Supporting Information.

Chemistry

^{1}H NMR spectra were measured on a Varian VXR-300S spectrophotometer using $CDCl_3$ as solvent with TMS as the internal standard. All chemical shifts are reported in ppm. Specific rotations were measured with a Perkin-Elmer 141 polarimeter. Column chromatography was performed with ICN silica gel 60A. Organic solutions were dried over anhydrous magnesium sulfate.

Dimethoxy-CBD (3)

CBD (3g, 9.95 mmol) was dissolved in DMF (55 ml). K_2CO_3 (7.35g, 53.3 mmol) and CH_3I (2.3 ml, 36.9 mmol) were added and the mixture was stirred at room temperature for 4 hours. The reaction was monitored by TLC (10% ether/light petroleum ether.) till the starting material disappeared. Then 200ml of water were added and the solution was extracted with Ether. The organic phase was washed with brine till neutral pH, dried on $MgSO_4$ and filtered. Removal of the solvent under reduced pressure afforded 3.2 g of the product (yield 98%).

Purity was established by thin layer chromatography (10% ether/ light petroleum ether) and one spot was observed.

(3): ^{1}H-NMR δ 6.344 (2H, s, Ar), 5.220 (1H, s, olefin), 4.460-4.436 (2H, d, J=7.2 Hz), 4.023-3.971 (1H, m, benzyl), 3.741 (6H, s, OCH_3), 2.960-2.869 (1H, td, J=11.5, 4.5 Hz, allyl), 2.717-2.569 (2H, t, J=7.5 Hz, benzyl), 2.259-2.144 (1H, m), 2.018-1.960 (1H, m), 1.789-1.722 (1H, m), 1.678 (3H, s, allyl CH_3), 1.568 (6H, br s), 1.352 (4H, m) 0.936-0.890 (3H, t, J=6.8 Hz, terminal CH_3).

IR: 2875, 1600, 1570, 1440, 1410, 1220, 1100, 880 cm^{-1}.

$[\alpha]_D$ -96.8 ^{0} (c 12.19 mg/ml, $CHCl_3$)
MS m/z (relative intensity): 342 (M^+, 14), 274 (100), 243 (27), 235 (10), 221 (40), 173 (16).
HR-MS for $C_{23}H_{35}O_2$: 342.2559, found 342.2551.

1,2 Oxido-dimethoxy-hexahydrocannabinol (4)

3-Chloro-perbenzoic acid (70% pure 1.2 g, 4.85 mmol) was dissolved in 50 ml CH_2Cl_2 and the solution was cooled to 0^{o}C. A solution of (**3**) (1.65 g, 4.82 mmol) in 10ml CH_2Cl_2 was slowly injected. The reaction mixture was stirred at 0^{o}C for 30 min and monitored by TLC (10% ether/ light petroleum ether.). The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ and the organic phase was separated by a separatory funnel, then the aqueous phase was extracted with ether. The combine organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Removal of the solvents under reduced pressure afforded a residue that was flash chromatographed (7% ether/ light petroleum ether) to give the epoxy-derivative (**4**) (yield 65%).
Purity was established by thin layer chromatography (10% ether/ light petroleum ether) and one spot was observed.

(4): ^{1}H-NMR δ 6.348-6.322 (2H, d, J=7.7 Hz, Ar), 4.369 (1H, s, olefin), 4.159 (1H, s, olefin), 3.803 (3H, s, OCH_3), 3.714 (3H, s, OCH_3), 3.612-3.571 (1H, d, J=12.2, Hz, H on epoxide ring), 2.574-2.522 (2H, t, J=7.9 Hz, benzyl), 2.293-2.201 (1H, m), 2.081-1.995 (1H, m), 1.882-1.757 (1H, m), 1.628-1.585 (6H, m), 1.364-1.313 (9H, m), 0.936-0.890 (3H, t, J=6.5 Hz, terminal CH_3).
IR: 2900, 1610, 1580, 1460, 1420, 1120, 760 cm^{-1}.

MS m/z (relative intensity): 358 (M^+, 26), 341 (5), 287 (7), 274 (16), 250 (29), 221 (100).
HR-MS for $C_{23}H_{34}O_3$: 358.2508, found 358.2531.

(3R,4R)-3-[2,6-Dimethoxy-4-pentylphenyl]-2-hydroxy-4-isopropenyl-1-methylenecyclohexane (5)

Butyllithium in hexane (5.6 ml, 14 mmol) was added to a 0°C solution of N-cyclohexylisopropylamine (1.85 ml, 11.3 mmol) in anhydrous toluene (10 ml, distilled over sodium) under N_2 atmosphere. After 15 min, methylmagnesium bromide in ether (3.8 ml, 11.4 mmol) was injected, and the reaction mixture was stirred for 45 min at room temperature. A solution of (**4**) (1g, 2.79 mmol) in dry toluene (3 ml) was added, and the mixture was heated to 40°C and stirred for two hours. Then the reaction was cooled to 0°C and quenched by the slow addition of 5M HCl. The organic phase was separated by a separatory funnel, and then the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Removal of the solvents under reduced pressure afforded an oily residue that on TLC (20% ether/light petroleum ether) showed only one spot, and by ^{1}H-NMR was proved to be (**5**) (yield 95%).

(5): ^{1}H-NMR δ 6.332 (2H, s, Ar), 5.083 (1H, s, olefin), 4.821 (1H, s, olefin), 4.662-4.622 (1H, d, J=11.8 Hz, CHOH), 4.387 (1H, s, olefin), 4.379 (1H, s, olefin), 3.798 (3H, s, OCH_3), 3.745 (3H, s, OCH_3), 3.200-3.154 (1H, td, J=11.2, 3.0 Hz, benzyl), 2.564-2.452 (3H, m), 2.255-1.625 (1H, m), 1.754-1.707 (1H, m), 1.609-1.350 (4H, m), 1.432 (3H, s, allyl CH_3), 1.350-1.313 (4H, m), 0.924-0.878 (3H, t, J=6.5 Hz, terminal CH_3).
IR: 3400, 2920, 1590, 1450, 1120, 900, 730 cm^{-1}.

$[\alpha]_D$ +62.3 ^{0} (c 15.36 mg/ml, $CHCl_3$)

(3R,4R)-3-[2,6-Dimethoxy-4-pentylphenyl]-2-acetoxy-4 isopropenyl-1-methylenecyclohexane (6)

(**5**) (0.9 g, 2.5 mmol) was dissolved in pyridine (2 ml) and acetic anhydride (2 ml) and the reaction was stirred for 18 hours at room temperature. Then the solution was poured onto iced water (20 ml) and extracted with ether. The combined organic extracts were washed successively with 1N HCl, aqueous sodium bicarbonate and brine, dried on $MgSO_4$ and filtered. Removal of the solvents under reduced pressure afforded an oily residue that on TLC (20% ether/ light petroleum ether.) showed only one spot, that by ^{1}H-NMR was proved to be (**6**) (yield ~100%).

(6): ^{1}H-NMR δ 6.281-6.267 (2H, d, J=4.2 Hz, Ar), 5.967-5.931 (1H, d, J=10.8 Hz, olefin), 4.767-4.721 (2H, d, J=13.7 Hz, olefin), 4.535 (1H, s, olefin), 4.419 (1H, s, olefin), 3.793 (3H, s, OCH_3), 3.745 (3H, s, OCH_3), 3.491-3.416 (1H, t, J=11.4 Hz), 3.286-3.197 (1H, td, J=11.4, 2.7, Hz, benzyl), 2.533-2.469 (2H, t, J=7.2 Hz), 2.325-2.249 (1H, m), 1.717 (3H, s, OAc), 1.625-1.447 (6H, m), 1.404-1.250 (6H, m), 0.924-0.878 (3H, t, J=6.5 Hz, terminal CH_3).

IR: 2910, 1750, 1450, 1360, 1240, 1120, 890 cm^{-1}.

MS m/z (relative intensity): 400 (M^+, 16), 340 (14), 314 (73), 234 (22), 221 (100).

HR-MS for $C_{25}H_{36}O_4$: 400.2613, found 400.2603.

7-Bromo-dimethoxy CBD (7)

(6) (1g, 2.5 mmol) was dissolved in dry CH_2Cl_2 (50 ml, distilled over CaH_2) under nitrogen atmosphere and TMSBr (1.6 ml, 12.1 mmol) was added. The reaction was stirred at r.t. for 4 hours, then it was shaken with a saturated aqueous solution of $NaHCO_3$ and the organic phase was separated by a separatory funnel, then the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Removal of the solvents afforded a residue that ^{1}H-NMR and TLC (20% ether/ light petroleum ether) showed predominantly a single component, that was used immediately with no purification. (yield 95%).

(7): ^{1}H-NMR δ 6.322 (2H, s, Ar), 5.736 (1H, s, olefin), 4.767 (1H, s, olefin), 4.454), 4.535 (1H, s, olefin), 4.006 (2H, s, CH_2Br), 3.736 (6H, s, OCH_3), 2.853-2.767 (1H, td, J=11.9, 3.2 Hz, benzyl), 2.565-2.512 (1H, t, J=7.9, Hz, benzyl), 2.397-2.359 (1H, m), 2.277-2.183 (1H, m), 1.870-1.662 (2H, m), 1.619 (3H, s, allyl CH_3), 1.439-1.237 (7H, m), 0.928-0.882 (3H, t, J=6.6 Hz, terminal CH_3).
IR: 2900, 1580, 1460, 1230, 1120 cm^{-1}.
MS m/z (relative intensity): 423 (M^+, 0.6), 342 (27), 340 (28), 287 (42), 274 (61), 221 (100).
HR-MS for $C_{23}H_{34}O_2{}^{81}Br$: 423.1722, found 423.1708.

7-Acetoxy-dimethoxy CBD (8)

(7) (570 mg, 1.35 mmol) was dissolved in acetone (15ml, stored on 4A^o molecular sieves) and tetrabutylammonium acetate (450 mg, 1.49 mmol). The mixture was stirred, refluxed and monitored by TLC (20% ether/ light petroleum ether). After 2 hours there was no more starting material. The acetone was removed under reduced pressure, and the residue was

diluted with water (20 ml) and extracted with ether. The combined organic extracts were washed with aqueous sodium bicarbonate and brine, dried on $MgSO_4$ and filtered. Removal of the solvents under reduced pressure afforded 520 mg of an oily residue (96% yield).
Purity was established by thin layer chromatography (20% ether/ light petroleum ether) and one spot was observed.

(8): ^{1}H-NMR δ 6.320 (2H, s, Ar), 5.581 (1H, s, olefin), 4.492-4.386 (4H, m, CH_2OAc + olefin), 4.040-3.986 (1H, m, benzyl), 3.715 (6H, s, OCH_3), 2.853-2.801 (1H, m), 2.195-2.071 (2H, m), 2.060 (3H, s, OAc), 1.823-1.695 (2H, m), 1.605 (5H, br s), 1.323 (4H, br s), 0.921-0.875 (3H, t, J=6.7 Hz, terminal CH_3).
IR: 2900, 1720, 1580, 1440, 1110 cm^{-1}.
$[\alpha]_D$ -135.2 ^{0} (c 15.95 mg/ml, $CHCl_3$)
MS m/z (relative intensity): 400 (M^+, 3), 332 (26), 331 (100), 241 (41), 221 (55), 208 (11).
HR-MS $C_{25}H_{36}O_4$: 400.2613, found 400.2609.

7-Hydroxy-dimethoxy CBD (9)

(**8**) (500 mg, 1.25 mmol) was dissolved in ethanol (20ml) and NaOH 1N (2 ml) was added and the reaction was refluxed for 1 hour. The ethanol was removed under reduced pressure, and the residue was diluted with water (20 ml) and HCl 2N was added to acid pH. The solution was extracted with ether. The combined organic extracts were washed brine, dried on $MgSO_4$ and filtered. Removal of the solvents under reduced pressure afforded 430 mg of an oily residue (96% yield).
Purity was established by thin layer chromatography (30% ether/ light petroleum ether) and one spot was observed.

(9): ^{1}H-NMR δ 6.328 (2H, s, Ar), 5.510 (1H, s, olefin), 4.458-4.414 (2H, d, J=13.2 Hz, olefin), 4.010 (2H, br s, CH_2OH), 3.728 (6H, s, OCH_3), 2.858-2.806 (1H, m, benzyl), 2.566-2.508 (2H, t, J=7.5 Hz, benzyl), 2.213 (2H, m), 1.817-1.582 (7H, m), 1.451-1.259 (5H, m), 0.924-0.878 (3H, t, J=6.5 Hz, terminal CH_3).

IR: 3300, 2900, 1580, 1440, 1220, 1110 cm^{-1}.

MS m/z (relative intensity): 358 (M^+, 7), 327 (52), 290 (80), 221 (100), 152 (33).

HR-MS for $C_{25}H_{38}O_3$: 358.2508, found 358.2511.

7-Hydroxy CBD (2)

A Grignard reagent was prepared with magnesium (100 mg, 4.17 mmol) and CH_3I (0.26 ml, 4.17 mmol) in dry ether (3ml, distilled over sodium) under N_2 atmosphere. (**9**) (420 mg, 1.17 mmol) in ether (1 ml) was slowly added to the stirred solution and the ether was distilled off. The residue was heated under N_2 atmosphere till 210^{o}C for 45 min. Then the flask was cooled till room temperature and the reaction was quenched with ice water. The aqueous solution was extracted with ether several times. The combine organic extracts were dried on $MgSO_4$ and filtered. Removal of the solvents under reduced pressure afforded a residue that was chromatographed on silica gel (30% ether/ light petroleum ether.) to give 150 mg of the pure (**2**) (yield 40 %).

Purity was established by thin layer chromatography (70% ether/ light petroleum ether) and HPLC (silica 5U column, normal phase, eluent isopropanol: n-hexane 5:95 v/v; flow=1ml/min; λ=220 nm). One spot was observed on TLC (R_f= 0.32) and one peak (10.6 min) was noted on HPLC.

(2): ^{1}H-NMR δ 6.200 (2H, s, Ar), 5.822 (1H, s, olefin), 4.629 (1H, s, olefin), 4.518 (1H, s, olefin), 4.075 (2H, s, CH_2OH), 3.962-3.923 (1H, m, benzyl), 2.567-2.484 (1H, td, J=13.3, 2.7 Hz, allyl), 2.435-2.384 (2H, t, J=7.5 Hz, benzyl), 1.882-1.734 (2H, m), 1.660 (6H, s. allyl CH_3), 1.584-1.487 (2H, m), 1.285-1.248 (6H, m), 0.886-0.843 (3H, t, J=6.3 Hz, terminal CH_3).

IR: 3300, 2900, 1620, 1580, 1440, 1240, 1020, 730 cm^{-1}.

$[\alpha]_D$ -67.3 ^{0} (c 19.51 mg/ml, $CHCl_3$)

MS m/z (relative intensity): 330 (M^+, 10), 312 (44), 299 (53), 284 (44), 244 (100), 231(56), 187 (29), 147 (13).

HR-MS for $C_{21}H_{30}O_3$: 330.21949, found 330.2211.