General Synthesis of Side Chain Derivatives of Cannabinoids

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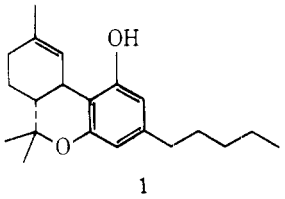
Synthesis of 2-(3′,5′-dihydroxyphenyl)-1,3-dithiane mono-*tert*-butyldimethylsilyl ether (**4b**) and BF_3·Et_2O catalyzed condensation with *p*-mentha-2,8-dien-1-ol afforded the cannabidiol analogue, 2-[4′-(*trans*-6a(*R*),10a(*R*)-metha-1″,8″-dien-3″-yl)-3′,5′-dihydroxyphenyl]-1,3-dithiane *tert*-butyldimethylsilyl ether (**6b**), in 30% overall yield. Acid-catalyzed cyclization of **6b** gave a 3:1 mixture of the Δ^9-THC analogue (6a*R*,10a*R*)-*trans*-3-[1′,3′-dithian-2′-yl]-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol *tert*-butyldimethylsilyl ether (**8b**), and an isomer in 60% yield. The structure of **8b** was confirmed by its conversion to Δ^9-THC by alkylation of the dithian-2-yl carbanion with butyl bromide and reductive cleavage of the 1,3-dithiopropane residue. The utility of **8b** as a precursor of side chain derivatives of cannabinoids was demonstrated by preparations of 1′-, 2′-, 3′-, and 4′-hydroxy-Δ^9-tetrahydrocannabinol, 3-carboxy-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol, and other side chain carboxy derivatives of pharmacological interest.

Modification of the *n*-pentyl side chain of *trans*-(−)-Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**), the active principal of marihuana,[1] has long been known to produce significant changes in psychotomimetic activity.[2] More recently, interest in side chain derivatives has been stimulated by their utility as haptens and radiolabel precursors,[3] and by reports that the *n*-pentyl group is a site of metabolic attack.[4] For example, Δ^9-THC, cannabinol, and cannabidiol are subject to microsomal hydroxylation at carbons 1′–5′ and, in the Δ^8-THC series, the biological activity has been shown to be dependent on the site of hydroxylation (**2d** > **2a** > **2e** > **2c** > **2b**).[4] Car-



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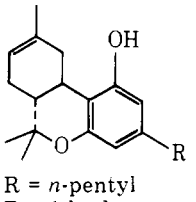
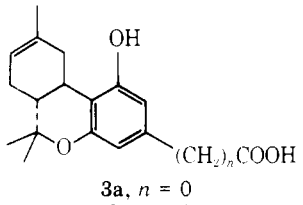


2a, R = *n*-pentyl
b, R = 1-hydroxypentyl
c, R = 2-hydroxypentyl
d, R = 3-hydroxypentyl
e, R = 4-hydroxypentyl



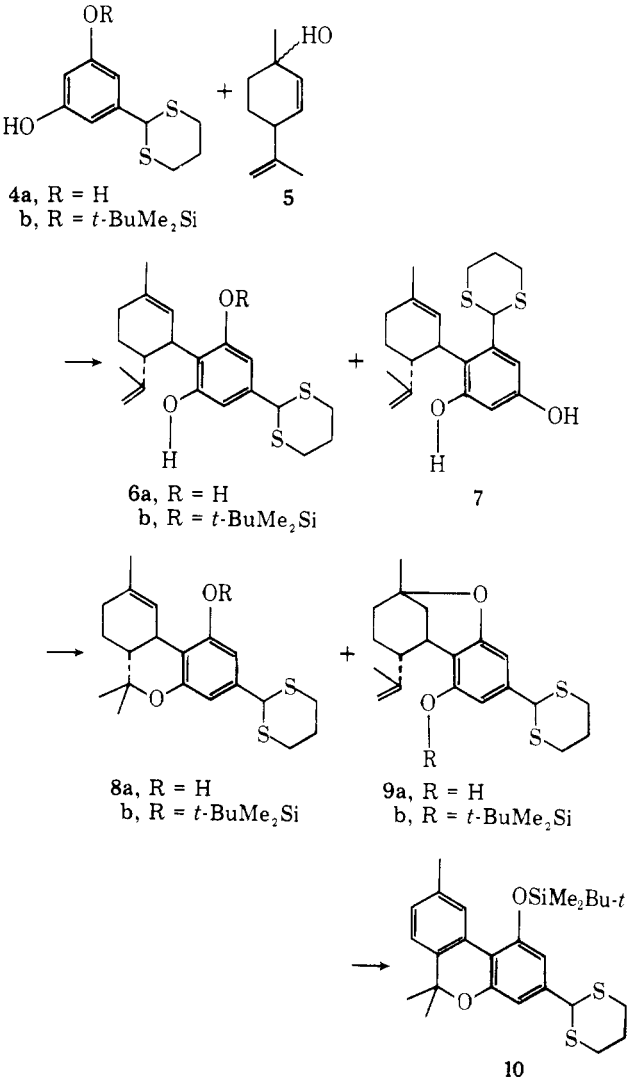
3a, *n* = 0
b, *n* = 1
c, *n* = 2
d, *n* = 3

boxylic acid metabolites, e.g., **3a–d**, formed by oxidative cleavage of the side chain, have also been identified.[5]

Syntheses of side chain derivatives of cannabinoids have generally been achieved by preparation of the requisite C-5 substituted resorcinol,[3,6] followed by acid-catalyzed condensation with a monoterpene, e.g., *p*-mentha-2,8-dien-1-ol.[7] However, this method is only compatible with a few functional groups in the side chain.[6] It also has the logistical disadvantage that each side chain derivative requires the development of an individual synthesis, attendant with difficult chromatographic separation of the isomers which invariably accompany construction of the cannabinoid skeleton.[8] These problems led us to study the synthesis and transformations of the 1,3-dithianyl derivatives **6**, **8**, and **10** shown in Chart I.[9] These dithianes constitute precursors of a wide variety of side chain derivatives of cannabidiol, Δ^9-THC, and cannabinol, respectively, by virtue of the well-documented synthetic transformations of dithianyl carbanions.[10]

2-(3′,5′-Dihydroxyphenyl)-1,3-dithiane (**4a**) was prepared in 50–60% yields by trimethylsilylation and then Vitride reduction of commercial methyl 3,5-dihydroxybenzoate, Jones oxidation of the resulting 3,5-dihydroxybenzyl alcohol,[11] and

Chart I



4a, R = H
b, R = *t*-$BuMe_2Si$

5

6a, R = H
b, R = *t*-$BuMe_2Si$

7

8a, R = H
b, R = *t*-$BuMe_2Si$

9a, R = H
b, R = *t*-$BuMe_2Si$

10

treatment of the aldehyde[12] with 1,3-propanedithiol/BF_3·Et_2O. Condensation of **4a** with *p*-mentha-2,8-dien-1-ol (**5**) was effected in the presence of either BF_3·Et_2O or *p*-toluenesulfonic acid, the latter being the catalyst of choice. The insolubility of **4a** in benzene, chloroform, and methylene chloride, the solvents generally used in this reaction,[8] necessitated the use of tetrahydrofuran as a cosolvent. Under these conditions, **4a** was relatively unreactive compared to olivetol, and *p*-mentha-2,8-dien-1-ol was largely dehydrated to *p*-cymene. This was compensated for by the stepwise addition of 3 equiv

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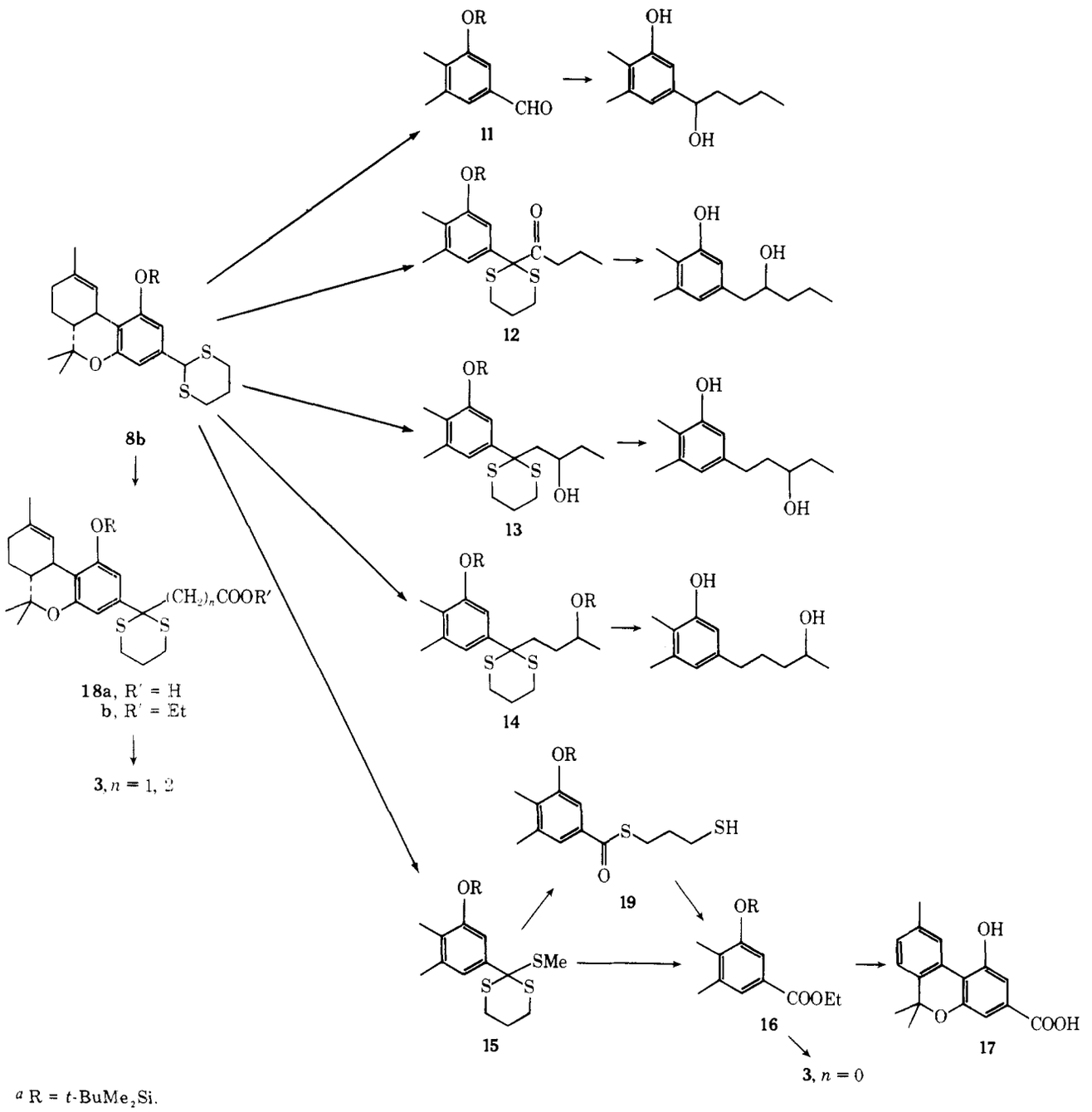
of the terpene to a 10% solution of **4a** and *p*-toluenesulfonic acid (1% w/w) in refluxing benzene/tetrahydrofuran (1:1) over a 3-h period. Three major products, identified as **6a, 7,** and a compound derived from condensation of 2 mol of the terpene with **4a**, were isolated in 20–25, 35–40, and 10–15% yields, respectively. The isolation of **6a**, to the exclusion of ring-closed products, e.g., **8a**, was unexpected since the *p*-toluenesulfonic acid catalyzed reaction of *p*-mentha-2,8-dien-1-ol with olivetol is known to proceed to Δ^8-THC, rather than stopping at cannabidiol. However, treatment of pure **6a** with 1% BF_3·Et_2O in methylene chloride at −15 °C resulted in cyclization to a 4:1 mixture of **8a** and **9a.**

Condensation with *p*-mentha-2,8-dien-1-ol was much improved when the poorly soluble **4a** was first converted to its mono-*tert*-butyldimethylsilyl ether **4b**. This more soluble derivative was prepared by either of two comparable methods, specifically (a) treatment of **4a** with 1 equiv of *t*-$BuMe_2SiCl$ and imidazole,[13] followed by chromatographic separation of unchanged **4a** (23%), **4b** (41%), and the disilyl ether (25%), or (b) quantitative conversion to the diether and then selective monodesilylation with fluoride ion[13] (74% yield). Condensation of **4b** and *p*-mentha-2,8-dien-1-ol in methylene chloride at −15 °C in the presence of BF_3·Et_2O and anhydrous magnesium sulfate[14] afforded 50% (based on recovered **4b**) of **6b** containing some (≤15%) of **8b**. Treatment of this mixture with BF_3·Et_2O in methylene chloride at −20 °C for 48 h gave 54–66% yields of a 3:1 mixture of **8b** and **9b**, which could be separated by elution chromatography. The structure of **8b** was confirmed by its conversion to Δ^9-THC (vide infra).

These results provide an interesting contrast to those observed with 2-(3′,5′-dihydroxyphenyl)-1,3-dithiolane, the five-membered heterocyclic analogue of **4a**. Razdan et al.[15] reported that the reaction of this compound and *p*-mentha-2,8-dien-1-ol in benzene catalyzed by *p*-toluenesulfonic acid afforded 53% of the Δ^8-analogue, 3-(1,3-dithiolan-2-yl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]-pyran-1-ol, with no mention of the cannabidiol or Δ^9-THC analogues. Evidently, the products of this method of con-

Chart II[a]



[a] R = *t*-$BuMe_2Si$.

struction of the cannabinoid skeleton are very sensitive to structure and/or reaction conditions. While the 1,3-dithiolanyl group is useful as a latent aldehyde functionality,[15] it does not have the synthetic versatility of the 1,3-dithianyl group. The utility of **8b** as a precursor of side chain derivatives of Δ^9-THC is demonstrated by the synthesis of a series of side chain hydroxy and carboxy derivatives (Chart II).

Hydroxy Derivatives. 1′-Hydroxy-Δ^9-THC. Hydrolysis of the dithiane group of **8b** with BF_3·Et_2O/HgO in aqueous dimethoxyethane afforded the corresponding aldehyde **11** (92%). Treatment of **11** with an excess of *n*-butyllithium followed by desilylation gave an equal mixture of the two diastereoisomers of 1′-hydroxy-Δ^9-THC. These diastereoisomers were easily separated chromatographically, but they were identical in other respect (MS, ^{1}H NMR, IR).

3′-Hydroxy-Δ^9-THC. Treatment of **8b** with *n*-butyllithium at −78 °C to generate the 1′ carbanion followed by addition of 1,2-epoxybutane gave the 3′-hydroxy compound **13** in 58% yield. Reductive cleavage of the dithiane residue with Raney nickel was quantitative, but this reagent also caused partial reduction of the 9,10 double bond. The latter reaction could be moderated but not reproducibly eliminated by using less active Raney nickel. Therefore, an alternative method of reductive cleavage was sought, using the bis(*tert*-butyldimethylsilyl) ether of **4a** as a model compound. Treatment with $LiAlH_4$ in the presence of zinc and cupric chloride failed, even though this reagent has been successfully applied to other dithianes.[16,17] Reductive cleavage using Wolf–Kishner conditions[18] was also unsuccessful. Fortunately, reduction with sodium in liquid ammonia and ether[19] proceeded without difficulty. This method was applied to **13**, and, after desilylation with fluoride, 3′-hydroxy-Δ^9-THC was obtained in 73% yield. No separation of diastereoisomers was observed.

2′-Hydroxy-Δ^9-THC. Treatment of **8b** with *n*-butyllithium and then *n*-butyryl chloride afforded unchanged **8b** (26%) and **12** (53%). Reductive cleavage of the dithiane residue of **12** with sodium in ammonia gave a mixture of 2′-oxo-Δ^9-THC (33%) and its *tert*-butyldimethylsilyl ether (52%). No reduction of the 2′-keto group was observed, probably because enolate formation is an intrinsic part of the reductive cleavage mechanism. Desilylation with fluoride ion and reduction with $LiAlH_4$ provided 2′-hydroxy-Δ^9-THC (76%).

4′-Hydroxy-Δ^9-THC. Alkylation of the 1′ carbanion of **8b** with 3-(*tert*-butyldimethylsilyloxy)butyl bromide and then cleavage of the dithiane and silyl groups provided this metabolite of Δ^9-THC in 71% overall yield.

Carboxy Derivatives. 3-Carboxy-1′,2′,3′,4′,5′-pentanor-Δ^9-THC (3a). Synthesis of the carboxylic acid equivalent **15** was achieved in 90% yield by treatment of the carbanion of **8b** with dimethyl disulfide. Solvolysis of **15** with 95% ethanol in the presence of HgO/$HgCl_2$ for 5 h at 78 °C gave 89% of the ethyl ester **16**, which was quantitatively converted to the title compound with KOH/aqueous MeOH. Solvolysis of **15** for only 1 h gave a mixture of **16** and a compound tentatively identified as **19**.

This method of preparation of the carboxy group[20] is preferred to treatment of the aldehyde **11** with standard oxidizing agents because of the sensitivity of the Δ^9-THC skeleton to oxidative degradation and acid-catalyzed isomerization to Δ^8-THC.

1′-Carboxy-2′,3′,4′,5′-tetranor-Δ^9-THC (3b). Addition of ethyl chloroformate to the carbanion of **8b** gave 46% of the ester **18b** (n = 0) and 25% of unchanged **8b**. The ester was saponified (100%) to the carboxylic acid to avoid reduction of the carbonyl group in the next step, reductive cleavage of the dithiane residue with sodium in ammonia. Alternatively, the free carboxy function was introduced directly in 54% yield by treatment of the carbanion of **8b** with carbon dioxide.

Reductive desulfurization of the carboxylic acid with sodium in ammonia and then disilylation with fluoride ion provided **3b** in 60% yield.

2′-Carboxy-3′,4′,5′-trinor-Δ^9-THC (3c). This side chain function was introduced by treatment of **8b** with *n*-butyllithium and then ethyl α-bromoacetate. The single product, **18b** (n = 1), obtained in 73% yield after purification, was saponified and reduced with sodium and ammonia to afford **3c** in 68% yield.

3′-Carboxy-1′,2′,3′,4′,5′-pentanorcannabinol (17). Two different approaches to the synthesis of side chain derivatives of cannabinol are feasible: aromatization of **8b** to the common precursor **10** and then elaboration of the side chain, or, alternatively, elaboration of the side chain of **8b** and then aromatization. The synthesis of **17** was achieved by sulfur aromatization of **3a** at 190 °C for 15 min (59% yield) and then saponification.

Sulfur aromatization of **8b** under similar conditions afforded only 28% of **10**, the major byproduct apparently arising from addition of sulfur to **10**.

Δ^9-THC. Alkylation of the carbanion of **8b** with *n*-butyl bromide, followed by cleavage of the dithiane and silyl groups, afforded Δ^9-THC (42%), identical with an authentic sample (TLC, GLC, MS, ^{1}H NMR).

Experimental Section

NMR spectra were obtained using a Varian HA-100 or EM-360 spectrometer with samples dissolved in deuteriochloroform unless specified otherwise (internal standard was tetramethylsilane). Infrared spectra were measured using a Perkin-Elmer Model 467 spectrophotometer. Mass spectroscopic analyses were carried out using either an AEI MS-902, a Finnigan 3300, or an LKB 9000 combined GLC mass spectrometer. Gas–liquid chromatographic analyses were performed using a Varian Model 1400 instrument, with columns (152 cm × 1.59 mm) containing 1.3% OV-17 on Gas Chrom-Q. Precoated silica gel 60 F-254 (Merck) plates and phosphomolybdic acid/ceric sulfate reagents were employed for TLC analysis. Ultraviolet spectra were obtained using a Cary 14 Model spectrophotometer. Optical rotations were measured using a Perkin-Elmer Model 141 polarimeter. The elemental composition of crystalline products was determined by combustion analysis (Micro-Tech Laboratories, Skokie, Ill.). The elemental composition of noncrystalline products was determined by high-resolution mass spectroscopy after verifying the purity of samples by TLC and GLC analysis. Solvents were dried over 3 Å molecular sieves by passage through Al_2O_3 or by distillation from either lithium aluminum hydride or calcium hydride. All reactions were carried out under a nitrogen or argon atmosphere. All of the compounds possessing the Δ^9-THC ring skeleton were unstable in air.

3,5-Dihydroxybenzyl Alcohol. A mixture of methyl 3,5-dihydroxybenzoate (25.3 g, 0.157 mol), hexamethyldisilazane (50 mL), and trimethylchlorosilane (2 mL) was heated at reflux for 5 h and then stirred overnight at 25 °C. Addition of ether (100 mL) gave a white precipitate which was removed by filtration. The filtrate was concentrated in vacuo, and the residual oil (50 g) in THF (100 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (7.6 g, 0.20 mol) in THF (500 mL). The mixture was heated at reflux for 4 h, left overnight at 25 °C, and then hydrolyzed by slow addition of aqueous ammonium chloride followed by concentrated hydrochloric acid. The mixture was filtered, and the solid was washed thoroughly with THF (~300 mL). The filtrate was concentrated to give 23.85 g (91% yield) of pure 3,5-dihydroxybenzyl alcohol as a white solid: mp 181–184 °C (lit.[11] mp 182–184 °C); ^{1}H NMR (acetone-d_6) δ 4.46 (s, 2 H, CH_2OH), 6.20 (m, 3 H, ArH).

3,5-Dihydroxybenzaldehyde. Jones reagent (90 mL, 0.90 M) was added dropwise to 3,5-dihydroxybenzyl alcohol (11.4 g, 0.817 mol) in acetone (120 mL) over a 1-h period. The mixture was then diluted with ether (1 L) and washed with aqueous sodium bicarbonate (in cases where an emulsion develops, it is helpful to filter through Celite). The aqueous phase was extracted with ether (3 × 150 mL), and the combined ether extracts were washed with brine (5 × 100 mL), dried, and concentrated to leave 6.15 g (55%) of 3,5-dihydroxybenzaldehyde as a tan-colored solid, mp 145–152 °C, pure by TLC and NMR. Crystallization from acetone/hexane raised the melting point to 162–163 °C; (lit.[12] mp 156–157 °C); IR (KBr) 3340 (OH), 1675 (C=O) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 9.73 (s, 1 H, CHO), 6.80 (d, J = 3 Hz, 2 H, 2,6-ArH_2), 6.52 (t, J = 3 Hz, 1 H, 4-H).

2-(3′,5′-Dihydroxyphenyl)-1,3-dithiane (4a). Propane-1,3-dithiol (21.2 mL, 212 mmol), 3,5-dihydroxybenzaldehyde (24.4 g, 177 mmol), and boron trifluoride etherate (10.9 mL, 88.4 mmol) in dry ether (530 mL) were stirred at room temperature for 4 h, seeded, and then stirred for an additional 2.5 h. The off-white crystals were washed with ether and dried (33.0 g, 82.5%). Concentration of the mother liquors to 150 mL afforded a further 1.5 g (3.8%): mp (Kofler) 241–244 °C dec.; R_f 0.40 (TLC; acetone/$CHCl_3$, 1:4); ^1H NMR δ 8.10 (s, 2 H, ArOH), 6.38 (d, J = 3 Hz, 2 H, 2′,6′-ArH_2), 6.18 (t, J = 3 Hz, 1 H, 4′-ArH), 5.05 (s, 1 H, SCHS), 3.0 (m, SCH_2); m/e 228 (M^+, base). Anal. Calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30. Found: C, 52.58; H, 5.28.

2-(3′,5′-Dihydroxyphenyl)-1,3-dithiane Mono-*tert*-butyldimethylsilyl Ether (4b). Method A. *tert*-Butyldimethylsilyl chloride (165 mg, 1.10 mmol), imidazole (170 mg, 2.50 mmol), and **4a** (228 mg, 1.00 mmol) in dry DMF (1 mL) were stirred overnight. The solution was diluted with ether, washed with water, dried (Na_2SO_4), and concentrated in vacuo. The residual oil was dissolved in a minimum of CH_2Cl_2, from which unchanged **4a** (52 mg, 23%) crystallized within 5 min. Elution of the concentrated liquors from silica gel 60 (6 g) with CH_2Cl_2 gave the disilyl ether (93 mg, 20%) and then **4b** (140 mg, 41%) as a white solid: mp 82–83 °C; R_f 0.68 (TLC; acetone/CH_2Cl_2, 5:95); ^1H NMR δ 6.56 (d, J = 2 Hz, 2 H, 2′,6′-ArH_2), 6.28 (t, J = 2 Hz, 1 H, 4′-ArH), 5.34 (br s, 1 H, ArOH), 5.03 (s, 1 H, SCHS), 2.93 (m, 4 H, SCH_2), 2.1 (m, 2 H, SCH_2CH_2), 0.95 (s, 9 H, $C(CH_3)_3$); IR (CCl_4) 3600 and 3380 (OH), 1015 (Si–O–C), 835 (Si–CH_3) cm^{-1}; m/e 342.1146 ($C_{16}H_{26}O_2S_2Si$ requires 342.1137) (M^+), 211 (base). Anal. Calcd for $C_{16}H_{26}O_2S_2Si$: C, 56.09; H, 7.65. Found: C, 56.53; H, 7.74.

Similar results were obtained on a 48-g scale.

Method B. *tert*-Butyldimethylsilyl chloride (40.7 g, 270 mmol), imidazole (18.4 g, 675 mmol), and **4a** (20.5 g, 90.0 mmol) in dry DMF (270 mL) were stirred overnight. The solvent was removed in vacuo, and the residue was redissolved in water and ether. The water phase was extracted with ether, and the combined organic extracts were washed with water and brine, diluted with water and brine, diluted with benzene, and concentrated. The residual oil (41.0 g, 100%) was homogeneous by TLC. A portion of this product (1.37 g, 3.00 mmol) was dissolved in dry THF (25 mL), and 1.8 mL of 20% tetra-*n*-butylammonium fluoride in THF was added slowly (1.75 h) to the solution at −20 °C until **4a** was just detectable (TLC). Hydrochloric acid (10 mL, 1 N) was added, and the solvent was removed in vacuo at 0 °C. The residue was extracted with ether, and the combined extracts were washed with water and brine and then dried (Na_2SO_4) and concentrated. Purification as described in method A afforded 757 mg (74%) of **4b**.

2-[4′-(*trans*-Mentha-1″,8″-dien-3″-yl)-3′,5′-dihydroxyphenyl]-1,3-dithiane Mono-*tert*-butyldimethylsilyl Ether (6b). Boron trifluoride etherate (184 μL) was added to a stirred slurry of **4b** (100 mg, 0.292 mmol), *p*-mentha-2,8-dien-1-ol (47 mg, 0.31 mmol), and anhydrous magnesium sulfate (57 mg) in CH_2Cl_2 (1.84 mL) at −10 °C. After 4 h, powdered $NaHCO_3$ (125 mg) was added. The mixture was stirred for 5 min, filtered, and concentrated. Elution from silica gel 60 (2 g) with CH_2Cl_2 gave impure **6b** and then unchanged **4b** (42 mg). The former was rechromatographed on a prepacked silica gel 60 column (Merck, size A), eluting with 40% $CHCl_3$ in hexane, to obtain 40.7 mg (29%) of **6b** as a yellow gum; R_f 0.37 (TLC; CH_2Cl_2/benzene, 1:1); ^1H NMR δ 6.55, 6.48 (d, d, J = 2 Hz, 2 H, ArH_2), 5.91 (br s, 1 H, ArOH), 5.48 (br, s, 1 H, C=CH), 4.98 (s, 1 H, SCHS), 4.55, 4.45 (s, s, 2 H, $C=CH_2$), 3.94 (br d, J = 10 Hz, 1 H, 3″-CH), 2.91 (m, 4 H, SCH_2), 2.09 (m, SCH_2CH_2), 1.76 (br s, $C=CCH_3$), 1.59 (s, $C=CCH_3$), 0.95 (s, $C(CH_3)_3$); IR (CH_2Cl_2) 3430 (OH), 1065 (Si-O-C), 840 (Si–CH_3) cm^{-1}; m/e 476.2232 ($C_{26}H_{40}O_2S_2Si$ requires 476.2239).

A large scale preparation using 26 g of **4b**, 1.2 mol equiv of *p*-mentha-2,8-dien-1-ol, 1.2% boron trifluoride etherate, and a temperature of −20 °C produced a similar yield (30%) of **6b**, but less recovered **4b**; some cyclization of **6b** to **8b** also occurred.

(6a*R*,10a*R*)-6a,7,8,10a-Tetrahydro-6,6,9-trimethyl-3-[1′,3′-dithian-2′-yl]-6*H*-dibenzo[*b,d*]pyran-1-ol *tert*-Butyldimethylsilyl Ether (8b). Boron trifluoride etherate (2 mL) was added slowly (10 min) to a stirred mixture of **6b** and **8b** (7.51 g, 15.8 mmol) in CH_2Cl_2 (188 mL) at −77 °C. The mixture was stirred at −20 °C until no **6b** was detected by TLC (2 days). Powdered $NaHCO_3$ (2 g) was added, and the mixture was allowed to warm to room temperature before filtering through 50% water saturated silica gel 60 (100 g, CH_2Cl_2 eluent). Concentration of the eluent afforded 6.06 g (81%) of a 1:3 mixture of **9b** and **8b** as a pale yellow foam. Elution of this mixture (5.55 g) from Florisil (1 kg) with ether (1–4%) in petroleum ether yielded first **9b** (0.55 g): R_f 0.42 (TLC; CH_2Cl_2/benzene, 1:1); ^1H NMR δ 6.52, 6.45 (d, d, J = 1 Hz, 2 H, ArH_2), 4.99, 4.95 (s, d, J = 5 Hz, 3 H, SCHS, $C=CH_2$), 3.52 (br s, 10a-H), 2.90 (m, 4 H, SCH_2), 1.83 (s, CH_3CO), 1.65 (br s, $C=CCH_3$), 0.96 (s, $C(CH_3)_3$); m/e 476.2232 ($C_{26}H_{40}O_2S_2Si$ requires 476.2239).

After mixtures of **9b** and **8b** (3.21 g), pure **8b** (1.12 g) was eluted as a light yellow gum: R_f 0.42 (TLC; CH_2Cl_2/benzene, 1:1); ^1H NMR δ 6.52 (br s, 2 H, ArH_2), 6.33 (br s, 1 H, C=CH), 4.99 (s, 1 H, SCHS), 2.91 (br m, 5 H, 10a-H, SCH_2), 2.08 (br, m, SCH_2CH_2), 1.63 (s, $C=CCH_3$), 1.37, 1.04 (s, s, $C(CH_3)_2$), 0.99 (s, $C(CH_3)_3$); m/e 476.2232 ($C_{26}H_{40}O_2S_2Si$ requires 476.2229) (base).

Subsequently it was found that elution from acidic Al_2O_3 (activity 1) with 20% ether/hexane gave a resolution of **8b** from **9b** that was much superior to that obtained on Florisil, although elution from the latter was still necessary to remove another impurity.

(6a*R*,10a*R*)-3-Formyl-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol *tert*-Butyldimethylsilyl Ether (11). A mixture of HgO (272 mg, 1.26 mmol) and BF_3·Et_2O (159 μL) in 85% dimethoxyethane/water (3 mL) was stirred for 10 min at room temperature followed by addition of **8b** (300 mg, 0.630 mmol) in DME (1.2 mL) over a 5-min period. At 30 min, after the reaction was shown to be complete by TLC, the mixture was filtered through Celite, washing the solids with DME and then ether. The combined filtrates were shaken with aqueous $NaHCO_3$, and the aqueous layer was extracted with ether. The combined organic phases were washed with brine until netural and dried (Na_2SO_4/CH_2Cl_2). Evaporation and elution from silica gel 60 (Merck prepacked column, size A) with CH_2Cl_2 yielded 223 mg (92%) of **11**: R_f 0.55 (TLC, CH_2Cl_2); ^1H NMR δ 9.73 (s, 1 H, CHO), 6.89, 6.82 (d, d, J = 2 Hz, 2 H, ArH_2), 6.24 (b, 1 H, C=CH), 3.18 (br d, J = 10 Hz, 1 H, 10a-H), 1.64 (br s, 11-CH_3), 1.41, 1.05 (s, s, $C(CH_3)_2$), 0.97 (s, $C(CH_3)_3$); IR (CH_2Cl_2) 1693 (C=O), 1065 (Si–O–C), 840 (Si–CH_3) cm^{-1}; m/e 386.2273 ($C_{23}H_{34}O_3Si$ requires 386.2268) (M^+), 329 ($M - C(CH_3)_3$, base).

1′-Hydroxy-Δ⁹-THC. *n*-Butyllithium in hexane (358 μL, 2.2 N, 0.79 mmol) was added to **11** (204 mg, 0.527 mmol) in dry THF (3 mL) under argon at −78 °C over a 5-min period. At 40 min, the reaction was diluted with ether (10 mL) and quenched with HCl (8 mL, 0.1 N). After warming to room temperature, the acidic mixture was extracted with ether. The combined organic layers were washed with $NaHCO_3$ and then water and dried (Na_2SO_4/CH_2Cl_2). Evaporation and elution from silica gel 60 (Merck prepacked column, size A) with CH_2Cl_2 yielded unchanged **11** (42 mg) and then a diastereoisomeric mixture of silylated 1′-hydroxy-Δ⁹-THC (137 mg, 74% based on consumed **8b**): R_f 0.21 (TLC, CH_2Cl_2); ^1H NMR δ 6.35 (m, 3 H, ArH_2, C=CH), 4.46 (t, J = 6 Hz, 1 H, 1′-CH), 3.12 (br d, J = 9 Hz, 1 H, 10a-H), 1.64 (br s, 11-CH_3), 1.38, 1.04 (s, s, $C(CH_3)_2$), 0.98 (s, $C(CH_3)_3$); IR (CH_2Cl_2) 3590 (OH), 1060 (Si–O–C), 840 (Si–CH_3) cm^{-1}; m/e 444.3052 ($C_{27}H_{44}O_3Si$ requires 444.3048) (base).

Tetra-*n*-butylammonium fluoride in THF (1.7 mL, 200 mg/mL) was added to a stirred solution of this product (124 mg, 0.279 mmol) in dry THF (2 mL) under argon at 0 °C over a 3-min period. After 2.5 h at room temperature, the reaction was complete (TLC), quenched with HCl (0.1 N to pH ~2), diluted with water, and extracted with ether. The combined organic layers were washed with water and brine and dried (Na_2SO_4/CH_2Cl_2). Evaporation and elution from silica gel 60 (Merck prepacked size A column) with 5% acetone/CH_2Cl_2 afforded approximately equal amounts of the two diastereoisomers of 1′-hydroxy-Δ⁹-THC (90 mg, 98%) as gums in the following order of elution. Isomer A: R_f 0.66 (TLC; acetone/CH_2Cl_2, 1:4); ^1H NMR δ 6.35 (m, 3 H, ArH_2, C=CH), 5.51 (br s, 1 H, ArOH), 4.49 (t, J = 6 Hz, 1 H, 1′-CH), 3.24 (br d, J = 10 Hz, 1 H, 10a-H), 1.67 (s, $C=CCH_3$), 1.40, 1.07 (s, s, $C(CH_3)_2$), 0.87 (t, J = 7 Hz, 5′-CH_3); IR (CH_2Cl_2) 3570, 3330 cm^{-1} (OH); $[\alpha]^{22}_D$ −155° (c 0.182, $CHCl_3$); UV (95% EtOH) 282.5 nm (ϵ 1660), 277.0 (1600); m/e 330.2197 ($C_{21}H_{30}O_3$ requires 330.2195).

Isomer B: R_f 0.58 (TLC; acetone/CH_2Cl_2, 1:4); ^1H NMR spectrum was identical with that of isomer A, with the exception of a poorly resolved pair of peaks at δ 6.3 and 6.4 (3 H, ArH_2, C=CH); $[\alpha]^{22}_D$ −169° (c 0.182, $CHCl_3$); UV (95% EtOH) 282.5 nm (ϵ 1525), 277.0 (1461); m/e 330.2197 ($C_{21}H_{30}O_3$ requires 330.2195).

2′-Hydroxy-Δ⁹-THC. *tert*-Butyllithium in pentane (1.16 mL, 1.04 M) was added slowly (20 min) to **8b** (476 mg, 1.00 mmol) in dry THF (2 mL) at −78 °C under argon. After stirring the resulting heavy suspension for 1.5 h, butyryl chloride (208 μL, 2.00 mmol) was added. The resulting clear solution was stirred for 1.5 h, quenched with hydrochloric acid (5 mL, 0.4 N), and allowed to warm to ambient temperature. The mixture was extracted with ether, and the combined organic extracts were washed with aqueous $NaHCO_3$ and brine and dried (Na_2SO_4/CH_2Cl_2). Concentration and elution from silica gel 60 (Merck prepacked column, size B) with CH_2Cl_2 afforded unchanged **8b** (123 mg, 26%) and then **12** (289 mg, 71% based on recovered **8b**) as a yellow gum: R_f 0.58 (TLC, CH_2Cl_2); ^1H NMR δ 6.70, 6.52 (d, d, J = 2 Hz, 2 H, ArH_2), 6.32 (br s, 1 H, C=CH), 3.0 (m, SCH_2), 2.35 (t, J = 7 Hz, 3′-CH_2), 1.65 (br s, $C=CCH_3$), 1.39, 1.04 (s, s, $C(CH_3)_2$), 0.98 (s, $C(CH_3)_3$), 0.79 (t, J = 7 Hz, 5′-CH_3); IR (CH_2Cl_2)

1705 cm^{-1} (C=O); *m/e* 546 (M^+), 475 (base).

A solution of **12** (289 mg, 0.529 mmol) in dry ether (20 mL) was added to sodium (92 mg, 4.0 mg-atom) in liquid ammonia (50 mL, distilled from sodium). The mixture was stirred for 15 min, when 1,2-dibromoethane in ether was added until the blue color was discharged. Ammonium chloride (350 mg) was added, and the ammonia was allowed to evaporate. The residual slurry was treated with 0.1 N hydrochloric acid (20 mL), and the aqueous phase was extracted with ether. The combined ether extracts were washed with aqueous $NaHCO_3$, dried (Na_2SO_4/CH_2Cl_2), and concentrated. Elution of the residual oil from silica gel 60 (Merck prepacked column, size A) with CH_2Cl_2 and 5% acetone in CH_2Cl_2 afforded first 122 mg (52%) of 2'-oxo-Δ^9-THC *tert*-butyldimethylsilyl ether as a yellow gum: R_f 0.46 (TLC, CH_2Cl_2); ^1H NMR δ 6.31 (br s, 2 H, C=CH, ArH), 6.21 (d, J = 2 Hz, 1 H, ArH'), 3.47 (s, 2 H, 1'-CH_2), 3.14 (br d, J = 10 Hz, 1 H, 10a-H), 2.40 (t, J = 7 Hz, 2 H, 3'-CH_2), 2.15 (m, 2 H, 8-CH_2), 1.66 (br s, C=CCH_3), 1.40, 1.06 (s, s, $C(CH_3)_2$), 0.99 (s, $C(CH_3)_3$), 0.85 (t, J = 7 Hz, 5'-CH_3), 0.23 (s, $Si(CH_3)_2$); *m/e* 442 (M^+), 385 (base).

Further elution gave 58 mg (33%) of 2'-oxo-Δ^9-THC as a yellow gum: R_f 0.13 (TLC, CH_2Cl_2); ^1H NMR δ 6.49 (s, 1 H, ArOH), 6.35 (br s, 1 H, C=CH), 6.24, 6.19 (d, d, J = 2 Hz, 2 H, ArH_2), 3.48 (s, 2 H, 1'-CH_2), 3.22 (br d, J = 10 Hz, 1 H, 10a-H), 2.42 (t, J = 7 Hz, 2 H, 3'-CH_2), 2.14 (br, 8-CH_2), 1.66 (br s, C=CCH_3), 1.38, 1.06 (s, s, $C(CH_3)_2$), 0.84 (t, J = 7 Hz, 5'-CH_3); *m/e* 328 (M^+, base).

Lithium aluminum hydride (20 mg) was added to 2'-oxo-Δ^9-THC *tert*-butyldimethylsilyl ether (122 mg, 0.275 mmol) in dry THF (1 mL). After stirring for 45 min, the mixture was quenched with 10% H_2SO_4 and extracted with ether, and the organic extracts were dried (Na_2SO_4/CH_2Cl_2) and concentrated. The residue was eluted from silica gel 60 (Merck prepacked column, size A) with CH_2Cl_2 to give 102 mg (84%) of the 2'-hydroxy compound as a yellow gum: R_f 0.36 (TLC, CH_2Cl_2); *m/e* 444 (M^+, base).

This product in THF (1 mL) was mixed with tetra-*n*-butylammonium fluoride (200 mg) in THF (1 mL). After stirring for 2 h, when no starting material remained (TLC), 0.1 N HCl (5 mL) was added and the mixture was extracted with ether. The combined extracts were washed with aqueous $NaHCO_3$ and then brine until neutral, dried (Na_2SO_4/CH_2Cl_2), and concentrated. Elution from silica gel 60 (Merck prepacked column, size A) with 10% acetone in CH_2Cl_2 gave 68 mg (90%) of 2'-hydroxy-Δ^9-THC as a yellow gum: R_f 0.43 (TLC; acetone/CH_2Cl_2, 1:9); ^1H NMR δ 6.37 (br s, 1 H, C=CH), 6.21 (br s, 2 H, ArH_2), 3.76 (b, 2'-CH), 3.22 (br d, J = 10 Hz, 1 H, 10a-H), 2.54 (m, 1'-CH_2), 1.66 (s, C=CCH_3), 1.38, 1.06 (s, s, $C(CH_3)_2$), 0.90 (t, J = 7 Hz, 5'-CH_3); IR (CH_2Cl_2) 3570, 3300 cm^{-1} (OH); *m/e* 330.2197 ($C_{21}H_{30}O_3$ required 330.2195). Similarly, reduction of 2'-oxo-Δ^9-THC with lithium aluminum hydride afforded 2'-hydroxy-Δ^9-THC in ~73% yield.

3'-Hydroxy-Δ^9-THC. *n*-Butyllithium in hexane (1.12 mL, 2.0 M, 2.24 mmol) was added to **8b** (722 mg, 1.52 mmol) in dry THF (5 mL) at −78 °C. After stirring for 0.5 h at −78 °C and 0.3 h at −25 °C, 1,2-epoxybutane (0.261 mL, 3.05 mmol) was added and the mixture was maintained at −26 °C. After 16 h, the mixture was diluted with ether and then 0.1 M HCl. The aqueous phase was extracted with ether, and the combined organic phase was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4/CH_2Cl_2), and concentrated. Elution of the residue from silica gel 60 (20 g) with 5% acetone in CH_2Cl_2 gave 480 mg (58%) of **13** as a yellow gum: R_f 0.60 (TLC; acetone/CH_2Cl_2, 1:19); ^1H NMR (acetone-d_6) δ 6.98 (br s, 2 H, ArH_2), 6.34 (br s, 1 H, C=CH), 3.66 (m, 3'-CH), 3.14 (br d, J = 9 Hz, 10a-H), 2.70 (m, SCH_2), 1.64 (br s, C=CCH_3), 1.40, 1.06 (s, s, $C(CH_3)_2$); *m/e* 548 (M^+), 476 (base).

Sodium (48 mg, 2.1 mg-atom) was added to a stirred solution of **13** (115 mg, 0.210 mmol) in dry ether (9 mL) and liquid ammonia (18 mL, distilled from sodium). After 15 min, the mixture was worked up as described above. Elution of the crude product from silica gel 60 (4 g) with 5% acetone in CH_2Cl_2 provided first 3'-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether (68 mg, 73%) as a yellow gum: R_f 0.64 (TLC; acetone/CH_2Cl_2, 1:19); ^1H NMR δ 6.2 (m, 3 H, ArH_2, C=CH), 3.50 (p, J = 6 Hz, 3'-CH), 3.07 (br d, 1 H, 10a-H), 2.55 (m, 1'-CH_2), 1.63 (s, C=CCH_3), 1.36 (s, *gem*-CH_3); *m/e* 444 (M^+), 372 (base). 3'-Hydroxy-Δ^9-THC (8 mg, 12%) was eluted subsequently.

3'-Hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether (68 mg, 0.15 mmol) in THF (0.5 mL) was mixed with tetra-*n*-butylammonium fluoride (100 mg) in dry THF (0.5 mL) at 0 °C. The mixture was stirred for 1.5 h and then worked up as described above. Elution of the crude product from silica gel 60 (2 g) with 5% acetone in CH_2Cl_2 followed by elution from silica gel 60 (Merck prepacked column, size A) with 7% acetone in CH_2Cl_2 afforded 33 mg (66%) of 3'-hydroxy-Δ^9-THC as a white foam: R_f 0.13 (TLC; acetone/CH_2Cl_2, 1:19); ^1H NMR (ethanol-d_6) δ 6.41 (br s, 1 H, C=CH), 6.15, 6.03 (d, d, J = 2 Hz, ArH_2), 5.13 (br s, OH), 2.5 (m, 1'-CH_2), 1.60 (br s, C=CCH_3), 1.35, 1.14 (s, s, $C(CH_3)_2$); IR (CH_2Cl_2) 3570, 3290 cm^{-1} (OH); *m/e* 330.2197 ($C_{21}H_{30}O_3$ requires 330.2195). 3'-Hydroxy-Δ^9-THC decomposed rapidly in air but was stable in ethanol under an inert atmosphere. In a subsequent desilylation on a 346-mg scale, where chromatography collecting tubes each contained a small amount of ethanol as a stabilizer and all glassware was acid-washed, a yield of 80% was obtained.

4'-Hydroxy-Δ^9-THC. *n*-Butyllithium in hexane (0.30 mL, 2.02 M) was added (30 min) to a stirred solution of **8b** (238 mg, 0.500 mmol) in dry THF (1 mL) at −78 °C. After 2.3 h, 3-(*tert*-butyldimethylsilyloxy)butyl bromide (0.19 mL, 0.75 mmol) was added to the resulting heavy suspension. The mixture was stirred for 2 h at −78 °C and then at −17 °C overnight. The resulting clear solution was worked up as described above, and the crude product was eluted from silica gel 60 (5 g) with CH_2Cl_2 to obtain 350 mg (105%) of **14** as a yellow gum: R_f 0.57 (TLC, benzene); ^1H NMR δ 6.86 (s, 2 H, ArH_2), 6.28 (br s, 1 H, C=CH), 4.2–3.3 (m, 4'-CH), 3.12 (br d, J = 10 Hz, 10a-H), 1.66 (s, C=CCH_3), 1.39, 1.06 (s, s, $C(CH_3)_2$), 1.00 (s, $C(CH_3)_3$), 0.82 (s, $C(CH_3)_3$); *m/e* 662 (M^+), 605 (base).

A solution of **14** (331 mg, 0.500 mmol) in dry ether (12 mL) was added to sodium (100 mg, 4.35 mg-atom) in ammonia (25 mL, distilled from sodium). After stirring for 15 min, the mixture was worked up as described previously. Elution of the crude product from silica gel 60 (5 g) with CH_2Cl_2 yielded 259 mg (93%) of 4'-hydroxy-Δ^9-THC bis(*tert*-butyldimethylsilyl) ether as a yellow oil: R_f 0.90 (TLC, CH_2Cl_2); ^1H NMR δ 6.25 (shoulder, C=CH), 6.18, 6.12 (d, d, J = 1 Hz, ArH_2), 3.76 (m, 4'-CH), 3.07 (br d, J = 9 Hz, 10a-H), 1.60 (s, C=CCH_3), 1.38 (s, *gem*-CH_3), 1.05 (shoulder, *gem*-CH_3), 1.02 (s, $C(CH_3)_3$), 0.88 (s, $C(CH_3)_3$); *m/e* 558 (M^+, base).

This product (259 mg, 0.464 mmol) and tetra-*n*-butylammonium fluoride (720 mg) in THF (3.6 mL) were stirred and refluxed for 2 h, at which time the reaction was complete (TLC). Standard workup and elution from silica gel 60 (10 g) with 3% acetone in CH_2Cl_2 provided 117 mg (76%) of 4'-hydroxy-Δ^9-THC as a white foam which discolored in air but was stable in ethanol: R_f 0.10 (TLC; acetone/CH_2Cl_2, 1:19); ^1H NMR δ 6.35 (s, 1 H, C=CH), 6.23, 6.11 (d, d, J = 1 Hz, 2 H, ArH_2), 5.54 (br s, 1 H, ArOH), 3.81 (m, J = 6 Hz, 1 H, 4'-CH), 3.22 (br d, J = 10 Hz, 1 H, 10a-H), 2.46 (t, J = 7 Hz, 2 H, 1'-CH_2), 2.16 (m, 8-CH_2), 1.67 (s, C=CCH_3), 1.39, 1.06 (s, s, $C(CH_3)_2$), 1.16 (d, J = 6 Hz, 5'-CH_3); IR (CH_2Cl_2) 3575, 3290 cm^{-1} (OH); *m/e* 330.2191 ($C_{21}H_{30}O_3$ requires 330.2195).

3-Carboxy-1',2',3',4',5'-pentanor-Δ^9-THC (3, *n* = 0). *n*-Butyllithium in hexane (0.57 mL, 2.1 M, 1.2 mmol) was added to **8b** (476 mg, 1.00 mmol) in dry THF (2 mL) under argon over a 25-min period at −78 °C with stirring. After 2 h, treatment with dimethyl disulfide (0.16 mL, 1.8 mmol) and removal of the dry ice bath after 15 min produced a viscous suspension as the system warmed. The mixture was quenched with HCl (0.1 N) and extracted with ether. The combined extracts were washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4/CH_2Cl_2), and evaporated to yield 0.55 g (105%) of **15** as an oil, R_f 0.71 (TLC, CH_2Cl_2). In another preparation the product was chromatographed on silica gel 60 (Merck prepacked column), eluting with 40% CH_2Cl_2 in hexane, to give a 90% yield of the purified product: ^1H NMR δ 6.94 (s, 2 H, ArH_2), 6.32 (br s, 1 H, C=CH), 3.3 (m, SCH_2 and 10a-H), 2.7 (m, SCH_2CH_2), 1.93 (s, S-CH_3), 1.63 (br s, 11-CH_3), 1.38, 1.04 (s, s, $C(CH_3)_2$), 0.97 (s, $C(CH_3)_3$); *m/e* 522.2111 ($C_{27}H_{42}O_2S_3Si$ requires 522.2106), 475 (M − SCH_3, base).

To **15** (112 mg, 0.215 mmol) in 95% ethanol (5.8 mL) was added HgO (75 mg, 0.35 mmol) and $HgCl_2$ (243 mg, 0.899 mmol). The mixture was refluxed for 5 h and then cooled and filtered through Celite, washing the solids with ethanol (10 mL) and CH_2Cl_2 (100 mL). The combined filtrates were shaken with water, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with 4 M NH_4Cl and with brine. Drying (Na_2SO_4), evaporation, and elution from silica gel 60 (4 g) with CH_2Cl_2 yielded 82 mg (89%) of **16** as an oil: R_f 0.45 (TLC, CH_2Cl_2); ^1H NMR δ 7.12, 7.03 (d, d, J = 2 Hz, 2 H, ArH_2), 6.29 (br s, 1 H, C=CH), 4.31 (q, J = 7 Hz, 2 H, OCH_2), 1.65 (br s, 11-CH_3), 1.41, 1.05 (s, s, $C(CH_3)_2$), 0.99 (s, $C(CH_3)_3$), 0.21 (s, $Si(CH_3)_2$); IR (CH_2Cl_2) 1709 cm^{-1} (CO_2Et); *m/e* 430.2535 ($C_{25}H_{38}O_4Si$ requires 430.2529), 373 (base).

When the solvolysis is carried out for only 1 h, the intermediate thioester **19** was also isolated: R_f 0.23 (TLC, CH_2Cl_2); ^1H NMR δ 7.08, 6.96 (d, d, J = 2 Hz, 2 H, ArH_2), 6.29 (s, 1 H, C=CH), 3.20 (t, J = 7 Hz, 5 H, 10a-H, SCH_2), 1.67 (br s, C=CCH_3), 1.43 (s, *gem*-CH_3), 1.07 (s, shoulder, *gem*-CH_3), 1.01 (s, $C(CH_3)_3$); IR (CH_2Cl_2) 1660 cm^{-1} (SC=O); *m/e* 492 (M^+), 385 (base). When **19** was resubjected to hydrolysis for 5 h in the presence of HgO/$HgCl_2$, additional **16** was obtained.

To **16** (62.4 mg, 0.145 mmol) in dioxane (2 mL) under argon was

added KOH (1.1 mL, 2 N) in 50% aqueous methanol, stirring at room temperature. After 20 h, the reaction was diluted with water and extracted with ether to remove the neutral products. The aqueous phase was cooled and acidified with HCl (concentrated) and then extracted with ether and CH_2Cl_2. The combined organic layers were washed with water and dried (Na_2SO_4). Evaporation and elution from silica gel 60 (Merck prepacked column, size A) with 50% acetone in CH_2Cl_2 yielded 41 mg (98%) of **3a**: R_f 0.26 (TLC; acetone/CH_2Cl_2, 1:1); ^1H NMR δ 7.14, 7.01 (br s, br s, 2 H, ArH_2), 6.30 (br s, C=CH), 3.18 (br d, J = 10 Hz, 1 H, 10a-H), 1.68 (br s, 11-CH_3), 1.41, 1.07 (s, s, $C(CH_3)_2$); IR (CH_2Cl_2) 3560 (OH), 3600–2400 (broad), 1685 (CO_2H) cm^{-1}; m/e 288.1366 ($C_{18}H_{22}O_4$ requires 288.1356).

3-Carboxy-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol (17). A mixture of **16** (43 mg, 0.10 mmol) and sulfur (7.0 mg, 0.22 mg-atom) was heated at 190 ± 3 °C for 10 min and then, after GLC analysis, for a further 5 min. Elution from Florisil (4 g) with 5% ether in hexane yielded 25 mg (59%) of 3-carbethoxy-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol *tert*-butyldimethylsilyl ether as a yellow gum: R_f 0.21 (TLC; ether/hexane, 1:19); ^1H NMR δ 8.28 (s, 1 H, 7-CH), 7.27, 7.22 (d, d, J = 2 Hz, 2 H, 2,4-CH), 7.10 (br s, 2 H, 8-CH, 10-CH), 4.34 (q, J = 7 Hz, 2 H, OCH_2CH_3), 2.35 (s, 3 H, 9-CH_3), 1.57 (s, 6 H, $C(CH_3)_2$), 1.37 (t, J = 7 Hz, OCH_2CH_3), 0.98 (s, $C(CH_3)_3$); m/e 426 (M^+), 411 (base); IR (CH_2Cl_2).

To this product (48 mg) in dioxane (2 mL) under nitrogen was added 50% aqueous methanolic KOH (1 mL, 2 N) at 0 °C. The mixture was stirred for 5 min at 0 °C and then overnight at ambient temperature, at which time no starting material was detected (TLC). If worked up at this point, the predominant product was the ethyl ester of **17**: R_f 0.73 (TLC; acetone/CH_2Cl_2, 1:4); IR (CH_2Cl_2) 3570 (OH), 1725 (C=O) cm^{-1}. Addition of more 50% aqueous methanolic KOH (1 mL, 2 N) and warming to 40–60 °C for ~2 h completed the saponification (TLC). Dilution with water and extraction with ether to remove the neutral compounds, followed by acidification to pH 1 with HCl and reextraction with ether, afforded the crude product. Slow evaporation of a CH_2Cl_2 solution gave **17** (14.1 mg, 44%) as white needles: mp 248–250 °C (Kofler); R_f 0.15 (TLC; acetone/CH_2Cl_2, 1:4); ^1H NMR δ 8.46 (s, 1 H, 10-CH), 7.30 (m, 1 H, 2- or 4-CH), 7.15 (m, 3 H, 2- or 4-CH, 7,8-CH), 2.35 (s, 3 H, 9-CH_3), 1.57 (s, 6 H, $C(CH_3)_2$); IR ($CHCl_3$) 3560 (OH), 3600–2400 (broad), 1685 (CO_2H) cm^{-1}; m/e 284.1045 ($C_{17}H_{16}O_4$ requires 284.1044). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.04; H, 5.64.

1′-Carboxy-2′,3′,4′,5′-tetranor-Δ^9-THC (3, n = 1). n-Butyllithium in hexane (119 μL, 2.2 N, 0.26 mmol) was added to **8b** (100 mg, 0.210 mmol) in stirred dry THF (2 mL) under argon over a 3-min period at −78 °C. After 2 h, the reaction vessel was flushed with dry CO_2 for 2 min, and a positive pressure of CO_2 was maintained for an additional 10 min. The mixture was stored at −26 °C overnight, quenched with NaOH (~0.2 mL, 0.1 N), and diluted with water (~15 mL). Surprisingly, after extraction with ether the product was detected (TLC) in the organic phase. The combined organic phases were washed with water and dried (Na_2SO_4). Evaporation and elution from silica gel 60 (3 g) with 50% acetone in CH_2Cl_2 yielded ~26 mg of starting material and 44 mg (54% based on consumed **8b**) of the carboxylic acid **18a** (n = 0) as a white solid: R_f 0.33 (TLC; acetone/CH_2Cl_2, 1:1); ^1H NMR δ 6.78, 6.71 (d, d, J = 2 Hz, 2 H, ArH_2), 6.30 (br s, 1 H, C=CH), 3.10 (br d, J = 10 Hz, 10a-H), 1.63 (br s, 11-CH_3), 1.38, 1.04 (s, s, $C(CH_3)_2$), 0.96 (s, $C(CH_3)_3$); IR (CH_2Cl_2) 3600–2400 (broad), 1700 (CO_2H), 1068 (Si–O–C), 840 (Si–CH_3) cm^{-1}; m/e 520.2133 ($C_{27}H_{40}O_4S_2Si$ requires 520.2127) (M^+), 475 ($M^+ - CO_2H$, base).

To a stirred solution of sodium (31 mg) in anhydrous ammonia (4 mL, distilled from sodium) was added **18a** (n = 0) (36 mg, 0.068 mmol) in dry THF (2 mL). After refluxing for 15 min, 1,2-dibromoethane in ether was added until the blue color was dissipated. Addition of NH_4Cl and evaporation of the ammonia under a stream of nitrogen were followed by dilution with NaOH (~15 mL, 0.1 N) and extraction with CH_2Cl_2/ether. The aqueous phase was acidified with HCl (10%) and extracted with CH_2Cl_2/ether. The extracts of the basic phase and those of the acidified phase were washed with water and dried (Na_2SO_4). The crude material (4.9 mg) extracted from the acidified aqueous phase was identified as **3** (n = 1). Evaporation of the combined extracts from the basic phase and elution from silica gel 60 (2 g) with 5% methanol in CH_2Cl_2 yielded 24.1 mg (85%) of the silyl ether of **3** (n = 1) as a gum: R_f 0.41 (TLC; MeOH/CH_2Cl_2, 1:9); ^1H NMR δ 6.35 and 6.29 (br s, br s, 3 H, ArH_2 and C=CH), 6.10 (b, CO_2H), 3.44 (br s, 2 H, $ArCH_2CO_2H$), 1.62 (br s, 11-CH_3), 1.37, 1.04 (s, s, $C(CH_3)_2$), 0.96 (s, $C(CH_3)_3$); IR (CH_2Cl_2) 3600–2400 (broad), 1705 (CO_2H), 840 (Si–CH_3) cm^{-1}; m/e 416.2386 ($C_{24}H_{36}O_4Si$ requires 416.2373) (M^+), 359 (base).

Tetra-*n*-butylammonium fluoride in THF (0.4 mL, 200 mg/mL) was added to the above compound (22 mg, 0.053 mmol) in stirred dry THF (0.5 mL) under argon at 0 °C. The mixture was allowed to warm to room temperature. After 2 h the reaction was complete (TLC). The mixture was diluted with HCl (0.1 N to pH 1) and extracted with ether, washing the combined organic layers with water and brine and drying (Na_2SO_4/CH_2Cl_2). The residue after evaporation was eluted from silica gel 60 (Merck prepacked column, size A) with 10% methanol in CH_2Cl_2 to afford 9.5 mg (60%) of **3** (n = 1) as a foam: R_f 0.15 (TLC; MeOH/CH_2Cl_2, 1:9); ^1H NMR δ 6.30 (b, ArH_2, C=CH), 5.06 (b, OH, CO_2H), 3.43 (s, $ArCH_2CO_2H$), 1.65 (br s, 11-CH_3), 1.37, 1.05 (s, s, $C(CH_3)_2$); IR (CH_2Cl_2) 3560 (OH), 3600–2400 (broad), 1710 (CO_2H) cm^{-1}; m/e 302.1517 ($C_{18}H_{22}O_4$ requires 302.1512).

2′-Carboxy-3′,4′,5′-trinor-Δ^9-THC (3, n = 2). n-Butyllithium in hexane (149 μL, 2.2 M, 0.33 mmol) was added to a stirred solution of **8b** (124 mg, 0.261 mmol) in dry THF (1 mL) under argon over a 5-min period at −78 °C. After 2 h, treatment with ethyl α-bromoacetate (58 μL, 0.52 mmol) was followed by slow warming to −25 °C overnight. The mixture was quenched with HCl (1 N) and extracted with ether. The combined extracts were washed with aqueous $NaHCO_3$ and brine and dried (Na_2SO_4/CH_2Cl_2). Evaporation and elution from silica gel 60 (Merck prepacked column, size A) with hexane/CH_2Cl_2 mixtures yielded 107 mg (73%) of **18b** (n = 1) as a foam: R_f 0.28 (TLC; Et_2O/petroleum ether, 1:4); ^1H NMR δ 6.98 (br s, 2 H, ArH_2), 6.35 (br s, 1 H, C=CH), 3.97 (q, J = 7 Hz, 2 H, $-CH_2CH_3$), 3.13 (br d, J = 10 Hz, 10a-H), 2.94 (s, 2′-CH_2), 1.65 (br s, 11-CH_3), 1.39, 1.05 (s, s, $C(CH_3)_2$); IR (CH_2Cl_2) 1725 (CO_2Et), 1065 (Si–O–C), 840 (Si–CH_3) cm^{-1}; m/e 562.2604 ($C_{30}H_{46}O_4S_2Si$ requires 562.2595) (base), 475 ($M^+ - CH_2CO_2Et$).

To **18b** (n = 1) (96 mg, 0.17 mmol) in dioxane (5 mL) under argon was added KOH (2.7 mL, 2 N) in 50% aqueous methanol, stirring at room temperature. At 20 h the reaction was complete (TLC). Dilution with water and extraction with ether to remove the neutral products were followed by acidification with HCl and extraction with ether and CH_2Cl_2. The combined organic layers were dried (Na_2SO_4/CH_2Cl_2) and evaporated. The residue was eluted from silica gel 60 (Merck prepacked column, size A) with 50% acetone in CH_2Cl_2 to yield 74 mg (103%) of the desilylated analogue of **18a** (n = 1) as a foam: R_f 0.20 (TLC; acetone/CH_2Cl_2, 1:1); ^1H NMR δ 6.91 (m, ArH_2), 6.6 (b, OH, CO_2H), 3.12 (d, J = 7 Hz, 10a-H), 3.06 (s, 2′-CH_2), 1.66 (br s, 11-CH_3), 1.39, 1.07 (s, s, $C(CH_3)_2$); IR (CH_2Cl_2) 3560 (OH), 3600–2300 (broad), 1710 (CO_2H) cm^{-1}; m/e 420.1425 ($C_{22}H_{28}O_4S_2$ requires 420.1422) (M^+, base), 361 ($M - CH_2CO_2H$).

This product (68.8 mg, 0.164 mmol) in dry THF/Et_2O (1:1, 6 mL) was added to a stirred solution of sodium (76 mg) in anhydrous ammonia (~9 mL, distilled from sodium). After refluxing for 15 min, the reaction was quenched with 1,2-dibromoethane in ether until the blue color was dissipated. Addition of NH_4Cl and evaporation of the ammonia under a stream of nitrogen were followed by dilution with NaOH (~15 mL, 0.1 N) and extraction with CH_2Cl_2/ether to remove the neutral products. The aqueous layer was acidified with HCl (10%) and extracted with CH_2Cl_2/Et_2O. The combined organic layers were washed with water and dried (Na_2SO_4). Evaporation and elution from silica gel 60 (Merck prepacked column, size A) with 10% MeOH in CH_2Cl_2 yielded 35 mg (68%) of **3** (n = 2) as a gum: R_f 0.31 (TLC; MeOH/CH_2Cl_2, 1:9); ^1H NMR δ 6.30 (br s, C=CH), 6.23, 6.16 (br s, br s, ArH_2), 5.8 (b, OH, CO_2H), 3.10 (br d, J = 10 Hz, 10a-H), 2.68 (m, $ArCH_2CH_2CO_2H$), 1.65 (br s, 11-CH_3), 1.37, 1.05 (s, s, $C(CH_3)_2$); IR (CH_2Cl_2) 3570 (OH), 3700–2400 (broad), 1711 ($-CO_2H$) cm^{-1}; m/e 316.1677 ($C_{19}H_{24}O_4$ requires 316.1668) (base).

Δ^9-THC. n-Butyllithium in pentane (0.16 mL, 1.04 M) was added to **8b** (65 mg, 0.14 mmol) in dry THF (1 mL) at −78 °C. After stirring for 2 h, n-butyl bromide (22 μL, 0.21 mmol) was added. After an additional 2 h, the mixture was worked up as described above. The crude product was purified by elution from 50% water saturated silica gel 60 (0.5 g) with CH_2Cl_2 and then from silica gel 60 (Merck prepacked column, size A) with 20% CH_2Cl_2 in hexane. The product (41 mg, 57%) in ether (2 mL) was added to sodium (16 mg, 0.70 mg-atom) in liquid ammonia (7 mL, distilled from sodium), and the mixture was stirred for 20 min. Workup using the standard procedure afforded 28 mg (85%) of Δ^9-THC *tert*-butyldimethylsilyl ether as a yellow gum. Desilylation with tetra-*n*-butylammonium fluoride (100 mg) in THF (1.5 mL) at 0 °C as already described and purification of the product from 50% water saturated silica gel 60 (14 g) with 0.8–6.8% CH_2Cl_2 in hexane afforded Δ^9-THC (18 mg, 42% overall yield), identical with an authentic sample (^1H NMR, MS, GLC, TLC).

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Registry No.—**3a**, 68582-79-6; **3b**, 61628-36-2; **3c**, 61628-35-1; **4a**,

66527-76-2; **4b**, 66527-81-9; **5**, 22771-44-4; **6b**, 68679-98-1; **8b**, 66527-84-2; **9b**, 66527-83-1; **11**, 68582-81-0; **12**, 66527-86-4; **13**, 66527-87-5; **14**, 66561-70-4; **15**, 66527-88-6; **16**, 66527-91-1; **17**, 60788-14-9; 17 ethyl ester, 68582-82-1; **18a** (n = 0), 68582-83-2; **18a** (n = 1, R = H), 68582-84-3; **18b** (n = 1), 68582-85-4; **19**, 68582-86-5; 1′-hydroxy-Δ^9-THC (isomer A), 66527-89-7; 1′-hydroxy-Δ^9-THC (isomer B), 66527-90-0; 2′-hydroxy-Δ^9-THC, 65372-82-9; 2′-oxo-Δ^9-THC *tert*-butyldimethylsilyl ether, 68582-87-6; 2′-oxo-Δ^9-THC, 68582-88-7; 3′-hydroxy-Δ^9-THC, 58434-44-9; 3′-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether, 68582-89-8; 4′-hydroxy-Δ^9-THC, 58434-43-8; 4′-hydroxy-Δ^9-THC bis(*tert*-butyldimethylsilyl) ether, 68582-90-1; 3-carbethoxy-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol *tert*-butyldimethylsilyl ether, 68582-91-2; Δ^9-THC, 1972-08-3; Δ^9-THC *tert*-butyldimethylsilyl ether, 61919-31-1; 1′-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether (isomer A), 68582-92-3; methyl 3,5-dihydroxybenzoate, 2150-44-9; 3,5-dihydroxybenzaldehyde, 26153-38-8; propane-1,3-dithiol, 109-80-8; 1′-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether (isomer B), 68582-93-4; *tert*-butyldimethylsilyl chloride, 18162-48-6; butyryl chloride, 141-75-3; 1,2-epoxybutane, 106-88-7; 3-(*tert*-butyldimethylsilyloxy)butyl bromide, 65566-22-5; 3,5-dihydroxybenzyl alcohol, 29654-55-5.

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Pentacyclic Steroids. 5. Total Synthesis of 4,6β-Ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol and 4,6α-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one

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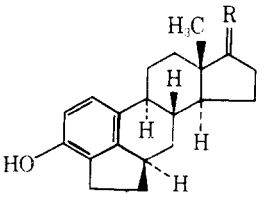
Total synthesis of the novel pentacyclic steroids 4,6β-ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (**5**) and 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**20**) is described. 7-Methoxy-1-tetralone (**6**) was converted in several steps into the key intermediate 8-methoxy-2a,3,4,5-tetrahydro-5-acenaphthenone (**14**). The latter ketone was converted into 4,6-ethano-3-methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (**17**) via the isothiouronium acetate (**16**). Ring cyclization of **17** led to a mixture of the stereoisomers 4,6β-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**19**) and 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**20**). The major isomer **19** was converted in four steps to the 4,6β-ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (**5**). The relative configuration of **5** was confirmed by an X-ray crystallographic study of the racemic mixture. The minor isomer **20** was converted into 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (**23**).

Introduction of a methyl group in the steroidal skeleton at position C-6 has led to useful oral contraceptives such as Provera (17α-acetoxy-6α-methylpregn-4-ene-3,20-dione) and megesterol acetate.[2,3] Recently, we have described[1,4-6] the synthesis of a new series of pentacyclic steroids containing an ethano bridge across C-4 and C-6. Our studies on 4,6β-ethanoestradiol (**1**) and 4,6β-ethanoestrone (**2**) have revealed that the fusion of the ethano bridge at positions C-4 and C-6 from the β face forces the B ring to assume a highly distorted conformation. This has been confirmed by X-ray crystallographic studies on the 17-*p*-bromobenzoate of 4,6β-ethanoestradiol (**3**).[4,5]

Studies with Drieding models show that the unusual strain on the B ring in 4,6β-ethanoestradiol could be somewhat relieved if the stereochemistry at C-6 or C-8 was reversed. We



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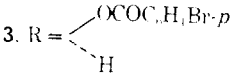
3. R = 

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