Acid-catalysed Terpenylations of Olivetol in the Synthesis of Cannabinoids

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Examination of the toluene-*p*-sulphonic acid-catalysed reaction of (1*S*,2*S*,3*R*,6*R*)-(+)-*trans*-car-2-ene epoxide with olivetol shows that, inconsistently with the accepted mechanism, (3*R*,4*R*)-(−)-*o*- and -*p*-cannabidiols are produced as well as (3*R*,4*R*)-(−)-Δ^1-and Δ^6-tetrahydrocannabinols. Evidence is now presented that, as in Petrzilka's reaction employing chiral *p*-mentha-2,8-dien-1-ols, the reacting species is the delocalised (4*R*)-*p*-mentha-2,8-dien-1-yl cation (**9**).

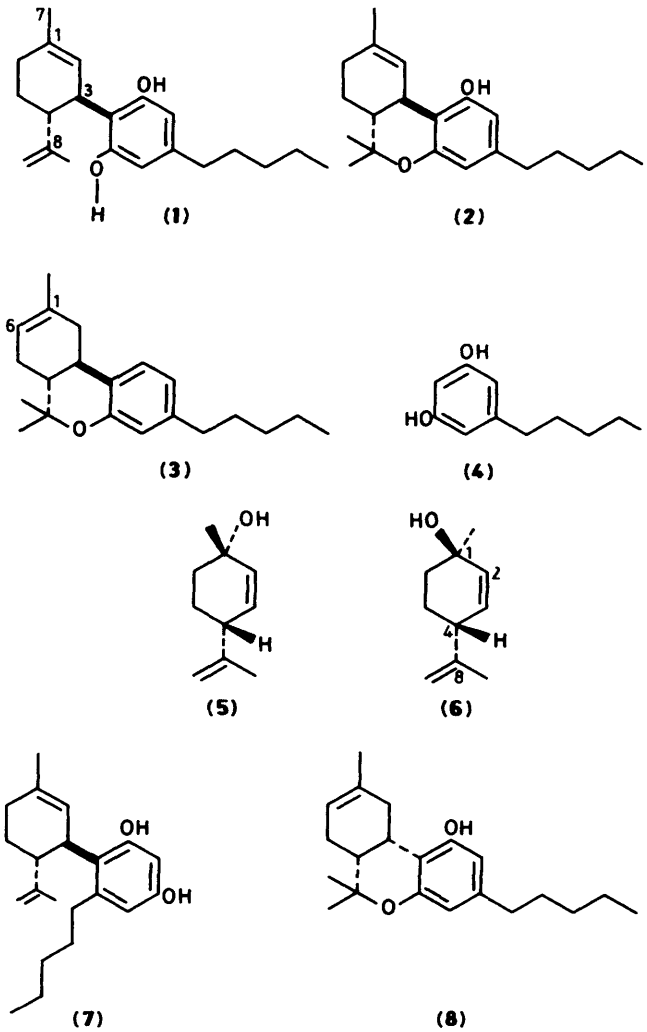
Similar terpenylation using (1*S*,3*S*,4*R*,6*R*)-(+)-*trans*-car-3-ene epoxide shows that besides the reported (−)-Δ^6-THC, *o*- and *p*-cannabidiols, Δ^1-THC and $\Delta^{4,8}$-iso-THC can also be produced. The nature of the products, the chirality, and the characteristics of the reaction implicate again the delocalised cation (**9**). Its formation *via* Kropp-type rearrangement is excluded and a pathway leading to (4*R*)-*p*-mentha-2,6,8-triene, which on protonation gives (**9**), is proposed. Protonated on C-8, the triene can be trapped and isolated as (4*R*)-*p*-mentha-2,6-dien-8-ol. The latter, made in (±)-form from citral, proved to be an excellent terpenylating agent for producing cannabinoids.

Terpenylation of olivetol by the pinanes (1*S*,4*S*,5*S*)-(−)-*cis*-verbenol and (1*R*,5*S*,7*R*)-(+)-*cis*-chrysanthenol is compared. A major drawback of the latter is partial racemisation which occurs in the verbenone–chrysanthenone isomerisation during its photochemical preparation. Whilst Δ^1-THC cannot be directly obtained from verbenol, its tertiary allylic cation permits a much higher yielding terpenylation than the secondary cation from chrysanthenol.

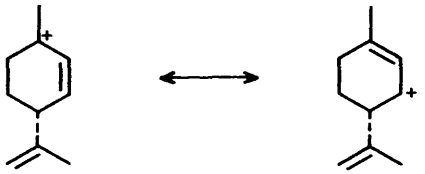
With some exceptions,[1] syntheses of the natural cannabinoids (3*R*,4*R*)-(−)-cannabidiol (CBD) (**1**), (3*R*,4*R*)-(−)-Δ^1-tetrahydrocannabinol (*trans*-Δ^1-THC) (**2**), and (3*R*,4*R*)-(−)-Δ^6-tetrahydrocannabinol (*trans*-Δ^6-THC) (**3**) draw upon the pool of natural chirality, using terpenylation reactions of olivetol (**4**). Similar approaches have been made to non-natural analogues.[2] Early terpenylation work employed acid-catalysed reactions of citral leading to racemates,[3] but the strongly chirality-dependent psychotomimetic effects of (3*R*,4*R*)-(−)-Δ^1-THC[4] have focussed interest on more appropriate chiral cyclic terpenes. It is the purpose of this paper[5] to contribute to mechanistic problems that have arisen in these terpenylation reactions of olivetol.

Acid-catalysed terpenylations of phenols frequently lead to a considerable number of products, reducing yields and complicating work-up. Although not completely free from these common defects, one of the most useful and most frequently used reagents is Petrzilka's (1*S*,4*R*)-(+)-*trans*- or (1*R*,4*R*)-(+)-*cis*-*p*-mentha-2,8-dien-1-ol (**5**) or (**6**):[6] a mixture may be employed since the C-1 chirality becomes irrelevant. The chirality derives from (+)-limonene and a mixture of (**5**) and (**6**) is obtained through sensitised photo-oxidation followed by reduction.[7]

Mild acid catalysis of the reaction betwen menthadienol and olivetol leads to (3*R*,4*R*)-(−)-*p*-cannabidiol (**1**)* and the corresponding unnatural *o*-compound (**7**).[6] Under stronger acidic conditions (3*R*,4*R*)-(−)-Δ^6-THC (**3**) is produced and during this process the kinetically favoured *o*-cannabidiol undergoes reversion to the more thermodynamically stable *p*-cannabidiol. Only small amounts of (3*S*,4*R*)-*cis*-Δ^6-THC (**8**) are formed.[6] It was later found that by closer control of the acid conditions the important (3*R*,4*R*)-(−)-*trans*-Δ^1-THC (**2**) could be obtained in acceptable yields,[8] though on more prolonged acid treatment it passes over to the stable (−)-Δ^6-compound (**3**). Petrzilka's terpenylation is considered to



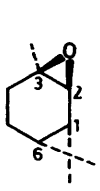
* The prefixes *ortho*- and *para*- are used with reference to the C_5-olivetol side chain. The former series are sometimes referred to as 'abnormal' and prefixed *abn*.



(9)

proceed *via* generation of the allylic cation (**9**) which by electrophilic attack on olivetol gives (**1**) [and (**7**)]: this then cyclises to Δ^1-THC (**2**) which further isomerises to Δ^6-THC (**3**), both processes involving carbonium ions.[9] The key importance of the allylic cation (**9**) will emerge in certain other terpenylations considered below.

Although producing Δ^1- and Δ^6-THC's along with products of the *cis*-series, the condensation of (1*S*,2*S*,3*R*,6*R*)-(+)-*trans*-car-2-ene epoxide (**10**) with olivetol, catalysed by toluene-*p*-sulphonic acid (PTSA), or boron trifluoride, is suggested by Razdan and Handrick[10] to be of a mechanistic type different from Petrzilka's reaction. In particular, no cannabidiols were found in the reaction, and in order to accommodate this, nucleophilic attack by a phenolic hydroxy group on the cyclopropane of car-2-ene epoxide as in (**11**) was postulated. Cyclisation as in (**12**) then ensues, followed by proton loss to



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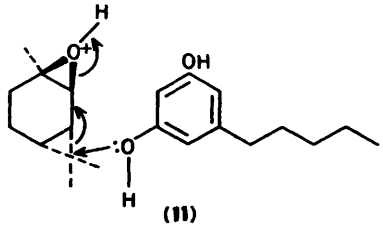

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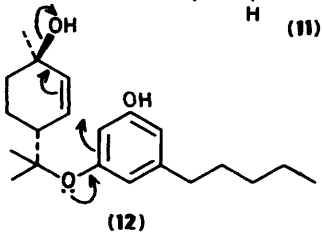


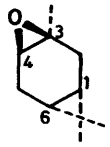
(12)

give (**2**). *cis*- and *trans*-Δ^1-THC's are thus claimed to be the first formed cannabinoids, with other products derived from them.[10] This mechanism is widely accepted in reviews.[11]

We have re-examined the reaction between (+)-*trans*-car-2-ene epoxide and olivetol in the presence of PTSA and find that contrary to the earlier report *p*-(**1**)- and *o*-(**7**)-cannabidiols are in fact the first-formed cannabinoid products of the reaction. Following the reaction at time intervals and at temperature intervals between 20 and 80 °C, monitoring by t.l.c. using Fast Blue Salt B spray and by g.l.c./m.s., it was shown that the two cannabidiols were formed in the early stages of all the reactions. Data shown in the Experimental section indicate that there is interconversion of *o*- to *p*-cannabidiol and that the latter is further converted first into Δ^1-THC and then into Δ^6-THC. Total yields of cannabinoids are rather poor, *ca.* 10% or less. The pattern of the reaction is similar to that involving the cation (**9**), though higher yields and fewer side-products are obtained when the latter is generated from *p*-menthadienol. This is hardly surprising, for car-2-ene epoxide under acidic conditions may also decompose by other than cannabinogenic pathways. Data for parallel experiments using car-2-ene epoxide and *p*-menthadienol are given in the Experimental section and suggest a common cannabinoid reaction profile and a large disparity in yields.

Treatment of car-2-ene epoxide with PTSA at 50 °C followed by quenching has allowed us to demonstrate by g.l.c. (Carbowax 20M)/m.s. that *cis*-*p*-menthadienol (**6**) is formed. This is in line with various reports that car-2-ene epoxide can be converted into *cis*-*p*-menthadienol under acid conditions.[12] In our opinion there are no grounds for the special mechanism (**11**)/(**12**). All our evidence points to involvement of the cation (**9**) and car-2-ene epoxide may be viewed as a surrogate for *p*-menthadienol in providing this. Because of other products produced, and in terms of yield, it provides a preparative route inferior to the *p*-menthadienol method.

Montero and Winternitz[13] have provided an interesting report that the PTSA-catalysed terpenylation of olivetol using (1*S*,3*S*,4*R*,6*R*)-(+)-*trans*-car-3-ene epoxide (**13**) [derived from the abundantly available natural terpene (+)-car-3-ene] gives (−)-Δ^6-THC (**3**) in 25% yield, but no products of the *cis*-THC series (*e.g.* iso-THC's). We have confirmed by isolation and measurement of the rotation that (−)-Δ^6THC is produced in



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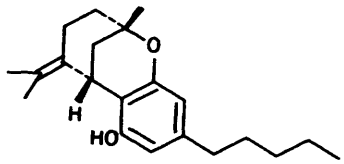

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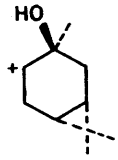

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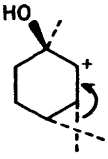
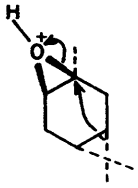


(16)

the reaction though in our hands yields were considerably lower (6—10%). In addition we have shown both by g.l.c./m.s. and by isolation that $\Delta^{4,8}$-iso-THC (**14**) is also produced in the reaction despite the earlier report. The fact that the Δ^6-THC belongs to the natural (3*R*,4*R*)-(−)-series poses an interesting stereochemical problem. In order to accommodate his results Montero[14] suggested that protonation of the epoxide (**13**) occurred giving (**15**), followed, in order to amend the chirality, by a 1,3-hydride shift to give (**16**). Opening of the homoallylic carbonium ion then gives the protonated form of the *p*-menthadienol (**6**). This explanation is not attractive as the epoxide opens to give a secondary in preference to a tertiary carbonium ion: there then follows a 1,3-hydride shift for which there seems to be no evidence. We have, therefore, sought a more satisfactory solution to the problem.

Our first thoughts turned to the possibility of a Kropp-type rearrangement.[15] This would lead *via* (**17**) to a homoallylic alcohol which on protonation (**18**) would give the carbonium ion (**19**) capable of terpenylating olivetol to give (−)-Δ^6-THC. In order to test this, the cyclopropyl alcohol (**24**) was made from carane-3β,4α-diol (**20**).[15] The latter was acetylated (**21**) and dehydrated with phosphorus oxychloride–pyridine to form a mixture of compounds (**23**) and (**25**). After deacetylation using lithium aluminium hydride, the two alcohols (**22**) and (**24**) were separated by preparative g.l.c. However, condensation of (**24**) with olivetol in the presence of PTSA gave no Δ^6-THC or other recognised cannabinoids under conditions that we would have expected to produce them. Examination of this reaction showed a number of products were formed and the two major ones were analysed spectroscopically and shown to have iridoid-type skeletal attachments. They are formulated, taking into account mechanistic and spectral information (see Experimental sec-



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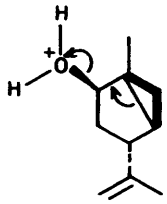

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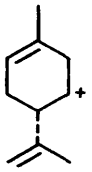

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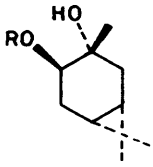

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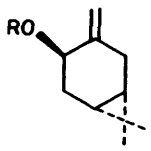
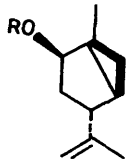
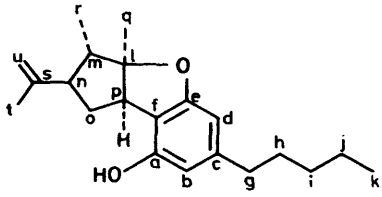
(21) R = Ac



(22) R = H
(23) R = Ac



(24) R = H
(25) R = Ac



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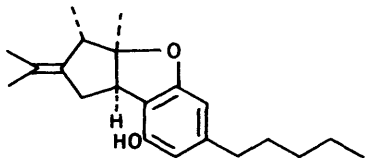

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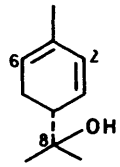
tion), as (**26**) and (**27**). Being apparently irrelevant to the problem on hand, the reaction was not studied further. Indeed further study of the PTSA-catalysed reaction between car-3-ene epoxide and olivetol cast doubt on the adequacy of the non-allylic cation (**19**) to explain our results since by varying conditions we were able to show that *o*- and *p*-cannabidiols as well as Δ^1-THC were produced under milder conditions. A different approach was therefore initiated.

(+)-*trans*-Car-3-ene epoxide was treated with PTSA in benzene for 30 min in the absence of olivetol and the products were examined. At least 33 compounds were found on the g.l.c. trace and the products were chromatographed using preparative h.p.l.c. on silica (eluant 5% ethyl acetate in hexane). 18 Fractions were taken and each was treated with olivetol and PTSA for cannabinoid formation. Cannabinogenic material was found to be confined essentially to fraction 13 and further purification by h.p.l.c. allowed isolation of the *exo*-methylene compound (**22**) identical with our synthetic specimen. Although it was a meagre producer of Δ^6-THC in the olivetol/*p*-TSA test, it was clear that a second and much better producer was present in this fraction. Continued h.p.l.c. work gave this second compound pure, and it was clearly a clean and abundant producer of Δ^6-THC. By spectroscopic analysis (u.v., ^{1}H and ^{13}C n.m.r.) and mass spectral information we were able to identify this compound as (*R*)-(−)-α-phellandren-8-ol (**28**).[16] Its identity was rigorously established by the preparation of a specimen of (±)-α-phellandren-8-ol through the condensation of citral, catalysed by dilute acid.[17] The reaction gives many products[18] and very careful h.p.l.c. separation with g.l.c. monitoring was required to isolate a pure specimen. Except for chirality, the compound from citral was identical in all respects with the sample isolated from car-3-ene epoxide.



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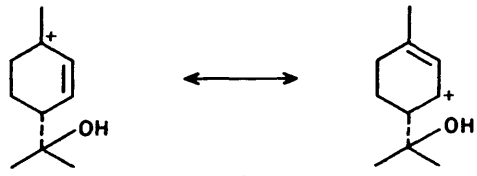
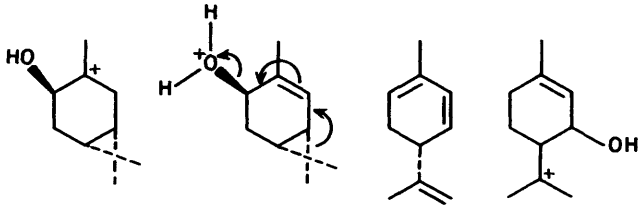
With a synthetic sample available, the reaction of α-phellandren-8-ol with olivetol in the presence of PTSA could be studied in more detail. As expected it forms, according to conditions, *o*- and *p*-cannabidiols, Δ^1-THC and Δ^6-THC, the latter in *ca.* 40% yield. Once again the allylic cation of the Petrzilka method is central to both the reactions of α-phellandren-8-ol, which gives by proton addition (**29**) and hence



(29)

(**9**), and the reaction of car-3-ene epoxide which presumably produces (**9**) *via* (**30**) and (**31**) and which can be trapped as (**28**) or which equilibrates with (**32**) and protonated species in the reaction mixture. Reactions using car-3-ene epoxide require for initiation rather stronger conditions than for the car-2-ene epoxide case, and this is understandable when the instability of the latter to acids, forming *p*-menthadienol, is considered. The mechanism proposed solves the stereochemical problem inherent in making (−)-THC's from (+)-*trans*-car-3-ene epoxide.



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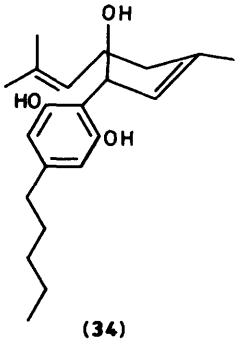
There remains the question of whether, in the acid-catalysed terpenylation of olivetol by citral,[3] which leads to (±)-cannabidiols and Δ^1- and Δ^6-THC's, cyclisation takes place before or after condensation with olivetol, *i.e.* whether (**33**) or (**34**) ⟶ (**35**) is involved. Tests show that under conditions used in one of our earlier papers (dichloromethane/PTSA)[19] citral in the absence of olivetol gives a fraction corresponding chromatographically with α-phellandren-8-ol which, completely free of citral, reacts with olivetol to form Δ^6-THC. The amount formed, however, was small and tends to indicate that both pathways are operative. Their relative significance will depend on reaction conditions.

Terpenylation by a pinane derivative was pioneered by Mechoulam and his colleagues[20] and is a well proved route to Δ^6-THC. In the presence of boron trifluoride–diethyl ether (1*S*,4*S*,5*S*)-(−)-*cis*-(**36**) [or (−)-*trans*] -verbenol condenses



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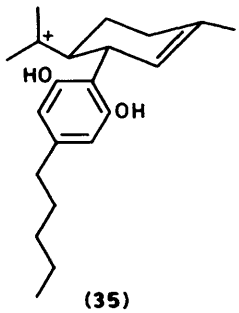
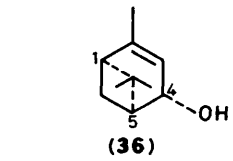


(35)

with olivetol to give (−)-Δ^6-THC in 44% yield. The process can be done in two stages forming first (**37**) with PTSA catalysis, and then converting the latter into (**3**) by BF_3 treatment. Δ^6-THC can be converted into Δ^1-THC by addition of hydrogen chloride and intramolecular elimination under kinetic control using the phenolic hydroxy group as base [*cf.* (**38**)].[1b]



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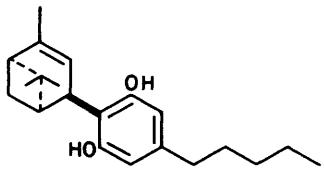

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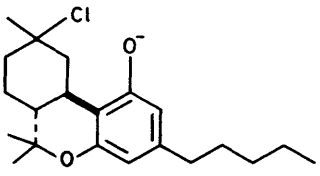

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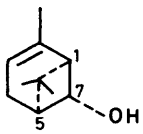

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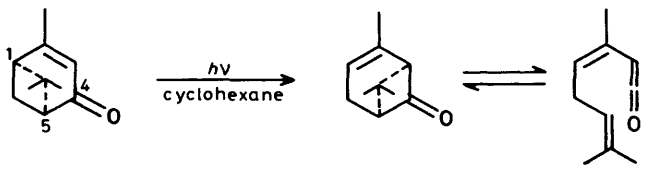
Prompted by Mechoulam's synthesis, a related method using (1*R*,5*S*,7*R*)-(+)-*cis*-chrysanthenol (**39**) which leads directly to Δ^1-THC was introduced by Razdan:[21] the yield was reported as 'moderate' [a resin containing *ca.* 25% Δ^1- (g.l.c.) and no Δ^6-THC was observed]. In repeating the synthesis of chrysanthenol we, like Razdan, had to prepare chrysanthenone (**41**) by photochemical isomerisation from verbenone (**40**) and it is in this step that a disadvantage emerges since substantial racemisation through photochemical equilibration with the ketone (**42**)

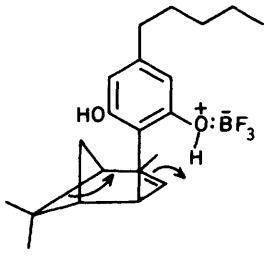


(40) (41) (42)

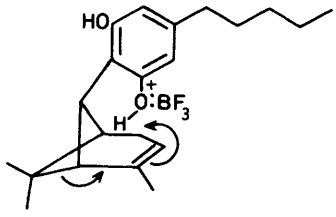
occurs.[22,23] Starting with verbenone of $[\alpha]_D^{24}$ −230° (*c* 0.7, $CHCl_3$) [lit. $[\alpha]_D^{24}$ −256° (*c* 0.0094, $CHCl_3$)] our sample of chrysanthenone had $[\alpha]_D^{24}$ −41.0° (*c* 3, $CHCl_3$) against a literature value[23] of $[\alpha]_D$ −108° (estimated) for chirally pure material (*i.e.* optical purity 38%). Razdan[21] reports his material as having 33% optical purity. Reduction of (**41**) with lithium aluminium hydride gave (+)-*cis*-chrysanthenol (**39**), $[\alpha]_D^{25}$ +11.2° (*c* 0.35, $CHCl_3$).

In a reaction of chrysanthenol using olivetol at 0 °C with 0.2% boron trifluoride–diethyl ether as catalyst, monitoring by g.l.c. at intervals, the g.l.c. yield of Δ^1-THC was *ca.* 5% at 45 min whereas with (−)-verbenol a g.l.c. yield of 50% Δ^6-THC was attained. Employing chrysanthenol at 20 °C with 1% boron trifluoride gave no Δ^1-THC, but at 30 min and at 1 h g.l.c./m.s. showed that Δ^6-THC was present in 15% yield at both times. The reaction is complex with a number of products being formed.

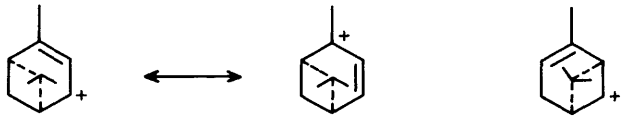
Verbenol gives a much smoother and higher-yielding reaction with olivetol in the presence of boron trifluoride than does chrysanthenol although under appropriate conditions the latter gives Δ^1-THC, unattainable directly from (**36**). The pinene–phenol intermediate corresponding to (**37**) has not been isolated in the chrysanthenol case, though it seems unlikely that the second stage terpene-rearrangement should differ markedly [*cf.* (**43**)] for verbenol and [*cf.* (**44**)] for chrysanthenol. The reactivity differences appear to lie in the formation, stability, and utilisation of the carbonium ion intermediates (**45**) (tertiary and allylic in the case of verbenol), and (**46**) (secondary and not allylic in the case of chrysanthenol).



(43)



(44)



(45) (46)

Experimental

Unless indicated otherwise, n.m.r. measurements refer to $CDCl_3$. ^1H N.m.r. spectra were mainly measured at 250 MHz and ^{13}C spectra at 62.9 MHz. The customary meanings apply to the abbreviations s, d, t, and q, and in the ^{13}C n.m.r. spectra these relate to off-resonance measurements. The general comments apply to the following papers also. Throughout ether refers to diethyl ether.

(1S,3S,4R,6R)-(+)-trans-*Car*-3-*ene Epoxide* (**13**).—Natural (1*S*,6*R*)-(+)-car-3-ene was purified by spinning-band distillation, b.p. 53—54 °C/16 mmHg, n_D^{22} 1.4716, $[\alpha]_D^{25}$ +17.0° (*c* 0.4, $CHCl_3$) [lit.,[24] 1.4726 $[\alpha]_D^{20}$ +15.6°]. Car-3-ene (5 g, 37 mmol) in dry ether (100 ml) at 0 °C was treated with *m*-chloroperoxybenzoic acid (80% active; 8.8 g, 40 mmol) and stirred at 0 °C (24 h). The product was well washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure to give (1*S*,3*S*,4*R*,6*R*)-(+)-*trans*-car-3-ene epoxide (4.08 g, 73%) pure by g.l.c., b.p. 29—30 °C/0.4 mmHg, n_D^{22} 1.4650, $[\alpha]_D^{22}$ +14.6 (*c* 0.41, $CHCl_3$) {lit.,[25] b.p. 77 °C/12 mmHg, n_D^{20} 1.4646, $[\alpha]_D^{24}$ +13.9° (*c* 3.5, $CHCl_3$)}; *m/z* 152 (M^+); δ_H 2.82 (1 H, br s), 2.22 (2 H, m), 1.58 (2 H, m), 1.26 (3 H, s), 1.02 (3 H, s), 0.72 (3 H, s), and 0.50 (2 H, s); δ_C 58.1 (C-4, d), 55.7 (C-3, s), 27.8 (C-10, q), 23.4 (C-5/2, t), 23.0 (C-8/9, q), 19.2 (C-5/2, C-7, t + s), 16.1 (C-1/6 br s), 14.6 (C-8/9, q), and 14.0 (C-1/6 br s).

(1S,2S,3R,6R)-(+)-trans-*Car-2-ene Epoxide* (**10**).—Car-3-ene (13.6 g, 0.1 mol) was added by syringe to stirred potassium t-butoxide (11 g, 0.1 mol) in dry dimethyl sulphoxide (50 ml) under nitrogen and the mixture was heated and stirred at 100 °C (4 h).[26] It was cooled (22 °C) and light petroleum (b.p. 40—60 °C; 20 ml) and water (5 ml) were added and the mixture shaken. Three layers separated and the two lower layers were extracted twice with light petroleum. The petroleum extracts were washed, dried, and evaporated to afford a product (10.0 g, 74%) which contained car-3-ene and car-2-ene in the ratio 3:2 (by g.l.c.). The oil was chromatographed on silica gel G (200 g) impregnated with silver nitrate (50 g) and eluted with light petroleum (b.p. 40—60 °C). Fractions were analysed by g.l.c. and those containing pure (1*S*,6*R*)-(+)-car-2-ene were combined, evaporated, and distilled to give a product (2 g, 15%), b.p. 50—51 °C/12 mmHg, n_D^{23} 1.4729, $[\alpha]_D^{23}$ +68.0° (*c* 0.27, $CHCl_3$), (lit.,[26] n_D^{20} 1.4762, $[\alpha]_D^{28.5}$ +76.36°); δ_H 5.56 (1 H, br s), 2.30—1.30 (4 H, m), 1.65 (3 H, s), 1.04 (3 H, s), 0.84 (3 H, s), and 1.0—0.7 (2 H, m). It was epoxidised as above to give (1*S*,2*S*,3*R*,6*R*)-(+)-*trans*- car-2-ene epoxide (**10**), b.p. 55 °C/2 mmHg, $[\alpha]_D^{23}$ +53.0° (*c* 0.25, $CHCl_3$) (lit.,[27] $[\alpha]_D^{20}$ +55.0); δ_H 3.03 (1 H, br s), 2.0—1.4 (5 H, m), 1.27 (3 H, s), 1.08 (6 H, s), and 0.70 (1 H, m); δ_C 58.1 (C-3, s), 57.8 (C-2,d) 29.0 (C-10, q), 27.3 (C-4, t), 23.8 (C-8/9, q), 22.1 (C-1, d), 21.2 (C-5, t), 20.8 (C-7, s), 16.6 (C-8/9, q), and 16.4 (C-6, d).

(1R,5S,7R)-(+)-cis-*Chrysanthenol* (**39**).—Active manganese dioxide (20 g) was vigorously stirred with (1*S*,4*S*,5*S*)-(−)-*cis*-verbenol (2 g) in light petroleum (b.p. 40—60 °C; 60 ml) for 2 h. The mixture was filtered, the filtrate evaporated, and the residue chromatographed on silica, eluting with ether–hexane (1:3) to give (1*S*,5*S*)-(−)-verbenone (**40**) (1.4 g, 71%), $\lambda_{max.}$ 250 nm, $[\alpha]_D^{24}$ −230° (*c* 0.7, $CHCl_3$) {lit.,[23] $[\alpha]_D$ −256° (*c* 0.0094, $CHCl_3$)}. Verbenone (1.3 g) in pure cyclohexane (130 ml) was flushed with nitrogen for 2 h and irradiated with an Hanovia 100-W lamp (7.5 h). The mixture was evaporated and the residue chromatographed on silica, eluting with ether–hexane (1:3) to give (1*R*,5*S*)-(−) chrysanthenone (**41**) (0.7 g, 54%), $[\alpha]_D^{24}$ −41.0° (*c* 3, $CHCl_3$) {lit.,[23] $[\alpha]_D^{30}$ −108° (estimated), *i.e.* 70%(−), 30%(+)}. Chrysanthenone (0.67 g) in ether (7 ml) was treated with lithium aluminium hydride (0.2 g) in ether (20 ml) and refluxed 1 h. Work-up with chromatography on silica (eluant $CHCl_3$) gave (1*R*,5*S*,7*R*)-(+)-*cis*-chrysanthenol[28,29] (**39**) (0.4 g, 59%) which formed a single peak on g.l.c. (1.5% OV 17, 5 ft, 100 °C); *m/z* 152 (M^+) $[\alpha]_D^{25}$ +11.2° (lit.,[21] $[\alpha]_D$ +8°). Neither sample is chirally pure; δ_H 5.22 (1 H, br s), 3.98 (1 H, s), 2.36 (1 H, s, D_2O exch.), 2.28 (2 H, br s), 2.00 (2 H, s), 1.68 (3 H, s), 1.60 (3 H, s), and 0.94 (3 H, s).

Treatment of Car-2-ene Epoxide (**10**) *with PTSA*.—The epoxide (10 mg) in benzene (0.5 ml) was heated with PTSA (*ca.* 4 mg) to 50 °C. A sample taken at 15 min was diluted with ether and the solution washed with aqueous sodium hydrogen carbonate and water, dried, evaporated, and subjected to g.l.c. [1.5% Carbowax 20M, 5 ft, programmed 60 °C (2 min) to 90 °C (at 4 °C/min)] to give a number of products, one of which had the correct retention time for *cis-p*-menthadienol (**6**). Its identity was confirmed by co-injection and by g.l.c./m.s. There was no evidence for *trans-p*-menthadienol.

Reaction of Car-2-ene Epoxide (**10**) *with Olivetol* (**4**) *in the Presence of Toluene*-p-*sulphonic Acid at Different Temperatures*.—*At* 40 °C. Freshly distilled olivetol (3.6 mg), dry (azeotroped) benzene (0.4 ml), toluene-*p*-sulphonic acid (2.0 mg; dried by azeotroping with benzene), and docosane (0.6 mg; g.l.c. standard) were mixed and car-2-ene epoxide (3.5 μl) added. The mixture was heated in one or more stirred reactivals, samples being removed at intervals and reaction stopped by syringing into aqueous sodium hydrogen carbonate. Aliquots were examined by t.l.c. [on silica, eluting with hexane–ether (3:1) and spraying with Fast Blue Salt B] and g.l.c. after silylation (SCOT OV225/200 °C). Peaks were identified by g.l.c./m.s. and by co-injection of authentic samples.

	40 °C 20 min	40 °C 45 min	40 °C 3 h
p-CBD	29%	24	—
o-CBD	47%	32	—
1-THC	24%	38	—
6-THC	—	6	100*

* Final yield based on olivetol was 8%. Peaks for other compounds increase with time.

At 50 °C. (a) Car-2-ene epoxide. The reaction mixture contained docosane (2.0 mg), olivetol (17.1 mg), PTSA (14 mg), benzene (2 ml), and car-2-ene epoxide (10 μl); conditions were similar to those described above.

	20 °C 20 min	50 °C 5 min	50 °C 15 min	50 °C 1 hr	50 °C 2.5 hr
p-CBD	42%	38	25	1	—
o-CBD	45%	59	56	2	—
1-THC	12%	3	6	30	—
6-THC	1%	—	13	67	100*

* Final yield 9%

(b) *p*-Menthadienol. The reaction mixture contained docosane (2.3 mg), olivetol (16.1 mg), PTSA (13.8), dry benzene (2 ml), and *p*-menthadienol (20 μl).

	20 °C 20 min	50 °C 5 min	50 °C 15 min	50 °C 1 hr	78 °C 15 min
p-CBD	48%	62	64	45	1
o-CBD	50%	34	28	19	1
1-THC	1%	3	6	27	19*
6-THC	1%	1	2	9	79*

* Combined yield 67%. The carene epoxide reaction gave eight or more peaks additional to the *p*-menthadienol reaction.

At 80 °C. The reaction mixture contained docosane (1.9 mg), olivetol (18.6 mg), PTSA (0.7 mg), benzene (4.5 ml), and car-2-ene epoxide (18 μl). Reaction at this PTSA concentration was slow (first column). The solution was cooled after 1.5 h and after 30 min at room temperature the concentration of PTSA was adjusted to 2.5 mg/ml and the mixture reheated to 80 °C.

	80 °C 1.5 h†	80 °C 0 min‡	80 °C 7 min‡	80 °C 15 min‡
p-CBD	40%	42	6	
o-CBD	60%	52	5	
1-THC		6		
6-THC			89	100*

* Final yield 6%. † Low acid concentration. ‡ High acid concentration.

Reaction Between Car-3-ene Epoxide (**13**) *and Olivetol*.—(+)-*trans*-Car-3-ene epoxide (1.9 g) and olivetol (1.8 g) in dry benzene (200 ml) were stirred and refluxed with PTSA (0.8 g) for 13.5 h. The product was worked up, washing with aqueous sodium hydrogen carbonate to give a brown oil (3.55 g). G.l.c. (OV 17, 220 °C) of a sample showed many peaks among which Δ^6-THC and $\Delta^{4,8}$-iso-THC (**14**) were identified by g.l.c./mass spectrometry.[30] Further confirmation of their formation was provided by g.l.c. [OV 225, 205 °C) of their silylated derivatives. T.l.c. data were also in agreement. Small but pure samples of Δ^6-THC and $\Delta^{4,8}$-iso-THC were isolated by preparative g.l.c. on OV 17 at 220 °C. Δ^6-THC had δ_H 6.27 (m, 1 H), 6.11 (m, 1 H), 5.41 (m, 1 H), 4.62 (br s, 1 H, D_2O exchg.) 3.3—3.1 (m, 1 H), 2.44

(t, 2 H, *J* 8 Hz), 1.71 (s, 3 H), 1.37 (s, 3 H), 1.10 (s, 3 H), and 0.88 (m, 3 H). $\Delta^{4,8}$-iso-THC had δ_H 6.30 (m, 1 H), 6.13 (m, 1 H), 4.45 (br s, 1 H, D_2O exchg.), 4.16 (br m, 1 H), 2.37 (m, 2 H), 1.94 (s, 3 H), 1.66 (s, 3 H), 1.35 (s, 3 H), 0.88 (m, 3 H), and 2.0—0.9 (br m). These data agree with literature reports.[3,6,31]

A sample of the brown oil (above) (0.95 g) was chromatographed on a dry silica column, eluting with ether–hexane (1:4). Fractions were monitored by g.l.c. and those containing mainly Δ^6-THC were rechromatographed on silica plates (20 × 20 cm), eluting four times with ether–hexane (1:8), to give a specimen of Δ^6-THC $[\alpha]_D^{25}$ −150° (*c* 0.1, $CHCl_3$) {lit.,[6] $[\alpha]_D^{18}$ −264° (*c* 0.1, EtOH)}.

In a further reaction car-3-ene epoxide (4.5 mg), olivetol (5.4 mg), and PTSA (3 mg) in dry benzene (0.5 ml) were heated at 60 °C the reaction being monitored at intervals by t.l.c. [silica, eluting with ether–hexane (1:3)] and g.l.c. (as TMS ethers on SCOT OV 225 column, 205 °C). After 30 min *o*- and *p*-cannabidiols and Δ^1-THC were detected. Their identities were confirmed by co-g.l.c. injections of authentic samples. A similar reaction was then run, products being separated by t.l.c. (system as for monitoring but 20 × 20 cm plates) monitoring by g.l.c. The identities of the separated *p*-cannabidiol, Δ^1-THC and a small amount of Δ^6-THC were then confirmed by g.l.c./mass spectrometry and co-injection with authentic samples.

Preparation of 4-exo-*Isopropenyl*-1-*methylbicyclo*[3.1.0]-*hexan*-2-endo-*ol* (**24**) *and Caren*-3β-*ol* (**22**).—Carane-3β,4α-diol (**20**) (15.8 g) and acetic anhydride (50 ml) in pyridine (50 ml) were stirred (16 h) at 20 °C. Work-up and crystallisation from hexane–chloroform gave the acetate (**21**) (16.5 g, 84%), m.p. 68—71 °C (lit.,[15] m.p. 73 °C); $\nu_{max.}$($CHCl_3$) 1 730 cm^{-1}. The acetate (4.85 g) was heated with phosphorus oxychloride (41 ml) and dry pyridine (41 ml) at 100 °C for 3 h under nitrogen. Work-up gave a mixture (2.5 g, 56%) of dehydrated acetates which were not further purified but dissolved in dry ether (20 ml) and deacetylated by dropwise addition to a suspension of lithium aluminium hydride (2.5 g) in ether (20 ml) at 0 °C. Work-up gave a mixture of the bicyclo compound (**24**) and the carenol (**22**) which was separated by preparative g.l.c. [Carbowax 20M (20%) at 150 °C]. The bicyclo compound (**24**) (450 mg, 24%) had δ_H 0.25—0.5 (2 H, m, CHCH_2C), 0.9—1.05 (1 H, m, C*H*CH_2C), 1.3 (3 H, s, CH_3C), 1.3—1.9 (2 H, m, CHCH_2CH), 1.75 (3 H, s, CH_3C=CH_2), 2.45 (1 H, s, OH, D_2O exchg.), 3.3 (1 H, m, CHC*H*CH), 4.15 (1 H, d, *J* 5 Hz, CHO), and 4.7—4.9 (2 H, m, C=CH_2). Carenol (**22**) (225 mg, 12%) had δ_H 0.65—0.9 (2 H, m, CHCH), 0.9 and 1.0 (6 H, 2 × s, 2 × MeC), 1.30—3.0 (5 H, m, CH_2CHCHCH_2 and OH, D_2O exchg.), 4.1 (1 H, t, CHO), and 4.8 (2 H, m, CH_2=C).

Condensation of the Bicyclo Compound (**24**) *with Olivetol* (**4**).—The terpene (**24**) (228 mg) was heated with olivetol (270 mg) and PTSA (150 mg) in dry benzene (25 ml) at 60 °C for 2 h. Work-up by chromatography on silica, eluting with light petroleum (b.p. 60—80 °C) and then light petroleum (b.p. 60—80 °C)–ether (9:1) gave two major fractions A and B. The latter contained a gum assigned structure (**26**) (25 mg, 5%) (Found: M^+, 314.2221. $C_{21}H_{30}O_2$ requires *M*, 314.2246); δ_H($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, CH_3CH_2) 1.1 (3 H, d, *J* 6.5 Hz, CH_3CH), 1.25—1.40 (4 H, m, CH_2CH_2), 1.45 (3 H, s, CH_3CO), 1.5—1.65 (2 H, m, CH_2), 1.65 (3 H, s, CH_3C=CH$_2$), 1.65—1.80 (1 H, d of q CH_3C*H*CH), 1.8—1.9 (2 H, m, ArCHCH_2CH), 2.15—2.3 (1 H, d of t, CHC*H*CH_2), 2.5 (2 H, t, *J* 7 Hz, ArCH_2CH), 3.45 (1 H, d of d, *J* 2.8, 7.3 Hz, ArC*H*CH$_2$), 4.7—4.8 (3 H, m, CH$_2$=C and OH, D_2O exchg.), and 6.1 and 6.2 (2 H, 2 × s, ArH); δ_H(C_6D_6) 0.85 (3 H, t, CH_3CH$_2$), 1.15 (3 H, d, *J* 7 Hz, CH_3CH), 1.15—1.4 (4 H, m, 2 × CH_2), 1.30 (3 H, s, CH_3CO), 1.45 (3 H, s, CH_3C=C), 1.5—1.6 (3 H, m, CH_2 and CH), 1.7 (1 H, d of t, ArCHC*H*CH), 3.05 (1 H, d of d, ArCHC*H*CH), 2.4 (1 H, m, CHC*H*CH), 2.45 (2 H, t, *J* 7 Hz, ArCH_2CH), 3.35 (1 H, d, *J* 8.8 Hz, ArC*H*CH$_2$), 4.2 (1 H, OH, D_2O exchg.), 4.6 and 4.75 (2 H, m, CH$_2$=C), and 5.85 and 6.45 (2 H, 2 × s, ArH); δ_C($CDCl_3$) 152.0s (a), 107.4d (b), 145.1s (c), 102.2 (d), 161.5s (e), 114.2s (f), 37.1t (g), 31.6t (h), 31.0t (i), 22.6t (j), 14.0q (k), 98.4s (1), 48.1d, 48.6d (m and n), 36.1t (o), 51.8d (p), 24.4q (q), 11.0q (r), 145.2s (s), 19.2 (t), and 111.4 (u). See formula (**26**) for lettering: assignments are tentative.

Fraction A was partly separated by h.p.l.c. on silica eluting with ethyl acetate–hexane (1:33), to give A1, a mixture of two components, and A2 (10 mg, 2%), a gum (Found: M^+, 314.2225. $C_{21}H_{30}O_2$ requires M^+, 314.2246. The latter (**27**) had δ_H($CDCl_3$) 0.8 (3 H, t, *J* 7 Hz, CH_3CH$_2$), 0.9 (3 H, d, *J* 7 Hz, CH_3CH), 1.15—1.3 (4 H, m, 2 × CH$_2$), 1.40 (3 H, s, CH$_3$CO), 1.45—1.55 (2 H, m, CH$_2$), 1.55 (3 H, s, CH$_3$C=C), 1.60 (3 H, fine d, CH$_3$C=C), 2.4 (3 H, m, ArCH_2CH$_2$ and ArCH–CH_a), 2.75 (1 H, q, *J* 7 Hz, CH_3CH), 2.9 (1 H, dd, *J*, 16.5 and 10.5 Hz, ArCHCH_bCH), 3.3 (1 H, dd, ArC*H*CH$_2$), 4.5 (1 H, br, OH, D_2O exchg.), and 6.05 and 6.15 (2 H, 2 × s, ArH); δ_H(C_6D_6) 0.85 (3 H, t, *J* 7 Hz, CH_3CH$_2$), 1.15 (3 H, d, *J* 7 Hz, CH_3CH), 1.2—1.3 (4 H, m, 2 × CH$_2$), 1.35 (3 H, s, CH$_3$CO), 1.50 (3 H, s, CH$_3$C=C), 1.55 (3 H, fine d, CH$_3$C=C), 2.4 (2 H, m, ArCH_2CH$_2$), 2.50 (1 H, m, ArCHCH_a), 2.75 (1 H, q, *J* 7 Hz, CH$_3$C*H*), 2.95 (1 H, dd, *J* 9.1, 16 Hz, ArCHCH_b), 3.3 (1 H, dd, *J* 9.1, 9.6 Hz, ArC*H*CH$_2$), 4.10 (1 H, br OH, D_2O exchg.), and 5.85 and 6.45 (2 H, 2 × s, ArH). There was no evidence (t.l.c. or g.l.c. using silylated or unsilylated samples) for the production of cannabidiols or Δ^1-or Δ^6-THC.

Isolation of α-*Phellandren*-8-*ol* (**28**) *from the Reaction Between Car*-3-*ene Epoxide* (**13**) *and Toluene*-p-*sulphonic Acid.*—Car-3-ene epoxide (50 μl) in dry benzene (4 ml) was treated with PTSA (38 mg) at 60 °C for 30 min. The mixture was quenched (aqueous sodium hydrogen carbonate) and worked up to provide a product which was chromatographed on a dry silica column (1 cm × 7 cm) eluting with a gradient of light petroleum (b.p. 60—80 °C)–20% ether in light petroleum (b.p. 60—80 °C). The mixture was resolved into 5 fractions and monitored by t.l.c. Small portions of each fraction were treated with PTSA and olivetol in benzene, heating at 60 °C for 30 min. Only fraction 6 produced Δ^6-THC as demonstrated by t.l.c. (pink-red Fast Blue Salt B colour) and g.l.c. of the silylated material.

Larger scale reactions were now carried out. In one of these car-3-ene epoxide (10 g) was heated with PTSA (4 g) in benzene (200 ml). Some *p*-cymene was noted in early fractions when subjected to preparative h.p.l.c. on silica (eluting with 5% ethyl acetate in hexane). 18 Fractions were taken and fraction 13 was identified as containing most of the cannabinoid-generating precursor. Further purifications of this using h.p.l.c. allowed the isolation of the *exo*-methylene alcohol (**22**) (identified by g.l.c. and n.m.r.) but tests for cannabinoid production using a synthetic sample of this terpene showed that it is a sluggish cannabinoid progenitor. Continued purification gave a second major component which when heated with olivetol and PTSA at 80 °C in benzene proved to be an excellent precursor for Δ^6-THC production. G.l.c./mass spectrum (e.i.) showed M^+ 152 ($C_{10}H_{16}O$ requires *M*, 152). The compound, recognised as α-phellandren 8-ol (**28**) had δ_H 1.21 and 1.22 (each 3 H, s, 9 and 10 Me's), 1.72 (3 H, d, *J* 2 Hz, 7-Me), 2.1—2.35 (3 H, m, 4- and 5-H$_2$), 5.49 (1 H, br m, 6-H), 5.83 and 5.87 (each 1 H, complex d, *J* 10 Hz, 2- and 3-H); δ_C 21.0 (q), 26.9 (q), and 27.5 (q) (3-Me's), 24.5 (t, C-5), 44.8 (d, C-4), 73.1 (s, C-8), 120.3 (d), 126.9 (d), and 129.2 (d) (C-2, -3, and -6), and 131.0 (s, C-1). Spectra were closely similar to the synthetic specimen below. Identity was confirmed by t.l.c. and h.p.l.c. comparisons on silica, eluting with ether–hexane and with hexane–ethyl acetate, and by g.l.c. R_t comparison.

Synthesis of (±)-α-*Phellandren*-8-*ol* (**28**) *from Citral.*—Citral (20 g) in water (300 ml; deaerated with N_2) was vigorously stirred at pH 2.5 (conc. HCl) in the dark and under nitrogen for 8 days.[17] After saturation with sodium chloride the mixture was extracted four times with ether and the extracts were washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated (17.8 g). Unchanged citral and less polar products were removed by h.p.l.c. on a Waters preparative silica column (R.I. detection) eluting with light petroleum (b.p. 60—80 °C)–ether (3:1). This yielded product (0.89 g) almost free of citral and further h.p.l.c. on the same column [eluant hexane–ether (4:1)] gave further purified material (0.48 g) which was totally free from citral (h.p.l.c. and t.l.c.). Fractions were monitored from this point by g.l.c. using a Carbowax column (5 ft × $\frac{1}{4}$ in, glass) but it is unsuitable whilst any citral remains, since citral and α-phellandren-8-ol are not effectively separated. G.l.c. indicated that the single h.p.l.c. peak contained six components, four in small amount only. Further purification was effected by repeated semi-preparative h.p.l.c. on silica (Waters Z-module) eluting at 3 ml/min with 15% ether in hexane, monitoring with g.l.c. (±)-α-Phellandren-8-ol had $\lambda_{max.}$ 261 nm (lit.,[17] $\lambda_{max.}$ 261 nm); δ_H 1.20, 1.21 (each 3 H, s, 9- and 10-Me's), 1.72 m (4 H, m, 7-Me and OH), 2.35—2.10 (3 H, m, 4-H and 5-H_2), 5.46 (1 H, br m, 6-H), 5.80 and 5.87 (each 1 H, complex d, *J* 10 Hz, 2- and 3-H); δ_C 21.0 (q), 26.9 (q), 27.5 (q) (3-Me's), 24.5 (t, C-5), 44.8 (d, C-4), 73.1 (s, C-8), 120.3 (d), 127.0 (d), 129.2 (d) (C-2, -3, and -6), and 130.9 (s, C-1).

When allowed to react with olivetol and PTSA in benzene at 80 °C for 1 h, the synthetic α-phellandren-8-ol formed Δ^6-THC (t.l.c., R_F and crimson with Fast Blue Salt B). This was confirmed by silylation and g.l.c. (SCOT, OV 225).

Reactions of α-*Phellandren*-8-*ol* (**28**) *with Olivetol* (**4**) *in the Presence of Toluene*-p-*sulphonic Acid.*—α-Phellandren-8-ol [(±)-made from citral)] (2.2 mg), olivetol (3.9 mg), and PTSA (1.5 mg) in benzene (0.25 ml) were kept at 25 °C and examined by g.l.c. at intervals. Nine peaks were observed and the major cannabinoids were identified and estimated quantitatively using a docosane standard:

Time	*p*-CBD	Δ^1-THC	Δ^6-THC
20 min	9.3%	4.8%	
45 min	5.5	10.1	
95 min	0.4	10.0	4.0%
220 min		7.0	8.2
23 h		4.4	18.5

% Yields are calculated on α-phellandren-8-ol.

α-Phellandren-8-ol (2.7 mg), olivetol (4.0 mg), docosane (standard, 0.9 mg), and PTSA (1.9 mg), in benzene (0.25 ml) were allowed to react at 52 °C.

Time	*p*-CBD	Δ^1-THC	Δ^6-THC
10 min	20.6%	4.4%	
35 min	2.5	21.3	6.3%
85 min		7.7	27.7
3½ h		4.3	38.7
5 h		4.1	34.0

α-Phellandren-8-ol (2.5 mg), olivetol (4.9 mg) and PTSA (1.6 mg) in benzene (0.25 ml) were allowed to react at 80 °C.

Time	*p*-CBD	Δ^1-THC	Δ^6-THC
9 min	0.6%	16.1%	13.0%
60 min	—	7.0	35.4

Treatment of Citral with Toluene-p-*sulphonic Acid in Dichloromethane.*—Citral (60 mg) was added to wet dichloromethane (3 ml) which had been allowed to equilibrate by shaking with PTSA at 20 °C. (These conditions were similar to those used in our earlier work[3] to obtain 27% *o*-cannabidiol and 21% *p*-cannabidiol *etc.* by allowing citral to react with olivetol.) The mixture was kept at 22 °C for 20 h, neutralised (aqueous $NaHCO_3$), and extracted into dichloromethane. Products were separated by semi-preparative h.p.l.c. on silica (eluant 15% ether in hexane), monitoring with t.l.c. and g.l.c. The fraction corresponding by h.p.l.c., t.l.c., and g.l.c. to α-phellandren-8-ol (0.6 mg) was allowed to react with olivetol and PTSA in benzene at 80 °C. T.l.c. after 15 min and after 1 h showed a spot corresponding in position and Fast Blue Salt B colour to Δ^6-THC. This was confirmed by neutralisation (aqueous sodium hydrogen carbonate) of the reaction mixture, evaporation of the dichloromethane, silylation of the residue (BSTFA + 1% TMCS), and g.l.c. of the product on a SCOT OV 225 column at 210 °C. A single peak corresponding to (±)-Δ^6-THC was found. The fraction eluting after citral but before the α-phellandren-8-ol gave no THC-like compound on reaction with olivetol and PTSA, indicating that the α-phellandren-8-ol was free of citral contaminant.

The amount of Δ^6-THC formed was small compared with total yields of cannabinoid compounds in our earlier work.

Reaction of Chrysanthenol (**39**) *with Olivetol* (**4**) *in the Presence of Boron Trifluoride.*—(+)-Chrysanthenol (2 mg) prepared as above, olivetol (2.4 mg), and docosane (0.32 mg, g.l.c. standard) were treated in dry benzene (0.25 ml) at 0 °C with 0.2% boron trifluoride–diethyl ether. Reaction was monitored by t.l.c. on silica [eluting with ether–hexane (1:3)] and, after conversion of the product to TMS ethers, by g.l.c./m.s. (OV 101 glass capillary), samples being taken at 5, 15, 30, and 45 min. Δ^1-THC was detected by t.l.c. at 30 min and in the four samples by g.l.c./m.s. The yield at 45 min (and earlier) did not exceed 5%. Under similar conditions (−)-verbenol gave a yield of 50% of Δ^6-THC.

(+)-Chrysanthenol (1.82 mg), olivetol (2.2 mg), and docosane (0.20 mg) were treated in dry benzene (0.2 ml) at 20 °C with 1% boron trifluoride–diethyl ether. Analysis by t.l.c. at 30 min and at 1 h showed no Δ^1-THC, but spots (amongst others) corresponding to Δ^6-THC. G.l.c./m.s. verified that at both times the major cannabinoid was 6-THC in *ca.* 15% yield.

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