

Synthesis of Lucidones

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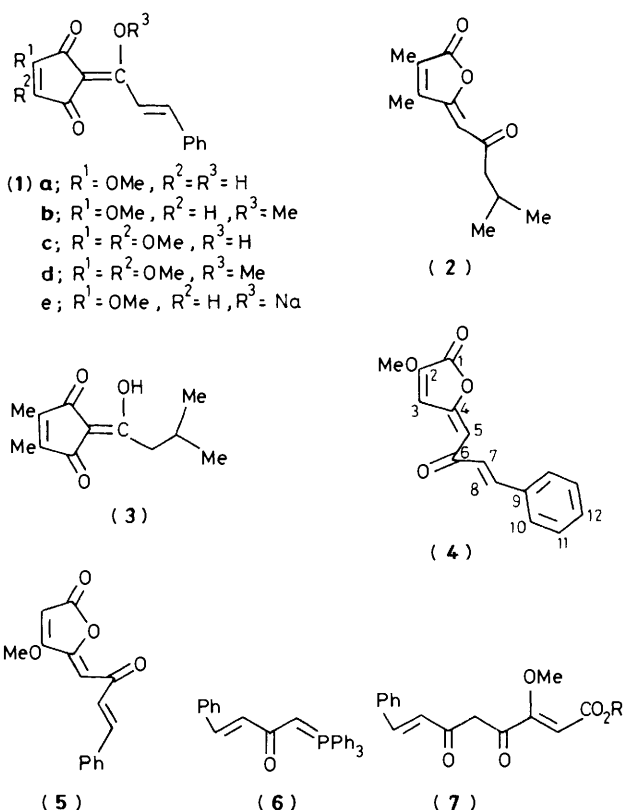
Reaction of 2-cinnamoyl-3-hydroxy-5-methoxy-1,4-benzoquinone (**10**) with acetic anhydride–dimethyl sulphoxide yielded (*E*)-4-(cinnamoylmethylene)-2-methoxybut-2-en-4-olide (**4**). Assignment of configuration of the exocyclic double bond in (**4**) is based on comparison of ¹H n.m.r. shift data and ³J(C-3,5-H) value with those of 4-ylidenebutenolides (**11**)—(**13**).

In the presence of sodium methoxide, (**4**) undergoes ready rearrangement affording lucidone (**1a**) and hence methyl-lucidone (**1b**).

Lucidone (**1a**)† and methyl-lucidone (**1b**)¹ are natural acylcyclopentenones isolated initially, with the structurally similar linderone (**1c**),² from the fruits of *Lindera lucida* (Lauraceae). They have since been found to be present also in the fruits of *Lindera erythrocarpa* Makino, together with the linderones (**1c** and **d**) and sodium lucidonate dihydrate (**1e**).³ It has been postulated that, biogenetically, these compounds might be derived from the appropriate acylphloroglucinol derivatives through ring-contraction reactions.⁴ Indeed the linderones had been synthesized from such a six-membered ring precursor.⁵ Recently, a novel method for the preparation of cyclopentenones which involves the base-catalysed rearrangement of isomeric 4-ylidenebutenolides has been developed.⁶ For example the butenolide (**2**) was readily converted by aqueous sodium hydrogen carbonate into the natural calythrone (**3**). This has led to the speculation that (i) the actual natural product from the oil of *Calythrix tetragona* might be (**2**), and (**3**) is an artifact from the isolation procedure used; and (ii) aromatic precursors might be implicated in the biosynthesis of cyclopentenones as they have been shown to be obligatory intermediates in the biogenetic route of several natural 4-ylidenebutenolides.⁷ In this paper, we describe the synthesis of lucidone (**1a**), and hence methyl-lucidone (**1b**) (since they are interconvertible), via a 4-ylidenebutenolide (**4**) derived from an acylphloroglucinol.

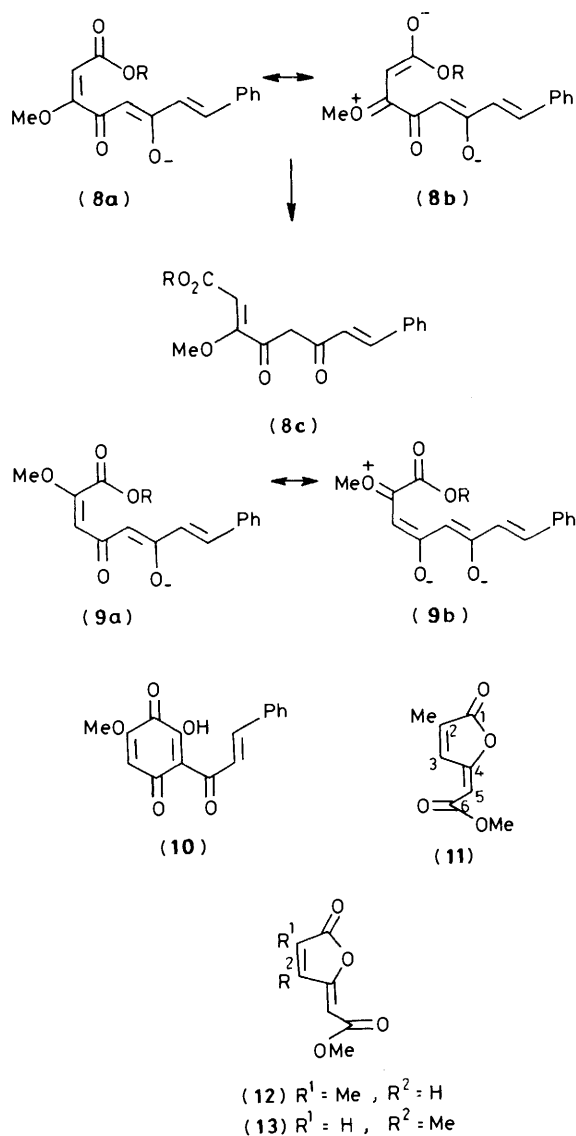
Attempts to rearrange 4-ylidenebutenolide (**5**), prepared by Wittig condensation of methoxymaleic anhydride and the phosphorane (**6**), to lucidone (**1a**) in the presence of various bases were reported to be unsuccessful.⁶ In each case, the only product, isolated in high yield, was the corresponding acyclic 4-oxo-unsaturated ester (**7**). The failure of (**5**) to yield (**1a**), in contrast to the generally ready base-catalysed rearrangement of 4-ylidenebutenolides to cyclopentenones, has been attributed to the importance of resonance structure (**8b**) of the intermediate (**8a**), which not only diminishes the electrophilicity of the carboxyl carbon, but also facilitates *E*–*Z* isomerization of the trisubstituted C-2 double bond to give (**8c**). Structure (**8c**) is sterically indisposed towards further ring-closure reaction. As a corollary to this observation, we reason that the inherent difficulty may be circumvented in the case of the isomeric 4-ylidenebutenolide (**4**) since the resonance contribution (**9b**) of the intermediate enolate (**9a**) would be relatively unimportant because of the resulting dipole repulsion. Enolate (**9a**) would be expected therefore to undergo subsequent intramolecular acylation readily leading to lucidone (**1a**).

Synthetic approaches to 4-ylidenebutenolides have been comprehensively reviewed.⁷ Considering the proposed mech-



anism for the reaction of dimethyl sulphoxide (DMSO)–acetic anhydride with hydroxyquinones to yield 4-ylidenebutenolides,⁸ it was thought that this oxidative rearrangement, applied to quinochalcone (**10**), might be the most expeditious way to the desired compound (**4**), especially since compound (**10**) had been prepared conveniently, in several steps, from pyrogallol.⁹ The reaction of quinochalcone (**10**) with acetic anhydride–DMSO for 1 h at 70–75 °C gave, indeed, a yellow solid, C₁₅H₁₂O₄, whose spectroscopic data are in agreement with the expected 4-ylidenebutenolide (**4**). The i.r. spectrum of the product shows absorptions at 1 625, 1 665, and 1 800 cm⁻¹, consistent with the presence of an α,β-unsaturated carbonyl as well as an *exo*-enol γ-lactone group.¹⁰ The ¹H n.m.r. spectrum shows a signal for three methoxy protons at δ 3.95. An AB pattern centres at δ 6.85 and 7.64 with *J* 16.1 Hz, which together with aromatic protons resonating between δ 7.3–7.7 are readily ascribed to the *trans*-cinnamoyl moiety. Two doublets at δ 6.39

† For convenience, only one enolic form is shown.



and 7.37, each with a splitting of 0.74 Hz, are assigned to the C-5 proton and C-3 proton respectively, based on comparison with the ^1H n.m.r. shift data of compounds (11) and (12) and other 4-ylidenebutenolides.¹¹ The relatively downfield position of the C-5 proton also indicates that compound (4) has the *E*-configuration since the vinylic H *cis* to the butenolide oxygen is more deshielded.¹²

In order to ascertain further the stereochemistry of the exocyclic double bond in (4), the ^{13}C n.m.r. spectra of (4) and (11)—(13) were determined (Table 1). The assignment of the ^{13}C chemical shifts is based generally on the proton-coupled and, where necessary, the selective proton-decoupled ^{13}C n.m.r. spectra. Some relevant carbon-proton coupling constants are shown in Table 2. Of significance are the values of the $^3J(\text{C}-3,5-\text{H})$ couplings. It has been noted that the values of *trans* C-H three-bonded couplings are usually much larger than those of the *cis* orientation.¹³ The value of $^3J(\text{C}-3,5-\text{H})$ obtained for (11), compared with the corresponding values for (12) and (13), follows this observed trend, and is in accord with the assigned stereochemistry (*E*-configuration for the former and *Z*-configuration for the latter two) as inferred from their ^1H n.m.r. shift data.¹¹ Since the $^3J(\text{C}-3,5-\text{H})$ value for (4) is very similar to that of (11), it is very likely that (4) also has the *E*-

Table 1. ^{13}C N.m.r. data (δ_{C} in p.p.m. from Me_4Si) of 4-ylidenebutenolides^a

Carbon atom	Compound			
	(4)	(11)	(12)	(13)
1	162.3	168.9	169.3	167.5
2	153.1	135.6	134.8	120.0
3	108.0	135.8	138.2	155.6
4	158.5	159.8	155.8	157.9
5	105.1	100.2	99.6	97.9
6	188.4	165.7	163.9	163.7
7 (Me)	127.7	11.1	10.9	11.9
8	143.4			
9	134.3			
10	128.5			
11	129.0			
12	130.8			
OMe	59.3	51.9	52.0	52.1

^a In CDCl_3 solution at concentration of $\leq 0.10\text{M}$. Uncertainties ± 0.1 p.p.m.

Table 2. $^{13}\text{C}-^1\text{H}$ and $^1\text{H}-^1\text{H}$ Coupling constants of 4-ylidenebutenolides

Compound	$J(\text{Hz})^a$					
	C-3, 3-H	C-3, 5-H	C-3, Me	C-5, 3-H	C-5, 5-H	3-H, 5-H
(4)	185.7	7.0		1.8	160.4	0.74
(11)	183.7	6.7	5.5	0	167.2	0.74
(12)	178.5	4.4	5.5	0	166.4	0
(13)		3.3	7.1		165.4	

^a Uncertainty in J_{HH} is ± 0.05 Hz and in J_{CH} ± 0.2 Hz. For other carbon-proton coupling constants, see Experimental section.

configuration. The observed value of 0 Hz for $^3J(\text{C}-5,7-\text{H})$ of (4) is also worthy of note, $^3J(\text{C},\text{CO},\text{C},\text{H})$ has been valuable in the conformational analysis of α,β -unsaturated ketones,¹⁴ and a value close to zero suggests that C-5 and 7-H have the *cis*-geometry as shown in the structural formula for (4).

Attempts to recrystallize (4) from methanol resulted in its decomposition to cinnamic acid. Reaction of (4) with aqueous sodium hydrogen carbonate gave, after acidification, the same product. Treatment of (4) with sodium methoxide in dry benzene or methanol for 1–1.5 h at their respective boiling points, however, yielded lucidone (1a) in 46–67% yield, identical in all respects (mixed m.p., i.r., ^1H n.m.r., and m.s.) with the natural compound. The instability of (4) in hot methanol appears to rule out its presence in the methanolic extracts¹⁵ of the fruits of *Lindera lucida* and hence excludes the possibility of (1a) as an artifact.

Experimental

I.r. and u.v.-visible spectra were measured in chloroform solutions with a Pye-Unicam SP1000 and a Perkin-Elmer model 551 spectrophotometer, respectively. Mass spectra were recorded at 70 eV with a VG Micromass 7035 instrument. Analytical t.l.c. and preparative t.l.c. (p.l.c.) were performed respectively on Merck pre-coated 0.25 mm and 0.5 mm Kieselgel 60 F₂₅₄ glass-backed plates; spots were located with iodine vapour or by u.v. illumination. Flash chromatographic separations were done according to published procedure.¹⁶ Hexane refers to the fraction of b.p. 64–68 °C. Elemental analyses were carried out by the Microanalytical Laboratory, National University of Singapore.

N.m.r. spectra were determined in CDCl_3 solutions in 5 mm

o.d. tubes at 28 °C on a JEOL FX-100 FT spectrometer operating at 100 MHz for ^1H and 25 MHz for ^{13}C . For ^1H spectra, the following accumulation parameters were used: data points 8K; spectral width 1 000 Hz; pulse angle 45°; acquisition time 2.0 s and pulse delay 3.0 s. For ^{13}C spectra, the following pulse modes were employed: proton-noise decoupling; proton-selective decoupling and gated decoupling for proton-coupled ^{13}C spectra. The accumulation parameters were: data points 8K; spectral width 4 000 Hz; pulse angle 45°; acquisition time 1.024 s and pulse delay 3.5 s. Resolution-enhancement procedures were adopted.

2-Cinnamoyl-3-hydroxy-5-methoxy-1,4-benzoquinone (10).⁹—To a solution of 2-hydroxy-3,4,6-trimethoxychalcone⁹ (3.5 g, 11 mmol) in glacial acetic acid (10 ml) at 65–70 °C was added conc. nitric acid (3.5 ml) and the red solution was stirred for 5 min before water (100 ml) was added. The precipitate was washed thoroughly with water and dried *in vacuo* over phosphorus pentoxide. Recrystallization from benzene afforded the pure product (10) (1.23 g) as dark orange plates, m.p. 175–177 °C (lit.⁹ 186–187 °C) (Found: C, 67.9; H, 4.4%; M^+ , 284.0686. Calc. for $\text{C}_{16}\text{H}_{12}\text{O}_5$: C, 67.6; H, 4.3% M , 284.0684; ν_{max} , 1 585 and 1 620 cm^{-1} ; δ 3.90 (3 H, s, OMe), 6.10 (1 H, s, 6-H), 7.35–8.3 (7 H, m, $\text{C}_6\text{H}_3\text{CH}=\text{CH}$), and 12.20 (1 H, br s, exchangeable, 3-OH); m/z 284 (84%), 256 (14), 227 (12), 171 (12), 153 (18), 131 (100), 115 (12), 106 (21), 104 (17), and 103 (60).

(E)-4-(Cinnamoylmethylene)-2-methoxybut-2-en-4-olide [(E)-5-(Cinnamoylmethylene)-3-methoxyfuran-2(5H)-one] (4).—A mixture of the preceding quinochalcone (10) (0.8 g, 2.8 mmol), acetic anhydride (3 ml) and DMSO (5 ml) was stirred and heated at 70–75 °C under nitrogen for 1 h, and then concentrated under reduced pressure. Flash chromatography (column diameter 40 mm; silica gel, 70 g) of the residue with methylene dichloride as eluant gave the butenolide (4) (320 mg) which crystallized from benzene as yellow rods, m.p. 140–142 °C (Found: C, 70.4; H, 4.75%; M^+ , 256.0732. $\text{C}_{15}\text{H}_{12}\text{O}_5$ requires C, 70.3; H, 4.7%; M , 256.0735; ν_{max} , 1 625, 1 665, and 1 800 cm^{-1} ; λ_{max} , 342 nm (log ϵ 4.35); δ 3.96 (3 H, s, OMe), 6.39 (1 H, d, J 0.74 Hz, 5-H), 6.85 and 7.64 (1 H each, d, J 16.1 Hz, $\text{PhCH}=\text{CHCO}$), 7.37 (1 H, d, J 0.74 Hz, 3-H), and 7.3–7.7 (5 H, m, Ph); $^3J(\text{C}-5,7\text{-H})$ 0 Hz, $^1J(\text{C}-7,7\text{-H})$ 155.5, $^1J(\text{C}-8,8\text{-H})$ 152.7, $^1J(\text{C}-12,12\text{-H})$ 161.5, and $^1J_{\text{CH(OMe)}}$ 147.2; m/z 256 (100%), 255 (73), 228 (13), 213 (19), 185 (31), 171 (12), 153 (45), 144 (26), 131 (35), 115 (18), 103 (54), and 84 (25).

Attempts to purify lactone (4) by recrystallizations from methanol gave cinnamic acid, m.p. and mixed m.p. 131–133 °C.

2-Cinnamoyl-4-methoxycyclopent-4-ene-1,3-dione (Lucidone) (1a).—A solution of the butenolide (4) (70 mg, 0.27 mmol) in dry benzene (6 ml) was added to a stirred solution of sodium methoxide [from NaH in 60% oil dispersion (10 mg) and methanol (1 ml)], and the mixture was heated to reflux under nitrogen for 1.5 h. Acidification (10% hydrochloric acid) in the cold and recrystallization of the yellow precipitate from methanol gave lucidone (1a) (32 mg) as bright yellow needles, m.p. and mixed m.p. 162–163 °C. The i.r., ^1H n.m.r., and mass spectra of the product are identical with those of the natural compound.

In a separate experiment, a solution of the butenolide (4) (60 mg, 0.23 mmol) in dry methanol (5 ml) was added to a stirred solution of sodium methoxide (from NaH in 60% oil dispersion) in methanol (5 ml) under nitrogen. The mixture was heated to reflux for 1 h, cooled, and acidified (10% hydrochloric acid). The product (40 mg) was identified as lucidone (1a) by m.p. and mixed m.p. (162–163 °C).

When the butenolide (4) (15 mg) was stirred in ether (5 ml) with 10% aqueous sodium hydrogen carbonate (5 ml) at room

temperature overnight, acidification of the mixture and isolation of the product with ether gave only cinnamic acid, m.p. and mixed m.p. 131–113 °C.

Wittig Reaction of 2-Methylmaleic Anhydride with Methoxycarbonylmethylenetriphenylphosphorane.—Following a published procedure,¹¹ the reaction mixture from 2-methylmaleic anhydride (1.87 g, 16.7 mmol) and methoxycarbonylmethylenetriphenylphosphorane¹⁷ (5.58 g, 16.7 mmol) was subjected to flash chromatography (column diameter 50 mm; silica gel, 100 g) with methylene dichloride as eluant to give (i) (E)-4-(methoxycarbonylmethylene)-2-methylbut-2-en-4-olide (11) (2.06 g) which crystallized from hexane as plates, m.p. 78–79 °C (lit.¹¹ 78–79 °C) (Found: M^+ , 168.0419. Calc. for $\text{C}_8\text{H}_8\text{O}_4$: M , 168.0422; ν_{max} , 1 670, 1 725, and 1 795 cm^{-1} ; λ_{max} , 284 nm (log ϵ 4.34); δ 2.09 (3 H, s, 2-Me), 3.77 (3 H, s, OMe), 5.81 (1 H, d, J 0.74 Hz, 5-H), and 8.07 (1 H, d, J 0.74 Hz, 3-H); $^1J_{\text{CH(Me)}}$ 129.3 Hz, $^1J_{\text{CH(OMe)}}$ 147.7 Hz, and $^3J[\text{C}(\text{Me}),3\text{-H}]$ 2.4 Hz; m/z 168 (22%), 137 (100), 136 (14), 110 (4.5), 97 (5), and 68 (11); and (ii) a mixture of butenolides (12) and (13) (0.2 g). This was further separated by p.l.c. [hexane-ethyl acetate (3:1 v/v), 4 developments] into pure (Z)-4-(methoxycarbonylmethylene)-2-methylbut-2-en-4-olide (12), m.p. 163–164 °C (20 mg) after sublimation at 110 °C (0.1 mm Hg) (Found: M^+ , 168.0419. $\text{C}_8\text{H}_8\text{O}_4$ requires M , 168.0422; ν_{max} , 1 675, 1 720, and 1 795 cm^{-1} ; λ_{max} , 282 nm (log ϵ 4.34); δ 2.08 (3 H, s, 2-Me), 3.79 (3 H, s, OMe), 5.36 (1 H, s, 5-H), and 7.07 (1 H, s, 3-H); $^1J_{\text{CH(Me)}}$ 130.0 Hz, $^1J_{\text{CH(OMe)}}$ 147.4 Hz, and $^3J[\text{C}(\text{Me}),3\text{-H}]$ 2.7 Hz; m/z 168 (64%), 138 (27), 137 (100), 136 (42), 110 (15), 97 (10), and 68 (36); and the more polar (Z)-4-(methoxycarbonylmethylene)-3-methylbut-2-en-4-olide (13) (120 mg), which after sublimation at 110 °C (0.1 mm Hg) had m.p. 94–95 °C (Found: M^+ , 168.0409. $\text{C}_8\text{H}_8\text{O}_4$ requires M , 168.0422; ν_{max} , 1 675, 1 720, and 1 805 cm^{-1} ; λ_{max} , 276 nm (log ϵ 4.22); δ 2.18 (3 H, s, 3-Me), 3.80 (3 H, s, OMe), 5.48 (1 H, s, 5-H) and 6.16 (1 H, s, 2-H); $^1J_{\text{CH(OMe)}}$ 147.2 Hz, $^1J_{\text{CH(Me)}}$ 129.6 Hz, and $^3J[\text{C}(\text{Me}),2\text{-H}]$ 2.7 Hz.

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