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Direct Indium-Promoted Preparation of α-Methylene-γ-lactones from 2-(Bromomethyl)acrylic Acid and Carbonyl Compounds

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Abstract

The reaction of 2-(bromomethyl)acrylic acid (**2**) with different carbonyl compounds **1** [CH_2O, (*E*)-CH_3CH=$CHCHO$, ^iPrCHO, ^tBuCHO, PhCHO, $CH_3(CH_2)_5CHO$, *c*-$C_6H_{11}CHO$, Ph_2CHCHO, $(CH_2)_5CO$, furfural, 1,4-cyclohexanedione, 2-chlorocyclohexanone, 2-hydroxybenzaldehyde, phthaldehyde, *N*-Boc-3-indolecarboxaldehyde, cholestanone, (1*R*)-(-)-myrtenal] and indium powder in a 1:1 THF:H_2O mixture at room temperature affords, after acidic work-up with 6M hydrochloric acid, the corresponding α-methylene-γ-lactones **3**.

Keywords: Indium and compounds; lactones; carbonyl compounds

I. Introduction

α-Methylene-γ-lactones are important biologically active natural products, which occur widely in nature: in fact, it is considered that around 10% of the described natural products contain this structural unit, especially in the field of sesquiterpene lactones [1,2]. Different methodologies have been developed in order to synthesise α-methylene-γ-lactones, the most useful being those involving methallylic derivatives, carbonyl compounds and a metal, because they avoid the use of multistep processes. For instance, this methodology has been successfully applied using zinc [3-5], tin [6,7] or chromium [8] as the metallic

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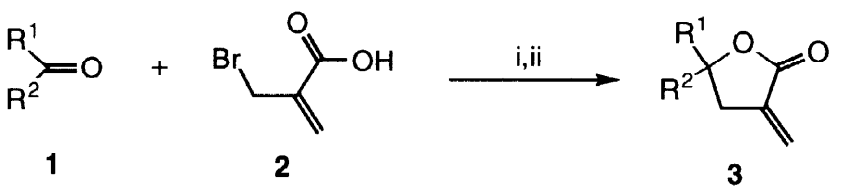
component in Reformatsky-type reactions [9].[1] On the other hand, in the last few years indium metal has been used to promote the allylation of carbonyl compounds under aqueous or non-aqueous reaction conditions [10-29]. In this paper we report a new simple one-pot methodology to prepare α-methylene-γ-lactones with indium metal as the metallic reagent and 2-(bromomethyl)acrylic acid and carbonyl compounds as the organic components under aqueous conditions [30].[2]

II. Results and Discussion

The reaction of different carbonyl compounds **1** with 2-(bromomethyl)acrylic acid **2** in the presence of indium metal (1:1.2:1.2 molar ratio) in a 1:1 mixture of THF and water at room temperature led, after hydrolysis with 6M hydrochloric acid, to the corresponding α-methylene-γ-lactone **3** (Scheme 1 and Table 1). In some cases the acidic treatment has to be prolonged for 3 or 6 h in order to achieve the final cyclisation (Table 1, footnotes b and e).



Scheme 1. *Reagents and conditions*: i, In powder, THF, H_2O, 20°C; ii, 6M HCl.

Some remarks concerning the results summarised in Table 1 are:

(1) In general, the yields of the isolated products **3**, after column chromatography, are good except in the case of the formaldehyde (used as a 30% aqueous solution) derivative **3a** (tulipalin A), probably due to its volatility. In fact, this was the only product isolated by distillation (Table 1, entry 1).

(2) In the case of using α,β-unsaturated systems, such as (*E*)-crotonaldehyde, only the corresponding product **3b** resulting from a 1,2-addition was obtained (Table 1, entry 2).

(3) In the reaction with a dicarbonyl compound as electrophile, a dilactone **3n** was isolated using double the amount of 2-(bromomethyl)acrylic acid (Table 1, entry 14 and footnote d). As a byproduct, the monolactone **3n'** was also isolated in 7% yield (Table 1, entry 14).

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1 When dimetallated methallyl alcohol was used instead of the corresponding acid or ester, it was necessary to carry out a final oxidation with MnO_2 in order to get the expected α-methylene-γ-lactones. See, for instance reference [9].

2 For preliminary communication see reference [30].

Table 1
Preparation of α-methylene-γ-lactones **3**

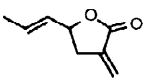
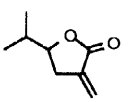
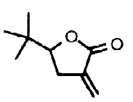
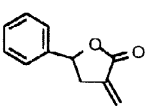
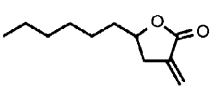
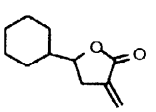
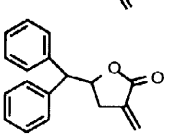
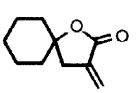
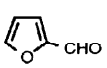
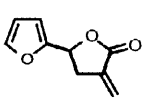
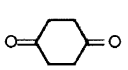
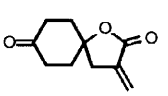
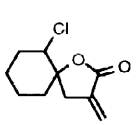
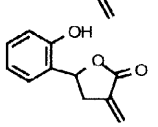
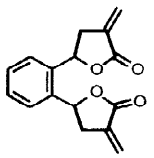
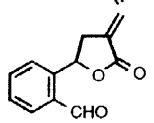
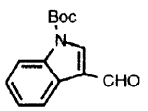
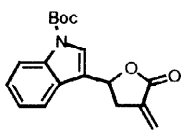
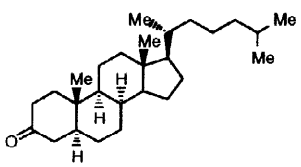
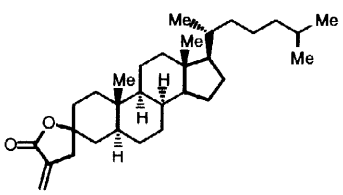
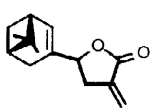
Entry	Carbonyl compound **1** R^1	R^2	Reaction time (h)	Product **3** Structure	No.	Yield (%)[a]
1	H	H	4.5		**3a**	40
2	(*E*)-CH_3CH=CH	H	3[b]		**3b**	77
3	^{i}Pr	H	3[b]		**3c**	69
4	^{t}Bu	H	6		**3d**	78
5	Ph	H	6		**3e**	75
6	$CH_3(CH_2)_5$	H	3[b]		**3f**	89
7	cC_6H_{11}	H	4[b]		**3g**	90
8	Ph_2CH	H	4.5[b]		**3h**	91
9	$(CH_2)_5$		4		**3i**	78
10			1.5[b]		**3j**	73
11			12[b]		**3k**	58
12	$ClCH(CH_2)_4$		16[b]		**3l**	65[c]
13	2-HO-C_6H_4	H	3[b]		**3m**	93

Table 1 (Cont.)

14	2-OHC-C_6H_4	H	2[b,d]		**3n**	58[c]
					**3n'**	7
15			1[e]		**3o**	73
16			24[f]		**3p**[g]	28[g]
17			3[b]		**3q**	96[c]

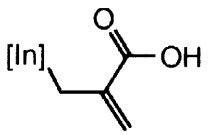
a Isolated yield unless otherwise noted, based on the starting carbonyl compounds **1**.
b The acidic hydrolysis was prolonged for 3h.
c A *ca.* 1:1 mixture of diastereoisomers was obtained (300 MHz ^{1}H NMR).
d Double amount of 2-(bromomethyl)acrylic acid was used in the reaction.
e The acidic hydrolysis was prolonged for 6 h.
f The reaction was carried out in THF and hydrolysis with 6M HCl in 1:1 MeOH-THF (8h).
g A sole diastereoisomer was isolated after column chromatography and recrystallisation.

(4) When a mixture of diastereoisomers was possible, a *ca.* 1:1 molar ratio was isolated (Table 1, entries 12, 14 and 17).

(5) For the cholestanone derivative **3p**, the reaction should be carried out only in THF and the final hydrolysis with hydrochloric acid in a 1:1 methanol-THF mixture due to solubility problems. In this case, even with a low yield, only one diastereoisomer was isolated after purification (column chromatography and recrystallisation). At this moment we are not able to assign the absolute configuration of the C-3 carbon atom, the new stereocenter formed (Table 1, entry 16 and footnote g).

Concerning a possible mechanistic pathway, in other indium promoted allylation reactions [31] allylindium sesquihalides of the type **I** have been proposed to be involved in

the process, being prepared, isolated and characterised in many cases. The reaction of this species with the carbonyl compound, followed by cyclisation during the acidic final treatment would afford the isolated lactones **3**.



I, [In]: $In_{2/3}Br$

III. Conclusion

From the results summarised in Scheme 1 and Table 1, we conclude that the methodology described here represents a versatile and simple method to prepare α-methylene-γ-lactones under very mild aqueous reaction conditions. In the case of the simplest reaction product **3a**, this is directly the natural product tulipaline A. The important feature of this process is that it is possible to prepare functionalised products as well as dilactones depending on the stoichiometry of the reaction.

IV. Experimental Section

IV.1. General.- Melting points are uncorrected. IR spectra were recorded using NaCl plates for neat liquids or KBr pellets for solid samples on a Nicolet 400 D-FT. Only the strongest and structurally most important peaks (IR, cm^{-1}) are listed. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker AC-300, using $CDCl_3$ as solvent and TMS (0.00 ppm, ^1H) and $CDCl_3$ (77.00 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (*J*) are measured in hertz. Low resolution mass espectra were recorded on a Shimadzu QP5000 and high resolution mass espectra were recorded on a Finnigan MAT95 S. The purity of volatile distilled products and the chromatographic analysis (GLC) were determined with a flame ionization detector. TLC was carried out on Schleicher&Schuell F1500/LS254 plates coated with a 0.2-mm layer of silica gel. A mixture of hexane/ethyl acetate was used as eluent; R_f values are given under these conditions. Microanalyses were performed by the Microanalyses Service at the University of Alicante. All reagents were commercially available (Aldrich) and of the best grade. Merck silica gel 60 (70-270 mesh) was employed for flash chromatography.

IV.2. Preparation of α-methylene-γ-lactones 3. General procedure. A mixture of the corresponding carbonyl compound **1**, 2-(bromomethyl)acrylic acid **2** and indium powder (1:1.2:1.2 molar ratio) in a mixture of THF (5 ml) and water (5 ml)[3] was stirred until the starting material disappeared (monitored by TLC and/or GLC; for

3 In the case of the reaction with cholestanone the reaction should be carried out in the absence of water in order to avoid solubility problems (Table 1, entry 16 and footnote f).

reaction times see Table 1). Then, the resulting mixture was treated with 6M HCl (4 ml),[4] extracted with ethyl acetate (3x20 ml) and the organic layer dried over anhydrous Na_2SO_4 and evaporated (15 Torr). The resulting residue was purified[5] by column chromatography (silica gel, hexane/ethyl acetate) to give the title compounds **3**. Structures and yields are indicated in Table 1; physical, spectroscopic and analytical data as well as literature references for known compounds follow.

2-Methylenebutyrolactone (Tulipalin A) (**3a**) [32]: colourless liquid, bp 75-77°C (1 Torr, Kugelrohr); ν_{max} (film) 2962, 2925, 1759 (C=O), 1665, 1261, 811 cm^{-1}; δ_H 2.95-3.02 (2H, m, $CH_2C=CH_2$), 4.37 (2H, t, J = 7.3, OCH_2), 5.67 (1H, t, J = 2.4, C=C*H*H), 6.26 (1H, t, J = 3.0, C=CH*H*); δ_C 27.3 ($CH_2C=CH_2$), 65.2 (OCH_2), 122.2 ($C=CH_2$), 133.5 ($C=CH_2$), 170.6 (C=O); *m/z* 98 (M+, 25%), 84 (10), 68 (54), 58 (10), 40 (100).

4-[(E)-1-Propenyl]-2-methylenebutyrolactone (**3b**): pale yellow oil, R_f 0.37 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2920, 1764 (C=O), 1667, 1270, 814 cm^{-1}; δ_H 1.74 (3H, dd, J = 6.4, 1.5, CH_3), 2.68 (1H, ddt, J = 17.1, 6.0, 3.0, CHCH*H*), 3.11 (1H, ddt, J = 17.1, 7.95, 2.5, CHC*H*H), 4.89 (1H, dd, J = 14.2, 7.0, OCH), 5.51 (1H, ddq, J = 15.2, 7.5, 1.5, CH_3CH), 5.62 (1H, t, J = 2.4, C=C*H*H), 5.78-5.90 (1H, m, $CH_3CH=CH$), 6.22 (1H, t, J = 3.0, C=CH*H*); δ_C 17.6 (CH_3), 34.1 (CH_2), 77.7 (CHO), 121.8 ($C=CH_2$), 129.0 ($CH_3CH=CH$), 130.7 ($CH_3CH=CH$), 134.5 ($C=CH_2$), 170.1 (C=O); *m/z* 138 (M+, 14%), 123 (13), 110 (18), 91 (10), 77 (22), 68 (100) (Found: M+, 138.0680. $C_8H_{10}O_2$ requires M, 138.0680).

4-Isopropyl-2-methylenebutyrolactone (**3c**): colourless oil, R_f 0.41 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2966, 1766 (C=O), 1669, 1278, 810 cm^{-1}; δ_H 0.94 (3H, d, J = 6.7, CH_3), 1.01 (3H, d, J = 6.7, CH_3), 1.86 [1H, octet, J = 6.7, $CH(CH_3)_2$], 2.64 (1H, ddt, J = 17.4, 6.0, 3.0, $CHCH_2$), 2.97 (1H, ddt, J = 17.4, 7.9, 2.4, $CHCH_2$), 4.25 (1H, dd, J = 14.3, 6.7, OCH), 5.62 (1H, t, J = 3.0, C=C*H*H), 6.21 (1H, t, J = 3.0, C=CH*H*); δ_C 17.2 (CH_3), 17.6 (CH_3), 31.0 ($CHCH_2$), 33.3 [$CH(CH_3)_2$], 82.1 (CHO), 121.6 ($C=CH_2$), 134.9 ($C=CH_2$), 170.4 (C=O); *m/z* 140 (M+, 6%), 125 (10), 112 (10), 97 (88), 69 (61), 41 (100) (Found: M+, 140.0837. $C_8H_{12}O_2$ requires M, 140.0837).

4-tert-Butyl-2-methylenebutyrolactone (**3d**): colourless oil, R_f 0.48 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2964, 1763 (C=O), 1664, 1282, 814 cm^{-1}; δ_H 1.01 [9H, s, $C(CH_3)_3$], 2.73 (1H, ddt, J = 17.7, 6.0, 3.0, CHC*H*H), 2.88 (1H, ddt, J = 17.0, 6.9, 2.45, CHCH*H*), 4.22 (1H, t, J = 6.7, OCH), 5.63 (1H, t, J = 3.0, C=C*H*H), 6.19 (1H, t, J = 3.0, C=CH*H*); δ_C 24.4 [$C(CH_3)_3$], 28.6 ($CHCH_2$), 34.0 [$C(CH_3)_3$], 84.4 (CHO), 121.3 ($C=CH_2$), 135.0 ($C=CH_2$), 170.3 (C=O); *m/z* 154 (M+, 1%), 139 (10), 126 (10), 97 (59), 69 (63), 57 (100), 41 (83) (Found: M+, 154.0994. $C_9H_{14}O_2$ requires M, 154.0993).

4 In some case it was necessary to stir for 3 or 6 additional hours under acidic conditions to complete the reaction (Table 1, footnotes b and e).

5 In the case of tulipaline A (**3a**), it was purified by distillation at reduced pressure (1 Torr) (Table 1, entry 1).

4-Phenyl-2-methylenebutyrolactone (**3e**) [33]: white solid, R_f 0.29 (silica gel, hexane/ethyl acetate: 5/1); mp 52-54°C (pentane/dichloromethane); ν_{max} (KBr) 3033, 2919, 1763 (C=O), 1665, 1277, 1127, 812 cm^{-1}; δ_H 2.88 (1H, ddt, J = 17.1, 6.0, 3.0, CHC*H*H), 3.38 (1H, ddt, J = 17.1, 7.95, 2.4, CHCH*H*), 5.49 (1H, t, J = 7.3, OCH), 5.66 (1H, t, J = 2.7, C=C*H*H), 6.27 (1H, t, J = 2.7, C=CH*H*), 7.26-7.40 (5H, m, ArH); δ_C 36.0 ($CHCH_2$), 77.8 (CHO), 122.2 (C=CH_2), 125.2, 128.4, 128.6 (ArC), 134.0 (C=CH_2), 139.7 (ArC), 170.0 (C=O); *m/z* 174 (M$^+$, 25%), 128 (10), 115 (10), 105 (10), 68 (100), 40 (92).

4-Hexyl-2-methylenebutyrolactone (**3f**) [9]: colourless oil, R_f 0.43 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2930, 2588, 1763 (C=O), 1665, 1276, 1116, 813 cm-1; δ_H 0.88 (3H, t, J = 6.7, CH_3), 1.25-1.55 [(10H, m, $CH_3(CH_2)_5$], 2.57 (1H, ddt, J = 17.1, 6.0, 3.0, C*H*HC=CH_2), 3.05 (1H, ddt, J = 17.1, 7.6, 2.4, CH*H*C=CH_2), 4.46-4.55 (1H, m , OCH), 5.62 (1H, t, J = 2.7, C=C*H*H), 6.21 (1H, t, J = 3.0, C=CH*H*); δ_C 13.9 (CH_3), 22.5, 24.7, 28.9, 31.6, 33.5 [$(CH_2)_5$], 36.2 (CH_2C=CH_2), 77.5 (CHO), 121.8 (C=CH_2), 134.8 (C=CH_2), 170.3 (C=O); *m/z* 182 (M$^+$, 2%), 164 (10), 140 (16), 112 (10), 68 (100).

4-Cyclohexyl-2-methylenebutyrolactone (**3g**): white solid, R_f 0.44 (silica gel, hexane/ethyl acetate: 5/1); mp 54-56°C (pentane/dichloromethane); ν_{max} (KBr) 2932, 2854, 1756 (C=O), 1667, 1446, 1278, 1125, 819 cm-1; δ_H 0.96-1.93 [11H, m, $(CH_2)_5CH$], 2.68 (1H, ddt, J = 17.4, 6.0, 3.0, CHC*H*H), 2.96 (1H, ddt, J = 17.1, 7.6, 2.45, CHCH*H*), 4.25 (1H, dd, J = 14.3, 7.0, OCH), 5.61 (1H, t, J = 2.75, C=C*H*H), 6.19 (1H, t, J = 2.75, C=CH*H*); δ_C 25.3, 25.5, 26.1, 27.5, 28.0 [$(CH_2)_5$], 31.1 (CH_2C=CH_2), 42.9 (CH_2CHCH_2), 81.3 (OCH), 121.41 (C=CH_2), 134.8 (C=CH_2), 170.3 (C=O); *m/z* 180 (M$^+$, 3%), 162 (10), 151 (10), 134 (10), 97 (82), 96 (19), 69 (72), 68 (43), 41 (100). Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.68; H, 9.10.

4-Benzhydryl-2-methylenebutyrolactone (**3h**): white solid, R_f 0.30 (silica gel, hexane/ethyl acetate: 5/1); mp 119-120°C (pentane/dichloromethane); ν_{max} (KBr) 3027, 3006, 2905, 1761 (C=O), 1667, 1454, 1282, 1127, 810 cm-1; δ_H 2.66 (1H, ddt, J = 17.4, 6.0, 3.0, CHC*H*H), 2.93 (1H, ddt, J = 17.0, 7.3, 2.75, CHCH*H*), 4.05 [1H, d, J = 7.95, $(Ph)_2CH$], 5.23 (1H, dt, J = 14.2, 7.9, OCH), 5.47 (1H, t, J = 2.7, C=C*H*H), 6.11 (1H, t, J = 2.7, C=CH*H*), 7.14-7.43 (10H, m, ArH); δ_C 32.6 ($CHCH_2$), 56.7 [$CH(Ph)_2$], 78.3 (CHO), 121.9 (C=CH_2), 126.9, 127.1, 128.4, 128.5, 128.6, 128.8 (ArC), 134.1 (C=CH_2), 139.8, 140.2 (ArC), 169.9 (C=O); *m/z* 264 (M$^+$, 2%), 215 (10), 167 (100), 152 (19), 128 (10), 97 (42) (Found: M$^+$, 264.1147. $C_{18}H_{16}O_2$ requires M, 264.1150).[6]

3-Methylene-1-oxaspiro[4.5]decan-2-one (**3i**) [9,33]: pale yellow oil, R_f 0.42 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2935, 2859, 1762 (C=O), 1664, 1448, 1275, 813 cm-1; δ_H 1.38-1.81 [10H, m, $(CH_2)_5$],

[6] For this compound it was not possible to obtain accurate microanalysis: **3h**: Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 83.60; H, 6.31. **3n**: Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.28; H, 5.00. **3p**: Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 82.99; H, 11.38.

2.72 (2H, t, J = 3.05, CH_2C=CH_2), 5.61 (1H, t, J = 2.4, C=CHH), 6.21 (1H, t, J = 2.4, C=CHH); δ_C 22.3, 24.6, 37.3 [$(CH_2)_5$], 39.4 (CH_2C=CH_2), 83.2 (OCCH_2), 121.9 (C=CH_2), 135.5 (C=CH_2), 169.7 (C=O); *m/z* 166 (M+, 20%), 138 (10), 124 (21), 110 (44), 68 (100), 40 (80).

4-(2-Furanyl)-2-methylenebutyrolactone (**3j**): brown oil, R_f 0.26 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2923, 1763 (C=O), 1669, 1279, 1132, 812 cm-1; δ_H 3.14-3.32 (2H, m, CHCH_2), 5.51 (1H, dd, J = 7.9, 6.7, OCHCH_2), 5.72 (1H, t, J = 2.4, C=CHH), 6.28 (1H, t, J = 3.05, C=CHH), 6.36 (1H, dd, J = 3.05, 1.8, CH=CHCH), 6.43 (1H, d, J = 3.05, CHCH=C), 7.42 (1H, d, J = 1.8, OCH=CH); δ_C 31.8 (CHCH$_2$), 71.1 (OCH), 109.4 (CH=CHCH), 110.4 (CH=CHCH), 122.3 (C=CH_2), 133.7 (C=CH_2), 143.5 (OCH=CH), 151.0 [OC(CH)=CH], 169.4 (C=O); *m/z* 164 (M+, 5%), 146 (10), 120 (10), 68 (87), 40 (100) (Found: M+, 164.0475. $C_9H_8O_3$ requires M, 164.0473).

3-Methylene-1-oxaspiro[4.5]decane-2,8-dione (**3k**): white solid, R_f 0.20 (silica gel, hexane/ethyl acetate: 2/1); mp 78-79°C (pentane/dichloromethane); ν_{max} (KBr) 2959, 1754 (C=O), 1716 (C=O), 1660, 1429, 1231, 1123, 811 cm-1; δ_H 1.97-2.40 [6H, m, $(CH_2)_3$], 2.73-2.84 (2H, m, CH_2), 2.87 (2H, t, J = 3.0, CH_2C=CH_2), 5.72 (1H, t, J = 3.05, C=CHH), 6.32 (1H, t, J = 3.05, C=CHH); δ_C 36.9, 37.0 [$(CH_2)_4$], 39.0 (CH_2C=CH_2), 80.5 (OCCH_2), 123.4 (C=CH_2), 134.2 (C=CH_2), 169.1 (C=O), 208.9 (C=O); *m/z* 180 (M+, 2%), 153 (10), 152 (10), 126 (10), 125 (12), 112 (10), 111 (13), 69 (40), 68 (84), 41 (35), 40 (100). Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.64; H, 6.80.

6-Chloro-3-methylene-1-oxaspiro[4.5]decan-2-one (**3l**): colourless oil, R_f 0.32 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2941, 1763 (C=O), 1667, 1448, 1434, 1275, 1178, 974, 808 cm-1; δ_H 1.21-2.15 [8H, m, $(CH_2)_4$], 2.62 (1H, dt, J = 17.7, 3.0, CHHC=CH_2), 3.15 (1H, dt, J = 17.7, 3.0, CHHC=CH_2), 3.87-3.92 (1H, m, CHCl), 5.62 (1H, t, J = 2.45, C=CHH), 6.24 (1H, t, J = 3.0, C=CHH); δ_C 21.0, 25.4, 32.7, 38.3 [$(CH_2)_4$], 38.4 (CH_2C=CH_2), 66.1 (CHCl), 82.5 (OCCH_2), 121.8 (C=CH_2), 134.7 (C=CH_2), 169.5 (C=O); *m/z* 202 (M++2, 5%), 201 (M++1, 3), 200 (M+, 16), 124 (10), 123 (90), 122 (11), 69 (35), 68 (94), 67 (43), 55 (100), 53 (21) (Found: M+, 200.0604. $C_{10}H_{13}ClO_2$ requires M, 200.0604).

4-(2-Hydroxylphenyl)-2-methylenebutyrolactone (**3m**): brown oil, R_f 0.43 (silica gel, hexane/ethyl acetate: 2/1); ν_{max} (film) 3711-2818 (OH), 2744, 1738 (C=O), 1662, 1460, 1508, 914, 812 cm-1; δ_H 2.93 (1H, ddt, J = 17.7, 6.0, 2.4, CHCHH), 3.40 (1H, ddt, J = 17.1, 8.5, 2.45, CHCHH), 5.64 (1H, t, J = 3.05, C=CHH), 5.77 (1H, dd, J = 8.2, 6.1, OCH), 6.26 (1H, t, J = 3.06, C=CHH), 6.81-6.93 (2H, m, ArH), 7.09-7.22 (2H, m, ArH), 7.36 (br s, OH); δ_C 34.5 (CHCH$_2$), 76.0 (OCH), 115.8, 120.0 (ArC), 122.6 (C=CH_2), 125.9, 126.0, 129.5 (ArC), 134.6 (C=CH_2), 153.3 (ArC), 172.0 (C=O); *m/z* 190 (M+, 12%), 172 (10), 144 (10), 118 (16), 68 (28), 40 (100) (Found: M+, 190.0630. $C_{11}H_{10}O_3$ requires M, 190.0629).

3-Methylene-5-[2-(4-methylene-5-oxotetrahydro-2-furanyl)phenyl]butyrolactone (**3n**): white solid, R_f 0.25

(silica gel, hexane/ethyl acetate: 2/1); mp 103-106°C (pentane/dichloromethane); ν_{max} (KBr) 3175, 2928, 2852, 1764 (C=O), 1279, 1247, 1127, 1020, 927, 876 cm-1; δ_H 3.05 [2H, ddt, J = 17.1, 6.0, 3.0, $(CHCHH)_2$], 3.49 [2H, ddt, J = 17.1, 7.9, 2.4, $(CHCHH)_2$], 5.73-5.79 [4H, m, $(C=CHH)_2$ and $(OCH)_2$], 6.32 [2H, t, J = 3.05, $(C=CHH)_2$], 7.34-7.45 (4H, m, ArH); δ_C 35.3 ($CHCH_2$), 74.3 (OCH), 122.9 ($C=CH_2$), 125.2, 129.2 (ArC), 133.7 ($C=CH_2$), 136.7 (ArC), 169.8 (C=O); *m/z* 270 (M^+, 3%), 242 (10), 234 (10), 224 (10), 202 (10), 68 (45), 40 (100) (Found: M^+, 270.0899. $C_{16}H_{14}O_4$ requires M, 270.0892).[6]

2-(4-Methylene-5-oxotetrahydro-2-furanyl)benzaldehyde (**3n'**): pale yellow oil, R_f 0.24 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 2924, 2854, 1769 (C=O), 1695 (C=O), 1578, 1281, 1247, 1124, 1025, 859, 815 cm-1; δ_H 2.59 (1H, ddt, J = 17.7, 6.0, 3.0, CHCHH), 3.74 (1H, ddt, J = 17.1, 8.55, 3.0, CHCHH), 5.64 (1H, t, J = 2.4, C=CHH), 6.30 (1H, t, J = 3.05, C=CHH), 6.36 (1H, dd, J = 8.55, 5.5, $CHCH_2$), 7.54-7.69 (3H, m, ArH), 7.87 (1H, d, J = 7.3, ArH), 10.08 (1H, s, HC=O); δ_C 36.0 ($CHCH_2$), 75.5 (OCH), 122.9 ($C=CH_2$), 124.9, 128.4 (ArC), 132.0 ($C=CH_2$), 133.8, 134.6, 136.1, 142.2 (ArC), 170.5 (C=O), 193.3 (CH=O); *m/z* 202 (M^+, 12%), 184 (10), 156 (10), 105 (28), 68 (16), 40 (100) (Found: M^+, 202.0628. $C_{12}H_{10}O_3$ requires M, 202.0629).

*4-[3-(*N-tert-*Butoxycarbonyl)indenyl]-2-methylenebutyrolactone* (**3o**): yellow oil, R_f 0.27 (silica gel, hexane/ethyl acetate: 5/1); ν_{max} (film) 3118, 2980, 2934, 1770 (C=O), 1744 (C=O), 1610, 1571, 1455, 1157, 1030, 855, 814 cm-1; δ_H 1.64 [9H, s, $OC(CH_3)_3$], 3.13 (1H, ddt, J = 17.1, 6.0, 2.4, CHCHH), 3.41 (1H, ddt, J = 17.1, 7.9, 2.4, CHCHH), 5.71-5.78 (2H, m, C=CHH and OCH), 6.33 (1H, t, J = 3.0, C=CHH), 7.21-7.51 (3H, m, ArH), 7.60 (1H, s, NCH), 8.16 (1H, d, J = 7.95, ArH); δ_C 28.0 $[C(CH_3)_3]$, 33.7 ($CHCH_2$), 72.5 (OCH), 84.1 $[OC(CH_3)_3]$, 115.4, 119.2 (ArC), 122.6 ($C=CH_2$), 122.8, 123.0, 124.9, 127.6 (ArC), 133.9 ($C=CH_2$), 135.8, 149.3 (ArC), 169.8 (C=O); *m/z* 313 (M^+, 4%), 257 (22), 213 (12), 83 (15), 57 (100) (Found: M^+, 313.1319. $C_{18}H_{19}NO_4$ requires M, 313.1314).

Cholestanone derivative (**3p**): white solid, R_f 0.57 (silica gel, hexane/ethyl acetate: 2/1); mp 193-198°C (pentane/dichloromethane); ν_{max} (KBr) 2932, 2867, 2850, 1751 (C=O), 1468, 1445, 1434, 1378, 1282, 1116, 982, 811 cm-1; δ_H 0.64 (3H, s, CH_3), 0.79 (3H, s, CH_3), 0.85-2.00 (46H, m), 2.66 (2H, t, J = 2.4, $CH_2C=CH_2$), 5.58 (1H, t, J = 2.4, C=CHH), 6.21 (1H, t, J = 3.05, C=CHH); δ_C 11.4, 12.1, 18.6, 20.9, 22.5, 22.8, 23.8, 24.1, 28.0, 28.2, 31.7, 33.8, 34.1, 35.2, 35.5, 35.8, 36.1, 39.5 ($CH_2C=CH_2$), 39.9, 40.5, 40.95, 41.0, 42.5, 53.8, 56.1, 56.4, 83.4 ($OCCH_2$), 122.0 ($C=CH_2$), 135.6 ($C=CH_2$), 170.0 (C=O); *m/z* 454 (M^+, 23%), 439 (18), 369 (10), 314 (10), 299 (60), 231 (13), 192 (12), 147 (13), 123 (19), 107 (26), 94 (10), 93 (26), 81 (42), 69 (35), 68 (30), 56 (10), 55 (77), 43 (100) (Found: M^+ 454.3818. $C_{31}H_{50}O_2$ requires M, 454.3810);[6] $[\alpha]_D^{25}$ = +9.2 [(c = 1.0, $(CHCl_3)$)].

4-{6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl}-2-methylenebutyrolactone (**3q**) (diastereoisomeric mixture): pale yellow oil, R_f 0.49 (silica gel, hexane/ethyl acetate: 2/1); ν_{max} (film) 2919, 1764 (C=O), 1669, 1275, 1126, 811

cm-1; δ_H 0.83, 0.84 (3H, 2s, CH_3), 1.19 [1H, dd, J = 14.0, 8.55, C*H*CH_2), 1.29 (3H, s, CH_3), 2.05-2.48 (5H, m), 2.55-2.72 (1H, m, OCHC*H*H), 2.91-3.08 (1H, m , OCHCH*H*), 4.87-4.92 (1H, m, OCH), 5.53-5.69 (1H, m, C=C*H*H), 6.21 (1H, t, J = 3.0, C=CH*H*); δ_C 21.0 (CH_3), 25.9 (CH_3), 30.9, 31.3, 31.5, 31.55 (CH_2), 38.0 [*C*(CH_3)$_2$], 40.55, 40.6, 40.95, 41.05 (*C*H), 78.3, 78.8 (CHO), 120.8 (C=*C*H), 121.6, 121.7 (C=*C*H_2), 134.5, 134.6 (*C*=CH), 144.9, 145.0 (*C*=CH_2), 170.3, 170.4 (C=O); m/z 218 (M^+, 5%), 203 (10), 174 (11), 130 (10), 68 (88), 41 (100), 40 (73) (Found: M^+ 218.1344. $C_{14}H_{18}O_2$ requires M, 218.1306): $[\alpha]_D^{25}$ = -36.2 [c = 1.0, ($CHCl_3$)].

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VI. References

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