Aust. J. Chem., 1984, **37**, 2339–48

Cannabinoid Studies. IV* Stereoselective and Regiospecific Syntheses of (±)-Δ^9-*trans*- and (±)-Δ^9-*cis*-6a,10a-Tetrahydrocannabinol

Michael Moore,[A] *Rodney W. Rickards*[A,B] *and Harald Rønneberg*[A]

[A] Research School of Chemistry, Australian National University, G.P.O. Box 4, Canberra, A.C.T. 2601.
[B] To whom correspondence should be addressed.

Abstract

Efficient syntheses of the title compounds are achieved through the intermediate alcohols (13) and (15), prepared by reaction of citral (10) with the lithiated olivetol dimethyl and di(methoxymethyl) ethers (4) and (6). Reaction of the alcohol (13) with boron tribromide yields (±)-Δ^9-*trans*-6a,10a-tetrahydrocannabinol (1) after regiospecific dehydrobromination of its hydrogen bromide adduct, whilst treatment of the alcohol (15) with trimethylsilyl bromide affords (±)-Δ^9-*cis*-6a,10a-tetrahydrocannabinol (11).

The complementary stereoselectivity of these reactions may provide insight into the nature of cannabinoid cyclization processes.

Introduction

Conventional syntheses of Δ^9-*trans*-6a,10a-tetrahydrocannabinol (Δ^9-*trans*-THC) (1), either as the racemate or as the laevorotatory enantiomer which is the principal psychoactive component of the resin from *Cannabis sativa*,[1] involve the condensation of olivetol (3) with an appropriately functionalized achiral or chiral monoterpene.[2] These routes are direct, but suffer from several disadvantages inherent in the use of Lewis or proton acids to catalyse the condensation of sensitive materials. The course of the reactions is critically dependent upon the nature and concentration of the catalyst, and upon the solvent and temperature used. Mixtures of difficultly separable products are invariably formed, resulting in yields which are low or at best moderate. In particular, the initial *C*-alkylation of the symmetrical phenolic ring is not regiospecific, and occurs at both possible sites. Furthermore, the undesired thermodynamically more stable Δ^8-*trans*-6a,10a-tetrahydrocannabinol (Δ^8-*trans*-THC)

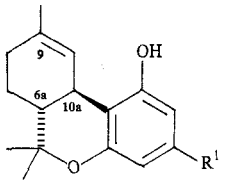
* Part III, *J. Org. Chem.*, 1984, **49**, 572.

[1] Mechoulam, R., (Ed.), 'Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects' (Academic Press: New York 1973); Nahas, G. G., (Ed.), 'Marihuana: Chemistry, Biochemistry and Cellular Effects' (Springer: New York 1976); Mechoulam, R., McCallum, N. K., and Burstein, S., *Chem. Rev.*, 1976, **76**, 75.

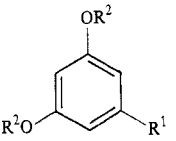
[2] Razdan, R. K., in 'The Total Synthesis of Natural Products' (Ed. J. ApSimon) p. 185 (Wiley–Interscience: New York 1981).

0004-9425/84/112339$02.00

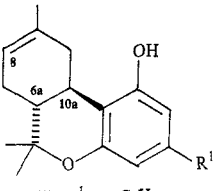
(8) is usually formed preferentially, and requires subsequent conversion into the desired Δ^9-isomer (1).[3]



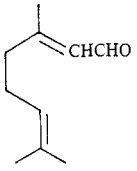
(1) $R^1 = n\text{-}C_5H_{11}$
(2) $R^1 = H$



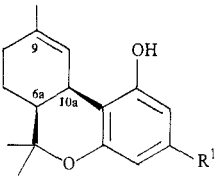
	R^1	R^2
(3)	$n\text{-}C_5H_{11}$	H
(4)	$n\text{-}C_5H_{11}$	Me
(5)	H	Me
(6)	$n\text{-}C_5H_{11}$	CH_2OMe
(7)	H	CH_2OMe



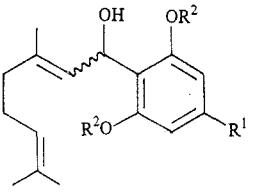
(8) $R^1 = n\text{-}C_5H_{11}$
(9) $R^1 = H$



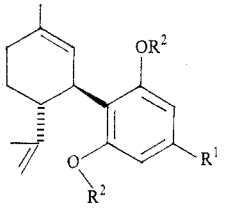
(10)



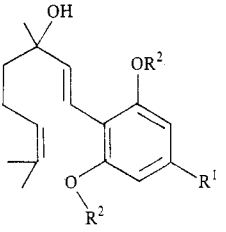
(11) $R^1 = n\text{-}C_5H_{11}$
(12) $R^1 = H$



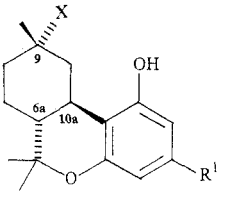
	R^1	R^2
(13)	$n\text{-}C_5H_{11}$	Me
(14)	H	Me
(15)	$n\text{-}C_5H_{11}$	CH_2OMe
(16)	H	CH_2OMe



	R^1	R^2
(17)	$n\text{-}C_5H_{11}$	Me
(18)	$n\text{-}C_5H_{11}$	H



	R^1	R^2
(19)	$n\text{-}C_5H_{11}$	Me
(20)	H	Me



	R^1	X
(21)	$n\text{-}C_5H_{11}$	Br
(22)	$n\text{-}C_5H_{11}$	Cl
(23)	H	Br

The most facile previous synthesis of racemic Δ^9-*trans*-THC (1) involves the reaction of olivetol (3) with citral (10) in the presence of 1% boron trifluoride etherate in methylene dichloride,[4] affording the product (1) in 20% yield together with 5% of the isomeric Δ^9-*cis*-6a,10a-tetrahydrocannabinol (Δ^9-*cis*-THC) (11). The sensitivity of the reaction is illustrated by alteration of the catalyst to 10% boron trifluoride etherate in benzene,[5] whereupon the double bond isomer Δ^8-*trans*-THC (8) is formed

[3] Petrzilka, T., and Sikemeier, C., *Helv. Chim. Acta*, 1967, **50**, 2111; Petrzilka, T., Haefliger, W., and Sikemeier, C., *Helv. Chim. Acta*, 1969, **52**, 1102; Razdan, R. K., Puttick, A. J., Zitko, B. A., and Handrick, G. R., *Experientia*, 1972, **28**, 121.

[4] Mechoulam, R., Braun, P., and Gaoni, Y., *J. Am. Chem. Soc.*, 1972, **94**, 6159.

[5] Taylor, E. C., Lenard, K., and Shvo, Y., *J. Am. Chem. Soc.*, 1966, **88**, 367; Gaoni, Y., and Mechoulam, R., *J. Am. Chem. Soc.*, 1966, **88**, 5673.

in 20% yield together with a doubly alkylated olivetol (10–20%) and an isocannabinoid (20%). The use of 0·0005 N hydrochloric acid in ethanol[5] affords Δ^9-*cis*-THC (11) in 12% isolated yield, with further impure *cis*-material containing some Δ^9-*trans*-THC (1).

In view of these problems associated with cationic condensations, we have examined the advantages of carbanionoid approaches to tetrahydrocannabinoids. Historically, the very first published synthesis of Δ^9-*trans*-THC (1) utilized an aryl carbanion.[4,6] The route involved the reaction of citral (10) with the lithium derivative of olivetol dimethyl ether (4) to give an intractable mixture, presumably containing the alcohol (13), which upon tosylation led to cannabidiol dimethyl ether (17) in 7% yield. Demethylation with dry methylmagnesium iodide was reported[4,6] to proceed in 80% yield, although other workers[7] could achieve a yield of only 50% based upon consumed dimethyl ether (17). The resulting cannabidiol (18) could then be cyclized efficiently to (±)-Δ^9-*trans*-THC (1), obtainable in *c.* 4% yield overall.

We describe here the development of an efficient, regiospecific synthesis of racemic Δ^9-*trans*-THC (1) from readily available citral (10) and lithiated olivetol dimethyl ether (4). Use of the corresponding di(methoxymethyl) ether (6) then permits extension of this carbanionoid approach to racemic Δ^9-*cis*-THC (11). This lesser known *cis*-isomer (11) has been formed previously in low yields in several syntheses of the *trans*-isomer (1),[2] including the citral–olivetol condensation described above,[4,5] and also in low yield from the reaction of dehydrolinalool acetate with olivetol bis(tetrahydropyranyl) ether homocuprate.[8] It is not psychoactive,[1] although one enantiomer, stated to have the 6a*S*,10a*R*-configuration, occurs naturally in *C. sativa*.[9]

Synthesis of (±)-Δ^9-*trans*-6a,10a-Tetrahydrocannabinol (1)

Olivetol dimethyl ether (4) was alkylated regiospecifically by reaction of its lithium derivative with citral (10), affording the alcohol (13). The product, a 1 : 2 mixture of *E* and *Z* isomers reflecting the parent citral composition, was obtained in 80% yield (99% after correcting for recovered ether) by chromatography on alkaline alumina. This material was extremely unstable, as observed also by Mechoulam and coworkers[4,6] who obtained a complicated mixture from which they were unable to isolate or characterize the presumed initial product (13). In our hands attempted chromatography on Florisil caused extensive decomposition, whilst silica promoted allylic rearrangement to the tertiary styryl alcohol (19).

With a view to effecting concomitant cyclization and demethylation to the desired Δ^9-*trans*-THC (1), the alcohol (13) was treated with three equivalents of boron tribromide[10] in methylene dichloride. Surprisingly, although ^{1}H n.m.r. analysis of the crude product showed little of either Δ^9-*trans*-THC (1) or its thermodynamically more stable Δ^8-isomer (8), column chromatography afforded mixtures of these compounds which varied in yield and composition with the absorbent used. The

[6] Mechoulam, R., and Gaoni, Y., *J. Am. Chem. Soc.*, 1965, **87**, 3273.
[7] Korte, F., Dlugosch, E., and Claussen, U., *Justus Liebigs Ann. Chem.*, 1966, **693**, 165.
[8] Luteijn, J. M., and Spronck, H. J. W., *J. Chem. Soc., Perkin Trans. 1*, 1979, 201.
[9] Smith, R. M., and Kempfert, K. D., *Phytochemistry*, 1977, **16**, 1088.
[10] McOmie, J. F. W., and Watts, M. L., *Chem. Ind. (London)*, 1963, 1658; McOmie, J. F. W., Watts, M. L., and West, D. E., *Tetrahedron*, 1968, **24**, 2289; McOmie, J. F. W., and West, D. E., *Org. Synth.*, 1969, **49**, 50.

acidic silica gel gave 40% yield of almost pure Δ^8-*trans*-THC (8), whilst the increasingly basic Florisil and alkaline alumina gave 57 and 66% yield, respectively, of 3 : 2 and 1 : 1 mixtures of Δ^8- and Δ^9-*trans*-THC (8) and (1). Clearly, the crude reaction product contained an intermediate which was converted into tetrahydrocannabinols on chromatography.

This intermediate, which was obtained without purification in almost quantitative yield but was too unstable for normal chromatography or satisfactory elemental analysis, was characterized spectroscopically after m.p.l.c. as the 9-bromo-*trans*-6a,10a-hexahydrocannabinol (21). Mass spectroscopy showed molecular ions corresponding to the formula $C_{21}H_{31}BrO_2$ at *m/z* 394 and 396, which suffered loss of HBr to give a base peak at *m/z* 314, further fragmentation of which closely resembled that of Δ^9-*trans*-THC (1). Confirmation of the structure (21) was obtained by detailed n.m.r. studies, and by comparison of the ^1H spectrum with that of the 9-chloro-*trans*-6a,10a-hexahydrocannabinol (22) described by Petrzilka *et al.*[3] and of the ^{13}C spectrum with spectra of Δ^9- and Δ^8-*trans*-THC.[11] These n.m.r. spectra indicate that the compound is a single isomer, which probably arises by the addition to a tetrahydrocannabinoid species of hydrogen bromide formed initially from reaction of the alcohol (13) with boron tribromide, or present as impurity in the reagent. Preferred *trans*-diaxial addition[12] to such a cyclohexene would be expected to yield predominantly the single axial bromide (21) depicted, in contrast to the two diastereoisomers which would result if the addition had occurred before ring closure. The addition would resemble the zinc chloride-catalysed reaction of hydrogen chloride with Δ^8- or Δ^9-*trans*-THC (8) or (1) to give a hydrochloride in which the C9 configuration was not defined,[3,4] but which is probably the axial chloride (22).

The direct production in high yield of the tertiary bromide (21) from the alcohol (13) now enabled the regiospecific introduction of the olefinic bond to form the required Δ^9-*trans*-THC (1). This process has precedent in the efficient base-induced elimination of hydrogen halide from the tertiary chloride (22),[3] and avoids the isomerization to the more stable Δ^8-isomer (8) which can occur when Δ^9-*trans*-THC (1) is formed in the presence of Lewis acids.[2]

The elimination step was first studied with the model tertiary bromide (23), which was prepared in high yield similarly to the pentyl homologue (21). Reaction of lithiated resorcinol dimethyl ether (5) with citral (10) yielded the unstable alcohol (14), which again rearranged to the tertiary styryl alcohol (20) on attempted silica chromatography. Treatment with boron tribromide gave the required model (23), which like its homologue (21) was very unstable but could be characterized spectroscopically after m.p.l.c. Treatment of the bromide (23) with potassium t-pentyloxide in warm benzene, conditions which promote nearly quantitative conversion of the chloride (22) into Δ^9-*trans*-THC (1),[3] gave predominantly the Δ^8-*trans*-THC analogue (9). In the belief that this result was largely due to uncontrolled intermolecular elimination of the more labile tertiary bromide, attempts were made to ensure initial formation of the phenoxide anion required to direct intramolecular dehydrohalogenation.[3,13] This was achieved by preliminary ionization at 5°C, at which temperature

[11] Wenkert, E., Cochran, D. W., Schell, F. M., Archer, R. A., and Matsumoto, K., *Experientia*, 1972, **28**, 250; Archer, R. A., Johnson, D. W., Hagaman, E. W., Moreno, L. N., and Wenkert, E., *J. Org. Chem.*, 1977, **42**, 490.

[12] Readio, P. D., and Skell, P. S., *J. Org. Chem.*, 1966, **31**, 753.

[13] Fahrenholtz, K. E., Lurie, M., and Kierstead, R. W., *J. Am. Chem. Soc.*, 1967, **89**, 5934.

little elimination occurred, subsequent brief warming at 60°C then leading to a 4 : 1 mixture of the Δ^9- and Δ^8-*trans*-THC analogues (2) and (9). The product still contained a trace of unchanged material (23), but ionization at room temperature or warming for a longer period resulted in increased formation of the Δ^8-isomer (9). The use of potassium t-butoxide under similar conditions to the t-pentyloxide caused complete elimination, and the resulting 85 : 15 ratio of the analogues (2) and (9) was less sensitive to the initial ionization temperature. In contrast, effective elimination with a tertiary nitrogen base, *s*-collidine, required heating to 130°C, the undesired Δ^8-isomer (9) then predominating.

Treatment of the unpurified tertiary bromide (21) with potassium t-butoxide gave the required Δ^9-*trans*-THC (1) together with its Δ^8-isomer (8) in an 87 : 13 ratio in 75% overall yield from the alcohol (13) after purification by m.p.l.c. This ratio of $\Delta^9 : \Delta^8$ isomers compares with the 95 : 5 ratio of $\Delta^9 : \Delta^{9(11)}$ *trans*-THC isomers reported by Razdan and coworkers[14] for the carefully optimized dehydrochlorination of the tertiary chloride (22) by potassium t-pentyloxide,[3] and presumably reflects the greater solvolytic tendency of the tertiary bromide relative to the tertiary chloride. Attempts to utilize this known dehydrochlorination by treating the alcohol (13) with boron trichloride rather than boron tribromide, in order to obtain the tertiary chloride (22), were not successful. Extensive decomposition resulted even under milder conditions than those involving concentrated boron trichloride which are commonly used for cleavage of unactivated aromatic ethers.[15]

Synthesis of (±)-Δ^9-*cis*-6a,10a-Tetrahydrocannabinol (11)

In order to examine the cyclization behaviour of a system carrying more readily removable phenolic protecting groups than those of the dimethyl ethers (13) and (14), we prepared the corresponding di(methoxymethyl) ether (16) by reaction of citral (10) with the regiospecifically C 2-lithiated resorcinol ether (7). Reaction of this ether (16) with trimethylsilyl chloride in the presence of tetraethylammonium bromide at 0°C,[16] followed by aqueous workup, gave *directly* the Δ^9-*cis*-THC homologue (12) in 72% yield. The structure of this product follows from the close similarity of the olefinic, benzylic and methyl proton resonances in its ^{1}H n.m.r. spectrum to the corresponding resonances for Δ^9-*cis*-THC (11).[5]

With this result in hand, we proceeded to the synthesis of racemic Δ^9-*cis*-THC (11) itself. The alcohol (15), a mixture of *E* and *Z* isomers, was prepared in 79% yield from citral (10) and the lithium derivative of olivetol di(methoxymethyl) ether (6). Cyclization and deprotection, as above, gave Δ^9-*cis*-THC (11) in 65% yield, with spectra in accord with published data.[5,11]

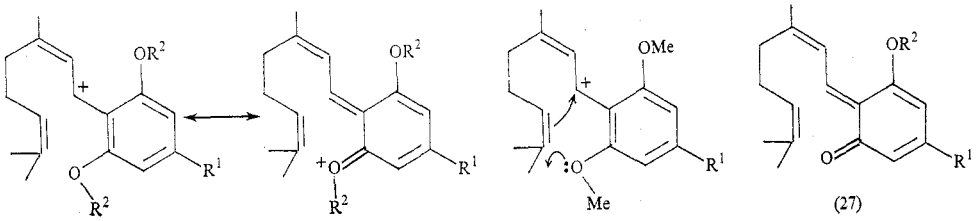
[14] Arthur D. Little, Inc., Technical Report 3 to National Institute of Mental Health, 1972, cited by Razdan, R. K., in ref. 2.

[15] Gerrard, W., and Lappert, M. F., *Chem. Rev.*, 1958, **58**, 1081.

[16] Woodward, R. B., Logusch, E., Nambiar, K. P., Sakan, K., Ward, D. E., Au-Yeung, B.-W., Balaram, P., Browne, L. J., Card, P. J., Chen, C. H., Chênevert, R. B., Fliri, A., Frobel, K., Gais, H.-J., Garratt, D. G., Hayakawa, K., Heggie, W., Hesson, D. P., Hoppe, D., Hoppe, I., Hyatt, J. A., Ikeda, D., Jacobi, P. A., Kim, K. S., Kobuke, Y., Kojima, K., Krowicki, K., Lee, V. J., Leutert, T., Malchenko, S., Martens, J., Matthews, R. S., Ong, B. S., Press, J. B., Rajan Babu, T. V., Rousseau, G., Sauter, H. M., Suzuki, M., Tatsuta, K., Tolbert, L. M., Truesdale, E. A., Uchida, I., Ueda, Y., Uyehara, T., Vasella, A. T., Vladuchick, W. C., Wade, P. A., Williams, R. M., and Wong, H. N.-C., *J. Am. Chem. Soc.*, 1981, **103**, 3213.

Discussion

Against the literature background of diverse cationic cyclizations leading to complex mixtures of isomeric cannabinoids referred to in the Introduction, the virtually exclusive production of either Δ^9-*trans*-THC (1) or Δ^9-*cis*-THC (11) in the present processes requires comment. We suggest that resonance-stabilized cations of the type (24) ↔ (25) are the primary intermediates in the formation of both the *trans* and the *cis* products. Formation of such cations (with R^2 = Me) from the methoxylated allylic-benzylic alcohols (13) and (14) on treatment with boron tribromide is unexceptional, and subsequent collapse then occurs, as shown in (26), to close the cyclohexanoid and benzopyranoid rings with subsequent demethylation of the resulting oxonium salt. We have observed a similar facile pyranoid ring closure with demethylation in a related system.[17] The thermodynamically more stable *trans* ring junctions of the products (21) and (23) result either directly from the cyclization process itself, or by boron tribromide-catalysed isomerization of any initially formed *cis* material. This latter process is known, and occurs in the presence of strong Lewis acids by opening and re-closing of the pyranoid ring with inversion of C 6a.[18] Demethylation to the free phenol also occurs, but participation of the olefinic bond in cyclization[2] and isomerization[19] processes is in this case prevented by the formation of its hydrogen bromide adduct.



(24) (25) (26) (27)

In formation of the *cis* products (11) and (12) we propose that trimethylsilyl chloride in the presence of tetraethylammonium bromide (forming trimethylsilyl bromide *in situ*[20]) reacts with the allylic-benzylic alcohols (15) and (16), perhaps after silylation of the hydroxyl group, to generate similar resonance-stabilized cations of the type (24) ↔ (25). Such benzylic–oxygen cleavage would closely resemble the known cleavage of methoxymethyl ethers $ROCH_2OMe$ by this reagent mixture[16] to yield the formal oxonium ion $CH_2{=}^+OMe$ together with the new trimethylsilyl ether $ROSiMe_3$, a process which will also effect transetherification at some stage in the present reaction. The resulting cations (24) ↔ (25) in these cases collapse by cleavage of one of the relatively labile methoxymethyl (or trimethylsilyl) ethers with formal loss of $CH_2{=}^+OMe$ (or Me_3Si^+) and generation of the corresponding quinone methides (27). Diels–Alder addition of olefins to such highly reactive species is known to occur at room temperature,[21] and would proceed intramolecularly in the present

[17] Rickards, R. W., and Rønneberg, H., *J. Org. Chem.*, 1984, **49**, 572.
[18] Razdan, R. K., and Zitko, B. A., *Tetrahedron Lett.*, 1969, 4947; Uliss, D. B., Handrick, G. R., Dalzell, H. C., and Razdan, R. K., *Tetrahedron*, 1978, **34**, 1885.
[19] Dalzell, H. C., Uliss, D. B., Handrick, G. R., and Razdan, R. K., *J. Org. Chem.*, 1981, **46**, 949.
[20] Schmidt, A. H., and Russ, M., *Ber. Dtsch. Chem. Ges.*, 1981, **114**, 1099.
[21] Wakselman, M., and Vilkas, M., *C. R. Acad. Sci.*, 1964, **258**, 1526.

cases to afford *cis* ring junction stereochemistry. Isomerization to *trans* does not occur since this particular reagent mixture does not even cleave acetonides[16] and therefore certainly *cannot re-open* the benzopyranoid ring. Isomerization of the double bond does not occur, since the conditions are mild and the Δ^9-position is thermodynamically preferred in *cis*-tetrahydrocannabinoid systems,[19] whilst the known reaction of this olefin with the neighbouring phenol to give various isotetrahydrocannabinoids[2] is prevented by the presence of the ether group. Aqueous workup subsequently hydrolyses the remaining silyl ether to yield Δ^9-*cis*-THC (11) and its homologue (12).

Concluding Remarks

The present carbanion-based syntheses of racemic Δ^9-*trans*-THC (1) and Δ^9-*cis*-THC (11) proceed through the single isolated intermediates (13) and (15) in greater than 50% overall yield from the olivetol dimethyl and di(methoxymethyl) ethers (4) and (6), respectively. Their high regiospecificity and stereoselectivity provide advantages over previous approaches to these tetrahydrocannabinoids in terms of simplicity of reaction mixtures, ease of product isolation, and yields obtainable. The reactions involved are not dependent upon critical concentrations of catalysts, and are thus readily reproducible. The nature of the processes may provide insight into the mechanism and control of cannabinoid cyclizations.

The extension of this carbanionoid approach to the synthesis of chiral Δ^9-*trans*-THC (1) is described elsewhere.[17]

Experimental

^{1}H and ^{13}C n.m.r. data were recorded for solutions in $CDCl_3$ with tetramethylsilane as internal reference on Bruker HFX-270 or Varian HA-100 spectrometers. Mass spectra were run on a VG Micromass 7070 instrument operating at 70 eV ionizing voltage. M.p.l.c. utilized a Merck LiChroprep Si 60 column. Light petroleum refers to the fraction b.p. 40–60°. Elemental analyses were carried out by the A.N.U. Analytical Services Unit.

Olivetol Dimethyl Ether (4)

Methylation[22] of olivetol (3) (3·0 g, 16·6 mmol) with dimethyl sulfate (6·3 g, 49·9 mmol) and potassium carbonate (6·9 g, 49·9 mmol) in acetone (30 ml) at reflux for 4 h, destruction of the excess of methylating agent with aqueous ammonia, extraction, washing and distillation gave the *dimethyl ether* (4) (3·09 g, 89%), b.p. 145°/2 mm. N.m.r. δ 0·89, t, CH_2CH_3; 1·25–1·38, m, CH_2CH_2Me; 1·53–1·7, m, CH_2Pr; 2·54, t, J 7·7 Hz, $ArCH_2$; 3·76, s, OCH_3; 6·25–6·4, m, ArH.

1-(2′,6′-Dimethoxy-4′-pentylphenyl)-3,7-dimethylocta-2,6-dien-1-ol (13)

To olivetol dimethyl ether (4) (0·63 g, 3 mmol) in dry tetrahydrofuran (15 ml) at 0° under argon was added butyllithium in hexane (2·2 ml, 1·6 M, 3·5 mmol). After 10 min at 0° and then 75 min at room temperature, mass spectrometry of a sample quenched with D_2O showed the recovered olivetol dimethyl ether to contain >92% D_1. The reaction mixture was cooled again to 0°, citral (10) (0·57 g, 3·8 mmol) in tetrahydrofuran (5 ml) was added, and the whole was left at room temperature overnight. The reaction was diluted with water, extracted with ether, and the extracts were washed (H_2O), dried ($MgSO_4$), and evaporated. The crude product (1·16 g) was chromatographed on basic alumina (Brockmann Grade II) in ether/light petroleum (1 : 2), yielding first a mixture (0·21 g, 2·7 : 6 by ^{1}H n.m.r.) of olivetol dimethyl ether and citral. Further elution gave the *alcohol* (13) (0·87 g, 80% or 99% corrected for recovered dimethyl ether) as an oil, a mixture of *E*

[22] Mirrington, R. N., and Feutrill, G. I., *Org. Synth.*, 1973, **53**, 90.

and *Z* isomers (Found: C, 76·5; H, 9·8. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%). *m/z* 342 (M−H_2O, 43%), 327 (70), 305 (35), 299 (86), 274 (28), 262 (47), 221 (100). N.m.r. δ 0·89, t, *J* 6·5 Hz, CH_2CH_3; 1·25–1·45, m, CH_2CH_2Me; 1·5–1·8, m, 11H, 3×C=CCH_3, CH_2Pr; 1·95–2·3, m, 2×C=CCH_2; 2·54, t, *J* 8 Hz, $ArCH_2$; 3·6, m, OH; 3·80, s, OCH_3; 5·0–5·24, m, H6; 5·6–5·78, m, H2; 5·8–5·98, m, H1; 6·28, s, ArH.

(6aR,9S*,10aR*)-9-Bromo-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydro-6H-dibenzo*[b,d]*pyran-1-ol* (*21*)

To the alcohol (13) (260 mg, 0·72 mmol) in dry dichloromethane (20 ml) under argon at −76° was added, with stirring, boron tribromide (542 mg, 2·16 mmol) in dichloromethane (0·6 ml, 3·6 M). The resulting deep red solution was allowed to warm to room temperature overnight, then diluted with ice-water and extracted with ether. The combined extracts were washed (5% aq. $NaHCO_3$, brine, H_2O), dried ($MgSO_4$) and evaporated to give the unstable tertiary *bromide* (21) (280 mg, 98%) as an oil. A sample purified by m.p.l.c. in ethyl acetate/light petroleum (15 : 85) gave a positive Br analysis. *m/z* 394/396 (M, 1·5%), 314 (M−HBr, 100), 299 (M−HBr−CH_3, 37), 271 (M−HBr−C_3H_7, 46), 258 (M−HBr−C_4H_8, 38), 231 (76). ^{1}H n.m.r. δ 0·88, t, CH_2CH_3; 1·15, s, 6α-CH_3; 1·2–1·38, m, CH_2CH_2Me; 1·39, s, 6β-CH_3; 1·4–1·8, m, H 6a,7,8β,10β, CH_2Pr; 1·89, s, 9-CH_3; 2·31, bd, $J_{8\alpha-8\beta}$ 11 Hz, H 8α; 2·43, t, *J* 8·25 Hz, $ArCH_2$; 3·12, dt, $J_{10a-6a,10\beta}$ 10·7 Hz, $J_{10a-10\alpha}$ 2·75 Hz, H 10a; 3·56, dt, $J_{10\alpha-8\alpha,10a}$ 2·75 Hz, $J_{10\alpha-10\beta}$ 14 Hz, H 10α; 6·09, d, 6·26, d, *J* 0·8 Hz, ArH. ^{13}C n.m.r. (assignments supported by gated decoupling) δ 14·0, CH_2CH_3; 19·2, 6α-CH_3; 22·5, CH_2Me; 25·0, C7; 27·7, 6β-CH_3; 30·6, CH_2Et; 31·6, CH_2Pr; 32·5, C10a; 35·4, $ArCH_2$; 35·9, C11; 43·7, C10; 46·3, C8; 48·9, C6a; 71·4, C9; 76·6, C6; 107·7, C4; 108·8, C10b; 110·2, C2; 143·0, C3; 154·5, 151·1, C1 and C4a.

1-(2′,6′-Dimethoxyphenyl)-3,7-dimethylocta-2,6-dien-1-ol (*14*)

Butyllithium in hexane (7 ml, 1·55 M) was added dropwise at room temperature with stirring to resorcinol dimethyl ether (5) (1·5 g, 10·86 mmol) in dry tetrahydrofuran (30 ml) under nitrogen. After stirring for 30 min, mass spectrometry of a sample quenched with D_2O showed recovered dimethyl ether to contain >90% D_1. Citral (10) (1·65 g, 10·86 mmol) was added dropwise and the reaction stirred overnight. Dilution with water, extraction with ether, and evaporation of the dried ($MgSO_4$) extracts gave a yellow liquid (3·1 g). Chromatography of a portion (700 mg) on Florisil in ether/light petroleum (3 : 2) yielded a mixture (115 mg) of resorcinol dimethyl ether and citral dimer, *m/z* 286 (M−H_2O, 22%). Further elution afforded the *alcohol* (14) (543 mg, 76% but quantitative if corrected for recovered dimethyl ether) as an oil, a mixture of *E* and *Z* isomers (Found: C, 74·5; H, 9·0. $C_{18}H_{26}O_3$ requires C, 75·0; H, 9·0%). *m/z* 290 (M, 2%), 273 (M−OH, 7), 272 (M−H_2O, 9), 232 (11), 229 (16), 207 (22), 167 (100), 165 (81), 151 (58). N.m.r. δ 1·5–1·8, m, 3×C=CCH_3; 1·88–2·35, m, 2×C=CCH_2; 3·68, m, OH; 3·80, s, OCH_3; 4·98–5·20, m, H6; 5·55–5·7, m, H2; 5·82–5·96, m, H1; 6·55, d, *J* 9 Hz, H3′,5′; 7·14, t, *J* 9 Hz, H4′.

1-(2′,6′-Dimethoxyphenyl)-3,7-dimethylocta-1,6-dien-3-ol (*20*)

The alcohol (14) (100 mg), subjected to dry column chromatography on silica gel in ether/light petroleum (2 : 3), gave first a mixture of unidentified compounds (23 mg) followed by the tertiary *styryl alcohol* (20) (65 mg, 65%) as an oil (Found: C, 74·6; H, 9·2. $C_{18}H_{26}O_3$ requires C, 75·0; H, 9·0%). *m/z* 290 (M, 7%), 272 (M−H_2O, 100), 207 (44), 204 (32), 173 (38), 167 (39), 165 (41), 151 (72), 138 (40). N.m.r. δ 1·36, s, CH_3COH; 1·59, bs, 1·63, bs, $(CH_3)_2C$=; 1·8–2·2, m, CH_2CH_2; 3·77, s, OCH_3; 5·04–5·28, m, H6; 6·51, d, *J* 9 Hz, H3′,5′; 6·74, ABq, *J* 17 Hz, CH=CH; 6·92–7·24, m, H4′.

(6aR,9S*,10aR*)-9-Bromo-6,6,9-trimethyl-6a,7,8,9,10,10a-hexahydro-6H-dibenzo*[b,d]*pyran-1-ol* (*23*)

Reaction of the alcohol (14) (1·0 g, 3·4 mmol) in dichloromethane (50 ml) with boron tribromide (2·6 g, 10·4 mmol) in dichloromethane (2·9 ml, 3·6 M), as described for the alcohol (13), gave the unstable tertiary *bromide* (23) (1·3 g), an oil R_F 0·73 on t.l.c. on silica in ethyl acetate/light petroleum (15 : 85) showing only two minor impurities. An aliquot was purified by m.p.l.c. on silica in ethyl acetate/light petroleum (15 : 85) for characterization (Found: C, 59·6; H, 6·7; Br, 21·2. $C_{16}H_{21}BrO_2$ requires C, 59·1; H, 6·5; Br, 24·6%). *m/z* 324/326 (M, 2%), 244 (M−HBr, 86),

201 ($M-HBr-C_3H_7$, 100), 161 (70). N.m.r. δ 1·15, s, 6α-CH_3; 1·4, s, 6β-CH_3; 1·45–1·85, m, H 6a,7,8β,10β; 1·9, s, 9-CH_3; 2·31, bd, $J_{8\alpha-8\beta}$ 11 Hz, H 8α; 3·12, dt $J_{10a-6a,10\beta}$ 10·8 Hz, $J_{10a-10\alpha}$ 2·6 Hz, H 10a; 3·57, dt, $J_{10\alpha-8\alpha,10a}$ 2·6 Hz, $J_{10\alpha-10\beta}$ 14·4 Hz, H 10α; 4·8, OH; 6·24, d, 6·41, d, J 8·2 Hz, H 2,4; 6·95, t, J 8·2 Hz, H 3.

(6aR,10aR*)-6,6,9-Trimethyl-6a,7,8,10a-tetrahydro-6H-dibenzo*[b,d]*pyran-1-ol (2)*

The tertiary bromide (23) (82 mg, 0·25 mmol) in dry benzene (1 ml) was added to a suspension of potassium t-butoxide (56 mg, 0·5 mmol) in dry benzene (5 ml) at 5°. After 75 min at 5°, the mixture was heated at 59–63° for 15 min. The mixture was saturated with carbon dioxide at 5°, diluted with ice-water, extracted with ether, and the extracts were washed (H_2O), dried ($MgSO_4$) and evaporated. M.p.l.c. on silica in ethyl acetate/light petroleum (15 : 85) gave an oily mixture (42 mg, 68%) of the 6a,7,10,10a-tetrahydro isomer (9) and the required Δ^9-*trans*-THC *analogue* (2). The ratio of isomers was estimated at 15 : 85 by ^1H n.m.r. spectroscopy, comparing the signal at δ 5·5 of H 8 in the Δ^8-isomer (9) to that at δ 3·24 of H 10a in the Δ^9-isomer (2). For the product (Found: C, 79·6; H, 8·6. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·3%). *m/z* 244 (M, 84%), 229 ($M-CH_3$, 53), 201 ($M-C_3H_7$, 100), 161 (100). N.m.r. of isomer (2) δ 1·07, s, 6α-CH_3; 1·39, s, 6β-CH_3; 1·67, bs, 9-CH_3; 1·75–1·9, m, H 7; 2·05–2·35, m, H 8; 3·24, bd, J 11 Hz, H 10a; 4·98, OH; 6·26, d, 6·4, d, J 8 Hz, H 2,4; *c.* 6·3, m, H 10; 6·92, t, J 8 Hz, H 3.

(6aR,10aR*)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-dibenzo*[b,d]*pyran-1-ol* (Δ^9-trans-THC) *(1)*

The tertiary bromide (21) (124 mg) was prepared from the alcohol (13) (100 mg, 0·28 mmol), as described above, and without purification was immediately dissolved in dry benzene (2 ml) and added to a suspension of potassium t-butoxide (63 mg, 0·56 mmol) in dry benzene (5 ml) at 5°. After 1 h at 5°, the mixture was heated at 60–64° for 10 min. Workup as described above for the analogue (2) and purification of the product by chromatography on Florisil with an increasing solvent gradient of ether in light petroleum gave an oily mixture (13 : 87 estimated by ^1H n.m.r. spectroscopy as above) (66 mg, 75%) of Δ^8-*trans*-THC (8) and Δ^9-*trans*-THC (1). The product showed *m/z* 314 (M, 86%), 299 ($M-CH_3$, 65), 271 ($M-C_3H_7$, 100), 231 (50). N.m.r. of isomer (1) δ 0·89, t, CH_2CH_3; 1·09, s, 6α-CH_3; 1·41, s, 6β-CH_3; 1·69, bs, 9-CH_3; 1·25–1·9, m, $CH_2CH_2CH_2Me$, H 7; 2·1–2·3, m, H 8; 2·45, t, J 7 Hz, $ArCH_2$; 3·23, bd, J 11 Hz, H 10a; 4·76, OH; 6·14, d, 6·28, d, J 1·5 Hz, H 2,4; 6·32, bs, H 10.

Di(methoxymethyl) Ethers (6) and (7)

Olivetol (3) (1·34 g, 7·4 mmol) in dimethylformamide (10 ml) was added to sodium hydride [from oil dispersion (55-60%, 1·26 g, *c.* 28 mmol), hexane-washed] at 0° in dimethylformamide (4 ml). After 15 min at 0° and 3 h at room temperature, the solution was cooled to 0° and chloromethyl methyl ether (2·14 g, 26·7 mmol) was added. After 15 min at 0°, the reaction was left overnight at room temperature. Addition of ice-water and extraction with ether gave, after washing the extracts (aqueous NaOH then brine) and drying ($CaCO_3$), *olivetol di(methoxymethyl) ether* (6) (1·64 g, 83%), b.p. 190° (bath temperature)/0·5 mm (Kugelrohr) (Found: C, 67·0; H, 8·8. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%). *m/z* 268 (M, 100%), 226 ($M-C_3H_6$, 23), 212 ($M-C_4H_8$, 79). N.m.r. δ 0·89, t, J 7 Hz, CH_2CH_3; 1·2–1·4, m, CH_2CH_2Me; 1·5–1·7, m, CH_2Pr; 2·53, t, J 8 Hz, $ArCH_2$; 3·46, s, OCH_3; 5·13, s, OCH_2OMe; 6·5–6·6, m, ArH.

Resorcinol di(methoxymethyl) ether (7) was prepared after Townsend *et al.*[23]

1-[2′,6′-Di(methoxymethyloxy)phenyl]-3,7-dimethylocta-2,6-dien-1-ol (16)

Butyllithium in hexane (0·97 ml, 1·55 M) was added dropwise at room temperature with stirring to resorcinol di(methoxymethyl) ether (7) (300 mg, 1·52 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. After stirring for 2 h, mass spectrometry of a sample quenched with D_2O showed the recovered ether to contain >90% D_1. Citral (10) (230 mg, 1·52 mmol) was added dropwise and the reaction stirred overnight. Workup and chromatography as for the alcohol (14) afforded first a

[23] Townsend, C. A., Davis, S. G., Christensen, S. B., Link, J. C., and Lewis, C. P., *J. Am. Chem. Soc.*, 1981, **103**, 6885; cf. Mamedov, Sh., and Mamedova, A. R., *Zh. Obshch. Khim.*, 1962, **32**, 407.

mixture (147 mg) of recovered ether and citral dimer followed by the alcohol (16) (320 mg, 60%, but quantitative if corrected for recovered ether) as an oil, a mixture of *E* and *Z* isomers (Found: C, 68·8; H, 8·8. $C_{20}H_{30}O_5$ requires C, 68·6; H, 8·6%). *m/z* 350 (M, 2%), 332 (M−H_2O, 12), 305 (M−CH_2OCH_3, 12), 287 (14), 274 (14), 205 (79), 161 (23), 69 (28), 45 (CH_3OCH_2, 100). N.m.r. δ 1·5–1·85, m, 3×C=CCH_3; 1·86–2·33 m, 2×C=CCH_2; 3·5, s, OCH_3; 3·65, OH; 5·0–5·3, m, OCH_2OMe, H6; 5·64–5·78, m, H2; 5·88–6·4, m, H1; 6·8, d, *J* 9 Hz, H3′,5′; 7·04–7·2, m, H4′.

(6aS,10aR*)-6,6,9-Trimethyl-6a,7,8,10a-tetrahydro-6H-dibenzo*[b,d]*pyran-1-ol* (*12*)

To the alcohol (16) (150 mg, 0·43 mmol) in stirred dichloromethane (20 ml) under nitrogen at room temperature was added trimethylsilyl chloride (270 mg, 2·47 mmol) and tetraethylammonium bromide (520 mg, 2·47 mmol). After 6 h, the reaction was diluted with water, extracted with ether and the extracts were washed (aqueous $KHCO_3$, then brine) and dried ($MgSO_4$). Evaporation and chromatography of the residue (102 mg) on silica in ether/light petroleum (2 : 3) gave the Δ^9-*cis*-THC *analogue* (12) as an oil (76 mg, 72%) (Found: C, 79·0; H, 8·1. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·3%). *m/z* 244 (M, 100%), 229 (M−CH_3, 39), 201 (68), 176 (14), 161 (97), 123 (13). N.m.r. δ 1·32, s, 1·44, s, 6-CH_3; 1·73, s, 9-CH_3; 1·6–1·8, m, H7; 1·8–2·12, m, H8; 3·64, bs, $W_{h/2}$ 14 Hz, H10a; 4·97, OH; 6·29, m, $W_{h/2}$ 12 Hz, H10; 6·35, d, 6·45, d, *J* 8 Hz, H2,4; 7·0, t, *J* 8 Hz, H3.

1-[2′,6′-Di(methoxymethyloxy)-4′-pentylphenyl]-3,7-dimethylocta-2,6-dien-1-ol (*15*)

Olivetol di(methoxymethyl) ether (6) (0·88 g, 3·3 mmol) in tetrahydrofuran (30 ml) was lithiated with butyllithium in hexane (2·3 ml, 1·6 M, 3·7 mmol) as for the dimethyl ether (4), but allowing 2 h at room temperature. Reaction with citral (10) (0·64 g, 4·2 mmol) in tetrahydrofuran (5 ml) and working up as for the dimethyl ether (13) gave the *alcohol* (15) (1·1 g, 79%) as an oily mixture of *E* and *Z* isomers (Found: C, 71·3; H, 9·7. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%). *m/z* 420 (M, 4%), 402 (M−H_2O, 17), 375 (M−CH_2OCH_3, 16), 275 (100). N.m.r. δ 0·89, t, *J* 6·5 Hz, CH_2CH_3; 1·22–1·42, m, CH_2CH_2Me; 1·52–1·85, m, 3×C=CCH_3, CH_2Pr; 1·92–2·3, m, 2×C=CCH_2; 2·53, t, *J* 8 Hz, ArCH_2; 3·5, s, OCH_3; 3·6, m, OH; 5·0–5·3, m, H6; 5·22, s, OCH_2OMe; 5·64–5·78, m, H2; 5·82–5·98, m, H1; 6·62, s, ArH.

(6aS,10aR*)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-dibenzo*[b,d]*pyran-1-ol* (Δ^9-cis-THC) (*11*)

To the alcohol (15) (177 mg, 0·42 mmol) in stirred dichloromethane (5 ml) under argon at 0° was added trimethylsilyl chloride (270 mg, 2·47 mmol) and tetraethylammonium bromide (520 mg, 2·47 mmol) in dichloromethane (15 ml). After 6 h at room temperature the reaction was poured into ice-water and worked up as for the analogue (12), to give a crude oil (153 mg). Chromatography of portion (96 mg) of this product on silica in ether/light petroleum (1 : 4) gave Δ^9-*cis*-THC (11) (54 mg, corresponding to 65%) as an oil. *m/z* 314 (M, 100%), 299 (M−CH_3, 52), 271 (M−C_3H_7, 43), 231 (76). N.m.r. δ 0·89, t, *J* 7 Hz, CH_2CH_3; 1·27, s, 1·38, s, 6-CH_3; 1·7, bs, 9-CH_3; 1·1–1·8, m, $CH_2CH_2CH_2$Me, H7; 1·8–2·1, m, H8, H6a (?); 2·45, t, *J* 7 Hz, ArCH_2; 3·56, bs, $W_{h/2}$ 12 Hz, H10a; 4·74, OH; 6·11, d, 6·25, d, *J* 2 Hz, ArH; 6·2, m, $W_{h/2}$ 6 Hz, H10.

Acknowledgments

We are indebted to Mr A. J. Herlt for expert technical assistance. Mass spectra were recorded by Messrs M. Chapman and W. Wheate, n.m.r. spectra by Mrs L. Harland, Mrs P. Culnane and Mr C. Blake.

Manuscript received 2 March 1984