and the solvent was evaporated under reduced pressure (25 °C, 12 Torr). The residue was purified by distillation to give 5,6-dihydro-2*H*-thiopyran: 1.31 g (65%); bp 58–60 °C (20 Torr).

Synthesis of (*Z*)-1-Phenyl-1-propene from (*E*)-1-Morpholino-1-phenyl-1-propene. The following procedure (A) for the preparation of (*Z*)-1-phenyl-1-propene is illustrative. To a stirred suspension of 9-BBN (2.44 g, 20 mmol) in THF (4 mL) was added (*E*)-1-morpholino-1-phenyl-1-propene (4.06 g, 20 mmol). The suspension became a clear solution after 3 h at 25 °C. The ^{11}B NMR spectrum of the solution indicated the absence of 9-BBN. The solvent THF was evaporated under reduced pressure (25 °C, 12 Torr). Methanol (0.8 g, 25 mmol) was added to the residue. A mildly exothermic reaction occurred, and the reaction mixture solidified. The solid was triturated with *n*-pentane (3 × 20 mL). The *n*-pentane solution was decanted and washed successively with water (2 × 10 mL), 3 N sodium hydroxide (3 × 10 mL), 3 N hydrochloric acid (3 × 10 mL), and water (2 × 10 mL) to remove *B*-methoxy-9-BBN and morpholine. The *n*-pentane layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure (25 °C, 12 Torr). The residue was purified by distillation to give isomerically pure (*Z*)-1-phenyl-1-propene: 1.90 g (81%); bp 62–64 °C (12 Torr).

Preparation of (*E*)-1-Phenyl-1-propene from (*E*)-1-Morpholino-1-phenyl-1-propene. The following procedure (B) for the preparation of (*E*)-1-phenyl-1-propene is typical. To a 1.0 M THF solution of (*E*)-1-morpholino-1-phenyl-1-propene (20 mL, 20 mmol), borane–methyl sulfide (2.0 mL, 20 mmol), was added at 25 °C with stirring. A yellow color developed immediately and faded completely within 0.25 h. The reaction mixture was stirred at 25 °C for 1 h and then methanolyzed. The solvent was evaporated under reduced pressure (25 °C, 12 Torr), and the resulting crude boronate ester was dissolved in THF so as to give a 1.0 M solution. It was oxidized using 30% hydrogen peroxide (2.3 mL), and the exothermic reaction was controlled by the rate of addition and by water-bath cooling to maintain the temperature below 30 °C. After 2 h, water (20 mL) and *n*-pentane (100 mL) were added to the reaction mixture. The organic phase was quickly washed with 3 N HCl (2 × 10 mL) and water (2 × 10 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated (25 °C, 12 Torr), and the residue was purified by distillation to give isomerically pure (*E*)-1-phenyl-1-propene: 1.77 g (75%); bp 72–74 °C (20 Torr).

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Supplementary Material Available: Physical properties and the spectra of the enamines used in this study are available as supplementary data (20 pages). Ordering information is given on any current masthead page.

Synthesis of Rotationally Restricted Tetrahydrocannabinol Ethers

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Two rotationally restricted tetrahydrocannabinol (THC) ethers were synthesized to test the concept that the psychopharmacological activity of cannabinoids derives, in part, from the orientation of the lone pairs of electrons of the phenolic hydroxyl oxygen. These compounds, *O*,2-propano-Δ^8-THC (**3**) and *O*,10-methano-Δ^9-THC (**12**), lock the orientation of the lone pairs of electrons toward and away from the cyclohexene ring, respectively, by restricting bond rotation through the formation of cyclic ethers. The synthesis of **3** was achieved by alkylation of the phenolic oxygen of Δ^8-THC (**1**) with 3-bromo-1-propanol followed by cyclodehydration in the presence of phosphorus pentoxide. The synthesis of **12** was achieved from a sequence of reactions that involved the cyclization of a chloroformate in a modification of the Darzens acylation of olefins. Thus, treatment of Δ^9-THC with phosgene in the presence of *N*,*N*-dimethylaniline afforded Δ^9-THC chloroformate. Subsequent intramolecular cycloaddition of the chloroformyl moiety to the Δ^9-unsaturation in the presence of $AlCl_3$ afforded the corresponding β-chloro ester **9**. Treatment of **9** with lithium aluminum hydride gave 10-(hydroxymethyl)-Δ^9-THC (**10**). Compound **12** and 10-methylene-Δ^8-THC (**11**) were obtained as a readily separable mixture by treatment of **10** with 3 mol of tosyl chloride in pyridine. ^{13}C NMR and ^1H NMR spectral assignments were made. A model study of the $TiCl_4$-mediated cleavage of the MEM ether of phenol demonstrated generation of the phenoxymethyl cation.

Two rotationally restricted tetrahydrocannabinol (THC) ethers were synthesized to test the hypothesis that the psychopharmacological activity of cannabinoids derives, in part, from the orientation of the lone pairs of electrons of the phenolic hydroxyl oxygen. Previous theoretical studies[2] have indicated that there are two minimum energy positions for the phenol hydroxyl in (−)-Δ^9-THC (**7**), the major psychopharmacologically active component of cannabis.[3] In these conformations, the lone pairs of electrons on the C1 oxygen are oriented toward and away from the cyclohexane ring. The two rotationally restricted THC ethers discussed here were designed to mimic the two phenol conformations of (−)-Δ^9-THC. Thus, *O*,2-propano-Δ^8-THC (**3**) and *O*,10-methano-Δ^9-THC (**12**) orient the lone pairs of electrons toward and away from the cyclohexane ring, respectively, by restricting bond rotation through the formation of cyclic ethers.

The accessible conformations of both **3** and **12** were calculated by using the method of molecular mechanics as encoded in the MMP2(85) program.[4] For **3**, two accessible minimum energy conformers were found that differend principally in the conformation of the new fourth ring. In the global minimum structure, the chroman ether

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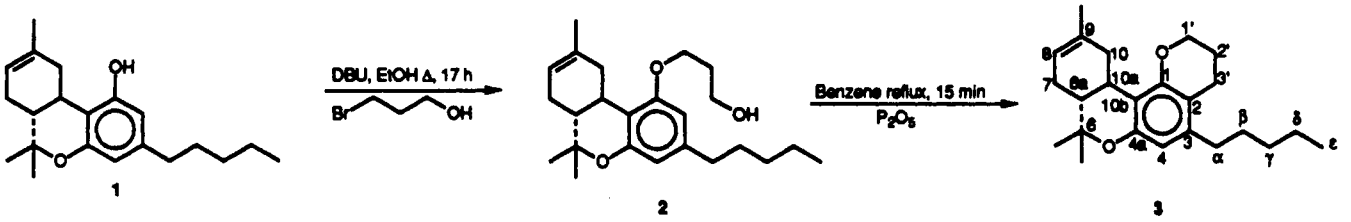
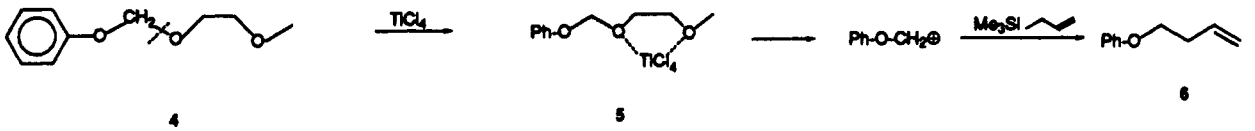
0022-3263/91/1956-1549$02.50/0

Scheme I



Scheme II



1′-CH_2 points into the α face of the molecule. In the second minimum energy conformer, which is 0.81 kcal/mol higher in steric energy than the global minimum conformer, the chroman ether 1′-CH_2 is puckered into the β face of the molecule.

For **12**, three accessible minimum energy conformers were found. Two low energy conformers (I and II) differed in steric energy by only 0.40 kcal/mol, while the third conformer (III) was 1.99 kcal/mol higher than the global minimum conformer (I). The first two conformers of **12** differed mainly in the conformation of the new fourth ring. In conformer I, the methylene bridge points into the β face of the molecule, while in conformer II, this bridge points into the α face of the molecule. In conformer III, the methylene bridge points into the α face of the molecule and further differs from conformers I and II in the pucker of the pyran ring. The details of these calculations, as well as a full description of the results will be published elsewhere.[5]

Molecular electrostatic potential (MEP) calculations[5] revealed that the accessible conformers of both **3** and **12** generate MEPs similar to those generated by (−)-Δ^9-THC in its two phenol conformations. Therefore, accessible conformers of **3** and **12** mimic the important structural features of active cannabinoids while separating the orientations of the lone pairs of electrons.

The synthesis of **3** was straightforward, following a general approach for the construction of the chroman ring system[6,7] (Scheme I). Alkylation of the phenolic oxygen of Δ^8-THC (**1**) with 3-bromo-1-propanol in the presence of DBU gave *O*-(3-hydroxypropyl)-Δ^8-THC (**2**) in 87% yield. Cyclization was mediated by P_2O_5 to provide **3** in 37% yield. The structures of these compounds were supported by their HRMS and ^{1}H NMR spectra, with **3** being further characterized by ^{13}C NMR, two dimensional heteronuclear correlation spectroscopy, and elemental analysis. The ^{13}C NMR spectrum (Table I) agreed closely with that of Δ^8-THC[8] with notable deviations for the C2, C3, and αCH_2 resonances, which exhibited shift changes of +4, −2.1, and −3.2 ppm, respectively. These positions are reasonably expected to show maximal changes for a new substituent at C2. The mass spectrum base ion at *m/e* 271 represented loss of five carbons of the cyclohexene ring from a retro-Diels–Alder fragmentation plus loss of a 6-methyl group, typical of Δ^8-cannabinoids.[9]

Table I. ^{13}C NMR Chemical Shift Assignments for Cannabinoids[a]

	3	7[b]	8	9	10	11	12
C1	154.1[c]	154.4[c]	150.2[c]	152.5[c]	155.2[c]	154.8[c]	153.2[c]
C2	111.6[d]	107.5	112.7	106.8	110.4[d]	108.9[d]	106.8[d]
C3	140.3	142.5	143.1	150.0	142.7	143.7[e]	142.9
C4	109.6	109.8	116.4	111.5	108.2[d]	110.7[d]	108.2[d]
C4a	152.1[c]	154.1[c]	154.7[c]	153.8[c]	154.4[c]	154.4[c]	152.9[c]
C10b	111.8[d]	108.9	114.4	144.3	109.8	106.6	*f*
C6	76.1	77.1	77.7	78.7	77.9	76.5	79.0
C6a	45.2	45.7	45.3	42.8	48.8	47.6	44.0
C7	28.0	25.0	24.7	23.0	22.9	29.3	23.4
C8	119.1	31.1	30.9	30.7	29.5	125.3	32.5
C9	135.0	133.8	135.4	64.0	135.6	133.8	128.0
C10	36.2	123.7	122.1	*g*	135.4	145.9[e]	122.8
C10a	31.9	33.6	33.8	35.1	35.4	38.0	30.4
6α-Me	18.3	19.2	19.3	21.2	18.3	18.4	22.1
6β-Me	27.5	27.5	27.3	27.5	27.3	27.0	28.1
9-Me	23.4	23.3	23.3	21.7	19.2	19.8	17.7
αC	32.2	35.4	35.2	35.7	35.6	35.5	35.8
βC	29.3	30.5	30.3	30.6	30.3	30.4	30.7
γC	31.9	31.4	31.3	31.2	31.3	31.4	31.4
δC	22.5	22.5	22.4	22.3	22.3	22.4	22.4
εC	13.9	14.0	13.8	13.8	13.7	13.9	13.8
O(10)			148.6	162.2	59.0	107.4	65.2
Pr1′	65.4						
Pr2′	*f*						
Pr3′	21.7						

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Data from ref 8. [c–e] Signals in any vertical column may be reversed. [f] Not observed as a resolved resonance, possibly due to overlap. [g] Not assigned from among the extra peaks in the spectrum of unstable **9**.

The synthesis of compound **12** offered more difficulties due to the unique chemistries of Δ^9-cannabinoids, which include preferred formation of or isomerization to the thermodynamically preferred Δ^8 structures.[10] The approach that we examined first to establish the bridged structure was the intramolecular cycloaddition of a phenoxymethyl cation to the Δ^9 unsaturation. Additions of chloromethyl ethers to olefins, presumably via the cation, have been reported.[11,12] However, the synthesis of the required cannabinoid chloromethyl ether could not be achieved by the approach applied to simpler phenols.[13,14]

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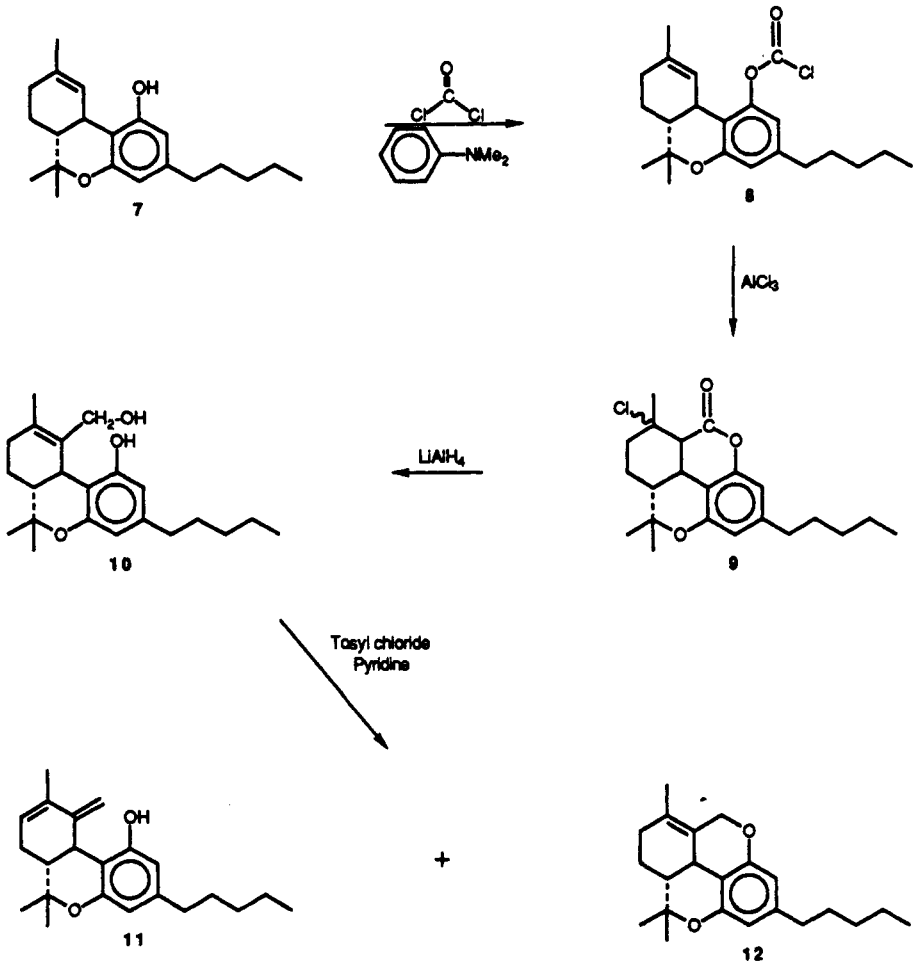
Scheme III



An alternative method of generating a phenoxymethyl cation was sought, using the cleavage of the (methoxyethoxy)methyl (MEM) ether of phenol (**4**, Scheme II) as a model system. The MEM ether, which was prepared by standard methods,[15] was treated with $TiCl_4$,[15,16] and the cation was trapped with allyl trimethylsilane. The product was shown to be 4-phenoxy-1-butene (**6**) (^1H NMR), demonstrating the production of the phenoxymethyl cation.

The MEM ether of Δ^9-THC was prepared and treated with $TiCl_4$ or $ZnBr_2$ by applying the above approach. Extensive degradation occurred when a range of stoichiometries of either Lewis acid was employed and a cyclized product could not be identified.

Intramolecular cyclization to establish the O-10 bridge and subsequent synthesis of **12** was achieved by employing Δ^9-THC chloroformate (**8**) as shown in Scheme III. The chloroformate was prepared by treatment of Δ^9-THC (**7**) with phosgene in the presence of *N,N*-dimethylaniline following standard methods.[17] Cyclization of **8** was achieved with $AlCl_3$ to afford the β-chloro ester **9** in a reaction that is analogous to the Darzens reaction of acid chlorides and anhydrides with olefins.[18] The acylation of olefins has generally been unsuccessful with chloroformates. Only one previous report[19] was made of such a reaction in which unexpected regiochemistry was obtained.[20] Successful acylation from **8** may, in part, be due to the use of an aryl chloroformate structure in contrast to the typically examined alkyl chloroformates, the latter being unstable to $AlCl_3$.

Elimination of HCl from **9** to give the corresponding α,β-unsaturated ester was attempted unsuccessfully with DBU, K_2CO_3, NaOMe, or by heat alone. The elimination and subsequent reduction to the allylic alcohol **10** was achieved directly, however, when **9** was treated with $LiAlH_4$. Dehydrohalogenation in preference to reduction is typical of tertiary halides treated with $LiAlH_4$.[21]

The method of cyclization of 1,5-diols to pyrans by heating in DMSO[22] was applied to **10**. The product, obtained in 60% yield, was identified as the diene **11** by elemental and spectral analyses. The assignment of the exocyclic methylene was supported by the heteronuclear correlation spectrum, which correlated the ^1H NMR δ 4.84 and 5.09 vinyl proton singlets with the ^{13}C NMR 107.4 ppm vinyl C1′ resonance. The above data, together with that of the δ 5.68 resonance for the 8-hydrogen, established the diene structure.

The cyclized product **12** was obtained as a readily separable mixture of **11** and **12** by treatment of **10** with 3 mol of *p*-toluenesulfonyl chloride in pyridine.[23] Elemental

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and HRMS analyses were in agreement with the structure of **12**. The ^1H NMR spectrum of **12** showed two doublets at δ 4.52 and 4.90 for the O,10 methylene bridge. The upfield doublet was broadened by further splitting, which must be of a long range nature such as a "W" relationship of protons. This is in agreement with molecular mechanics calculations, which indicated that in two of the accessible conformations of **12** the methylene was puckered back to the α face of the cannabinoid such that the β proton assumes a "W" relationship with the 10a proton. The ^{13}C NMR spectrum resonance at 65.2 ppm was assigned to the O,10 methylene bridge and correlated with the above proton resonances by heteronuclear correlation spectroscopy. These data and the absence of both an OH absorption in the IR spectrum and a vinyl proton resonance in the ^1H NMR spectrum established the bridged structure with a Δ^9 unsaturation.

In addition to providing compounds of defined conformations for biological testing, the above syntheses introduce the potential of expanding the utility of the Darzens reaction by its extension to acylation with aryl chloroformates.

Experimental Section

The ^1H NMR, ^{13}C NMR, and 2D NMR spectra were recorded on a Bruker 250 spectrometer except for the noted single spectrum recorded on a Varian 90-MHz EM390 spectrometer. IR spectra were run in NaCl cells on a Shimadzu Model IR-460 spectrophotometer. Whatman K6F silica gel was employed for thin-layer chromatography with detection by UV and phosphomolybdic acid/ceric sulfate sprays.

(6a*R*-*trans*)-3-[(6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-yl)oxy]-1-propanol (2) [*O*-(3-Hydroxypropyl)-Δ^8-THC]. Δ^8-THC (1.33 g, 4.24 mmol) in 20 mL of absolute EtOH was treated with DBU (1.89 mL, 12.6 mmol) and 3-bromo-1-propanol (1.18 mL, 13.0 mmol) under N_2 and heated at reflux for 17 h. The volatiles were evaporated in vacuo, and the residue was dissolved in EtOAc and washed with H_2O, 0.1 N HCl, and H_2O. Drying over $MgSO_4$ and evaporation of solvent left a resin that was dissolved in CH_2Cl_2 and evaporated in vacuo onto siliga gel. This was loaded onto a 70-g silica gel column and eluted with a gradient of hexane to 66% CH_2Cl_2/hexane to yield 972 mg (62%) of the title compound: HRMS, calcd for $C_{24}H_{36}O_3$ 372.266, found 372.266; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.7 Hz, ϵCH_3), 1.09 (s, 3 H, 6α-Me), 1.37 (s, 3 H, 6β-Me), 1.69 (br s, 3 H, 9-Me), 2.49 (t, 2 H, J = 7.7 Hz, αCH_2), 2.65 (dt, 1 H, J = 4.5, 10.8 Hz, 10a-H), 3.17 (dd, 1 H, J = 4.8, 16.2 Hz, 10α-H), 3.88 (t, 2 H, J = 6.1 Hz, C*H*$_2$OH), 4.12 (m, 2 H, ArOC*H*$_2$), 5.42 (br d, 1 H, J = 3.8 Hz, 8-H), 6.27 (br s, 1 H, ArH), 6.31 (bs, 1 H, ArH').

On half the above scale, where the workup was addition of silica gel to the cooled reaction mixture followed by evaporation of solvent, the yield was 87%.

(8a,*R*-*trans*)-3,4,8a,9,12,12a-Hexahydro-8,8,11-trimethyl-5-pentyl-2*H*,8*H*-[2]benzopyrano[3,4-*b*]-1-benzopyran (3) [*O*,2-Propano-Δ^8-THC]. *O*-(3-Hydroxypropyl)-Δ^8-THC (935 mg, 2.51 mmol) in 15 mL of dry benzene was added to a stirred suspension of P_2O_5 (631 mg) in 10 mL of dry benzene under N_2. After being heated at reflux for 30 min, the starting material was completely consumed as shown by TLC (5% EtOAc/toluene) and the reaction mixture was cooled to room temperature and filtered. The filtrate was diluted with EtOAc and washed with 0.1 N NaOH, H_2O, and brine and dried over $MgSO_4$. The residue upon evaporation was dissolved in CH_2Cl_2, mixed with 1 g of silica gel, freed of solvent in vacuo, and loaded onto a 50-g silica gel column. Elution with CH_2Cl_2/hexane (1:5) afforded the TLC homogeneous product (CH_2Cl_2/hexane, 1:1), which was distilled in vacuo (190 °C, 0.045 mmHg) to yield 325 mg (36%) of the title compound: HRMS, calcd for $C_{24}H_{34}O_2$ 354.255, found 354.256, UV (absolute EtOH), ϵ_{289} = 1800 L/mol·cm. ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.9 Hz, ϵCH_3), 1.09 (s, 3 H, 6α-Me), 1.36 (s, 3 H, 6β-Me), 1.70 (br s, 3 H, 9-Me), 2.43 (t, 2 H, J = 7.9 Hz, αCH_2), 2.64 (t + m, 3 H, J = 6.6 Hz, $ArCH_2$ [pr] + 10a-H), 3.17 (dd, 1 H, J = 3.6, 17.4 Hz, 10α-H), 4.09 (m, 1 H, ArOCH), 4.17 (m, 1 H, ArOCH'), 5.42 (br s, 1 H, 8-H), 6.28 (s, 1 H, ArH). Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.66. Found: C, 81.21; H, 9.66.

Carbonochloridic Acid, (6a*R*-*trans*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-yl Ester (8) [Δ^9-THC Chloroformate]. Δ^9-THC (1.15 g, 3.67 mmol) in 10 mL of dry CH_2Cl_2 was treated with 20% phosgene in toluene (1.93 M) (3.80 mL, 7.34 mmol) at 0 °C under N_2. After 5 min dry *N*,*N*-dimethylaniline (0.93 mL, 7.34 mmol) was added with stirring. The reaction was stirred at 0 °C for 0.5 h and ambient temperature for 22 h. The reaction was quenched with ice and extracted with water, 1 N HCl, and brine (2×). Drying over Na_2SO_4 and evaporation of solvent afforded a resin, which was eluted from 10 g of silica gel with 20% CH_2Cl_2/heptane. Removal of solvent in vacuo yielded 1.30 g (94%) of the title compound. The compound decomposes upon brief standing on a TLC plate, showing a streak to a spot with the R_f of Δ^9-THC: HRMS, calcd for $C_{22}H_{29}O_3Cl$ 376.181, found 376.180; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.8 Hz, ϵCH_3), 1.08 (s, 3 H, 6α-Me), 1.42 (s, 3 H, 6β-Me), 1.70 (br s, 3 H, 9-Me), 2.50 (t, 2 H, J = 7.7 Hz, αCH_2), 3.16 (br d, 1 H, J = 10.9 Hz, 10a-H), 5.96 (br s, 1 H, 10-H), 6.53 (d, 1 H, J = 1.6 Hz, H-2), 6.61 (d, 1 H, J = 1.3 Hz, H-4).

6-Chloro-5a,7,8,8a,9,10c-hexahydro-6,9,9-trimethyl-2-pentyl-5*H*,6*H*-[2]benzopyrano[5,4,3-*cde*][1]benzopyran-5-one (9) [*O*,10-Carbonyl-9-chlorohexahydrocannabinol]. Δ^9-THC chloroformate (16.5 g, 43.9 mmol) in dry CH_2Cl_2 (72 mL) was added in one portion to a stirring suspension of $AlCl_3$ (17.5 g, 132 mmol) in dry CH_2Cl_2 (231 mL) under N_2. The reaction mixture turned dark red and nearly all the $AlCl_3$ appeared to dissolve. At 40 min the reaction was quenched by the rapid addition of K_2CO_3 (36.4 g, 264 mmol) in 35 mL of H_2O with vigorous stirring. After the boiling subsided, the granular precipitate was filtered through a course fritted filter. The amount of H_2O employed in the quenching process was limited to avoid the formation of a difficult to filter pasty solid. The resin obtained after removing the solvent in vacuo was eluted from 600 g of silica gel with 40% CH_2Cl_2/hexane to yield 8.47 g (51%) of the title compound: HRMS, calcd for $C_{22}H_{29}O_3Cl$ 376.181, found 376.180; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, ϵCH_3), 1.24 (s, 3 H, 6α-Me), 1.47 (s, 3 H, 6β-Me), 2.17 (d, 3 H, J = 2.5 Hz, 9-Me), 2.50 (t, overlap, J = 7.6 Hz, αCH_2), 3.36 (br d, 1 H, J = 11.0 Hz, 10a-H), 6.39 (d, 1 H, J = 1.2 Hz, ArH), 6.42 (d, 1-H, J = 1.2 Hz, ArH').

(6a*R*-*trans*)-6a,7,8,10a-Tetrahydro-1-hydroxy-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-10-methanol (10) [10-(Hydroxymethyl)-Δ^9-THC]. *O*,10-Carbonyl-9-chlorohexahydrocannabinol (8.28 g, 22.0 mmol) dissolved in dry ether (83 mL) was added to $LiAlH_4$ (0.83 g, 22.0 mmol) suspended in 83 mL of dry ether with vigorous stirring under N_2 at a rate not to exceed maintaining control of the vigorus reaction (1.5 min). After 35 min the reaction was quenched by sequential addition of 0.83 mL of H_2O, 0.83 mL of 15% (w/v) NaOH, and 2.49 mL of H_2O with stirring. The precipitate was filtered with the aid of Celite and evaporated in vacuo and reevaporated from CH_2Cl_2/MeOH to afford a foam. Elution from 500 g of silica gel with 3% acetone/CH_2Cl_2 afforded 3.21 g (42%) of the title compound as pale yellow crystals. The compound could be recrystallized from CH_3CN, mp 160–3 °C: HRMS, calcd for $C_{22}H_{32}O_3$ 344.235, found 344.326; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.6 Hz, ϵCH_3), 1.04 (s, 3 H, 6α-Me), 1.33 (s, overlap, 6β-Me), 1.86 (br s, 3 H, 9-Me), 2.46 (t, 3 H, J = 7.7 Hz, αCH_2), 3.14 (br d, br s, 2 H, J = 10.2 Hz, 10a-H, OH), 3.75 (d, 1 H, J = 11.9 Hz, C*H*-OH), 4.12 (d, 1 H, J = 11.9 Hz, C*H'*-OH), 6.30 (s, 2 H, ArH_2).

(6a*R*-*trans*)-6a,7,10,10a-Tetrahydro-6,6,9-trimethyl-10-methylene-3-pentyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol (11) [10-Methylene-Δ^8-THC]. 10-(Hydroxymethyl)-Δ^9-THC (48 mg, 0.14 mmol) in 0.7 mL of anhydrous DMSO, degassed under vacuum in a septum-sealed reacti-vial, was heated at 132 °C for 1 h. TLC (1:1 CH_2Cl_2/hexane) showed the reaction to be complete and the solvent was removed in vacuo at 50 °C. The residue was chromatographed on silica gel, eluting with 35% CH_2Cl_2/hexane, to yield 27 mg (60%) of the title compound. This material was also obtained as a byproduct of the *p*-toluenesulfonyl chloride/pyridine-mediated cyclization of 10-(hydroxymethyl)-Δ^9-THC (see below). Bulb-to-bulb distillation afforded the product as a water

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white resin, bp 170 °C/0.04 mmHg: HRMS, calcd for $C_{22}H_{30}O_2$ 326.225, found 326.224; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.8 Hz, ϵCH_3), 1.09 (s, 3 H, 6α-Me), 1.36 (s, 3 H, 6β-Me), 1.91 (d, 3 H, J = 1.1 Hz, 9-Me), 2.49 (t, 2 H, αCH_2), 3.18 (d, 1 H, J = 11.0 Hz, 10a-H), 4.84 (s, 1 H, =CH), 4.99 (s, 1 H, OH, D_2O exchangeable), 5.09 (s, 1 H, =CH′), 5.68 (br d, 1 H, J = 3.4 Hz, 8-H), 6.35 (d, 1 H, J = 1.4 Hz, ArH), 6.38 (d, 1 H, J = 1.5 Hz, ArH′); IR (CH_2Cl_2) 3510 cm^{-1} (OH). Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.71; H, 9.31.

(5a*R*-*trans*)-5a,7,9,10c-Tetrahydro-5,5,8-trimethyl-2-pentyl-5*H*,6*H*-[2]benzopyrano[5,4,3-*cde*][1]benzopyran (12) [*O*,10-Methano-Δ^9-THC]. 10-(Hydroxymethyl)-Δ^9-THC (3.1 g, 9.0 mmol) in dry pyridine (50 mL) was treated with *p*-toluenesulfonyl chloride (5.14 g, 27.0 mmol) in dry pyridine (10 mL) over a period of 0.5 min with stirring. After being stirred for 2.2 h, the reaction was quenched by the addition of H_2O (6 mL) and stirred for 10 min. Volatiles were evaporated in vacuo and the residue was dissolved in CH_2Cl_2 and extracted twice with saturated $NaHCO_3$, 1 N HCl, and H_2O. Drying over Na_2SO_4 and removing the solvent in vacuo afforded a foam that was eluted from silica gel (30 g) with CH_2Cl_2. The product-containing fractions were combined and rechromatographed from a Merck size C silica gel column, eluting with 20% CH_2Cl_2/hexane, to afford 534 mg (18%) of the title compound followed by 338 mg (12%) of 10-methylene-Δ^8-THC. The title compound was distilled bulb-to-bulb to afford a pale yellow resin, bp 175 °C/ 0.04 mmHg. On exposure to air, this material yellowed and showed degradation products by HPLC (Waters RCM C-18, 85% CH_3CN/H_2O, 280 nm): HRMS, calcd for $C_{22}H_{30}O_2$ 326.225, found 326.225; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 6.7 Hz, ϵCH_3), 1.26 (s, 3 H, 6α-Me), 1.42 (s, 3 H, 6β-Me), 1.69 (d, 3 H, J = 0.88 Hz, 9-Me), 2.17 (m, 2 H, 8-CH_2), 2.45 (t, 2 H, J = 7.6 Hz, αCH_2), 3.10 (br d, 1 H, J = 9.6 Hz, 10a-H), 4.52 (br d, 1 H, J = 13.2 Hz, *O*,10-CH), 4.90 (d, 1 H, J = 13.0 Hz, *O*,10-CH′), 6.20 (d, 1 H, J = 1.3 Hz, ArH), 6.23 (d, 1 H, J = 1.3 Hz, ArH′). Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.63; H, 9.07.

Cleavage of (β-Methoxyethoxy)methyl Phenyl Ether (5). (β-Methoxyethoxy)methyl phenyl ether (207 mg, 1.13 mmol) and allyltrimethylsilane (0.27 mL, 1.71 mmol) in 5 mL of dry CH_2Cl_2 were cooled to −20 °C under N_2 and treated with $TiCl_4$ (0.15 mL, 1.37 mmol) in five portions over 10 min with stirring. After being stirred for 1 h at −20 °C, the reaction was quenched with aqueous $NaHCO_3$ and extracted with ether (2×). The combined ether extracts were washed with H_2O (3×), dried over $MgSO_4$, and evaporated to a light yellow liquid (275 mg) after pumping at high vacuum. Elution from silica gel (12 g) with 9 to 11% CH_2Cl_2/hexane afforded 4-phenoxy-1-butene (36 mg, 22%) as the major and earliest eluting product: ^{1}H NMR, 90 MHz ($CDCl_3$) δ 2.60 (q, [dt], 2 H, J = 6 Hz, 3-CH_2), 4.10 (t, 2 H, J = 6.5 Hz, 0-CH_2), 5.20 (m, 2 H, =CH_2), 6.02 (m, 1 H, CH=), 7.01 (m, 3 H, ArH_3), 7.36 (m, 2 H, ArH_2). The compound was unstable to GC and MS at 80 °C.

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Supplementary Material Available: 2D heteronuclear correlation spectra of 3 and 12 (2 pages). Ordering information is given on any current masthead page.

Synthesis of 1- and 1,2,2′-Deuteriated Deoxyribose and Incorporation into Deoxyribonucleosides

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Thymidine, deoxycytidine, deoxyadenosine, and deoxyguanosine have been prepared with deuterium substitution at position 1′ and at positions 1′, 2′, and 2″ from deuteriated deoxyribose. The synthetic strategy involved reduction of the bis(*tert*-butyldimethylsilyl) derivative **4a** of 2-deoxyribonolactone (**3a**) with Dibal-D followed by deprotection (HCl/MeOH and tetrabutylammonium fluoride) to give 1-deuterio methyl glycoside **7a** which was converted to the 1-deuterio 3,5-ditoluoyl methyl glycoside **8a**. Preliminary exchange of 2-deoxyribonolactone with NaOMe/MeOD brought about 2,2′-dideuteriation; treatment as above gave the 1,2,2′-trideuterio 3,5-ditoluoyl methyl glycoside **8b**. **8a** and **8b** were condensed with heterocyclic bases via α-chloro derivatives **9a** and **9b** to form deoxynucleosides. New methods were utilized for preparation of deoxycytidine and deoxyguanosine which are improvements over published procedures.

The investigation of interactions of both small and large molecules with oligonucleotides as models of their interactions with genomic DNA is a rapidly expanding field of study[1] due to the ready availability of sequence-specific DNA oligomers via automated DNA synthesis[2] and to the development of highly sophisticated instrumentation and software for analysis of solution structure, particularly in the area of NMR spectroscopy.[3] Two-dimensional NMR correlated spectroscopy (COSY) allows the spectral assignment of protons connected via small numbers of bonds

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