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2-(Chlorocarbonyl)-2-mesitylketene, a new building block for the synthesis of 4-hydroxy-3-mesityl tetronic acids

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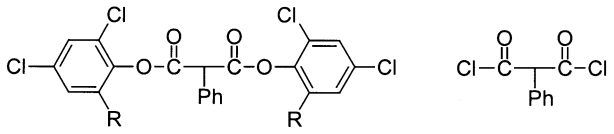
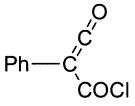
Abstract—Investigation of the reaction of (chlorocarbonyl)mesitylketene with ketones led to the discovery of a new synthetic pathway which yields 4-hydroxy-3-mesityl tetronic acids. Depending on the reaction conditions and the substitution pattern of the starting ketone, the expected products, i.e. 4-hydroxy-3-mesitylpyrones, can nevertheless be obtained.

Phenylmalonic acid derivatives such as activated diesters **1a**,**b**[1–6] and the diacyl chloride **2**[7,8] have often been described as versatile bifunctional reagents for the synthesis of numerous heterocycles. Phenyl-substituted chlorocarbonylketene **3**, first described by Nakanishi,[9] represents a highly reactive equivalent of phenylmalonic acid. However, the use of **3** as starting material was only seldom reported.[10–13]



1 **a** R= H
b R= Cl

2



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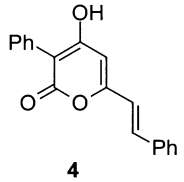

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Reaction of malonic acid derivatives with ketones is known[14–16] to yield the corresponding 4-hydroxy-pyrones. For instance, the characteristic structural design of kawalactones such as **4** may be obtained from reaction of phenylmalonic ester **1b** with 4-phenyl-3-buten-2-one.[17]

Using (chlorocarbonyl)mesitylketene **6** as synthetic equivalent of **1** in the reaction with ketones was therefore aimed at the synthesis of various 4-hydroxy-3-mesityl-pyrones. However, reaction of ketene **6** with acyclic α-substituted ketones **5a–e** afforded 4-hydroxy-3-mesityl tetronic acids **9a–e** in good yields in place of the expected pyrones **7a–e** (Scheme 1). The structural identity of the product probably resulting from a rearrangement as well as its configuration was confirmed by X-ray analysis of **9a** (Fig. 1).[18] Pyrones **7**, expected to arise from condensation and subsequent cyclisation could be obtained in good yield starting from silyl enol ethers **8** which were themselves derived from the corresponding ketones **5**, following House's method (excess TMSCl in DMF).[19] Under these conditions, tetronic acids **9** were only formed as by-products.

Formation of both the expected annulated pyrones **11a–e** and the spirotetronic acids **12a–e** occurred in the reaction of chlorocarbonylketene **6** with α-substituted cycloalkanones **10a–e** (Scheme 2). The structure of **12a** was confirmed by X-ray analysis (Fig. 2).[18]

The pyrone/tetronic acid ratio is influenced by the substitution pattern of the starting ketone. Only traces of pyrones **11a** and **11b** could be isolated under standard reaction conditions (i.e., reflux of xylene) whereas pyrones **11d** and **11e** could be obtained in higher yield. Reaction temperature also plays a key role in product distribution. Under heating of the two reactants for 5h to 200°C in the absence of solvent, formation of pyrone is then favoured. Under such reaction conditions pyrone **11b** is obtained as sole product.

A new synthetic pathway yielding versatile, highly functionalized tetronic acids was reported here. The scope of the novel methodology is not limited to the use of (chlorocarbonyl)mesitylketene **6**. Moreover, this reaction can be carried out with a large variety of ketones. Further

Keywords: (chlorocarbonyl)mesitylketene; 4-hydroxy-3-mesitylpyrones; 4-hydroxy-3-mesityl tetronic acids.

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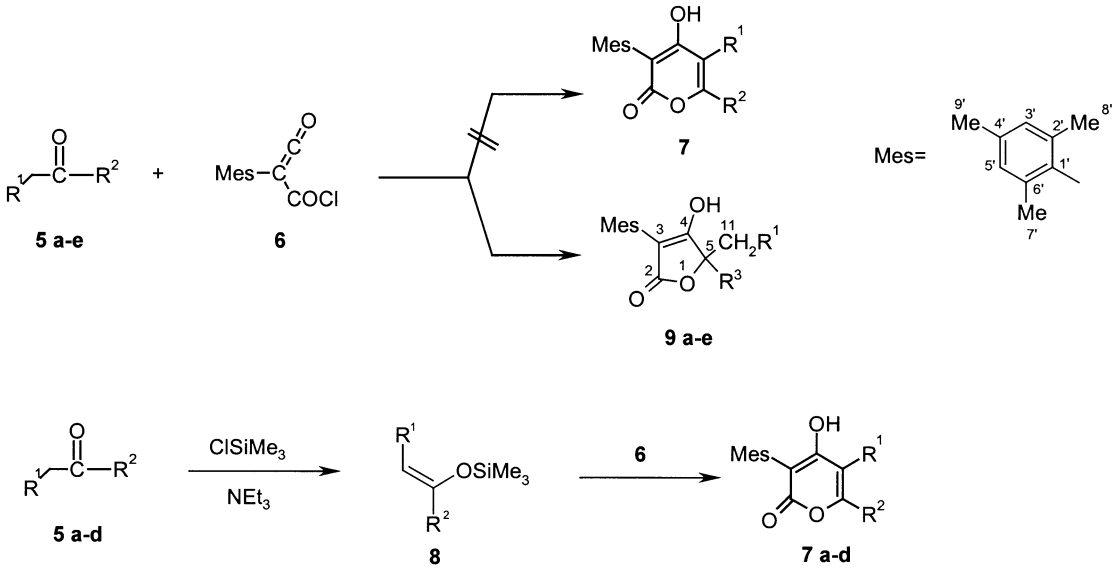


	R^1	R^2	R^3	9^a (%)	7^b (%)
a	H	cyclopentyl	cyclopenten-1-yl	60	48
b	H	cyclohexyl	cyclohexen-1-yl	85	71
c	H	cycloheptyl	cycloheptyl-1-yl	61	54
d	CH_3	cyclopentyl	cyclopenten1-yl	53	
e	H	-$CHMe_2$	-C(Me)=CH_2	69	

[a] Obtained from **5** and **6**; [b] Obtained from **8** and **6**

Scheme 1.

investigations with thioketones and imines as starting materials are currently under way.

1. Experimental

All commercially available solvents and reagents were used without further purification. 2-(Chlorocarbonyl)-2-mesitylketene **6** was prepared according to Nakanishi's method.[9] Thin layer chromatography was performed on silica gel $60F_{254}$ plates from Merck, Darmstadt, Germany.

Unless otherwise stated, ^1H NMR and ^{13}C NMR spectra were recorded either at 200 MHz on a XL 200 spectrometer or at 400 MHz on a Bruker DPX 400 Ultra Shield spectrometer using TMS as internal reference. High-resolution

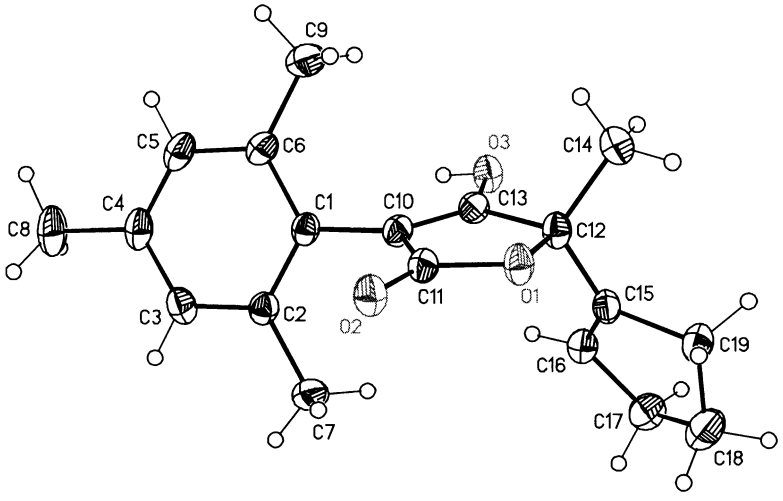
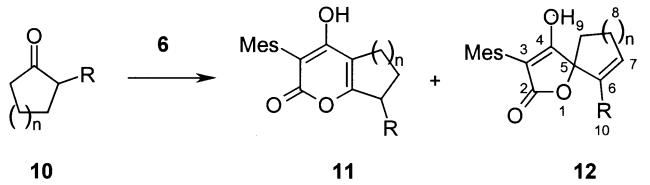


Figure 1. X-Ray structure of 4-hydroxy-3-mesityl tetronic acid **9a**.



	R	n	11 (%)	12 (%)
a	Me	1	trace 16[a]	57 26[a]
b	Me	2	trace 56[a]	62 trace[a]
c	Et	2	trace	71
d	*t*-Bu	2	22	58
e	Cl	2	20	15

a= 200°C, 5h, neat

Scheme 2.

mass spectrometry was carried out on a FTICR-MS Bruker Daltonik Bio Apex 7T spectrometer using electrospray ionisation (ESI). Crystal analysis was performed on a Bruker-Smart-CCD surface detection system, using $Mo_{K\alpha}$-radiation, a graphite monochromator and a rotation anode M18X-HF from MACScience Co., Ltd.

1.1. General procedure for the reaction of ketene 6 with acyclic α-substituted ketones and the corresponding silyl enol ethers

In a typical procedure, ketone **5** (40 mmol) dissolved in 10 ml abs. xylene was added dropwise at 20°C to a solution of 2-(chlorocarbonyl)-2-mesitylketene **6** (8.80 g, 40 mmol) in 80 ml abs. xylene. The reaction mixture was then heated to reflux for 8h. The precipitate obtained upon cooling was recrystallised from toluene/cyclohexane to yield compound **9**.

Silyl enol ethers **8** obtained according to House's method[19] were treated in a similar manner to yield products **7**.

1.1.1. 5-(1-Cyclopenten-1-yl)-4-hydroxy-3-mesityl-5-methyl-2(5*H*)-furanone (9a). Yield: 60%; white solid, mp 204–206°C; ^{1}H NMR (400 MHz, $CDCl_3$) d 1.61 (s, 3H, H11), 1.82–1.92 (p, 2H, J=3.7 Hz, H9), 1.95 (s, 3H), 1.97 (s, 3H) (H7', H8'), 2.10–2.40 (m, 7H, H8, H10 and H9'), 5.78 (t, *J*= 1.2 Hz, 1H, H7), 6.78 (s, 2H, H3' and H5'), enol-OH not observed.[13]C NMR (100 MHz, 80% $CDCl_3$ + 20% *d6*-DMSO) d 20.16 and 20.53 (C7', C8'), 21.51 (C9'), 22.38 (C11), 23.57 (C9), 31.30 and 33.17 (C8, C10), 83.56 (C5), 100.91 (C3), 123.88 (C1'), 128.5 and 128.54 (C3', C5'), 131.13 (7), 138.08, 138.36 and 138.48 (C2', C4', C6'), 140.91 (C6), 174.43 (C2), 178.37 (C4); HR-MS: $C_{19}H_{22}O_3$ calcd for $[M+H]^+$ 299.16147, found m/z 299.16410 for $[M+H]^+$.

1.1.2. 5-(1-Cyclohexen-1-yl)-4-hydroxy-3-mesityl-5-methyl-2(5*H*)-furanone (9b). Yield: 85%; white solid, mp 229–230°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.5–1.75 (m, 4H, CH_2), 1.70 (s, 3H, CH_3), 1.8–2.0 (m, 2H, CH_2), 2.0–2.3 (m, 2H, CH_2), 2.10 (s, 3H, mesityl CH_3), 2.12 (s, 3H, mesityl CH_3), 2.26 (s, 3H, mesityl CH_3), 5.96 (m, 1H, **H**C=C), 6.90 (s, 2H, aromatic); HR-MS: $C_{20}H_{24}O_3$ calcd for $[M+H]^+$313.17982, found m/z 313.17981.

1.1.3. 5-(1-Cyclohepten-1-yl)-4-hydroxy-3-mesityl-5-methyl-2(5*H*)-furanone (9c). Yield: 61%; white solid, mp 206-209°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35–1.6 (m, 6H, CH_2), 1.75 (s, 3H, CH_3), 1.7–1.85 (m, 2H, CH_2), 2.15 (s, 3H, mesityl CH_3), 2.18 (s, 3H, mesityl CH_3), 2.15–2.3 (m, 2H, CH_2), 2.3 (s, 3H, mesityl CH_3), 6.18 (t, 1H, J= 7.5 Hz, **H**C=C), 6.92 (s, 2H, aromatic); HR-MS: $C_{21}H_{26}O_3$ calcd for $[M+H]^+$327.19547, found m/z 327.19532.

1.1.4. 5-(1-Cyclopenten-1-yl)-5-ethyl-4-hydroxy-3-mesityl-2(5*H*)-furanone (9d). Yield: 53%; white solid, mp 209–211°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3H, J= 7.5 Hz, CH_3), 1.75–2.1 (m, 4H, CH_2), 2.0 (s, 3H, mesityl CH_3), 2.02 (s, 3H, mesityl CH_3), 2.22 (s, 3H, mesityl CH_3), 2.25–2.45 (m, 4H, CH_2), 5.78 (t, 1H, J= 7.5 Hz, **H**C=C), 6.78 (s, 2H, aromatic); HR-MS: $C_{20}H_{24}O_3$ calcd for $[M+H]^+$ 313.17982, found m/z 313.17973.

1.1.5. 4-Hydroxy-5-isopropenyl-3-mesityl-5-methyl-2(5*H*)-furanone (9e). Yield: 69%; white solid, mp 196–198°C; ^{1}H

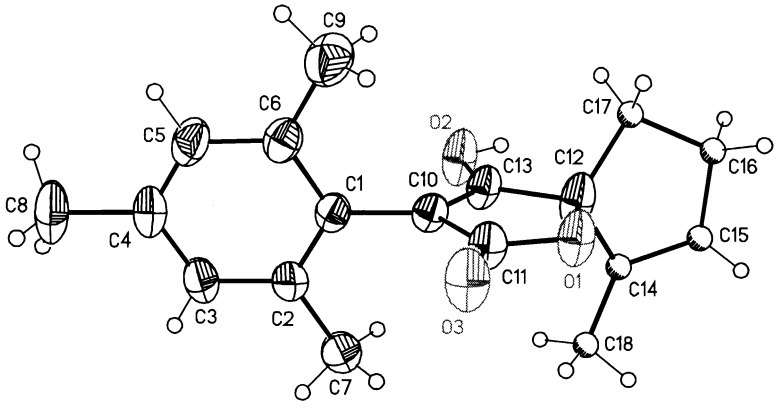


Figure 2. X-Ray structure of 3-mesityl-spirotetronic acid **12a**.

NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.00 (s, 3H, mesityl CH_3), 2.02 (s, 3H, mesityl CH_3), 2.22 (s, 3H, mesityl CH_3), 5.08 and 5.15 (s, 1H, H_2C=C), 6.8 (s, 2H, aromatic); HR-MS: $C_{17}H_{20}O_3$ calcd for $[M+H]^+$ 273.14852, found m/z 273.14854.

1.1.6. 6-Cyclopentyl-4-hydroxy-3-mesityl-2*H*-pyran-2-one (7a). Yield: 48%; mp 200–202°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.6–1.85 (m, 6H, CH_2), 1.9–2.1 (m, 2H, CH_2), 2.12 (s, 6H, mesityl CH_3), 2.28 (s, 3H, mesityl CH_3), 2.9 (m, 1H, C**H**-C=CH), 6.0 (s, 1H, **H**C=C), 6.95 (s, 2H, aromatic); HR-MS: $C_{19}H_{22}O_3$ calcd for $[M+H]^+$ 299.16417, found m/z 299.16408.

1.1.7. 6-Cyclohexyl-4-hydroxy-3-mesityl-2*H*-pyran-2-one (7b). Yield: 71%; mp 234–236°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15–1.45 (m, 4H, CH_2), 1.65–1.9 (m, 4H, CH_2), 1.95–2.05 (m, 2H, CH_2), 2.1 (s, 6H, mesityl CH_3), 2.25 (s, 3H, mesityl CH_3), 2.35–2.5 (m, 1H, C**H**-C=CH), 5.95 (s, 1H, **H**C=C), 6.95 (s, 2H, aromatic); HR-MS: $C_{20}H_{24}O_3$ calcd for $[M+H]^+$ 313.17982, found m/z 313.17992.

1.1.8. 6-Cycloheptyl-4-hydroxy-3-mesityl-2*H*-pyran-2-one (7c). Yield: 54%; mp 216–218°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4–1.9 (m, 9H, CH_2), 1.9–2.1 (m, 2H, CH_2), 2.1 (s, 6H, mesityl CH_3), 2.1–2.2 (m, 1H, CH_2), 2.3 (s, 3H, mesityl CH_3), 2.6 (m, 1H, C**H**-C=CH), 5.95 (s, 1H, **H**C=C), 6.95 (s, 2H, aromatic); HR-MS: $C_{21}H_{26}O_3$ calcd for $[M+H]^+$ 327.19547, found m/z 327.19533.

1.2. General procedure for the reaction of ketene 6 with cycloalkanones

In a typical procedure, cycloalkanone **10** (40 mmol) dissolved in 10 ml abs. xylene was added dropwise at 20°C to a solution of 2-(chlorocarbonyl)-2-mesitylketene **6** (8.80g, 40 mmol) in 80 ml abs. xylene. The reaction mixture was then heated to reflux for 8h. The precipitate (spiro-tetronic acid **12**) obtained upon cooling was recrystallised from toluene/cyclohexane (3:1). Pyrone **11** could be isolated after evaporation of xylene and subsequent flash chromatography of the residue with toluene/acetone.

When the reaction was conducted neat, purification was performed by flash chromatography (vide supra).

1.2.1. 4-Hydroxy-3-mesityl-7-methyl-6,7-dihydrocyclopenta[*b*]pyran-2(5*H*)-one (11a). Brown solid, mp 216–218°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (d, 3H, J= 7.5 Hz, CH_3), 1.67–1.85 (m, 2H, CH_2), 2.12 (s, 3H, mesityl CH_3), 2.14 (s, 3H, mesityl CH_3), 2.35 (s, 3H, mesityl CH_3), 2.7 (m, 2H, CH_2), 3.1–3.35 (m, 1H, CH), 5.75 (bs, 1H, OH), 7.0 (s, 2H, aromatic); HR-MS: $C_{18}H_{20}O_3$ calcd for $[M+H]^+$ 285.14852, found m/z 285.14849.

1.2.2. 4-Hydroxy-3-mesityl-8-methyl-5,6,7,8-tetrahydro-2*H*-chromen-2-one (11b). White solid, mp 123–125°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, 3H, J= 7.5 Hz, CH_3), 1.50–2.05 (m, 6H, CH_2), 2.12 (s, 3H, mesityl CH_3), 2.13 (s, 3H, mesityl CH_3), 2.30 (s, 3H, mesityl CH_3), 2.45 (dt, 2H, J= 7.5 Hz, J= 3 Hz, CH_2), 2.7–2.85 (m, 1H, CH), 5.75 (bs, 1H, OH), 7.0 (s, 2H, aromatic); HR-MS: $C_{19}H_{22}O_3$ calcd for $[M+H]^+$ 299.16417, found m/z 299.16415.

11c could not be isolated. However, the presence of **11c** was deduced from HPLC analysis by analogy with the other products.

1.2.3. 8-tert-Butyl-4-hydroxy-3-mesityl-5,6,7,8-tetrahydro-2*H*-chromen-2-one (11d). Yellow solid, mp 172–175°C; ^{1}H NMR (200 MHz, CD_3OD) δ 1.12 (s, 9H, *t*-Bu), 1.45–1.80 (m, 3H, CH_2), 1.85–2.05 (m, 2H, CH_2), 2.08 (s, 3H, mesityl CH_3), 2.10 (s, 3H, mesityl CH_3), 2.30 (s, 3H, mesityl CH_3), 2.50–2.65 (m, 2H, CH_2), 6.95 (s, 2H, aromatic); HR-MS: $C_{22}H_{28}O_3$ calcd for $[M+H]^+$ 341.21112, found m/z 341.21109.

1.2.4. 8-Chloro-4-hydroxy-3-mesityl-5,6,7,8-tetrahydro-2*H*-chromen-2-one (11e). White solid, mp 156–158°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85–2.15 (m, 1H, CH_2), 2.12 (s, 3H, mesityl CH_3), 2.15 (s, 3H, mesityl CH_3), 2.05–2.25 (m, 2H, CH_2), 2.32 (s, 3H, mesityl CH_3), 2.30–2.42 (m, 2H, CH2), 2.60–2.75 (m, 1H, CH2), 4.85 (t, 1H, J=4 Hz, CH), 6.0 (bs, 1H, OH), 6.95 (s, 2H, aromatic); HR-MS: $C_{18}H_{19}ClO_3$ calcd for $[M+H]^+$ 319.10955, found m/z 319.10953.

1.2.5. 4-Hydroxy-3-mesityl-6-methyl-1-oxaspiro[4.4]nona-3,6-dien-2-one (12a). White solid, mp 214–216°C; ^{1}H NMR (400 MHz, $CDCl_3$) d 1.66 (d, *J*= 0.8Hz, 3H, H10), 2.11(s, 3H) and 2.14 (s, 3H) H7' and H8', 2.22–2.32 (m, 4H, H9', H9a), 2.36–2.61 (m, 3H, H9b, H8), 5.85–5.9 (m, 1H, H7), 6.66 (s, 2H, H3', H5'), enol-OH not observed. ^{13}C NMR (100 MHz, 80% $CDCl_3$ + 20% *d6*-DMSO) δ 11.46 (C10), 19.79 and 20.19 (C7', C8'), 21.09 (C9'), 30.02 (C8), 33.16 (C9), 95.69 (C5), 101.48 (C3), 124.42 (C1'), 128.17 and 128.19 (C3', C5'), 134.46 (C7), 136.03(C6), 138.16, 138.26 and 138.30 (C2', C4', C6'), 172.76 (C2), 175.26 (C4). HR-MS: $C_{18}H_{20}O_3$ calcd for $[M+H]^+$ 285.14852, found m/z 285.14849.

1.2.6. 4-Hydroxy-3-mesityl-6-methyl-1-oxaspiro[4.5]deca-3,6-dien-2-one (12b). White solid, mp 223–225°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60 (s, 3H, CH_3), 1.70–1.90 (m, 3H, CH_2), 2.05 (s, 3H, mesityl CH_3), 2.08 (s, 3H, mesityl CH_3), 1.90–2.15 (m, 3H, CH_2), 2.24 (s, 3H, mesityl CH_3), 5.90 (m, 1H, C**H**=CCH_3), 6.82 (s, 2H, aromatic); HR-MS: $C_{19}H_{22}O_3$ calcd for $[M+H]^+$ 299.16417, found m/z 299.16409.

1.2.7. 6-Ethyl-4-hydroxy-3-mesityl-1-oxaspiro[4.5]deca-3,6-dien-2-one (12c). White solid, mp 255–257°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (t, 3H, J= 7.5Hz, CH_3), 1.75–1.95 (m, 6H, CH_2), 2.00 (s, 3H, mesityl CH_3), 2.04 (s, 3H, mesityl CH_3), 2.0–2.18 (m, 3H, CH_2), 2.22 (s, 3H, mesityl CH_3), 5.90 (m, 1H, C**H**=CCH_3), 6.80 (s, 2H, aromatic); HR-MS: $C_{20}H_{24}O_3$ calcd for $[M+H]^+$ 313.17982, found m/z 313.17981.

1.2.8. 6-tert-Butyl-4-hydroxy-3-mesityl-1-oxaspiro[4.5]-deca-3,6-dien-2-one (12d). White solid, mp 273–275°C; ^{1}H NMR (200 MHz, CD_3OD) δ 1.20 (s, 9H, *t*-Bu), 1.70–2.0 (m, 4H, CH_2), 2.0–2.25 (m, 2H, CH_2), 2.15 (s, 3H, mesityl CH_3), 2.25 (s, 3H, mesityl CH_3), 2.28 (s, 3H, mesityl

CH_3), 6.25 (t, 1H, J= 7.5 Hz, **H**C=CCH_3), 6.90 (s, 2H, aromatic); HR-MS: $C_{22}H_{28}O_3$ calcd for $[M+H]^+$ 341.21112, found m/z 341.21109.

1.2.9. 6-Chloro-4-hydroxy-3-mesityl-1-oxaspiro[4.5]deca-3,6-dien-2-one (12e). White solid, mp 260–263°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.60–2.10 (m, 4H, CH_2), 2.08 (s, 3H, mesityl CH_3), 2.15 (s, 3H, mesityl CH_3), 2.15–2.30 (m, 2H, CH_2), 2.25 (s, 3H, mesityl CH_3), 6.42 (m, 1H, **H**C=CCH_3), 6.90 (s, 2H, aromatic); HR-MS: $C_{18}H_{19}ClO_3$ calcd for $[M+H]^+$ 319.10955, found m/z 319.10967.

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18. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 158087 & 158088. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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