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Synthesis of 5',11-Dihydroxy-Δ^8-tetrahydrocannabinol

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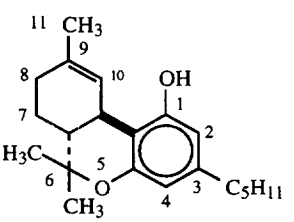
Abstract: The synthesis of a polar cannabinoid, 5',11-dihydroxy-Δ^8-tetrahydrocannabinol (**2**), has been carried out. A key step in the synthesis is the reaction of an aryllithium derived from 1-(*tert*-butyldimethylsilyloxy)-5-(3,5-dimethoxyphenyl)pentane with apoverbenone. Subsequent conversions provided diol **2**, which has significantly less affinity for the cannabinoid receptor than Δ^8-THC.

INTRODUCTION

A comprehensive set of structure activity relationships (SAR) has been developed for cannabinoids which is based on the effect of structural variations in analogues of Δ^9-tetrahydrocannabinol (**1**, Δ^9-THC, the numbering system is indicated on the structure; the C-3 side chain is numbered beginning with the benzylic carbon as C-1'), the principal psychoactive component of marijuana.[1,2] In the course of developing these SAR it was observed that THC metabolites with a hydroxyl group on the side chain also have cannabinoid activity.[1] In particular, it was reported that 1'- and 2'-hydroxy-Δ^8-THC were less potent than Δ^8-THC, while the 3'- and 4'-hydroxy analogues were more potent. The 5'-isomer was approximately equal to the parent cannabinoid in activity.[3] Both 3'*R*- and 3'*S* -hydroxy-Δ^9-THC have been evaluated individually, and the 3'*R*-isomer was found to be considerably more potent than the 3'*S*-analogue.[4]



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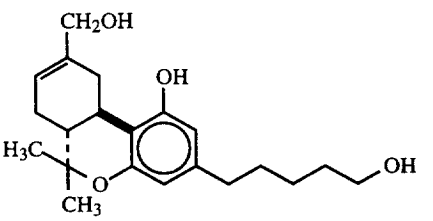

2

Although the hydroxylated side chain metabolites of THC have been synthesized, and evaluated for their cannabinoid activity, the only dihydroxy metabolite which appears to have been reported is 3',11-dihydroxy-Δ^9-THC which was found to be considerably less potent than Δ^9-THC.[5] Several other dihydroxy-THC analogues were described recently by Tius *et al.*, in which a hydroxyalkyl group is appended to C-6, and there

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is either a 9- or 11-hydroxyl group.[6] Those compounds in this series in which there is an 11-hydroxy, a 1,1-dimethylheptyl side chain, and a 6β-hydroxyalkyl moiety have high affinity for the cannabinoid brain (CB1) receptor.[6b]

In order to further explore the effect upon cannabinoid activity of the combination of a second polar hydroxyl on the alkyl side chain, and to examine the scope and limitations of the cannabinoid synthesis developed in these laboratories, the synthesis of 5',11-dihydroxy-Δ^8-THC (**2**) has been carried out. In this synthetic protocol, an appropriately substituted 1,3-dialkoxy-5-alkylbenzene is selectively lithiated; the aryllithium is condensed with apoverbenone, a monoterpene derivative, and subsequent transformations provide the target cannabinoid.[7]

RESULTS

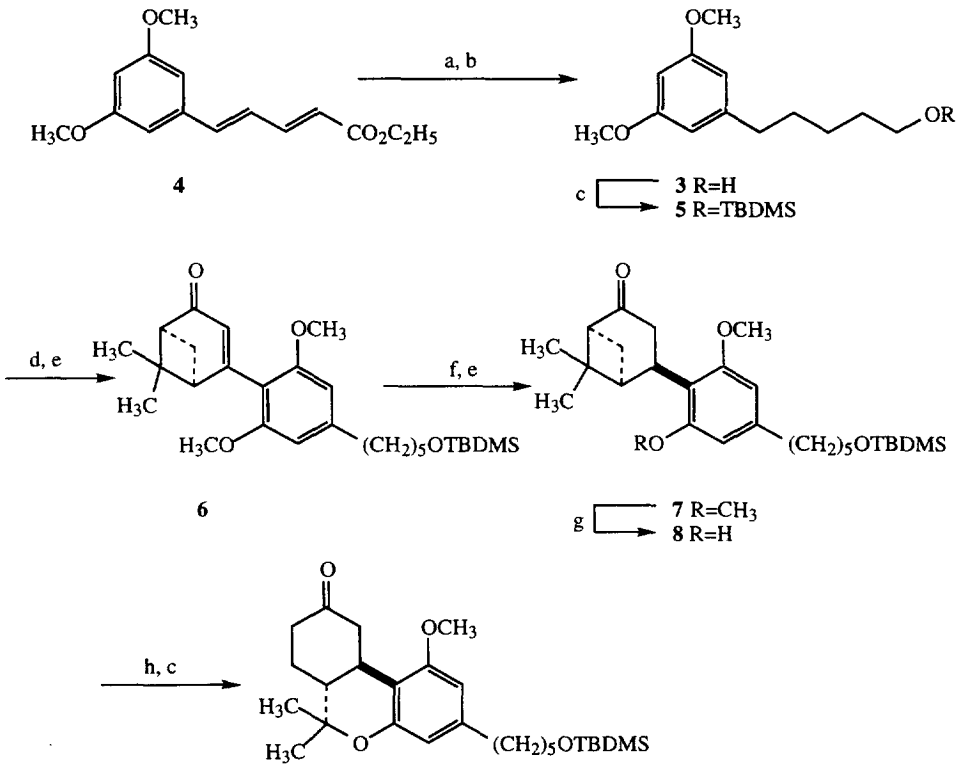
For the synthesis of cannabinoid **2**, the aromatic substrate of choice appeared to be an ether derived from 5-(3,5-dimethoxyphenyl)-1-pentanol (**3**). Alcohol **3** (Scheme I) was prepared by a variation of the procedure employed by Pitt *et al.* for the synthesis of 1-bromo-5-(3,5-dimethoxyphenyl)pentane.[8] In the Pitt procedure, 3,5-dimethoxybenzaldehyde was reacted with a Wittig ylide derived from 1-bromo-4-phenoxybutane to provide a mixture of *E* and *Z*-alkenes which were hydrogenated in excellent yield to the pentane derivative. Reaction of the ylide derived from the triphenylphosphonium salt of ethyl 4-bromocrotonate with 3,5-dimethoxybenzaldehyde proceeded smoothly, however considerable difficulty was encountered in removing the last traces of phosphorus containing impurities from the reaction product. These impurities were very effective catalyst poisons, which seriously hindered the subsequent hydrogenation step. This problem was avoided by carrying out a Horner-Emmons condensation using triethyl 4-phosphonocrotonate, which provided ester **4** in 76% yield. Catalytic hydrogenation followed by $LiAlH_4$ reduction gave alcohol **3** in 97% yield for the two steps. Initially, the hydroxyl group was protected as the benzyl ether, however attempted metalation with *n*-butyllithium gave only 5-(3,5-dimethoxyphenyl)-1-pentene.[9]

Protection of the primary alcohol as the *tert*-butyldimethylsilyl ether proceeded smoothly to give **5**, which reacted with *n*-butyllithium to afford the expected aryllithium. Reaction with apoverbenone gave the tertiary allylic alcohol which, without purification, was oxidized with PDC to provide enone **6** in 55% yield for three steps.[7] In analogy to earlier syntheses, the oxidation was initially attempted using PCC, however this reagent was sufficiently acidic that cleavage of the silyl ether occurs and the overall yield of **6** was only 5%. Dissolving metal reduction of **6** afforded ketone **7**, stereoselectively, in 80% yield, after reoxidation with PDC.[7] Selective cleavage of one of the aromatic methyl ethers was effected with sodium thiopropoxide to afford phenol **8** as a somewhat air sensitive oil. Considerable difficulty was encountered in the rearrangement of **8** to ketone **9**, primarily due to the sensitivity of the *tert*-butyldimethylsilyl ether to the Lewis acid used to accomplish this transformation. Ultimately, the reaction was accomplished in 56% yield using $AlCl_3$ in CH_2Cl_2, followed by reprotection of the primary hydroxyl group. This rearrangement probably proceeds in two discrete steps: cationic rearrangement of the bicyclo[3.1.1]hexane to the *cis*-isomer of **9**, followed by isomerization to the *trans* fused ketone.[7]

The initial synthetic approach to the target diol was to proceed from ketone **9** to vinyl triflate **10** (Scheme II), and then *via* palladium mediated carbonylation to ester **11**.[7a,10] Attempted formation of triflate **10**

by trapping of the derived enolate with N-phenyltriflimide[11] or the pyridine derived triflating agents developed by Comins[12] provided only recovered ketone. Deuterium trapping experiments indicated that strong base (LDA, LHMDS or KHMDS) produced the enolate of ketone **9**, however the enolate failed to react with any of the standard triflating reagents. It was originally thought that the lack of reactivity of this enolate at oxygen was probably due to steric effects associated with the aromatic methoxyl, but it was subsequently found that a structurally similar enolate lacking this methoxyl was also unreactive toward these triflating agents.[13]

Scheme I

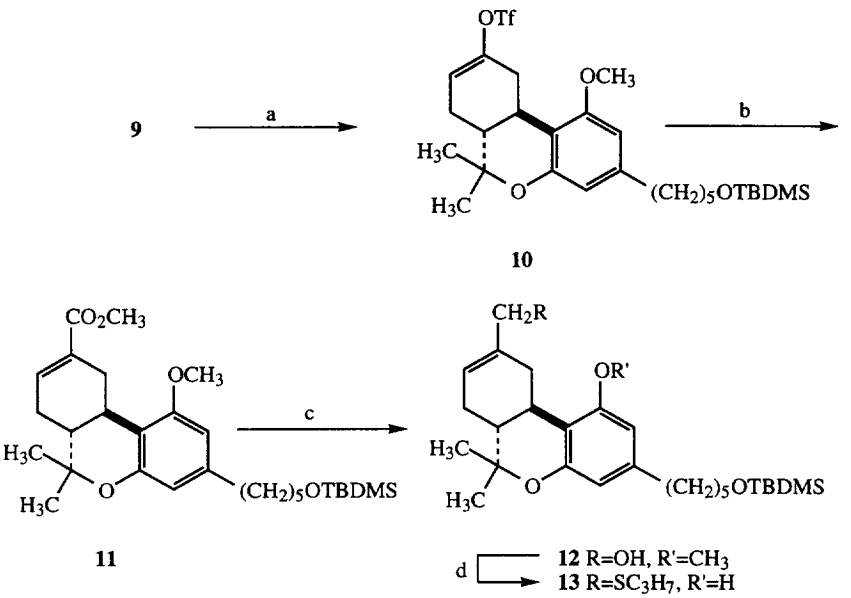


a) H_2, Pd/C, EtOH, 48 h, 98%; b) $LiAlH_4$, Et_2O, 0 °C, 36 h, 99%; c) *t*-$BuMe_2SiCl$, imidazole, DMF, reflux, 5 h, 99%; d) *n*-BuLi, THF, 25 °C, 3 h, then (+)-apoverbenone, 18 h; e) PDC, CH_2Cl_2, 25 °C, 3 h, 55% (two steps); f) Li, NH_3 (liq.), -60 °C, 1 h, 80% (two steps); g) NaH, nPrSH, DMF, 120 °C, 3 h, 85%; h) $AlCl_3$, CH_2Cl_2, 24 h, 56% (two steps).

Triflate **10** was finally prepared in 71% yield by the reaction of ketone **9** with triflic anhydride using conditions developed by Stang.[14] Palladium catalyzed carbonylation to form methyl ester **11** proceeded

routinely, as did reduction to a doubly protected derivative of diol **2** (**12**). However, attempted nucleophilic cleavage of the methyl ether using thiopropoxide, generated from propanethiol and sodium hydride, provided an air sensitive sulfur containing compound. On the basis of NMR and mass spectral data (see Experimental) this compound was allylic sulfide **13**, the result of the desired transformation accompanied by the nucleophilic displacement of hydroxyl. The use of milder conditions for the ether cleavage gave only recovered starting material, and even in the presence of excess sodium hydride **13** was the only identifiable product.

Scheme II



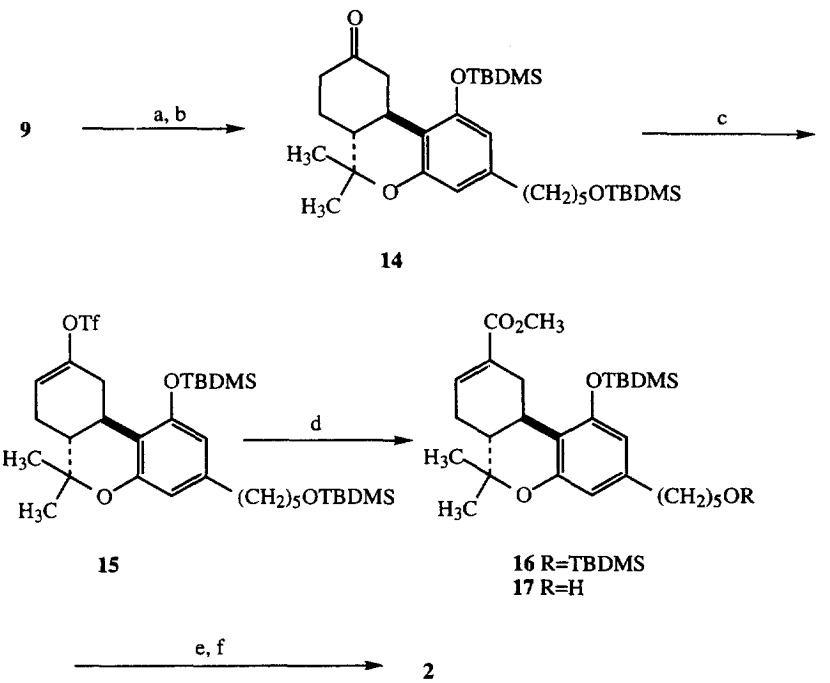
a) 2,6-di-*t*-butyl-4-methylpyridine, Tf_2O, CH_2Cl_2, 25 °C, 3.5 h, 71%; b) $Pd(OAc)_2$, PPh_3, CO, Et_3N, MeOH, DMF, 36 h, 53%; c) $LiAlH_4$, Et_2O, 0 °C, 18 h, 91%; d) NaH, nPrSH, DMF, 120 °C, 3 h, 51%.

This problem was successfully circumvented by appropriate manipulation of the protecting group on the phenolic hydroxyl. Nucleophilic cleavage of the aryl ether present in ketone **9** (Scheme III) gave the corresponding phenol which was reprotected as the *tert*-butyldimethylsilyl ether (**14**). Conversion to the corresponding triflate (**15**) by the method employed for the preparation of **10** proceeded in only 47% yield, apparently due to partial cleavage of the TBDMS ether by the acidic pyridinium salt formed as a by-product in this procedure. Considerable difficulty was encountered in carrying out the carbonylation to ester **16**. The conditions used to prepare **11** provided **16** in only 14% yield. The use of a longer reaction time (28 hours) provided ester **17** in which the primary silyl ether has been cleaved, but the yield remained an unsatisfactory 25%. Intermediate reaction times gave mixtures of **16** and **17** plus a number of decomposition products. If the reaction time exceeded 28 hours the yield was decreased due to decomposition of the product. Although the

conversion of ketone **14** to ester **16** or **17** could not be effected in satisfactory yield, the synthesis of **2** was completed by $LiAlH_4$ reduction of **17** to provide the target diol.

The affinity of diol **2** for the cannabinoid brain (CB1) receptor was determined by measuring the ability of the compound to displace the very potent cannabinoid, [^{3}H] CP 55,940, from its binding site in a membrane preparation.[15] For diol **2**, K_i=235±82 nM, approximately 20% of that of Δ^8-THC, which is consistent with the observation that 3',11-dihydroxy-Δ^9-THC is a less potent cannabinoid than Δ^9-THC.[5,16] Since the presence of either a 3'*R*- or an 11-hydroxyl group increases potency, a possible explanation for the lack of affinity of diol **2** for the CB1 receptor may be due to the presence of polar groups on both the side chain and at C-11.

Scheme III



a) NaH, nPrSH, DMF, 120 °C, 3 h, 59%; b) $tBuMe_2SiCl$, imidazole, DMF, 25 °C, 20 h, 57%; c) 2,6-di-t-butyl-4-methylpyridine, Tf_2O, CH_2Cl_2, 25 °C, 6 h, 47%; d) $Pd(OAc)_2$, PPh_3, CO, Et_3N, MeOH, DMF, 4h, **16** (14%); 28 h, **17** (25%); e) $LiAlH_4$, Et_2O, 0 °C, 20 h; f) TBAF, THF, 25 °C, 1 h, 76% from **15**.

The synthesis of diol **2** by the protocol developed for the synthesis of 11-nor-9-carboxy-Δ^9-THC,[7a] which was refined in the synthesis of nabilone[7b] and used subsequently in the synthesis of 1-deoxy-3-(1,1-dimethylheptyl)-11-hydroxy-Δ^8-THC[13] indicates that this method is of general utility for the synthesis of a variety of structurally diverse cannabinoids. Although somewhat longer than the traditional Petrzilka synthesis from a resorcinol derivative and a monoterpene,[17] this procedure permits the inclusion of acid labile functional

groups in the target cannabinoids. It should be noted that the presence of two *tert*-butyldimethylsilyl protecting groups would appear to be the limit in terms of at least silicon containing moieties. This is indicated by the poor yields obtained in the conversion of ketone **14** to esters **16** or **17**.

EXPERIMENTAL

General. IR spectra were obtained using Nicolet 5DX or Magna spectrometers; ^1H and ^{13}C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett-Packard 5890A gas chromatograph with a mass sensitive detector, and HRMS data were provided by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Universal silica gel (32-63μ) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and ^{13}C NMR.

Ethyl 5-(3,5-dimethoxyphenyl)penta-2,4-dienoate (4). A solution of 19.9 g (79.4 mmol) of triethyl 4-phosphonocrotonate in 20 ml of dry THF at 0 °C was added slowly to a suspension of 2.60 g (86.6 mmol) of NaH in 200 ml of dry THF. The reaction was stirred for 0.5 h, and 12.0 g (72.2 mmol) of 3,5-dimethoxybenzaldehyde in 20 ml of THF were added dropwise. After stirring at room temperature for 0.5 h the reaction was heated at reflux for 20 min, quenched with 500 ml of water, and extracted with three portions of ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product which was chromatographed (petroleum ether/ethyl acetate, 20:1) to give 14.38 g (76%) of ester **4**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H), 3.81 (s, 6H), 4.23 (q, J=7.1 Hz, 2H), 5.98 (d, J=15.2 Hz, 1H), 6.43 (t, J=2.1 Hz, 1H), 6.60 (d, J=2.2 Hz, 2H), 6.81-6.83 (m, 2H), 7.38-7.47 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 55.3, 60.2, 101.2, 105.1, 121.5, 126.6, 137.9, 140.2, 144.2, 160.9, 166.9; HRMS Calcd for $C_{15}H_{18}O_4$: 262.1205, Found 262.1209.

Ethyl 5-(3,5-dimethoxyphenyl)pentanoate. To a solution of 14.38 g (54.8 mmol) of ester **4** in 300 ml of ethanol was added 2.16 g of 10% Pd/C, and the mixture was shaken under an atmosphere of H_2 (45 psi) for 48 h. The reaction mixture was filtered through celite and the ethanol was evaporated *in vacuo* to give 14.35 g (98%) of ester as a pale yellow oil which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 1.62-1.68 (m, 4H), 2.32 (t, J=7.1 Hz, 2H), 2.57 (t, J=7.2 Hz, 2H), 3.78 (s, 6H), 4.12 (q, J=7.1 Hz, 2H), 6.30 (t, J=2.2 Hz, 1H), 6.34 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 24.6, 30.6, 34.2, 35.8, 55.2, 60.2, 97.7, 106.4, 144.6, 160.7, 173.6.

1-(*tert*-Butyldimethylsilyloxy)-5-(3,5-dimethoxyphenyl)pentane (5). A solution of 14.9 g (55.7 mmol) of ethyl 5-(3,5-dimethoxyphenyl)pentanoate in 60 ml of dry ether was added dropwise to a suspension of 5.29 g (139 mmol) of $LiAlH_4$ in 600 ml of ether at 0 °C in a N_2 atmosphere. The reaction mixture was stirred for 36 h and allowed to slowly warm to room temperature. The reaction was quenched by the cautious addition of 5.29 ml of H_2O, 5.29 ml of 15% aqueous NaOH, followed by 15.9 ml of H_2O. The precipitated salts were filtered off, washed with ether, the combined ether solutions were washed with H_2O and brine, dried ($MgSO_4$) and the solvent removed at reduced pressure to give 12.4 g (99%) of crude alcohol **3** which was used in the next step without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 1.34-1.44 (m, 2H), 1.51 (br s, 1H), 1.55-

1.68 (m, 4H), 2.56 (t, J=7.5 Hz, 2H), 3.63 (t, J=6.5 Hz, 2H), 3.78 (s, 6H), 6.30 (t, J=2.2 Hz, 1H), 6.34 (d, J=2.2 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.3, 30.9, 32.5, 36.1, 55.1, 62.8, 97.5, 106.4, 144.9, 160.6.

To a solution of 12.4 g (55.3 mmol) of 5-(3,5-dimethoxyphenyl)pentan-1-ol in 20 ml of DMF was added 10.54 g (155 mmol) of imidazole and 10.42 g (69.1 mmol) of *t*-butyldimethylsilyl chloride. The reaction mixture was heated at reflux for 5 h, cooled, diluted with ether, washed with brine, dried ($MgSO_4$), and the solvent removed *in vacuo*. After chromatography (petroleum ether/ether, 5:1) there was obtained 18.7 g (99%) of pure (TLC, ^{13}C nmr) **5** as a viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.34-1.41 (m, 2H), 1.50-1.67 (m, 4H), 2.55 (t, J=7.5 Hz, 2H), 3.60 (t, J=6.6 Hz, 2H), 3.77 (s, 6H), 6.29 (t, J=2.3 Hz, 1H), 6.34 (d, J=2.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 25.5, 25.9, 31.0, 32.6, 36.2, 55.1, 63.1, 97.5, 106.4, 145.1, 160.6; IR (neat) 1699 cm^{-1}; HRMS Calcd for $C_{19}H_{34}O_3Si$: 338.2277, Found 338.2283.

(1*R*,5*S*)-(-)-4-[2,6-Dimethoxy-4-(5-*tert*-butyldimethylsilyloxypentyl)phenyl]-6,6-dimethylbicyclo[4.1.1]hept-3-en-2-one (6). To a stirred solution of 8.77 g (25.9 mmol) of TBDMS ether **5** in 120 ml of dry THF at ambient temperature was added 14.54 ml (28.5 mmol) of 1.1 M *n*-butyllithium. After stirring for 3 h the mixture was cooled to 0 °C and 3.52 g (25.9 mmol) of (+)-apoverbenone in 45 ml of THF were added dropwise. The solution was allowed to warm to ambient temperature and stirred for 18 h. After quenching with H_2O, the layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude adduct was dissolved in 10 ml of CH_2Cl_2 and added dropwise to a solution of 14.6 g (38.8 mmol) of pyridinium dichromate (PDC) in 45 ml of CH_2Cl_2. The reaction was stirred at room temperature for 3 h, diluted with ether, filtered and the dark residue washed thoroughly with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by chromatography (petroleum ether/ether, 9:1) to give 6.72 g (55%) of enone **6** as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.16 (s, 3H), 1.37-1.45 (m, 2H), 1.50 (s, 3H), 1.54-1.70 (m, 4H), 2.34 (d, J=9.1 Hz, 1H), 2.60 (t, J=7.4 Hz, 2H), 2.67-2.74 (m, 2H), 2.83-2.90 (m, 1H), 3.62 (t, J=6.4 Hz, 2H), 3.76 (s, 6H), 5.99 (t, J=1.2 Hz, 1H), 6.39 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 22.4, 25.5, 25.9, 26.9, 31.1, 32.6, 36.6, 41.5, 50.5, 54.3, 55.6, 57.8, 63.0, 104.1, 114.7, 125.0, 145.4, 156.9, 163.9, 204.7; IR (neat) 1669, 1609 cm^{-1}; MS (CI) *m/z* 473 (100); $[\alpha]_D^{20}$ -88.7° (c=1.37, $CHCl_3$); Anal. Calcd for $C_{28}H_{44}O_4Si$: C, 71.14; H, 9.38; Found: C, 71.04; H, 9.36.

(1*R*,4*R*,5*S*)-4-[2,6-Dimethoxy-4-(5-*tert*-butyldimethylsilyloxypentyl)phenyl]-6,6-dimethylbicylo[4.1.1]heptan-2-one (7). To a solution of 0.27 g (39 mg/atoms) of Li in 300 ml of liquid NH_3 at -60 °C was added dropwise a solution of 1.84 g (3.89 mmol) of enone **6** in a mixture of 60 ml of dry THF and 0.73 ml of *t*-butyl alcohol. The reaction was stirred at -60 °C for 1 h, quenched with solid NH_4Cl, and the NH_3 was evaporated. The solid residue was taken up in water, extracted with ether; the ether extracts were dried ($MgSO_4$), and the solvent removed *in vacuo* to give a mixture of epimeric alcohols. The crude mixture was dissolved in 6 ml of CH_2Cl_2 and added to a suspension of 2.2 g of PDC in 12 ml of CH_2Cl_2. The oxidation was carried out and the product isolated as described above for the preparation of **6**. After chromatography (petroleum ether/ether, 9:1) there was obtained 1.48 g (80%) of ketone **7** as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 0.93 (s, 3H), 1.35 (s, 3H), 1.28-1.69 (m, 7H), 2.54-2.70

(m, 6H), 3.04-3.08 (m, 1H), 3.27-3.38 (m, 1H), 3.61 (t, J=6.5 Hz, 2H), 3.68-3.75 (m, 1H), 3.77 (s, 6H), 6.34 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 14.1, 23.5, 25.6, 25.9, 26.5, 29.1, 31.2, 32.6, 35.3, 36.3, 40.1, 42.0, 46.2, 55.1, 58.1, 63.1, 104.1, 117.2, 142.1, 158.2, 215.5; IR (neat) 1690, 1600 cm^{-1}; MS (CI) *m/z* 475 (100); Anal. Calcd for $C_{28}H_{46}O_4Si$: C, 70.22; H, 9.69; Found: C, 70.21; H, 9.66.

(1*R*,4*R*,5*S*)-4-[2-Methoxy-6-hydroxy-4-(5-*tert*-butyldimethylsilyloxypentyl)phenyl]-6,6-dimethylbicyclo[4.1.1]heptan-2-one (8). To a stirred suspension of 4.4 g (150 mmol) of NaH (80% suspension in mineral oil) in 100 ml of dry DMF at ambient temperature was added dropwise 15.0 ml (166 mmol) of 1-propanethiol. The mixture was stirred at this temperature for 20 min, and a solution of 3.95 g (8.32 mmol) of ketone **7** in 25 ml of DMF was added. The mixture was stirred at 120 °C for 3 h, cooled, poured into water and extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil which was purified by chromatography (petroleum ether/ethyl acetate, 5:1) to give 3.27 g (85%) of phenol **8** as a pale yellow, somewhat air sensitive oil which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 0.95 (s, 3H), 1.35-1.39 (m, 2H), 1.38 (s, 3H), 1.50-1.62 (m, 6H), 2.47 (t, J=7.6 Hz, 2H), 2.60-2.84 (m, 3H), 3.10-3.13 (m, 1H), 3.45 (q, J=10.0 Hz, 1H), 3.60 (t, J=6.5 Hz, 2H), 3.76 (s, 3H), 6.23 (d, J=5.0 Hz, 2H), 6.93 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 25.4, 25.6, 25.9, 26.4, 28.8, 31.0, 32.6, 35.3, 35.7, 40.3, 41.6, 45.9, 54.9, 58.1, 63.1, 103.3, 109.0, 115.4, 142.4, 155.0, 158.4, 218.5; IR (neat) 3300, 1690, 1600 cm^{-1}; MS (CI) *m/z* 461 (100).

(6a*R*,10a*R*)-(-)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-6a,7,10,10a-tetrahydro-1-methoxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9(8*H*)-one (9). To a stirred solution of 1.60 g (3.48 mmol) of phenol **8** dissolved in 50 ml of dry CH_2Cl_2 was added 2.30 g (17.4 mmol) of $AlCl_3$. The reaction mixture was stirred at ambient temperature for 24 h, poured over ice and the phases were separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude reaction product was dissolved in 10 ml of dry DMF to which was added 0.66 g (9.73 mmol) of imidazole and 0.69 g (4.58 mmol) of *tert*-butyldimethylchlorosilane. The reaction was heated at reflux for 5 h, cooled, diluted with H_2O and extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was purified by preparative TLC (petroleum ether/ethyl acetate, 9:1) to give 0.90 g (56%) of ketone **9**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.05 (s, 3H), 1.34-1.41 (m, 2H), 1.46 (s, 3H), 1.46-1.63 (m, 6H), 1.89 (dt, J=10.2, 2.0 Hz, 1H), 2.06-2.17 (m, 2H), 2.41-2.57 (m, 4H), 2.82 (dt, J=12.5, 2.3 Hz, 1H), 3.60 (t, J=6.4 Hz, 2H), 3.77 (s, 3H), 6.24 (d, J=1.2 Hz, 1H), 6.31 (d, J=1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 18.7, 25.6, 25.9, 26.6, 27.8, 30.8, 32.7, 34.5, 36.0, 40.7, 45.8, 47.5, 55.0, 63.1, 76.6, 103.0, 109.6, 110.0, 143.1, 154.2, 158.4, 211.2; IR (neat) 1719, 1625 cm^{-1}; $[\alpha]_D^{20}$ -54.0° (c=1.24, $CHCl_3$); HRMS Calcd for $C_{27}H_{44}O_4Si$: 460.3009. Found 460.3005.

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-9-trifluoromethanesulfonyloxy-6a,7,10,10a-tetrahydro-1-methoxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (10). To a stirred solution of 0.28 g (1.37 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine in 5 ml of dry CH_2Cl_2 was quickly added 0.20 ml (1.20 mmol) of trifluoromethanesulfonic anhydride. After stirring for 5 min, a solution of 0.32 g (0.687 mmol) of ketone **9** in 3 ml of CH_2Cl_2 was added dropwise. The reaction was stirred for 3.5 h, with monitoring by TLC. Upon completion of the reaction, the solvent was removed *in vacuo*, the residue was dissolved in ether, and

filtered to remove the pyridinium salts. The solvent was removed *in vacuo*, and the crude triflate was purified by flash chromatography (petroleum ether/ether, 27:1) to give 0.29 g (71%) of triflate **10** as a yellow oil, which was used in the subsequent step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.10 (s, 3H), 1.36-1.46 (m, 5H), 1.80-2.02 (m, 2H), 2.11-2.21 (m, 1H), 2.31-2.36 (m, 1H), 2.52 (t, J=7.6 Hz, 2H), 2.80 (dt, J=11.0, 4.9 Hz, 1H), 3.58-3.62 (m, 3H), 3.78 (s, 3H), 5.79-5.81 (m, 1H), 6.25 (s, 1H), 6.31 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 25.6, 26.0, 27.5, 30.9, 31.8, 32.7, 33.3, 36.0, 43.8, 55.1, 63.1, 76.0, 103.1, 116.5, 120.1, 122.1, 143.3, 149.5, 154.1, 158.6.

(6a*R*,10a*R*)-(-)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-9-carbomethoxy-6a,7,10,10a-tetrahydro-1-methoxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (11). To a solution of 0.29 g (1.01 mmol) of triflate **10** in 4.2 ml of dry DMF was added 0.28 ml (2.02 mmol) of triethylamine, 0.0068 g (0.030 mmol) of $Pd(OAc)_2$, 0.0159 g (0.061 mmol) of triphenylphosphine and 1.92 ml of methanol. The reaction flask was purged for 10 min with carbon monoxide, then stirred in an atmosphere of carbon monoxide for 36 h at ambient temperature. The reaction mixture was poured into H_2O and extracted with ether. After drying ($MgSO_4$) the ether was removed *in vacuo* to give an oil which was chromatographed (petroleum ether/ethyl acetate, 20:1) to give 0.101 g (53%) of ester **11** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.10 (s, 3H), 1.33-1.43 (m, 5H), 1.50-1.69 (m, 5H), 1.76-2.04 (m, 3H), 2.35-2.41 (m, 1H), 2.52 (t, J=7.7 Hz, 2H), 2.58-2.66 (m, 1H), 3.60 (t, J=6.5 Hz, 2H), 3.69 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 6.25 (s, 1H), 6.30 (s, 1H), 6.99 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.2, 18.4, 25.6, 26.0, 27.5, 28.5, 30.4, 30.9, 31.4, 32.7, 36.0, 44.4, 51.6, 55.2, 63.2, 75.9, 103.2, 110.2, 110.9, 131.2, 137.5, 142.7, 154.7, 158.9, 167.8; IR (neat) 1721, 1622, 1579 cm^{-1}; $[\alpha]_D^{20}$ -121.9° (c=0.457, $CHCl_3$); HRMS Calcd for $C_{29}H_{46}O_5Si$: 502.3119. Found 502.3115.

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-6a,7,10,10a-tetrahydro-9-hydroxymethyl-1-methoxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (12). To a stirred suspension of 0.017 g (0.46 mmol) of $LiAlH_4$ in 8 ml of dry THF at 0 °C was added dropwise 0.115 g (0.229 mmol) of ester **11** in 2 ml of dry THF. The reaction was stirred for 18 h at 0 °C, then quenched by the addition of 0.017 ml of H_2O and 0.017 ml of 15% aqueous NaOH, followed by 0.051 ml of H_2O. The white solid was filtered off, washed with ether and the combined organic phases washed with H_2O and brine. After drying ($MgSO_4$) the solvents were removed *in vacuo* to give 0.096 g (91%) of alcohol **12** which was used in subsequent reactions without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.09 (s, 3H), 1.25 (s, 3H), 1.35-1.43 (m, 5H), 1.80-1.85 (m, 2H), 2.17-2.22 (m, 1H), 2.51 (t, J=8.1 Hz, 2H), 2.63-2.70 (m, 1H), 3.31-3.38 (m, 1H), 3.60 (t, J=6.5 Hz, 2H), 3.79 (s, 3H), 4.04 (s, 1H), 5.73 (br s, 1H), 6.24 (d, J=1.2 Hz, 1H), 6.30 (d, J=1.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 25.5, 25.9, 27.5, 27.6, 29.6, 30.8, 31.5, 31.8, 32.7, 36.0, 45.2, 55.1, 63.1, 66.9, 72.2, 103.0, 110.2, 111.4, 120.5, 138.5, 142.4, 154.2, 158.9; MS (Negative ion CI) *m/z* 473 (4), 385 (3), 370 (4), 308 (11), 168 (13), 166 (100).

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsiloxypentyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-9-thiopropylmethyl-6*H*-dibenzo[*b*,*d*]pyran (13). The nucleophilic ether cleavage was carried out in the manner described above for the preparation of phenol **8**. From 0.055 g (0.12 mmol) of alcohol **12**, there was obtained, after chromatography (petroleum ether/ethyl acetate, 20:1), 0.022 g (51%) of sulfide **13** as an air sensitive yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 0.97 (t, J=7.3 Hz, 3H), 1.10 (s, 3H), 1.38 (s, 3H), 1.51-1.62 (m, 6H), 1.80-2.04 (m, 5H), 2.19-2.24 (m, 1H), 2.37-

2.44 (m, 4H), 2.67 (dt, J=11.0, 4.9 Hz, 1H), 3.11 (s, 2H), 3.42-3.47 (m, 1H), 3.58-3.67 (m, 3H), 5.60 (br s, 1H), 6.10 (s, 1H), 6.25 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.2, 13.5, 14.1, 18.4, 22.6, 25.5, 26.0, 27.5, 27.9, 29.7, 30.7, 31.5, 32.5, 33.1, 35.4, 39.0, 44.9, 62.9, 63.2, 107.7, 109.8, 110.3, 122.5, 134.9, 142.5, 154.7, 155.0; MS (EI) *m/z* 518 (8), 461 (23), 385 (66), 329 (21), 265 (78), 132 (48), 75 (100).

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9(8*H*)-one. The nucleophilic ether cleavage was carried out in the manner described above for the preparation of phenol **8**. From 0.20 g (0.44 mmol) of ketone **9** there was obtained 0.115 g (59%) of phenol as a colorless oil after flash chromatography (petroleum ether/ethyl acetate, 9:1) which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.12 (s, 3H), 1.31-1.39 (m, 2H), 1.47 (s, 3H), 1.49-1.63 (m, 5H), 1.97 (td, J=12.1, 2.4 Hz, 1H), 2.08-2.21 (m, 2H), 2.45 (t, J=8.0 Hz, 2H), 2.47-2.55 (m, 1H), 2.62-2.67 (m, 1H), 2.89 (td, J=11.1, 3.3 Hz, 1H), 3.60 (t, J=6.6 Hz, 2H), 4.11-4.19 (m, 1H), 6.23 (s, 1H), 6.26 (s, 1H), 7.83 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -5.3, 18.3, 18.8, 25.5, 25.9, 26.9, 27.8, 30.8, 32.6, 34.8, 35.5, 40.8, 44.8, 47.4, 63.2, 76.5, 107.7, 107.9, 109.0, 143.2, 154.5, 155.4, 214.8.

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-6a,7,10,10a-tetrahydro-1-*tert*-butyldimethylsilyloxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9(8*H*)-one (14). To a stirred solution of 0.321 g (0.72 mmol) of phenol in 4 ml of DMF was added 0.4 g (2.65 mmol) of *t*-butyldimethylsilyl chloride, followed by 0.4 g (5.88 mmol) of imidazole. The solution was stirred at 25 °C for 20 h, diluted with brine and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a residue which was purified by flash chromatography (petroleum ether/ethyl acetate, 95:5) to give 0.228 g (57%) of silyl ether **14** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.16 (s, 3H), 0.25 (s, 3H), 0.89 (s, 9H), 1.00 (s, 9H), 1.09 (s, 3H), 1.26-1.39 (m, 2H), 1.46 (s, 3H), 1.49-1.60 (m, 5H), 1.94 (td, J=11.0, 2.6 Hz, 1H), 2.06-2.17 (m, 2H), 2.40-2.54 (m, 4H), 2.71 (td, J=11.4, 3.2 Hz, 1H), 3.59 (t, J=6.5 Hz, 2H), 3.74-3.79 (m, 1H), 6.19 (d, J=1.3 Hz, 1H), 6.31 (d, J=1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -5.3, -4.2, -3.8, -3.6, 18.2, 18.3, 18.5, 25.4, 25.9, 26.8, 27.7, 30.6, 32.6, 35.1, 35.5, 40.7, 45.6, 47.8, 63.0, 76.4, 110.5, 111.8, 112.3, 142.6, 154.3, 154.4, 210.2; MS *m/z* (rel intensity) 560 (17), 503 (90), 379 (22), 73 (100); HRMS Calcd for $C_{32}H_{56}O_4Si_2$: 560.3717. Found 560.3719.

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-9-trifluoromethanesulfonyloxy-6a,7,10,10a-tetrahydro-1-*tert*-butyldimethylsilyloxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (15). Ketone **14** (0.26 g, 0.46 mmol) in 3 ml of CH_2Cl_2 was added to a mixture of 0.16 g (0.69 mmol) of 2,6-di-t-butyl-4-methylpyridine and 0.17 g (0.60 mmol) of triflic anhydride in 3 ml of CH_2Cl_2. The solution was stirred at 25 °C for 6 h; the solvent was removed *in vacuo*; the residue was taken up in ether, and filtered. The filtrate was washed with cold 10% aqueous HCl, dried ($MgSO_4$) and solvent removed *in vacuo*. The residue was purified by flash chromatography (petroleum ether, followed by petroleum ether/ethyl acetate, 98:2) to give 0.15 g (47%) of triflate **15** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.21 (s, 3H), 0.28 (s, 3H), 0.91 (s, 9H), 1.01 (s, 9H), 1.12 (s, 3H), 1.35-1.44 (m, 2H), 1.45 (s, 3H), 1.51-1.65 (m, 4H), 1.86 (td, J=11.2, 3.8 Hz, 1H), 1.95-2.06 (m, 1H), 2.18-2.23 (m, 1H), 2.43-2.50 (m, 1H), 2.48 (t, J=7.6 Hz, 2H), 2.76 (td, J=10.9, 4.6 Hz, 1H), 3.62 (t, J=6.5 Hz, 2H), 3.63-3.69 (m, 1H), 5.82-5.83 (m, 1H), 6.24 (s, 1H), 6.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -5.3, -4.0, -3.8, 18.1, 18.3, 25.4, 25.6, 25.9, 26.0, 27.5, 30.7, 32.2, 32.7, 33.5, 35.6, 44.0, 63.1, 75.8, 110.7, 111.7, 112.0, 116.7, 142.9, 149.2, 154.3, 154.7; MS

m/z (rel intensity) 692 (2), 635 (12), 485 (8), 379 (15); HRMS Calcd for $C_{33}H_{55}F_3O_6SSi_2$: 692.3210. Found 692.3209.

(6a*R*,10a*R*)-3-(5-*tert*-Butyldimethylsilyloxypentyl)-9-methoxycarbonyl-6a,7,10,10a-tetrahydro-1-*tert*-butyldimethylsilyloxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (16). The carbonylation was carried out as described above for the preparation of **11**, but for 4 h. From 0.049 g (0.07 mmol) of triflate **15** there was obtained, after, flash chromatography (petroleum ether/ethyl acetate, 9:1), 0.006 g (14%) of ester **16** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.14 (s, 3H), 0.29 (s, 3H), 0.90 (s, 9H), 0.98 (s, 9H), 1.10 (s, 3H), 1.34-1.39 (m, 2H), 1.40 (s, 3H), 1.48-1.65 (m, 5H), 1.76-2.10 (m, 2H), 2.34-2.58 (m, 4H), 3.60 (t, J=6.6 Hz, 2H), 3.74 (s, 3H), 3.80-3.88 (m, 1H), 6.22 (s, 1H), 6.30 (s, 1H), 7.00-7.05 (m, 1H); MS *m/z* (rel intensity) 602 (13, M^+), 545 (9), 513 (9), 379 (24), 367 (24); HRMS Calcd for $C_{34}H_{58}O_5Si_2$: 602.3823. Found 602.3822.

(6a*R*,10a*R*)-3-(5-Hydroxypentyl)-9-methoxycarbonyl-6a,7,10,10a-tetrahydro-1-*tert*-butyldimethylsilyloxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran (17). When the carbonylation was carried out as described above, but for 28 h, there was obtained from 0.165 g (0.20 mmol) of triflate **15**, 0.029 g (25%) of ester **17** as a colorless oil after chromatography: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.28 (s, 3H), 0.98 (s, 9H), 1.10 (s, 3H), 1.39 (s, 3H), 1.25-1.43 (m, 2H), 1.52-1.67 (m, 5H), 1.78-2.05 (m, 2H), 2.40-2.58 (m, 4H), 3.64 (t, J=6.6 Hz, 2H), 3.73 (s, 3H), 3.79-3.89 (m, 1H), 6.22 (s, 1H), 6.30 (s, 1H), 7.00-7.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -4.4, -3.6, -0.1, 18.0, 18.2, 25.3, 25.8, 27.3, 28.5, 30.2, 30.6, 31.7, 32.6, 35.5, 44.5, 51.4, 62.9, 75.8, 110.5, 111.7, 131.0, 137.8, 142.1, 154.4, 167.6.

5',11-Dihydroxy-Δ^8-Tetrahydrocannabinol (2). To a stirred suspension of 0.008 g (0.21 mmol) of $LiAlH_4$ in 2 ml of dry ether was added a solution of 0.029 g (0.06 mmol) of ester **17** in 0.5 ml of dry ether at 0 °C. The resulting solution was allowed to warm to room temperature, and stirred overnight. The reaction was quenched by the addition of 10 μl of water, followed sequentially by 10 μl of 10% aqueous NaOH, and 30 μl of water. The solid was filtered off, the filtrate was dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give the crude alcohol which was used in the next step without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.24 (s, 3H), 0.84-0.93 (m, 1H), 0.99 (s, 9H), 1.10 (s, 3H), 1.38 (s, 3H), 1.25-1.44 (m, 2H), 1.50-1.63 (m, 5H), 1.68-1.85 (m, 3H), 2.21-2.28 (m, 1H), 2.47 (dd, J=8.0, 5.9 Hz, 2H), 2.59 (td, J=11.0, 4.4 Hz, 1H), 3.31-3.37 (m, 1H), 3.64 (t, J=6.6 Hz, 2H), 4.03 (br s, 2H), 5.72-5.75 (m, 1H), 6.20 (s, 1H), 6.30 (s, 1H).

The crude alcohol was dissolved in 1 ml of dry THF, and 0.2 ml of TBAF (1.0 M in THF) was added. The resulting solution was stirred at 25 °C for 1 h, the solvent was then removed *in vacuo*, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1; then ethyl acetate) to give 0.015 g (73%) of 5',11-dihydroxy-Δ^8-THC (**2**) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83-0.96 (m, 1H), 1.08 (s, 3H), 1.37 (s, 3H), 1.29-1.41 (m, 2H), 1.53-1.60 (m, 4H), 1.75-1.90 (m, 4H), 2.17-2.23 (m, 1H), 2.44 (t, J=7.4 Hz, 2H), 2.69 (td, J=10.7, 4.0 Hz, 1H), 3.42-3.51 (m, 1H), 3.63 (t, J=6.5 Hz, 2H), 4.06 (br s, 1H), 5.71-5.74 (m, 1H), 6.13 (s, 1H), 6.23 (s, 1H); $[\alpha]_D^{25}$ -4.35° (c=0.7, $CHCl_3$); MS *m/z* (rel intensity) 346 (92), 328 (22), 313 (28), 285 (25), 274 (31), 247 (100); HRMS Calcd for $C_{21}H_{30}O_4$: 346.2144. Found 346.2142.

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