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Halogenated Cannabinoid Synthesis

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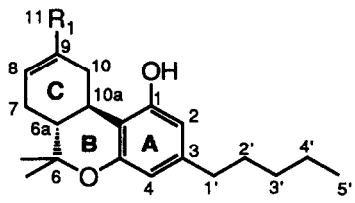
Abstract: A convenient synthesis of several tricyclic and bicyclic fluoro- and iodo analogs of cannabinoids has been reported. A new, mild methodology for the synthesis of vinyl fluorides from vinylstannanes has also been demonstrated. These C9 halo-functionalized cannabinoid analogs, along with (-) and (+)-Δ^9-THC carboxylic acids, were screened for anti-inflammatory activity in the mouse ear edema assay. It was interesting to find that both enantiomers of Δ^9-THC carboxylic acid were moderately active as anti-inflammatories. The bicyclic vinyl iodide (**18C**) also showed appreciable anti-inflammatory activity.

The discovery of the non-classical cannabinoids and the early recognition of their activities have shed light on the structural requirements for activity.[1] There is very little information on the synthesis of halogen substituted cannabinoids or the effect of halogen substitution on cannabinoid activity.[2] Tetrahydrocannabinol (THC) analogs with a halogen substituent at C9 are apparently unknown. Very recently, the pharmacological activities and relative cannabinoid receptor site(s) binding affinities of (-)-Δ^8-THC [**1**, $R_1 = CH_3$] analogs with a halogen substituent at C11 (**1**, $R_1 = CH_2F$) and C5′ (**2**, X = F, Br, I) have been described.[2b] Another analog (**2**, X = ^{18}F), has been used to study the biodistribution of cannabinoids in primate brain by positron emission tomography (PET) technique.[3] Because of the low binding affinity of (-)-5′-^{18}F-Δ^8-THC, the PET experiment was unable to distinguish between the specific and the non-specific binding sites for cannabinoids. One of the significant features in determining the activity is the presence of a hydroxyl substituent either at C9 or C11 in the C ring.[4] It would be useful to prepare C9 halogen substituted THC derivatives because unlike the oxygen substituted cannabinoids, in which the hydroxyl can act as a donor or an acceptor of a hydrogen bond, halogens act only as hydrogen bond acceptors. The steric and electronic effects of halogen substitution on cannabinoid structure-activity relationships can be dissected by using fluoro- and iodo substituents.



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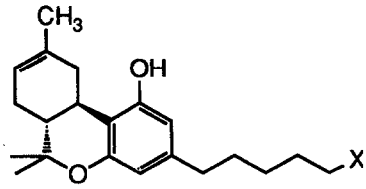
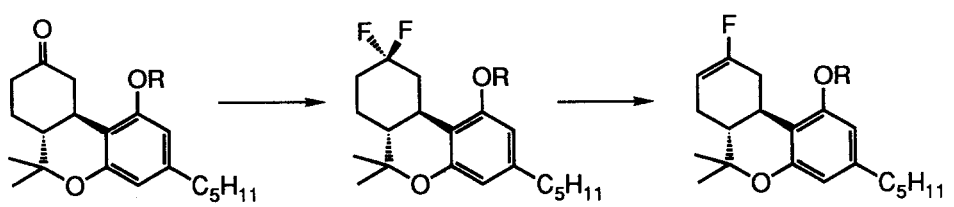


2

This paper describes the synthesis and some properties of novel fluorine and iodine substituted cannabinoids. The application of a new method of electrophilic fluorination to a difficult case is also described. The fluorination of ketones and alcohols with dialkylaminosulfur trifluoride and its analogs is well precedented.[5] Therefore, (-)-11-nor-9-keto-hexahydrocannabinol (HHC) (**3a**)[6] was an ideal starting material for 9-fluoro-HHC analogs (scheme 1). The phenolic hydroxyl in **3a** was protected as the acetate (**3b**) in 83% yield. Treatment of **3b** with 10 equivalents of dimethylaminosulfur trifluoride (methyl-DAST) in dichloromethane (CH_2Cl_2) under nitrogen at ambient temperature for 2 days afforded bis-fluoride **4a** in excellent yield along with a trace of vinyl fluoride **5a**, which presumably is formed through loss of an α-hydrogen from the fluoro-carbocation intermediate. Acetate hydrolysis in **4a** with potassium carbonate in methanol at 22 °C gave **4b** in 80% yield. The ^{13}C NMR spectrum of **4b** proved interesting. Fluorine-bearing carbon C9 showed not only the expected coupling to the fluorine atoms (triplet, J = 240.7 Hz) but also long-range coupling to C8, C10 (triplets, J = 24.4 Hz) and C7 and C10a (doublets, J = 10.4 Hz). Examination of Drieding models indicated that both C7 and C10a form dihedral angles of 180° and 90° with the equatorial and axial fluorine respectively. This observation proved to be useful for the assignment of stereochemistry at C9 for monofluoro HHCs. All attempts to increase the ratio of vinyl fluoride **5a** to **4a** during the fluorination of **3b** by using a polar solvent, such as tetrahydrofuran (THF), 1,2-dimethoxyethane (DME) and N-methylpyrrolidone were unsuccessful. Therefore, a two step procedure for the synthesis of **5a** was envisioned. Elimination of hydrogen fluoride from **4a** using neutral activated alumina at 120 °C in a sealed tube for two days[7] afforded vinyl fluoride **5b** in 37% yield. It should be noted that hydrolysis of the acetate also took place during the elimination reaction. The formation of the Δ^8-isomer is not surprising as it is thermodynamically more stable than the Δ^9-isomer.[8]

In order to prepare 9-nor-9α-fluoro-HHC (**7b**), ketone **3b** was reduced with sodium borohydride in a mixture of THF and isopropanol (9:1) at 22 °C to afford 9-nor-9β-hydroxy HHC (**6**) in 80% yield (scheme 2).[4a] Fluorination of the alcohol **6** with methyl-DAST in CH_2Cl_2 at -78 °C gave 42% yield of the desired axial

Scheme 1



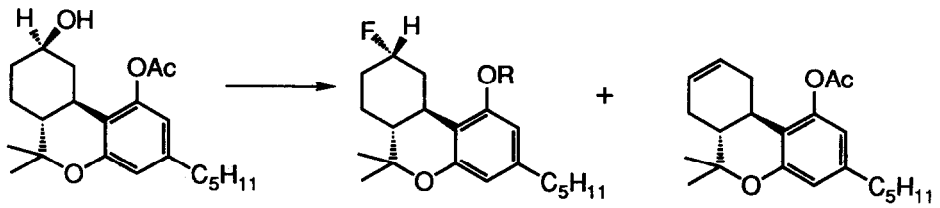
3a R = H
3b R = Ac

4a R = Ac
4b R = H

5a R = Ac
5b R = H

monofluoride acetate (**7a**) along with 21% of **8**.[9] The hydrolysis of **7a** with potassium carbonate in methanol produced phenol **7b** in 88% yield. The stereochemistry at the fluorine-bearing carbon in **7b** was determined by examination of the ^{19}F spectrum which showed a quartet of triplets (J = 46.6, 11.3 Hz) because of vicinal coupling to each of the *trans* diaxial hydrogens. Furthermore, the absence of 3-bond coupling of C7 and C10a to the fluorine atom in the ^{13}C NMR spectrum is consistent with an axial fluorine substituent. Attempts to synthesize the other isomer, 9-nor-9β-fluoro-HHC, from 9-nor-9α-OH-HHC[4a] acetate using methyl-DAST under identical conditions resulted in a mixture of products. Cyclic alcohols in which the hydroxyl group is axial and which possess a neighboring anti-periplanar hydrogen often undergo facile elimination reactions and/or rearrangements giving rise to a mixture of products.[10]

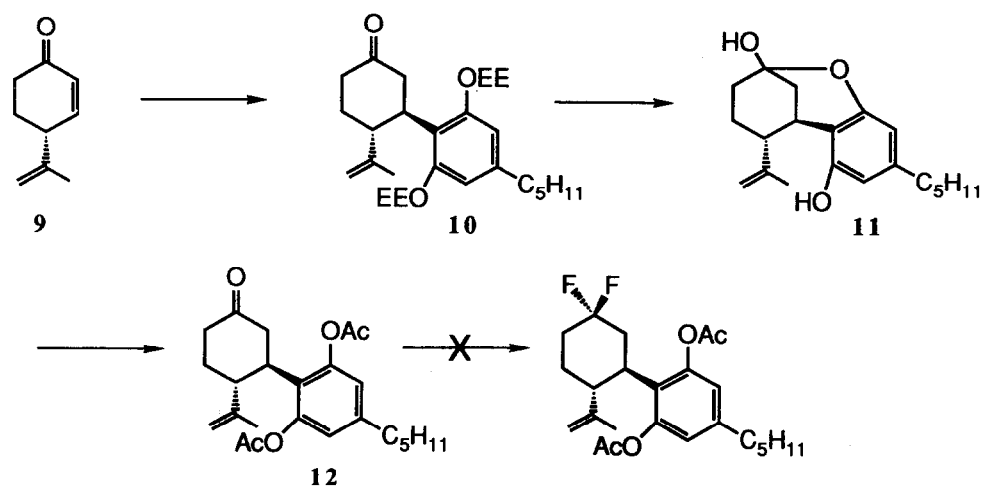
Scheme 2



6 **7a** R = Ac, **7b** R = H **8**

Bicyclic C9 halogen substituted cannabinoids were the next targets for synthesis. The synthetic pathway is summarized in Scheme 3. Ketone **10** was obtained from the reaction between racemic enone **9** and the mixed higher-order cuprate[11] derived from bis-(ethoxyethyl)ether of olivetol and lithium-2-thienylcyanocuprate.[12] Enone **9** was prepared from commercially available racemic perillaldehyde according to Razdan's procedure.[13]

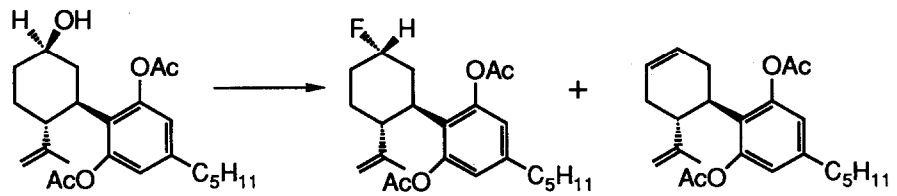
Scheme 3



9 **10** **11** **12**

The fluorination of **10** with methyl-DAST was not successful, perhaps due to the acid-labile ethoxyethyl ether protecting groups. Hydrolysis of the ethoxyethyl ether groups with catalytic p-toluenesulfonic acid in wet THF gave the hemiketal **11** which was subsequently rearranged and protected using pyridine and acetic anhydride in CH_2Cl_2 in the presence of catalytic DMAP to afford bis acetate **12** in 80% yield. The formation of the hemiketal, though unexpected, was not surprising as such acid catalyzed reactions are known.[6] Fluorination of **12** with methyl-DAST failed to give the desired geminal difluoride. Instead, a complicated mixture was produced from which no identifiable products were isolated. Fluorination of the alcohol **13** which was obtained from the reduction of **12** with sodium borohydride afforded only 9% of monofluoride **14** with an approximately equal amount of the elimination product **15** (scheme 4). The difficulty which we encountered in our attempts to prepare these fluoro analogs in acceptable yield, and the limitations of methyl-DAST as a fluorinating agent for these systems, provided the impetus for the development of a mild alternative method for the introduction of fluorine.

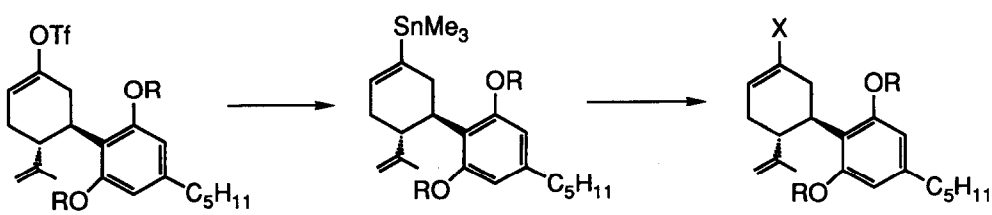
Scheme 4



13 **14** **15**

Exposure of vinyltrimethylstannanes to xenon difluoride in the presence of silver(I) salts leads to the rapid, stereospecific replacement of tin by fluorine.[14] Recent unpublished work in our laboratory has led to significant improvements in the yield for this process. This methodology appeared to be ideal for the synthesis of fluorovinyl cannabinoids. Treatment of ketone **10** with lithium diisopropylamide (LDA) in THF at 0 °C followed by N-phenyltriflimide in freshly distilled DME gave cyclohexenyl triflate **16a** (scheme 5).[15] The position of the double bond was determined by 2D-NMR (HMQC, HMBC) correlations. Hydrolytic cleavage of the ethoxyethyl ether protecting groups with pyridinium tosylate (PPTs) in methanol afforded **16b** in 57% overall yield from **10**. Palladium(0) catalyzed stannylation of the cyclohexenyl triflate (**16b**) with hexamethyl-

Scheme 5



16a R = EE
16b R = H

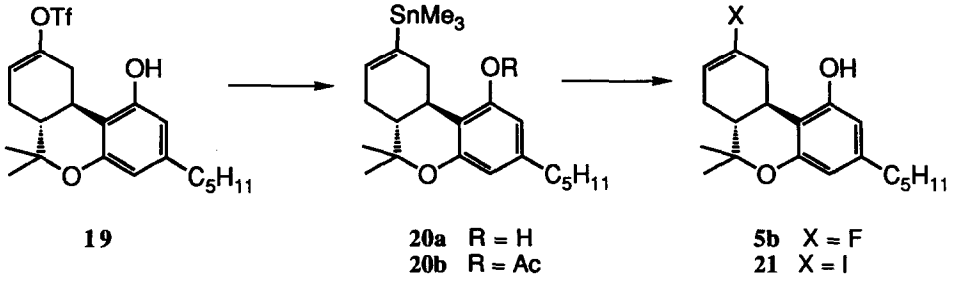
17a R = H
17b R = Ac

18a X = F, R = Ac
18b X = F, R = H
18c X = I, R = H

distannane in the presence of lithium chloride and lithium carbonate produced **17a** in 73% yield.[16] The phenolic hydroxyls in **17a** were protected as the acetates to give **17b** in 65% yield. The conversion of vinyl stannane **17b** to vinyl fluoride **18a** was carried out with silver triflate formed *in situ* from silver carbonate and trifluoromethanesulfonic acid, and xenon difluoride in CH_2Cl_2 at 22 °C.[17] Fluorination was fast (ca. 3 min) and gave rise to a mixture (5:1 ratio) of vinyl fluoride **18a** and alkene (**15**) respectively. The separation of **18a** from alkene using flash chromatography on silica gel was difficult. Separation of the free resorcinols was much easier. Hydrolysis of the acetates in the mixture followed by purification using flash chromatography produced **18b** contaminated with traces of the alkene in 57% overall yield. The fluorination of **17a** took place in lower yield (ca. 30%), and the product mixture in this case contained a number of polar byproducts. Nonetheless, the remarkable fact that **18b** could be isolated from the reaction demonstrates the utility of the method. The survival of the electron rich resorcinol in the presence of xenon difluoride is unusual and testifies to the mildness of the method.[18] This methodology was next applied to cyclohexenyl triflate **19** (scheme 6).[11] Stannylation and protection of the phenolic hydroxyl as the acetate gave **20b** in 60% overall yield from **19**. The fluorination of **20b** and subsequent hydrolysis gave (-)-9-fluoro-Δ^8-THC (**5b**) and the corresponding alkene as a 5:1 mixture in 62% yield.

Vinyl stannanes **17a** and **20a** are excellent starting materials for the preparation of vinyl iodides via a metal halogen exchange. Treatment of the vinyl stannanes **17a** and **20a** with a dilute solution of iodine in CH_2Cl_2 at 0 °C gave rise to **18c** (78% yield) and **21** (83% yield) respectively.

Scheme 6



19

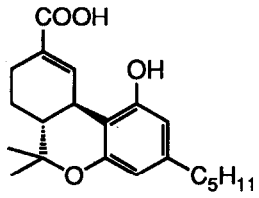
20a R = H
20b R = Ac

5b X = F
21 X = I

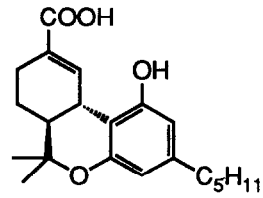
Burstein has suggested that Δ^9-THC carboxylic acid (**22**) may act as a non-steroidal anti-inflammatory agent.[19] In order to learn whether other C9-functionalized cannabinoids share this activity, and in particular whether the halogenated analogs act as anti-inflammatory agents, several were evaluated in the mouse ear edema assay.[20] The results are summarized in Table 1, and confirm that **22** is in fact active. It is interesting that **23**,[21] the enantiomer of **22**, was active at approximately the same level. This insensitivity to molecular chirality may suggest the cell membrane as the drug target, rather than the cannabinoid receptor[22] which would presumably discriminate between the two enantiomers. Iodo cannabinoid **18c** also showed appreciable activity in this assay.

In conclusion, a convenient synthesis of several fluoro- and iodo analogs of cannabinoids has been accomplished. A mild, new method for the introduction of fluorine has been demonstrated. The ready availability of fluorinated cannabinoids through this method will make the thorough pharmacological evaluation

of these compounds possible.



22



23

Table 1. Effect of Topical Application of Various Cannabinoid Analogs on Phorbol-12-myristate-13-acetate - induced Edema of the Mouse Ear [a]

compound	Percent Inhibition of Inflammation[b]
22	52%
23	69%
21	15%
7b	17%
4b	19%
18c	45%

[a] Compounds were topically applied in acetone to the inside pinnae of the ears of mice in a solution containing phorbol-12-myristate-13-acetate (PMA). PMA alone (2 μg/ear) or in combination with 50 μg/ear of test compound was applied to the left ears and acetone was applied to all right ears. After 3 hours 20 minutes incubation, the mice were sacrificed, the ears removed, bores taken and the difference in weight between the two ears recorded. Per cent inhibition of inflammations relative to the PMA control were calculated.

[b] Mean values are based on 5 mice.

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EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz ^1H (75.5 MHz ^{13}C) or 500 MHz ^1H (125.8 MHz ^{13}C) in either deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^1H, 77.00 ppm ^{13}C) or deuteriobenzene (C_6D_6) with benzene (7.15 ppm ^1H, 128.00 ppm ^{13}C) as an internal reference. ^{19}F NMR spectra were recorded on a Nicolet NT-300 instrument, and chemical shifts are reported upfield from fluorotrichloromethane (0.00 ppm) as an external standard. Chemical shifts are given in δ; multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were performed on a VG-70 SE mass spectrometer. Mass spectral data are reported in the form of m/e (intensity relative to base =100).

Thin-layer chromatography (TLC) was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash column chromatography was performed on Brinkmann silica gel (0.040-0.063 mm). Tetrahydrofuran (THF), diethyl ether, 1,2-dimethoxyethane (DME) were distilled from sodium-benzophenone ketyl, N,N-dimethylformamide (DMF), triethylamine (Et_3N) and boron trifluoride-etherate ($BF_3.Et_2O$) from calcium hydride, carbon tetrachloride (CCl_4), dichloromethane (CH_2Cl_2) from phosphorus pentoxide. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. The purity and homogeneity of the products on which the high resolution mass spectral data are reported are determined on the basis of 300 MHz ^1H NMR (>94%) and multiple elution TLC analysis, respectively.

3-[4-Pentyl-2,6-bis(2-ethoxyethyl)phenyl]-4-isopropenyl-cyclohexan-1-one (10).

To a solution of the bis-(ethoxyethyl)ether of olivetol (765 mg, 2.35 mmol) in anhydrous THF (30 ml) was added n-butyllithium in hexane (1.45 ml, 2.21 mmol) at 0 °C during 20 min. The reaction mixture was stirred at 0 °C for 10 min and then at 25 °C for 2.5 h. In a separate flask, a solution of lithium 2-thienylcyanocuprate (23.5 ml, 2.35 mmol) was cooled to -78 °C. The lithiated olivetol diether was transferred via cannula to the cuprate solution over 15 min. Following addition, the reaction was placed in an ice bath for 10 min, cooled to -78 °C, and stirred for 1.5 h. To this mixed higher-order cuprate solution at -78 °C, was added a mixture of **9** (200 mg, 1.47 mmol) and $BF_3.Et_2O$ (0.20 ml,1.63 mmol) in THF (3 ml). The progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was diluted with ether, washed with concentrated NH_4OH/saturated NH_4Cl (1/9) solution, extracted with ether (3x50 ml), and dried ($MgSO_4$). Evaporation of the solvent followed by purification by flash chomatography on silica gel eluting with 10% ethyl acetate in hexane produced 500 mg (74% yield) of **10** as a mixture of diastereomers due to the asymmetric center on each of the two ethoxyethyl protecting groups.

Hemiketal 11.

To a solution of ketone **10** in THF and H_2O (5:1) at 23 °C was added catalytic p-TSA and was stirred at 23 °C until TLC showed complete consumption of starting material (10 h). The reaction mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). Evaporation of the solvent followed by purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane produced the hemiketal **11** (97% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.29 (s, 1H), 6.15 (s, 1H), 5.01 (s, 1H), 4.94 (s, 1H), 4.73 (s, 1H, exchangeable with D_2O), 3.62 (br s, 1H), 2.83 (s, 1H, exchangeable with D_2O), 2.46 (dd, J = 7.8, 7.5 Hz, 2H), 2.34 (br s, 1H), 2.09 (t, J = 12.6 Hz, 1H), 2.05-1.91 (br m, 2H), 1.88 (s, 3H), 1.67-1.52 (m, 4H), 1.35-1.26 (m, 5H), 0.88 (dd, J = 6.9, 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 152.2, 145.4, 143.2, 111.1, 110.5, 107.6, 106.8, 98.7, 42.7, 35.7, 35.3, 31.5, 31.2, 30.8, 30.4, 22.5, 21.6, 14.0; IR (neat) 3470, 2950, 2920, 2850, 1625, 1585, 1435, 1140, 1070 cm^{-1}; mass spectrum m/e (relative intensity) 316(M^+, 30), 248(11), 233(100), 204(19), 150(33). Exact mass calculated for $C_{20}H_{28}O_3$: 316.2038, found: 316.2013.

3-[4-Pentyl-2,6-bis(acetoxy)phenyl]-4-isopropenyl-cyclohexan-1-one (12).

To a solution of hemiketal **11** (130 mg, 0.41 mmol) in CH_2Cl_2 at 0 °C was added pyridine (0.10 ml, 1.23 mmol), catalytic DMAP and acetic anhydride (0.10 ml, 1.03 mmol). The reaction mixture was stirred at 0 °C for 30 min and warmed to ambient temperature. The progress of the reaction was monitored by TLC for the

disappearance of the starting material (5 h). The reaction was diluted with CH_2Cl_2, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and purification of the crude product by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave **12** (80% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.78 (br s, 2H), 4.62 (s, 1H), 4.59 (s, 1H), 3.25 (td, J = 12.0, 4.8 Hz, 1H), 2.96 (td, J = 11.4, 3.3 Hz, 1H), 2.76 (t, J = 14.4 Hz, 1H), 2.54 (dd, J = 8.1, 7.8 Hz, 2H), 2.51-2.39 (m, 2H), 2.32 (br s, 6H), 2.10-2.02 (m, 1H), 1.78 (qd, J = 13.2, 4.8 Hz, 1H), 1.63-1.57 (m, 1H), 1.54 (s, 3H), 1.32-1.25 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 168.5 (br s), 149.3 (br s), 145.5, 142.8, 123.0, 120.9, 119.9, 112.4, 47.4, 45.0, 41.4, 39.1, 35.2, 31.6, 31.5, 30.2, 29.7, 29.4, 22.4, 19.2, 14.0; IR (neat) 2920, 2850, 1765, 1720, 1570, 1195, 1175 cm^{-1}; mass spectrum m/e (relative intensity) 400(M^+, 11), 341(35), 298(26), 272(78), 231(67), 206(74), 150(49), 117(100). Exact mass calculated for $C_{24}H_{32}O_5$: 400.2250, found: 400.2234.

(-)-trans-3-Pentyl-6,6a,7,8,10,10a-hexahydro-1-acetoxy-6,6-dimethyl-9H-dibenzo-[b,d]-pyran-9-one (3b).

Compound **3b** was prepared from **3a** according the procedure described for **12**. Spectral data for **3b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.58 (s, 1H), 6.41 (s, 1H), 3.28 (dt, J = 14.7, 2.7 Hz, 1H), 2.71 (td, J = 11.6, 3.3 Hz, 1H), 2.60-2.54 (m, 1H), 2.49 (t, J = 7.8 Hz, 2H), 2.45-2.36 (m, 1H), 2.32 (s, 3H), 2.29-2.11 (m, 2H), 1.95 (td, J = 12.0, 2.4 Hz, 1H), 1.60-1.49 (m, 2H), 1.47 (s, 3H), 1.36-1.25 (m, 4H), 1.11 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 169.0, 154.3, 149.3, 143.7, 115.4, 114.6, 114.0, 76.4, 47.5, 45.9, 40.6, 35.4, 34.9, 31.5, 30.4, 27.7, 26.7, 22.5, 21.2, 18.8, 14.0; IR (neat) 2940, 2910, 2840, 1760, 1705, 1620, 1560, 1420, 1360, 1195, 1175 cm^{-1}; mass spectrum m/e (relative intensity) 358(M^+, 26), 316(100), 299(33), 260(61), 233(61), 206(15), 150(42), 69(55). Exact mass calculated for $C_{22}H_{30}O_4$: 358.2144, found: 358.2113.

9-Nor-9,9-bisfluoro-hexahydrocannabinol acetate (4a).

To a solution of ketone **3b** (12 mg, 0.033 mmol) in dry CH_2Cl_2 under a static atmosphere of nitrogen was added methyl-DAST (0.04 ml, 0.330 mmol) and the mixture was stirred at ambient temperature. The progress of the reaction was monitored by TLC. Upon complete disappearance of the starting material (1-2 d), water was added and the reaction was stirred for a few minutes. The organic layer was separated and the aqueous layer was extracted with several portions of CH_2Cl_2. The combined organic extracts were washed once with distilled water and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by flash column chromatography on silica gel eluting with 2-5% ethyl acetate in hexane. The yield of the reaction was 12 mg (96%). Spectral data for **4a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.56 (s, 1H), 6.41 (s, 1H), 3.12-2.99 (m, 1H), 2.62 (t, J = 11.4 Hz, 1H), 2.50 (t, J = 8.1 Hz, 2H), 2.32 (s, 3H), 2.30-2.23 (m, 1H), 1.93-1.69 (m, 2H), 1.60-1.49 (m, 4H), 1.41 (s, 3H), 1.35-1.25 (m, 5H), 1.08 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 154.6, 149.5, 143.5, 123.1 (t, J = 241.4 Hz), 115.4, 114.5, 113.7, 76.9, 47.9, 38.6 (t, J = 23.1 Hz), 35.4, 34.1 (t, J = 24.0 Hz), 32.3 (d, J = 11.1 Hz), 31.5, 30.4, 27.6, 24.2 (d, J = 11.1 Hz), 22.5, 21.0, 18.9, 13.9; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -91.1 (d, J = 236.6 Hz), -99.1 (dm, J = 238.0 Hz).

9-Nor-9,9-bisfluoro-hexahydrocannabinol (4b).

A stream of argon was bubbled through a solution of **4a** (7 mg, 0.018 mmol) in methanol (5 ml) at 23 °C

(15 min) followed by rapid addition of powdered potassium carbonate. The reaction mixture was stirred at ambient temperature for 15 min during which time TLC showed complete disappearance of starting material. The mixture was filtered into a separatory funnel with ether (20 ml), washed with 1N HCl (2x10 ml) and saturated aqueous sodium bicarbonate before drying over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography on silica gel with 5% ethyl acetate in hexane gave 5 mg (80% yield) of **4b**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.26 (d, J = 1.3 Hz, 1H), 6.08 (d, J = 1.3 Hz, 1H), 4.73 (s, 1H, exchangeable with D_2O), 3.66-3.59 (m, 1H), 2.77 (tt, J = 11.5, 2.6 MHz, 1H), 2.43 (td, J = 7.1, 2.2 Hz, 2H), 2.29-2.23 (m, 1H), 1.92-1.87 (m, 1H), 1.81 (dtt, J = 35.7, 13.4, 4.9 Hz, 1H), 1.59-1.26 (series of multiplets, 9H), 1.41 (s, 3H), 1.10 (s, 3H), 0.88 (t, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.0, 154.4, 143.3, 123.6 (t, J = 240.7 Hz), 110.2, 108.0, 107.7, 76.6, 47.7, 37.9 (t, J = 24.4 Hz), 35.4, 34.3 (t, J = 24.4 Hz), 32.0 (d, J = 10.4 Hz), 31.5, 30.5, 27.8, 24.2 (d, J = 10.5 Hz), 22.5, 19.0, 13.9; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -91.4 (d, J = 238.1 Hz), -99.8 (dm, J = 247.7 Hz); IR (neat) 3390, 2950, 2920, 2870, 2850, 1620, 1575, 1425, 1365, 1090 cm^{-1}; mass spectrum m/e (relative intensity) 338(M^+, 67), 318(9), 295(29), 282(100), 262(19), 235(15), 193(27). Exact mass calculated for $C_{20}H_{28}F_2O_2$: 338.2057, found: 338.2063.

4-[2,6-Dihydroxy-4(pentyl)phenyl]-5-isopropenyl-2-(((trifluoromethyl)sulfonyl)-oxy)-cyclohex-1-ene (16b).

To a solution of lithium diisopropylamide (LDA) at 0 °C, prepared from 0.37 ml (2.60 mmol) of diisopropylamine, 2.43 mmol of n-butyllithium and 20 ml of THF, was added a solution of 400 mg (0.87 mmol) of **10** in THF (5 ml). The solution was stirred at 0 °C for 45 min and treated with a solution of N-phenyltriflimide (930 mg, 2.60 mmol) in DME (4 ml). After stirring at 0 °C for 30 min, the reaction mixture was diluted with ether (15 ml) and washed with saturated aqueous $NaHCO_3$, and extracted with ether (2x10 ml). The organic layer was dried ($MgSO_4$) and concentrated to give crude **16a**, in which the ethoxyethyl groups were removed hydrolytically by treatment with catalytic pyridinium tosylate in methanol at 23 °C. The crude diol **16b** was purified by flash column chromatography on silica gel, eluting with 7% ethyl acetate in hexane. The overall yield of **16b** from **10** was 57%. Spectral data for **16b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.10 (s, 2H), 5.82 (br s, 1H), 4.74 (s, 1H), 4.62 (s, 2H, exchangeable with D_2O), 4.56 (s, 1H), 3.58 (td, J = 11.3, 5.4 Hz, 1H), 3.24 (td, J = 11.3, 5.4 Hz, 1H), 3.06 (br t, J =12.6 Hz, 1H), 2.41 (dd, J = 8.1, 7.5 Hz, 2H), 2.34-2.17 (br m, 3H), 1.57 (s, 3H), 1.54-1.52 (m, 2H), 1.31-1.25 (br m, 4H), 0.89 (dd, J = 6.9, 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7 (br s), 148.5, 146.9, 143.0, 117.7, 112.5, 111.6, 108.5, 43.1, 35.3, 34.4, 31.9, 31.5, 30.5, 29.9, 22.5, 18.3, 14.0; IR (CCl_4) 3450, 2960, 2920, 2850, 1620, 1590, 1410, 1240, 1205, 1140, 1035 cm^{-1}; mass spectrum m/e (relative intensity) 448(M^+, 45), 392(30), 299(15), 247(35), 231(99), 193(100), 149(48), 109(25), 81(39). Exact mass calculated for $C_{21}H_{27}F_3O_5S$: 448.1531, found: 448.1522.

Stannylation of cyclohexenyl triflates. 4-[2,6-Dihydroxy-4-(pentyl)phenyl]-5-isopropenyl-2-trimethylstannyl-cyclohex-1-ene (17a).

To a suspension of anhydrous lithium carbonate (0.22 mmol) and lithium chloride (1.56 mmol) in THF (5 ml) under a static nitrogen atmosphere, was added a solution of **16b** (0.22 mmol) in THF (2 ml). The mixture

was heated to a gentle reflux. After 30 min, a solution of hexamethyldistannane (0.22 mmol) in THF (2 ml) was added via cannula followed by catalytic tetrakis(triphenylphosphine)palladium(0) in THF (1 ml). The reaction mixture was heated at 60 °C for 12 h, during which time TLC indicated the complete consumption of starting material. The reaction was diluted with ether (20 ml), washed with saturated aqueous sodium bicarbonate (1 x 20 ml) and dried (Na_2SO_4). Solvent evaporation produced the crude product, which was purified by flash chromatography on silica gel eluting with ethyl acetate:hexane:triethyl amine (86:10:4 ratio) to give **17a** (73% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.13 (s, 2H), 5.93 (br s, 1H), 4.72 (s, 1H), 4.54 (s, 1H), 3.38 (td, J = 11.1, 5.1 Hz, 1H), 3.18 (td, J = 11.1, 5.1 Hz, 1H), 2.83-2.71 (m, 1H), 2.42 (dd, J = 8.1, 7.5 Hz, 2H), 2.34-2.13 (br m, 3H), 1.59 (s, 3H), 1.55-1.50 (m, 2H), 1.31-1.25 (m, 4H), 0.89 (dd, J = 6.9, 6.6 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (C_6D_6, 75 MHz) δ 149.1, 141.7, 140.6, 136.7, 115.3, 110.8, 108.5 (br s), 44.9, 36.8, 35.8, 35.7, 34.8, 31.9, 31.0, 22.9, 18.8, 14.2, -10.4; IR (CCl_4) 3450, 2960, 2920, 2850, 1620, 1585, 1425 cm^{-1}.

1-Hydroxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-9-trimethylstannyl-6H-dibenzo[b,d]-pyran (20a).

The stannylation of **19** was carried out according to the procedure described for **17a**. Spectral data for **20a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.27 (s, 1H), 6.10 (s, 1H), 5.87 (br s, 1H), 4.67 (s, 1H, exchangeable with D_2O), 3.50 (br d, J = 16.2 Hz, 1H), 2.70 (td, J = 10.5, 4.2 Hz, 1H), 2.43 (dd, J = 8.1, 6.9 Hz, 2H), 2.26-2.20 (m, 1H), 2.06-1.81 (br m, 2H), 1.36 (s, 3H), 1.32-1.25 (m, 4H), 1.09 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H), 0.10 (s, 9H).

The phenolic hydroxyls in these vinyl stannanes **17a** and **20a** were protected as the acetates **17b** and **20b** respectively according to the procedure described for **12**.

4-[4-Pentyl-2,6-bis(acetoxy)phenyl]-5-isopropenyl-2-trimethylstannyl-cyclohex-1-ene (17b). ^{1}H NMR (C_6D_6, 300 MHz) δ 6.98 (br s, 1H), 6.77 (br s, 1H), 5.98 (s, 1H), 4.95 (s, 1H), 4.73 (s, 1H), 3.38 (td, J = 10.5, 6.6 Hz, 1H), 3.21 (td, J = 10.5, 5.7 Hz, 1H), 2.74-2.66 (m, 2H), 2.42-2.31 (m, 2H), 2.28 (dd, J = 8.1, 7.2 Hz, 2H), 1.79 (br s, 6H), 1.69 (s, 3H), 1.39-1.32 (m, 2H), 1.12-1.08 (m, 4H), 0.77 (t, J = 6.3 Hz, 3H), 0.09 (s, 9H); IR (CCl_4) 2960, 2920, 2840, 1765, 1195, 1175 cm^{-1}.

1-Acetoxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-9-trimethylstannyl-6H-bibenzo[b,d]-pyran (20b). ^{1}H NMR (C_6D_6, 300 MHz) δ 6.87 (d, J = 1.5 Hz, 1H), 6.58 (d, J = 1.5 Hz, 1H), 5.78 (br s, 1H), 3.25 (dd, J = 17.1, 2.1 Hz, 1H), 2.76 (td, J = 10.8, 4.5 Hz, 1H), 2.39 (dd, J = 7.9, 7.5 Hz, 2H), 2.14-2.03 (m, 1H), 1.93 (s, 3H), 1.86-1.76 (m, 1H), 1.65-1.60 (m, 1H), 1.53-1.43 (m, 2H), 1.25(s, 3H), 1.19-1.14 (m, 4H), 1.03 (s, 3H), 0.79 (t, J = 6.9 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (C_6D_6, 75 MHz) δ 168.0, 155.4, 150.7, 143.0, 140.3, 135.5, 116.7, 115.8, 114.9, 76.4, 45.2, 37.3, 35.7, 33.0, 31.7, 31.0, 30.4, 27.4, 22.8, 20.8, 18.5, 14.2, -10.5; IR (C_6D_6) 2950, 2920, 2850, 1765, 1620, 1565, 1420, 1365, 1200, 1175cm^{-1}.

Fluorination of vinyl stannanes. 1-Hydroxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-9-fluoro-6H-dibenzo[b,d]pyran (5b).

To a suspension of silver carbonate (0.042 mmol) in CH_2Cl_2 (1 ml) under a static atmosphere of nitrogen at 22 °C was added trifluoromethanesulfonic acid (0.059 mmol) and stirred for 30 min.[23] The solution of vinyl stannane **20b** (0.039 mmol) in CH_2Cl_2 (1.5 ml) and an equimolar amount of xenon difluoride in CH_2Cl_2[24]

(1.0 ml) was added in rapid succession via cannula using positive nitrogen pressure. The progress of the reaction was monitored by TLC for the complete disappearance of starting material (ca. 3 min). The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and filtered through a short pad of silica gel. After solvent evaporation, the products were purified by flash chromatography on silica gel eluting with 2% ethyl acetate in hexane gave a mixture of **5a** and alkene **8** (5:1 ratio based on ^1H NMR integration). The hydrolysis of the ester group in **5a** according to the procedure described for **4a** followed by purification using flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave **5b** contaminated with a small amount of alkene (17:1). Spectral data for **5b**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.28 (d, J = 1.3 Hz, 1H), 6.09 (d, J = 1.6 Hz, 1H), 5.23 (ddt, J = 16.1, 5.7, 2.0 Hz, 1H), 4.69 (s, 1H, exchangeable with D_2O), 3.50 (dddd, J = 16.7, 8.1, 4.8, 1.6 Hz, 1H), 2.83 (td, J = 11.3, 5.2 Hz, 1H), 2.44 (td, J = 7.5, 3.2, 2H), 2.22-2.17 (m, 1H), 2.12-2.05 (m, 1H), 1.90-1.85 (m, 1H), 1.80 (td, J = 11.5, 3.9, 1H), 1.59-1.53 (m, 2H), 1.40(s, 3H), 1.34-1.25 (m, 4H), 1.12 (s, 3H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.5 (d, J = 255.3 Hz), 154.4, 154.2, 142.9, 109.7, 108.8, 107.2, 99.7 (d, J = 16.7 Hz), 76.1, 43.9, 35.0, 31.1, 31.0, 30.9 (d, J = 16.7 Hz), 30.2, 27.3, 24.1 (d, J = 9.7 Hz), 22.1, 18.1, 13.6; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -103.1 (m); IR (neat) 3399, 2957, 2930, 2871, 2856, 1706, 1625, 1580, 1427, 1366, 1257, 1185, 1132, 1129, 1081, 1007, 811 cm^{-1}; mass spectrum m/e (relative intensity) 319(22), 318(M^+, 100), 275(20), 262(74), 246(12), 231(55), 193(29). Exact mass calculated for $C_{20}H_{27}FO_2$: 318.1995, found: 318.1982.

4-[2,6-Bis(acetoxy)-4(pentyl)phenyl]-5-isopropenyl-2-fluorocyclohex-1-ene (18a).
^1H NMR ($CDCl_3$, 300 MHz) δ 6.78 (br s, 2H), 5.25 (td, J = 16.5, 1.8 Hz, 1H), 4.63 (s, 1H), 4.58 (s, 1H), 3.15 (td, J = 11.4, 5.7 Hz, 1H), 2.86 (td, J = 11.1, 6.6 Hz, 1H), 2.55 (dd, J = 8.1, 7.5 Hz, 2H), 2.52-2.45 (m, 1H), 2.33 (s, 6H), 2.31-2.24 (m, 1H), 2.14-2.12 (m, 2H), 1.63-1.58 (m, 2H), 1.52 (s, 3H), 1.33-1.25 (m, 4H), 0.88 (dd, J = 6.9, 6.6 Hz, 3H); ^{19}F NMR ($CDCl_3$, 283 MHz) δ -104.04 (m); IR (CCl_4) 2920, 2850, 1770, 1370, 1200, 1180 cm^{-1}; mass spectrum m/e (relative intensity) 402(M^+, 49), 384(9), 360(41), 318(78), 263(24), 235(50), 193(100). Exact mass calculated for $C_{24}H_{31}FO_4$: 402.2206, found: 402.2202.

4-[2,6-Dihydroxy-4(pentyl)pheny]-5-isopropenyl-2-fluorocyclohex-1-ene(18b).
^1H NMR ($CDCl_3$, 300 MHz) δ 6.11 (s, 2H), 5.25 (dd, J = 16.5, 5.4 Hz, 1H), 4.73 (s, 1H), 4.62 (s, 2H, exchangeable with D_2O), 4.54 (s, 1H), 3.52 (td, 11.7, 5.7 Hz, 1H), 3.18 (td , J = 11.1, 5.1 Hz, 1H), 2.89 (br t, J = 14.4 Hz, 1H), 2.42 (dd, J = 8.1, 7.5 Hz, 2H), 2.28-2.05 (br m, 3H), 1.57 (s, 3H), 1.55-1.51 (m, 2H), 1.31-1.26 (m, 4H), 0.89 (dd, J = 6.9, 6.0 Hz, 3H); IR (CCl_4) 3420, 2960, 2920, 2840, 1620, 1580, 1430, 1120 cm^{-1}; mass spectrum m/e (relative intensity) 319(14), 318(62), 300(11), 263(27), 231(100), 193(99). Exact mass calculated for $C_{20}H_{27}FO_2$: 318.1995, found: 318.2005.

9-Nor-9β-hydroxy-hexahydrocannabinol acetate (6).

To a solution of ketone **3b** (0.06 mmol) in THF and isopropanol (9:1) at ambient temperature under a static atmosphere of nitrogen was added sodium borohydride (1.05 mmol) portionwise and the mixture was stirred for 10 min, during which time TLC indicated the complete consumption of starting material. The reaction was quenched with water, acidified carefully with 1N HCl and extracted with ether (3x15 ml). The combined ether extracts were washed once with 1N HCl, saturated aqueous sodium bicarbonate, and brine and dried

($MgSO_4$). Evaporation of the solvent gave the crude alcohol which was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane to give the alcohol **6** as single isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.55 (s, 1H), 6.38 (s, 1H), 3.74 (tt, J = 11.4, 4.2 Hz, 1H), 2.90 (br d, J = 12.3, 1H), 2.49 (t, J = 7.8 Hz, 2H), 2.37 (td, J = 11.7, 2.4 Hz, 1H), 2.30 (s, 3H), 2.16 (br d, J = 9.9 Hz, 1H), 1.88 (dd, J = 12.6, 3.0 Hz, 1H), 1.62-1.42 (m, 5H), 1.38 (s, 3H), 1.35-1.09 (m, 6H), 1.06 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); IR (neat) 3388, 2932, 2871, 2860, 1767, 1626, 1426, 1371, 1208, 1184, 1136, 1052, 1038 cm^{-1}; mass spectrum m/e (relative intensity) 360(M^+, 56), 342(10), 319(21), 318(100), 300(29), 262(31), 257(40), 193(34). Exact mass calculated for $C_{22}H_{32}O_4$ 360.2300, found: 360.2304.

Compound 13.

The reduction of ketone **12** was carried out according to the above procedure to give **13** in 90% yield. Spectral data for **13**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 1H), 6.69 (s, 1H), 4.58-4.47 (m, 2H), 3.68-3.58 (m, 1H), 2.80 (td, J = 11.9, 3.0 Hz, 1H), 2.61-2.41 (m, 1H), 2.53 (t, J = 8.4 Hz, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.11-1.96 (m, 2H), 1.83-1.25 (m, 11H), 1.51 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); IR (neat) 3489, 3348, 2954, 2932, 2859, 1770, 1645, 1624, 1573, 1450, 1370, 1201, 1180, 1029, 888 cm^{-1}; mass spectrum m/e (relative intensity) 402 (M^+, 2), 384(2), 360(6), 342(4), 318(5), 300(7), 261(8). Exact mass calculated for $C_{24}H_{34}O_5$ 402.2407, found: 402.2384.

Fluorination of alcohols. 9-nor-9α-Fluoro-hexahydrocannabinol acetate (7a).

To the solution of **6** (0.05 mmol) in CH_2Cl_2 (3 ml) under a static atmosphere of nitrogen at -78 °C was added methyl-DAST (5.10 mmol) and was stirred at -78 °C. The reaction was monitored by TLC. Upon completion of the reaction (ca. 4h), water was added and reaction mixture was warmed to 23 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x15 ml). The combined organic extracts were washed once with distilled water and dried ($MgSO_4$). Evaporation of the solvent followed by purification by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 2:1 mixture of **7a** (42% yield) and elimination product **8** (21% yield). **7a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.55 (d, J =1.5 Hz, 1H), 6.39 (d, J = 1.5 Hz, 1H), 4.95 (d, J = 46.5 Hz, 1H), 3.04-2.94 (m, 1H), 2.79-2.71 (m, 1H), 2.49 (t, J = 7.5 Hz, 2H), 2.30 (s, 3H), 2.23-2.14 (m, 1H), 1.74-1.66 (m, 1H), 1.64-1.41 (m, 5H), 1.39 (s, 3H), 1.32-1.27 (m, 5H), 1.09 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2, 154.8, 149.5, 143.0, 115.3, 115.1, 114.3, 89.0 (d, J = 168.4 Hz), 77.2, 48.6, 35.7 (d, J = 19.7 Hz), 35.4, 31.5, 31.2 (d, J = 21.1 Hz), 30.4, 29.7, 27.3, 22.9, 22.5, 21.0, 18.9, 14.0; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -181.4 (br q, J = 44.2 Hz); IR (neat) 2932, 2872, 2858, 1769, 1568, 1427, 1367, 1206 cm^{-1}; mass spectrum m/e (relative intensity) 362(M^+, 13), 343(15), 342(69), 321(10), 320(20), 300(100), 283(53), 257(67), 244(55), 231(75). Exact mass calculated for $C_{22}H_{31}FO_3$: 362.2257, found: 362.2297.

Compound 14.

Alcohol **13**, when subjected to the same conditions employed for the synthesis of **7a** as above, afforded **14** in poor yield (9%) along with an approximately equivalent amount of alkene. Spectral data for **14**: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.78 (br s, 1H), 6.71 (br s, 1H), 4.90 (br d, J = 48.7 Hz, 1H), 4.58 (s, 1H), 4.53 (m, 1H), 3.25 (td, J = 12.3, 3.6 Hz, 1H), 2.65 (tm, J = 11.8, 1H), 2.54 (t, J = 8.7 Hz, 2H), 2.33 (s, 6H), 2.17-2.12 (m, 1H), 2.08-2.02 (m, 1H), 1.87-1.72 (m, 2H), 1.64-1.57 (m, 3H), 1.56 (s, 3H), 1.31-1.25 (m,

5H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.4, 168.5, 149.7, 149.2, 147.4, 142.2, 124.7, 121.0, 119.7, 111.1, 88.6 (d, J = 169. Hz), 48.0, 35.4 (d, J = 23.8 Hz), 35.2, 33.1, 31.5, 31.0 (d, J = 20.6 Hz), 30.2, 26.9, 22.5, 20.8, 19.0, 14.0; ^{19}F NMR (CDCl3, 283 MHz) δ -186.1 (qt, J = 47.8, 9.6 Hz); IR (neat) 3075, 2952, 2930, 2856, 1771, 1646, 1625, 1574, 1457, 1440, 1429, 1368, 1199, 1181, 1033 cm $^{-1}$ mass spectrum m/e (relative intensity) 404(M^+, 11), 384(21), 362(34), 342(20), 341(15), 320(89), 299(26), 277(45). Exact mass calculated for $C_{24}H_{33}FO_4$: 404.2363, found: 404.2380.

9-nor-9α-Fluoro-hexahydrocannabinol (7b).

Hydrolysis of the ester group was carried out according to the procedure described for **4a**. Spectral data for **7b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.26 (s, 1H), 6.08 (s, 1H), 4.98 (br d, J = 47.4 Hz, 1H), 4.70 (s, 1H, exchangeable with D_2O), 3.55-3.45 (m, 1H), 2.91 (td, J = 10.9, 2.7 Hz, 1H), 2.43 (t, J = 7.2 Hz, 2H), 2.24-2.16 (m, 1H), 1.74-1.69 (m, 1H), 1.61-1.51 (m, 4H), 1.39 (s, 3H), 1.32-1.26 (m, 6H), 1.10 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 154.5, 142.8, 110.2, 109.3, 107.7, 89.4 (d, J = 167.3 Hz), 76.6, 48.6, 35.4, 35.2 (d, J = 21.1 Hz), 31.5, 31.4 (d, J = 22.6 Hz), 30.4, 29.4, 27.5, 22.8, 22.4, 19.0, 13.9; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -180.7 (qt, J = 46.6, 11.3 Hz); IR (neat) 3532, 3410, 2932, 2858, 1624, 1578, 1427, 1133, 1039 cm^{-1}; mass spectrum m/e (relative intensity) 320(M^+, 9), 300(82), 281(100), 257(49), 244(49), 231(74). Exact mass calculated for $C_{20}H_{29}FO_2$: 320.2151, found: 320.2184.

Iodination of vinyl stannanes. 4-[2,6-(Dihydroxy)-4-(pentyl)phenyl]-5-isopropenyl-2-iodo-cyclohex-1-ene (18c).

To a solution of vinyl stannane in CH_2Cl_2 under a static nitrogen atmosphere at 0 °C was added a dilute solution of iodine in CH_2Cl_2 dropwise with vigorous stirring until a permanent light pink color remained in the reaction mixture. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate followed by brine and dried (Na_2SO_4). Solvent evaporation produced the crude product, which was purified by flash chromatography on silica gel eluting with 2% ethyl acetate in hexane to give **18c** in 78% yield. Spectral data for **18c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.37 (br s, 1H), 6.09 (s, 2H), 4.72 (s, 1H), 4.64 (s, 2H), 4.54 (s, 1H), 3.58 (td, J = 11.1, 5.1 Hz, 1H), 3.26 (td, J = 11.1, 5.1 Hz, 1H), 3.14 (m, 1H), 2.61 (dd, J = 17.1, 4.2 Hz, 1H), 2.40 (dd, J = 8.1, 7.5 Hz, 2H), 2.34-2.24 (m, 1H), 2.17-2.05 (m, 1H), 1.57 (s, 3H), 1.30-1.26 (m, 4H), 0.88 (dd, J = 6.9, 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.0, 147.9, 142.7, 136.8, 122.9, 113.3, 111.1, 108.6, 95.7, 43.9, 42.9, 36.9, 35.5 35.3, 31.5, 30.5, 22.5, 18.4, 14.0; IR (CCl_4) 3450, 2950, 2920, 2840, 1620, 1580, 1420 cm^{-1}; mass spectrum m/e (relative intensity) 426(M^+, 31), 370(8), 299(25), 231(82), 193 (55), 71(88), 69(100) Exact mass calculated for $C_{20}H_{27}IO_2$ 426.1056, found: 426.1025.

1-Hydroxy-6a,7,10,10a-tetrahydro-6,6-dimethyl-9-iodo-6H-dibenzo[b,d]pyran (21).

Iodination of **20a** according to the procedure described above gave **21** in 83% yield. Spectral data for **21**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.36 (br s, 1H), 6.26 (s, 1H), 6.09 (s, 1H), 4.79 (s, 1H, exchangeable with D_2O), 3.87 (td, J = 17.7, 4.2 Hz, 1H), 2.89 (td, J = 10.8, 4.5 Hz, 1H), 2.43 (dd, J = 8.4, 6.9 Hz, 2H), 2.36-2.28 (m, 1H), 2.27-2.16 (m, 1H), 1.99-1.72 (m, 2H), 1.57-1.53 (m, 2H), 1.36 (s, 3H), 1.31-1.28 (m, 4H), 1.09 (s, 3H), 0.88 (dd, J = 6.0, 6.9 Hz, 3H); IR (CCl_4) 3390, 2950, 2920, 2850, 1620, 1570, 1425 cm^{-1}; mass spectrum m/e (relative intensity) 426(M^+, 8), 370(3), 300(6), 231(11), 169(14), 111(40), 69(100). Exact

mass calculated for $C_{20}H_{27}IO_2$ 426.1056, found: 426.1040.

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