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Conformationally Restricted Hybrids of CP-55,940 and HHC: Stereoselective Synthesis and Activity

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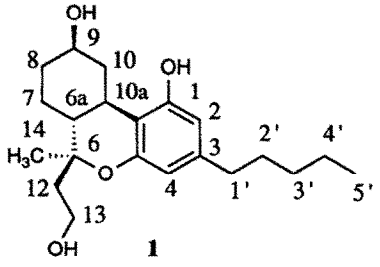
Abstract: A stereoselective total synthesis of each of the two diastereomeric C6-hydroxyethyl analogs of (-)-9-nor-9β-hydroxyhexahydrocannabinol has been reported. Control of the stereochemistry at C6 during the key step is accomplished through an intramolecular oxymercuration reaction. The prediction that the analogs would exhibit different degrees of binding to the cannabinoid receptor was borne out. This observation sheds light on the stereochemical requirements of the receptor.

The recent recognition of the presence of a cannabinoid receptor,[1] and the subsequent discovery of its endogenous ligand[2] have provided new inspiration for workers in the area. A particularly interesting early discovery is related to the development of a class of synthetic, non-classical cannabinoids based on the structure of (-)-9-nor-9β-hydroxyhexahydrocannabinol (HHC).[3] HHC is equivalent to morphine in analgesic potency, and provided the model for an extensive search for potent, non-opiate analgesics.[4] One of the most exciting structures to come out of this pioneering work was CP-55,940, in which the pyran ring associated with the



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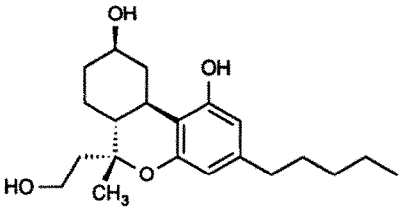
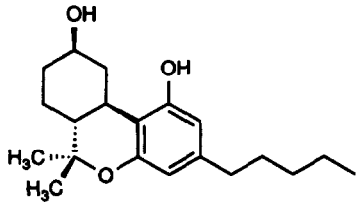


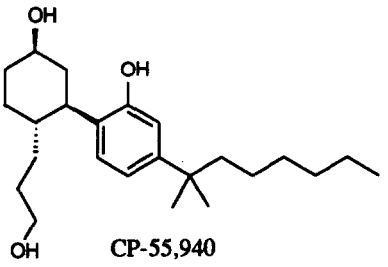
2

natural series and HHC was replaced by a hydroxypropyl group.[5] This analog was significantly more active as an analgesic than morphine, the increase in potency being attributed in part to the introduction of the new hydroxypropyl binding component in the southern portion of the molecule. Significantly, both the aryl-cyclohexyl bond and the hydroxypropyl groups are not conformationally restricted. A partially restricted

analog of CP-55,940, in which rotation about the benzylic carbon-carbon bond was allowed, showed enhanced potency.[5] In this work we report the total synthesis and the receptor binding properties of hybrid structures **1** and **2** which combine the structural elements of CP-55,940 and HHC, and for which rotation about the benzylic carbon-carbon bond is precluded by the dihydrobenzopyran ring. In these two diastereomers partial restriction of the hydroxypropyl group is also imposed.



HHC

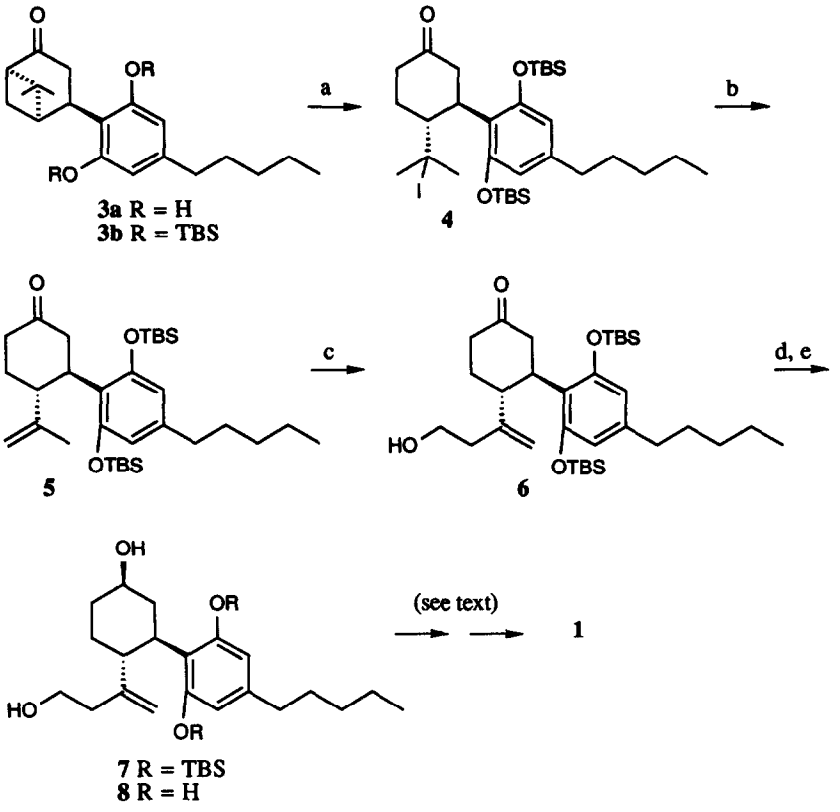


CP-55,940

Control of the stereochemistry at C6 poses a challenge for the chemist. Several non-stereoselective routes to **1** and **2** can be imagined, however our goal was to define a route which would be both selective and easily modified to produce either of the two isomers. The point of departure is ketone **3a** (Scheme 1) which was prepared from (-)-β-pinene according to the published procedure.[6] Exposure to *tert*-butyldimethylsilyl chloride (TBS-Cl) and imidazole in N,N-dimethylformamide at 23 °C produced the *bis*-TBS ether **3b** in 85% yield. Cleavage of the cyclobutane ring in **3b** under the influence of trimethylsilyl iodide (generated *in situ* from allyltrimethylsilane and iodine) at 0 °C gave rise to tertiary iodide **4** which was immediately converted to **5** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at 23 °C.[7] The overall yield for the two steps was 52%. The regiochemical course of the elimination reaction had been predicted based upon our earlier work.[8] The next task formally required appending a hydroxymethyl group to the isopropenyl methyl of **5**. An obvious approach was to make use of an acid catalyzed ene reaction with formaldehyde. With dimethylaluminum chloride as the Lewis acid[9] limited success was realized: yields were low (ca. 20%) and the reaction did not proceed to completion. Yamamoto's methylaluminum *bis*(2,6-diphenylphenoxide)-formaldehyde reagent led to an efficient (50-55% yield) conversion of **5** to hydroxyethyl derivative **6**.[10] Carbonyl reduction with sodium borohydride in tetrahydrofuran (THF)-isopropanol (9:1) at 23 °C led to the equatorial alcohol **7** in 88% yield. Removal of the TBS protecting groups was accomplished in 90-96% yield by brief exposure to tetra-*n*-butylammonium fluoride in THF. Tetraol **8** is a potential intermediate for the synthesis of both **1** and **2**.

The stereochemically determining step in the synthesis of **1** or **2** is the acid catalyzed ring-closure of **8**, or of a similar intermediate, to form the dihydrobenzopyran. The stereochemistry of the product would presumably depend upon which of the two diastereotopic faces of the alkene was presented to the phenolic hydroxyl. Cyclization via conformer **8a** would lead to **2**, whereas cyclization through **8b** would lead to **1**.

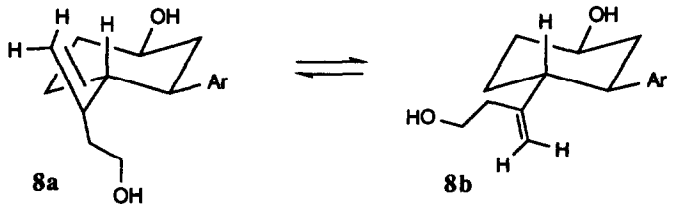
Scheme 1



(a) allyltrimethylsilane, I_2, CCl_4, 0 °C; (b) DBU, benzene, 23 °C; 52% yield overall from **3b**; (c) MAPH, sym-trioxane, CH_2Cl_2, 0 °C; 50-55% yield; (d) $NaBH_4$, THF/*i*-PrOH (9:1), 23 °C; 88% yield; (e) *n*-Bu_4NF, THF, 23 °C; 90-96% yield.

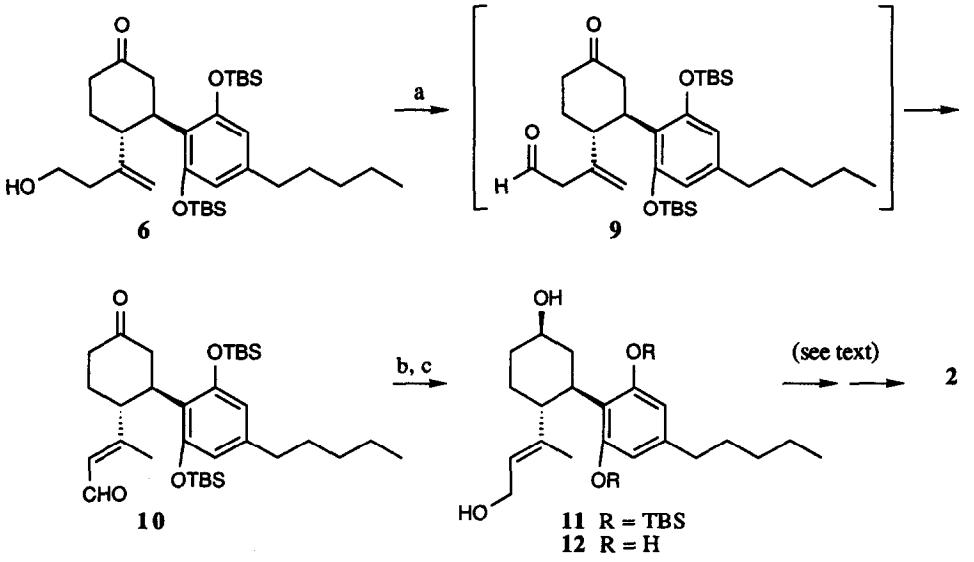
Control of the stereochemical course of the cyclization was predicted to pose a difficult challenge, since there was no reason *a priori* to expect any conformational preference. In fact, exposure of **8** to *p*-toluenesulfonic acid in refluxing toluene was non-stereospecific, and led to a 1:1 mixture of **1** and **2**. Protonation of the alkene presumably led to a tertiary carbocation which was intercepted by the phenolic hydroxyl with a complete lack of stereochemical bias.[11] This result with proton as the electrophile was disheartening, but it suggested that the problem might be surmounted by altering the mechanism, through the use of an alternative electrophile. Indeed, treatment of **8** with mercuric acetate in THF at 0 °C, followed by reductive demercuration with sodium borohydride in aqueous sodium hydroxide,[12] led to a 86:14 (hplc: 25 cm, 10 μ Econosil column; 80/20 ethyl acetate/hexanes) mixture of **1** and **2** in 75% yield. The determination of stereochemistry was made on the basis of nOe: irradiation of the pseudoaxial methyl group (δ = 1.10 ppm) in isomer **1** led to enhancement of the C10a benzylic methine signal (δ = 2.52 ppm).[13] Irradiation of the C-14

methylene group in isomer **2** led to enhancement of the same signal. This assignment of stereochemistry is also supported by the observation in various THC derivatives that the 6β-methyl is always at lower field than the 6α-methyl.[14] The 6β-methyl in **2** appears at 1.42 ppm whereas the 6α-methyl in **1** appears at 1.10 ppm. The approach provided a satisfying route to **1**; it remained to be determined whether a minor variation would provide **2** as the major product.



Swern oxidation[15] of **6** (Scheme 2) led to β,γ-unsaturated aldehyde **9** which underwent spontaneous isomerization to a single conjugated isomer. No coupling between the vinylic methyl and hydrogen was observed in the ^{1}H nmr spectrum at 300 MHz; the geometry of the double bond in **10** was assumed to be *E*. Reduction of both carbonyl groups in **10** with sodium borohydride, followed by cleavage of the phenolic protecting groups with tetra-*n*-butylammonium fluoride, led to tetraol **12**. Mercuration of **12** and reductive demercuration with sodium borohydride led to a 85:15 mixture of **2** and **1** in 80% yield.

Scheme 2

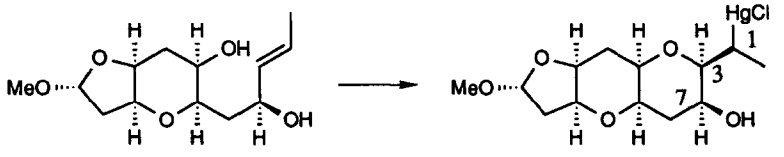


(a) DMSO, oxalyl chloride, CH_2Cl_2, -78 °C; 85% yield; (b) $NaBH_4$, THF/*i*-PrOH (9:1), 23 °C; 72% yield; (c) *n*-Bu_4NF, THF, 23 °C; 92% yield.

This demonstrated that each of the two diastereomers was available selectively, however the origin of the stereoselectivity is not easily rationalized. Some of the earlier results in the area are contradictory. Sinaÿ has shown that intramolecular oxymercuration of **13** produces axial CH_2HgCl in high yield.[16] The stereochemistry was attributed to coordination by the benzyloxy groups to the incoming mercurio species. On the other hand, Ganem reported only equatorial product from the intramolecular aminomercuration of **14**, even though an adjacent benzyloxy group to direct the axial stereochemistry was present.[17] In Kozikowski's synthesis of the dactylomelynes, the high degree of stereoselectivity during the cyclization of **15** was attributed to the equatorial preference of the bulky alkylmercurial group in a chair-like transition state.[18] It is perhaps significant that in the solid state of the product, rotation about the C1-C3 bond places the chloromercury group *syn* to the C7 hydroxyl, suggesting that in this case, the stereoselectivity may in fact be traced to a directing effect by hydroxyl. In the case of both **8** and **12**, oxymercuration took place so as to place the alkylmercurial group axial in the developing dihydrobenzopyran ring. In the absence of any heteroatomic directing effect, the stereochemical preference may be due to the anomeric effect of the positively charged mercurio species in the transition state. The mercury is clearly exercising a profound effect on the stereochemistry, as evidenced by the observation that fluorodesilylation of **10**, followed by reduction with sodium borohydride, produced a 1:1 mixture of **1** and **2**. Attribution of the stereochemical course of a reaction to any single factor in a complex system is undoubtedly an oversimplification, nevertheless this provides a working hypothesis to be tested.

13 *[Sinay, 1981]*

14 *[Ganem, 1985]*



15 *[Kozikowski, 1990]*

Compounds **1** and **2** as well as their uncyclized precursor (**12**) were tested for their affinities for the cannabinoid receptor using rat brain membranes and [^{3}H]-CP-55,940 as the radioligand. Of these, **1**, in which the hydroxyethyl group has a β-equatorial relative configuration, was shown to possess considerable affinity

(IC_{50}=100nM) while **2** and **12** exhibited much weaker affinities (IC_{50}=3.2μM; >10μM, respectively). The above biochemical data demonstrate the strict stereochemical requirements for a favorable ligand:receptor interaction imposed by the cannabinoid receptor on the hydroxypropyl pharmacophore.

Acknowledgement is made to NIDA (AM for DA7215 and DA3081; MAT for DA06731) for generous support. XLZ thanks Dr. Thomas Hemscheidt for assistance.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz ^{1}H (75 MHz ^{13}C) or 500 MHz ^{1}H (125 MHz ^{13}C) in either deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) or acetone-d_6 with acetone (2.04 ppm ^{1}H, 29.8, 206.5 ppm, ^{13}C) as an internal reference. Chemical shifts are given in δ; multiplicities are indicated as br (broadened), s (singlet), 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-70SE 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, were distilled from sodium-benzophenone ketyl, N,N-dimethylformamide (DMF), triethylamine (Et_3N) 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 were determined on the basis of 300 MHz ^{1}H-NMR (94%) and multiple elution TLC analysis, respectively.

4-[4-Pentyl-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-6,6-dimethylbicyclo [3.1.1]-hept-2-one (3b).

To a solution of ketone **3a** (158 mg, 0.50 mmol) and *tert*-butyldimethylsilyl chloride (453 mg, 3.00 mmol) in 10 ml N,N-dimethylformamide (DMF) at 23 °C was added imidazole (410 mg, 6.00 mmol). The mixture was stirred at 23 °C for 16 h and 50 ml ether was added. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to give 231 mg (85% yield) of **3b**: (oil); IR (neat) 2960, 2860, 1710, 1600, 1560, 1460, 1420 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 2H), 3.98 (m, 1H), 3.75 (d, J = 6.9 Hz, 1H), 3.68 (d, J = 6.9 Hz, 1H), 2.56-2.36 (m, 6H), 2.21 (m, 1H), 1.56-1.30 (m, 2H), 1.55 (s, 3H), 1.32 (s, 3H), 0.98 (s, 6H), 0.86 (s, 18H), 0.02 (s, 12H); mass spectrum m/e (relative intensity) 544(M^+, 7), 487(67), 377(33), 73(100). Exact mass calculated for $C_{32}H_{56}O_3Si_2$: 544.3767, found: 544.3748.

3-[4-Pentyl-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-isopropenylcyclohexane-1-one (5).

A solution of iodine (343 mg, 1.35 mmol) and allyltrimethylsilane (156 mg, 1.37 mmol) in 5 ml CCl_4 was stirred at 0 °C for 2 h. Ketone **3b** (480 mg, 0.88 mmol) in 3 ml CCl_4 was added. The reaction mixture was stirred at 0 °C for 30 min, then quenched by adding aqueous saturated $Na_2S_2O_3$. The mixture was extracted with ether. The organic solution was dried ($MgSO_4$) and evaporated. The crude product **4** was dissolved in 5 ml benzene at 23 °C and excess DBU (ca. 4 mmol) was added. The solution was stirred for 2 h at 23 °C and diluted with 20 ml ether. The organic solution was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) on silica gel to give 250 mg (52% overall yield) of **5**: (oil); IR (neat) 3010, 2960, 1720, 1610, 1560, 1470 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1H), 6.20 (s, 1H), 4.66 (d, J = 0.3 Hz, 1H), 4.52 (s, 1H), 3.70 (m, 1H), 3.47 (td, J = 12.0, 3.0 Hz, 1H), 3.17 (dd, J = 14.1, 13.5 Hz, 1H), 2.48 (m, 3H), 2.33-1.67 (m, 6H), 1.56 (s, 3H), 1.32 (m, 4H), 1.06 (s, 9H), 0.98 (s, 9H), 0.88 (dd, J = 6.9, 6.6 Hz, 3H), 0.35 (s, 3H), 0.32 (s, 3H), 0.23 (s, 3H), 0.16 (s, 3H); mass spectrum m/e (relative intensity) 544(M^+, 6), 487(69), 379(33), 73(100). Exact mass calculated for $C_{32}H_{56}O_3Si_2$: 544.3767, found: 544.3794.

3-[4-Pentyl-2,6-bis(*tert*-butyldimethylsilyloxy)phenyl]-4-[3'-(1'-hydroxy-3',4'-butenyl]-cyclohexane-1-one (6).

To a solution of 2,6-diphenylphenol (134 mg, 0.55 mmol) in 2 ml CH_2Cl_2 was added 0.17 ml of a 1.6 M solution of trimethylaluminum in toluene (0.27 mmol) at 23 °C. The solution turned light brown and was stirred for 1 h at 23 °C, cooled to 0 °C, and trioxane (11 mg, 0.12 mmol) in 1 ml CH_2Cl_2 was added. The mixture was stirred for 1 h at 0 °C. Ketone **5** in 2 ml CH_2Cl_2 was added and the solution was stirred for an additional 2 h. Saturated aqueous $NaHCO_3$ was used to quench the reaction. The reaction was extracted with CH_2Cl_2 and the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to give 58 mg (50-55% yield) of **6**: (oil); IR (neat) 3450, 2980, 2860, 1710, 1570, 1420, 1100 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.20 (s, 1H), 4.97 (s, 1H), 4.68 (s, 1H), 3.75 (m, 1H), 3.58 (q, J = 12.3, 12.0 Hz, 2H), 3.36 (m, 2H), 2.48-2.05 (m, 6H), 1.71-1.50 (m, 3H), 1.55 (s, 3H), 1.30-1.25 (m, 3H), 1.05 (s, 9H), 0.99 (s, 9H), 0.88 (dd, J = 6.9, 6.6 Hz, 3H), 0.36 (s, 3H), 0.32 (s, 3H), 0.24 (s, 3H), 0.16 (s, 3H); mass spectrum m/e (relative intensity) 574(0.1), 487(57), 379(26), 73(100), 69(25). Exact mass calculated for $C_{33}H_{58}O_4Si_2$: 574.3957, found 574.3915.

3-[4-Pentyl-2,6-(*tert*-butyldimethylsilyloxy)phenyl]-4-[3'-(1-hydroxy-3',4'-butenyl)]-cyclohexane-1-ol (7).

To a solution of ketone **6** (80 mg, 0.14 mmol) in 10 ml of a mixture of THF and isopropanol (9:1) at 23 °C was added sodium borohydride (8 mg, 0.21 mmol) portionwise, and the mixture was stirred for 30 min. The reaction was quenched with water and the mixture was extracted with ether. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel to give 70 mg (85-88% yield) of alcohol **7**: (oil); IR (neat) 3340, 2970, 2880, 1600, 1420, 1050 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1H), 6.18 (s, 1H), 4.91 (s, 1H), 4.61 (s, 1H),

3.69 (m, 1H), 3.54 (tt, J = 5.7, 5.7 Hz, 2H), 3.35 (m, 1H), 2.89 (m, 1H), 2.41 (dd, J = 7.8, 7.5 Hz, 2H), 2.09 (m, 3H), 1.86 (m, 1H), 1.55 (s, 3H), 1.57-1.24 (m, 7H), 1.06 (s, 9H), 1.02 (s, 9H), 0.88 (dd, J = 6.0, 5.7 Hz, 3H), 0.33 (s, 3H), 0.32 (s, 3H), 0.25 (s, 3H), 0.17 (s, 3H).

Tetraol (8).

To a solution of **7** (40 mg, 0.07 mmol) in 6 ml THF at 23 °C was added tetra-*n*-butylammonium fluoride hydrate (73 mg, 0.28 mmol) portionwise. The mixture was stirred for 1 h and 30 ml ether was added. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (80% ethyl acetate in hexanes) on silica gel to give 23 mg (90-96% yield) of **8**: (oil); IR (neat) 3350, 2960, 2880, 1620, 1590, 1420, 1040 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3COCD_3) δ 8.00 (br, 1H, exchangeable with D_2O), 6.16 (s, 1H), 6.14 (s, 1H), 5.61 (s, 1H, exchangeable with D_2O), 4.84 (d, J = 1.5 Hz, 1H), 4.47 (s, 1H), 3.64 (m, 1H), 3.54-3.31 (m, 3H), 3.03 (m, 1H), 2.33 (dd, J = 8.1, 6.9 Hz, 2H), 2.15 (m, 2H), 1.79 (m, 2H), 1.55-1.19 (m, 10H), 0.86 (dd, J = 6.9, 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CD_3COCD_3) δ 157.6, 156.0, 151.1, 141.7, 115.8, 109.8, 108.5, 107.6, 71.1, 61.6, 46.4, 40.4, 38.6, 37.1, 36.7, 36.0, 32.9, 32.2, 31.5, 23.1, 14.2; mass spectrum m/e (relative intensity) 348(M^+, 56), 257(31), 217(53), 207(46) 193(100). Exact mass calculated for $C_{21}H_{32}O_4$: 348.2300, found: 348.2290.

α,β-Unsaturated aldehyde (10).

Dimethylsulfoxide (0.52 mmol) was added to the solution of oxalyl chloride (0.35 mmol) in 2 ml CH_2Cl_2 at -78 °C. After 8 min, 48 mg of **6** (0.08 mmol) in 1 ml CH_2Cl_2 was added slowly. The mixture was stirred for 15 min, then triethylamine (0.22 mmol) was added at -78 °C. The mixture was warmed to 23 °C and stirring was continued for 12 h. The reaction was quenched with water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) on silica gel to give 41 mg (85% yield) of ketoaldehyde **10**: (oil); IR (neat) 2980, 2880, 1720, 1680, 1605, 1570, 1100 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.82 (d, J = 7.9 Hz, 1H), 6.22 (s, 1H), 6.18 (s, 1H), 5.86 (d, J = 7.9 Hz, 1H), 3.76 (m, 1H), 3.56 (m, 1H), 3.20 (dd, J = 13.5, 11.2 Hz, 1H), 2.41 (m, 3H), 2.05 (m, 1H), 1.99 (s, 3H), 1.80-1.57 (m, 5H), 1.25 (m, 4H), 1.06 (s, 9H), 0.99 (s, 9H), 0.88 (t, J = 6.9, 6.6 Hz, 3H), 0.36 (s, 3H), 0.33 (s, 3H), 0.25 (s, 3H), 0.17 (s, 3H); mass spectrum m/e (relative intensity) 572(M^+, 0.4), 516(38), 515(76), 445(36), 405(39), 377(68), 100(83), 95(61), 73(100). Exact mass calculated for $C_{33}H_{56}Si_2O_4$: 572.3717, found: 572.3741.

Tetraol (12).

The same procedure was followed as in the conversion of **6** to **8**. Ketoaldehyde **10** (25 mg) was converted to diol **11** (18 mg, 72% yield). Desilylation produced 10 mg (92% yield) of **12**: (oil); IR (neat) 3400, 3010, 2980, 1600, 1420, 1100 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3COCD_3) δ 7.60 (br d, exchangeable with D_2O, 1H), 6.15 (s, 1H), 6.12 (s, 1H), 5.34 (dd, J = 6.6, 6.0 Hz, 1H), 3.88 (m, 1H), 3.76 (m, 1H), 3.64 (m, 1H), 3.33 (td, J = 11.7, 3.3 Hz, 1H), 2.33 (dd, J = 7.8, 7.5 Hz, 2H), 2.17-1.96 (m, 3H), 1.84 (m, 1H), 1.65 -1.23 (m, 9H), 1.48 (s, 3H), 0.86 (dd, J = 7.2, 6.6 Hz, 3H); mass spectrum m/e (relative intensity) (no M^+), 330(M^+-H_2O, 60), 312(30), 217(24), 194(24), 193(100), 150(52), 79(33).

12β-Hydroxymethyl-9-nor-9β-hydroxyhexahydrocannabinol (1).

Mercuric acetate (28 mg, 0.06 mmol) was added to a solution of tetraol **8** (20 mg, 0.06 mmol) in 3 ml THF in one portion at 23 °C. The mixture was stirred for 18 h. Excess sodium borohydride (0.12 mmol) in 0.5 ml 2.5 M aqueous NaOH was added, and the mixture was stirred for an additional 10 h. Saturated aqueous Na_2CO_3 (0.5 ml) was added and the mixture was stirred for another 4 h. The reaction mixture was decanted from the metallic mercury and was partitioned between ether and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel to give 15 mg (75% yield) of a 86:14 mixture of products **1** and **2**. The pure product **1** was purified by hplc (80% ethyl acetate in hexanes): (oil); IR (neat) 3400, 2980, 1600, 1480, 1350, 1050 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.21 (d, J = 1.5 Hz, 1H), 6.11 (br, 1H, exchangeable with D_2O), 6.10 (d, J = 1.5 Hz, 1H), 3.97-3.81 (m, 3H), 3.55-3.52 (m, 1H), 2.86 (br, 1H, exchangeable with D_2O), 2.52 (td, J = 11.1, 2.1 Hz, 1H), 2.41 (dd, J = 8.5, 7.0 Hz, 2H), 2.16 (m, 1H), 1.95 (t, J = 5.8 Hz, 2H), 1.84 (m, 1H), 1.66-1.52 (m, 4H), 1.40-1.26 (m, 5H), 1.14-1.01 (m, 1H), 1.10 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 155.1, 153.9, 142.9, 109.6, 109.0, 108.2, 79.9, 70.9, 58.9, 46.3, 41.1, 38.6, 35.5, 35.4, 33.2, 31.6, 30.6, 25.7, 22.5, 17.8, 14.0; mass spectrum m/e (relative intensity) 348(M^+, 39), 257(37), 193(42), 167(32), 150(33), 149(100). Exact mass calculated for $C_{21}H_{32}O_4$: 348.2300, found: 348.2308.

14α-Hydroxymethyl-9-nor-9β-hydroxyhexahydrocannabinol (2).

Compound **2** (8 mg) was prepared in 80% yield from 10 mg of **12** by the same procedure as described for **1**. The ratio of **1**:**2** was 15:85: (oil); IR (neat) 3400, 2980, 1610, 1450, 1100 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20 (d, J = 0.9 Hz, 1H), 6.09 (d, J = 0.9 Hz, 1H), 5.97 (br, exchangeable with D_2O, 1H), 3.87 (m, 2H), 3.73 (m, 1H), 3.48 (m, 1H), 2.53 (td, J = 11.4, 2.0 Hz, 1H), 2.44 (m, 2H), 2.18 (m, 1H), 1.97-1.83 (m, 4H), 1.42 (s, 3H), 1.58-1.33 (m, 8H), 1.05 (q, J = 6.9, 7.2 Hz, 1H), 0.87 (dd, J = 7.2, 6.9 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 155.1, 154.2, 143.2, 109.2(2C), 108.3, 78.5, 70.8, 59.1, 49.7, 38.8, 35.7, 35.4, 32.8, 32.7, 31.5, 30.6, 25.7, 24.7, 22.5, 14.0; mass spectrum m/e (relative intensity) 348(M^+, 72), 285(47), 257(71), 231(34), 217(28), 193(100), 149(51). Exact mass calculated for $C_{21}H_{32}O_4$: 348.2300, found: 348.2295.

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