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Synthesis of 5′-($^2H_3$)-(−)-11-Nor-9-carboxy-Δ^9-Tetrahydrocannabinol Methyl Ester Methyl Ether

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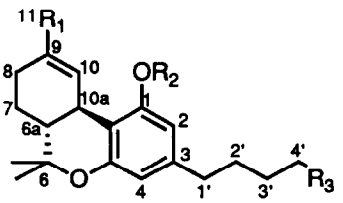
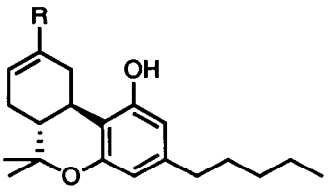
Abstract: A synthesis of 5′-($^2H_3$)-(-)-11-nor-9-carboxy-Δ^9-tetrahydrocannabinol methyl ester methyl ether (**4**) has been accomplished from α-bromoenone **10**. The key steps are the stereocontrolled cyclobutane ring opening of the cuprate adduct **18** and the cyclization of the cyclohexenyl triflate **21** with excess iodotrimethylsilane to produce Δ^9-cyclohexenyl triflate **22**. An efficient, stereospecific synthesis of optically active (-)-11-nor-9-keto-hexahydrocannabinol (**8**) has also been accomplished.

Δ^9-Tetrahydrocannabinol (Δ^9-THC) (**1**), the primary psychoactive constituent of marijuana (*Cannabis sativa*), its metabolites and synthetic analogs have been studied extensively for the last two decades. These studies have established a wide spectrum of useful pharmacological properties[1], of which the most promising activities are associated with the antiemetic, antiglaucoma and analgesic effects. Interest in this family of compounds has been heightened by the recent identification of a cannabinoid binding site in the rat brain.[2] In addition, concern over the abuse of marijuana has led to the development of a number of immunological screening tests for the detection of THC metabolites in biological fluids.[3] The major metabolic pathway for Δ^9-THC when marijuana is smoked involves hepatic microsomal oxidation giving rise to 11-nor-9-carboxy-Δ^9-



1 $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_3$
2 $R_1 = COOH$; $R_2 = H$; $R_3 = CH_3$
3 $R_1 = COOH$; $R_2 = H$; $R_3 = CD_3$
4 $R_1 = COOCH_3$; $R_2 = CH_3$; $R_3 = CD_3$



5 $R = CH_3$
6 $R = COOH$

THC (2). The acid 2 is then excreted as the glucuronide in urine.[4] The trideuterio 11-nor-9-carboxy-Δ^9-THC acid (3) is commonly used as an internal standard for the unambiguous confirmation and quantification of THC metabolites by gas chromatographic - mass spectrometric (GC/MS) analysis.[3] Derivatization of the carboxylic acid by conversion to 4 is advantageous for conferring thermal stability and to avoid on-column losses during GC/MS analysis. For all these reasons there is considerable interest in improved routes to the synthesis of Δ^9-THC metabolites and labelled analogs.

Many of the earlier published routes to Δ^9-THC metabolites have suffered from two major problems. Firstly, the cycloaddition of olivetol with an appropriate monoterpene under cationic conditions leads to a ca. 1/1 mixture of regioisomers derived from the substitution at both C2 and C4 of olivetol.[5] This lack of regiospecificity compromises the efficiency of the synthesis and leads to unacceptable losses of material when an expensive labelled olivetol derivative is utilized. Secondly, the non-stereospecific cyclization reaction gives rise to a mixture of *trans:cis* ring junction isomers which cannot be separated by flash column chromatography. Recently, Huffman and co-workers have reported a very elegant synthetic route to acid 2 which overcomes the lack of regiospecificity.[6] The major disadvantage of this synthetic sequence was the formation of a mixture of ring junction isomers (*trans:cis*, 3:1). Difficulties in the synthesis of metabolites of Δ^9-THC also arise due to the instability of the double bond at C9, which undergoes facile isomerization to the thermodynamically more stable Δ^8-THC (5) series.[7] Futhermore, cannabinoids in general are sensitive to oxidation, particularly in basic media.

Our synthetic strategy was aimed at an efficient route to the Δ^9-cyclohexenyl triflate (A), which not only avoids an oxidation for the conversion of the corresponding alcohol and/or aldehyde to acid 2, but which also might provide access to cannabinoids labelled at C11. There are potentially two approaches to the formation of subunit A (Figure 1). The first was through the regiospecific enolization of cyclized ketone B (X = H) leading

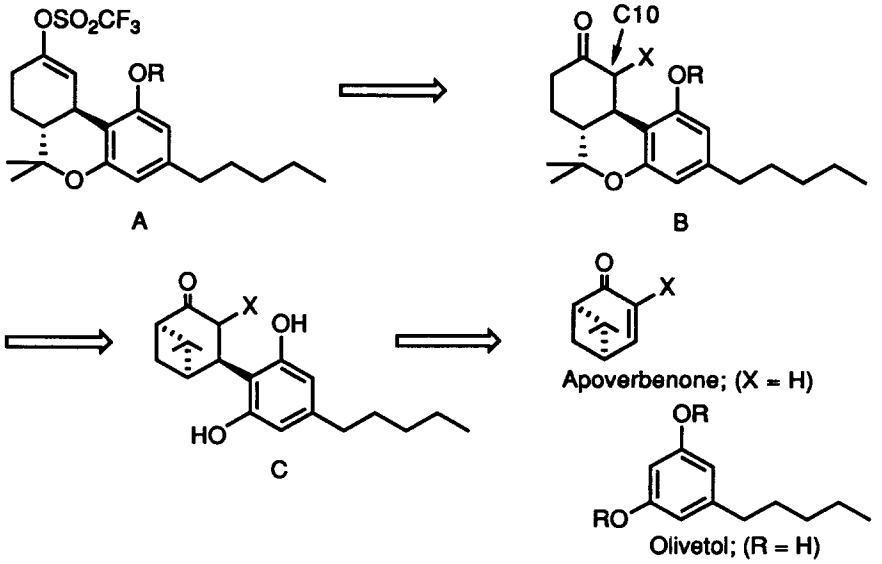
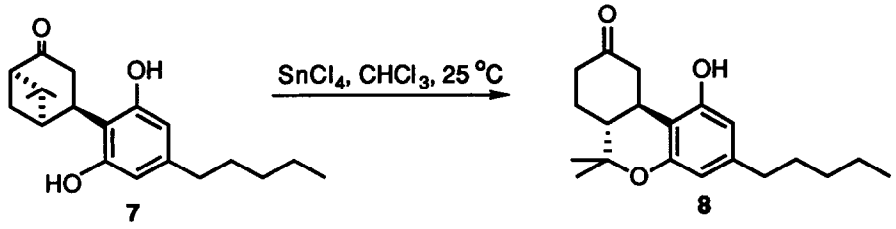


Figure 1. Disconnective analysis of Δ^9-cyclohexenyl triflate

specifically to the Δ^9-series. Cyclic ketone B can be envisioned to arise from the cationic cyclization of resorcinol C (X = H) which in turn can be prepared through the use of a mixed higher-order cuprate as described in the synthesis of the methyl ester of Δ^8-THC acid (6).[8] It was clear at the outset that the formation of the Δ^9-enolate with specificity is difficult. However, the apparent simplicity and directness of the approach suggested that enolization of B was worth examining under both kinetic and thermodynamic enolization conditions. The second was to utilize a heteroatomic substituent (X = halogen, alkoxy) at C10 of ketone B as a control element to generate the unsaturation leading to the Δ^9-series. The substitution at C10 could be introduced either through the use of the substituted apoverbenone in the cuprate reaction or by intercepting the enolate formed from the apoverbenone with a heteroatomic electrophile.

Resorcinol **7** was synthesized as a single isomer from apoverbenone and the bis-(ethoxyethyl)ether of olivetol in 52% overall yield.[8] Treatment of **7** with stannic chloride in anhydrous chloroform ($CHCl_3$) at 25 °C produced optically active ketone **8** in 72% yield. These conditions are analogous to those described by Archer and co-workers in the synthesis of nabilone.[9] The phenol functionality in **8** was protected either as the ethoxyethyl ether (ethyl vinyl ether, cat. p-toluenesulfonic acid, ether) or as the *tert*-butyldimethylsilyl ether (*tert*-butyldimethylsilyl chloride, imidazole, N,N-dimethylformamide). The enolization of these two protected ketones with variety of bases (lithium diisopropylamide, potassium hexamethyldisilylamide, triethylamine, 2,4,6-trimethylpyridine, diisopropylaminomagnesium bromide) followed by trapping the enolate either as the silyl ether or as the triflate in all cases resulted in Δ^8-enol ether with no detectable formation of the Δ^9-isomer.



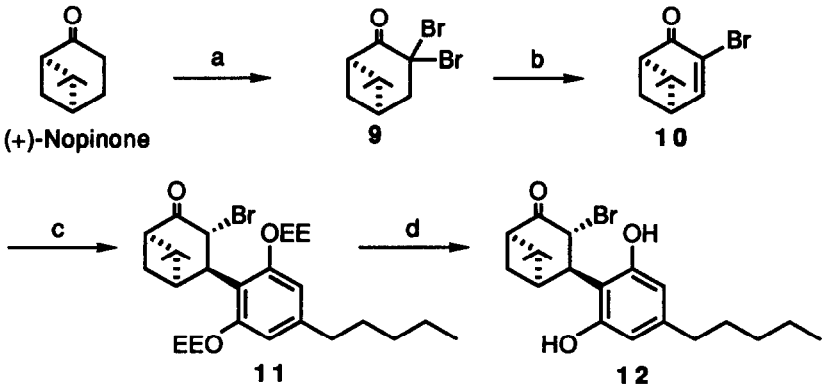
7 **8**

Attention was next focused on the alternative strategy for the Δ^9-enolate. (+)-Nopinone, readily obtainable in large quantities by ozonolysis of (−)-β-pinene,[10] was brominated with excess N-bromosuccinimide (NBS) in carbon tetrachloride (CCl_4) at 75 °C in the presence of catalytic benzoyl peroxide. Bis-bromonopinone (**9**) was formed with mono-bromonopinone as a 3:2 mixture which was separated by flash column chromatography on silica gel. The dehydrobromination was carried out in N,N-dimethylformamide (DMF) with lithium carbonate and lithium bromide at 130 °C to afford the α-bromoenone (**10**) as pale yellow crystals in 76% yield.[11] Attempts to carry out the dehydrobromination reaction with 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) in dichloromethane (CH_2Cl_2) at room temperature and potassium *tert*-butoxide in tetrahydrofuran (THF) at varying temperatures resulted in a mixture of products and a lower yield of **10**. The initial synthetic strategy envisioned that the ethoxyethyl ether would serve as a protecting group for olivetol during cuprate addition. Regiospecific lithiation of olivetol bis-(ethoxyethyl)ether[12] was carried out with n-butyllithium in THF at 22 °C. The lithiated olivetol derivative was transferred to lithium 2-thienylcyanocuprate[13] in THF at -78 °C and stirred for 1.5 h. The mixed higher-order cuprate was treated with a solution of **10** and boron trifluoride etherate (1/1) in THF to furnish **11** in 55-60% yield. The ^1H nmr

spectrum of **11** indicated a mixture of diastereoisomers, due to the asymmetric center on each of the ethoxyethyl ether protecting groups. Hydrolytic removal of the ethoxyethyl ether with catalytic pyridinium tosylate (PPTs) in methanol produced resorcinol **12** as a single isomer in 90% yield (Scheme 1).

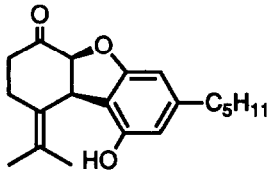
The next phase involved the cyclization of **12**, the crucial step in the synthetic sequence. A number of methods were investigated to effect cyclization of **12** unsuccessfully, including treatment with stannic chloride in $CHCl_3$[9] or aqueous CH_2Cl_2, boron trifluoride etherate in CH_2Cl_2,[9] perchloric acid in aqueous trifluoroethanol, lithium perchlorate in ether[14] and zinc bromide in ether in the presence of lithium bromide.

Scheme 1



(a) NBS, cat. $(PhCO_2)_2$, CCl_4, 75 °C; (b) Li_2CO_3, LiBr, DMF, 130 °C; (c) see text; (d) cat. PPTs, methanol

These conditions resulted no detectable reaction at lower temperatures (-78 °C to 22 °C) and partial decomposition at elevated temperatures (60 °C to 110 °C). When the reaction was carried out with excess titanium tetrachloride in $CHCl_3$ at 60 °C, **13** was isolated as the major product in 42% yield (unoptimized). Attempted cyclization of **12** with p-toluenesulfonic acid in $CHCl_3$ in either ethanol[6] or methanol provided the corresponding ketals **14a** and **14b** in good yield. These ketals could not be converted to the cyclized ketone



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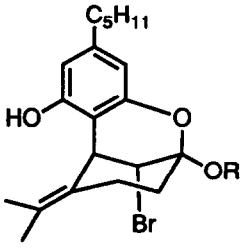
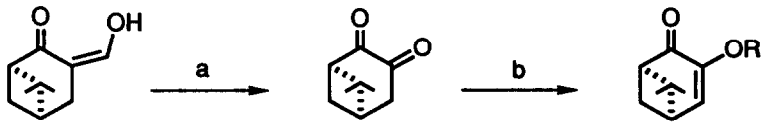


14a R = CH_2CH_3
14b R = CH_3

with stannic chloride in CH_2Cl_2, although the conversion of the corresponding non-halogenated cannabinoid methyl ketal to the cyclized ketone with *cis* ring junction has been reported.[9] Apparently the electronic effect of the bromine substituent adversely influences the cationic cyclization process.

The difficulties encountered with **12** suggested that an α-alkoxy substituent be examined. The formation of 1,2-diketones via ozonolysis of α-hydroxymethylene ketones is precedented.[15] Treatment of (+)-nopinone with ethyl formate and sodium hydride in ether in the presence of catalytic ethanol produced the salt of the α-hydroxymethylene ketone[16] which was acidified carefully with 1N HCl and extracted with ether to afford **15** in 73% yield (Scheme 2). Ozonolysis of **15** in CH_2Cl_2:pyridine (v/v 1:1) at -78 °C gave a bright yellow solution which was treated with methyl sulfide to afford **16** in 56% yield. Enones **17a** and **17b** were prepared from **16** by trapping the enolate formed with potassium *tert*-butoxide in THF at -50 °C with methyl iodide and acetic anhydride respectively. Surprisingly, the cuprate addition of olivetol diether to either **17a** or **17b** was unsuccessful even in the presence of monodentate and bidentate Lewis acids such as boron trifluoride etherate or stannic chloride, respectively.

Scheme 2



15 **16** **17a** R = CH_3 **17b** R = $COCH_3$

(a) O_3, pyridine:CH_2Cl_2, -78 °C then $(CH_3)_2S$; (b) $K^+ {}^-OBu^t$, THF, -50 °C then CH_3I or $(CH_3CO)_2O$

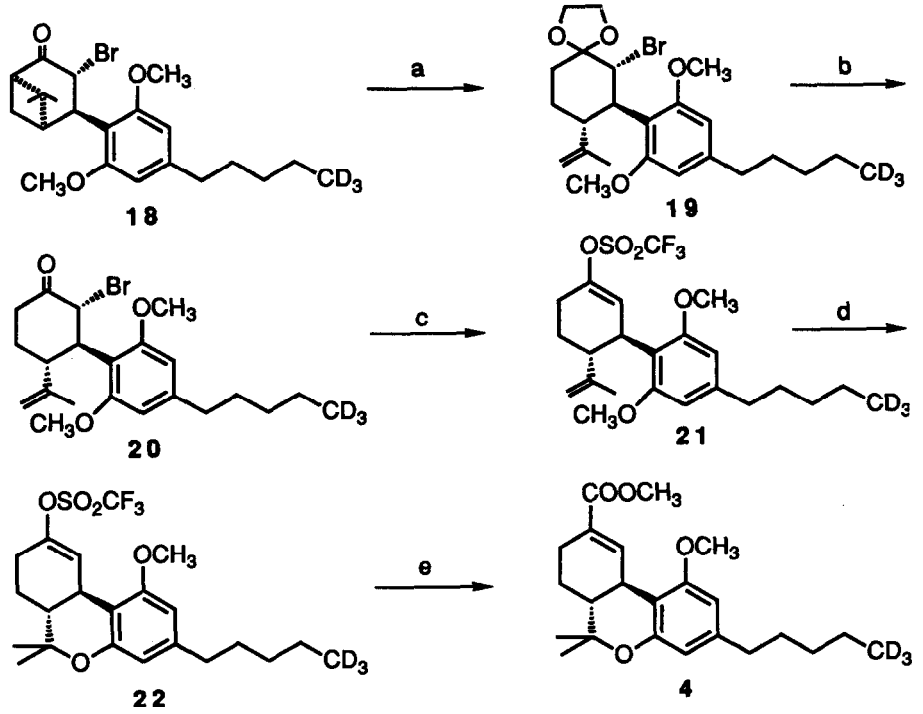
These failures prompted a rethinking of the chemistry outlined in Scheme 1. Ketals **14a** and **14b** presumably arise from intramolecular attack of the phenolic oxygen on the carbonyl carbon. To avoid the ketal formation it was therefore necessary to use an oxygen protecting group on olivetol which would be robust enough to survive the acid-catalyzed conditions for the cleavage of the cyclobutane ring of the cuprate adduct. 5'-($^2H_3$)-Olivetol dimethyl ether[17] was metalated with n-butyllithium in THF at 25 °C and was converted to the mixed higher-order cuprate as before, by transferring to an equivalent of lithium-2-thienylcyanocuprate in THF -78 °C. The cuprate solution was next treated with a solution of α-bromoenone **10** in the presence of boron trifluoride etherate (1/1) in THF to produce **18** in 83% yield (Scheme 3). The stereospecific ring opening of **18** was carried out with excess 1,2-bis(trimethylsilyloxy)ethane in CH_2Cl_2 at 22 °C using an equivalent of trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give **19** in 65% yield. When the reaction was carried out with catalytic TMSOTf,[18] initial ketalization took place, followed by cyclobutane ring opening to **19** upon addition of more TMSOTf. A related rearrangement of a pinane with ethylene glycol and p-toluenesulfonic acid in benzene at 100 °C has also been reported.[19] Exposure of **18** to these conditions produced traces of **19**. It is worthy of note that ketalization and cyclobutane ring opening of α-bromonopinone formed 2-bromo-4-isopropylidene cyclohexan-1-ethylene ketal exclusively; none of the isopropenyl isomer could be detected. The formation of the isopropenyl substituent in the case of **18** is due to a stereoelectronic effect by the aryl substituent at C4: In the carbocationic intermediate **18a**, the steric bulk of the aryl group prevents the

alignment of the 2p orbital on C6 with the C6a-H bonding orbital. Consequently, proton loss takes place from the methyl group in **18b**, leading to the isopropenyl group of the product.

18a **18b**

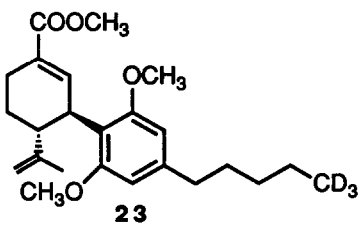
Hydrolysis of ketal **19** with 50% aqueous perchloric acid in acetone[20] at 40 °C gave ketone **20** in 66-71% yield. The reductive debromination of **20** was carried out with lithium dimethylcuprate in ether[21] at 0 °C and the derived enolate was trapped with N-phenyltriflimide in freshly distilled 1,2-dimethoxyethane (DME) to

Scheme 3



(a) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2; (b) 50% aqueous $HClO_4$, acetone; (c) lithium dimethylcuprate, ether, 0 °C, then N-phenyltriflimide, DME, 0 °C; (d) iodotrimethylsilane, $CHCl_3$, 22 °C; (e) Et_3N, $Pd(OAc)_2$, triphenylphosphine, methanol, DMF, CO.

produce **21** in 75-81% yield. Pd-catalyzed carbonylation of **21** gave the methyl ester **23** in 80% yield.[22] The next task was to demethylate **23** and cyclize the dihydrobenzopyran ring. As anticipated, cleavage of the methyl ester to the corresponding carboxylate took place rapidly. When **23** was fused with pyridine hydrochloride at 200 °C, a clean reaction took place leading to the carboxy analog of cannabifuran **24**. Other reaction conditions for the cleavage of methyl ether groups, such as boron tribromide in dichloromethane at -78 °C followed by warming to 0 °C and sodium thioethoxide in DMF at 120 °C[23] were accompanied by isomerization of isopropenyl to isopropylidene and/or conjugate addition of phenoxide to form dihydrobenzofuran. Attempted cleavage of the methyl ether of **19** with sodium thioethoxide in DMF at 120 °C[23] gave only the dihydrobenzofuran derivatives **25a** and **25b**. The stereochemistry of the dihydrobenzofuran derivatives **25a** and **25b** was established by n.O.e experiments.



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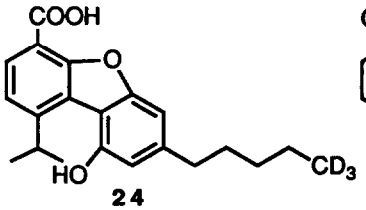

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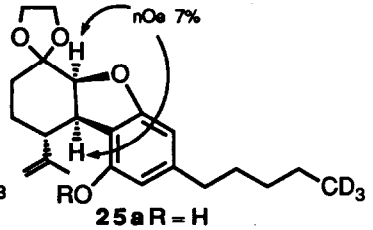
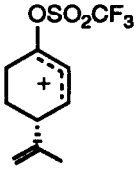


25a R = H
25b R = CH_3

Alkenyl triflates are chemically robust, and it was gratifying to note that cyclohexenyl triflate **21** was a suitable substrate for the demethylation and cyclization. Treatment of **21** with excess iodotrimethylsilane[24] (purchased from Aldrich Chemical Co.) in anhydrous $CHCl_3$ at 22 °C, followed by purification by flash column chromatography, gave a mixture of *trans* (**22**) and *cis* stereoisomers in the approximate ratio of 17:1 (by ^1H NMR spectral integration of the proton at C10) in 47% yield. Attempts to improve the yield using various methods for *in situ* generation of iodotrimethysilane, such as sodium iodide or lithium iodide and trimethylchlorosilane in acetonitrile, hexamethyldisilane[25] or allylsilane[26] and iodine, gave either lower yields of **22** or a higher percentage of the *cis* stereoisomer. The *cis* isomer probably arises from acid-catalyzed isomerization of the isopropenyl to the isopropylidene followed by cyclization. The major reaction byproduct, 5'-($^2H_3$)olivetol dimethyl ether, presumably arises from initial transfer of a proton to the electron-rich aromatic ring of **21**, followed by carbon-carbon bond cleavage with generation of allylic carbocation **26**. It is interesting that the presence of the electron-withdrawing triflate group on **26** is not sufficient to inhibit this cleavage reaction. Both the side reaction leading to **26** as well as the cyclization to **22** apparently require catalysis by HI because the conversion of **21** to **22** did not proceed when iodotrimethylsilane was used in the presence of an acid scavenger, such as pyridine or methylcyclohexene, or when excess allylsilane and hexa-



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methyldisilane and iodine were used to form iodotrimethylsilane *in situ*. Cyclohexenyl triflate **22** and the *cis* isomer were treated with carbon monoxide and methanol under palladium catalysis to afford *trans* (**4**) and *cis* unsaturated methyl esters in 82% combined yield.[22] The *trans* isomer was separated and purified by HPLC (Phenomenex Ultracarb 5 ODS 30 column, 250x10 mm, flow rate 2.5 ml/min, methanol). The specific rotation for **4** was $[\alpha]^{21}_D = -237^o$ (c = 0.005 g/ml, ethanol) and the ^1H NMR spectral data closely paralleled those of the racemic, undeuterated **4** reported in literature.[6] The benzylic proton at C10a in **4** appeared at δ 3.31 ppm as a doublet of doublets (J = 1.5, 11.4 Hz), as expected for a *trans* relationship of the C6a and C10a protons.

In conclusion, a synthesis of 5'-($^2H_3$)-(-)-11-nor-9-carboxy-Δ^9-THC methyl ester methyl ether has been accomplished in six steps from bromoenone **10**, and olivetol dimethyl ether. The stereocontrol exercized in the pinane ring opening to produce the desired isopropenyl substituent in **19**, and also the use of the cyclohexenyl triflate as a stable equivalent of the Δ^9-enolate, are noteworthy features of this synthesis. Dihydrobenzofuran ketal **25a** is potentially an important precursor to the C9 and C11 functionalized Δ^9-THC derivatives.

Acknowledgement is made to NIDA (DA06731) for generous support and to the East West Center for financial assistance provided to G.S.K.K. in the form of a scholarship.

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. 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, except for those reactions utilizing water as a solvent, which were run in air.

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

To a solution of 125 mg (0.40 mmol) of resorcinol **7** in anhydrous $CHCl_3$ (12 ml) was added 0.42 ml (3.60 mmol) of stannic chloride at 25 °C. The resulting mixture was stirred at 25 °C for ca. 24 h at which time TLC indicated the complete consumption of the starting material. The reaction mixture was poured onto ice and extracted with ether (3x30 ml). The combined ether extracts were washed with a saturated aqueous solution of

sodium bicarbonate (1x20 ml) followed by brine, dried ($MgSO_4$), and concentrated under reduced pressure. The purification of the crude compound by flash column chromatography eluting with 10% ethyl acetate in hexane produced 90 mg (72% yield) of **8** as a white foam. $[\alpha]^{25}_D$ = -43.7° (c = 2.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 6.22 (s, 1H, exchangeable with D_2O), 6.18 (s, 1H), 3.99 (br d, J = 15.0 Hz, 1H), 2.88 (ddd, J = 11.7, 11.4, 3.0 Hz, 1H), 2.64-2.48 (m, 2H), 2.44 (dd, J = 8.1, 7.5 Hz, 2H), 2.18-2.09 (m, 3H), 1.96 (t, J = 12.3 Hz, 1H), 1.59-1.53 (m, 2H), 1.47 (s, 3H), 1.31-1.26 (m, 4H), 1.12 (s, 3H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 215.19, 156.59, 155.45, 143.79, 109.67, 108.62, 108.26, 76.37, 47.21, 44.98, 40.43, 36.09, 35.05, 31.85, 31.31, 27.85, 26.59, 22.88, 18.95, 14.21; IR (CCl_4) 3260, 2940, 2920, 2840, 1685, 1615, 1570, 1420, 1350, 1250, 1175, 1090, 1030 cm^{-1}; mass spectrum m/e (relative intensity) 316(100), 301(35), 273(29), 260(70), 245(36), 233(93), 150(78), 95(30), 83(36), 69(77), 57(85). Exact mass calculated for $C_{20}H_{28}O_3$: 316.2038, found: 316.2034.

(1R,5R)-3,3-Dibromo-6,6-dimethylbicyclo[3.1.1]-heptan-2-one (**9**).

A solution of (+)-nopinone (2.00 g, 14.49 mmol) in CCl_4 (10 ml) was added to a stirred solution of recrystallized N-bromosuccinimide (7.74 g, 43.48 mmol) and benzoyl peroxide (0.36 g, 1.49 mmol) in CCl_4 (20 ml) in a nitrogen atmosphere. The resulting solution was heated at reflux, and the progress of the reaction was monitored by TLC. After 2 days, TLC indicated the formation of both mono- and bis-bromonopinone (ca. 2:3 ratio). The reaction mixture was cooled, diluted with water (50 ml), and extracted with CH_2Cl_2 (2x100 ml). The combined CH_2Cl_2 extracts were washed successively with saturated aqueous sodium bicarbonate (2x100 ml) and brine (2x50 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Bis-bromonopinone was separated from mono-bromonopinone by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexane to afford 2.35 g (55% yield). **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (dd, J = 15.9, 4.2 Hz, 1H), 3.39 (d, J = 15.9 Hz, 1H), 2.99 (t, J = 5.7 Hz, 1H), 2.75-2.68 (m, 1H), 2.60 (d, J = 1.1 Hz, 1H), 2.27-2.22 (m, 1H), 1.43 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.08, 59.58, 57.30, 48.97, 44.24, 42.29, 25.71, 25.36, 23.75; IR ($CHCl_3$) 2980, 2960, 2920, 1730, 1450 cm^{-1}; mass spectrum m/e (relative intensity) 296(2), 217(10), 215(11), 173(7), 136(8), 110(62), 95(63), 83(100). Exact mass calculated for $C_9H_{12}OBr$ (M^+–Br): 215.0071, found: 215.0063.

(1R,5R)-3-Bromo-6,6-dimethylbicyclo[3.1.1]-hept-3-en-2-one (**10**).

To a suspension of anhydrous lithium carbonate (1.77 g, 23.89 mmol), anhydrous lithium bromide (1.45 g, 16.74 mmol) in freshly distilled DMF (20 ml) under nitrogen, equipped with a reflux condenser at 100 °C, was added a solution of bis-bromonopinone (**9**) (2.35 g, 7.96 mmol) in DMF (10 ml) by cannula. The reaction mixture was stirred at 130 °C for 6 h, at which time TLC indicated the complete consumption of starting material. The reaction mixture was cooled, diluted with water (50 ml) and extracted with ether (3x75 ml). The combined ether extracts were washed with brine (2x50 ml), and dried ($MgSO_4$). Solvent evaporation produced the crude product, which was purified by flash column chromatography on silica gel, eluting with 5% ethyl acetate in hexane, to afford 1.29 g (76% yield) of the α-bromoenone. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.2 Hz, 1H), 2.93 (dd, J = 12.6, 6.0 Hz, 1H), 2.87 (dd, J = 15.0, 5.4 Hz, 1H), 2.65 (dd, J = 12.6, 6.9 Hz, 1H), 2.23 (d, J = 9.3 Hz, 1H), 1.52 (s, 3H), 1.03(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.89, 156.29, 119.76, 58.28, 56.34, 45.88, 41.63, 26.33, 22.49; IR ($CHCl_3$) 2960, 1695, 1580, 1460,

1305, 1240 cm^{-1}; mass spectrum m/e (relative intensity) 216(13), 214(14), 201(28), 199(29), 176(45), 174(45),135 (85), 83(100).

3-Bromo-4-[4-pentyl-2,6-bis(2-ethoxyethyl)phenyl)]-6,6-dimethylbicyclo[3.1.1]-hept-2-one (**11**).

To a solution of the bis-(ethoxyethyl)ether of olivetol (650 mg, 2.20 mmol) in anhydrous THF (30 ml) was added n-butyllithium in hexane (1.45 ml, 2.20 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 (22.00 ml, 2.20 mmol) was cooled to -78 °C. The lithiated olivetol diether was transferred via cannula to the cuprate solution over a 15 min period. Following addition, the reaction mixture 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 **10** (268 mg, 1.25 mmol) and $BF_3.Et_2O$ (0.15 ml, 1.25 mmol) in THF (2 ml). The mixture was stirred at -78 °C until TLC showed the disappearence of starting material (5-6 h). The reaction was diluted with ether, washed with concentrated NH_4OH/saturated NH_4Cl (1/9) solution, extracted with ether (2x50 ml), and dried ($MgSO_4$). Evaporation of the solvent followed by purification by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 375 mg (56% yield) of **11** (mixture of ethoxyethyl diastereomers). ^1H NMR (300 MHz, $CDCl_3$) 6.59 (br s, 2H), 6.27 (d, J = 9.0 Hz, 1H), 5.56-5.35 (br m, 2H), 4.42 (d, J = 9.0 Hz, 1H), 3.81-3.65 (br m, 2H), 3.59-3.51 (br m, 1H), 2.83 (dd, J = 6.3, 5.4 Hz, 1H), 2.61-2.43 (br m, 2H), 2.53 (t, J = 6.9 Hz, 2H), 2.14-2.11 (m, 1H), 1.49 (d, J = 2.7 Hz, 6H), 1.37 (s, 3H), 1.18 (t, J = 6.9 Hz, 6H), 1.01 (s, 3H), 0.88 (t, J = 6.6 Hz, 3H); IR (CCl_4) 2960, 2920, 2870, 1725, 1605, 1580, 1440, 1380, 1350, 1080, 1050 cm^{-1}.

3-Bromo-4-[(2,6-dihydroxy-4-pentyl)phenyl]-6,6-dimethylbicyclo[3.1.1]-hept-2-one (**12**).

To a solution of **11** (375 mg, 0.69 mmol) in methanol (20 ml) was added pyridinium tosylate (ca. 35 mg). The reaction was strirred vigorously at 22 °C until TLC indicated that all the starting material had been consumed (ca. 8 h). The reaction mixture was extracted with ether (3x75 ml), and the combined ether extracts were washed with brine (2x50 ml) and dried ($MgSO_4$). Solvent evaporation, followed by purification by flash column chromatography on silica gel eluting with 10% ethyl acetate in hexane afforded 246 mg (90% yield) of the resorcinol. **12**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (d, J = 8.7 Hz, -CHBr, 1H), 6.24 (s, 2H), 5.66 (br s, 2H, exchangeable with D_2O), 4.28 (d, J = 8.7 Hz, 1H), 2.84 (dd, J = 5.4, 5.2 Hz, 1H), 2.62 (d, J = 11.1 Hz, 1H), 2.49-2.47 (m, 1H), 2.42 (t, J = 7.8 Hz, 2H), 2.20 (t, J = 5.7 Hz, 1H), 1.59-1.50 (m, 2H), 1.36 (s, 3H), 1.32-1.24 (m, 4H), 1.01 (s, 3H), 0.88 (dd, J = 6.9, 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.71, 155.15, 143.42, 110.79, 108.95, 57.73, 52.61, 48.92, 44.10, 42.18, 35.28, 31.50, 30.50, 25.49, 23.72, 22.50, 22.49, 13.98; IR ($CHCl_3$) 3400, 2960, 2940, 2850, 1710, 1620, 1590, 1430, 1350, 1260 cm^{-1}; mass spectrum m/e(relative intensity) 396(2), 394(2), 314(48), 258(30), 231(42), 204(50), 148(49), 83(100). Exact mass calculated for $C_{20}H_{27}O_3Br$: 394.1140, found: 394.1144.

3-Bromo-4-[(2,6-dimethoxy-4-(5'-($^2H_3$)pentyl))phenyl]-6,6-dimethylbicyclo[3.1.1]-hept-2-one (**18**).

The cuprate reaction was carried out in the same manner as that described for the preparation of **11**, using 1.20 g (5.77 mmol) of 5'-($^2H_3$)olivetol dimethyl ether and 770 mg (3.60 mmol) of **10**, to produce 1.27 g (82% yield) of the cuprate adduct. **18**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 2H), 6.14 (d, J = 9.0 Hz,

-CHBr, 1H), 4.37 (d, J = 9.0 Hz, 1H), 3.80(s, 6H), 2.84-2.81 (m, 1H), 2.57 (dd, J = 8.1, 7.5 Hz, 2H), 2.46 (dd, J = 4.5, 3.0 Hz, 2H), 2.09 (br t, J = 4.5 Hz, 1H), 1.65-1.58 (m, 2H), 1.41-1.25 (m, 4H), 1.37 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.93, 158.57, 143.39, 113.69, 104.72, 57.60, 55.71, 52.87, 48.88, 43.82, 41.23, 36.33, 31.46, 30.89, 25.44, 23.69, 22.42, 22.17; IR (CCl_4) 2920, 2850, 1725, 1605, 1575, 1450, 1420, 1120 cm^{-1}; mass specturm m/e (relative intensity) 427(4), 425(5), 346(11), 250(29), 224(18), 137(27), 95(53), 83(100). Exact mass calculated for $C_{22}H_{28}O_3D_3Br$: 425.1600, found: 425.1606.

2-Bromo-3-[(2,6-dimethoxy-4-(5'-(^{2}H3)pentyl))phenyl]-4-isopropenyl-cyclohexan-1-ethylene ketal **(19).**

To a solution of 1,2-bis(trimethylsilyloxy)ethane (5.75 ml, 23.64 mmol) in CH_2Cl_2 (2 ml) at 22 °C was added trimethylsilyl trifluoromethanesulfonate (0.25 ml, 1.26 mmol). After 15 min, a solution of **18** (500 mg, 1.18 mmol) in CH_2Cl_2 (5 ml) was added and stirred vigorously at 22 °C. The progress of the reaction was monitored by TLC. After 60 h, the TLC indicated nearly complete disappearence of the starting material. The reaction mixture was extracted with CH_2Cl_2 (4x50 ml), and the combined CH_2Cl_2 extracts were washed successively with saturated aqueous sodium bicarbonate (2x50 ml), brine (1x50 ml), and dried ($MgSO_4$). Solvent evaporation, followed by separation of the product from the unreacted starting material by flash column chromatography, eluting with 2% ethyl acetate in hexane afforded 360 mg (65% yield) of ketal. **19**: ^{1}H NMR (300MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.30 (s, 1H), 5.11 (d, J = 12.0 Hz, 1H), 4.42 (s, 1H), 4.37 (s, 1H), 4.33-4.29 (m, 1H), 4.25-4.16 (m, 1H), 4.06-3.99 (m, 2H), 3.92 (dd, J = 12.0, 11.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.97 (ddd, J = 11.4, 11.1, 3.0 Hz, 1H), 2.53 (dd, J = 8.1, 7.5 Hz, 2H), 2.04-1.99 (m, 1H), 1.83-1.71 (m, 2H), 1.63-1.56 (m, 3H), 1.55 (s, 3H), 1.32-1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.62, 158.30, 147.75, 142.60, 115.43, 110.62, 108.34, 104.37, 104.13, 66.24, 65.41, 61.95, 56.01, 55.14, 48.36, 43.82, 36.47, 35.40, 31.61, 30.77, 28.45, 22.27, 18.72; IR (CCl_4) 2920, 2850, 1605, 1575, 1450, 1120 cm^{-1}; mass spectrum m/e (relative intensity) 471(4), 469(5), 388(7), 308(9), 224(52), 154(60), 99(50), 86(100). Exact mass calculated for $C_{24}H_{32}D_3O_4Br$: 469.1907, found: 469.1879.

2-Bromo-3-[(2,6-dimethoxy-4-(5'-(^{2}H3)pentyl))phenyl]-4-isopropenyl-cyclohexan-1-one **(20).**

To a solution of **19** (250 mg, 0.53 mmol) in acetone (100 ml) was added 50% aqueous perchloric acid (10 ml). The reaction mixture was stirred vigorously at 40 °C, and the progress of the reaction was monitored by TLC. After 48 h, the reaction mixture was cooled to room temperature and neutralized carefully with saturated aqueous sodium bicarbonate, extracted with ether (3x75 ml), and dried ($MgSO_4$). Evaporation of the solvent followed by purification by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane produced 160 mg (71% yield) of ketone. **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (s, 2H), 5.48 (d, J = 11.4 Hz, -CHBr, 1H), 4.51 (s, 1H), 4.45 (s, 1H), 3.98 (dd, J = 11.4, 11.1 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.33 (ddd, J = 11.7, 11.4, 4.2 Hz, 1H), 2.77 (ddd, J = 14.1, 3.6, 3.1 Hz, 1H), 2.62 (dd, J = 13.5, 6.6 Hz, 1H), 2.54 (dd, J = 8.1, 7.5 Hz, 2H), 2.03-1.82 (br m, 2H), 1.63-1.57 (m, 2H), 1.52 (s, 3H), 1.32-1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.89, 158.19, 157.93, 146.19, 143.38, 114.52, 111.55, 104.39, 104.09, 60.07, 55.86, 55.11, 48.09, 47.03, 40.19, 36.44, 31.49, 30.75, 30.59, 22.19, 18.46; IR (CCl_4) 2920, 2850, 1725, 1605, 1580, 1450, 1420, 1230, 1120 cm^{-1}; mass spectrum m/e (relative intensity)

427(11), 425(12), 346(100), 317(13). Exact mass calculated for $C_{22}H_{28}O_3D_3Br$: 425.1600, found: 425.1631.

3[(2,6-dimethoxy-4-(5'-($^2H_3$)pentyl))phenyl]-4-isopropenyl-1-(((trifluoromethyl)sulfonyl)oxy)-cyclohex-1-ene (**21**).

A solution of methyllithium (0.59 ml, 0.71 mmol) was added dropwise to a suspension of anhydrous cuprous iodide (68 mg, 0.36 mmol) in ether (6 ml) at 0 °C. The reaction mixture was stirred at 0 °C 10 min. A solution of ketone **20** (105 mg, 0.25 mmol) in ether (4 ml) was added to the lithium dimethylcuprate solution at 0 °C during 30 sec. The reaction mixture turned bright yellow after ca. 10 sec. A solution of N-phenyltriflimide (176 mg, 0.49 mmol) in freshly distilled DME (3 ml) was added immediately after the appearence of the bright yellow color. The solution was stirred at 0 °C for 5 h. The reaction was diluted with ether (20 ml), washed with concentrated NH_4OH/ saturated NH_4Cl (1/9) solution, extracted with ether (2x25 ml), and dried ($MgSO_4$). Evaporation of the solvent followed by purification by flash column chromatography on silica gel by eluting with 5% ethyl acetate in hexane produced 90 mg (76% yield) of the enol triflate. **21**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (s, 2H), 5.67 (dd, J = 2.3, 2.1 Hz, 1H), 4.49 (dd, J = 2.9, 1.5 Hz, 1H), 4.39 (br d, J = 1.5 Hz, 1H), 4.15 (dm, J = 10.1 Hz, 1H), 3.74 (s, 6H), 2.84 (dd, J = 15.5, 7.8 Hz, 1H), 2.67-2.58 (br m, 1H), 2.54 (dd, J = 7.9, 7.7 Hz, 2H), 2.37 (dm, J = 15.5 Hz, 1H), 1.91-1.86 (br m, 2H), 1.62-1.58 (br m, 2H), 1.61 (s, 3H), 1.34-1.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.48, 158.39, 147.14, 146.89, 143.08, 124.01, 115.11, 103.99, 55.46, 44.48, 36.51, 34.78, 31.57, 31.01, 28.83, 28.12, 22.26, 18.79; IR ($CHCl_3$) 2920, 2860, 1605, 1580, 1450, 1420, 1210, 1150, 1120, 1050, 980 cm^{-1}; mass spectrum m/e (relative intensity) 479(2), 411(11), 329(39), 278(100), 224(73), 205(32), 190(15), 152(24), 119(12), 91(14). Exact mass calculated for $C_{23}H_{28}D_3F_3O_5S$: 479.2033, found: 479.2061.

1-methoxy-3-(5'-($^2H_3$)pentyl)-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-(((trifluoromethyl)sulfonyl)oxy)-6H-dibenzo[b,d]-pyran (**22**).

To a solution of **21** (100 mg, 0.21 mmol) in distilled $CHCl_3$ (10 ml) was added iodotrimethylsilane (purchased from Aldrich Chemical Co., 0.45 ml, 3.14 mmol) at 22 °C. After stirring for 12 h at 22 °C, more iodotrimethylsilane (0.45 ml, 3.14 mmol) was added as the TLC of the reaction mixture indicated the presence of starting material. After 10 h, the reaction was quenched with saturated aqueous sodium sulfite, and extracted with CH_2Cl_2 (3x50 ml). The combined CH_2Cl_2 extracts were washed successively with saturated aqueous sodium bicarbonate (3x50 ml), brine (2x50 ml) and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel eluting with 2% ethyl acetate in hexane to afford 46 mg (47% yield) of cyclized cyclohexenyl triflate. The major by-product was 5'-($^2H_3$)-olivetol dimethyl ether. Examination of the ^1H NMR spectrum of the product showed the presence of both *trans* and *cis* ring junction isomers (*trans:cis*, 17:1). The mixture was used in the succeeding step without further separation. Spectral data for the *trans* isomer, **22**. ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (br s, 1H), 6.32 (s, 1H), 6.27 (s, 1H), 3.82 (s, 3H), 3.39 (dd, J = 10.9, 2.1 Hz,1H), 2.56-2.52 (m, 2H), 2.51 (dd, J = 8.1, 7.5 Hz, 2H), 2.06 (br d, J = 12.6 Hz, 1H), 1.78 (dt, J = 11.7, 2.1 Hz, 1H), 1.61-1.49 (m, 3H), 1.43 (s, 3H), 1.31-1.28 (m, 4H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.93, 154.24, 148.50, 143.62, 122.47, 110.33, 107.37, 102.98, 76.62, 55.07, 44.27, 36.03, 32.93, 31.48, 30.79, 28.32, 27.59, 24.29, 22.26,

19.13; IR ($CDCl_3$) 2920, 2850, 1615, 1570, 1410, 1205, 1140 cm^{-1}; mass spectrum m/e (relative intensity) 465(15), 406(7), 332(75), 211(20), 152(100), 69(42). Exact mass calculated for $C_{22}H_{26}D_3F_3O_5S$: 465.1876, found: 465.1890.

Dihydrobenzofuran ketal (**25a**).

To 16 mg (0.67 mmol) of NaH (85% dispersion in mineral oil, washed with dry hexane) suspended in dry DMF (10 ml) at ambient temperature under nitrogen was added 0.04 ml (0.64 mmol) of ethanethiol in dry DMF (2 ml). After stirring for 15 min, a solution of 30 mg (0.064 mmol) of **19** in 5 ml of DMF was added. The mixture was heated to reflux for 4 h, cooled to 0 °C and acidified with 10% aqueous HCl. The mixture was extracted with ether, the extracts were dried ($MgSO_4$), and the solvent was removed to afford the crude product, which after flash column chromatography on silica gel gave 12 mg (53% yield) of **25a** and 6 mg (24% yield) of **25b**. Spectral data for **25a**: ^1H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 1H), 6.27 (s, 1H), 5.32 (s, 1H, exchangeable with D_2O), 5.07 (s, 1H), 5.03 (s, 1H), 4.21 (dd, J = 6.2, 1.8 Hz, 1H), 4.17-4.13 (brm, 1H), 4.10-3.98 (brm, 3H), 3.37 (dd, J = 10.8, 6.2 Hz, 1H), 2.48 (t, J = 7.6 Hz, 2H), 2.06-2.01 (m, 1H), 1.97-1.91 (m, 1H), 1.83 (s, 3H), 1.81-1.76 (brm, 1H), 1.71-1.66 (m, 2H), 1.58-1.53 (m, 2H), 1.3-1.23 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.83, 152.43, 151.69, 145.08, 116.18, 111.78, 109.81, 106.80, 103.59, 84.39, 65.41, 65.10, 47.92, 44.21, 35.97, 31.36, 31.16, 30.88, 28.25, 22.30, 22.25; IR (CCl_4) 3450, 2920, 2850, 1630, 1605, 1430, 1200 cm^{-1}; mass spectrum m/e (relative intensity) 361(6), 154(41), 99(21), 86(100). Exact mass calculated for $C_{22}H_{27}O_4D_3$: 361.2332, found: 361.2331.

(-)-trans-1-methoxy-3-(5'-($^2H_3$)pentyl)-6a,7,8,10a-tetrahydro-6,6-dimethyl-9-carbomethoxy-6H-dibenzo[b,d]-pyran (**4**).

A solution of 46 mg (0.10 mmol) of the mixture of *trans* and *cis* ring junction isomers of the cyclohexenyl triflate, 0.03 ml of Et_3N, 1.0 mg of $Pd(OAc)_2$, 2.0 mg of triphenylphosphine, and 0.2 ml of methanol in 0.5 ml of DMF was purged with carbon monoxide for 5 min and then stirred under a carbon monoxide atmosphere. The progress of the reaction was monitored by TLC. After 12 h, the reaction mixture was poured into water, and extracted with ether (2x50 ml). The ether extracts were dried ($MgSO_4$) and solvent was evaporated. The purification of the crude product by flash column chromatography on silica gel eluting with 5% ethyl acetate in hexane afforded 30 mg of a mixture of *trans* and *cis* esters. These stereoisomers were separated by HPLC (Phenomenex Ultracarb 5 ODS 30 column, 250 x 10 mm, flow rate 2.5 ml/min, methanol). The specific rotation for the *trans* isomer **4** was $[\alpha]^{21}D$ = -237° (c= 0.005 g/ml, ethanol). Spectral data for **4**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.81(br s, 1H), 6.31(s, 1H), 6.28 (s, 1H), 3.87 (s, 3H), 3.73 (s, 3H), 3.31 (dd, J = 11.4, 1.5 Hz, 1H), 2.59-2.53 (br m, 1H), 2.50 (dd, J = 8.1, 7.2 Hz, 2H), 2.47-2.39 (m, 1H), 2.00 (dd, J = 12.6, 7.5 Hz, 1H), 1.71 (ddd, J = 12.6, 11.4, 1.8 Hz, 1H), 1.63-1.54 (br m, 2H), 1.43 (s, 3H), 1.41-1.36 (m, 1H), 1.33-1.28 (br m, 4H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.16, 158.16, 154.39, 143.26, 143.24, 128.87, 110.28, 108.15, 102.99, 77.55, 55.27, 51.54, 44.53, 36.04, 34.57, 31.46, 30.82, 27.49, 25.43, 24.37, 22.27, 18.94; IR ($CHCl_3$) 2980, 2915, 2860, 1720, 1620, 1575, 1420, 1120, 1100 cm^{-1}; mass spectrum m/e (relative intensity) 375(26), 360(41), 356(24), 316(74), 272(12), 258(24), 229(25), 210(100), 185(40). Exact mass calculated for $C_{23}H_{29}D_3O_4$: 375.2489, found: 375.2492.

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