Structural Revision and Synthesis of LL-D253α: a Chromanone Metabolite of *Phoma pigmentivora*

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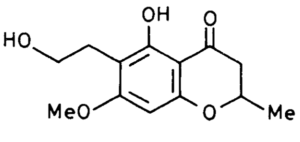
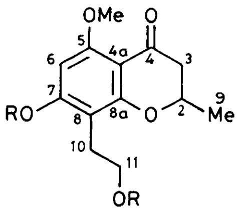
LL-D253α, a chromanone metabolite of *Phoma pigmentivora,* has been shown by analysis of the ^{1}H-coupled ^{13}C n.m.r. spectrum and by synthesis to be 7-hydroxy-8-(2-hydroxyethyl)-5-methoxy-2-methylchromanone.

LL-D253α was first isolated from *Phoma pigmentivora* and was assigned the chromanone structure (**1**) on the basis of spectroscopic and degradative studies.[1] It has also been isolated along with a number of related co-metabolites from *Phoma violacea* and *Sclerotinia fructigena.*[2] We now report ^{13}C n.m.r. studies on LL-D253α, carried out as a preliminary to biosynthetic labelling experiments,[3] which necessitate revision of the structure to (**2**) on the basis of a full analysis of the fully ^{1}H-coupled ^{13}C n.m.r. spectrum of LL-D253α diacetate (**3**). This has been confirmed by unambiguous syntheses of both structures (**1**) and (**2**).



(**1**)



(**2**) R = H

(**3**) R = Ac

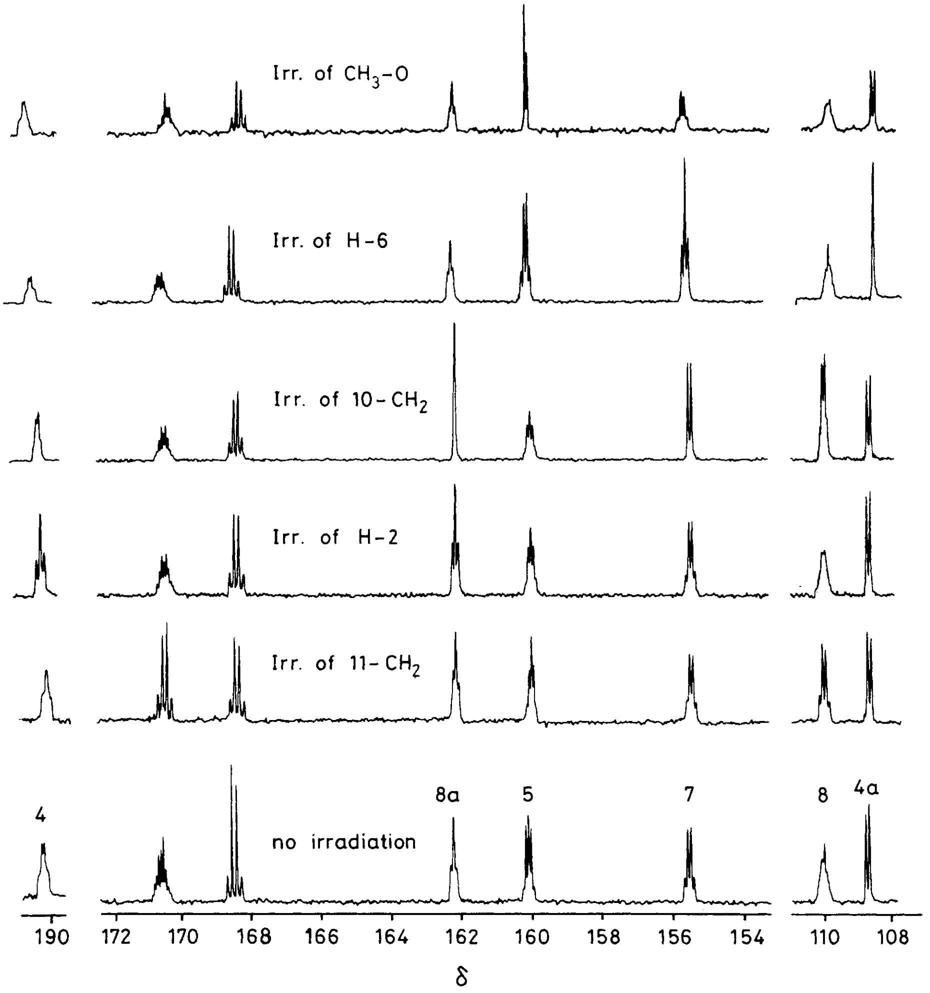


Figure 1. The high-frequency region of the fully ^{1}H-coupled 200 MHz ^{13}C n.m.r. spectrum of LL-D253α diacetate, and results of selective low-power ^{1}H decoupling experiments.

Figure 1 shows the high frequency region of the fully ^{1}H-coupled ^{13}C n.m.r. spectrum of LL-D253α diacetate (**3**) and the results of a series of specific low-power decoupling experiments.[4] All the aromatic carbons give characteristic multiplet patterns.† The hydroxyethyl side chain must be placed at C-8 rather than C-6 of the chromanone skeleton as irradiation of the benzylic methylene hydrogens (10-CH_2) and H-2 respectively caused the multiplet resonance at δ 162.1 to sharpen to a broad singlet and a sharp triplet (Figure 1). These results, along with the chemical shift, indicate that this resonance must therefore be assigned to C-8a, showing 3-bond couplings to 10-CH_2 and H-2. Similarly the phenolic acetate must be placed at C-7 as irradiation of 10-CH_2 and H-6 respectively change the quartet at δ 155.1 to a doublet and a triplet; and the methoxy substituent must be placed at C-5 as the quintet at δ 160.0 collapses to a quartet and doublet respectively on irradiation of H-6 and OCH_3. The complex multiplet at δ 110.0 is assigned to C-8 as it sharpens to a quartet on irradiation of either 10-CH_2 or 11-CH_2. It also sharpens slightly and shows an intensity increase on irradiation of H-6 due to removal of the expected 3-bond coupling. C-4a also shows a 3-bond coupling to H-6. The carbon–hydrogen couplings revealed by these experiments are summarised in Figure 2. Although these effectively define structure (**2**) for LL-D253α, confirmatory evidence was provided by unambiguous syntheses of both (**1**) and (**2**) from 5,7-dihydroxy-2-methylchromanone (**4**)[5] as outlined in Scheme 1. Allylation of the non-chelated hydroxy group on C-7 followed by methylation gave (**5**), which on heating to melting underwent a Claisen rearrangement to furnish (**6**).‡ In

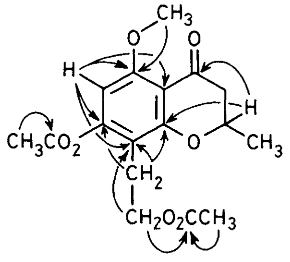


Figure 2. Long range ^{1}H–^{13}C couplings in LL-D253α diacetate selectively removed by low-power ^{1}H decoupling experiments.

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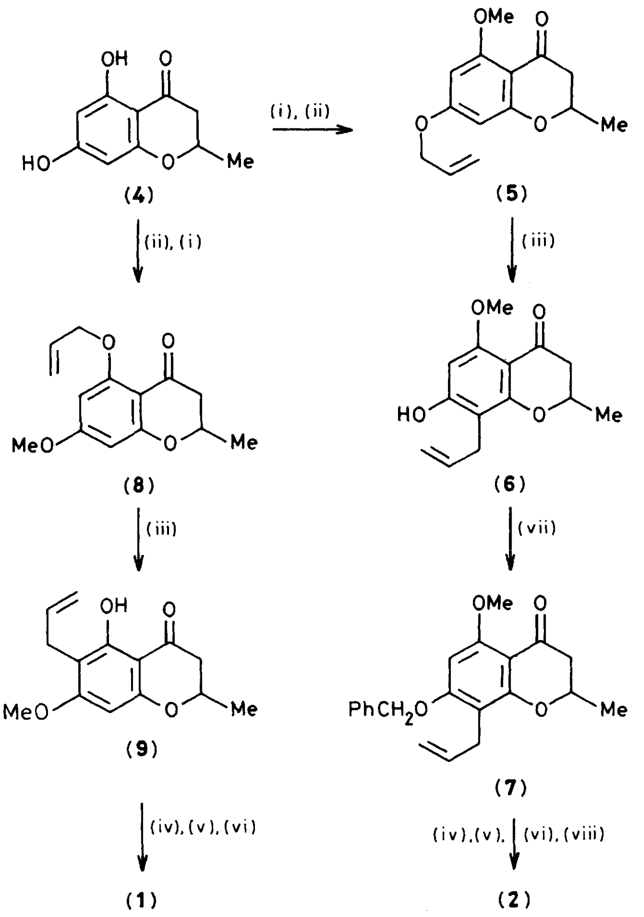
† C-6 gives a doublet [^1J(^{13}C–^{1}H) 126 Hz] and exhibits no long-range couplings.

‡ There is much precedent in the literature for Claisen rearrangement of 7-allyl ethers in chromone and chromanone systems to give mainly or exclusively the 8-allyl derivatives.[6]



Scheme 1. *Reagents and conditions:* (i) $H_2C{=}CHCH_2Br$, K_2CO_3; (ii) MeI, K_2CO_3; (iii) heat; (iv) OsO_4; (v) $NaIO_4$; (vi) $NaBH_4$; (vii) $PhCH_2Br$, K_2CO_3; (viii) H_2, Pd(C).

the presence of the free 7-hydroxy group all attempts to cleave the double bond oxidatively gave intractable mixtures. However, after protection as the benzyl ether (**7**), osmium tetroxide oxidation to the vicinal diol, periodate cleavage, and borohydride reduction of the resultant aldehyde, compound (**2**) was obtained in acceptable overall yield [16% from (**4**)] on hydrogenolysis of the benzyl protecting group. This was identical in all respects to natural LL-D253α. Structure (**1**) was obtained from (**4**) by methylation followed by allylation to give (**8**), which underwent Claisen rearrangement to (**9**). The allyl moiety was cleaved to the hydroxyethyl moiety as above without protection of the chelated hydroxy group being necessary. The overall yield of (**1**) from (**4**) was 44%. In contrast to LL-D253α, compound (**1**) was readily soluble in $CDCl_3$ and its ^1H n.m.r. spectrum showed the presence of a chelated hydroxy proton at δ 12.17, whereas the ^1H n.m.r. spectrum of LL-D253α in $CDCl_3$ showed that no chelated hydroxy group was present.

The ^1H-coupled ^{13}C n.m.r. spectra of (**1**) and a third isomer have been obtained and will be reported in full elsewhere.

Received, 5th March 1984; Com. 295

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