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Development of Agonists, Partial Agonists and Antagonists in the Δ^8-Tetrahydrocannabinol Series

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Abstract: Synthetic sequences were developed (Schemes 1 to 6) for the syntheses of various Δ^8-THC analogs with either a rigid acetylenic linkage or a *cis*-double bond in different positions in the side chain. Various alkyne and *cis*-ene-Δ^8-THC analogs were also synthesized carrying a functional group such as a cyano, isothiocyano, azido, amino, nitro, bromo, hydroxy, fluoro and a methoxy group at the chain terminal. The *in vitro* and *in vivo* pharmacology of these unique analogs have provided several ligands which are partial agonists or antagonists of the cannabinoid receptor CB1. The 2'-position in the side chain was found to be optimum for activity.

Keywords: Cannabinoids; Alkynes; Alkenes; Pharmacologically active compounds

Introduction

It is well established that the active constituent of marijuana is Δ^9-tetrahydrocannabinol (THC) which produces its central nervous system (CNS) effects by interaction with a G-protein-coupled receptor CB1[1]. The endogenous ligand for this CB1 receptor has been identified as anandamide, an arachidonic acid derivative[2]. Another cannabinoid subtype receptor CB2 has been identified which is expressed mainly in the periphery (macrophages in the spleen) and its ligand is shown to be 2-arachidonyl glycerol (2-Ara-Gl). 2-Ara-Gl has also been identified in the brain[3-6]. The current increase in interest in the cannabinoid field can be attributed to recent reports on the biochemical role of these two ligands[7-10]. Other cannabimimetics are known which have diverse chemical structures, such as the non-classical THC's (e.g. CP 55,940)[11], indole derivatives (e.g. Win 55,212-2)[12] and the antagonists SR141716A and SR144528 for CB1 and CB2 respectively which are pyrazole derivatives[13,14]. This raises the intriguing question; how do such a myriad of chemical structures interact with the same receptor? There is evidence that suggests that the ligand-receptor interaction is not identical in every class of ligands. It is very likely that further SAR studies of the lipophilic side chain of THCs which plays an extraordinary role in the binding affinity and efficacy of these compounds[15,16] will lead to clarification of the interaction of the CB1 receptor with the cannabinoids. Some time ago, as part of an ongoing program on the modification of side chain of THCs, we reported[17] on some 2'-yne-Δ^8-THC analogs as a preliminary exploration of this series. All analogs showed high binding affinities (4-11 nM) and some showed low *in vivo* potency suggesting a compound with antagonist properties. Encouraged by these results, we designed similar compounds, inserting the rigid acetylenic

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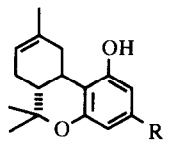
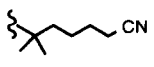
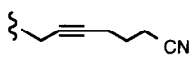
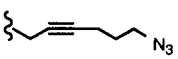
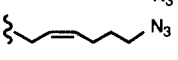
linkage throughout the side chain or replacing this region by a *cis* double bond, thus introducing a bend or an angle and confering different degrees of restricted rotation in the chain. In addition we incorporated functional groups at the chain terminal which are known to influence other classes of ligands[18]. From this series of compounds some unique ligands have emerged which are either partial agonists or show antagonist properties. This represents the first example of a THC agonist being transformed to a partial agonist/antagonist by manipulation of the side chain. A few examples are given in Table 1. We have recently reported[19] the detailed pharmacological evaluation (*in vivo*) of these compounds and the efficacy of some of the analogs in the GTPγS binding assay[20]. Furthermore in *in vitro* studies, compound **21** (O-823) was shown[21] to be a potent partial agonist (CB1) in mouse vasa deferentia, and in the guinea-pig myenteric plexus preparation it antagonized Win 55,212-2 and CP 55,940 with a K_D value of 0.27 nM. Similarly **23** (O-1184) behaved as an antagonist (CB1) in the guinea-pig myenteric plexus preparation[22]. At human CB1 and CB2 receptors, **23** was found to be a partial agonist at CB1 but showed inverse cannabimimetic effects at CB2 receptors. In CB2 cells, **23** enhanced cyclic AMP production whereas **34** (O-1238) behaved as a weak partial agonist[23].

Table 1. Effect on the Pharmacological Activity of THCs by Manipulation of their Side Chain



Compound No.	R	Ki(nM) CB1	in vivo Tetrad Tests	GTPγS
O-581		0.36 ± 0.14	agonist	-
21 (O-823)		0.77 ± 0.05	inactive	antagonist
23 (O-1184)		2.14 ± 0.44	partial agonist	antagonist
34 (O-1238)		3.32 ± 0.59	agonist	partial agonist

The differences observed between **23** and **34** suggest that, although increasing the rigidity of the side chain of THCs has little effect on CB1 or CB2 (9.2 nM) receptor affinity, it can markedly affect the magnitude or direction of the changes initiated by such compounds at cannabinoid receptors. This provides a lead for the development of a novel class of antagonists that will block the actions of both CB1 and CB2 receptor agonists[23].

In summary the biological evaluation of these analogs has provided several conclusions which are noteworthy for SAR studies, e.g. (a) several high affinity acetylenic derivatives, especially with a cyano substitution, were partial agonists or were inactive in the tetrad tests; (b) some of these low efficacy high affinity ligands elicited antagonist activity; (c) the 2'-position for the acetylene/*cis* double bond was found to be optimum for activity; (d) none of the -ynyl analogs studied (**19**, **21**, **23**, **27**) stimulated GTPγS binding and they antagonized the stimulatory effects of cannabinoid receptor agonists; (e) the -enyl compounds in general showed higher potency than the corresponding

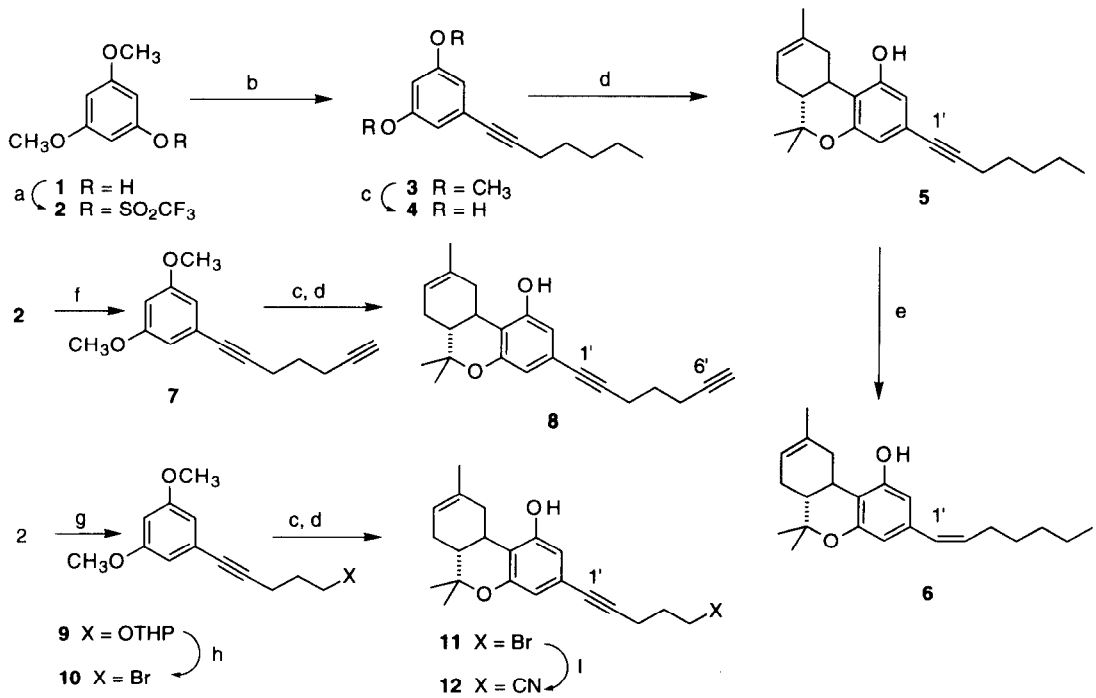
acetylene analogs in the mouse tetrad tests, but in the GTPγS binding assay all the -enyl compounds tested (**32-34**) stimulated binding, acting as partial agonists.

This series of THC analogs is important and unique and in this paper we describe the development of synthetic routes to these compound.

Results

The THCs discussed in this paper were prepared by standard synthetic methodology (see the reaction schemes and the Experimental Section for the precise synthetic procedures used to prepare each THC). In general, this involved synthesizing the appropriate resorcinol precursors (*i.e.*, possessing the side chains desired for the THCs in the 5-position of the resorcinol), followed by condensation[24] with *cis-p*-menth-2-ene-1,8-diol to give a mixture of isomeric products from which the desired THCs were isolated by silica gel chromatography. In a few cases,the condensation product i.e. the Δ^8-THC derivative was merely an intermediate in the synthesis of the desired product, and in that case further reactions were performed on the condensation product with/without protection of the phenol. The resorcinol precursors were synthesized in a protected form, as their bismethyl ethers, and then

Scheme 1

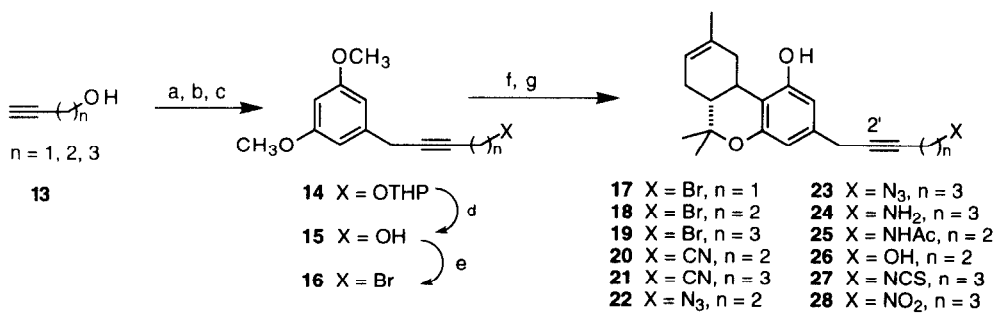


(a) Tf_2O, pyridine, CH_2Cl_2, 0° C, 1h, 70%; (b) 1- heptyne, $Pd(PPh_3)_4$, piperidine, 80° C, 2h, 70%; (c) BBr_3, CH_2Cl_2, -78°→25° C, 1h, 80%; (d) p-menth-2-ene-1,8-diol, TsOH, C_6H_6, 80° C, 2h, 5%; (e) Lindlar catalyst, H_2, 19%; (f) 1,6-heptadiyne, $Pd(PPh_3)_4$, piperidine, 80° C, 2h, 50%; (g) $Pd(PPh_3)_4$, piperidine, O-tetrahydropyranyl-4-pentyn-1-ol, 80° C, 2h, 90%; (h) CBr_4, PPh_3, CH_2Cl_2, 0°→25° C, 12h, 55%; (i) NaCN, DMSO, 50° C, 3h, 70%.

deprotected (demethylated) with BBr_3[25] before condensing with menthenediol to give the THC analogs. During the synthesis, low yields were encountered on several occasions especially during the formation of the THC ring system. Low yields during this step are well known in the cannabinoid field[17,24] but we stress that in this study, no attempt was made to optimize the yields since the primary objective was to obtain the target compounds in sufficient quantity and of high purity, for biological testing. The given yields of target compounds relate to GC pure materials only.

1'-Alkyne-Δ^8-THC analogs (**5**, **8** and **12**) were synthesized (Scheme **1**) from 3,5-dimethoxyphenol **1** by activation of the phenol as the triflate **2**[26] and carrying out the coupling[27] with the appropriate yne-compound in the presence of Pd° as a catalyst. Thus treatment of **2** with 1-heptyne gave **3**. It is noteworthy that the synthesis of **3** was reported by Busch-Petersen et al.[28] albeit by a different route. Ether cleavage with BBr_3[25], followed by acid catalyzed condensation with *cis-p*-menth-2-ene-1,8-diol, according to our procedure[24], furnished the target THC analog **5**. Similarly **2** formed **7** with 1,6-heptadiyne, which was transformed to the THC analog **8** following the same sequence as used in the conversion of **3** to **5**. Compound **9** was synthesized similarly from **2** and was directly converted[29] to the bromo derivative **10** using $CBr_4/PPh_3/CH_2Cl_2$. Intermediate **10** was then transformed to the THC analog **11** as described in the formation of **5** from **3**. Treatment of **11** with NaCN gave analog **12**. The *cis*-alkene analog **6** was prepared from the corresponding alkyne **5** by partial reduction, using Lindlar's catalyst.[30]

Scheme 2

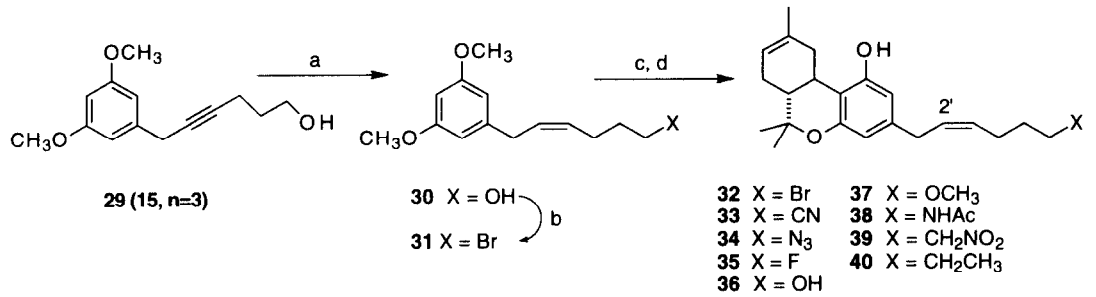


(a) dihydropyran, H^+; (b) BuLi, THF, -78°→25° C, 1h ; (c) 3,5-dimethoxybenzyl bromide, LiI, THF, reflux, 2h, 25-75%; (d) TsOH, MeOH, 25° C, 1h, 70-80%; (e) CBr_4, Oct_3P, ether, 0°→25° C, 12h, 75-90%; (f) BBr_3, CH_2Cl_2, -78°→25° C, 1h; (g) p-menth-2-ene-1,8-diol, TsOH, C_6H_6, 5-20%.

The preparation of 2'-yne-THCs was reported by us previously[17] but the procedure for the alkylation of terminal alkynes with 3,5-dimethoxybenzyl bromide has since been modified. The details are given as a 'general procedure' in the Experimental Section. Analogs of 2'-yne-Δ^8-THC with a substituent at the terminal end of the chain (**17** to **28**) were synthesized as shown in Scheme 2. The commercially available alkynols (**13**, n = 1,2,3) were protected as their tetrahydropyranyl (THP) ethers[31] before alkylation[32] of their lithium salts with 3,5-dimethoxybenzyl bromide using LiI to give the corresponding dimethyl resorcinols **14**. These were deprotected[33] to give the alcohols **15** which were converted to the bromides **16** using CBr_4/Oct_3P/ether[34]. After demethylation with BBr_3/CH_2Cl_2 they were condensed with *cis-p*-menth-2-ene-1,8-diol as before to give the THCs **17-19**.

Treatment of **18** and **19** with NaCN/DMSO, as in the preparation of **11** to **12**, furnished the target analogs **20** and **21**. The azides **22** and **23** were obtained from the corresponding bromides by treatment with NaN_3/DMSO. Reduction of **23** with $LiAlH_4$/ether gave the amine **24** whereas treatment of **22** with Zn powder in

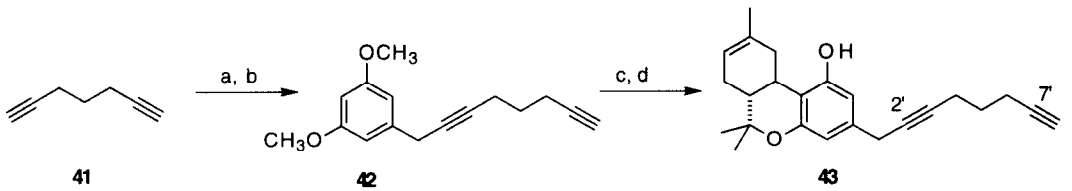
Scheme 3



(a) Lindlar catalyst, H_2, MeOH, 76%; (b) CBr_4, Oct_3P, ether, 73%; (c) BBr_3, CH_2Cl_2; (d) TsOH, p-menth-2-ene-1,8-diol, C_6H_6, 17%.

acetic acid followed by acetylation (Ac_2O/py) formed **25**. Analog **26** was formed as a by-product during the synthesis of **28** from **18** by treatment with nitromethane/CH_3ONa/ethanol. Reaction of thiophosgene on the amine **24** furnished the analog **27**.

Scheme 4

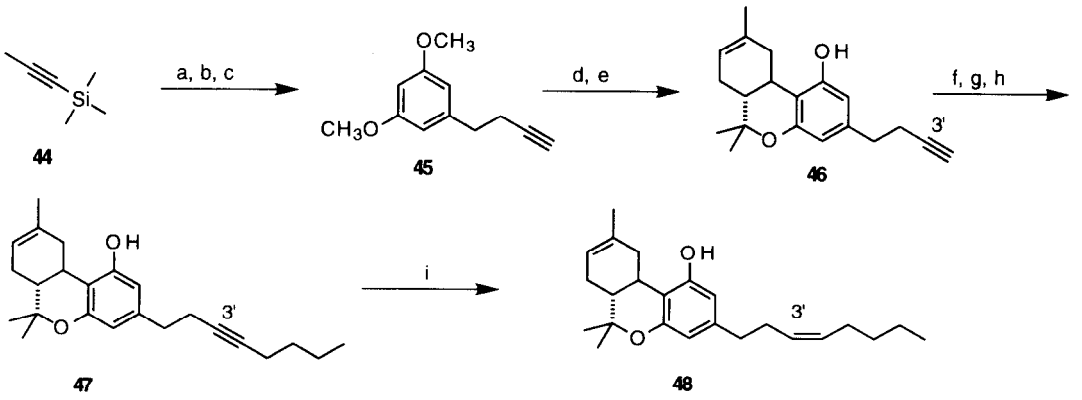


(a) BuLi, THF, -78°→25° C, 1h; (b) 3,5-dimethoxybenzyl bromide, LiI, THF, reflux, 2h, 70%; (c) BBr_3, CH_2Cl_2; (d) p-menth-2-ene-1,8-diol, TsOH, C_6H_6, 8%.

Various 2'-alkene-Δ^8-THC analogs with a substituent at the terminal end of the chain (**32** to **40**) were synthesized from the alkyne **29** (**15** n=3) as shown in Scheme 3. Partial reduction of the alkyne (Lindlar catalyst)[30] in methanol formed **30**. Conversion of the alcohol group to the bromide **31**, followed by demethylation and condensation with *cis-p*-menth-2-ene-1,8-diol formed the THC analog **32**. This was transformed into **33**, **34**, **38** and **39** following the same procedures as described above in the 2'-yne-THC series. The fluoroalkane analog **35** was synthesized from **32** by treatment with tetrabutylammonium fluoride solution in THF under reflux for 18h. The hydroxyl analog **36** was formed as a by-product in the preparation of **39** as well as the fluoroalkane analog **35**. The methoxy analog **37** was prepared from the bromide **32** by treatment with CH_3ONa/methanol. Analog **40** was synthesized from the corresponding 2-yne-Δ^8-THC[17] by partial reduction, using Lindlar catalyst.

The 2',7'-diyne-Δ^8-THC analog **43** was prepared (Scheme 4) from 1,6-heptadiyne **41** by alkylation of its monolithium salt with 3,5-dimethoxybenzyl bromide. The dimethyl resorcinol **42** was formed which was transformed to the corresponding THC analog **43** as described before.

Scheme 5

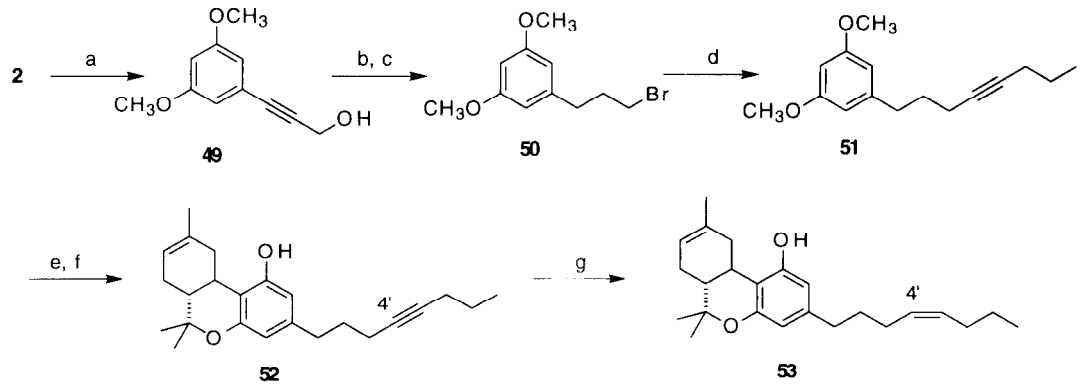


(a) BuLi, TMEDA, ether, -20° C, 4h; (b) 3,5-dimethoxybenzyl bromide, -20°→25° C, 15h; (c) KF•$2H_2O$, DMF, 25° C, 4h, 73%; (d) BBr_3, CH_2Cl_2; (e) p-menth-2-ene-1,8-diol, TsOH, C_6H_6, 38%; (f) CH_3OCH_2Cl, K_2CO_3, CH_3CN, 25° C, 6h, 94%; (g) BuLi, THF, -78°→25° C, 2h, BuI, 25° C, 17h, 49%; (h) TsOH, ethanol, 50° C, 1.5h, 63%; (i) Lindlar catalyst, H_2, 87%.

The synthetic route to 3'-alkyne-Δ^8-THC **47** and the corresponding *cis*-alkene analog **48** (Scheme 5) was achieved from the commercially available 1-trimethylsilyl-1-propyne **44**. It was alkylated[35] as its lithium salt with 3,5-dimethoxybenzyl bromide[36] and then desilylated[37] using KF/DMF to give the resorcinol **45**. This was transformed to the THC derivative **46** and the side chain was extended by protection of the phenol hydroxyl as the MOM ether followed by deprotonation of the terminal alkyne (BuLi). The acetylide anion thus formed was alkylated with iodobutane and then MOM deprotected[33] to give the desired analog **47**. Partial reduction of the triple bond of **47** furnished the 3'-*cis*-ene-Δ^8-THC analog **48**.

The sequence developed for the synthesis of 4'-alkyne-Δ^8-THC **52** and its 4'-*cis*-ene-Δ^8-THC analog **53** is shown in Scheme 6. Palladium coupling[27] of the triflate **2** (Scheme 1) with propargyl alcohol formed **49**. Reduction of the triple bond (Pd/C/H_2) followed by conversion of the alcohol to the bromide gave **50**. This was alkylated by the acetylide anion of 1-pentyne to form the resorcinol **51** which was transformed to the THC analogs **52** and **53** as described before.

Scheme 6



(a) propargyl alcohol, $Pd(PPh_3)_4$, piperidine, 80° C, 2h, 50%; (b) Pd-C, H_2, methanol, 25° C, 2h, 100%; (c) PBr_3, pyridine, toluene, reflux, 40%; (d) 1-pentyne, BuLi, THF, LiI, THF, reflux, 3h, 75%; (e) BBr_3, CH_2Cl_2; (f) TsOH, C_6H_6, p-menth-2-ene-1,8-diol, 40%; (g) Lindlar catalyst, H_2, 5%.

Experimental Section

^1H NMR spectra were recorded on either a Bruker 100 or a Varian XL400 spectrophotometer using $CDCl_3$ as the solvent with tetramethylsilane as an internal standard. Thin layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was accomplished with either iodine vapour, UV exposure or treatment with phosphomolybdic acid (PMA). Flash chromatography was carried out on EM Science Silica Gel 60. Elemental Analyses were performed by Atlantic Microlab, Atlanta, GA. The THCs were purified by monitoring the fractions by GC and the yields given relate to GC pure material. The high-resolution mass spectral data (HRMS) were carried out at Boston University, MA and are reported on materials that were determined to be pure by GC, TLC and ^1H NMR analysis. The analyses by gas chromatography (GC) were performed on a Perkin Elmer 8500 instrument equipped with a 25 meter fused silica capillary column, 0.53 mm i.d. with 0.25 mm film thickness (007 Methyl Phenyl (5%) Silicone; Quadrex Corp.). A typical temperature program for THCs is as follows: injector at 250° C, oven at 150 ° C and detector at 300° C when the sample was injected; after maintaing the oven temperature for 1 min it was increased to 200° at 25°/min, then held there for 8 min, then increased to 250° at 25°/min and held there for 2 min before returning to 150° for the next run. The GC purity is indicated in parenthesis. All intermediates and products were stored under nitrogen in a freezer (-20° C). All alkyne starting materials used were purchased from either Aldrich Chemical Co. or Farchan Laboratories (GFS Chemicals), Gainesville, Fl. *Cis-p*-menth-2-ene-1,8-diol was supplied by Firmenich & Co. NJ.

3,5-Dimethoxyphenyl trifluoromethanesulfonate (2).[26] Trifluoromethanesulfonic anhydride (22 mL, 131 mmol) was added dropwise over 45 min to a stirred solution of 3,5-dimethoxyphenol (**1**, 9.77 g, 63 mmol) and pyridine (16 mL, 198 mmol) in anhyd. CH_2Cl_2 (100 mL) at 0° C under N_2 . After stirring for an additional hour at 0° C, the reaction was quenched by adding H_2O and stirring for 10 min. The mixture was concentrated, and the residue was extracted with Et_2O. The extract was washed with H_2O several times, then washed with satd. NaCl, dried over $MgSO_4$, filtered, concentrated, and the residue chromatographed (3% to 5%

EtOAc/hexanes) to afford triflate **2** (12.67 g, 70%) as a pale yellow, low-melting solid: ^{1}H NMR δ 3.80 (s, 6H), 6.43 (br s, 3H).

1-(3,5-Dimethoxyphenyl)-1-heptyne (3).[27,28] Tetrakis(triphenylphosphine)palladium(0) (47 mg, 0.041 mmol) was added to a stirred solution of triflate **2** (270 mg, 0.94 mmol) and 1-heptyne (180 mg, 1.9 mmol) in piperidine (3 mL). Under nitrogen the mixture was heated for 2 h at 85° C (oil bath) then cooled to room temperature and quenched by adding half-satd. NH_4Cl. It was extracted with Et_2O, washed with 1 *M* HCl, H_2O, satd. $NaHCO_3$, and satd. NaCl. After drying it was concentrated, and then chromatographed (2% EtOAc/hexanes) to afford alkyne **3** (176 mg, 80%) as a clear, colorless liquid: ^{1}H NMR δ 0.92 (t, *J* = 8 Hz, 3H), 1.15-1.80 (m, 6H), 2.39 (t, *J* = 7 Hz, 2H), 3.77 (s, 6H), 6.40 (t, *J* = 2 Hz, 1H), 6.56 (d, *J* = 2 Hz, 2H).

1-(3,5-Dihydroxyphenyl)-1-heptyne (4).[25] Boron tribromide (1 *M* in CH_2Cl_2, 9.0 mL, 9.0 mmol) was added dropwise over 2 min to a stirred solution of ether **3** (778 mg, 3.4 mmol) in anhyd. CH_2Cl_2 (7 mL) at -78° under N_2. After stirring at -78° for an additional 10 min, the cooling bath was removed, and the mixture allowed to warm to room temperature while stirring for 1 h. Then the mixture was quenched by transferring the solution by cannula into rapidly stirred satd. $NaHCO_3$ solution. After stirring for 10 min, the mixture was extracted with Et_2O, washed with satd. $NaHCO_3$ and satd. NaCl, dried over $MgSO_4$, filtered, concentrated, and then chromatographed (20% to 30% EtOAc/hexanes) to afford resorcinol **4** (541 mg, 79%) as a clear, brown oil: ^{1}H NMR δ 0.92 (t, *J* = 7 Hz, 3H), 1.1-1.9 (m, 6H), 2.37 (t, *J* = 7 Hz, 2H), 4.76 (br s, 2H), 6.29 (t, *J* = 2.3 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 2H).

(6a*R*, 10a*R*)-3-(1-Heptynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (5).[24] A solution of resorcinol **4** (357 mg, 1.8 mmol), *cis*-*p*-menth-2-ene-1,8-diol (247 mg, 1.5 mmol), and *p*-toluenesulfonic acid monohydrate (TsOH•H_2O, 12 mg, 0.06 mmol) in benzene (50 mL) was refluxed for 2 h under N_2 while removing water with a Dean-Stark trap. After cooling, excess $NaHCO_3$ was added to quench the TsOH. After stirring for 30 min, the mixture was concentrated, and the residue chromatographed (4% EtOAc/hexanes) to afford THC **5** (22 mg, 5%) as a clear, light yellow oil: GC 92% purity; ^{1}H NMR[38] (400 MHz) δ 0.91 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 3H), 1.30-1.46 (m, 4H), 1.37 (s, 3H), 1.53-1.61 (m, 2H), 1.70 (br s, 3H), 1.76-1.88 (m, 3H), 2.10-2.18 (m, H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.70 (td, *J* = 10.8, 4.8 Hz, 1H), 3.17 (dd, *J* = 15.8, 4.0 Hz, 1H), 4.68 (s, 1H), 5.42 (br d, *J* = 5 Hz, 1H), 6.30 (d, *J* = 1.5 Hz, 1H, H-2), 6.49 (d, *J* = 1.5 Hz, 1H, H-4); ^{1}H NMR (400 MHz, C_6D_6) δ 6.10 (d, *J* = 1.5 Hz, 1H, H-2), 7.06 (d, *J* = 1.5 Hz, 1H, H-4); HRMS (CI) calcd. for $C_{23}H_{31}O_2$ (MH^+) 339.2324, found 339.2310.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(1-heptenyl)-6*H*-dibenzo[b,d]pyran (6).** To a stirred solution/suspension of 235 mg (0.69 mmol) of alkyne **5** and 40 mg of Lindlar catalyst (5% Pd-$CaCO_3$ poisoned with lead, used as obtained from Aldrich Chemical Co.) in 5 mL of reagent alcohol was added one drop of quinoline. The reaction flask was flushed with N_2, then flushed with H_2, and an atmosphere (balloon) of H_2 was applied. After stirring for 2 days at 25° C, TLC analysis indicated only partial consumption of the starting material. The reaction was stopped at this point, and the product was isolated as follows. The H_2 atmosphere was removed by flushing with N_2, the mixture was filtered through diatomaceous earth (Celite® 545), the filtrate was concentrated on the rotary evaporator and the residue was chromatographed twice eluting with 1% → 2% EtOAc/hexanes to afford 46 mg (19%) of the product, as a clear, yellow oil: R_f 0.60 (eluted three times with 1:19 EtOAc/hexanes; SM at 0.55); GC 88% purity; ^{1}H NMR δ 0.88 (t, *J* = 6 Hz, 3H), 1.10 (s, 3H), 1.38 (s, 3H), 1.71 (br s, 3H), 2.2-2.5 (m, 2H), 2.72 (td, *J* = 10, 5 Hz, 1H), 3.20 (dd, *J* = 16, 5

Hz, 1H), 4.69 (s, 1H), 5.43 (br s, 1H), 5.57 (dt, J = 12, 7 Hz, 1H), 6.20 (br d, J = 12 Hz, 1H), 6.21 (d J = 1.5 Hz, 1H), 6.39 (d, J = 1.4 Hz, 1H); HRMS (CI) calcd. for $C_{23}H_{33}O_2$ (MH^+) 341.2481, found 341.2469.

1-(3,5-Dimethoxyphenyl)-1,6-heptadiyne (7). Prepared from triflate **2** and 1,6-heptadiyne by the procedure used to prepare alkyne **3** to afford alkyne **7** (689 mg, 50%) as a clear, yellow liquid: ^{1}H NMR δ 1.83 (pentet, J = 6.9 Hz, 2H), 1.99 (t, J = 2.6 Hz, 1H), 2.39 (td, J = 6.7, 2.5 Hz, 2H), 2.55 (t, J = 7.0 Hz, 2H), 3.78 (s, 6H), 6.41 (t, J = 2.0 Hz, 1H), 6.56 (d, J = 2.0 Hz, 2H).

(6a*R*, 10a*R*)-3-(1,6-Heptadiynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (8). Prepared from ether **7** by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **8** (12 mg, 2%) as a clear, light brown oil: GC 85% purity; ^{1}H NMR δ 1.08 (s, 3H), 1.37 (s, 3H), 1.71 (br s, 3H), 1.97 (t, J = 2.6 Hz, 1H), 2.36 (td, J = 6.8, 2.6 Hz, 2H), 2.50 (t, J = 7.0 Hz, 2H), 2.70 (td, J = 11, 4 Hz, 1H), 3.18 (dd, J = 15.5, 3.8 Hz, 1H), 4.83 (br s, 1H), 5.42 (br d, J = 3 Hz, 1H), 6.30 (d, J = 1.4 Hz, 1H), 6.49 (d, J = 1.4 Hz, 1H); HRMS (CI) calcd. for $C_{23}H_{27}O_2$ (MH^+) 335.2011, found 335.1976.

***O*-tetrahydropyranyl-5-(3,5-dimethoxyphenyl)-4-pentyn-1-ol (9).** Prepared from triflate **2** and *O*-tetrahydropyranyl-4-pentyn-1-ol (prepared from 4-pentyn-1-ol and DHP) by the procedure used to prepare alkyne **3**, to afford alkyne **9** (3.68 g, 88%): ^{1}H NMR δ 1.4-1.8 (m, 6H), 1.90 (pentet, J = 7 Hz, 2H), 2.53 (t, J = 7 Hz, 2H), 3.4-3.7 (m, 2H), 3.78 (s, 6H), 3.8-4.0 (m, 2H), 4.62 (br s, 1H), 6.40 (t, J = 2 Hz, 1H), 6.55 (d, J = 2 Hz, 2H).

1-(3,5-Dimethoxyphenyl)-5-bromo-1-pentyne (10).[29] Triphenylphosphine (2.05 g, 7.8 mmol) was added to a stirred solution of **9** (1.07 g, 3.5 mmol) and CBr_4 (1.56 g, 4.7 mmol) in anhyd. CH_2Cl_2 (17 mL) at 0° C under N_2. The mixture was allowed to warm to 25° C while stirring overnight. After stirring for 14 h, the mixture was filtered through silica gel washing with CH_2Cl_2; the filtrate was concentrated and the residue chromatographed (5% EtOAc/hexanes) to afford bromide **10** (563 mg, 57%) as a cloudy, pale yellow liquid: ^{1}H NMR δ 2.14 (pentet, J = 6.4 Hz, 2H), 2.61 (t, J = 6.7 Hz, 2H), 3.59 (t, J = 6.5 Hz, 2H), 3.78 (s, 6H), 6.42 (t, J = 2.1 Hz, 1H), 6.56 (d, J = 2.2 Hz, 2H).

(6a*R*, 10a*R*)-3-(5-Bromo-1-pentynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (11). Prepared from ether **10** by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **11** (52 mg, 8%) as a clear, light yellow oil: ^{1}H NMR δ 1.08 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.10 (pentet, J = 6.5 Hz, 2H), 2.57 (t, J = 6.7 Hz, 2H), 2.67-2.87 (m, 1H), 3.18 (dd, J = 15.3, 4.4 Hz, 1H), 3.56 (t, J = 6.4 Hz, 2H), 4.9 (br s, 1H), 5.43 (br d, J = 3 Hz, 1H), 6.31 (d, J = 1.5 Hz, 1H), 6.49 (d, J = 1.5 Hz, 1H).

(6a*R*, 10a*R*)-3-(6-Nitrilo-1-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (12). Prepared from **11** by the procedure used to prepare nitrile **20** (n=2) to afford nitrile **12** (30 mg, 68%) as a cloudy, colorless oil: GC 90% purity; ^{1}H NMR δ 1.08 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 1.93 (pentet, J = 6.8 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 2.56 (t, J = 6.1 Hz, 2H), 2.71 (td, J = 11.2, 5.5 Hz, 1H), 3.20 (dd, J = 16.1, 4.5 Hz, 1H), 5.33 (s, 1H), 5.42 (br d, J = 3 Hz, 1H), 6.33 (d, J = 1.3 Hz, 1H, H-2), 6.48 (d, J = 1.4 Hz, 1H, H-4); ^{1}H NMR (100 MHz, C_6D_6) δ 6.45 (d, J = 1.5 Hz, 1H, H-2), 7.07 (d, J = 1.5 Hz, 1H, H-4); HRMS (CI) calcd. for $C_{22}H_{26}NO_2$ (MH^+) 336.1963, found 336.2012.

General procedure for the alkylation of terminal alkynes with 3,5-dimethoxybenzyl bromide.[32,36] nBuLi/hexanes solution (3.0 equiv.) was added dropwise over 5 min to a stirred solution of the terminal alkyne (2.0 equiv.) in anhyd. THF at 0° C under N_2. After stirring for 30 min at 0° C, the cooling bath

was removed, and the solution stirred for 1 h at 25° C. Then a solution of 3,5-dimethoxybenzyl bromide (1 equiv.) in anhyd. THF was added followed by a solution of anhyd. lithium iodide (1 equiv.) in anhyd. THF. The resulting mixture was refluxed for 2 h under N_2, then cooled, and quenched with H_2O. After extraction with Et_2O, it was washed with H_2O and satd. NaCl, dried over $MgSO_4$, filtered, concentrated, and then chromatographed.

***O*-(2-Tetrahydropyranyl)-4-(3,5-dimethoxyphenyl)-2-butyn-1-ol (14, n=1).** nBuLi (2.5 *M* in hexanes, 17 mL, 43 mmol) was added dropwise over 15 min to a stirred solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (6.0 mL, 43 mmol) in anhyd. THF (120 mL) at 0° C under N_2. After stirring for 10 min, the cooling bath was removed and the mixture stirred for 2 h at 25° C. 3,5-Dimethoxybenzyl bromide (5.0 g, 22 mmol) and LiI (2.9 g, 22 mmol) were added with anhyd. THF (50 mL). The mixture was heated to reflux for 2 h, cooled, and then quenched with aq. NH_4Cl and extracted with Et_2O. The extract was washed with H_2O and satd. NaCl, dried and concentrated, and then chromatographed (10% to 20% EtOAc/hexanes) to afford alkyne **14** (n=1, 4.53 g, 72%) as a clear, yellow liquid: ^{1}H NMR δ 1.4-1.9 (m, 6H), 3.59 (br s, 2H), 3.79 (s, 6H), 4.26-4.38 (m, 2H), 4.83 (br s, 1H), 6.33 (t, *J* = 2 Hz, 1H), 6.51 (d, *J* = 2 Hz, 2H).

***O*-(2-Tetrahydropyranyl)-5-(3,5-dimethoxyphenyl)-3-pentyn-1-ol (14, n=2).** Prepared from *O*-(2-tetrahydropyranyl)-3-butyn-1-ol (prepared from 3-butyn-1-ol and DHP) and 3,5-dimethoxybenzyl bromide by the procedure used to prepare alkyne **14** (n=1) to give alkyne **14** (n=2, 2.59 g, 24%) as a clear, yellow liquid: ^{1}H NMR δ 1.4-1.9 (m, 6H), 2.53 (tt, *J* = 7.1, 2.4 Hz, 2H), 3.4-4.0 (m, 4H), 3.52 (t, *J* = 2.4 Hz, 2H), 3.78 (s, 6H), 4.64 (br s, 1H), 6.33 (t, *J* = 2.2 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 2H).

***O*-(2-Tetrahydropyranyl)-6-(3,5-dimethoxyphenyl)-4-hexyn-1-ol (14, n=3).** TsOH•H_2O (36 mg, 0.19 mmol) was added to a stirred solution of 4-pentyn-1-ol (15 mL, 163 mmol) and dihyropyran (30 mL, 329 mmol) in anhyd. THF (150 mL) at 0° C under N_2. The mixture was stirred overnight (16 h), during which time the temperature was allowed to rise to 25° C. The mixture was then cooled to 0° C before adding nBuLi (2.5 *M* in hexanes, 50 mL, 125 mmol). After stirring at 0° C for 30 min then at 25° for 2.5 h, a solution of 3,5-dimethoxybenzyl bromide (18.2 g, 79 mmol) and LiI (10.0 g, 75 mmol) in anhyd. THF (75 mL) was added. The resulting mixture was then heated at reflux for 3 h. The mixture was quenched by adding 1:1 H_2O and satd. NH_4Cl then extracted with Et_2O. The extract was washed with H_2O followed by satd. NaCl, then dried over $MgSO_4$. After concentration, the residue was chromatographed (5% to 15% EtOAc/hexanes) to afford alkyne **14** (n=3, 27.6 g, 25.1 g theoretical) as a clear, yellow liquid: ^{1}H NMR δ 1.4-1.8 (m, 6H), 1.82 (pentet, *J* = 6.5 Hz, 2H), 2.35 (tt, *J* = 6.8, 2.3 Hz, 2H), 3.3-3.6 (m, 4H), 3.7-3.9 (m, 2H), 3.79 (s, 6H), 4.58 (br s, 1H), 6.33 (t, *J* = 2.2 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 2H).

4-(3,5-Dimethoxyphenyl)-2-butyn-1-ol (15, n=1). Prepared from **14** (n=1) by the procedure used to prepare alcohol **15** (n=3) to afford alcohol **15** (n=1, 1.26 g, 70%) as a clear, dark yellow oil: ^{1}H NMR δ 3.58 (br t, *J* = 1.9 Hz, 2H), 3.79 (s, 6H), 4.3 (br s, 2H), 6.34 (t, *J* = 2.3 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 2H).

5-(3,5-Dimethoxyphenyl)-3-pentyn-1-ol (15, n=2). Prepared from **14** (n=2) by the procedure used to prepare alcohol **15** (n=3) to afford alcohol **15** (n=2, 1.52 g, 81%) as a clear, light brown liquid: ^{1}H NMR δ 1.80 (t, *J* = 6.1 Hz, 1 H), 2.50 (tt, *J* = 6.2, 2.4 Hz, 2 H), 3.54 (t, *J* = 2.4 Hz, 2 H), 3.6-3.8 (m, 2 H), 3.79 (s, 6 H), 6.34 (t, *J* = 2.2 Hz, 1 H), 6.50 (d, *J* = 2.2 Hz, 2 H).

6-(3,5-Dimethoxyphenyl)-4-hexyn-1-ol (15, n=3). TsOH•H_2O (0.32 g, 2 mmol) was added to a stirred solution of **14** (n=3, 15.41 g, 48 mmol) in MeOH (200 mL) at 25° C. After stirring for 1 h, $NaHCO_3$ was added

to quench the TsOH. After stirring 30 min the mixture was concentrated and the residue was chromatographed (30% to 45% EtOAc/hexanes) to afford alcohol **15** (n=3, 9.66 g, 85%) as a clear, yellow liquid: ^{1}H NMR δ 1.78 (pentet, J = 6.5 Hz, 2H), 2.35 (tt, J = 6.8, 2.5 Hz, 2H), 3.51 (t, J = 2.5 Hz, 2H), 3.77 (t, J = 6.1 Hz, 2H), 3.79 (s, 6H), 6.33 (t, J = 2.3 Hz, 1H), 6.50 (d, J = 2.3 Hz, 2H).

4-(3,5-Dimethoxyphenyl)-1-bromo-2-butyne (16, n=1).[34] Tri-*n*-octylphosphine (5.5 mL, 12 mmol) was added to a stirred solution of alcohol **15** (n=1, 1.26 g, 6 mmol) and CBr_4 (4.41 g, 13 mmol) in anhyd. Et_2O (30 mL) at 0° C under N_2. The mixture was allowed to warm to 25° C while stirring overnight, then concentrated, and the residue chromatographed (4% EtOAc/hexanes) to afford bromide **16** (n=1, 1.24 g, 76%) as a clear, light yellow liquid: ^{1}H NMR δ 3.61 (br t, J = 2.4 Hz, 2H), 3.79 (s, 6H), 3.98 (t, J = 2.4 Hz, 2H), 6.35 (t, J = 2.2 Hz, 1H), 6.49 (d, J = 2.3 Hz, 2H).

1-Bromo-5-(3,5-dimethoxyphenyl)-3-pentyne (16, n=2). Prepared from alcohol **15** (n=2) by the procedure used to prepare bromide **16** (n=1) to afford bromide **16** (n=2, 1.76 g, 90%) as a clear, light brown liquid: ^{1}H NMR δ 2.80 (tt, J = 7.1, 2.4 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H), 3.54 (br s, 2H), 3.79 (s, 6H), 6.34 (t, J = 2.2 Hz, 1H), 6.52 (d, J = 2.3 Hz, 2H).

1-Bromo-6-(3,5-dimethoxyphenyl)-4-hexyne (16, n=3). Prepared from alcohol **15** (n=3) by the procedure used to prepare bromide **16** (n=1) to afford bromide **16** (n=3, 1.79 g, 89%): ^{1}H NMR δ 2.06 (pentet, J = 7 Hz, 2H), 2.43 (tm, J_t = 7 Hz, 2H), 3.52 (br s, 2H), 3.55 (t, J = 7 Hz, 2H), 3.80 (s, 6H), 6.34 (t, J = 2 Hz, 1H), 6.51 (d, J = 2 Hz, 2H).

(6a*R*, 10a*R*)-3-(4-Bromo-2-butynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (17, n=1). Prepared from bromide **16** (n=1) by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **17** (n=1, 51 mg, 3%) as a clear, yellow oil: GC 87% purity; ^{1}H NMR δ 1.11 (s, 3H), 1.38 (s, 3H), 1.71 (br s, 3H), 2.71 (td, J = 10.5, 4.6 Hz, 1H), 3.21 (dd, J = 16.0, 4.3 Hz, 1H), 3.55 (br t, J = 2.5 Hz, 2H), 4.84 (t, J = 2.6 Hz, 2H), 4.93 (s, 1H), 5.43 (br d, J = 3.9 Hz, 1H), 6.19 (d, J = 1.5 Hz, 1H, H-2), 6.35 (d, J = 1.5 Hz, 1H, H-4); ^{1}H NMR (100 MHz, C_6D_6) δ 5.74 (d, J = 1.5 Hz, 1H, H-2), 6.63 (d, J = 1.3 Hz, 1H, H-4); HRMS (CI) calcd. for $C_{20}H_{24}BrO_2$ (MH^+) 375.0959, found 375.0951.

(6a*R*, 10a*R*)-3-(5-Bromo-2-pentynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (18, n=2). Prepared from bromide **16** (n=2) by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **18** (n=2, 493 mg, 20%) as a clear, dark yellow oil: GC 91% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.38 (s, 3H), 1.70 (br s, 3H), 2.77 (tt, J = 7.2, 2.0 Hz, 2H), 3.21 (dd, J = 17.6, 5.1 Hz, 1H), 3.3-3.6 (m, 4H), 4.91 (s, 1H), 5.43 (br d, J = 3.5 Hz, 1H), 6.30 (d, J = 1.6 Hz, 1H, H-2), 6.40 (d, J = 1.5 Hz, 1H, H-4); ^{1}H NMR (100 MHz, C_6D_6) δ 5.83 (d, J = 1.6 Hz, 1H, H-2), 6.74 (d, J = 1.6 Hz, 1H, H-4); HRMS (CI) calcd. for $C_{21}H_{26}BrO_2$ (MH^+) 389.1116, found 389.1100.

(6a*R*, 10a*R*)-3-(6-Bromo-2-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (19, n=3). Prepared from bromide **16** (n=3) by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **19** (n=3, 57 mg, 18%): ^{1}H NMR δ 1.10 (s, 3H), 1.38 (s, 3H), 1.70 (br s, 3H), 1.9-2.2 (m, 2H), 2.3-2.5 (m, 2H), 2.70 (td, J = 11, 4 Hz, 1H), 3.21 (dd, J = 17, 5 Hz, 1H), 3.41 (br s, 2H), 3.54 (t, J = 7 Hz, 2H), 4.85 (br s, 1H), 5.45 (br d, J = 4 Hz, 1H), 6.30 (br s, 1H), 6.40 (br s, 1H); MS (CI) 402 (M^+, ^{79}Br), 404 (M^+, ^{81}Br).

(6a*R*, 10a*R*)-3-(6-Nitrilo-2-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (20, n=2). A mixture of bromide **18** (n=2, 216 mg, 0.56 mmol) and NaCN (262 mg,

5.4 mmol) in DMSO (5 mL) under N_2 was heated at 50° C for 3 h. After cooling it was diluted with Et_2O and the Et_2O extract was washed with H_2O and satd. NaCl. After drying it was concentrated then chromatographed (15% EtOAc/hexanes) to afford nitrile **20** (n=2, 42 mg, 23%) as a clear, light yellow oil: GC 93% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.59 (s, 4H), 2.71 (td, J = 11.6, 4.0 Hz, 1H), 3.23 (dd, J = 15.4, 3.8 Hz, 1H), 3.44 (br s, 2H), 5.25 (br s, 1H), 5.42 (br d, J = 4 Hz, 1H), 6.33 (d, J = 1.0 Hz, 1H), 6.56 (d, J = 1.1 Hz, 1H); HRMS (CI) calcd. for $C_{22}H_{26}NO_2$ (MH^+) 336.1963, found 336.1993.

(6a*R*, 10a*R*)-3-(7-Nitrilo-2-heptynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (21, n=3). Prepared from bromide **19** (n=3) by the procedure used to prepare nitrile **20** (n=2) to afford nitrile **21** (n=3, 409 mg, 89%): GC 92% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.38 (s, 3H), 1.72 (br s, 3H), 1.65-2.00 (m, 2H), 2.40 (tm, J_t = 7 Hz, 2H), 2.51 (t, J = 7 Hz, 2H), 2.70 (td, J = 10, 3 Hz, 1H), 3.22 (dd, J = 17, 5 Hz, 1H), 3.42 (br s, 2H), 5.40 (br s, 1H), 5.45 (s, 1H), 6.30-6.38 (m, 2H); HRMS (CI) calcd. for $C_{23}H_{28}NO_2$ (MH^+) 350.2120, found 350.2107.

(6a*R*, 10a*R*)-3-(5-Azido-2-pentynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (22, n=2). Alternate name (3-(5-Azido-2-pentynyl)-Δ^8-THC). Prepared from bromide **18** (n=2) by the procedure used to prepare nitrile **20** (n=2) except using NaN_3 rather than NaCN to afford 177 mg (85%) of the product, as a clear, colorless oil: R_f 0.5 (1:4 EtOAc/hexanes); IR (neat on NaCl plate) 2100 cm^{-1} (N_3); ^{1}H NMR (400 MHz) δ 1.08 (s, 3H), 1.36 (s, 3H), 1.68 (br s, 3H), 1.75-1.87 (m, 3H), 2.09-2.17 (m, 1H), 2.50 (tt, J = 6.8, 2.4 Hz, 2H), 2.68 (td, J = 10.8, 4.8 Hz, 1H), 3.17 (dd, J = 15.8, 3.8 Hz, 1H), 3.39 (t, J = 6.8 Hz, 2H), 3.42 (br s, 2H), 4.71 (br s, 1H), 5.41 (br d, J = 4 Hz, 1H), 6.27-6.28 (m, 1H), 6.37-6.38 (m, 1H); Anal. for $C_{21}H_{25}N_3O_2$•0.05 $CHCl_3$: calcd. 70.74% C, 7.06% H, 11.76% N; found 70.74% C, 7.16% H, 11.59% N.

(6a*R*, 10a*R*)-3-(6-Azido-2-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (23, n=3). Alternate name (3-(6-Azido-2-hexynyl)-Δ^8-THC). Prepared from the bromide **19** (0.3 g, 0.74 mmol) by the procedure used to prepare **22**. It was purified by chromatography eluting with 10% EtOAc/hexanes to afford 0.24 g (91%) of **23** as a colorless oil; ^{1}H NMR δ 1.08 (s, 3H), 1.36 (s, 3H), 1.68 (br s, 3H), 1.75-1.95 (m, 5H), 2.09-2.40 (m, 3H), 2.55-2.90 (m, 1H), 3.15 (dd, J = 15, 4 Hz, 1H), 3.30-3.55 (m, 4H), 4.90 (br s, 1H), 5.42 (br d, J = 4 Hz, 1H), 6.27 (m, 1H), 6.40 (m, 1H); Anal. for $C_{22}H_{27}O_2N_3$•0.6H_2O: calcd. 70.16% C, 7.55% H, 11.16% N; found 70.04% C, 7.27% H, 11.14% N.

(6a*R*, 10a*R*)-3-(6-Amino-2-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (24, n=3). Alternate name (3-(6-Amino-2-hexynyl)-Δ^8-THC). To a stirred solution of the azide **23** (0.25 g, 0.7 mmol) in 22 mL of dry Et_2O, was added 6 mL (6 mmol) of 1 *M* $LiAlH_4$ solution in Et_2O and the mixture was refluxed under N_2 for 4h. The reaction was decomposed by the addition of satd. Na_2SO_4 solution and the Et_2O layer was separated. It was washed with H_2O, dried and evaporated to leave a gum which was purified by chromatography, eluting with 30% MeOH/$CHCl_3$. The product **24** (179 mg, 65%) was obtained as a foam: ^{1}H NMR δ 1.08 (s, 3H), 1.36 (s, 3H), 1.69 (br s, 3H), 1.8-2.4 (m, 9H), 2.55-3.0 (m, 1H), 3.15-3.60 (m, 7H), 5.45 (br s, 1H), 6.25-6.6 (m, 2H); HRMS (CI) calcd. for $C_{22}H_{30}NO_2$ (MH^+) 340.2270, found 340.2268.

(6a*R*, 10a*R*)-3-(5-Acetamido-2-pentynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (25, n=2). Alternate name (3-(5-Acetamido-2-pentynyl)-Δ^8-THC). Zinc powder (105 mg, 1.6 g-mmol, 5 equiv.) was added to a stirred solution of 115 mg (0.33 mmol) of azide **22** (n=2) in 2

mL HOAc under N_2. After stirring for 20 h, the mixture was filtered through diatomaceous earth washing with MeOH and EtOAc. The filtrate was concentrated on the rotary evaporator and the residue was repeatedly dissolved in EtOAc and concentrated to remove most of the AcOH azeotropically. Then 2 mL each of pyridine and Ac_2O was added to the residue. After stirring for 3 h, the mixture was diluted with Et_2O. The organic layer was washed with several portions of 1 *M* HCl, then with H_2O and satd. $NaHCO_3$. After concentration the residue was dissolved in 5 mL of MeOH and excess K_2CO_3 was added. After stirring for 30 min, the mixture was diluted with Et_2O and the organic layer was washed twice with H_2O and satd. NaCl and dried over $MgSO_4$. It was concentrated and then chromatographed, eluting with 50% EtOAc/hexanes to afford 38 mg (32%) of the product, as a colorless foam: R_f 0.3 (7:3 EtOAc-hexanes); GC 86% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.36 (s, 3), 1.71 (br s, 3H), 2.03 (s, 3H), 2.43 (tt, *J* = 6, 3 Hz, 2H), 2.57-2.88 (m, 1H), 3.2-3.4 (m, 1H), 3.42 (br s, 2H), 3.55 (q, *J* = 6 Hz, 2H), 5.41 (br d, *J* = 3 Hz, 1H), 5.79 (br t, *J* = 5 Hz, 1H), 6.24 (d, *J* = 1 Hz, 1H), 6.50 (d, *J* = 1 Hz, 1H), 7.13 (s, 1H); HRMS (CI) calcd. for $C_{23}H_{30}NO_3$ (MH^+) 368.2226, found 368.2208.

(6a*R*, 10a*R*)-3-(5-Hydroxy-2-pentynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (26, n=2). Alternate name (3-(5-Hydroxy-2-pentynyl)-Δ^8-THC). Prepared from bromide **18** (n=2) as a by-product in the preparation of nitroalkane **28** (n=3) (see below), to afford 9 mg (9%) of alcohol **26**, as a clear, light yellow oil: R_f 0.3 (2:3 EtOAc/hexanes); GC 94% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.37 (s, 3H), 1.69 (br s, 3H), 2.50 (tt, *J* = 6, 2 Hz, 2H), 2.6-2.9 (m, 1H), 3.21 (dd, *J* = 17, 4 Hz, 1H), 3.43 (br s, 2H), 3.74 (t, *J* = 6 Hz, 2H), 5.42 (br d, *J* = 4 Hz, 1H), 5.6 (br s, 1H), 6.30-6.45 (m, 2H).

(6a*R*, 10a*R*)-3-(6-Isothiocyano-2-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (27, n=3). Alternate name (3-(6-Isothiocyano-2-hexynyl)-Δ^8-THC). To a stirred solution of **24** (119 mg, 0.35 mmol) in 35 mL of $CHCl_3$ was added 14 mL of a satd. solution of $NaHCO_3$ followed by 42 μL (0.55 mmol) of thiophosgene. The mixture was stirred at 25° C for 4h after which it was washed with satd. $NaHCO_3$ solution, dried and evaporated to leave a residue. After chromatography, eluting with 10% EtOAc/hexanes, a brown gum, **27** (50 mg, 37%) was obtained: ^{1}H NMR δ 1.10 (s, 3H), 1.40 (s, 3H), 1.71 (br s, 3H), 1.8-2.2 (m, 6H), 2.3-2.8 (m, 3H), 3.22 (dd, *J* = 15, 4 Hz, 1H), 3.45 (br s, 2H), 3.7 (t, *J* = 6 Hz, 2H), 5.0 (br s, 1H), 5.4 (br s, 1H), 6.32 (br s, 1H), 6.40 (br s, 1H); HRMS (CI) calcd. for $C_{22}H_{28}NO_2S$ (MH^+) 382.1840, found 382.1841.

(6a*R*, 10a*R*)-3-(6-Nitro-2-hexynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (28, n=3). Alternate name (3-(6-Nitro-2-hexynyl)-Δ^8-THC). A stirred mixture of 115 mg (0.30 mmol) of bromide **18** (n=2) and 195 mg (3.6 mmol) of $NaOCH_3$ in 4 mL of 1:1 CH_3NO_2-reagent alcohol under N_2 was heated to reflux for 16 h. The mixture was cooled, diluted with Et_2O and the layers were separated. The EtO_2 extract was washed with H_2O and satd. NaCl, dried and concentrated, then chromatographed eluting with 5% → 25% EtOAc/hexanes to afford 14 mg (13%) of **28** as a clear, light yellow oil. (Alcohol **26** (n=2) was isolated (in 9% yield) as a by-product of this preparation.): R_f 0.3 (1:4 EtOAc/hexanes); GC 95% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.56-2.82 (m, 1H), 2.93 (tt, *J* = 7, 2 Hz, 2H), 3.20 (dd, *J* = 16, 5 Hz, 1H), 3.40 (br s, 2H), 4.50 (t, *J* = 7 Hz, 2H), 5.01 (br s, 1H), 5.42 (br d, *J* = 4 Hz), 6.24 (d, *J* = 1.5 Hz, 1H), 6.34 (br s, 1H); Anal. for $C_{22}H_{27}NO_4$•0.4 Et_2O: calcd. 71.02% C, 7.83% H, 3.51% N; found 71.19% C, 7.72% H, 3.17% N; the presence of Et_2O was confirmed by NMR.

***Z*-6-(3,5-Dimethoxyphenyl)-4-hexen-1-ol (30).** Prepared from alkyne **15** (n=3) by partial reduction as described above for the preparation of alkene **6**, except that MeOH was used as the solvent, to afford the crude product which was chromatographed eluting with 20% → 30% EtOAc/hexanes to give 1.62 g (76%) of the product, as a clear, colorless liquid: R_f 0.53 (1:1 EtOAc/hexanes); ^{1}H NMR δ 1.28 (br t, J = 6 Hz, 1H), 1.67 (pentet, J = 7 Hz, 2H), 2.25 (q, J = 7 Hz, 2H), 3.35 (d, J = 6 Hz, 2H), 3.68 (q, J = 6 Hz, 2H), 3.78 (s, 6H), 5.44-5.70 (m, 2H), 6.27-6.41 (m, 3H).

***Z*-1-(3,5-Dimethoxyphenyl)-6-bromo-2-hexene (31).** Prepared from alcohol **30** by the procedure used to prepare bromide **16** (n=1) to afford 8.01 g (73%) of the product, as a clear, light yellow liquid: R_f 0.7 (3:7 EtOAc/hexanes); ^{1}H NMR δ 1.8-2.1 (m, 2H), 2.32 (q, J = 6.5 Hz, 2H), 3.37 (d, J = 6.3 Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 3.78 (s, 6H), 5.3-5.8 (m, 2H), 6.28-6.44 (m, 3H).

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(6-bromo-2-hexenyl)-6*H*-dibenzo[b,d]pyran (32).** Alternate name (*cis*-3-(6-Bromo-2-hexenyl)-Δ^8-THC). Prepared from *O,O*-dimethylresorcinol **31** by the procedures used to prepare resorcinol **4** and tetrahydrocannabinol **5** to afford 342 mg (17%) of the product, as a clear, light yellow oil: R_f 0.6 (1:4 EtOAc/hexanes); GC 94% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.28 (q, J=7 Hz, 2H), 2.70 (td, J=10, 4 Hz, 1H), 3.1-3.3 (m, 1H), 3.26 (d, J = 6 Hz, 2H), 3.42 (t, J = 7 Hz, 2H), 4.81 (s, 1H), 5.27-5.79 (m, 3H), 6.12 (br s, 1H, H-2), 6.27 (br s, 1H, H-4); ^{1}H NMR (100 MHz, C_6D_6) δ 5.72 (d, J = 1.6 Hz, 1H, H-2), 6.59 (br s, 1H, H-4); HRMS (CI) calcd. for $C_{22}H_{29}BrO_2$ (M^+) 404.1351, found 404.1332.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(7-nitrilo-2-heptenyl)-6*H*-dibenzo[b,d]pyran (33).** Alternate name(*cis*-3-(6-Cyano-2-hexenyl)-Δ^8-THC). Prepared from bromide **32** by the procedure used to prepare nitrile **20** (n=2) to afford 86 mg (34%) of the product, as a clear, colorless oil: R_f 0.2 (1:4 EtOAc/hexanes); GC 94% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.18-2.47 (m, 4H), 2.70 (td, J = 11, 5 Hz, 1H), 3.0-3.3 (m, 1H), 3.25 (d, J = 7 Hz, 2H), 4.85 (s, 1H), 5.24-5.83 (m, 3H), 6.14 (d, J = 1.7 Hz, 1H), 6.26 (d, J = 1.6 Hz, 1H); HRMS (CI) calcd. for $C_{23}H_{29}NO_2$ (M^+) 351.2198, found 351.2230.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(6-azido-2-hexenyl)-6*H*-dibenzo[b,d]pyran (34).** Alternate name (*cis*-3-(6-Azido-2-hexenyl)-Δ^8-THC). Prepared from bromide **32** by the procedure used to prepare nitrile **20** (n=2) except using NaN_3 rather than NaCN to afford 148 mg (78%) of the product, as a clear, light yellow oil: R_f 0.49 (1:19 EtOAc/hexanes); IR (neat on NaCl plates) 2104 cm^{-1} (N_3); ^{1}H NMR δ 1.10 (s, 3H), 1.37 (s, 3H), 1.69 (br s, 3H), 2.1-2.4 (m, 2H), 2.70 (td, J = 11, 4 Hz, 1H), 3.1-3.3 (m, 1H), 3.24 (d, J = 7 Hz, 2H), 3.30 (t, J = 7 Hz, 2H), 4.79 (br, 1H), 5.3-5.8 (m, 3H), 6.10 (d, J = 1.6 Hz, 1H), 6.28 (d, J = 1.5 Hz, 1H); HRMS (CI) calcd. for $C_{22}H_{30}N_3O_2$ (MH^+) 368.2338, found 368.2329.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(6-fluoro-2-hexenyl)-6*H*-dibenzo[b,d]pyran (35).** Alternate name (*cis*-3-(6-Fluoro-2-hexenyl)-Δ^8-THC). A solution of 214 mg (0.53 mmol) of bromide **32** in 5 mL 0.5 *M* Bu_4NF in THF under N_2 was refluxed for 18 h. After cooling, the mixture was diluted with Et_2O and the layers were separated. The Et_2O solution was washed with H_2O and satd. NaCl, dried, and concentrated, then chromatographed eluting with 2% EtOAc/hexanes to afford 33 mg (18%) of the product, as a clear, light yellow resin: R_f 0.36 (1:19 EtOAc/hexanes); ^{1}H NMR δ 1.10 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.70 (td, J = 11, 4 Hz, 1H), 3.1-3.3 (m, 1H), 3.24 (d, J = 6 Hz, 2H), 4.46 (dt, J = 47, 6 Hz,

2H), 4.76 (s, 1H), 5.3-5.7 (m, 3H), 6.10 (d, J = 1.6 Hz, 1H), 6.28 (d, J = 1.5 Hz, 1H); HRMS (CI) calcd. for $C_{22}H_{30}FO_2$ (MH^+) 345.2230, found 345.2237.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(6-hydroxy-2-hexenyl)-6*H*-dibenzo[b,d]pyran (36).** Alternate name (*cis*-3-(6-Hydroxy-2-hexenyl)-Δ^8-THC). Alcohol **36** was formed as a by-product in the preparation of fluoroalkane **35** and nitroalkane **39**. The batches were combined and rechromatographed to afford 70 mg of alcohol **36**, as a clear, yellow resin: R_f 0.4 (2:3 EtOAc/hexanes); GC 96% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.37 (s, 3H), 1.68 (br s, 3H), 2.69 (td, J = 11, 4 Hz, 1H), 3.1-3.3 (m, 1H), 3.23 (d, J = 6 Hz, 2H), 3.69 (t, J = 6 Hz, 2H), 5.3-5.6 (m, 4H), 6.11 (d, J = 1.4 Hz, 1H), 6.26 (br s, 1H); HRMS (CI) calcd. for $C_{22}H_{31}O_3$ (MH^+) 343.2273, found 343.2262.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(6-methoxy-2-hexenyl)-6*H*-dibenzo[b,d]pyran (37).** Alternate name (*cis*-3-(6-Methoxy-2-hexenyl)-Δ^8-THC). Prepared from bromide **32** by the procedure used to prepare nitroalkane **28** (n=3) except using MeOH as the solvent rather than CH_3NO_2-reagent alcohol mixture, to afford 125 mg (65%) of the product, as a clear, light yellow oil: R_f 0.46 (1:4 EtOAc/hexanes); GC 98% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.36 (s, 3H), 1.68 (br s, 3H), 2.0-2.4 (m, 2H), 2.69 (td, J = 11, 4 Hz, 1H), 3.1-3.3 (m, 1H), 3.22 (d, J = 6 Hz, 2H), 3.35 (s, 3H), 3.41 (t, J = 6 Hz, 2H), 5.3-5.6 (m, 4H), 6.09 (d, J = 1 Hz, 1H), 6.26 (d, J = 1 Hz, 1H); HRMS (CI) calcd. for $C_{23}H_{33}O_3$ (MH^+) 357.2430, found 357.2418.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(6-acetamido-2-hexenyl)-6*H*-dibenzo[b,d]pyran (38).** Alternate name (*cis*-3-(6-Acetamido-2-hexenyl)-Δ^8-THC). Prepared from azide **34** by the procedure used to prepare acetamide **25** (n=2) to afford 32 mg (18%) of the product, as a clear, colorless oil: R_f 0.3 (3:2 EtOAc/hexanes); GC 94% purity; ^{1}H NMR δ 1.09 (s, 3H), 1.36 (s, 3H), 1.70 (br s, 3H), 1.98 (s, 3H), 2.1-2.4 (m, 2H), 2.70 (td, J = 10, 4 Hz, 1H), 3.1-3.5 (m, 5H), 5.4-5.9 (m, 4H), 6.22 (s, 2H), 7.46 (s, 1H); ^{1}H NMR (100 MHz, DMSO-d_6) δ 5.3-5.5 (m, 3H), 6.00 (d, J=1 Hz, 1H), 6.14 (d, J=1 Hz, 1H), 7.80 (br s, 1H), 9.23 (s, 1H); HRMS (CI) calcd. for $C_{24}H_{34}NO_3$ (MH^+) 384.2539, found 384.2530.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(7-nitro-2-heptenyl)-6*H*-dibenzo[b,d]pyran (39).** Alternate name (*cis*-3-(7-Nitro-2-heptenyl)-Δ^8-THC) . Prepared from bromide **32** by the procedure used to prepare nitroalkane **28** (n=3) to afford 29 mg (16%) of the product, as a clear, yellow oil: R_f 0.4 (1:4 EtOAc/hexanes); GC 93% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.0-2.3 (m, 4H), 2.70 (td, J = 11, 4 Hz, 1H), 3.1-3.3 (m, 1H), 3.21 (d, J = 7 Hz, 2H), 4.38 (t, J = 7 Hz, 2H), 4.90 (s, 1H), 5.3-5.8 (m, 3H), 6.08 (d, J = 1 Hz, 1H), 6.25 (d, J = 1 Hz, 1H); HRMS (CI) calcd. for $C_{23}H_{32}NO_4$ (MH^+) 386.2331, found 386.2318.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(2-octenyl)-6*H*-dibenzo[b,d]pyran (40).** Alternate name (*cis*-3-(2-Octenyl)-Δ^8-THC). Prepared from the corresponding 2'-yne-Δ^8–THC[17] by partial reduction as described above for the preparation of alkene **6**, to afford 206 mg (40%) of the product, as a clear, dark yellow oil: R_f 0.5 (1:9 EtOAc/hexanes); GC 99% purity; ^{1}H NMR δ 0.89 (t, J = 6 Hz, 3H), 1.10 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.69 (td, J = 11, 4 Hz, 1H), 3.05-3.35 (m, 1H), 3.23 (d, J = 5 Hz, 2H), 4.74 (s, 1H), 5.3-5.6 (m, 3H), 6.10 (d, J = 1 Hz, 1H), 6.28 (d, J = 1 Hz, 1H); HRMS (CI) calcd. for $C_{24}H_{35}O_2$ (MH^+) 355.2637, found 355.2610.

8-(3,5-Dimethoxyphenyl)-1,6-octadiyne (42). Prepared from 1,6-heptadiyne (**41**) and 3,5-dimethoxybenzyl bromide by the procedure used to prepare alkyne **14** (n=1) to afford alkyne **42** (755 mg, 71%) as a clear, yellow liquid: ^{1}H NMR δ 1.75 (pentet, J = 7 Hz, 2H), 1.96 (t, J = 3 Hz, 1H), 2.24-2.48 (m, 4H), 3.52 (br s, 2H), 3.79 (s, 6H), 6.34 (t, J = 2 Hz, 1H), 6.51 (d, J = 2 Hz, 2H).

(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(2,7-octadiynyl)-6*H*-dibenzo[b,d]pyran (43). Prepared from **42** by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **43** (82 mg, 8%) as a clear, light yellow oil: GC 91% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.38 (s, 3H), 1.64-1.90 (m, 5H), 1.70 (br s, 3H), 1.98 (t, J = 2.7 Hz, 1H), 2.11-2.19 (m, 1H), 2.31-2.38 (m, 4H), 2.70 (td, J = 10.7, 4.3 Hz, 1H), 3.19 (dd, J = 16.2, 4.6 Hz, 1H), 3.43 (br s, 2H), 4.73 (s, 1H), 5.43 (br d, J = 4 Hz, 1H), 6.30 (s, 1H), 6.40 (s, 1H); HRMS (CI) calcd. for $C_{24}H_{29}O_2$ (MH^+) 349.2168, found 349.2168.

4-(3,5-Dimethoxyphenyl)-1-butyne (45).[35,37] nBuLi (2.5 *M* in hexanes, 7.0 mL, 18 mmol) was added to an oven-dried flask under N_2 and N_2 was flushed through the flask until most of the hexane had evaporated. The flask was cooled to -20° C before adding anhyd. Et_2O (25 mL), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 2.5 mL, 17 mmol), and 1-trimethylsilyl-1-propyne (**44**, 2.5 mL, 17 mmol). The resulting mixture was stirred for 4 h at -20° C. 3,5-Dimethoxybenzyl bromide (2.6 g, 11 mmol) was added using anhyd. THF (2 × 5 mL). After stirring for 1 h at -20° C, the cooling bath was removed and the solution stirred at 25° C overnight. The mixture was quenched with aq. NH_4Cl and extracted with Et_2O. The extract was washed with 1 *M* HCl, H_2O, satd. $NaHCO_3$, satd. NaCl, then dried and concentrated to afford the crude 4-(3,5-dimethoxyphenyl)-1-trimethylsilyl-1-butyne, as a clear, yellow liquid: ^{1}H NMR δ 0.15 (s, 9H), 2.49 (tm, J_t = 7 Hz, 2H), 2.78 (tm, J_t = 7 Hz, 2H), 3.78 (s, 6H), 6.29-6.42 (m, 3H).

Potassium fluoride dihydrate (3.1 g, 33 mmol) was added to a stirred solution of crude 4-(3,5-dimethoxyphenyl)-1-trimethylsilyl-1-butyne (11 mmol, theoretical) in DMF (40 mL). After stirring the suspension for 4 h at 25° C, the mixture was quenched with aq. NH_4Cl and extracted with Et_2O. The combined extract was washed with H_2O and satd. NaCl, dried and concentrated then chromatographed (3% EtOAc/hexanes) to afford alkyne **45** (1.55 g, 73% two-step yield) as a clear, light yellow liquid: ^{1}H NMR δ 1.99 (t, J = 2.5 Hz, 1H), 2.47 (tm, J_t = 7.2 Hz, 2H), 2.80 (tm, J_t = 7.1 Hz, 2H), 3.78 (s, 6H), 6.31-6.46 (m, 3H).

(6a*R*, 10a*R*)-3-(3-Butynyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran (46). Prepared from **45** by the procedures used to prepare resorcinol **4** and THC **5** to afford crude THC **46** (486 mg, 38%, >80% purity by GC) as a clear, yellow oil which was used in the following preparations without further purification. A sample of this compound was purified twice to obtain a high purity sample for characterization and bio-assay: GC 95% purity; ^{1}H NMR δ 1.10 (s, 3H), 1.38 (s, 3H), 1.71 (br s, 3H), 1.98 (t, J = 2.5 Hz, 1H), 2.41 (tm, J_t = 7 Hz, 2H), 2.55-2.88 (m, 3H), 3.20 (br dd, J = 17, 4 Hz, 1H), 5.43 (br d, J = 4 Hz, 1H), 6.15 (d, J = 1.6 Hz, 1H, H-2), 6.29 (d, J = 1.6 Hz, 1H, H-4); ^{1}H NMR (100 MHz, C_6D_6) δ 5.61 (d, J = 1.7 Hz, 1H, H-2), 6.58 (d, J = 1.6 Hz, 1H, H-4); HRMS (CI) calcd. for $C_{20}H_{25}O_2$ (MH^+) 297.1855, found 297.1821.

(6a*R*, 10a*R*)-3-(3-Butynyl)-6a,7,10,10a-tetrahydro-1-methoxymethoxy-6,6,9-trimethyl-6*H*-dibenzo[b,d]pyran. Chloromethyl methyl ether (MOM-Cl, 0.50 mL, 6.6 mmol) was added to a stirred suspension of THC **46** (479 mg, 1.6 mmol) and K_2CO_3 (895 mg, 6.5 mmol) in anhyd. CH_3CN (10 mL) at 25° C under argon. After stirring for 6 h, H_2O was added to quench the excess MOM-Cl. After stirring for 15 min, the mixture was extracted with Et_2O and the extract was washed with H_2O and satd. NaCl. It was dried,

concentrated, then chromatographed (5% EtOAc/hexanes) to afford the MOM-THC (515 mg, 94%) as a clear, yellow oil: ^{1}H NMR δ 1.09 (s, 3H), 1.37 (s, 3H), 1.71 (br s, 3H), 1.98 (t, J = 2.5 Hz, 1H), 2.43 (tm, J_t = 7 Hz, 2H), 2.75 (t, J = 7 Hz, 2H), 3.18 (dd, J = 16, 5 Hz, 1H), 3.50 (s, 3H), 5.17 (s, 2H), 5.43 (br d, J = 4 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.50 (d, J = 1.6 Hz, 1H).

(6a*R*, 10a*R*)-6a,7,10,10a-tetrahydro-1-methoxymethoxy-6,6,9-trimethyl-3-(3-octynyl)-6*H*-dibenzo[b,d]pyran. nBuLi (2.5 *M* in hexanes, 0.30 mL, 0.75 mmol) was added to a stirred solution of MOM-THC (see above; 197 mg, 0.58 mmol) in anhyd. THF (4 mL) at -78° C under N_2. After stirring for 15 min at -78° C, the cooling bath was removed. After stirring for 2 h at 25° C, iodobutane (0.15 mL, 1.3 mmol) was added and the mixture was further stirred for 17h. The mixture was then quenched with satd. NH_4Cl and extracted with Et_2O. The extract was washed with H_2O and satd. NaCl, dried, concentrated, then chromatographed (3% EtOAc/hexanes) to afford MOM-THC (83 mg, 36%) as a clear, light yellow oil: ^{1}H NMR δ 0.90 (t, J = 7 Hz, 3H), 1.09 (s, 3H), 1.37 (s, 3H), 1.70 (br s, 3H), 2.0-2.3 (m, 2H), 2.3-2.5 (m, 2H), 2.6-2.9 (m, 3H), 3.17 (dd, J = 16, 4 Hz, 1H), 3.49 (s, 3H), 5.17 (s, 2H), 5.43 (br d, J = 3 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.49 (d, J = 1.5 Hz, 1H).

(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(3-octynyl)-6*H*-dibenzo[b,d]pyran (47).[33] TsOH•H_2O (56 mg, 0.29 mmol) was added to a stirred solution of MOM-THC (see above; 102 mg, 0.26 mmol) in EtOH (2 mL). The flask was flushed with N_2, then heated to 50° C for 1.5 h. K_2CO_3 was added to quench the TsOH, and the mixture was diluted with H_2O and extracted with Et_2O. The extract was washed with satd. $NaHCO_3$ and satd. NaCl, dried and concentrated, then chromatographed (5% EtOAc/hexanes) to afford THC **47** (57 mg, 63%) as a clear, light yellow oil: GC 88% purity; ^{1}H NMR d 0.90 (t, J = 6.5 Hz, 3H), 1.10 (s, 3H), 1.37 (s, 3H), 1.71 (br s, 3H), 2.03-2.26 (m, 2H), 2.26-2.50 (m, 2H), 2.54-2.78 (m, 3H), 3.19 (dd, J = 16, 4 Hz, 1H), 4.67 (br s, 1H), 5.43 (br d, J = 4 Hz, 1H), 6.14 (d, J = 1.5 Hz, 1H), 6.29 (d, J = 1.5 Hz, 1H); HRMS (CI) calcd. for $C_{24}H_{33}O_2$ (MH^+) 353.2481, found 353.2501.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(3-octenyl)-6*H*-dibenzo[b,d]pyran (48).** Alternate name (*cis*-3-(3-Octenyl)-Δ^8-THC). Prepared from alkyne **47** by partial reduction as described above for the preparation of alkene **6**, to afford 115 mg (87%) of the product, as a clear, yellow oil: R_f 0.4 (1:9 EtOAc/hexanes); GC 98% purity; ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.88 (t, J = 6 Hz, 3H), 1.10 (s, 3H), 1.2-1.4 (m, 4H), 1.37 (s, 3H), 1.71 (br s, 3H), 2.2-2.5 (m, 4H), 2.69 (td, J = 11, 4 Hz, 1H), 3.19 (dd, J = 16, 4 Hz, 1H), 4.66 (s, 1H), 5.3-5.5 (m, 3H), 6.12 (d, J = 1.6 Hz, 1H), 6.29 (d, J = 1.5 Hz, 1H); HRMS (CI) calcd. for $C_{24}H_{35}O_2$ (MH^+) 355.2637, found 355.2654.

3-(3,5-Dimethoxyphenyl)-2-propyn-1-ol (49). Prepared from triflate **2** and propargyl alcohol by the procedure used to prepare alkyne **3**. It afforded alkyne **49** (2.06 g, 49%) as a yellow solid: ^{1}H NMR δ 1.65 (t, J = 6.3 Hz, 1H), 3.78 (s, 6H), 4.50 (d, J = 6.1 Hz, 2H), 6.45 (t, J = 2.3 Hz, 1H), 6.60 (d, J = 2.3 Hz, 2H).

3-(3,5-Dimethoxyphenyl)-1-bromopropane (50). A solution of alkyne **49** (2.06 g, 11 mmol) in MeOH (20 mL) was reduced with H_2 (40 psi) over 5% palladium on charcoal (137 mg) in a Parr hydrogenation apparatus. After 2 h, the mixture was filtered through diatomaceous earth washing with MeOH, and the filtrate was concentrated and placed under high vacuum to afford the crude product 3-(3,5-dimethoxyphenyl)-1-propanol (2.36 g, 2.11 g theoretical) as a clear, yellow oil: ^{1}H NMR δ 1.36 (br s, 1H), 1.88 (pentet, J = 6.6 Hz, 2H), 2.67 (t, J = 7.5 Hz, 2H), 3.69 (t, J = 6.7 Hz, 2H), 3.78 (s, 6H), 6.29-6.43 (m, 3H).

Phosphorus tribromide[36] (0.5 mL, 5 mmol) was added dropwise over 3 min to a stirred solution of 3-(3,5-dimethoxyphenyl)-1-propanol (2.1 g, 11 mmol) and pyridine (0.5 mL, 6 mmol) in anhyd. toluene (30 mL) under N_2 to afford an off-white suspension. The stirred mixture was then heated to reflux for 10 min, cooled, then quenched with H_2O and extracted with Et_2O. The extract was washed with H_2O and satd. NaCl, dried, and concentrated, and chromatographed (10% EtOAc/hexanes) to give **50** (1.06 g, 38%) as a clear, light yellow liquid: ^{1}H NMR δ 2.15 (pentet, J = 7.0 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 3.40 (t, J = 6.5 Hz, 2H), 3.78 (s, 6H), 6.35 (br s, 3H).

1-(3,5-Dimethoxyphenyl)-4-octyne (51). 1-Pentyne (2 mL, 20 mmol) was added to a stirred solution of nBuLi (2.5 *M* in hexanes, 6.0 mL, 15 mmol) in anhyd. THF (20 mL) at 0° C under N_2. After stirring for 1 h at 0° C, an additional 1 mL (10 mmol) of 1-pentyne was added. After stirring for 1 h at 0° C, a solution of bromide **50** (1.06 g, 4.1 mmol) and LiI (0.63 g, 4.7 mmol) in anhyd. THF (20 mL) was added. The mixture was heated at reflux for 3 h, cooled, quenched with aq. NH_4Cl and extracted with Et_2O. The extract was washed with H_2O and satd. NaCl, dried, concentrated, and chromatographed (4% EtOAc/hexanes) to afford alkyne **51** (775 mg, 77%) as a clear, yellow liquid: ^{1}H NMR δ 0.99 (t, J = 7.2 Hz, 3H), 1.49 (pentet, J = 7.3 Hz, 2H), 1.78 (pentet, J = 7.2 Hz, 2H), 2.02-2.29 (m, 4H), 2.67 (t, J = 7.4 Hz, 2H), 3.78 (s, 6H), 6.28-6.43 (m, 3H).

(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(4-octynyl)-6*H*-dibenzo[b,d]pyran (52). Prepared from ether **51** by the procedures used to prepare resorcinol **4** and THC **5** to afford THC **52** (123 mg, 13%): GC 95% purity; ^{1}H NMR δ 0.98 (t, J = 7.1 Hz, 3H), 1.10 (s, 3H), 1.38 (s, 3H), 1.71 (br s, 3H), 2.0-2.3 (m, 4H), 2.57 (t, J = 7.4 Hz, 2H), 2.70 (td, J = 11, 5 Hz, 1H), 3.21 (br dd, J = 14, 4 Hz, 1H), 4.66 (s, 1H), 5.43 (br d, J = 5 Hz, 1H), 6.12 (d, J = 1.2 Hz, 1H), 6.29 (d, J = 1.2 Hz, 1H); HRMS (CI) calcd. for $C_{24}H_{33}O_2$ (MH^+) 353.2481, found 353.2489.

***Z*-(6a*R*, 10a*R*)-6a,7,10,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-(4-octenyl)-6*H*-dibenzo[b,d]pyran (53).** Alternate name (*cis*-3-(4-Octenyl)-Δ^8-THC). Prepared from alkyne **52** by partial reduction as described above for the preparation of alkene **6**, to afford 14 mg (5%) of the product, as a clear, yellow oil: R_f 0.5 (1:9 EtOAc-hexanes); GC 90% purity; ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.89 (t, J = 7.1 Hz, 3H), 1.10 (s, 3H), 1.37 (s, 3H), 1.71 (br s, 3H), 2.47 (t, J = 7.7 Hz, 2H), 2.70 (td, J = 11.1, 4.6 Hz, 1H), 3.20 (dd, J = 16.0, 3.5 Hz, 1H), 4.70 (s, 1H), 5.3-5.5 (m, 3H), 6.10 (d, J = 1.6 Hz, 1H), 6.28 (d, J = 1.6 Hz, 1H); HRMS (CI) calcd. for $C_{24}H_{35}O_2$ (MH^+) 355.2637, found 355.2617.

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