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A General Synthesis of (±)-γ-Substituted γ-Butyrolactones Using a Kinetic Alkylation-Ozonolysis Procedure

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A GENERAL SYNTHESIS OF (±)-γ-SUBSTITUTED γ-BUTYROLACTONES USING A KINETIC ALKYLATION - OZONOLYSIS PROCEDURE.

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Abstract: A synthesis of (±)-γ-substituted γ-butyrolactones is described in which the key intermediates, γ-ketoesters, are prepared from the readily available 6-methyl-5-hepten-2-one using a kinetic alkylation-ozonolysis procedure; the method allows terminal ester and *Z*-alkene groups to be incorporated into the side-chain and thus can be used for the synthesis of (±)-γ-jasmolactone as well as other naturally occurring lactones.

The lactone functional group is a commonly encountered sub-unit of many natural products and indeed many simple lactones are also of importance as they function as insect pheromones[1] or occur in the essential oils of plants[2]. This importance is reflected in the wide range of methods available for the synthesis of lactones[3]. γ-Substituted γ-butyrolactones (5-substituted 2(3*H*)-furanones) are among the most important of the simpler lactones and a variety of synthetic procedures have been developed for their construction[4,5].

In a previous paper[6] we reported that 2-substituted 2-cyclopenten-1-ones could be synthesised from the readily available 6-methyl-5-hepten-2-one **(1)** using a kinetic alkylation-ozonolysis procedure **(Scheme 1)**; this method has the advantage that it allows desireable structural features such as terminal ester and *Z*-alkene groups to be

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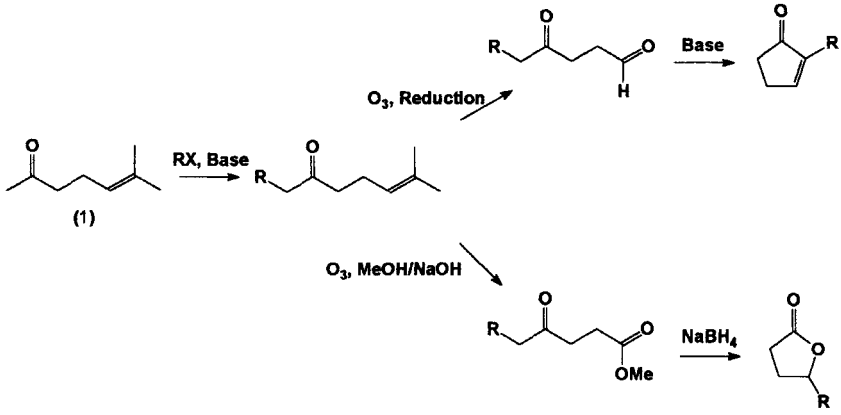
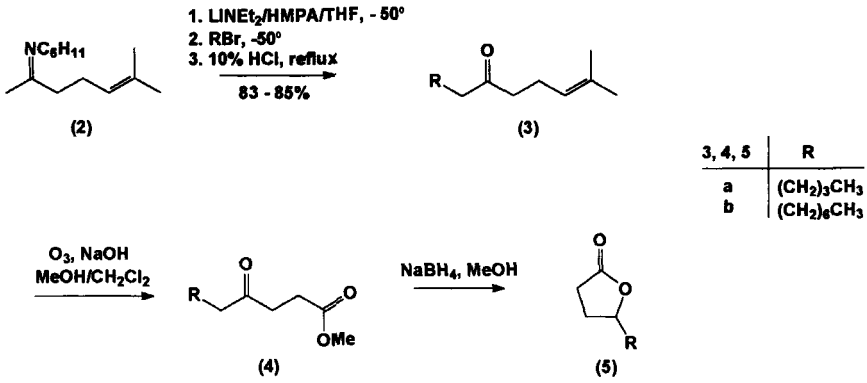
incorporated into the side-chain on the cyclopentenone ring. The present paper describes how this procedure can be adapted, using a recently published method for the direct conversion of olefins into esters[7], to allow γ-substituted γ-lactones with functionalised side-chains to be efficiently synthesised.



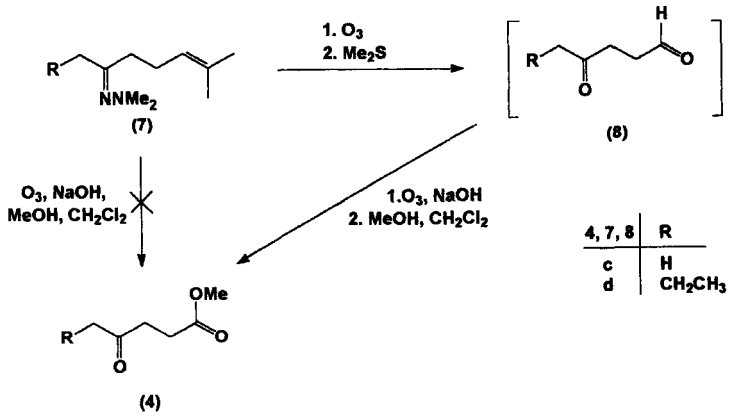
Scheme 1

The potential of the procedure for the synthesis of γ-lactones with saturated side-chains in the γ-position is shown by the synthesis of 3,4-dihydro-5-pentyl-2(3*H*)-furanone (**5a**) and 3,4-dihydro-5-octyl-2(3*H*)-furanone (**5b**) **(Scheme 2)**, an optically active form of the latter being used as a pheromone by the rove beetle[8]. Thus the unsaturated ketone (**3**), formed by kinetic alkylation of the cyclohexylimine of 6-methyl-5-hepten-2-one (**1**), is converted to the ketoester (**4**) by ozonolysis in a solution of methanolic sodium hydroxide in dichloromethane; reduction of (**4**) with sodium borohydride gives the lactone (**5**) directly. The alternative approach of alkylating (**1**) as its *N,N*-dimethylhydrazone proved to be of value in the synthesis of cyclopentenones[6] as ozonolysis of the alkylated hydrazone resulted in simultaneous cleavage of the alkene and regeneration of the ketone, thus affording the desired γ-ketoaldehyde without the use of the dilute aqueous acid required for the hydrolysis of the imine.



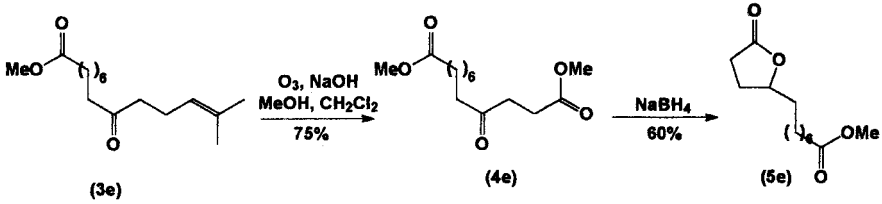
Scheme 2

Although in this case the direct ozonolysis of the alkylated *N,N*-dimethylhydrazone (**7**) in methanolic sodium hydroxide/dichloromethane solution leads to a complex mixture which contains little if any of the ketoester (**4c**), the transformation can be achieved, in what is effectively a one-pot procedure, using ozone and methyl sulphide to form the ketoaldehyde (**8**) which can then be converted to (**4c**) by ozonolysis in methanolic sodium hydroxide/dichloromethane solution **(Scheme 3)**.



Scheme 3

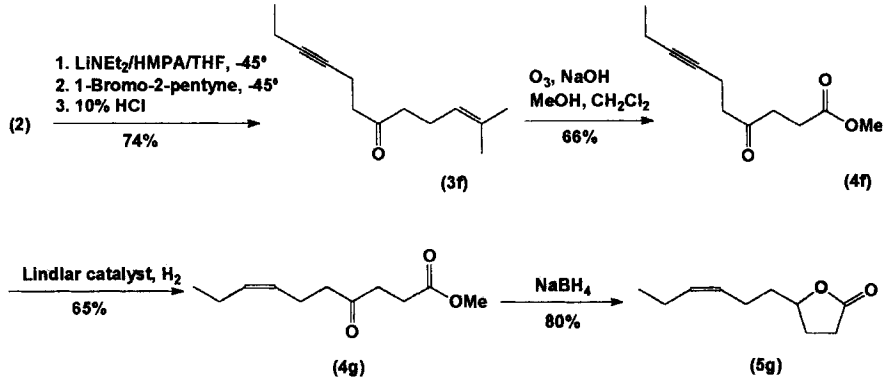
The procedure can also be extended **(Scheme 4)** to lactones possessing side-chains with terminal ester groups as the unsaturated ketoester **(3d)**[6] can be oxidatively cleaved to give the ketodiester **(4e)** which on reduction cyclises regioselectively to give the γ-lactone **(5e)**.



Scheme 4

The synthesis of γ-jasmolactone **(5g)** **(Scheme 5)**, one of the constituents of the essential oil of jasmin flowers[2], demonstrates the potential of the kinetic alkylation - ozonolysis procedure for the synthesis of γ-lactones with *Z*-unsaturated side-chains in the γ-position, which are of considerable synthetic importance because of their diverse biological activity[1,9]. The acetylenic enone **(3f)** is formed from the imine **(2)** and is converted to the ketoester **(4f)** in an ozonolysis step which must be carefully monitored (GLC) to prevent reaction at the alkyne bond. The stereoselective partial hydrogenation of the triple bond must also be monitored by GLC as excessively long reaction times lead to alkane formation and *Z-E* isomerization of the alkene bond in the product **(4g)**. Borohydride reduction completes the synthesis of γ-jasmolactone **(5g)**.

Thus the synthetic procedure described here offers a direct and versatile route to a wide range of γ-substituted γ-lactones using the readily available 6-methyl-5-hepten-2-one as starting material. A method for the synthesis of an appropriate starting material for δ-lactones, 7-methyl-6-octen-2-one, is available in the literature[10] and thus these lactones should also be accessible using the procedure described here.



Scheme 5

Experimental

^{1}H- and ^{13}C-NMR were recorded at 270MHz and 60MHz, respectively. All starting materials and solvents were dried and distilled before use.

Alkylated Ketones (3):

The preparation of the ketones **(3a)**, **(3e)** and **(3f)** has been described previously[6]. **2-Methyl-2-tetradecen-6-one (3b)** was prepared using the same procedure; yield: 87%; bp 98-103^0/1.0mmHg.

$C_{15}H_{28}O$: Calc. 80.30, H 12.58; Found C 80.41, H 12.62.

IR (film): ν = 1715 (C=O); 830 cm^{-1} (olefinic C-H).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.87 (t, 3H, J = 7.20 Hz); 1.2 (m, 12H); 1.58 (s, 3H); 1.63 (s, 3H); 2.23 (m, 2H); 2.41 (m, 4H); 5.03 (br s,1H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.1, 17.2, 22.65, 22.7, 23.9, 25.8, 29.15, 29.2, 29.3, 31.7, 42.8, 43.0, 123.1, 133.0, 210.0.

γ-Ketoesters (4); General Procedure:

Ozone is passed through a gas dispersion tube into a stirred solution of the unsaturated ketone **(3)** in CH_2Cl_2 (50ml) and 2.5M methanolic NaOH (10ml) at -70^0 until

Table. Preparation of γ-Ketoesters (**4**) and γ-Lactones (**5**).

Compound	Ketoester (**4**)			Lactone (**5**)		
	Yield[a,b]	bp (°C)/ mmHg	Molecular Formula or Lit. bp (°C)/ mmHg	Yield[a,b]	bp (°C)/ mmHg	Molecular Formula or Lit. bp (°C)/ mmHg
a	70	100-105/0.2	$C_{10}H_{18}O_3$	82	130-135/15	105-107/2[15]
b	73	105-110/0.2	$C_{13}H_{24}O_3$	86	140-144/0.1	148/0.5[15]
c	55[c]	60-65/15	85-86/14[11]	-	-	-
d	58[c]	80-85/15	130/30[12]	-	-	-
e	75	150-165/0.1	143-146/0.15[13]	60	140-150/0.1	$C_{13}H_{22}O_4$
f	66	100-110/0.1	$C_{11}H_{16}O_3$	-	-	-
g	65	95-100/0.1	150/0.05[14]	80	128-135/0.5	110/0.35[14]

[a] Yield of product after distillation; the purity was ≥ 96% by GLC (3% OV 17, 160°).
[b] Satisfactory elemental analyses were obtained: C ± 0.3, H ± 0.3.
[c] Chromatography on silica required before distillation.

the solution turns blue. The ozonolysis of 2-methyldodec-2-en-9-yn-6-one (**3f**) is monitored carefully by GLC and the reaction is terminated at 97% conversion in order to prevent reaction at the triple bond. Water (30ml) and ether (30ml) were then added and, after warming to room temperature, the mixture is extracted with ether (3 x 20ml). The combined ether extracts are dried over $MgSO_4$ and the solvent evaporated to give (**4**) as a yellow oil which is purified by Kugelrohr distillation.

Methyl 4-Oxononanoate (4a): yield: 70%; bp 100-105°/0.2mmHg.

$C_{10}H_{18}O_3$: Calc. C 64.49, H 9.74; Found C 64.65, H 10.00.

IR (film): ν = 1740 (COOMe); 1715 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.87 (t, 3H, *J* = 6.23 Hz); 1.3 (m, 4H); 1.57 (m, 2H);

2.42 (t, 2H, J = 7.50Hz); 2.56 (t, 2H, J = 6.78Hz); 2.70 (t, 2H, J = 6.50Hz); 3.65 (s, 3H, COOMe).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.8, 22.4, 23.45, 27.7, 31.3, 37.0, 42.7, 51.6, 173.0, 209.0.

Methyl 4-Oxododecanoate (4b): yield: 73%; bp 105-110^0/0.2mmHg.

$C_{13}H_{24}O_3$: Calc. C 68.38, H 10.59; Found C 68.29, H 10.74.

IR (film): ν = 1740 (COOMe); 1715 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.88 (t, 3H, J = 7.20 Hz); 1.25 (m, 10H); 1.60 (m, 2H); 2.46 (t, 2H, J = 7.40Hz); 2.59 (t, 2H, J = 6.50Hz); 2.74 (t, 2H, J = 6.41Hz); 3.68 (s, 3H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.1, 22.6, 23.8, 27.7, 29.1, 29.3, 31.3, 31.7, 37.0, 42.7, 51.7, 173.0, 209.0.

Dimethyl 4-Oxododecanedioate (4e): yield: 70%; bp 150-165^0/0.1mmHg (lit.[13] 143-146^0/0.15mmHg).

$C_{14}H_{24}O_5$: Calc. C 61.74, H 8.88; Found C 61.97, H 9.16.

IR (film): ν = 1738 and 1732 (COOMe); 1716 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.35 (m, 10H); 2.30 (t, 2H, J = 7.5); 2.45 (t, 2H, J = 7.50Hz); 2.61 (t, 2H, J =7.50Hz); 2.76 (t, 2H, J = 7.5Hz); 3.67 (s, 3H,); 3.68 (s, 3H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 23.5, 24.7, 27.6, 28.8, 29.5, 33.9, 36.9, 42.5, 51.25, 51.6, 173.2, 174.0, 209.0.

Methyl 4-Oxodec-7-ynoate (4f): yield: 65%; bp 100-110^0/0.1mmHg.

$C_{11}H_{16}O_3$: Calc. C 67.32, H 8.22; Found C 67.00, H 8.28.

IR (film): ν = 1736 (COOMe); 1716 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.09 (t, 3H, 7.51Hz); 2.13 (tq, 2H, J = 7.5 and 0.9Hz); 2.42 (tt, 2H, J = 7.50 and 0.9Hz); 2.75 (t, 2H, J =7.30Hz); 2.67 (t, 2H, J =

7.3Hz); 2.61 (t, 2H, J = 7.2Hz); 3.68 (s, 3H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 12.2, 13.3, 14.0, 27.6, 37.0, 41.9, 51.6, 77.6, 82.2, 173.0, 207.0.

γ-Ketoesters (4); from hydrazones (7); general procedure:

A solution of hydrazone **(7)** (7.5mmol) in CH_2Cl_2 (50ml) is cooled to -78^0 and ozone is passed in through a gas dispersion tube until the solution turns blue. After the solution is swept with N_2 gas for 15min, methyl sulphide (5.4ml, 144mmol) is added and the solution is stirred at room temperature overnight. The solvent and excess methyl sulphide are then evaporated off under reduced pressure (T < 40^0) and the residue is dissolved in 2.5M methanolic NaOH (14.6ml, 36.5mmol) and CH_2Cl_2 (50ml). Ozone is passed in as before at -78^0 until the solution turns blue, water (50ml) and ether (50ml) are added and the stirred solution is allowed to warm to room temperature. The mixture is extracted with ether and the combined ether extracts are dried over $MgSO_4$; evaporation of the solvent, chromatography on silica gel (eluent: gradient, 10-90% ether in 40-60^0 pet.spirit) and Kugelrohr distillation gives the γ-ketoester **(4)**.

Methyl Levulinate (4c): yield: 50%; bp 60-65^0/15mmHg (lit.[11] 85-86^0/14mmHg).

IR (film): ν = 1739 (COOMe); 1718 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.19 (s, 3H); 2.70 (m, 4H); 3.68 (s, 3H)

Methyl 4-Oxoheptanoate (4d): yield: 58%; bp 80-85^0/15mmHg (lit.[12] .130^0/30mmHg).

IR (film): ν = 1742 (COOMe); 1716 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.92 (t, 3H, J = 6.85 Hz); 1.63 (m, 2H); 2.60 (m, 4H); 3.67 (s, 3H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.3, 16.9, 27.4, 36.6, 44.2, 51.3, 172.95, 208.6.

Methyl 4-Oxodec-7-enoate (4g):

Methyl 4-oxodec-7-ynoate **(4f)** (0.2g, 1.02mmol) is added to MeOH (20ml) containing quinoline (0.03ml) and Lindlar catalyst. The mixture is stirred under a hydrogen atmosphere and the reaction is stopped at 98% conversion (GLC). The catalyst and quinoline are removed by filtering the reaction mixture through silica and the solvent is evaporated to give **(4g)** which is purified by Kugelrohr distillation: yield: 0.13g (65%); bp 95-105^0/0.1mmHg (lit.[14] 150^0/0.05mmHg).

IR, ^{1}H-NMR spectroscopic data in agreement with lit. data[14].

^{13}C-NMR ($CDCl_3$/TMS): δ = 12.7, 18.9, 20.0, 26.2, 35.65, 41.1, 50.2, 125.6, 131.4, 172.8, 206.8.

Lactones (5); General Procedure:

$NaBH_4$ (0.089g, 2.3mmol) and $Na_2HPO_4.12H_2O$ (0.104g, 0.31mmol) are added to MeOH (15ml) and the mixture is cooled to 0^0. The ketoester **(4)** in MeOH (15ml) is added dropwise and after being kept at 0^0 for a further 5 min, the mixture is stirred at room temperature until the reaction is complete (IR, GLC), *c.* 24h. Water is then added and the product mixture is extracted with ether (3 x 20ml). The combined ether extracts are dried over $MgSO_4$ and the solvent is removed to give the lactone **(5)** which is further purified by Kugelrohr distillation.

Dihydro-5-pentyl-2(3*H*)-furanone (5a): yield: 82%; bp 120-130^0/15mmHg (lit.[15] 105-107^{0}2mmHg).

IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic data in agreement with lit. data[16,17].

Dihydro-5-octyl-2(3H)-furanone (5b): yield: 86%; bp 140-144^0/0.1mmHg (lit.[15] 148^0/0.5mmHg)

IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic data in agreement with lit. data[16,17].

Dihydro-5-(6-methoxycarbonylheptyl)-2(3*H*)-furanone (5e): yield: 60%; bp

135-145^0/0.1mmHg.

$C_{13}H_{22}O_4$: Calc. C 71.98, H 6.71; Found C 72.03, H 7.00

IR (film): ν = 1775 (lactone), 1737 cm^{-1} (COOMe).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.45 (m, 14H); 2.31 (m, 2H); 2.54 (t,2H, J = 6.9Hz); 3.67 (s, 3H); 4.60(m, 1H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 17.7, 24.6, 24.9, 27.7, 28.55, 28.7, 28.76, 28.8, 33.7, 35.3, 51.1, 80.7, 173.8.

Dihydro-5-[(*Z*)-3-hexenyl]-2(3*H*)-furanone (γ-jasmolactone) (5g): yield: 85%; bp 128-135^0/0.1mmHg (lit.[14] 165^0/0.2mmHg).

IR, ^{1}H-NMR spectroscopic data in agreement with lit. data[14].

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.2, 20.5, 23.0, 27.95, 28.8, 35.6, 80.3, 127.1, 133.1, 177.1.

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