

A One-Step Method for the α -Arylation of Camphor. Synthesis of (-)-Cannabidiol and (-)-Cannabidiol Dimethyl Ether

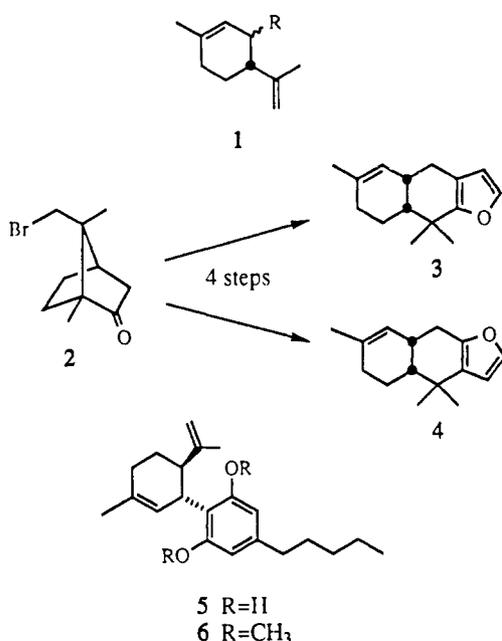
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The syntheses of (-)-cannabidiol and (-)-cannabidiol dimethyl ether were accomplished via fragmentation of an appropriately substituted 9-bromocamphor derivative. A new method of α -arylation of 3,9-dibromocamphor was shown to provide a variety of α -arylated camphor derivatives in good yields.

A wide variety of naturally occurring compounds possess the structural features of limonene derivatives of type 1. Recently,¹ we have shown that these structural features as well as several variations of the terpene skeleton are readily accessible from fragmentation reactions of 9-bromocamphor (2), which were exploited in enantiospecific syntheses of (-)-furodysin (3) and (-)-furodysin (4).



These fragmentation reactions appeared to be of general synthetic utility; however, they were limited by the constraints of effective C-3 functionalization of camphor. Previously, it had been shown that camphor and its brominated derivatives undergo aldol reactions to yield adducts in good yields with fair to good exo selectivity.² It has also been shown that camphor and its derivatives undergo alkylation at C-3 with alkyl halides in only poor to fair yields with endo selectivity, with the exception of methyl iodide which provides good yields of adducts with exo selectivity.³ To more fully realize the synthetic potential of the camphor system, new methods for manipulation of the various carbons, especially C3, are necessary. In this article, we detail recent work in this area which includes a new α -arylation technique resulting in the synthesis of terpenylated phenols.

Cannabidiol (5) is one such molecule which possesses the terpene structural unit 1. Various strategies for the synthesis of cannabidiol and tetrahydrocannabinol can be found in the literature.⁴ These include a Diels-Alder approach,⁵ anionic⁶ or cuprate⁷ additions of olivetol to terpenes, and the acid-catalyzed condensation of olivetol and a terpene which is normally followed by in situ cationic cyclization.⁸ The first two strategies produce racemic products. The latter approaches suffer from the general problem that cyclization to tetrahydrocannabinol derivatives is difficult to prevent under these conditions. Herein, we report a convenient enantiospecific synthesis of (-)-cannabidiol (5) and (-)-cannabidiol dimethyl ether (6) via the fragmentation of a brominated camphor derivative.

In order to synthesize cannabidiol from camphor, a new method for the introduction of substituted aromatic groups at the C-3 position of camphor had to be developed. Hamon and Levisalles⁹ had previously shown that the reaction of 3-bromocamphor with methylcuprate in a mixed solvent system of DMSO/Et₂O gave rise to nonselective methylation at the C-3 position with subsequent displacement of bromine. We knew from previous studies that the stereochemical outcome of this reaction was irrelevant because exo substituents at this position could be equilibrated to the desired endo position. The reaction of 3,9-dibromocamphor with a variety of aryl and heteroaryl cuprates was found to be a very general one (see Table I). The desired α -aryl ketone was formed in all cases in good yields (63-79%). When sterically demanding aryl cuprates (9 and 11) were used, the reaction proceeded with exclusive endo selectivity. When sterically less demanding cuprates (7 and 13) were used, the reaction provided a mixture of the exo and endo α -aryl ketones. At this time, we know very little about the mechanism of this arylation; however, we have found that the reaction is sensitive to both air and an excess of lithium base. We have also found that the cosolvent is important. A pure ethereal solvent yields only 9-bromocamphor, whereas a 1:1 mixture of the

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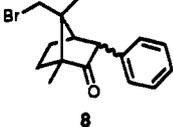
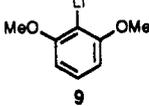
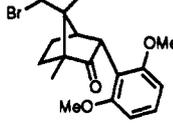
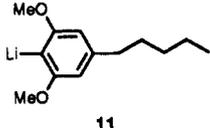
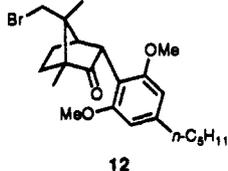
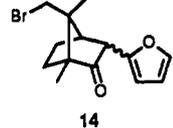
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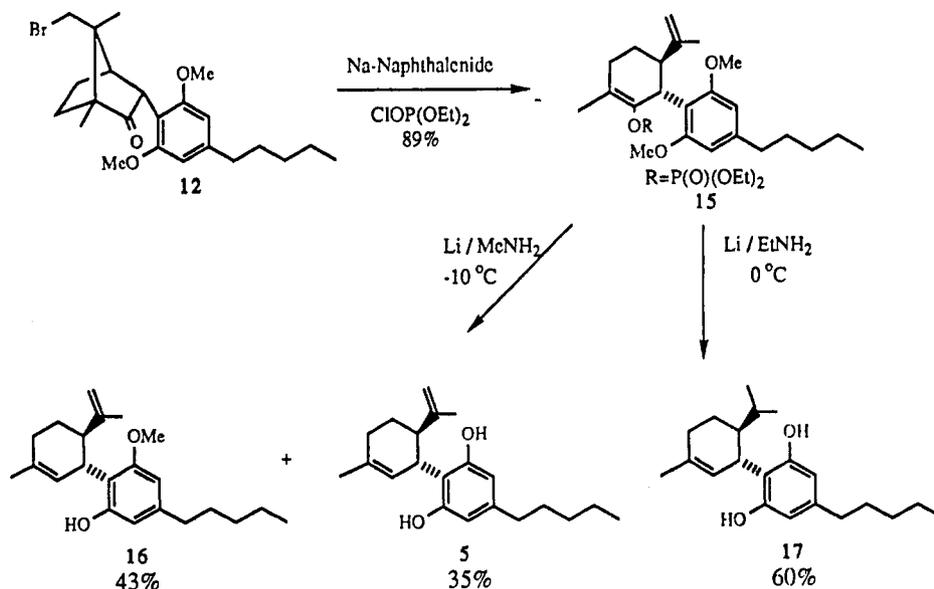
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Table I. Reactions of 3,9-Dibromocamphor with Aryl Cuprates

organolithium	condns	product	% yield
	CuI Et ₂ O/DMSO (1:1)		63 (4.5:1 endo:exo)
	CuI Et ₂ O/DMSO (1:1)		79
	CuI THF/DMSO (1:1)		71
	CuI THF/DMSO (1:1)		71 (5.5:1 endo:exo)

Scheme I. Synthesis of Cannabidiol (5) and Cannabidiol Methyl Ether (16)



ethereal solvent and either DMF or DMSO yields the desired α -aryl ketone.

With these results in hand, the task of completing the cannabidiol synthesis was begun. The first attempted synthesis paralleled the previously reported (-)-furodysin synthesis. Starting from α -aryl ketone 12, fragmentation by treatment with sodium naphthalenide and trapping of the resulting enolate afforded the enol phosphate 15 in 89% yield. Reductive cleavage of the vinyl phosphate was accompanied by mono- and bis-deprotection by treatment with an excess of lithium in monomethylamine at -10°C furnishing (-)-cannabidiol methyl ether (16) in 43% yield and (-)-cannabidiol (5) in 35% yield that was spectroscopically identical to an authentic sample. Attempts to improve the yield of cannabidiol by using monoethylamine at 0°C resulted in overreduction to furnish 17 in 60% yield.

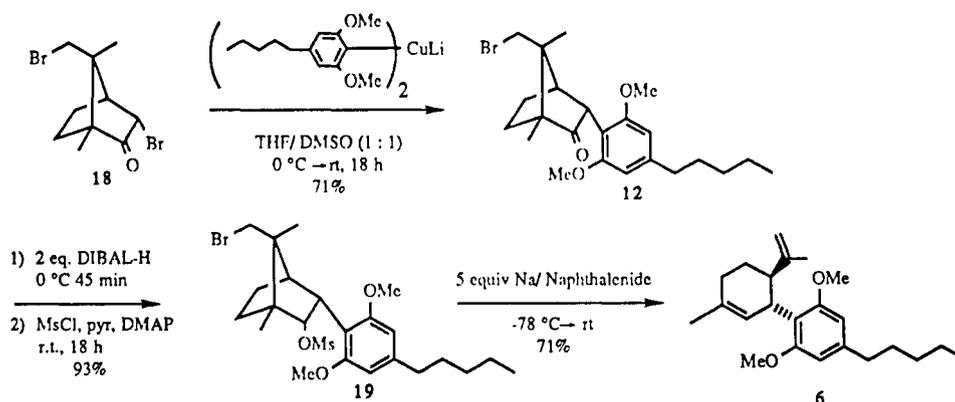
An alternative route for the synthesis of cannabidiol was subsequently explored. The α -aryl ketone 12 was reduced using 2 equiv of DIBAL in toluene. A variety of other

reducing agents were tried, but these resulted in significantly poorer yields. The resulting alcohol was then mesylated to give 19. We have previously demonstrated that an endo mesylate possesses the correct orientation to undergo fragmentation of the C1-C7 camphor bond.¹⁰ Addition of 19 to a large excess of a 0.4 M Na-naphthalenide/0.4 M tetraethyleneglycol dimethyl ether solution in THF resulted in fragmentation of the C1-C7 bond to form (-)-cannabidiol dimethyl ether (6) in 71% yield.¹¹ The major byproduct of this reaction was the

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(11) Two methods for the demethylation of cannabidiol dimethyl ether deprotection have been reported. The first utilizes molten MeMgI at $155-160^\circ\text{C}$ and is reported to proceed in an 80% yield. (Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* 1965, 87, 3273.) The second procedure involves concomitant monodemethylation and cyclization to tetrahydrocannabinol followed by further demethylation and is reported to proceed with a 75% yield. (Rickards, R. W.; Ronnenberg, H. *J. Org. Chem.* 1984, 49, 572.) Alternative methods of demethylation including lithium iodide, trimethylsilyl iodide, boron tribromide, and *B*-bromo-9-borabicyclo[3.3.1]nonane failed in our hands.

Scheme II. Synthesis of Cannabidiol Dimethyl Ether (6)



product of simple debromination at the C-9 position.

In summary, a convenient three-step synthesis of (-)-cannabidiol and a corresponding four-step synthesis of (-)-cannabidiol dimethyl ether were achieved starting from (+)-3,9-dibromocamphor which is readily accessible in one step from commercially available 3-bromocamphor. A method of arylating the C-3 position of camphor was also developed and found to be general for a variety of aryl cuprates. The generality of this methodology is currently being studied, and the results will be reported in due course.

Experimental Section

General. ^1H NMR data were measured at 300 MHz and ^{13}C data at 75 MHz. Infrared spectroscopic samples were prepared as neat oils (liquids) or as KBr pellets (solids). All electron-impact high-resolution mass spectral (HRMS) data were measured at 70 eV. Optical rotations were measured at the designated concentrations at 25 °C on a Perkin-Elmer Model 241MC polarimeter. All experiments were carried out under an atmosphere of dry argon or nitrogen in flame-dried flasks fitted with addition funnels of the pressure equilibrating type. THF and diethyl ether were freshly distilled from sodium/benzophenone ketyl and were transferred via syringes. CuI was purified by continuous extraction with THF for 12 h. Alkyl lithium reagents were obtained from the Aldrich Chemical Co. as standard solutions. Anhydrous DMSO was obtained from Aldrich Chemical Co. High-performance liquid chromatography (HPLC) was performed on either a Varian 5000 liquid chromatograph or a semipreparative component system obtained from the Rainin Instrument Corp. HPLC separations were performed on 250- \times -20-mm 8- μm silica Magnum semipreparative columns obtained from Rainin Instruments.

General Procedure for the Arylation of 3,9-Dibromocamphor. The desired cuprate was generated by treating 0.286 g (1.5 mmol) of CuI in 3 mL dry THF (Et_2O in the case of PhLi)¹² at 0 °C with 3 mmol of the required aryl lithium in 3 mL of THF (Et_2O in the case of PhLi).¹³ After 30 min, 6 mL of anhydrous DMSO was added and the resulting solution was transferred via cannula to a solution of 0.310 g (1 mmol) of 3,9-dibromocamphor in 1 mL of THF and 1 mL of DMSO at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of 5 mL of a saturated aqueous NH_4Cl solution. The aqueous layer was extracted three times with Et_2O . The combined organic layers were washed three times with brine and dried over Na_2SO_4 , and the solvent was removed in vacuo. The crude product was chromatographed on silica eluting with hexane-EtOAc (98:2) to yield the desired product which could be further purified by recrystallization from EtOH.

(12) The reactions involving phenyllithium were performed in Et_2O since the phenyllithium was obtained from Aldrich Chemical Co. as a solution in Et_2O /cyclohexane.

(13) Phenyllithium was purchased from the Aldrich Chemical Co. Furryllithium and 2,6-dimethoxyphenyllithium were prepared by treatment of furan or resorcinol dimethyl ether in 3 mL of dry THF with 1 equiv of *n*-butyllithium at 0 °C for 1 or 3 h, respectively.

3-Phenylcamphor (8): yield 0.194 g (63%); mp 113–116 °C; 4.5:1 mixture of endo-exo isomers; ^1H NMR (CDCl_3) δ 0.78 (s, 3 H, minor), 0.98 (s, 3 H, minor), 1.04 (s, 3 H, major), 1.18 (s, 3 H, major), 1.20–1.80 (overlapping multiplet, 7 H, major and minor), 2.05–2.15 (m, 1 H, minor), 2.72 (t, $J = 4$ Hz, 1 H, major), 3.12 (d, $J = 4$ Hz, 1 H, minor), 3.19 (d, $J = 10$ Hz, 1 H, minor), 3.29 (overlapping multiplet, 2 H, major and minor), 3.60 (d, $J = 10$ Hz, 1 H, minor), 3.69 (d, $J = 10$ Hz, 1 H, major), 3.81 (d, $J = 4.5$ Hz, 1 H, major), 7.20–7.33 (overlapping multiplet, 9 H, major and minor), 7.50 (d, $J = 7.6$ Hz, 1 H, minor); ^{13}C NMR δ 9.6, 10.0, 16.6, 18.5, 20.3, 27.6, 29.2, 29.5, 39.6, 40.3, 44.1, 47.4, 49.9, 51.2, 54.6, 56.3, 58.1, 60.0, 126.1, 126.7, 127.5, 127.6, 128.0, 128.5, 136.7, 137.5, 215.8; IR (KBr pellet) 2954, 2879, 1731, 1449, 1390, 1243, 1032, 750, 697, 656 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{19}\text{BrO}$ 306.0620, found 306.0621.

3-(2-Furyl)camphor (14): yield 0.209 g (71%); mp 94–96 °C; 5.7:1 mixture of endo-exo isomers; ^1H NMR (CDCl_3) δ 0.80 (s, 3 H, minor), 0.96 (s, 3 H, minor), 0.99 (s, 3 H, major), 1.10 (s, 3 H, major), 1.25–1.82 (overlapping multiplet, 7 H, major and minor), 2.04 (m, 1 H, minor), 2.76 (t, $J = 4.5$ Hz, 1 H, major), 2.98 (d, $J = 4$ Hz, 1 H, minor), 3.14 (d, $J = 10$ Hz, 1 H, minor), 3.24 (d, $J = 10.5$ Hz, 1 H, major), 3.29 (overlapping multiplet, 1 H, minor), 3.54 (d, $J = 10$ Hz, 1 H, minor), 3.62 (d, $J = 10.5$ Hz, 1 H, major), 3.75 (d, $J = 5$ Hz, 1 H, major), 6.14 (d, $J = 3$ Hz, 1 H, major), 6.20 (d, $J = 2$ Hz, 1 H, minor), 6.27–6.30 (overlapping multiplet, 2 H, major and minor), 7.30 (s, 1 H, minor), 7.32 (s, 1 H, major); ^{13}C NMR δ 9.6, 9.7, 16.5, 17.2, 20.8, 27.3, 29.2, 29.7, 39.2, 40.0, 44.7, 46.2, 49.5, 49.8, 51.0, 52.1, 58.0, 59.1, 105.1, 107.6, 110.1, 110.4, 141.0, 141.9, 150.6, 213.1, 213.6; IR (KBr pellet) 2972, 1739, 1583, 1485, 1454, 1390, 1237, 1149, 1072, 1025, 996, 808, 726, 626, 591 cm^{-1} ; HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{BrO}_2$ 296.0412, found 296.0414.

endo-3-(2,5-Dimethoxyphenyl)camphor (10): yield 0.291 g (79%); mp 181–182 °C; $\alpha_D^{25} = +132$ (c = 0.627 g/100 mL, CHCl_3); ^1H NMR (CDCl_3) δ 1.02 (s, 3 H), 1.18 (s, 3 H), 1.42 (t, $J = 10$ Hz, 1 H), 1.59–1.7 (overlapping multiplet, 2 H), 1.87 (t, $J = 10$ Hz, 1 H), 2.57 (t, $J = 4$ Hz, 1 H), 3.29 (d, $J = 10$ Hz, 1 H), 3.74–3.78 (overlapping multiplet, 7 H), 3.92 (dd, $J = 4$, 1 Hz, 1 H), 6.54 (d, $J = 8$ Hz, 2 H), 7.18 (t, $J = 8$ Hz, 1 H); ^{13}C NMR (CDCl_3) δ 10.4, 17.1, 21.5, 30.7, 40.5, 46.9, 47.2, 50.4, 55.7, 60.1, 104.4, 113.6, 128.3, 158.9, 216.3; IR (KBr pellet) 2971, 2933, 1737, 1587, 1469, 1247, 1103, 1031, 783 cm^{-1} ; HRMS calcd for $\text{C}_{18}\text{H}_{25}\text{BrO}_3$ 366.0830, found 366.0824.

endo-3-(2,5-Dimethoxy-4-*n*-pentylphenyl)camphor (12). A solution of 2.08 g (10 mmol) of olivetol dimethyl ether in 10 mL of dry THF under nitrogen was cooled to -10 °C. To this was added dropwise 8.82 mL (15 mmol, 1.5 equiv) of *tert*-butyllithium (1.7 M in hexanes). The resulting solution was allowed to stir for 3 h. This solution was then cooled back to 0 °C and transferred dropwise via cannula to a solution of 0.952 g (5 mmol) of CuI in 5 mL dry THF at 0 °C. The resulting solution was allowed to stir for 20 min, and then 15 mL of anhydrous DMSO was added. The solution was then transferred dropwise via cannula to a solution of 1.41 g (4.54 mmol) of 3,9-dibromocamphor in 5 mL of dry THF and 5 mL of DMSO at 0 °C. The reaction was then allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of 20 mL of saturated aqueous NH_4Cl . The aqueous layer was extracted three times with Et_2O . The combined organic layers were washed

three times with brine and dried over Na_2SO_4 , and the solvent was removed in vacuo. The crude product was chromatographed on silica eluting with hexane-EtOAc (95:5) and the major product recrystallized from EtOH to yield 1.332 g (71%) of the desired acrylated product as white crystals: mp 124–125 °C, $\alpha_D^{25} = +108$ ($c = 0.50$ g/100 mL, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 0.90 (t, $J = 7$ Hz, 3 H), 1.01 (s, 3 H), 1.16 (s, 3 H), 1.33 (m, 4 H), 1.43 (m, 1 H), 1.62 (m, 4 H), 1.86 (m, 1 H), 2.55 (overlapping multiplet, 3 H), 3.28 (d, $J = 10$ Hz, 1 H), 3.77–3.72 (overlapping multiplet, 7 H), 3.88 (d, $J = 4$ Hz, 1 H), 6.37 (s, 2 H); $^{13}\text{C NMR}$ δ 10.4, 14.0, 17.0, 21.4, 22.5, 30.6, 31.0, 31.5, 36.1, 40.5, 46.9, 47.1, 50.3, 55.6, 60.1, 104.7, 110.8, 143.6, 158.7, 216.5; IR (thin film) 1962, 2921, 2858, 1743, 1611, 1582, 1456, 1422, 1118 cm^{-1} ; HRMS exact mass calcd for $\text{C}_{23}\text{H}_{33}\text{BrO}_3$ 436.1613, found 436.1608.

Vinyl Phosphate 15. A solution of 0.436 g (1 mmol) of the arylated 9-bromocamphor derivative 12 in 5 mL of dry THF under nitrogen was cooled to -78 °C. The solution was titrated with ca. 7.5 mL of a freshly prepared 0.4 M Na-naphthalenide/0.4 M tetraethyleneglycol dimethyl ether solution in THF (as prepared below) until a deep green color persisted. To the mixture was then added 0.22 mL (1.5 mmol) of diethyl chlorophosphate and 0.30 mL (1.7 mmol) of HMPA. The resulting solution was allowed to warm to -20 °C and quenched by the addition of 5 mL of saturated aqueous NH_4Cl . The aqueous layer was extracted three times with Et_2O . The combined organic layers were washed twice with saturated aqueous NaHCO_3 and once with brine and dried over Na_2SO_4 , and the solvent was removed in vacuo. The crude product was chromatographed through a short silica column, eluting first with hexane-EtOAc (95:5) followed by hexane-EtOAc (75:25) to yield 0.437 g of the desired enol phosphate as a colorless oil (89%): $\alpha_D^{25} = -72$ ($c = 1.484$ g/100 mL, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 0.81 (t, $J = 6$ Hz, 3 H), 1.02 (t, $J = 7$ Hz, 3 H), 1.09 (t, $J = 7$ Hz, 3 H), 1.24 (m, 4 H), 1.48 (m, 4 H), 1.59 (s, 3 H), 1.68 (s, 3 H), 1.98 (bm, 1 H), 2.17 (bm, 1 H), 2.43 (t, $J = 7$ Hz, 2 H), 2.60 (dt, $J = 3, 13$ Hz, 1 H), 3.55 (q, $J = 7$ Hz, 2 H), 3.64 (s, 6 H), 3.71 (td, $J = 2, 7$ Hz, 2 H), 4.22 (br s, 1 H), 4.26 (br s, 1 H), 4.35 (br s, 1 H), 6.20 (s, 1 H), 6.22 (s, 1 H); $^{13}\text{C NMR}$ δ 13.8, 15.7, 15.6, 16.5, 18.3, 22.3, 27.8, 30.3, 31.0, 31.3, 36.1, 37.9, 48.1, 55.3, 55.8, 62.8 (d, $J = 6$ Hz), 63.2 (d, $J = 6$ Hz), 103.7, 104.8, 110.4, 115.5, 117.8 (d, $J = 7$ Hz), 142.0, 142.1 (d, $J = 12$ Hz), 147.5, 158.8, 159.1; IR (neat) 3072, 2931, 2861, 1701, 1652, 1616, 1581, 1455, 1420, 1279, 1230, 1117, 1040, 977 cm^{-1} ; HRMS exact mass calcd for $\text{C}_{27}\text{H}_{43}\text{O}_6\text{P}$ 494.2797, found 494.2801.

(-)-Cannabidiol (5) and (-)-Cannabidiol Monomethyl Ether (16). A total of 0.049 g (0.1 mmol) of the vinyl phosphate 15 in 0.5 mL of dry THF and 0.03 mL (0.3 mmol, 3 equiv) of *t*-BuOH was added dropwise to an excess of lithium foil (ca. 0.25 g) in MeNH_2 (ca. 10 mL) at -78 °C. When addition was complete, the -78 °C bath was replaced by a -10 °C ice-salt bath. The reaction was allowed to stir at -10 °C for 1 h. The bath was then removed, and the reaction was allowed to warm until all of the amine had boiled off. The reaction was then quenched by addition of 2 mL of a saturated aqueous NH_4Cl solution, diluted with Et_2O , and transferred to a separatory funnel. The mixture was made acidic by dropwise addition of 1 M HCl. The acidic aqueous layer was extracted three times with Et_2O . The combined organic layers were washed twice with saturated aqueous NaHCO_3 and twice with brine and dried over Na_2SO_4 , and the solvent was removed in vacuo. The crude reaction mixture was chromatographed on neutral alumina, and eluted first with hexane-EtOAc (95:5) to yield 0.014 g (43%) of (-)-cannabidiol monomethyl ether (16): $\alpha_D^{25} = -135$ ($c = 0.238$ g/100 mL, EtOH); $^1\text{H NMR}$ (CDCl_3) δ 0.88 (t, 3 H, $J = 7$ Hz), 1.25–1.35 (m, 4 H), 1.54–1.82 (overlapping multiplet, 4 H), 1.66 (s, 3 H), 1.78 (s, 3 H), 2.0–2.3 (bm, 2 H), 2.35–2.45 (m, 1 H), 2.49 (t, $J = 7.5$ Hz, 2 H), 3.70 (s, 3 H), 3.95–4.05 (bm, 1 H), 4.31 (s, 1 H), 4.48 (m, 1 H), 5.57 (s, 1 H), 6.00 (s, 1 H), 6.21 (d, $J = 1$ Hz, 1 H), 6.30 (d, $J = 1$ Hz, 1 H); $^{13}\text{C NMR}$ (CDCl_3) δ 14.1, 18.7, 22.5, 23.7, 28.1, 30.3, 30.8, 31.5, 35.4, 36.0, 46.6, 55.5, 103.1, 109.5, 110.8, 115.0, 124.5, 139.5, 142.6, 147.2, 155.6, 158.1; IR (thin film) 3437, 2948, 2916, 2852, 1617, 1580, 1453, 1431, 1208, 1101 cm^{-1} ; HRMS calcd for $\text{C}_{22}\text{H}_{32}\text{O}_2$ 328.2402, found 328.2407. Further elution with hexane-EtOAc (90:10) yielded 0.011 g (35%) of (-)-cannabidiol (5) which was spectroscopically identical to an authentic sample (and published IR and MS data^{6a}): $\alpha_D^{25} = -116$ ($c = 2.43$ g/100 mL, EtOH) (lit.¹⁴ $\alpha_D^{18} = -129$ ($c = 0.45$ g/100 mL,

EtOH); $^1\text{H NMR}$ (CDCl_3) δ 0.89 (t, $J = 7$ Hz, 3 H), 1.22–1.38 (m, 2 H), 1.48–1.84 (olm, 4 H), 1.63 (s, 3 H), 1.82 (s, 3 H), 2.02–2.44 (olm, 3 H), 2.39 (t, $J = 7.5$ Hz, 4 H), 3.7–3.9 (m, 1 H), 4.49 (s, 1 H), 4.56 (t, $J = 1.5$ Hz, 1 H), 5.54 (s, 1 H), 5.9–6.4 (bm, 2 H), exchanges D_2O to a broad singlet at δ 6.22; $^{13}\text{C NMR}$ (CDCl_3) δ 14.0, 20.5, 22.5, 23.7, 28.4, 30.3, 30.6, 31.4, 35.4, 37.2, 46.1, 107.9 (broad), 109.7 (broad), 110.8, 113.7, 124.0, 140.0, 143.0, 149.4; IR (thin film) 3426, 2960, 2929, 2856, 1629, 1583, 1147, 1378, 1237, 1219, 1053, 1025, 884 cm^{-1} ; MS m/e 314 (16), 246 (34), 231 (100), 193 (10), 174 (9), 121 (10); HRMS calcd for $\text{C}_{21}\text{H}_{30}\text{O}_2$ 314.2246, found 314.2248.

Reduction of 15 with Monoethylamine (15 \rightarrow 17). This reaction was run in the same manner as the reaction above except monoethylamine was used in place of monomethylamine. The crude $^1\text{H NMR}$ spectrum of the reaction showed essentially one product. Chromatography on alumina, eluting with hexane-EtOAc (90:10) yielded 0.019 g of 17 as the major reaction product: $^1\text{H NMR}$ (CDCl_3) δ 0.82–0.92 (m, 9 H), 1.20–1.46 (m, 6 H), 1.76 (s, 3 H), 1.52–1.84 (m, 4 H), 2.00–2.20 (m, 2 H), 2.44 (t, $J = 8$ Hz, 2 H), 3.80 (m, 1 H), 4.62 (broad s, OH), 5.52 (s, 1 H), 6.20 (broad s, 2 H + OH); IR (thin film) 3419, 2942, 2928, 2871, 1628, 1580, 1440, 1219, 1022 cm^{-1} ; HRMS calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2$ 316.2404, found 316.2400.

Endo Mesylate (19). A solution of 0.501 g (1.15 mmol) of the aryl ketone 12 in 3 mL of dry toluene was cooled to 0 °C. To this was added dropwise 1.53 mL of a 1.5 M DIBAL solution in toluene (2.29 mmol, 2 equiv). The resulting solution was allowed to stir at 0 °C for 45 min and then quenched by the addition of 0.15 mL of MeOH and 0.10 mL of saturated aqueous NH_4Cl . The resulting solution was stirred for an additional hour. The mixture was then diluted with Et_2O and filtered, and the solvent was removed in vacuo to yield quantitatively the desired alcohol which was used without further purification for subsequent reactions: mp 79–81 °C; $^1\text{H NMR}$ (CDCl_3) δ 0.92 (t, $J = 7$ Hz, 3 H), 0.95 (s, 3 H), 1.26 (s, 3 H), 1.33 (m, 5 H), 1.99 (m, 1 H), 2.10 (s, 1 H), 2.57 (t, $J = 7$ Hz, 2 H), 3.29 (d, $J = 10$ Hz, 1 H), 3.78 (d, $J = 10$ Hz, 1 H), 3.83 (s, 6 H), 4.19 (s, 2 H), 4.74 (broad s, 1 H), 6.45 (s, 2 H); $^{13}\text{C NMR}$ δ : 13.91, 13.95, 15.3, 22.1, 22.4, 26.4, 30.8, 31.4, 36.1, 37.5, 42.4, 50.1, 50.7, 51.7, 55.7, 79.2, 105.2, 113.6, 142.7, 158.4; IR (thin film) 3475, 2957, 2931, 1609, 1576, 1547, 1232, 1118 cm^{-1} ; HRMS, exact mass calcd for $\text{C}_{23}\text{H}_{35}\text{BrO}_3$ 438.1769, found 438.1775.

A solution of the crude alcohol from above (ca. 1.15 mmol) in 5 mL of dry CH_2Cl_2 was cooled to 0 °C. To this was added 0.01 g of 4-(dimethylamino)pyridine, 0.922 mL (11.5 mmol, 10 equiv) of pyridine, and 0.44 mL (5.7 mmol, 5 equiv) of methanesulfonyl chloride. The resulting solution was allowed to warm to room temperature and stirred for 18 h. The mixture was condensed and the crude product chromatographed on silica and eluted with hexane-EtOAc (90:10) to yield 0.550 g (93% from ketone) of the desired mesylate 19 as a viscous oil: $\alpha_D^{25} = -40$ ($c = 0.535$ g/100 mL, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 0.89 (t, $J = 7$ Hz, 3 H), 1.07 (s, 3 H), 1.23 (s, 3 H), 1.32 (m, 5 H), 1.60 (quintet, $J = 7$ Hz, 2 H), 1.76 (m, 1 H), 1.96 (m, 2 H), 2.55 (overlapping multiplet, 3 H), 2.61 (s, 3 H), 3.31 (d, $J = 10$ Hz, 1 H), 3.76–3.80 (overlapping multiplet, 7 H), 3.85 (m, 1 H), 5.26 (dd, $J = 1, 10$ Hz, 1 H), 6.32 (s, 1 H), 6.39 (s, 1 H); $^{13}\text{C NMR}$ δ 14.0, 14.3, 17.0, 22.5, 22.9, 27.1, 31.0, 31.6, 36.2, 38.2, 39.7, 41.5, 48.1, 51.52, 51.55, 55.3, 55.6, 89.8, 103.3, 105.3, 111.0, 143.1, 158.6, 159.2; IR (neat) 2957, 2934, 2857, 1609, 1576, 1454, 1417, 1339, 1177, 1128, 948 cm^{-1} ; HRMS exact mass calcd for $\text{C}_{24}\text{H}_{37}\text{BrO}_5\text{S}$ 516.1545, found 516.1540.

Preparation of 0.4 M Na-Naphthalenide/0.4 M Tetraethylene Glycol Dimethyl Ether Solution in THF. A 50-mL three-neck flask equipped with an addition funnel was charged with 1.41 g (11 mmol) of naphthalene and 25 mL of dry THF. To this was added 0.23 g (10 mmol) of sodium metal. The mixture was allowed to stir for 2 h, and then 2.41 mL of tetraethylene glycol dimethyl ether was added. The mixture was allowed to stir an additional hour at room temperature before use.

Cannabidiol Dimethyl Ether (6). To 7.4 mL (2.95 mmol, 5 equiv) of a freshly prepared 0.4 M Na-naphthalenide/0.4 M tetraethylene glycol dimethyl ether solution in THF at 0 °C was added dropwise a solution of 0.303 g (0.59 mmol) of the endo mesylate 19 in 1.5 mL dry THF. The resulting solution was

(14) Petrzilka, T.; Haefliger, W.; Sikemeier, C.; Ohlogg, G.; Eschenmoser, A. *Helv. Chim. Acta.* 1967, 50, 719.

