Simple Synthesis of Hexahydrocannabinoids using Phenylboric Acid Catalyst

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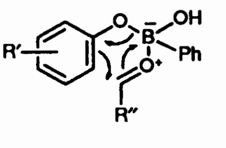
Common activated phenols, such as sesamol, undergo a one-pot annulation to hexahydrocannabinoids on being heated with citronellal, phenylboric acid and an excess of acetic acid. Benzodioxaborines **2** are shown to be intermediates and are proposed to undergo conversion into quinonemethides under the acid conditions employed. Generally the more stable equatorial-*trans*-stereoisomer is formed in better than 95% purity.

Phenylboric acid is a useful reagent for protecting[1] 1,2- and 1,3-*cis*-diols and in differentiating[2] between these and the corresponding *trans*-diols in carbohydrates,[3] anthracylinones[4] and steroids.[5] The *ortho*-specific attack on phenols by aldehydes catalysed by phenylboric acid was first reported in 1976.[6] Full details were later presented by Nagata,[7] who proposed a [3.3]-sigmatropic rearrangement pathway (structure **1**) and ultimately isolated benzodioxaborines **2**. Broadhurst and Hassall[4] applied this methodology successfully to the synthesis of anthracyclinones. They subsequently found[8] that this reagent was capable of converting benzylic 1,3-*trans*-diols into the corresponding epimers in the presence of acid, probably *via* a carbocationic pathway.



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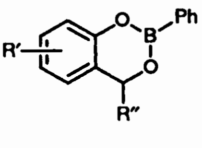

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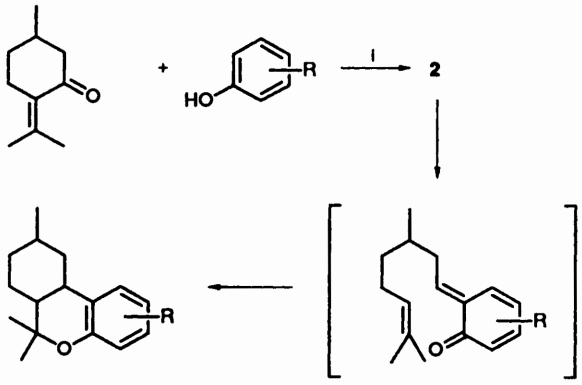
The possibility arose, therefore, that a benzodioxaborine such as structure **2** would lead to a protonated quinonemethide, and ultimately a transient quinonemethide, if heated with an appropriate protic acid. The trapping of quinonemethides both by nucleophiles[9] and by cycloaddition[10] have formed the basis of many recent elegant synthetic studies. We were interested, therefore, in investigating the reactions of intermediates **2**, prepared *in situ* from the corresponding phenol and aldehyde.

We now report the results of our investigation of the reaction of 3,7-dimethyloct-7-enal (citronellal) with phenols and phenylboric acid.[11] Our choice of aldehyde stemmed from the above considerations together with the capability of citronellal to act also as a dienophile. If citronellal reacted initially to form a borate ester **2**, then intramolecular cycloaddition to a subsequently formed quinonemethide functionality might follow under appropriate experimental conditions (Scheme 1).

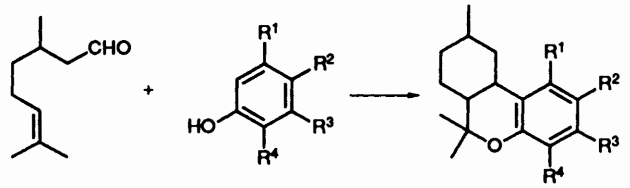
The general procedure which we employed involved heating to reflux the phenol with one mole equivalent each of citronellal and phenylboric acid in toluene with excess of acetic acid. As predicted, hexahydrocannabinoids, the cycloadducts of the proposed transient quinonemethides, were formed. Results are summarised in Table 1. Although the yields were variable, they were not optimised. 2′,4′-Dihydroxyacetophenone (resacetephenone), phenol, *p*-methoxyphenol, phloroglucinol, and catechol did not undergo condensation.

The structure of the products was consistent with attack at the more electrophilic position *ortho* to the hydroxy group. Ring fusion was invariably *trans* with the methyl group adopting the equatorial position. As an example, 3,5-dimethoxyphenol **8** reacted to give a good yield of the product **14**. Reaction involving the hydroxy group was readily apparent from the IR spectrum. Formation of a pyran ring was indicated by the chemical shift of the geminal methyl groups at δ_H 1.05 and 1.36. This was substantiated by the occurrence, in the C NMR spectrum, of a singlet at δ_C 77.12 due to the quaternary carbon bonded to the oxygen atom. 3-H Is observed as a doublet of triplets at δ_H 2.37. The coupling constants ($J_{3,4}$ 10.7, $J_{2\beta,3}$ 12.1, $J_{2\alpha,3}$ 3.0 Hz) are consistent only with *trans*-fusion.[12,13] This is confirmed by the observation of a signal for 2-H$^\alpha$ at δ_H 2.97 as a doublet of doublets ($J_{2\alpha,2\beta}$ 12.4, $J_{2\alpha,3}$ = $J_{1,2\alpha}$ = 3.0 Hz). The low chemical shift of this proton is due to the in-plane deshielding of the methoxy group, an effect useful for the assignment of the orientation of unsymmetrical aryl rings (see below).[12,13] 2-H$^\beta$ Is observed as a quartet at δ_H 0.68



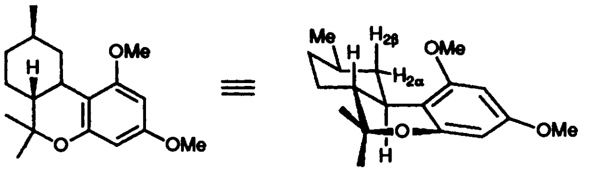
Scheme 1 *Reagent:* i, $PhB(OH)_2$

Table 1 Synthesis of hexahydrocannabinoids from citronnellal and phenols in the presence of phenylboric acid and an excess of acetic acid

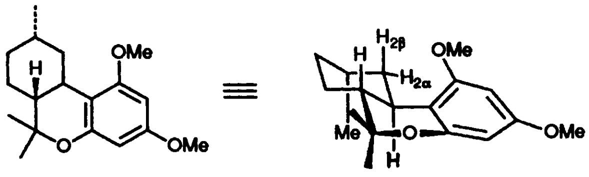


Phenol	Products and yield (%)	Epimeric ratio equatorial:axial
3 $R^1R^2 = C_6H_4$, $R^3 = R^4 = H$	**9** (52)	95:5
4 $R^1 = R^2 = H$, $R^3R^4 = C_6H_4$	**10** (52)	96:4
5 $R^1 = R^2 = R^4 = H$, $R^3 = OH$	**11** (43)	95:5
6 $R^1 = R^2 = R^4 = H$, $R^3 = OMe$	**12** (71)	97:3
7 $R^1 = R^4 = H$, $R^2R^3 = OCH_2O$	**13** (90)	100:0
8 $R^1 = R^3 = OMe$, $R^2 = R^4 = H$	**14** (86)	90:10

($J_{2\alpha,2\beta}$ 12.5, $J_{1,2\beta} = J_{2\beta,3}$ = 12.1 Hz), consistent with an equatorial methyl group at C-1.[12,13] The latter is observed as a sharp doublet at δ_H 0.94 (J 6.2 Hz). The presence of the C-1 epimer is indicated by the doublet of triplets at δ_H 2.6 (ratio 9:1).[14] The results with α-naphthol **4**, β-naphthol **3**, 3-methoxyphenol **6** and sesamol **7** were similar. The epimeric ratios are summarised in Table 1.

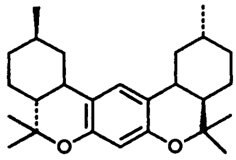


14 equatorial



14 axial

The results with 3,5-dihydroxyanisole and resorcinol **5** were more complicated, largely as a result of the presence of the two hydroxy groups. When resorcinol **5** was treated with 1 mol equiv. of citronellal, the tricyclic product **11** was formed together with a low percentage of its C-1 epimer. The structure of the main product was established as above. The orientation of substitution of the aryl ring was determined by the absence of deshielding for 2-H$^\alpha$, which was observed at δ_H 1.80. With 2 mol equiv. of citronellal, resorcinol **5** underwent bis-condensation. The coupling constant between the two aryl protons in this case was 1.5 Hz and thereby established the structure of the product as **15**. A much larger coupling constant would be expected between the aryl protons of the alternative product **16**. However, an additional doublet absorption in the aryl region of the ^{13}C spectrum suggests the presence of an impurity. The presence of an epimer was not detected.



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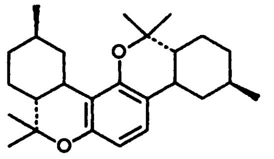

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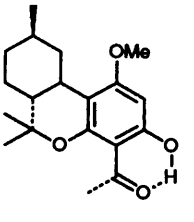
3.5-Dihydroxyanisole when treated with 1 mol equiv. of citronellal under normal conditions, gave four products (**17**–**20**). The stereochemistry of products **17** and **18** was determined as described earlier. Aryl acetylation was indicated by the absence of an OH absorption in the IR spectrum, combined with a low carbonyl absorption at ~1615 cm^{-1}. This proposal was confirmed by a one-proton singlet at δ_H 5.99 in the proton NMR spectrum combined with a singlet at δ_C 203.43 in the ^{13}C NMR spectrum. The structures of these two products were differentiated by NOE spectroscopy. A 20% enhancement of the aryl proton and a 10% enhancement of the acetyl singlet were observed when the methoxy absorption of the solid product was irradiated. The compound was therefore assigned the structure **18**. The mixture of products **19** and **20** was found to be inseparable. However, spectroscopic analysis of this mixture was unambiguous and enabled the assignment of structures to the two components.

When 4-methoxyphenol was treated with citronellal under the usual experimental conditions, no condensation occurred as noted earlier. However, 4-methoxyphenyl acetate was formed. As expected, when the reaction was repeated in the absence of citronellal the same product was isolated. When these results are coupled with the observation that acetylated products are formed in the reaction of 3,5-dihydroxyanisole it appears that phenylboric acid has the capability of catalysing the *O*-acetylation of phenols and inducing a subsequent Fries rearrangement, if the aryl ring is sufficiently activated. This proposal has yet to be investigated.



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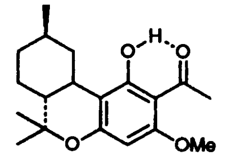

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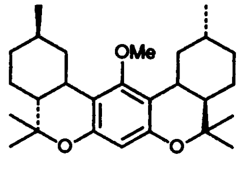

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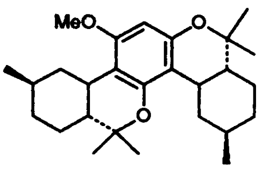

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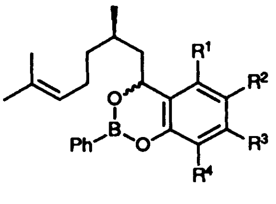
Nagata's rationale[7] satisfactorily explains invariable substitution *ortho* to the phenolic hydroxy group, namely initial mixed borate complex formation between the phenol, phenylboric acid, and citronellal. Aromatic substitution ensues *via* a [3.3]-sigmatropic rearrangement. If it is assumed that the carbonyl group in this complex is highly polarised, then it may be anticipated that the transition state will reflect this and make the extent of activation of the aryl ring important, as was observed.

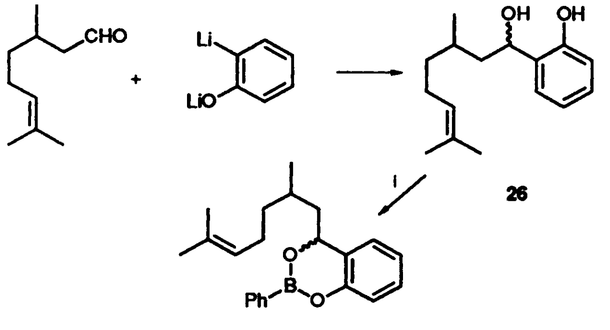
Since formation of stable borate esters from the immediate product of the [3.3]-sigmatropic rearrangement is predicted, isolation of these dioxaborine esters was attempted. The conditions employed were the same as those described above with the difference that only a catalytic quantity of acetic acid was employed. In the case of β-naphthol **3** (63%), α-naphthol **4** (38%), 3-methoxyphenol **6** (39%), and 3,5-dimethoxyphenol **8** (47%) the corresponding benzodioxaborines **21**–**24** were readily isolable, could be purified by chromatography, and were stable. The structures of these esters were assigned unambiguously by spectroscopic methods. In the case of sesamol **7**, the borate ester could not be isolated under the conditions employed to induce reaction of the other phenols. The corresponding hexahydrocannabinoid was isolated instead. The phenols catechol, hydroquinone, 4-methoxyphenol, phenol, and pyrogallol did not undergo any reaction.



21 $R^1R^2 = C_6H_4$, $R^3 = R^4 = H$
22 $R^1 = R^2 = H$, $R^3R^4 = C_6H_4$
23 $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
24 $R^1 = R^3 = OMe$, $R^2 = R^4 = H$

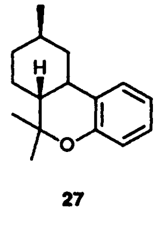
With regard to the mechanism of formation of hexahydrocannabinoids, we propose by analogy with others' results,[10,12,15] an acid-catalysed decomposition of the intermediate borate esters to a quinonemethide followed by a rapid intramolecular cycloaddition of the terminal double bond to this functionality. This reaction will additionally be driven by the regain of aromaticity. It could be anticipated that the overall conversion of the borate into the cannabinoid would be relatively insensitive to substituent effects. To test this proposal the dioxaborines which had been synthesized from α-naphthol **4** and β-naphthol **3** were heated to reflux in toluene with an excess of acetic acid. A 95% and 98% conversion into the corresponding cannabinoid, respectively, was observed. These results are consistent with our proposed mechanism. The influence of substituent effects was investigated by treatment of the dioxaborine **25**—the synthesis of which is described below—to the same conditions. The corresponding cannabinoid **27** was isolated in 35% yield. A similar yield of hexahydrocannabinoid was obtained when the diol **26** was heated in refluxing toluene with 2 mol equiv. of ethylmagnesium bromide, an established route to quinonemethides.[15] It thus appears that the overall efficiency of the combination of *o*-quinonemethide formation and cycloaddition is dependent on substituent effects. It should be noted, however, that a protonated quinonemethide intermediate[16] is a reasonable alternative consistent with these substituent effects. We have not discarded this possibility.

The dioxaborine **25** was readily prepared by heating the diol **26**, which had been synthesized by Talley's method[16] with phenylboric acid in toluene in the presence of a catalytic quantity of acetic acid (see Scheme 2).



Scheme 2 *Reagents:* i, $PhB(OH)_2$, H^+

With the exception of 3,5-dimethoxyphenol **8**, the percentage of C-1 epimer formed during synthesis of the hexahydrocannabinoids was in the range 3–5%; see Table 1. To explain this, we have adopted Vollhard's proposal,[17] since employed by others,[9b,10,12] which he used to explain the stereospecificity of intramolecular cycloaddition of an *o*-xylylene. If it is assumed that the (*E*)-*exo*-quinonemethide is formed, then from inspection of models the most favourable pseudochair transition state is equatorial-*trans*, structure **28**. By comparison, transition states in which the methyl group adopts an axial conformation or which lead to *cis*-fusion[18,19] involve either additional strain due to *gauche* interactions or steric interaction between a terminal methyl group and the aryl ring.



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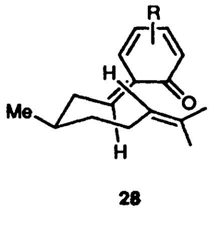

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Experimental

TLC and preparative TLC (PLC) were achieved on glass-backed silica gel plates employing silica gel HF_{254} and PF_{254}, respectively. Flash column chromatography was effected by using silica gel PF_{254}. Solvents were dried and purified before use by standard methods. M.p.s were achieved on a Reichet microscope hot-stage melting point apparatus and are uncorrected. Elemental analyses were accomplished at the Microanalytical Laboratory University College, Cork, employing a Perkin-Elmer 240 elemental analyser. IR spectra were recorded from samples as KBr discs for solids and thin films on sodium chloride plates for liquids, by using a Perkin-Elmer 682 IR spectrometer. ^1H NMR spectra were acquired at 15 MHz on a JEOL JNM-FX60 Fourier transform spectrometer at 24 °C. Deuteriated chloroform ($CDCl_3$) was employed as a solvent in all cases, unless otherwise stated. Tetramethylsilane (TMS) was utilised as internal standard, in reference to which positive chemical shifts were downfield. *J*-Values are given in Hz. The 270 MHz ^1H NMR spectra were recorded at University College, Galway on a JEOL GX spectrometer.

General Procedure for the Reaction and Work-up Procedures for the Phenylboric Acid-catalysed Reactions.—To dry toluene (50 cm^3) were added the phenol (3 mmol) and citronellal (3 mmol). Phenylboric acid (3 mmol) in an excess of glacial acetic acid (15 cm^3) was then added. This solution was heated to reflux for the appropriate number of hours (20–40) with a Dean–Stark apparatus fitted, during which the reaction was followed by TLC [developer ethyl acetate–hexane (1:9)]. The reaction mixture was then cooled, the solvent evaporated off under reduced pressure, and the product extracted with diethyl ether. The combined extracts were washed successively with water, aq. sodium hydrogen carbonate, and brine. The ethereal solution was then dried with magnesium sulfate, filtered, and evaporated. Purification was achieved by flash chromatography with ethyl acetate–hexane (1:9) as eluent and then by PLC with diethyl ether–hexane (1:19) as developer.

Reaction with β-Naphthol **3**.—A crystalline *solid* **9** (52%), m.p. 113–114 °C (Found: C, 85.5; H, 8.8. $C_{20}H_{24}O$ requires C, 85.7; H, 8.6%); ν_{max}/cm^{-1} 3060, 2960, 2930, 2870, 1640, 1600 and 1505; δ_H 0.79 (1 H, q, $J_{2a.2e} = J_{2a.1a} = J_{2a.3a}$ = 11.93, 2-H^{β}), 0.91 (3 H, d, *J* 6.41), 1.02 (3 H, s, 8-Me^{α}), 1.41 (3 H, s, 8-Me^{β}), 0.90–2.06 (6 H, m), 1.86 (1 H, br m, *J* 11.73, 2-H^{α}), 2.77 (1 H, dt, 3-H), 6.99 (1 H, d, ArH), 7.23 (1 H, t, ArH), 7.38 (1 H, t, ArH), 7.52 (1 H, d, ArH), 7.69 (1 H, d, ArH) and 7.79 (1 H, d, *J* 8.25, ArH); δ_C 18.26 (q), 22.48 (q), 27.48 (q), 28.26 (q), 33.14 (d), 35.93 (t), 36.58 (t), 42.36 (t), 51.09 (d), 76.86 (s), 117.28 (s), 119.87 (d), 122.41 (d), 124.03 (d), 125.07 (d), 127.87 (d), 128.65 (d), 129.56 (s), 132.29 (s) and 151.39 (s).

Reaction with α-Naphthol **4**.—A crystalline *solid* **10** (52%); m.p. 72–74 °C (Found: C, 85.5; H, 8.6. $C_{20}H_{24}O$ requires C, 85.7; H, 8.6%); ν_{max}/cm^{-1} 3050, 2970, 2920, 2860, 1630, 1600, 1570 and 1505; δ_H 0.86 (1 H, q, $J_{2a.2e} = J_{2a.3a} = J_{2a.3a}$ = 12.2, 2-H^{β}), 0.95 (3 H, d, *J* 6.22, 1-Me), 1.10 (3 H, s, 8-Me^{α}), 1.46 (3 H, s, 8-Me^{β}), 0.95–1.94 (6 H, m), 1.76 (1 H, br d, *J* 9.89, 2-H^{α}), 2.44 (1 H, dt, *J* 10.26 and 3.5, 3-H), 7.31 (4 H, m), 7.66 (1 H, m, ArH) and 8.22 (1 H, m, ArH); δ_C 20.14 (q), 22.61 (t), 27.55 (d), 27.94 (d), 32.62 (q), 34.89 (t), 35.93 (q), 39.76 (t), 47.11 (d), 77.58 (s), 118.45 (s), 118.71 (d), 122.02 (d), 124.03 (d), 124.75 (d), 125.53 (s), 127.15 (d), 133.13 (s) and 147.88 (s).

Reaction of Resorcinol **5** *with* 1 *Mol Equiv. of Citronellal.*—A crystalline *solid* **11** (43%); m.p. 140–141 °C (Found: C, 77.7; H, 9.0. $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.0%); ν_{max}/cm^{-1} 3200, 2940, 2920, 2870, 2830, 1620 and 1580; δ_H 0.85 (1 H, q, $J_{2a.2e}$ 13.2, $J_{2a.1a} = J_{2a.3a}$ = 12.1, 2-H^{β}), 0.97 (3 H, d, *J* 6.23, 1-Me), 1.12 (3 H, s, 8-Me$^{\alpha}$), 1.37 (3 H, s, 8-Me$^{\beta}$), 0.92–1.55 (6 H, m), 1.80 (1 H, br d, *J* 13.19, 2-H$^{\alpha}$), 2.36 (1 H, dt, *J* 12.1, 3-H), 6.26 (1 H, d, *J* 2.57, ArH), 6.27 (1 H, dd, 4′-OH), 6.36 (1 H, dd, ArH) and 7.05 (1 H, d, ArH); δ_C 20.21 (q), 22.61 (q), 27.55 (d), 27.94 (q), 32.36 (d), 34.89 (t), 35.09 (t), 39.76 (t), 46.98 (d), 77.90 (s), 103.63 (d), 107.40 (d), 118.06 (s), 126.89 (d), 153.99 (s) and 154.90 (s).

Reaction with 3-*Methoxyphenol* **6**.—A clear, viscous *oil* **12** (71%) (Found: C, 78.8; H, 9.2. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%); ν_{max}/cm^{-1} 2940, 2920, 2850, 1615, 1580 and 1500; δ_H 0.83 (1 H, q, $J_{2a.2e}$ 13.2, $J_{2a.1a}$ = $J_{2a.3a}$ = 12.1, 2-H$^{\beta}$), 0.96 (3 H, d, *J* 6.23, 1-Me), 1.10 (3 H, s, 8-Me$^{\alpha}$), 1.36 (3 H, s, 8-Me$^{\beta}$), 0.90–1.53 (6 H, m), 1.79 (1 H, br d, *J* 11.36, 2-H$^{\alpha}$), 2.34 (1 H, dt, *J* 12.1, 3-H), 3.69 (3 H, s, 4′-OMe), 6.32 (1 H, d, ArH), 6.41 (1 H, dd, ArH) and 7.07 (1 H, d, ArH); δ_C 20.08 (q), 22.61 (q), 27.48 (d), 27.94 (q), 32.29 (d), 34.83 (t), 35.02 (t), 39.70 (t), 46.98 (q), 54.90 (d), 77.38 (s), 101.55 (d), 106.56 (d), 117.60 (s), 126.20 (d), 154.05 (s) and 158.99 (s).

Reaction with Sesamol **7**.—A crystalline *solid* **13** (90%), m.p. 97–99 °C (Found: C, 74.1; H, 8.0. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.1%); ν_{max}/cm^{-1} 2990, 2940, 2920, 2900, 2880, 2860, 2770, 1630, 1515, 1510 and 1490; δ_H 0.85 (1 H, q, $J_{2a.2e}$ = $J_{2a.1a}$ = $J_{2a.3a}$ = 12.1, 2-H$^{\beta}$), 0.97 (3 H, d, *J* 6.6, 1-Me), 1.01 (3 H, s, 8-Me$^{\alpha}$), 1.34 (3 H, s, 8-Me$^{\beta}$), 1.09–1.82 (6 H, m), 1.79 (1 H, br d, *J* 12.1 and 2.96, 2-H$^{\alpha}$), 2.27 (1 H, dt, *J* 12.1, 3-H), 5.83 (2 H, AB quartet, *J* 0.5, OCH$_2$O), 6.31 (1 H, s, ArH) and 6.69 (1 H, s, ArH); δ_C 19.74 (q), 22.55 (d), 27.48 (q), 27.81 (q), 32.36 (d), 34.83 (t), 35.74 (t), 40.02 (t), 46.98 (d), 76.99 (s), 98.76 (d), 100.51 (t), 105.00 (d), 116.89 (s), 141.06 (s), 146.25 (s) and 147.81 (s).

Reaction with 3,5-*Dimethoxyphenol* **8**.—A clear, viscous *oil* **14** (86%) (Found: C, 74.6; H, 9.2. $C_{18}H_{26}O_3$ requires C, 74.5; H, 9.1%); ν_{max}/cm^{-1} 2980, 2950, 2930, 2880, 1620, 1590 and 1495; δ_H 0.68 (1 H, q, $J_{2a.2e}$ 12.46, $J_{2a.1a}$ = $J_{2a.3a}$ = 12.1, 2-H$^{\beta}$), 0.94 (3 H, d, *J* 6.23, 1-Me), 1.05 (3 H, s, 8-Me$^{\alpha}$), 1.36 (3 H, s, 8-Me$^{\beta}$), 0.92–2.02 (6 H, m), 2.37 (3 H, dt, $J_{3.0}$ and 12.1, 3-H), 2.97 (1 H, br d, *J* 3.0 and 12.46, 2-H$^{\alpha}$), 3.71 (1 H, s, 2′-OMe), 3.75 (3 H, s, 4′-OMe), 5.99 (1 H, d, *J* 2.56, ArH) and 6.02 (1 H, d, *J* 2.56, ArH); δ_C 18.91 (q), 22.68 (q), 27.77 (q), 28.07 (d), 32.81 (d), 35.41 (t), 35.67 (t), 39.37 (t), 49.32 (d), 55.10 (q), 77.12 (s), 91.74 (d), 94.01 (d), 107.07 (s), 155.22 (s), 159.32 (s) and 159.90 (s).

Reaction of Resorcinol **5** *with* 2 *Mol Equiv. of Citronellal.*—A *solid* **15** (20%) (Found: C, 81.4; H, 10.2. $C_{26}H_{38}O_2$ requires C, 81.6; H, 10.0%); ν_{max}/cm^{-1} 2960, 2920, 2850, 1620, 1605 and 1580; δ_H 0.86 and 0.87 (1 H each, q, $J_{2a.2e}$ = $J_{2a.1a}$ = $J_{2a.1a}$ = 12.1, 2- and 2′-H$^{\beta}$), 0.97 and 1.00 (3 H each, d, *J* 6, 1- and 1′-Me), 1.11 and 1.13 (3 H each, s, 8- and 8′-Me$^{\alpha}$), 1.33 (6 H, s, 8- and 8′-Me$^{\beta}$), 0.78–1.74 (12 H, m), 1.82 (2 H, br d, $J_{2e.2a}$ 12.1, $J_{2e.1a}$ = $J_{2e.3a}$ = 2.5, 2- and 2′-H$^{\alpha}$), 2.38 (2 H, dt, $J_{3a.2a}$ 12.1, $J_{3a.4a}$ 11.3, $J_{3a.2e}$ 2.5, 3- and 3′-H), 6.18 (1 H, d, *J* 1.5, ArH) and 7.03 (1 H, d, *J* 1.5, ArH); δ_C 20.27 (q), 22.68 (q), 27.68 (d), 28.07 (q), 32.42 (d), 34.96 (t), 35.28 (t), 39.83 (t), 47.17 (d), 77.06 (s), 104.35 (d), 117.08 (s), 122.54 (d), 122.86 (d) and 152.43 (s).

Reaction of 3,5-*Dihydroxyanisole.*—A *solid* **19** plus **20** (16%) (Found: C, 78.5; H, 9.6%. $C_{27}H_{40}O_3$ requires C, 78.6; H, 9.8%); ν_{max}/cm^{-1} 2970, 2910, 2850, 1605, 1580 and 1560; δ_H 0.65 and 0.68 (2 H, q, $J_{2a.2e}$ = $J_{2a.1a}$ = $J_{2a.3a}$ = 12.1, 2- and 2′-H$^{\beta}$), 0.91 (6 H, d, *J* 6.2, 1- and 1′-Me), 1.05 and 1.09 (6 H, 8- and 8′-Me$^{\alpha}$), 1.35, 1.37 and 1.39 (6 H, 8- and 8′-Me$^{\beta}$), 0.80–1.95 (12 H, m), 2.36 (2 H, dt, $J_{3a.2a}$ 12.1, $J_{3a.4a}$ 11.3, $J_{3a.2e}$ 2.5, 3- and 3′-H), 2.94, 3.06 and 3.20 (2 H, $J_{2e.2a}$ 12.1, $J_{2e.1a}$ = $J_{2e.3a}$ = 2.5, 2- and 2′-H$^{\alpha}$), 3.71 (3 H, s, OMe) and 5.89 and 5.95 (1 H, ArH); δ_C 18.99 (q), 22.69 (q), 27.80 (q), 28.15 (d), 32.83 (d), 35.56 (t), 35.72 (t), 39.74 (t), 49.37 (d), 54.81 (q), 76.67 (s), 92.18 (d), 92.73 (d), 106.86 (s), 152.57 (s), 153.05 (s), 153.85 (s) and 157.69 (s).

A clear, viscous *oil* **17** (16%) (Found: C, 71.6; H, 8.2. $C_{19}H_{26}O_4$ requires C, 71.7; H, 8.2%); ν_{max}/cm^{-1} 2960, 2920, 2860 and 1615; δ_H 0.63 (1 H, q, $J_{2a.2e}$ = $J_{2a.1a}$ = $J_{2a.3a}$ = 12.1, 2-H$^{\beta}$), 0.93 (3 H, d, *J* 6.2, 1-Me), 1.08 (3 H, s, 8-Me$^{\alpha}$), 1.43 (3 H, s, 8-Me$^{\beta}$), 0.80–1.90 (6 H, m), 2.34 (1 H, dt, $J_{3a.2a}$ 12.1, $J_{3a.4a}$ 11.2, $J_{3a.2a}$ 2.5, 3-H), 2.61 (3 H, s, Ac), 2.82 (1 H, br d, $J_{2e.2a}$ 12.1, $J_{2e.1a}$ = $J_{2e.3a}$ = 2.5, 2-H$^{\alpha}$), 3.80 (3 H, s, OMe) and 5.99 (1 H, s, ArH); δ_C 19.04 (q), 22.61 (q), 27.48 (q), 27.74 (d), 32.75 (q), 33.33 (d), 35.22 (t), 35.48 (t), 39.63 (t), 48.80 (d), 55.29 (q), 78.81 (s), 92.13 (d), 105.39 (s), 106.43 (s), 156.72 (s), 164.77 (s), 165.29 (s) and 203.43 (s).

A *solid* **18** (23%) (Found: C, 71.5; H, 8.0. $C_{19}H_{26}O_4$ requires C, 71.7; H, 8.2%); ν_{max}/cm^{-1} 2960, 2920, 2860 and 1615; δ_H 0.61 (1 H, q, $J_{2a.2e}$ = $J_{2a.1a}$ = 12.1, 2-H$^{\beta}$), 0.93 (3 H, d, *J* 6.2, 1-Me), 1.07 (3 H, s, 8-Me$^{\alpha}$), 1.38 (3 H, s, 8-Me$^{\beta}$), 0.78–1.90 (6 H, m), 2.40 (1 H, dt, $J_{3a.2a}$ 12.1, $J_{3a.4a}$ 11.3, $J_{3a.2e}$ 2.5, 3-H), 2.57 (3 H, s, Ac), 3.18 (1 H, br d, $J_{2e.2a}$ 12.1, $J_{2e.1a}$ = $J_{2e.3a}$ = 2.5, 2-H$^{\alpha}$), 3.79 (3 H, s, OMe) and 5.81 (1 H, s, ArH); δ_C 1930 (q), 22.55 (q), 27.48 (q), 27.94 (d), 32.62 (d), 32.88 (t), 34.76 (t), 35.54 (t), 38.46 (d), 49.06 (q), 55.23 (s), 78.94 (d), 91.48 (d), 105.39 (s), 105.84 (s), 161.01 (s), 161.20 (s), 166.27 (s) and 203.04 (s).

Generation of Dioxaborines. A General Procedure.—The phenol (3 mmol) was dissolved in dry toluene (50 cm^3). Citronellal (0.46 g, 0.54 cm^3, 3 mmol), phenylboric acid (0.37 g, 3 mmol) and a trace of acetic acid (0.1 cm^3) were added. The reaction mixture was heated under reflux for the appropriate number of hours, with a Dean–Stark apparatus fitted, and was monitored by TLC [ethyl acetate–hexane (1:9)]. When the reaction was complete, the solvent was evaporated under reduced pressure. The residual oil was diluted with diethyl ether, washed successively with sodium hydrogen carbonate and brine and dried with magnesium sulfate. The solvent was then evaporated off under reduced pressure. The product was isolated by PLC, with the solvent mixture (1:19) ethyl acetate–hexane.

1-(2′,6′-*Dimethylhept*-5′-*enyl*)-3-*phenyl*-1H-*naphtho*[2,1-d]-[1,3,2]*dioxaborine* **21**.—A clear, viscous *oil* **21** (63%) (Found: C, 81.1; H, 7.3. $C_{26}H_{29}BO_2$ requires C, 81.3; H, 7.6%); ν_{max}/cm^{-1} 3070, 3050, 3020, 2960, 2920, 2870, 2850, 1625, 1600 and 1515; δ_H 0.97 (3 H, d, *J* 6.2, 2′-Me), 1.53 (3 H, d, *J* 4.8, Me*Me*C=CH), 1.70 (3 H, d, *J* 6.0, *Me*MeC=CH), 0.78–2.14 (7 H, m), 5.03 and 5.23 (1 H, m, 1-H), 5.87 (br m, Me$_2$C=C*H*CH$_2$), 7.22–7.57 (6 H, m, naphthyl), 7.57–7.84 (3 H, m, Ph) and 7.96–8.13 (2 H, m, Ph); δ_C 19.01 (q), 20.58 (q), 25.36 (q), 25.51 (q), 28.51 (d), 29.30 (d), 35.72 (t), 37.80 (t), 46.00 (t), 46.42 (t), 68.91 (d), 69.37 (d), 119.13 (d), 119.22 (s), 119.28 (s), 121.51 (d), 121.58 (d), 124.09 (d), 126.73 (d), 127.76 (d), 128.82 (d), 129.10 (d), 129.53 (s), 129.56 (s), 130.42 (d), 131.49 (s), 134.48 (d) and 146.52 (s).

4-(2′,6′-*Dimethylhept*-5′-*enyl*)-2-*phenyl*-4H-*naphtho*[1,2-d]-[1,3,2]*dioxaborine* **22**.—A clear, viscous *oil* **22** (38%) (Found: C, 81.2; H, 7.7%); ν_{max}/cm^{-1} 3070, 3050, 3020, 2960, 2920, 2870, 2850, 1635, 1600, 1580 and 1510; δ_H 0.99 (3 H, d, *J* 6.2, 2′-Me), 1.54 (3 H, s, Me*Me*C=CH), 1.59 (3 H, s, *Me*MeC=CH), 5.06 and 5.14 (1 H, t, *J* 6.1, 4-H), 5.38 (1 H, br d, *J* 8.3, Me$_2$C=C*H*CH$_2$), 7.05 (1 H, d, naphthyl), 7.26–7.62 (4 H, m), 7.77 (1 H, d, naphthyl), 8.11 (3 H, d, ArH) and 8.45 (2 H, d, ArH); δ_C 19.32 (q), 20.76 (q), 25.41 (q), 25.62 (q), 28.59 (d), 29.02 (d), 36.10 (t), 37.94 (t), 47.29 (t), 71.25 (t), 71.60 (d), 118.89 (s), 120.85 (s), 121.79 (d), 122.55 (d), 122.69 (d), 124.91 (d), 125.12 (d), 126.05 (d), 126.31 (d), 127.42 (d), 127.96 (d), 131.49 (s), 133.65 (s), 134.58 (d) and 143.86 (s).

4-(2′,6′-*Dimethylhept*-5′-*enyl*)-7-*methyl*-4H-*benzo*[d][1,3,2]-*dioxaborine* **23**.—A clear, viscous *oil* **23** (39%) (Found: C, 75.8; H, 7.8. $C_{23}H_{29}BO_3$ requires C, 75.8; H, 8.0%); ν_{max}/cm^{-1} 3070, 3050, 3020, 2950, 2920, 2860, 1620, 1600, 1585 and 1500; δ_H 1.06 (3 H, d, *J* 6.2, 2′-Me), 1.54 (3 H, s, Me*Me*C=CH), 1.63 (3 H, s, *Me*MeC=CH), 0.73–2.10 (7 H, m), 3.78 (3 H, s, OMe), 5.06 (1 H, t, *J* 6.01, 4-H), 5.23 (1 H, dd, *J* 8.2, Me$_2$C=C*H*CH$_2$), 6.59 (1 H, dd, *J* 8.4 and 2.6, 6-H), 6.64 (1 H, d, *J* 2.6, 8-H), 6.88 (1 H, d, *J* 8.4, 5-H), 7.32–7.54 (3 H, m, ArH) and 7.87–8.03 (2 H, m, ArH); δ_C 17.65 (q), 19.21 (q), 20.49 (q), 25.40 (q), 28.28 (t), 37.78 (t), 47.46 (t), 55.25 (d), 55.38 (q), 77.03 (d), 77.51 (d), 103.25 (d), 109.33 (d), 119.18 (s), 124.55 (s), 124.66 (d), 125.80 (d), 127.68 (d), 131.37 (d), 134.37 (d), 147.71 (s) and 159.85 (s).

4-(2′,6′-*Dimethylhept-5′-enyl*)-5,7-*dimethoxy*-4H-*benzo*[d]-[1,3,2]*dioxaborine* **24**.—A clear, viscous *oil* **24** (47%) (Found: C, 72.7; H, 8.1. $C_{24}H_{31}BO_4$ requires C, 73.1; H, 7.9%); ν_{max}/cm^{-1} 3080, 3050, 2960, 2920, 2870, 2850, 1635, 1600, 1580 and 1510; δ_H 0.95 (2 H, t, *J* 7.8, 2′-Me), 1.06 (2 H, t, *J* 7.8), 1.51 (3 H, s, Me*Me*C=CH), 1.58 (3 H, s, *Me*MeC=CH), 0.82–2.12 (7 H, m), 3.73 (3 H, s, OMe), 3.75 (3 H, s, OMe), 5.04 and 5.16 (1 H, t, *J* 6.2, 4-H), 5.36 (1 H, dd, *J* 8.3 and 1.2, Me$_2$=C*H*CH$_2$), 6.15 (1 H, d, *J* 2.6, ArH), 6.28 (1 H, d, *J* 2.6, ArH), 7.30–7.52 (3 H, m, ArH) and 7.87–8.03 (2 H, m, ArH); δ_C 17.87 (q), 18.93 (q), 20.72 (q), 25.49 (t), 28.57 (d), 37.88 (t), 45.74 (t), 55.30 (q), 55.38 (q), 67.87 (d), 68.23 (d), 93.69 (d), 94.96 (d), 108.32 (s), 124.82 (d), 127.68 (d), 131.03 (s), 131.33 (d), 134.39 (d), 150.25 (s), 156.15 (s) and 160.33 (s).

4-(2′,6′-*Dimethylhept-5′-enyl*)-4H-*benzo*[d][1,3,2]*dioxaborine* **25**.—A clear, viscous *oil* **25** (56%) (overall) (Found: C, 78.9; H, 8.2. $C_{22}H_{27}BO_2$ requires C, 79.0; H, 8.1%); ν_{max}/cm^{-1} 3060, 3040, 3020, 2960, 2920, 2870, 1605, 1590 and 1490; δ_H 0.97 (3 H, d, *J* 6.3, 2′-Me), 1.59 (3 H, s, Me*Me*C=CH), 1.69 (3 H, s, *Me*MeC=CH), 0.76–2.13 (7 H, m), 5.05 and 5.13 (1 H, t, *J* 5.8, 4-H), 5.24 (1 H, m, Me$_2$C=C*H*CH$_2$), 6.73–7.24 (4 H, m, ArH), 7.33–7.52 (3 H, m, Ph) and 7.97 (2 H, d, Ph); δ_C 17.62 (q), 19.16 (q), 20.47 (q), 25.28 (t), 28.73 (t), 36.03 (t), 37.75 (t), 70.67 (d), 71.09 (d), 117.99 (d), 122.95 (d), 124.65 (d), 124.72 (d), 125.24 (d), 125.28 (s), 127.68 (d), 128.45 (d), 128.81 (s), 131.37 (d), 134.39 (d) and 148.81 (s).

Conversion of the 1,3,2-*Benzodioxaborinane Intermediates* **21** *and* **22** *into the Corresponding Tetracyclopyrans* **9** *and* **10**.—(a) *By heating in acetic acid.* The intermediate (0.2 g, 0.5 mmol) was dissolved in dry toluene (20 cm^3). An excess of acetic acid (5 cm^3) was added. This solution was heated to reflux and the reaction was monitored by TLC. When the reaction was finished the solvent was removed under reduced pressure. The crude product was purified by PLC [(1:9) ethyl acetate–hexane].

The reactants **21** and **22** were converted into products **9** and **10** in 98 and 95% yield, respectively. The two products had the same physical, analytical, and spectral properties as found earlier.

Conversion of Compound **25** *into the Corresponding Hexahydrocannabinoid* **27**.—(a) *By heating with ethylmagnesium bromide.* A solution of the dioxaborine **25** (0.4 g, 1.6 mmol) in diethyl ether (5 cm^3) was added to a solution of ethylmagnesium bromide (3.2 mmol) in diethyl ether (5 cm^3). The ether was removed under reduced pressure and was replaced with dry toluene (25 cm^3). The solution was heated under reflux for 20 h. The solvent was removed under reduced pressure. The residue was diluted with diethyl ether and quenched with saturated aq. ammonium chloride. After being washed with brine, the diethyl ether was evaporated off. Purification was achieved by PLC, with (1:9) ethyl acetate–hexane.

The product **27** (0.14 g, 38%) was isolated. It is clear, viscous *oil* (Found: C, 83.9; H, 9.8. $C_{10}H_{22}O$ requires C, 83.5; H, 9.6%); ν_{max}/cm^{-1} 3070, 3050, 3020, 2940, 2920, 2850, 1725, 1645, 1605 and 1575; δ_H 0.85 (1 H, q, $J_{2a,2e} = J_{2a,1a} = J_{2a,3a} = 12.1$, 2-H$^\beta$), 0.93 (3 H, d, *J* 6.4, 1-Me), 1.10 (3 H, s, 8-Me$^\alpha$), 1.42 (3 H, s, 8-Me$^\beta$), 0.80–1.61 (6 H, m), 1.80 (1 H, br d, *J* 12.1, 2-H$^\alpha$), 2.43 (1 H, dt, $J_{3a,2a}$ 12.1, $J_{3a,4a}$ 10.63, $J_{3a,2e}$ 2.5, 3-H) and 6.76–7.23 (4 H, m, ArH); δ_C 20.14 (q), 22.16 (q), 27.61 (d), 28.00 (q), 32.42 (d), 34.83 (t), 35.54 (t), 39.50 (t), 49.78 (d), 77.12 (s), 117.08 (d), 125.33 (s), 125.92 (d) and 153.14 (s).

(b) *By heating with phenylboric acid and toluene*-p-*sulfonic acid.* The phenol **26** (0.4 g, 1.6 mmol) was heated under reflux in toluene (25 cm^3) with phenylboric acid (0.19 g, 1.6 mmol) and toluene-*p*-sulfonic acid (0.13 g, 0.8 mmol) for 20 h. The product **27** was isolated in 35% yield.

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