A synthesis of 11-nor-9-ketohexahydrocannabinol[1]

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A 12-step synthesis of 11-nor-9-keto-hexahydrocannabionol (**3**) from dimethoxyolivetol (**4**) is described, together with some ancillary synthetic steps. The key step in this route is the reaction of the unsaturated dinitrile **6** with the Danishefsky diene **10**.

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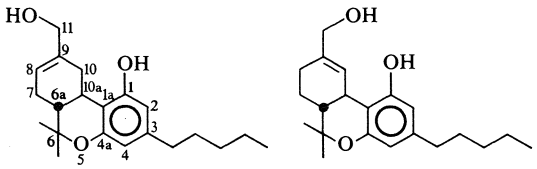
On décrit une synthèse en 12 étapes du nor-11 céto-9 hexahydrocannabionol (**3**) à partir du diméthoxyolivétol (**4**); on décrit aussi quelques étapes connexes. La réaction du dinitrile insaturé **6** avec le diène de Danishefsky **10** est l'étape principale de cette synthèse.
[Traduit par le journal]

As part of a wider project aimed at the total synthesis of a variety of metabolites of cannabinoids (1) such as the 11-hydroxylated derivatives of Δ^8 and Δ^9 THC (**1** and **2** respectively), together with the possible requirement for the labelling of such species at nonexchangeable sites (see Scheme 1), we have examined routes proceeding via 11-nor-9-ketohexahydrocannabinol **3** (2).

In this report we describe our studies towards a direct, rational approach to the total synthesis of **3**. Although the final step in the route is of modest yield only, all of the other operations are extremely efficient.



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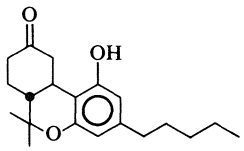

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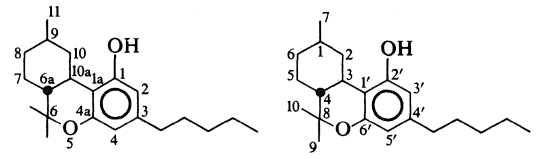
The basis strategy of our approach is outlined in Scheme 1. The key steps foreseen in such a tactic involve a Diels–Alder reaction between a coumarin and a 2-oxygenated butadiene (3). Precedent for construction of the carbon skeleton of the basic cannabinoid system by a Diels–Alder route is reported (4), but the work described does not involve incorporation of oxygen at the 9-position. In our proposal, this oxygen atom is delivered to the correct site in the form of a trapped enol in the diene synthon. Other efficient routes to the target compound (**3**) must also be noted (3, 5).

The overall pathways studied are outlined in Schemes 2 and 3. That described first, proceeding via cyanocoumarin **7***a* or **7***b*, was not amenable to the elaboration of cannabinoid-like compounds; however, a slight modification of the strategy involved enabled **3** to be prepared.

The first synthetic plan devised for the preparation of **3** is summarized in Scheme 2. The *cis*-ring junction that would be generated in the proposed Diels–Alder reaction of 2-methoxy-1,3-butadiene **8** with the cyanocoumarin **7** presents no problem since decarboxylation (after hydrolysis of the nitrile function), proceeding through an enolate, should cause equilibration to the preferred *trans*-fusion. Both the carbocyclic ring and the requisite oxygen function would be efficiently introduced via the cycloaddition process. Incorporation of the *gem*-dimethyl grouping would involve the action of two equivalents of a methyl Grignard reagent on the lactone, affording a tertiary alcohol. Under acidic conditions, cyclization ensues, yielding the pyran ring. This sequence has been successfully performed with similar substrates, although not with the

[1]Two numbering systems are in use today. One is based on the formal chemical rules for numbering of benzopyran. The second system has a biogenetic basis, regarding cannabinoids as substituted monoterpenes. The former is used exclusively in this work. The naturally occurring enantiomer (6aR, 10aR) is shown for convenience although structures of synthetic materials described herein represent racemates.



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[3]Portions of this work are taken from the M.Sc. thesis of A.H., Carleton University, 1976.

[4]Portions of this work are taken from the M.Sc. thesis of I.J., Carleton University, 1981.

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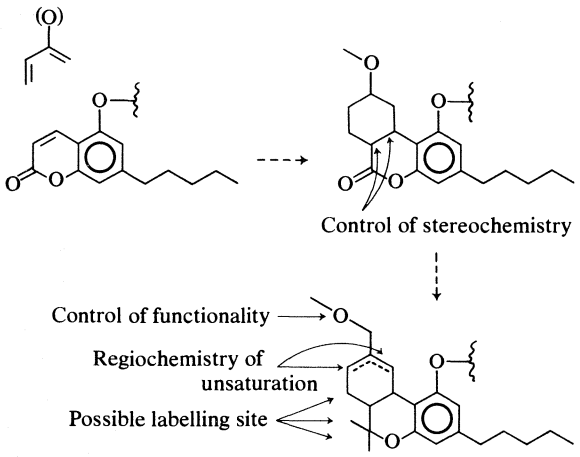


SCHEME 1. Synthetic strategy used in this study.

compounds studied in this work (For a summary of previous synthetic efforts in the cannabinoid field, see ref. 3.).

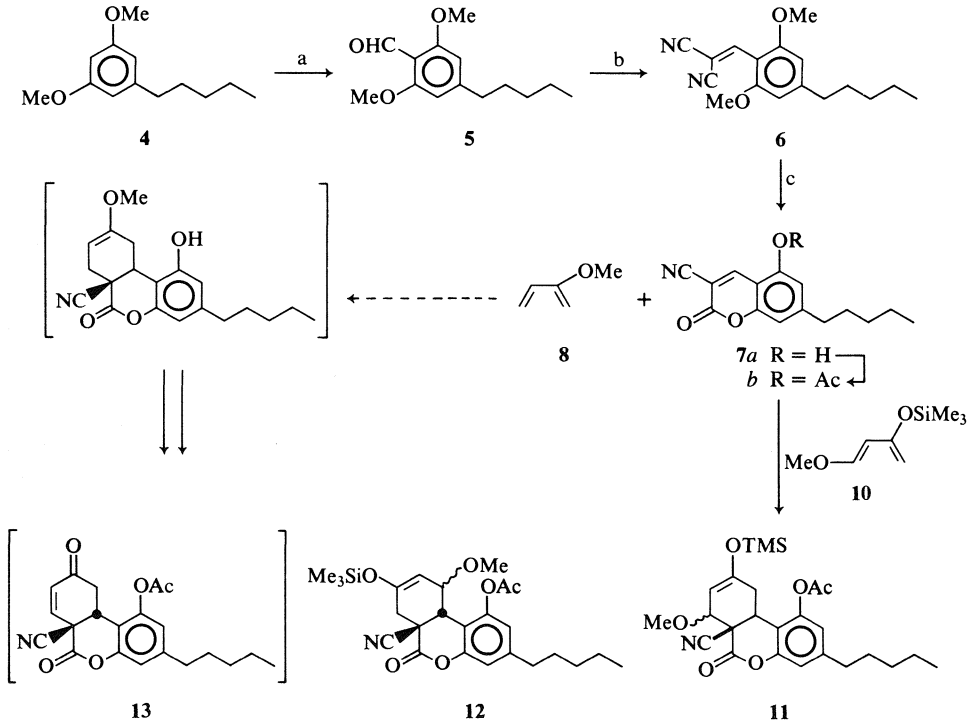
Routes towards 11-nor-9-ketohexahydrocannabinol ***3***

Olivetol dimethyl ether **4** was prepared via the two-step transformation developed by Bailey (6).

Introduction of the aldehyde function to give **5** was achieved through the known procedure (4, 7) involving metallation of **4** and reaction with *N*-methylformanilide. Addition of piperidine to a mixture of **5** and malononitrile initiated an exothermic reaction, producing a homogeneous mass (8) which after purification gave **6**. Cleavage of the methyl ethers of **6** was next undertaken. Refluxing of the dinitrile and aluminum chloride in chlorobenzene for 4 h (9) did not produce the dihydroxy analog of **6**, but instead yielded only the cyanocoumarin **7**. Formation of the lactone presumably occurred as outlined in Scheme 3.

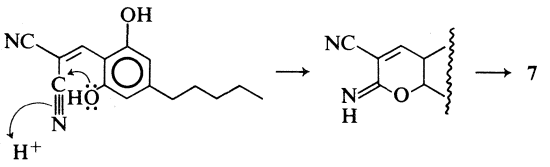
The only difficulty associated with this step occurred in larger-scale preparations, when the solid mass produced during work-up interfered with complete recovery of **7**. The cyanocoumarin **7** was considered a suitable precursor for elaboration to tricyclic material, via a cycloaddition reaction with 2-methoxy-1,3-butadiene (**8**) synthesized using the two-step method of Degraw *et al.* (10).

Heating cyanocoumarin (**7**) in the presence of the substituted butadiene (**8**) failed to produce a Diels–Alder adduct as indicated by the persistence of the nmr resonance (δ 8.56) of the highly deshielded



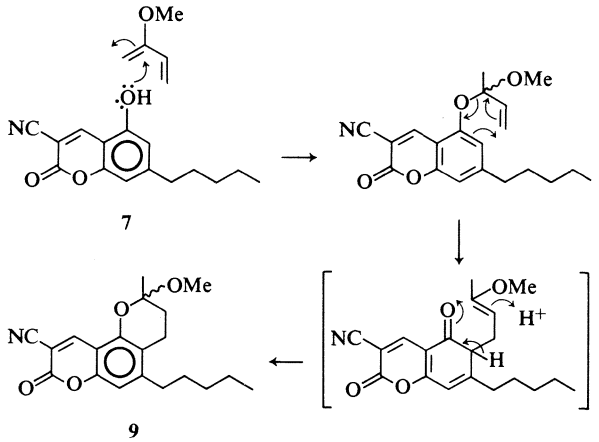
Reagents: a, *n*-BuLi, *N*-methylformanilide; b, malononitrile, piperidine; c, $AlCl_3$, chlorobenzene, reflux; d, Ac_2O,H_2SO_4

SCHEME 2



SCHEME 3

proton of the disubstituted styrene. Other features of the nmr spectrum of the product indicated that it possessed one aromatic proton (s, δ 6.76), an ether methyl group (s, δ 3.30), which was not of the enol ether variety, and another methyl group (s, δ 1.68) not coupled to other hydrogens. The ir spectrum showed no hydroxyl absorption, and the mass spectrum indicated a molecular ion of *m/e* 341. In addition, the ultraviolet (uv) absorption of the compound was in agreement with a species possessing extended conjugation to an aromatic system. All of the spectral data are in accord with structure **9**, the formation of which can be accounted for by addition of the phenol to the double bond of the diene, followed by a Claisen rearrangement as indicated in Scheme 4. Analogous processes have been cited (11).



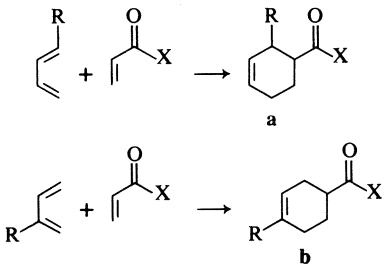
SCHEME 4

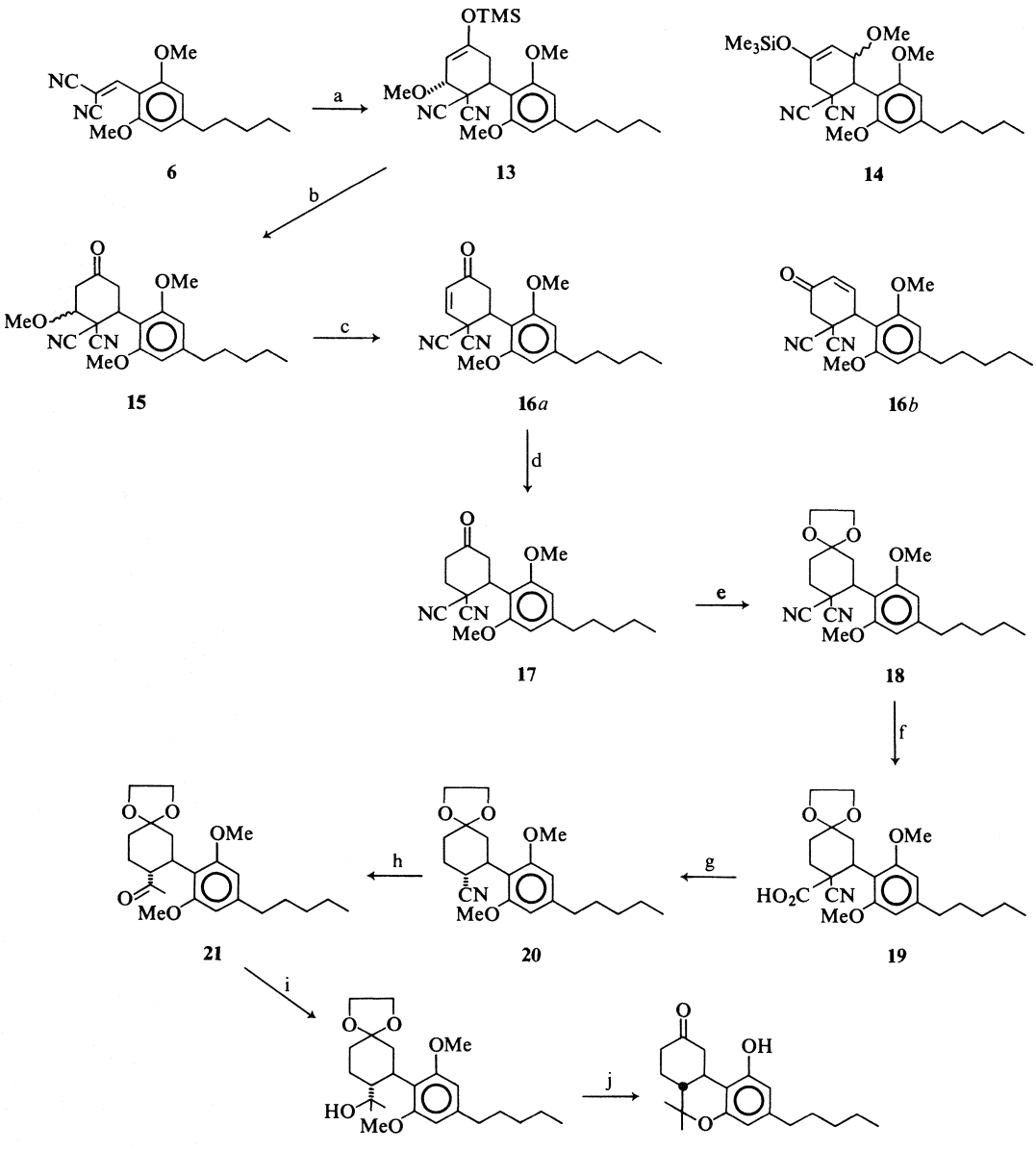
The hydroxy function of **7** was next masked as the acetate in order to block the Claisen process, and thereby prevent competition with the Diels–Alder reaction. The acetoxycoumarin **7***b* and the diene **8** resisted all efforts to carry out the cycloaddition reaction. A sealed vessel was used to avoid loss of the relatively volatile diene (bp 74–77°C), and several attempts involved Lewis acid catalysis, known to alter the facility and regioselectivity of Diels–Alder reactions (e.g. ref. 12). The lack of reactivity of this diene–dienophile combination was rather surprising, as both compounds are activated, the former by virtue of an electron-donating function and the coumarin with two electron-withdrawing groups.

At this juncture, the Danishefsky diene (13), 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (**10**), was examined in view of its ready reaction with a variety of dienophiles, exhibiting a high degree of selectivity in the orientation of addition to unsymmetrical olefins.

Refluxing a benzene solution of the diene **10** and the acetoxycoumarin **7***b* under a nitrogen atmosphere led to complete consumption of starting material as indicated by the disappearance in the nmr spectrum of the crude reaction mixture of the olefinic proton resonance at δ 8.26. Also, the ir spectrum of the product exhibited a carbonyl absorption at 1785 cm^{-1}. This Diels–Alder adduct was assigned structure **11**, a conclusion based upon consideration of the "*ortho* and *para* rules".[5] Danishefsky had found that, in all reactions of **10** studied (13), there was a high degree of selectivity in the formation of the isomer in accord with these postulates. Both possible configurations of the methoxyl substituent appear to be generated, a result attributable to competition between the *exo* and *endo* modes of approach of the reactants (14). The nmr spectrum exhibited two singlets (δ 3.57, 3.61), with intensities corresponding to a product ratio of 1.0:1.4. The formation of a diastereomeric mixture in no way affects the outcome of the synthetic route, as the asymmetric centre β to the ketone would be destroyed upon hydrolysis and elimination to give the sought after enone **13**. This conversion was the next goal of the synthesis but, contrary to the previously reported (13, 15) facile hydrolyses to α,β-unsaturated systems, this step presented unforeseen difficulties. The mild conditions (0.005 *N* HCl, THF, 0°C, 10 min) employed by Danishefsky and Kitahara (15) indicated no

[5]These rules are based on the observation that an unsymmetrically substituted diene would orient itself in adding to acrolein or acrylates to produce a predominance of the adduct *a* with a 1-substituted diene, and an excess of *b* with a group at the 3-position of the diene. In the reaction of **7***b* with **10**, both these tendencies favour formation of the positional isomer **11**, rather than **12**.





Reagents: a, diene **10**; b, HCl, MeOH, H_2O; c, *p*-toluene sulfonic acid, benzene; d, H_2, Pd/C; e, $HOCH_2CH_2OH$, *p*-TSA; f, 10 *N* NaOH/EtOH; g, NaOH, DMF, 150°C; h, MeMgI, Et_2O,6 h; i, MeMgBr; j, Ph_2PLi, THF

SCHEME 5

reaction occurring. Attempts at forcing the process with 6 *N* hydrochloric acid in methanol or other reaction conditions produced a complex reaction mixture, with no evidence of the existence of the enone **13**.

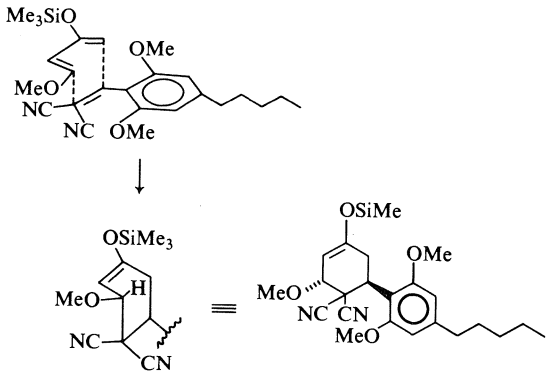
In view of these problems, which rendered this synthetic approach unattractive, the scheme was abandoned in favour of the parallel Diels–Alder process between **10** and the unsaturated dinitrile **6** (see Scheme 5).

Reaction of **6** and **10** in dry benzene at reflux caused a high yield conversion to a crystalline bicyclic species that had a proton nmr spectrum consistent with the adduct **13**, but not with the

positional isomer **14**. The benzylic methine proton appears as a doublet of doublets (J = 5, 12 Hz), coupled to the hydrogens of the allylic methylene group. In **14** a single splitting would be expected for this proton (coupled only to the allylic methine hydrogen). The large paramagnetic shift of the benzylic proton is likely due to the anisotropy of the neighbouring nitrile functions. The methine proton α to the ether oxygen atom is coupled solely to the olefinic hydrogen, providing further support for the assignment of **13** as the correct representation of the reaction product. The coupling constant of 6 Hz relates to a dihedral angle of 30 to 40° between the methine and olefinic hydrogens, indicating that the former is an equatorial substituent (i.e. the *O*-methyl group is axial). This is the configuration one would expect to arise from *exo* approach of the diene and dienophile (14) (see Scheme 6). Thus, structure **13** was assigned to the Diels–Alder adduct. This adduct was allowed to stand at room temperature for 30 min in a 5:3 mixture of acetone and 6 *N* hydrochloric acid. A β-methoxy ketone (**15**), rather than an enone, was again inferred from the spectral data. The infrared spectrum included a carbonyl absorption at 1735 cm^{-1}, and a three-proton singlet at δ 3.53 in the nmr spectrum confirmed that hydrolysis of the enol ether was not accompanied by elimination of methanol. Each methine proton β to the ketone appeared as a doublet of doublets, a result consistent with structure **15**.

Elimination of methanol to give the α,β-unsaturated ketone **16***a* was accomplished in excellent yield by refluxing **15** in benzene in the presence of *p*-toluenesulfonic acid. The ^1H nmr pattern of the olefinic protons reinforces the earlier statement that the orientation of the Diels–Alder cycloaddition was that required to generate **13**. The double bond hydrogens give rise to a pair of doublets centred at δ 6.32 and δ 6.90, with a coupling constant of 10 Hz. The alternative enone **16***b* would be expected to exhibit a more complex pattern for the resonance of the olefinic proton β to the ketone, as it would be coupled to the benzylic methine proton in addition to the neighbouring olefinic hydrogen.

A sharp six proton singlet at δ 3.82 in the proton nmr spectrum of **16***a* is a result of the methoxy groups. It is interesting to note that elimination of the aliphatic *O*-methyl substituent causes a collapse to this singlet from the two singlets seen for the enol silyl ether **13**, and the broad multiplet found with the β-methoxy ketone **15**. This variance is attributed to an increase in the ease of rotation about the inter-annular bond. Molecular models of



13

SCHEME 6

the compounds involved show that the axial methoxy substituent and the aromatic methoxyls experience severe steric interactions. Hydrogenation of **16***a* in ethanol at atmospheric pressure with palladium on charcoal as a catalyst gave dinitrile ketone **17** in a 99% yield as an unstable solid with a melting point of 54–55°C. The instability of **17** was probably due to aerial oxidation at room temperature leading to aromatization of the C-ring. Ketalization with ethylene glycol gave a colorless solid **18** in a yield of 93% (mp 104–106°C), which proved to be much more stable.

At this point cleavage of the methyl ether groups was, as anticipated, the major obstacle. In the earlier cannabinoid work by Adams *et al.* (4) this problem proved to be insurmountable.

In cannabinoid work, a variety of reagents have been used for this process (3) and recently a large variety of reagents have been reported for effective demethylation of phenol methyl ethers (16). In this study no satisfactory result was obtained on treatment of **17** or **18** with any of these reagents.

A variation in the synthetic route was next studied. Thus, heating **18** in 10 *N* sodium hydroxide and ethanol (1:1) resulted in the hydrolysis of only one nitrile group. The product **19** exhibited a molecular ion in its mass spectrum of *m/e* 417 as well as exhibiting the expected spectral data. This acid (**19**) was decarboxylated by stirring over ground sodium hydroxide in DMF at 150°C to give **20** in an 80% yield from **18**. After 2 h the decarboxylation was complete and analysis of the product **20** by gas chromatography (gc) showed that the two possible epimers about position 6a were present in a ratio of 2:3. After further heating of the reaction for an additional 8 h, the ratio had become 9:1. The thermodynamically more stable *trans*-isomer was assumed to predominate in the final product. The above reaction demonstrated that the nitrile **20** was relatively unreactive, so it appeared that demeth-

ylation might again be attempted. Demethylation of **20** could lead to the intramolecular hydrolysis of the nitrile and lactonization following a route similar to that observed in the formation of **7***a*.

When **20** was treated with a variety of reagents (16) no useful reaction was observed. Finally treatment of **20** with 30 equivalents of methylmagnesium iodide in ether at gentle reflux for 6 h formed the methyl ketone **21** in a 40% conversion and 60% yield based on recovered starting material.

The methyl ketone **21** was easily methylated with methylmagnesium bromide to give alcohol **22** in a 95% yield. This represents a 28% overall yield of **22** from dimethoxyolivetol (**4**) in eleven steps with an average yield of 89% per step.

Demethylation of alcohol **22** was accomplished following the method of Ireland and Walba (16*f*) with lithium diphenylphosphide. Acidic work-up was used to invoke cyclization and deketalization when a modest yield of ketone **3** was obtained which was identical in all respects with an authentic sample of ketone **3** (prepared following the method of Archer *et al.* (5)). Thus, a total synthetic route to ketone **3** has been completed. Although existing routes would appear better suited to large scale work (3, 5) the present route reveals some useful and interesting chemistry capable of leading to a variety of modified cannabinoids.

Experimental

Melting points were determined with a Fisher–Johns melting point block and are uncorrected. A Perkin–Elmer 237B Infracord spectrophotometer was used for recording infrared (ir) spectra. Absorptions are noted as strong (s), medium (m), weak (w), or shoulder (sh). Nuclear magnetic resonance (nmr) spectra were taken on a Varian Associates Model T-60A with deuteriochloroform solvent (unless otherwise stated), and tetramethylsilane as internal standard. The following designations are used in characterizating nmr signals: singlet (s), doublet (d), triplet (t), doublet of doublets (dd), multiplet (m), and broadened (br). Gas chromatographs were recorded using a Perkin–Elmer 990 Gas Chromatograph, with a 5.5 ft column of 3% OV-17 at 285°C, with nitrogen as the carrier gas or using a Hewlett Packard 5840B Gas Chromatograph using a 25 M, SP-2100 microcapillary column with nitrogen as the carrier gas. Mass spectra were recorded using an AEI MS12 instrument at Trent University.

Preparative hplc was done using a Waters Prep 500 with two PrepPac silica gel columns. Thin-layer and preparative thin-layer chromatography (tlc and ptlc respectively) were carried out on Merck 60 F-254 precoated silica gel plates of 0.25 mm thickness. Bands were visualized by (*i*) viewing under an ultraviolet (uv) source or (*ii*) spraying with ceric ammonium sulfate and charring the plate. Florosil (activated magnesium silicate, J. T. Baker Chemical Co., 100–200 mesh) was the adsorbent used for column chromatography.

Tetrahydrofuran (THF) was distilled from sodium and stored over 4A molecular sieves (J. T. Baker Chemical Co.) under nitrogen. Azeotropic removal of water followed by distillation afforded dry benzene which was stored over sodium. Anhydrous ether was stored under nitrogen over sodium. Anhydrous dimethylformamide was prepared by drying ACS Spec. grade solvent over molecular sieves (4A).

*((2,6-Dimethoxy-4-pentylphenyl)methylidene)malononitrile (**6**)*

Piperidine (10 mL) was added to a mixture of the 2,6-dimethoxy-4-pentylbenzaldehyde **5** (10.50 g, 44.4 mmol) and malononitrile (3.10 g, 46.9 mmol), causing the mass to become hot and homogeneous. After the red solution had cooled, it was acidified with 6 *N* hydrochloric acid, and extracted with three portions of chloroform. The combined organic solutions were washed with water (×2) and saturated aqueous sodium chloride, before being dried ($MgSO_4$) and concentrated under vacuum. Addition of a little methanol to the resultant oil, accompanied by chilling of the solution, yielded a crop of yellow crystals (2.61 g). Recrystallization from methanol afforded pure **6**, mp 64–65°C; uv: 348 nm (ε 21 500) and 203 nm (28 500); ir (KBr): 2215 (m, conjugated C≡N), 1617 (s, C=C), and 825 (m, trisubstituted C=C) cm^{-1}; nmr (100 MHz, CCl_4) δ: 0.93 (br, t, J = 6 Hz, 3H, terminal CH_3), 1.25–1.83 (m, 6H, $3CH_2$'s), 2.61 (br, t, J = 7 Hz, 2H, benzylic CH_2), 3.90 (s, 6H, $2ArOCH_3$), 6.15 (s, 2H, aromatic), 7.74 (s, 1H, olefinic CH); *m/e* (relative intensity): 284 (40), 242 (12), 241 (10), 229 (20), 228 (100), 227 (10). *Anal.* calcd. for $C_{17}H_{20}N_2O_2$: C 71.81, H 7.09, N 9.85; found: C 71.86, H 7.05, N 9.92.

Chromatography of the mother liquors on silica gel (elution with benzene) gave a further 8.38 g of product. The total yield of **6** was 87%.

*5-Hydroxy-2-oxo-7-pentyl-2H-1-oxanapthalene-3-carbonitrile (**7***a*)

Employing the demethylation procedure of Bruce and Sutcliffe (9*b*), the dinitrile **6** (1.10 g, 3.87 mmol) was dissolved in chlorobenzene (125 mL), aluminum chloride (3.7 g, 28 mmol) was added to the solution, and the reaction mixture was refluxed under a nitrogen atmosphere for 3.5 h. 2 *N* Hydrochloric acid (100 mL) was added to the cooled flask, and the yellow solid present was removed by filtration. The aqueous layer of the filtrate was separated, and extracted with ether (×4). The pooled ethereal extracts were washed with water and aqueous sodium chloride (saturated), after which this organic solution was added to the chlorobenzene layer, previously washed in the same manner. Drying over $MgSO_4$ and evaporation of solvent afforded **7***a* as a yellow powder (570 mg).

The filter cake separated above was extracted with ether (×4). Work-up (as above) of the combined organic solutions produced a further 381 mg of material, which was combined with the product already isolated. The pooled material (951 mg, 96%) was homogeneous by tlc ($CHCl_3$/EtOAc, 80:20). Ultraviolet: 340 (ε 37 500), 250 (9 000), and 209 nm (28 000); ir (neat): 3345 (m, OH), 2230 (w, conjugated C≡N), 1695 (s, C=O), and 1625 (m, C=C) cm^{-1}; ir (KBr): 3270 (sh), 3205 (s, OH), 2255, 2225 (m, conjugated C≡N), 1745, 1705 (s, C=O), and 1635 (s, C=C) cm^{-1}; nmr (100 MHz) δ: 0.89 (br t, J = 6 Hz, 3H, terminal CH_3), 1.13–1.83 (m, 6H, $3CH_2$'s), 2.65 (br t, J = 7 Hz, 2H, benzylic CH_2), 6.69 (m, 2H, aromatic), and 8.61 (s, 1H, olefinic CH); *m/e* (relative intensity): 257 (33), 215 (10), 214 (11), 202 (17), 201 (100), 200 (14). The analytical sample (mp 179–181°C) was prepared by sublimation (170–175°C/0.1 Torr). Compound **7***a* recrystallized with difficulty; benzene was the most effective solvent. *Anal.* calcd. for $C_{15}H_{15}NO_3$: C 70.02, H 5.88, N 5.44; found: C 70.08, H 5.88, N 5.45.

*7,8-Dihydro-6-methoxy-6-methyl-2-oxo-9-pentyl-2H,6H-1,5-dioxaphenanthrene-3-carbonitrile (**9**)*

The cyanocoumarin **7***a* (202 mg, 0.785 mmol), 2-methoxy-1,3-butadiene (**8**, 143 mg, 1.70 mmol), and hydroquinone (53 mg) were combined with xylenes (50 mL) in a sealed pressure vessel, then heated to 165°C (sand bath). After 70 h at this temperature,

the reaction mixture was cooled and concentrated *in vacuo*. The residue was chromatographed on silica gel. From the early benzene–ether (95:5) fractions was isolated **9** (193 mg, 72%), as white needles. Recrystallization from methanol gave the analytical sample, mp 160–160.5°C; uv: 342 (ε 18 500), 250 (4 000), and 209 nm (35 000); ir (KBr): 2855 (m, $ROCH_3$), 2230 (m, conjugated C≡N), 1745 (s, C=O), and 1625 (s, C=C) cm^{-1}; nmr (100 MHz) δ: 0.86 (br t, J = 6 Hz, 3H, terminal CH_3), 1.2–1.7 (m, 6H, $3CH_2$'s), 1.68 (s, 3H, CH_3COR), 2.65 (br t, J = 7 Hz, 2H, benzylic CH_2), 3.30 (s, 3H, OCH_3), 6.76 (s, 1H, aromatic), 8.56 (s, 1H, olefinic CH); *m/e* (relative intensity): 341 (100), 310 (57), 309 (37), 204 (42), 270 (23), 269 (92), 252 (31), 240 (24), 214 (35), 213 (24). *Anal.* calcd. for $C_{20}H_{23}NO_4$: C 70.36, H 6.79, N 4.10; found: C 70.43, H 6.69, N 4.04.

*5-(Ethanoyloxy)-2-oxo-7-pentyl-2*H*-1-oxanaphthalene-3-carbonitrile (7*b*)*

The cyanocoumarin **7***a* (1.25 g, 4.86 mmol) was covered with distilled acetic anhydride (12.41 g, 122 mmol). Concentrated sulfuric acid (0.5 mL) was added to the mixture, which immediately became hot, forming a tan paste. This material was dissolved in chloroform, and allowed to stand for 0.5 h before water was added. The aqueous layer was separated, and extracted with chloroform (×3). These extracts were combined with the original chloroform phase, which was then washed with water (×2) and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated *in vacuo*, yielding **7***b* (1.41 g, 97%). Three recrystallizations from methanol afforded the analytical sample, mp 155–155.5°C; uv: 318 (ε 15 500) and 203 nm (32 500); ir (KBr): 2235 (m, conjugated C≡N), 1777 (s, aryl acetate), 1738 (s, C=O), and 1627 (s, C=C) cm^{-1}; nmr (100 MHz) δ: 0.90 (br, t, J, 6 Hz, 3H, terminal CH_3), 1.17–1.84 (m, 6H, $3CH_2$'s), 2.45 (s, 3H, acetate), 2.73 (t, J = 7 Hz, 2H, benzylic CH_2), 7.03 (br s, 2H, aromatic), and 8.26 (s, 1H, olefinic CH); *m/e* (relative intensity): 299 (27), 258 (19), 257 (100), 215 (9), 214 (10), 202 (15), 201 (98), 200 (14). *Anal.* calcd. for $C_{17}H_{17}NO_4$: C 68.22, H 5.72, N 4.68; found: C 68.07, H 5.63, N 4.58.

Attempted reaction of **7**b *with 2-methoxy-1,3-butadiene (**8**)*

Attempt 1

2-Methoxy-1,3-butadiene (**8**, 19 mg, 0.23 mmol), **7***b* (68 mg, 0.23 mmol), and hydroquinone (22 mg) were dissolved in 50 mL of xylenes, and heated in a sealed vessel at 160–165°C. After 87 h, the flask was cooled to room temperature and the contents were concentrated at reduced pressure to give a solid, which was recrystallized from methanol. The spectral characteristics of the crystalline substance were identical with those of **7***b*.

Attempt 2

A solution of **8** (16.5 mg, 0.20 mmol) and **7***b* (62 mg, 0.21 mmol) in dry benzene (25 mL) was heated (150–152°C) in a sealed vessel for 18 h. Removal of solvent *in vacuo* afforded pure **7***b* with the same physical properties previously reported.

Attempt 3

To a solution of **7***b* (28.9 mg, 0.097 mmol) in anhydrous ether (25 mL), stirred under a nitrogen atmosphere, was added boron trifluoride etherate (40 μL, 0.33 mmol), followed after 15 min by the diene **8** (119 mg, 1.41 mmol). After 72 h at ambient temperature, the reaction mixture was poured into water. Extraction with chloroform (×3), washing of the combined extracts with water and aqueous sodium chloride (saturated), drying of the organic solution ($MgSO_4$), and evaporation of solvent gave a white solid that was identical with **7***b* in all respects.

Attempt 4

The reaction was repeated as in Attempt 3, except that it was carried out in dry benzene rather than ether. The quantities of the reactants were: **7***b* (21.5 mg, 0.072 mmol), **8** (90 mg, 1.1 mmol), boron trifluoride etherate (30 μL, 0.24 mmol). Again, only the starting coumarin was recovered.

*4-(Ethanoyloxy)-4b,5,8,8a-tetrahydro-8-methoxy-9-oxo-2-pentyl-6-(trimethylsiloxy)-9*H*-10-oxaphenanthrene-8a-carbonitrile (**11**)*

The acetoxycoumarin **7***b* (301 mg, 1.01 mmol) and the diene **10** (239 mg, 1.39 mmol) were dissolved in benzene (60 mL), then refluxed under nitrogen for 65 h. The cooled solution was concentrated *in vacuo* to give 458 mg (99%) of an oil, which eventually solidified on standing. Although tlc ($CHCl_3$) showed only one major spot, recrystallization from various solvent systems proved difficult. The product (**11**), mp 119–125°C (dec.), exhibited the following physical properties: ir (neat): 2245 (w, C≡N), 1785 (s, C=O), 1775 (s, aryl acetate), and 1662 (m, enol ether) cm^{-1}; nmr (100 MHz) δ: 0.23 (s, 9H, $OSi(CH_3)_3$), 0.94 (br, t, J = 6 Hz, 3H, terminal CH_3), 1.21–1.80 (m, 6H, $3CH_2$'s), 2.39 (s, 3H, acetate), 2.64 (br t, J = 7.5 Hz, 2H, benzylic CH_2), 2.4–2.9 (obscured m, 2H, allylic CH_2), 3.57, 3.61 (two s, ratio 1.0:1.4, 3H total, OCH_3), 3.83 (dd, J = 7 Hz, J' = 11 Hz, 1H, benzylic CH), 4.55 (m, 1H, $CHOCH_3$), 5.14 (m, 1H, olefinic CH), and 6.84 (m, 2H, aromatic); *m/e*: 399 ($M^+ - 72$) (relative intensity 22), 358 (24), 357 (100), 325 (10), 301 (29), 299 (15), 258 (12), 257 (40), 201 (35).

*2-(2,2-Dicyano-3-methoxy-5-(trimethylsiloxy)-4-cyclohexenyl)-1,3-dimethoxy-5-pentylbenzene (**13**)*

A mixture of the dinitrile **6** (515 mg, 1.81 mmol) and the diene **10** (480 mg, 2.79 mmol), in 50 mL of dry benzene, was refluxed under nitrogen for 2 h. Evaporation of the cooled solution left **13** as a solid (817 mg, 99%), which was recrystallized from hexanes. Two further recrystallizations afforded the analytical sample, mp 118.5–119.5°C; ir (KBr): 2240 (w, C≡N), 1655 (s, enol ether), and 1615 (s, C=C) cm^{-1}; nmr (100 MHz) δ: 0.25 (s, 9H, $OSi(CH_3)_3$), 0.91 (br t, J = 6 Hz, 3H, terminal CH_3), 1.23–1.81 (m, 6H, $3CH_2$'s), 2.23 (dd, J = 5 Hz, J' = 18 Hz, 1H, allylic CH_2 proton), 2.58 (t, J = 7.5 Hz, 2H, benzylic CH_2), 2.99 (dd, J = 12 Hz, J' = 18 Hz, 1H, allylic CH_2 proton), 3.58 (s, 3H, $ROCH_3$), 3.81 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 4.30 (d, J = 6 Hz, 1H, $CHOCH_3$), 4.52 (dd, J = 5 Hz, J' = 12 Hz, 1H, benzylic CH), and 6.38 (s, 2H, aromatic); *m/e* (relative intensity): 456 (12), 384 (15), 353 (11), 285 (10), 284 (42), 242 (13), 234 (25), 229 (17), 228 (100), 227 (12). *Anal.* calcd. for $C_{25}H_{36}N_2O_4Si$: C 65.75, H 7.95, N 6.13; found: C 65.74, H 7.91, N 6.09.

*2-(2,2-Dicyano-3-methoxy-5-oxocyclohexyl)-1,3-dimethoxy-5-pentylbenzene (**15**)*

To an acetone solution (50 mL) of the adduct **13** (724 mg, 1.50 mmol) was added 6*N* hydrochloric acid (30 mL). The solution was allowed to stand at room temperature for 45 min before the organic solvent was removed *in vacuo*. Work-up of the residual liquid yielded the β-methoxy ketone **15** (577 mg, 94%), of sufficient purity (tlc ($CHCl_3$/EtOAc, 80:20)) for use in the next synthetic step. Chromatography on silica gel gave, in the benzene/ether (99:1) fractions, pure **15**, from which the analytical sample was obtained by evaporative distillation at 115–120°C (0.1 Torr); ir (neat): 2240 (w, C≡N) and 1735 (s, C=O) cm^{-1}; nmr (100 MHz) δ: 0.91 (br t, J = 6 Hz, 3H, terminal CH_3), 1.24–1.81 (m, 6H, $3CH_2$'s), 2.59 (t, J = 7.5 Hz, 2H, benzylic CH_2), 2.73–3.14 (m, 4H, CH_2's α to carbonyl), 3.53 (s, 3H, $ROCH_3$), 3.61–3.86 (m, 6H, $2ArOCH_3$'s), 4.03 (dd, J = 5 Hz, J' = 8 Hz, 1H, $CHOCH_3$), 4.68 (dd, J = 5 Hz, J' = 7 Hz, 1H, benzylic CH), and 6.39 (br s, 2H, aromatic); *m/e* (relative intensity): 384 (75), 354 (13), 353 (49), 328 (10), 261 (10), 251 (10), 236 (10), 235 (57), 234 (100), 228 (14), 221 (13). *Anal.* calcd. for $C_{22}H_{28}N_2O_4$: C 68.73, H 7.34, N 7.29; found: C 68.59, H 7.46, N 7.27.

*2-(2,2-Dicyano-5-oxo-3-cyclohexenyl)-1,3-dimethoxy-5-pentylbenzene (**16**a)*

The ketone **15** (577 mg, 1.50 mmol) was refluxed in benzene (70 mL) under nitrogen, in the presence of a large excess of

p-toluenesulfonic acid (723 mg, 3.80 mmol). After 2.5 h, water was added to the cooled reaction mixture. The benzene layer was separated, washed with water (×3) and aqueous sodium chloride (saturated), dried ($MgSO_4$), and evaporated to a white crystalline solid (481 mg, 91%). In chromatographing the product on silica gel, **16***a* (mp 84–87°C) was eluted with benzene. As recrystallization proved to be troublesome, the analytical sample was prepared by high-vacuum sublimation (134°C/0.1 Torr), ir (KBr): 2250, 2225 (w, C≡N), and 1695 (s, conjugated C=O) cm^{-1}; nmr (100 MHz) δ: 0.93 (br t, J = 6 Hz, 3H, terminal CH_3), 1.22–1.83 (m, 6H, $3CH_2$'s), 2.61 (br t, J = 7 Hz, 2H, benzylic CH_2), 2.78–2.96 (m, 2H, CH_2 α to carbonyl), 3.82 (s, 6H, $2ArOCH_3$'s), 4.52–4.75 (m, 1H, benzylic CH), 6.32 (d, J = 10 Hz, 1H, olefinic CH α to carbonyl), 6.41 (s, 2H, aromatic), and 6.90 (d, J = 10 Hz, 1H, olefinic CH β to carbonyl); *m/e* (relative intensity): 352 (26), 310 (5), 284 (8), 235 (22), 234 (100), 228 (17), 178 (28), 177 (8). *Anal.* calcd. for $C_{21}H_{24}N_2O_3$: C 71.57, H 6.86, N 7.95; found: C 71.65, H 6.72, N 7.88.

2-(2,2-Dicyano-5-oxocyclohexyl)-1,3)-dimethoxy-5-pentylbenzene (17)

The enone **17** (1.90 g, 5.4 mmol) in ethanol (250 mL) over 10% palladium on charcoal (50 mg) was stirred under hydrogen for 6 h. Filtration through Celite and concentration yielded a yellow oil. Column chromatography on Florisil (benzene) gave **17** as an unstable white solid (1.90 g, 99%), mp 54–55°C; ir ($CHCl_3$): 2240 (w, C≡N), 1710 (s, C=O) cm^{-1}; nmr δ: 0.90 (br t, J = 6 Hz, 3H, terminal CH_3), 1.2–1.8 (m, 7H, $4CH_2$'s), 2.60 (br t, J = 8 Hz, 2H, benzylic CH_2), 2.70–3.25 (m, 4H, $2CH_2$'s, α to carbonyl), 3.80 (s, 6H, $2ArOCH_3$'s), 4.50 (t, J = 6 Hz, 1H, benzylic CH), and 6.40 (s, 2H, aromatic); *m/e* (relative intensity): M^+ 354 (81), 324 (100), 298 (29), 262 (41), 234 (95), 221 (47), 178 (62), 91 (35). *Anal.* calcd. for $C_{21}H_{26}N_2O_3$: C 71.16, H 7.39, N 7.90; found: C 71.05, H 7.41, N 7.72.

2-(2,2)Dicyano-5-ethylenedioxycyclohexyl)-1,3-dimethoxy-5-pentylbenzene (18)

Ketone **17** (1.90 g, 5.4 mmol), ethylene glycol (1.15 g, 18.5 mmol), and *p*-toluenesulfonic acid (0.2 g) were refluxed in benzene (100 mL) for 4 h with a Dean–Stark trap fitted. The reaction mixture was cooled and the solvent removed *in vacuo*. Chromatography on Florisil (benzene) yielded a yellow oil which was crystallized from hexane to give **18** (1.98 g, 93%) as a colorless solid, mp 104–106°C; ir (KBr): 2250 (w, C≡N) cm^{-1}; nmr δ: 0.90 (br t, J = 6 Hz, 3H, terminal CH_3), 1.20–2.30 (m, 12H, $6CH_2$'s), 2.50 (br t, J = 6 Hz, 2H, benzylic CH_2), 3.80 (s, 6H, $ArOCH_3$), 3.95 (4H, 2 ketal CH_2's), 4.20 (dd, J = 3 Hz, J' = 14 Hz, 1H, benzylic CH), 6.40 (s, 2H, aromatic); *m/e* (relative intensity): 398 (68), 305 (20), 228 (13), 178 (15), 165 (31), 164 (93), 99 (24), 86 (100). *Anal.* calcd. for $C_{23}H_{30}N_2O_4$: C 69.32, H 7.59, N 7.03; found: C 69.11, H 7.52, N 7.01.

2(2-Cyano-5-ethylenedioxy-2-cyclohexylcarboxylic acid)-1,3-dimethoxy-5-pentylbenzene (19)

To a solution of ketal (**18**) (1.07 g, 2.7 mmol) in ethanol (200 mL) was added 10 *N* aqueous sodium hydroxide (200 mL). The mixture was refluxed for 20 h. The organic solvent was removed *in vacuo* and the aqueous residue was cooled to below 0°C. The solution was acidified to pH 3 by dropwise addition of *concentrated* hydrochloric acid, maintaining the temperature below 5°C. The aqueous layer was extracted with ether (×3) using ice to maintain the temperature at 0°C. The combined organic layers were dried ($MgSO_4$) and concentrated to give acid **19** as a white foam (1.05 g, 94%). Analysis of the product on tlc (ethyl acetate) showed one trace impurity which later proved to be **20**. The physical properties exhibited were ir (KBr): 3200 (s, acidic OH), 2240 (w, C≡N), 1750, 1720 (acid, C=O) cm^{-1}; nmr δ: 0.90 (br t, J = 6 Hz, terminal CH_3), 2.60 (br t, J = 6 Hz, 2H, benzylic CH_2), 3.80 (s, 6H, a $ArOCH_3$'s), 3.95 (s, 4H, $2CH_2$'s of ketal), 6.40 (s, 2H), aromatic, variable, D_2O exchangeable (s or br s, 1H, acid OH); *m/e* (relative intensity): M^+ 417 (13), 373 (23), 315 (32), 234 (14), 183 (55), 139 (58), 86 (100).

2(2-Cyano-5-ethylenedioxycyclohexyl)-1,3-dimethoxy-5-pentylbenzene (20)

A stirred solution of acid **19** (555 mg, 1.3 mmol) in 100 mL of dimethylformamide was stirred at reflux over ground sodium hydroxide (2 pellets) under a nitrogen atmosphere for 8 h. The reaction mixture was cooled and poured into water (300 mL). The mixture was cooled to 0°C, acidified with dilute hydrochloric acid, and then extracted with ether (×3, 200 mL). The combined extracts were washed with water (×3), dried ($MgSO_4$), and concentrated *in vacuo*. Filtration through Florisil (20 g; ethyl acetate/benzene, 2:98) afforded mononitrile **20** (435 mg, 88%) as a clear oil; ir (neat): 2225 (m, C≡N) cm^{-1}; nmr δ: 0.90 (br t, J = 6 Hz, 3H, terminal CH_3), 2.60 (br t, H = 6 Hz, 2H, benzylic CH_2), 3.80 (s, 6H, $2ArOCH_3$), 4.00 (s, 4H, $2CH_2$'s of ketal), 6.40 (s, 2H, aromatic); *m/e* (relative intensity): M^+ 373 (51), 342 (12), 329 (15), 305 (40), 285 (48), 140 (10), 139 (94), 99 (31), 86 (100). *Anal.* calcd. for $C_{22}H_3NO_4$: C 70.75, H 8.37, N 3.75; found: C 70.51, H 8.17, N 3.54.

2(2-Ethyloxy-5-ethylenedioxycyclohexyl)-1,3-dimethoxy-5-pentylbenzene (21)

To oven dried magnesium turnings (0.162 g, 6.7 mmol) covered with anhydrous ether in an oven dried flask, fitted with a condenser, under a dry nitrogen atmosphere, was added methyl iodide (1.04 g, 7.3 mmol) in anhydrous ether (15 mL) via syringe. After 10 h, mononitrile **20** was added to the ice-cooled Grignard reagent. The solution was gently refluxed for 6 H. The reaction was then cooled in an ice bath and saturated aqueous ammonium chloride (10 mL) followed by water (10 mL) were added. After separation the aqueous layer was extracted with ether (×2). The combined ether layers were dried ($MgSO_4$) and concentrated *in vacuo*. Preparative tlc (ethyl acetate/benzene, 10:90) afforded the methyl ketone (28 mg, 40%) as a clear oil, and starting nitrile (18 mg). This represents a yield of 60% based on recovered starting material; ir (neat): 1700 (s, C=O) cm^{-1}; nmr δ: 0.90 (br t, J = 6 Hz, 3H, terminal CH_3), 1.90 (s, 3H, methyl ketone), 3.85 (s, 6H, $2ArOCH_3$'s), 4.00 (s, 4H, 2 ketal CH_2's), 6.40 (s, 2H, aromatic); *m/e* (relative intensity): M^+ 390 (24), 359 (39), 347 (12), 305 (21), 289 (10), 245 (12), 221 (9), 156 (22), 139 (9.4), 124 (12), 99 (31), 86 (100). *Anal.* calcd. for $C_{23}H_{34}O_5$: C 70.74, H 8.78; found: C 70.25, H 9.39.

2(2(1-Hydroxyisopropyl)-5-ethylenedioxycyclohexyl)-1-3-dimethoxy-5-pentylbenzene (22)

To a stirred, ice-chilled solution of methyl ketone **21** (51 mg, 0.13 mmol) in anhydrous ether (20 mL), under argon, was added methyl magnesium bromide (0.1 mL, 0.6 mmol) and the solution was refluxed 1 h. The reaction was cooled in an ice bath and saturated aqueous ammonium chloride (10 mL) was added dropwise, followed by water. The mixture was separated and the aqueous layer was extracted with ether (×2). The combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo* before ptlc (ethyl acetate/benzene, 10:90) gave 50 mg of alcohol **22** (95%) as a clear oil; ir (neat): 3500 (OH) cm^{-1}; nmr δ: 0.90 (br t, J = 6 Hz, 3H, terminal CH), 1.10 (s, 6H, 2CH's α to alcohol), 3.85 (s, 6H, $2ArOCH_3$), 6.40 (br s, 2H, aromatic); *m/e* (relative intensity): M^+ 406 (10), 305 (30), 221 (25), 178 (10), 154 (62), 152 (10), 139 (15), 99 (22), 86 (100).

11-Nor-9-ketohexahydrocannabinol (3)

To a solution of diphenylphosphine (0.05 mL, 0.29 mmol) in dry THC (2.5 mL) was added 0.25 mL (0.40 mmol) of cold 1.6 *M* *n*-butyllithium – hexane solution via syringe. The reaction was stirred for 15 min before the addition of alcohol **22** (32 mg, 0.08 mmol) in dry THF (2.5 mL) via syringe. The solution was

stirred at room temperature for 2 h before being added to 20 mL of 5% hydrochloric acid and stirred for an additional 2 h. The aqueous mixture was extracted with ether (×3) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Separation by ptlc (ethyl acetate/benzene, 10:90) afforded a material **16** (2 mg) identical in all respects to an authentic sample of **1**, prepared by M. Guiver following the method of Archer *et al.* (5).

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