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# SYNTHESIS OF D,L-CANNABICHROMENE, FRANKLINONE AND OTHER NATURAL CHROMENES*

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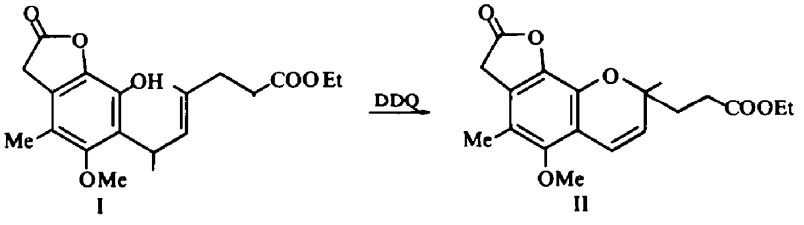
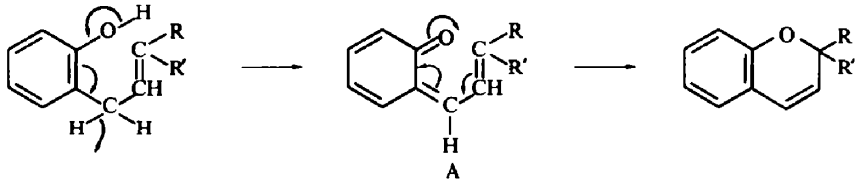
**Abstract**—The natural chromenes D,L-cannabichromene, franklinone, alloevodionol, evodionol methyl ether and the trimethyl ether of flemingin C were synthesized by cyclodehydrogenation of the corresponding isoprenylphenols with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or *via* the chromanes and dehydrogenation with DDQ. The biogenetical interest of this route is emphasized.

A RECENT paper[1] described the cyclization of a phenol with an ortho isoprenic side chain (ethyl mycophenolate, I) to the corresponding chromene (ethyl mycochromenate, II) by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). This result does not seem to have received the attention that it deserves.




I II

It is probably the first experimental reproduction *in vitro* of the biogenesis of natural chromenes in the modification—proposed by Turner—of the well-known hypothesis of Ollis and Sutherland:[3]




A

* Part VII of a series on Natural Chromenes, Part VI: G. Cardillo and L. Merlini, *Gazz. Chim. Ital.* **98**, 191 (1968).

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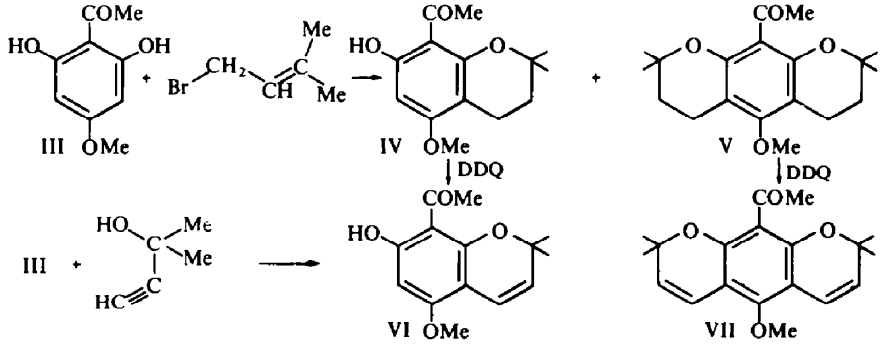
Abstraction of a hydride ion by DDQ[4] gives the unstable intermediate quinone methide A,* which immediately isomerizes to chromene.

Moreover, when coupled with prenylation of phenols, this method may be the mildest and most efficient synthesis of 2,2-dimethylchromenes, and especially 2-methyl-2′(4′-methylpent-3′-enyl) chromenes or higher isoprenylated homologues. The other usual methods[5] for the synthesis of 2,2-dimethylchromenes require the use of reagents (LAH or Grignard) which can interfere with possible reactive functional groups of the phenol. The direct Späth–Nickl[6,7] synthesis from phenols and alkynes gives low yields (< 5%) which are even lower in the case of the $C_{10}$ alkyne, dehydrolinalool.[8] Good results have been attained, in two very recent examples,[9,10] by synthesis of the chromanes, followed by dehydrogenation with DDQ.

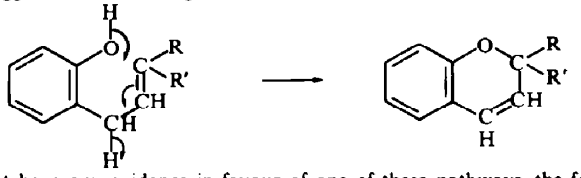
We wish to report here the successful synthesis, by cyclodehydrogenation with DDQ or *via* the chromanes, of some representative natural chromenes, D,L-cannabichromene,[11] the elusive[12] franklinone,[13] alloevodionol,[14] evodionol methyl ether[14,13] and the trimethyl ether of flemingin C.[15,8]

In the preparation of the intermediate phenols, the conditions—heterogeneous medium, non-polar solvent, and maximum coordinating power of the cation[16]—were selected, in order to obtain the maximum C-alkylation. The allylic bromide was thus added to the lithium salt of the phenol, which is easily prepared in benzene by reaction with commercially available butyl-lithium. The C-alkylated derivatives only were obtained in 15–20% yield, without O-alkylated by-products. In some cases, only the chromanes formed by cyclization of the isoprenylphenol could be isolated after chromatography through silica gel. These chromanes were dehydrogenated with DDQ to the chromenes.

In the first case, 2,6-dihydroxy-4-methoxyacetophenone (III) lithium salt was treated with dimethylallyl bromide in benzene. Chromatography of the reaction products through silica gel afforded directly the chromanes dihydroalloevodionol (IV) and tetrahydrofranklinone (V):



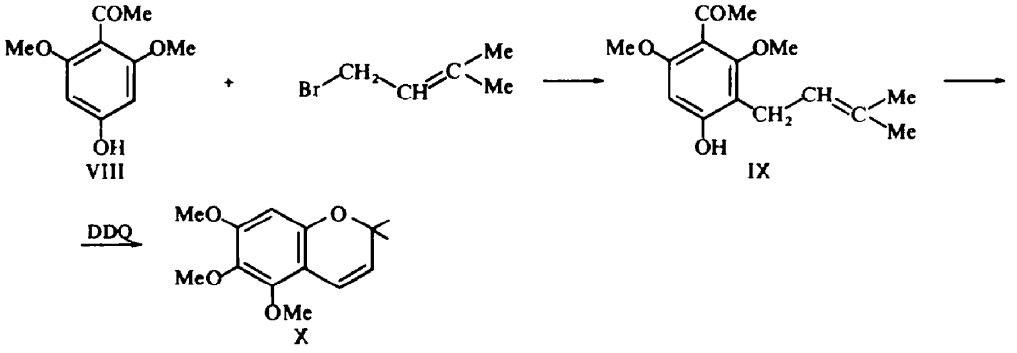

* A referee has suggested the following alternative mechanism:




Although we do not have any evidence in favour of one of these pathways, the formation of an intermediate quinone methide has been proposed in many oxidations of phenols, even with DDQ.[2,4]

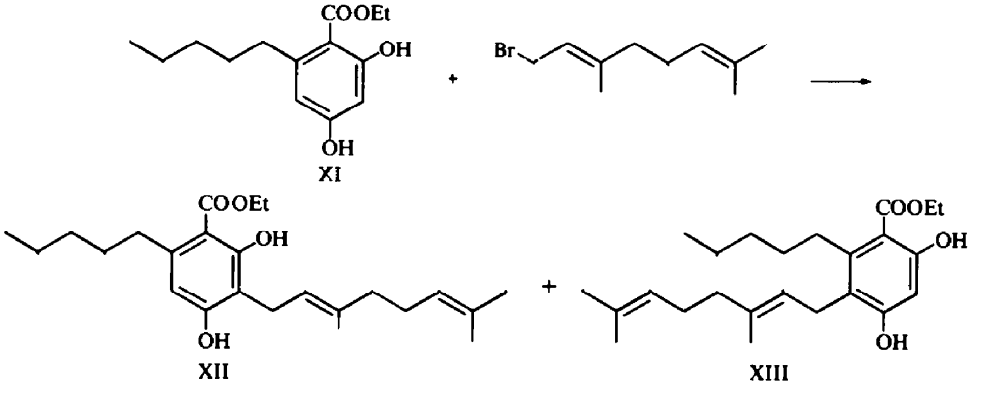
No open-chain derivative was isolated. Dehydrogenation of these chromanes with DDQ in benzene gave the expected *alloevodionol* (VI) and *franklinone* (VII) in 40–50% yield. The m.ps and spectral data of the compounds prepared are in agreement with those for the natural products or their derivatives. This synthesis establishes definitely the symmetrical structure VII for franklinone. Alloevodionol could also be prepared in low yield by direct reaction of III with 2-methyl-but-3-yn-2-ol and $ZnCl_2$. No franklinone was formed under these conditions.

The alkylation of 4-hydroxy-2,6-dimethoxyacetophenone (VIII) with dimethylallyl bromide gave instead the alkylated phenol IX:



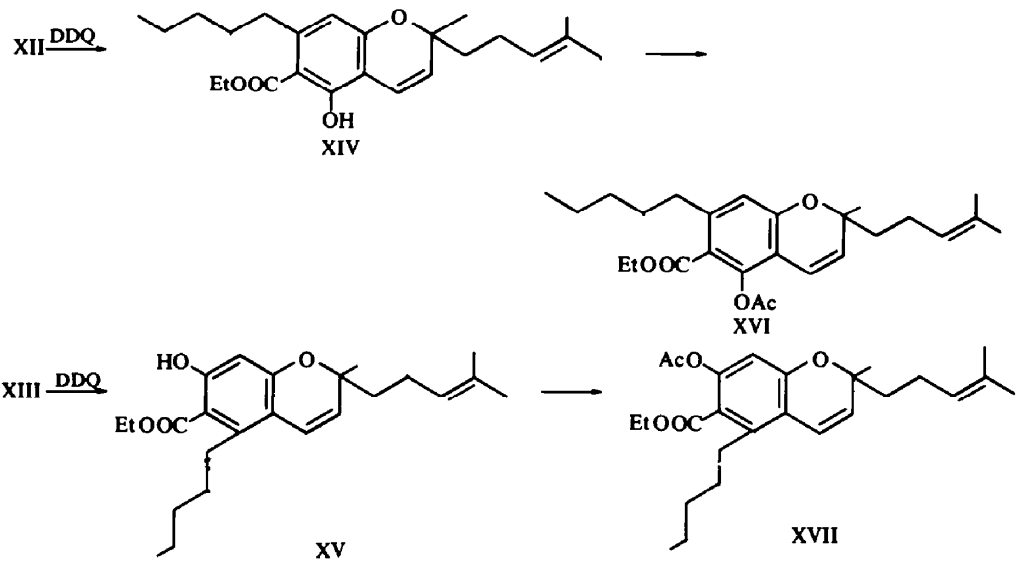

the reaction of which with DDQ in benzene gave the expected *evodionol methyl ether* (X).

The next effort was directed toward the synthesis of D,L-cannabichromene, a constituent of hashish,[17] which contains a 2-methyl-2'(4'-methylpent-3'-enyl)-chromene system. Alkylation of 6-carbethoxyolivetol (XI) with geranyl bromide in the usual way afforded two geranyl derivatives, XII and XIII, which could be separated by chromatography. The similarity of UV, mass and NMR spectra does

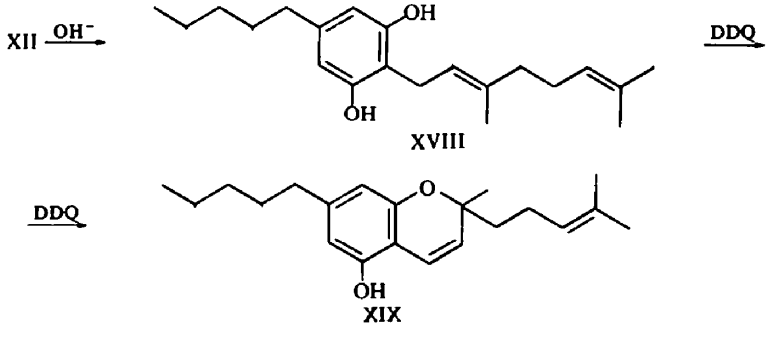



not allow a distinction between the two isomers. However, cyclization with DDQ should afford a 5-hydroxy- (XIV) and a 7-hydroxychromene (XV)* respectively:

* We have observed that the chelated OH is much less reactive in these cyclizations than the free OH. Thus the other possible isomers are not formed.



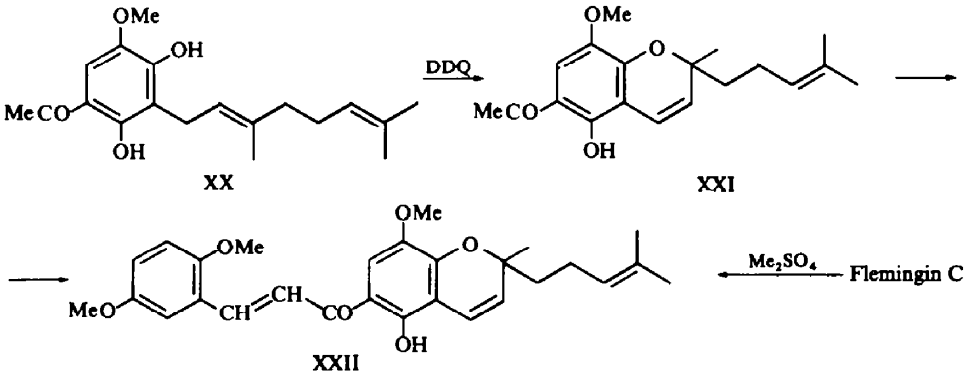

Compounds XIV and XV could be distinguished by the different chemical shift of $H_4$ (Experimental), on which the *peri* OH induces a remarkable deshielding effect in XIV.[18] Moreover, as we have already shown in a number of natural chromenes,[18] acetylation brings about a marked diamagnetic shift on $H_4$ in XIV, if it is a 5-hydroxychromene, and not in XV. This was indeed the case, and the structures of XIV and XV were thus assigned. Compound XII is, therefore, the ethyl ester of cannabigerolic acid.[19] It was hydrolysed under the conditions given[19] to cannabigerol* (XVIII), which was cyclized by DDQ to D,L-*cannabichromene* (XIX). UV and NMR spectra of XX are identical with those reported[11,17] for the natural product. This synthesis



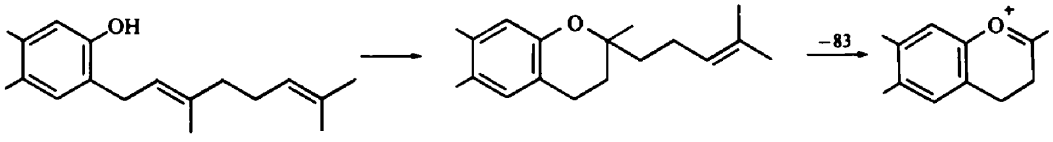

is not only a confirm of the structure of cannabigerol and cannabichromene, but it suggests an alternative path of biosynthesis of cannabichromene, with respect to that proposed by Gaoni and Mechoulam.[17]

* Cannabigerol has been already synthesized by reaction of olivetol with geraniol in boiling decaline.[20] The alkylation of olivetol with geranyl bromide gave even smaller yields than *ria* the cannabigerolic ester, and the separation of cannabigerol from other products was more difficult and required repeated chromatography. Only traces of the isomer 4-geranyl-5-pentylresoreinol were obtained by preparative TLC and identified by the mass spectrum.

Finally, the trimethyl ether of flemingin C, one of the chalcones recently isolated from the drug Wars[15] was synthesized. Cyclodehydrogenation of 2,4-dihydroxy-3-geranyl-5-methoxyacetophenone (XX) with DDQ afforded in 40% yield the expected XXI, which was condensed with 2,5-dimethoxybenzaldehyde to give *flemingin C trimethyl ether* (XXII), identical to the product obtained by methylation of natural flemingin C:




NMR and mass spectra (Experimental) are consistent with all the structures given. The mass spectra of chromanes show the known fragmentation schemes,[21] i.e. easy formation of pyrilium ions and retro Diels–Alder cleavages. In the case of phenols with ortho $C_5$ or $C_{10}$ isoprenic chains (e.g. IX, XII, XVIII) the loss of fragments with mass units 15 and 83 respectively could be interpreted with a prior cyclization* to chromane, followed by fragmentation:




## EXPERIMENTAL

UV spectra ($\lambda_{max}$ in nm) were measured in 95% EtOH soln, with a Beckman DK-2 apparatus, NMR spectra (values in $\delta$, $J$ in Hz) in $CCl_4$ soln with a Varian A-60 (TMS as internal standard), and mass spectra with a Hitachi–Perkin Elmer RMU6D spectrometer. Column chromatography was performed with a Merck 0·05–0·20 mm silica gel, and TLC with Merck $HF_{254}$.

*Dihydroalloevodionol* (IV). To 3 g 2,6-dihydroxy-4-methoxyacetophenone in 150 ml dry benzene, 16 ml 15% BuLi in hexane were added. After boiling for 1 hr, 10·5 g γ,γ-dimethylallylbromide were added slowly, and the mixture refluxed overnight. Decomposition with ice and 1N HCl, extraction with ether gave a crude product, which was chromatographed with hexane–AcOEt, 99:1 to give 1 g IV, m.p. 78° (aq. EtOH), UV: 223, 291, 334 (ε 16,100, 16,400, 2800). Mass: 250, 235 (M—Me), 207 (M—Me—CO), 195 (M—$C_4H_7$), 167. NMR: $Me_2$—C(—O)— (1·36), —$CH_2$—$CH_2$— (two rough triplets of ca. 7 Hz, 1·72 and 2·50), MeCO (2·52), OMe (3·77), 1 arom. H (5·86), 1 chel. OH (10·36).

*Tetrahydrofranklinone* (V) m.p. 124–127° (hexane), was obtained (850 mg) from the preceding chromatography, by elution with hexane–AcOEt. NMR: 2 $Me_2C$—O— (1·27), 2 Ar—$CH_2$—$CH_2$— (two rough

* The same behaviour has been observed in the case of chalcones, which give mass spectra very similar to the corresponding flavanones: see H. Audier, *Bull. Soc. Chim. Fr.* 2892 (1966).

tripl. of ca. 7 Hz, 1·70 and 2·64), MeCO (2·26), OMe (3·67). Mass: 318, 303 (M—Me), 263 (M—$C_4H_7$), 247, 207.

*Alloevodionol* (VI). (a) Compound IV (300 mg) and DDQ (300 mg) in 50 ml dry benzene were refluxed 1 hr. Filtration and evaporation gave 130 mg VI. (b) 2,6-Dihydroxy-4-methoxyacetophenone (800 mg), 2-methylbut-3-yn-2-ol (4 g) and $ZnCl_2$ (1 g) were heated 30 min at 120° and for 1 hr at 140°. The mixture extracted with ether and 1N HCl, the extract chromatographed with hexane–AcOEt 98:2, to give 70 mg VI m.p. 67–69°. (Found: C, 68·43; H, 6·94. Calc. for $C_{14}H_{16}O_4$: C, 67·73; H, 6·50%); UV: 222, 278, 356 (ε 10,900, 19,800, 2250). NMR: ($Me_2\underset{|}{C}$—O— (1·47), MeCO (2·50), OMe (3·83), CH=CH (5·30, 6·47, $J$ = 10), 1 H arom. (s, 5·89), 1 chel. OH (13·50).

*Franklinone* (VII). Compound V (300 mg) was dehydrogenated with 500 mg DDQ in 50 ml boiling dry benzene. Filtration and evaporation gave a pure product, m.p. 128–129°; Mass: 314, 299 (M—Me). NMR: 2 $Me_2C$—O— (1·41), MeCO (2·37), OMe (3·71), 2 CH=CH (5·43, 6·43, $J$ = 10).

*2,6-Dimethoxy-4-hydroxy-3-(3'-methylbut-2'-enyl) acetophenone* (IX). 2,6-Dimethoxy-4-hydroxyacetophenone (1 g) in 50 ml dry benzene was alkylated with 3 ml γ,γ-dimethylallyl bromide as described. After extraction with benzene and chromatography with hexane–AcOEt 9:1 80 mg IX, m.p. 66–68° was obtained; UV: 274, ~305 (ε4100, 2500); Mass: 264, 249 (M—Me), 221 (M—Me—CO), 209 (M—$C_4H_7$), 193, 181; NMR: 2 Me—$\underset{|}{C}$= (1·67, 1·74), MeCO (2·42), Ar—$CH_2$—CH= (3·2, d of ca. 7 Hz), 2 Me (3·54, 3·64), —$CH_2$—CH= (m, 5·0–5·2), 1 arom. H (6·10), 1 OH (7·1).

*Evodionol methylether* (X). Compound IX (60 ml) in 30 ml dry benzene was refluxed 1 hr with 60 mg DDQ. Filtration and evaporation gave X, m.p. 76–77°; UV: 228, 254 (ε 10,700, 8700); NMR: 2 Me—$\underset{|}{C}$—O— (1·38), MeCO (2·38), 2 OMe (3·69, 3·75), CH=CH (5·42, 6·42, $J$ = 10) 1 arom. H (6·07).

*Ethyl cannabigerolate* (XII) and *2,4-dihydroxy-5-geranyl-6-pentylbenzoate* (XIII). To 3·5 g 6-carbethoxyolivetol[22] in 70 ml dry benzene, 15 ml 15% BuLi in hexane was added. After 1 hr, 3 g geranyl bromide was added, and the mixture refluxed overnight. Decomposition with dil HCl, extraction with benzene and chromatography gave 1·1 g XII (eluted with hexane–AcOEt 99:1) and 0·35 g XIII (eluted with hexane–AcOEt 80:20). Both had to be rechromatographed under the same conditions. Compound XII, oil, UV: 223, 272, 308 (ε 23,000, 11,300, 4100); Mass: 388, 305 (M—$C_6H_{11}$), 273, 265 (M—$C_9H_{15}$), 231, 219; NMR: $C\underline{H}_3CH_2CH_2$— (t, 0·90), $C\underline{H}_3CH_2O$— (t, 1·38, $J$ = 7), 3 $CH_3$—$\underset{|}{C}$= (1·57, 1·66, 1·78) $\diagdown$—$CH_2$—$CH_2$—$\diagup$ (1·9–2·1), Ar—$C\underline{H}_2$—$CH_2$— (2·7), Ar—$C\underline{H}_2$—CH= (3·56, d of ca. 7 Hz), $MeC\underline{H}_2O$— (q, 4·35, $J$ = 7), 2 CH= (m, 4·9–5·3) 1 arom. H (s, 6·11), 1 chel. OH (12·0). Compound XIII, oil, UV: 219, 269, 311 (ε 23,800, 9700, 4650); Mass: 388, 305, 265; NMR: $CH_3CH_2CH_2$— (0·90), $C\underline{H}_3CH_2O$— (t, 1·40, $J$ = 7), 3 $CH_3$—C= (1·57, 1·65, 1·73), $\diagdown$—$CH_2$—CH—$\diagup$ (1·9–2·1), $ArC\underline{H}_2CH_2$ (2·7–2·9), Ar—$C\underline{H}_2CH$= (d, 3·26, $J$ = 7), $CH_3C\underline{H}_2O$— (q, 4·38, $J$ = 7), 2 CH= (m, 4·8–5·2), 1 arom. H (6·05), 1 OH (7·1), 1 chel. OH (11·5).

*2-Methyl-2'(4'-methylpent-3'-enyl)5-hydroxy-6-carbethoxy-7-pentylchromene* (XIV). Cyclization of 200 mg XII with 200 mg DDQ in 30 ml boiling dry benzene for 16 hr gave, after chromatography, XIV; UV: 256, 263 (ε 35,000, 36,500); NMR: 25 H (0·80–2·20), $ArC\underline{H}_2CH_2$— (2·75), $CH_3C\underline{H}_2O$— (q, 4·38, $J$ = 7), 1 CH= (m, 4·8–5·2), CH=CH (5·35, 6·72, $J$ = 10), 1 arom. H (s, 6·08), 1 chel. OH (11·84). The acetate XVI was prepared by reaction with $Ac_2O$ and AcONa for 1 hr on a water bath; UV: 233, 280, 308, 320 (ε 28,700, 4300, 2850, 2350); NMR: 22 H (0·8–2·1), MeCO (2·18), $ArC\underline{H}_2CH_2$ (2·65), $MeC\underline{H}_2O$— (q, 4·24, $J$ = 6), 1 CH= (m, 4·8–5·2), CH=CH (5·45, 6·22, $J$ = 10), 1 arom. H (s, 6·47).

*2-Methyl-2'-(4'methylpent-3'-enyl)5-pentyl-6-carbethoxy-7-hydroxychromene* (XV). This was prepared in the same way as XIV; NMR: 22 H (0·8–2·2), $ArC\underline{H}_2CH_2$— (2·85), $MeC\underline{H}_2O$— (q, 4·38, $J$ = 6), 1 CH= (m, 4·8–5·2), CH=CH (5·43, 6·47, $J$ = 10), 1 arom. H (s, 6·18), 1 chel. OH (11·2). Acetate XVII: UV: 231, 280 sh, 310, 320 (ε 20,600, 3550, 2000, 1800); NMR: 22 H (0·8–2·2), MeCO (2·13), $ArCH_2CH_2$ (2·60), $MeCH_2O$— (q, 4·26, $J$ = 6), 1 CH= (m, 4·8–5·2), CH=CH (5·53, 6·47, $J$ = 10) 1 arom. H (6·45).

D,L-*Cannabichromene* (XIX). Compound XIV (150 mg) was hydrolised and decarboxylated[19] to give 33 mg of XVIII, the UV, NMR and mass spectra of which are identical to those reported.[17] Cyclization of XVIII with DDQ in the usual way and chromatography with hexane–AcOEt afforded XIX as an oil,

UV: 230, 280 (ε 19,500, 7400), mass: 314, 299, 243; 231; NMR: $C\underline{H}_3CH_2$— (0·88), $CH_3\overset{|}{C}(-O-)-$ (1·32), 2 $CH_3$—C= (1·55, 1·62), $ArC\underline{H}_2CH_2$— (2·38, rough triplet of ca. 7 Hz), 1 CH= (m, 4·9–5·1), CH=CH (5·37, 6·52, $J$ = 10), 2 meta arom. protons (5·95, 6·10).

*2-Methyl-2'(4'-methylpent-3'-enyl)5-hydroxy-6-acetyl-8-methoxychromene* (XXI). Compound XX[15] (47 mg) in 10 ml dry benzene was refluxed 1 hr with 56 mg DDQ. Filtration, evaporation and chromatography with hexane–AcOEt 95:5 afforded 20 mg XXI; UV: 259, 324 (ε 17,400, 5600); Mass: 316, 301 (M—$CH_3$), 233 (M—$C_6H_{11}$); NMR: $CH_3-\overset{|}{C}(-O-)$ (1·26), $Me_2C$= (1·55, 1·63), 4 H (1·6–2·2), MeCO (2·47), OMe (3·75), 1 CH= (m, 4·8–5·2), CH=CH (5·44, 6·72, $J$ = 10), 1 H arom. (s, 6·93), 1 chel. OH (12·65).

*Flemingin C trimethylether* (XXII). A soln of 120 mg XXI and 70 mg 2,5-dimethoxybenzaldehyde in 2 ml ethanol was added under $N_2$ atmosphere and with cooling to 1 g KOH in 2 ml MeOH. After 3 days at room temp, dilution, acidification, extraction with ether and chromatography with hexane–AcOEt 98:2 afforded XXII, identical by thin-layer comparison and spectral data to the sample prepared by methylation of flemingin C.[8]

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