 1.31 (2H, hex., $J = 7.5$ Hz), 0.91 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (75

MHz, CDCl₃) δ : 210.5 (C-4), 208.2 (C-7), 178.6 (C-1), 47.9, 43.5, 37.9, 37.1 (C-2, C-3, C-5, C-6), 28.8 (C-8), 27.0 (C-9), 23.4 (C-10), 13.9 (C-11).

4,7-Dioxododecanoic acid (3e), Off white triangular plates (32.7%); m.p. 87.5-88.2 °C (lit.⁷ 92-93 °C); ¹H NMR (300 MHz, CDCl₃) δ : 8.20 (1H br. s), 2.80-2.53 (8H, m), 2.42 (2H, t, J = 7.5 Hz), 1.36-1.11 (6H, m), 0.88 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ : 205.2 (C-4), 202.8 (C-7), 173.5 (C-1), 38.3, 32.5, 31.7, 31.5 (C-2, C-3, C-5, C-6), 26.9 (C-8), 23.4 (C-9), 19.1 (C-10), 18.0 (C-11), 9.5 (C-12).

Preparation of 7-hydroxy-γ-lactones: A solution of sodiumborohydride (3 mmol) in 99% ethanol (20 mL) was added dropwise while stirring at room temperature to a solution of 4,7-dioxocarboxylic acid **3a**, **3b**, **3c**, **3d** or **3e** (0.3 mmol) in 99% ethanol (20 mL) within 20 min. Stirring was continued for a further 3-5 h. The mixture was quenched with ice water (10 mL) and hydrochloric acid (10M for solution of **3a** and 1M for solution of **3b**, **3c**, **3d** or **3e**). The excess ethanol was removed under reduced pressure and the mixture was extracted with dichloromethane. Evaporation of the solution gave the product as a light yellow viscous liquid. The crude product was subjected to silica gel column chromatography, using a gradient elution with hexane-chloroform-ethyl acetate to obtain the corresponding 7-hydroxy-γ-lactone.

7-Hydroxyoctan-4-olide (4a), (48.5%); IR ν^{KBr} cm⁻¹: 3430, 1780 ; ¹H NMR (200 MHz, CDCl₃) δ: 4.55 (1H, m, H-4), 3.86 (1H, m, H-7), 2.58 (2H, m, H-2), 2.40 (1H, m, H-3a), 2.20 (1H, broad singlet, OH), 1.90 (1H, m, H-3b), 1.84 (2H, m, H-5), 1.61 (2H, m, H-6), 1.23 (3H, d, J = 6 Hz H-8); ¹³C NMR (50 MHz, CDCl₃) δ : 177.5 (C-1), 80.8 & 81.2 (C-4), 67.4 & 67.2 (C-7), 34.7 & 34.3 (C-6), 31.9 & 31.5 (C-5), 28.7 (C-2), 27.9 & 27.8 (C-3), 23.5 & 23.4 (C-8); GCMS m/z (rel. int.): 159, M+1, (1), 143 (2), 125 (10), 114 (48), 97 (10), 85 (100), 73 (38), 55 (68), 31 (12).

7-Hydroxynonan-4-olide (4b), (55.0%); IR ν^{KBr} cm⁻¹: 3420, 1770; ¹H NMR (200 MHz, CDCl₃) δ: 4.59 (1H, m, H-4), 3.80 (1H, broad singlet, OH), 3.53 (1H, m, H-7), 2.54 (2H, m, H-2), 2.36 (1H, m, H-3a), 2.01-1.61 (5H, m, H-3b, H-5, H-6), 1.46 (2H, m, H-8), 0.90 (3H, t, J = 7.2 Hz, H-9); ¹³C NMR (50 MHz, CDCl₃) δ : 177.4 (C-1), 81.1 & 80.6 (C-4), 71.8 & 71.5 (C-7), 31.8 & 31.4, 29.5 & 29.4 (C-5, C-6), 31.2 & 30.9 (C-8), 28.2 (C-2), 27.3 & 27.2 (C-3), 9.3 (C-9); GCMS m/z (rel. int.): 173, M+1, (1), 143 (21), 125 (86), 114 (67), 97 (43), 85 (81), 73 (59), 55 (100), 31 (71).

7-Hydroxydecan-4-olide (4c), (33.3%); IR ν^{KBr} cm⁻¹: 3440, 1780; ¹H NMR (300 MHz, CDCl₃) δ: 4.54 (1H, m,

H-4), 3.76 (1H, m, H-7), 2.55 (2H, m, H-2), 2.34 (1H, m, H-3a), 1.85 (1H, m, H-3b), 1.60 (2H, m, H-5), 1.43-1.26 (6H, m, H-6, H-8, H-9), 0.92 (3H, t, J = 6.6 Hz, H-10); ¹³C NMR (75 MHz, CDCl₃) δ : 177.3 (C-1), 81.3 & 80.7 (C-4), 71.3 & 70.9 (C-7), 39.9 & 39.8, 33.3 & 32.8 (C-6, C-8), 32.1 & 31.6 (C-5), 28.9 & 28.8 (C-2), 28.2 & 28.0 (C-3), 18.9 (C-9), 14.1 (C-10).

7-Hydroxyundecan-4-olide (4d), (61.0%); IR ν^{KBr} cm⁻¹: 3420, 1750 ; ¹H NMR (300 MHz, CDCl₃) δ: 4.54 (1H, m, H-4), 3.61 (1H, m, H-7), 2.54 (2H, m, H-2), 2.34 (1H, m, H-3a), 1.84 (1H, m, H-3b), 1.72 (2H, m, H-5), 1.58 (2H, m, H-6), 1.44 (2H, m, H-8), 1.34 (2H, m, H-9), 1.16 (2H, m, H-10), 0.91 (3H, t, J = 6.6 Hz, H-11); ¹³C NMR (75 MHz, CDCl₃) δ : 177.3 (C-1), 82.3 & 81.7 (C-4), 72.6 & 71.2 (C-7), 38.5 & 38.4 (C-8), 34.2 & 33.7 (C-6), 33.2 & 32.7 (C-5), 29.9 & 29.8 (C-2), 29.2 & 29.0 (C-3), 28.9 & 28.8 (C-9), 23.8 (C-10), 15.1 (C-11); GCMS m/z (rel. int.): (M⁺+1) 201 (1), 143 (30), 125 (100), 114 (74), 97 (33), 85 (52), 73 (52), 55 (79), 31 (19).

7-Hydroxydodecan-4-olide (4e), (75.0%); IR ν^{KBr} cm⁻¹: 3500, 1780 ; ¹H NMR (300 MHz, CDCl₃) δ: 4.48 (1H, m, H-4), 3.56 (1H, m, H-7), 2.49 (2H, m, H-2), 2.30 (1H, m, H-3a), 1.90-1.45 (9H, m, H-3b, H-5, H-6, H-8, H-9), 1.89 (2H, m, H-10), 1.20 (2H, m, H-11), 0.92 (3H, t, J = 6.6 Hz, H-12); ¹³C NMR (75 MHz, CDCl₃) δ : 172.7 (C-1), 76.9 & 76.4 (C-4), 66.9 & 66.6 (C-7), 33.2 & 33.1, 28.7 & 28.2, 23.6 & 23.5, 20.9 (C-5, C-6, C-8, C-9), 27.6 (C-2), 27.4 & 27.1 (C-3), 24.5 & 24.4 (C-10), 18.2 (C-11), 9.6 (C-12); GCMS m/z (rel. int.): (M⁺+1) 215 (26), 143 (95), 125 (98), 114 (100), 97 (71), 85 (73), 73 (48), 55 (100), 31 (17).

Preparation of 7-acetoxy-γ-lactones: The 7-hydroxy-γ-lactone **4a**, **4b**, **4c**, **4d** or **4e** (0.13 mmol) was dissolved in dry pyridine (0.4 mL). Acetyl chloride (0.4 mL) was added drop-wise to the mixture on an ice bath with shaking and allowing to cool to room temperature. The reaction mixture was warmed for 2 min on a boiling water bath and then acidified with 0.5 M hydrochloric acid (2 mL) and extracted with CH₂Cl₂. The CH₂Cl₂ extract was washed with aqueous NaHCO₃ and dried with anhydrous Na₂SO₄. Evaporation of the solution under reduced pressure gave the product as a pale yellow viscous liquid. The crude product was subjected to silica gel column chromatography, using a gradient elution with hexane-chloroform-ethyl acetate to obtain the corresponding 7-acetoxy-γ-lactone.

7-Acetoxyoctan-4-olide (5a), (46.0%); IR ν^{KBr} cm⁻¹: 1790, 1740 ; ¹H NMR (200 MHz, CDCl₃) δ: 4.96 (1H, m, H-7), 4.50 (1H, m, H-4), 2.55 (2H, m, H-2), 2.34 (1H, m, H-3a), 2.05 (3H, s, OCOCH₃), 1.97-1.54 (5H, m, H-3b,

H-5, H-6) 1.24 (3H, d, $J = 6.3$ Hz, H-8); ^{13}C NMR (50 MHz, CDCl_3) δ : 176.9 (C-1), 170.6 (OCOCH_3), 80.5 & 80.2 (C-4), 70.3-69.9 (C-7), 31.7 & 31.6, 31.5 & 31.3 (C-5, C-6), 28.7 (C-2), 27.9 (C-3), 21.2 (C-8), 19.2 (OCOCH_3); GCMS m/z (rel. int.): ($\text{M}^+ + 1$) 201 (1), 185 (1), 125 (10), 114 (28), 97 (18), 85 (90), 73 (11), 55 (29), 43 (100), 31 (3).

7-Acetoxynonan-4-olide (5b), (46.2%); IR ν^{KBr} cm^{-1} : 1790, 1740; ^1H NMR (200 MHz, CDCl_3) δ : 4.80 (1H, m, H-7), 4.49 (1H, m, H-4), 2.54 (2H, m, H-2), 2.35 (1H, m, H-3a), 2.05 (3H, s, OCOCH_3), 1.97-1.51 (7H, m, H-3b, H-5, H-6, H-8), 0.90 (3H, t, $J = 7.3$ Hz, H-9); ^{13}C NMR (50 MHz, CDCl_3) δ : 176.9 (C-1), 170.9 (OCOCH_3), 80.7 & 80.2 (C-4), 74.9 & 74.3 (C-7), 31.7 & 31.3, 29.9 & 29.4, 28.8 & 28.7 (C-5, C-6, C-8), 27.9 (C-2), 27.0 & 26.9 (C-3), 21.1 (OCOCH_3), 9.5 (C-9); GCMS m/z (rel. int.): ($\text{M}^+ - \text{C}_2\text{H}_5$) 185 (1), 125 (10), 114 (10), 97 (4), 85 (29), 73 (4), 55 (14), 43 (100), 31 (5).

7-Acetoxydecan-4-olide (5c), Light yellow viscous liquid (8.1%); IR ν^{KBr} cm^{-1} : 1780, 1740; ^1H NMR (300 MHz, CDCl_3) δ : 4.90 (1H, m, H-7), 4.45 (1H, m, H-4), 2.60 (2H, m, H-2), 2.35 (1H, m, H-3a), 2.05 (3H, s, OCOCH_3), 1.91 (1H, m, H-3b) 1.81-1.20 (8H, m, H-5, H-6, H-8, H-9), 0.91 (3H, t, $J = 6.9$ Hz, H-10).

7-Acetoxyundecan-4-olide (5d), (45.2%); IR ν^{KBr} cm^{-1} : 1770, 1735; ^1H NMR (300 MHz, CDCl_3) δ : 4.92 (1H, m, H-7), 4.47 (1H, m, H-4), 2.54 (2H, m, H-2), 2.32 (1H, m, H-3a), 2.05 (3H, s, OCOCH_3), 1.82 (1H, m, H-3b), 1.63 (2H, m, H-5), 1.41-1.15 (6H, m, H-6, H-8, H-9), 1.19 (2H, m, H-10), 0.89 (3H, t, $J = 6.9$ Hz, H-11); ^{13}C NMR (75 MHz, CDCl_3) δ : 176.9 (C-1), 170.5 (OCOCH_3), 80.6 & 80.1 (C-4), 73.7 & 73.2 (C-7), 33.9 & 33.8, 31.6 & 31.3, 27.4 & 27.3 (C-6, C-8, C-9), 30.1 & 29.4 (C-5), 28.8 & 28.7 (C-2), 27.9 & 27.8 (C-3), 22.5 (OCOCH_3), 21.2 & 21.1 (C-10), 13.9 (C-11); GCMS m/z (rel. int.): ($\text{M}^+ + 1$) 243 (1), 185 (3), 125 (24), 114 (30), 97 (14), 85 (45), 73 (8), 55 (21), 43 (100).

7-Acetyldodecan-4-olide (5e), (33.0%); IR ν^{KBr} cm^{-1} : 1780, 1740; ^1H NMR (300 MHz, CDCl_3) δ : 4.85 (1H, m, H-7), 4.43 (1H, m, H-4), 2.85 (2H, m, H-2), 2.35 (1H, m, H-3a), 2.05 (3H, s, OCOCH_3), 1.90 (1H, m, H-3b), 1.85-1.55 (6H, m, H-6, H-8, H-9), 1.63 (2H, m, H-5), 1.52 (2H, m, H-10), 1.30 (2H, m, H-11), 0.90 (3H, t, $J = 6.9$ Hz, H-11); ^{13}C NMR (75 MHz, CDCl_3) δ : 176.6 (C-1), 170.5 (OCOCH_3), 76.2 & 75.8 (C-4), 69.3 (C-7), 29.7, 24.4 & 24.3, 20.5 (C-6, C-8, C-9), 27.4 (C-2), 27.2 & 27.0 (C-3), 25.7 (C-10), 23.6 & 23.5 (C-5), 18.1 (OCOCH_3), 16.8 (C-11), 9.6 (C-12); GCMS m/z (rel. int.): ($\text{M}^+ + 1$) 257 (1), 185 (3), 125 (24), 114 (30), 97 (14), 85 (45), 73 (8), 55 (21), 43 (100).

Preparation of 7-oxo- γ -lactones: Jones reagent⁸ (1.25 mL, 0.6 mmol) was added dropwise while stirring at room temperature to 7-hydroxy gamma lactone **4a**, **4b**, **4c**, **4d** or **4e** (1.8 mmol) within 15 min. Stirring was continued for a further 2 h and then the reaction mixture was extracted with CH_2Cl_2 . The CH_2Cl_2 extract was washed with aqueous NaHCO_3 solution and dried with anhydrous Na_2SO_4 . Evaporation of the solution under reduced pressure gave the product as a pale yellow viscous liquid. The crude product was subjected to silica gel column chromatography, using a gradient elution with hexane-chloroform-ethyl acetate to obtain the corresponding 7-oxo- γ -lactone.

7-Oxo-octan-4-olide (6a), (32.6%); IR ν^{KBr} cm^{-1} : 1780, 1740; ^1H NMR (200 MHz, CDCl_3) δ : 4.58 (1H, m, H-4), 2.68 (2H, t, $J = 6.8$ Hz, H-6), 2.52 (2H, m, H-2), 2.42 (1H, m, H-3a), 2.18 (3H, s, H-8), 2.01 (1H, m, H-5a), 1.91 (1H, m, H-3b), 1.83 (1H, m, H-5b); ^{13}C NMR (50 MHz, CDCl_3) δ : 207.3 (C-7), 176.8 (C-1), 79.7 (C-4), 39.0 (C-6), 29.9 (C-8), 29.0 (C-5), 28.6 (C-2), 27.8 (C-3); GCMS m/z (rel. int.): ($\text{M}^+ + 1$) 157 (2), 141 (1), 113 (24), 99 (61), 85 (57), 71 (24), 57 (19), 43 (100).

7-Oxononan-4-olide (6b), (35.3%); IR ν^{KBr} cm^{-1} : 1780, 1750; ^1H NMR (200 MHz, CDCl_3) δ : 4.51 (1H, m, H-4), 2.63 (2H, t, $J = 7.5$ Hz, H-6), 2.57 (2H, m, H-2), 2.46 (2H, q, $J = 7.3$ Hz, H-8), 2.40 (1H, m, H-3a), 2.01 (1H, m, H-5a), 1.91 (1H, m, H-3b), 1.83 (1H, m, H-5b), 1.05 (3H, t, $J = 7.3$ Hz, H-9); ^{13}C NMR (50 MHz, CDCl_3) δ : 201.1 (C-7), 176.8 (C-1), 79.8 (C-4), 37.6 (C-6), 35.8 (C-8), 29.4 (C-5), 28.5 (C-2), 27.8 (C-3), 7.6 (C-9); GCMS m/z (rel. int.): (M^+) 170 (5), 141 (19), 113 (48), 99 (67), 85 (60), 71 (38), 57 (100), 43 (36).

7-Oxodecan-4-olide (6c), (35.3%); IR ν^{KBr} cm^{-1} : 1780, 1740; ^1H NMR (300 MHz, CDCl_3) δ : 4.40 (1H, m, H-4), 3.01-2.50 (4H, m, H-6, H-8), 2.50-2.20 (3H, m, H-2, H-3a), 2.01 (1H, m, H-5a), 1.70 (1H, m, H-3b), 1.50-1.00 (3H, m, H-9, H-5a), 0.92 (3H, t, $J = 6.6$ Hz, H-10).

7-Oxoundecan-4-olide (6d), (41.0%); IR ν^{KBr} cm^{-1} : 1760, 1740; ^1H NMR (300 MHz, CDCl_3) δ : 4.45 (1H, m, H-4), 2.62 (2H, t, $J = 7.5$ Hz, H-6), 2.55 (2H, m, H-2), 2.42 (2H, t, $J = 7.3$ Hz, H-8), 2.38 (1H, m, H-3a), 2.01 (1H, m, H-5a), 1.84 (1H, m, H-3b), 1.56 (1H, m, H-5b), 1.30 (2H, m, H-9), 0.94-0.86 (5H, m, H-10, H-11); ^{13}C NMR (75 MHz, CDCl_3) δ : 207.5 (C-7), 176.5 (C-1), 80.9 (C-4), 43.2 (C-6), 39.2 (C-8), 37.8 (C-9), 35.6 (C-5), 30.8 (C-10), 29.7 (C-2), 29.6 (C-3), 15.1 (C-11); GCMS m/z (rel. int.): ($\text{M}^+ + 1$) 199 (4), 141 (14), 113 (38), 99 (36), 85 (98), 71 (32), 57 (100), 43 (31).

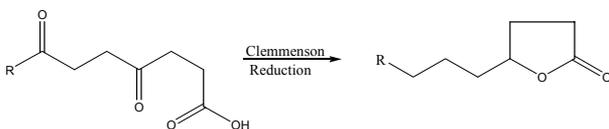
7-Oxododecan-4-olide (6e), (51%); IR $\nu_{\text{KBr}} \text{ cm}^{-1}$: 1780, 1760; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 4.45 (1H, m, H-4), 2.55 (2H, t, $J = 6$ Hz, H-6), 2.45 (2H, m, H-2), 2.35 (2H, t, $J = 6$ Hz, H-8), 2.25 (1H, m, H-3a), 1.95 (1H, m, H-5a), 1.85 (1H, m, H-3b), 1.75 (1H, m, H-5b), 1.52 (2H, m, H-9), 1.25-1.11 (4H, m, H-10, H-11), 0.80 (3H, t, $J = 6.9$ Hz, H-12); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ : 205.2 (C-7), 172.3 (C-1), 75.5 (C-4), 38.5 (C-6), 33.7 (C-8), 26.9 (C-5), 24.9 (C-2), 24.2 (C-3), 23.5 (C-9), 19.1 (C-10), 17.9 (C-11), 9.4 (C-12); GCMS m/z (rel. int.): ($M^+ + 1$) 213 (16), 141 (48), 113 (84), 99 (97), 85 (69), 71 (100), 57 (29), 43 (98).

RESULTS AND DISCUSSION

Furfural was condensed with a series of methyl ketones (**1a-1e**) (**Scheme II**) to obtain furfurylidene ketones (**2a-2e**), which were subjected to acid catalysed hydrolytic ring cleavage to provide 4,7-dioxocarboxylic acids (**3a-3e**). Spectral details for compounds (**2b-2e**) and (**3b-3e**) are being reported here for the first time. Although the conversion of furfurylidene ketones to 4,7-dioxocarboxylic acids by aqueous acids has been known for over a century, there have been no reports on the mechanism of the reaction. A mechanism for the reaction has been proposed involving the initial protonation of the carbonyl oxygen and nucleophilic attack by a water molecule at the C-1 position of the furan ring⁶.

The reduction of 4,7-dioxocarboxylic acids by the Clemmenson reagent to gamma lactones bearing saturated alkyl chains in the 4-position has been reported earlier⁹ (**Scheme I**). In the Clemmenson reduction a carbonyl group is reduced to a methylene group *via* a hydroxy group. In the reported reaction, the carbonyl group at the 7-position is reduced to a methylene group while the intermediate hydroxy group at the 4-position is not subjected to further reduction as it undergoes an intramolecular reaction with the carboxylic acid group and cyclizes to a lactone under the acidic reaction conditions.

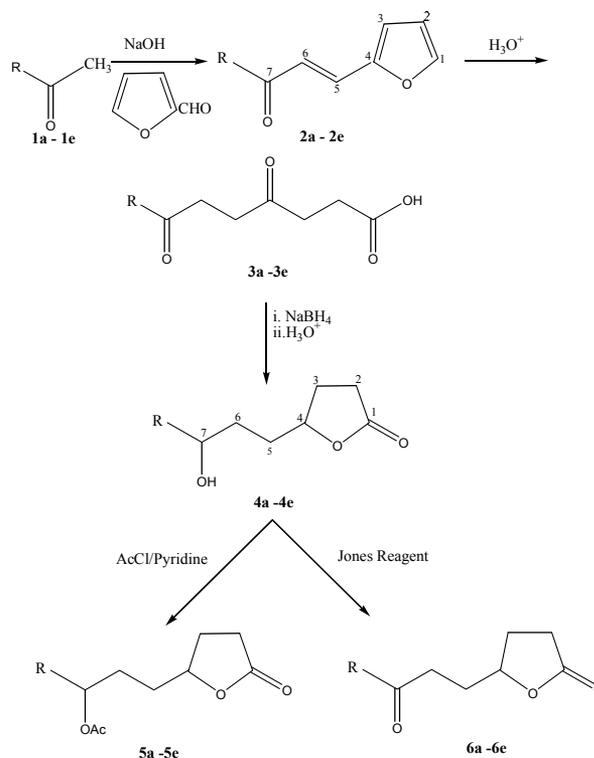
Our synthetic strategy was to use a reagent with a lower reducing potential to retain the intermediate hydroxy group at the 7-position in the product. Thus, the reduction of the 4,7-dioxocarboxylic acids (**3a-3e**) with sodium borohydride followed by acidification gave 7-hydroxy- γ -lactones (**4a-4e**) (**Scheme II**). The hydroxy



Scheme I: Synthesis of gamma lactones with saturated alkyl chains

lactones were extracted into dichloromethane, after acidification of the reaction mixture with 1 M HCl. All the 4,7-dioxocarboxylic acids gave moderate to high yields (33%-75%) of the corresponding 7-hydroxy- γ -lactone with this procedure except **3a** (~20%). However, the yield of the product **4a** could be increased (48%) by strongly acidifying the reaction mixture with 10 M HCl and heating at 60 °C for 2 h prior to the extraction into the organic layer. There was no corresponding increase in the yield observed when the reaction mixtures from the other 4,7-dioxocarboxylic acids were treated similarly. It would appear that the 4,7-dihydroxy acid from **3a** requires a lower pH than the other 4,7-dihydroxy acids, for total conversion to the corresponding 7-hydroxy- γ -lactone.

The 7-hydroxy group provides a convenient handle for manipulation of the side chain functionality (**Scheme II**). Thus, the 7-hydroxy group was easily acetylated to obtain the 7-acetoxy- γ -lactones (**5a-5e**) or oxidized to a keto group to obtain the corresponding 7-oxo- γ -lactones (**6a-6e**). For both transformations only mild conditions were used, so as to avoid reactions at the gamma lactone ring.



Scheme II: Synthesis of 7-functionalized gamma lactones

The structures of all the new compounds were established by IR, ^1H and ^{13}C NMR, 2D NMR (COSY and HETCOR) spectroscopy and GC-MS. The 7-hydroxy and 7-acetoxy lactones each have two chiral centres (C4 and C7), and are formed as equimolar mixtures of diastereomers. This was reflected in the fact that most of the ^{13}C signals of these compounds were found as finely separated pairs, which transform into single peaks in the 7-oxo series of compounds. However, the diastereotopic C-5 protons were found to be better differentiated in the ^1H NMR spectrum in the 7-oxo series than in the 7-hydroxyl and 7-acetoxy series. For example, the methylene protons at C-5 of compound **4a**, appeared as a single multiplet at δ 1.84, while the same protons in compound **6a** appeared as two sets of multiplets at δ 1.83 (1H, m) and δ 2.01 (1H, m).

The GCMS of 7-hydroxy lactones (**4a-4e**) displayed a low intensity peak for $[\text{M}+1]^+$ ion for all homologues, a feature which is common to oxygen bearing compounds. The peak at m/z 85 could be attributed to the ion arising from the loss of the 4-substituent from M^+ while loss of the terminal alkyl group arising from cleavage of the C7-C8 bond could give rise to the peak at m/z 143. Peaks were also observed at m/z 114 and 125 for the loss of CHO and H_2O respectively from m/z 143. The 7-acetoxy lactones gave the fragment ion $[\text{CH}_3\text{CO}]^+$ as the base peak at m/z 43.

The reaction pathway described is a convenient one for synthesizing 7-functionalized γ -lactones in moderate yields. Work on further elaboration of the 7-functionality is in progress.

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