The Synthesis of Hexahydro-6*H*-dibenzo[*b*,*d*]pyrans: Derivatives of 9-Nor-9β-hydroxyhexahydrocannabinol

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To assess the importance of the phenol functionality in cannabinoids for analgetic activity a new series of 9-nor-9β-hydroxyhexahydrocannabinoids was prepared. The synthesis of 1-substituted (H, CH_2OH, OH, NH_2) 6aβ,7,8,9,10,10aα-hexahydro-9β-hydroxy-6,6-dimethyl-3-[1-methyl-4-phenylbutoxy]-6*H*-dibenzo[*b*,*d*]pyrans from 3,5-dihydroxystilbene, 3,3',5,5'-tetrahydroxystilbene or 1,3,5-trihydroxybenzene is described. Relative stereochemistry and structure confirmations were obtained by nmr and X-ray crystal analysis.

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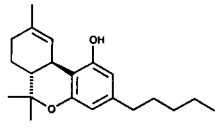
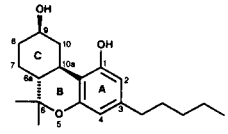
Discussion.

The report that Δ^9-tetrahydrocannabinol (THC) possesses, among others, analgetic activity [2] has made cannabinoids an intriguing lead in the field of analgetic research. The first clear indication for pursuit of a THC derived analgetic came when 9-nor-9β-hydroxyhexahydrocannabinol (HHC) was reported to possess potent analgesia in rodents without opiate effects [3]. Many structure activity relationship (SAR) studies involving cannabinoids had appeared previously [4] but heretofore none contained the



THC

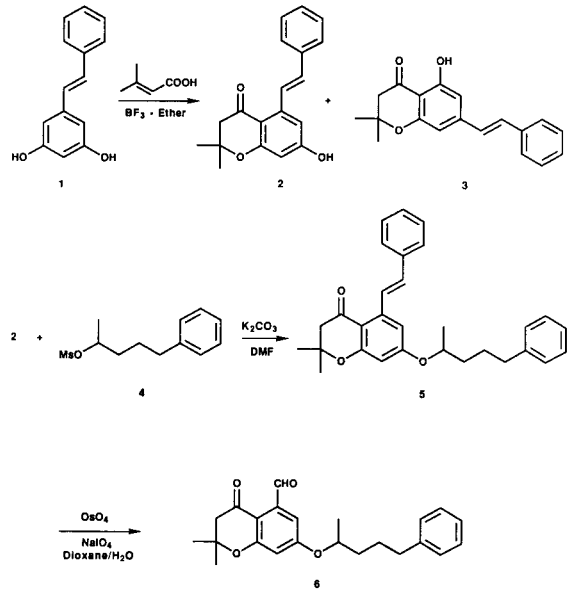


HHC

9-nor-9β-hydroxy modification of HHC. In search of potent non-opiate analgetics, we pursued key SAR points about HHC with the objective of defining those structural variables most congruous with analgesia. The synthetic routes and chemistry utilized to synthesize and characterize some of these novel substances are reported here.

Our earliest idea for a molecular model to rationalize a cannabinoid-receptor mediated analgetic effect predicted that the alcohol, phenol and C-3 chain of compounds such as HHC were all necessary for receptor recognition. Furthermore, the C-1 phenol in HHC was expected to play a key role in our three-point receptor hypothesis [5] that would guide our design of potential therapeutants. Thus, we decided to prepare bioisosteric 1-substituted HHC derivatives to determine if indeed retaining the phenol was a prerequisite for potent analgetic activity. We had previously discovered that the 1-methyl-4-phenylbutoxy C-3 sidechain (*e.g.* compound **39**) gave superior biological activity when compared to the *n*-C_5H_{11} sidechain of natural cannabinoids [5]. The 1-methyl-4-phenylbutoxy sidechain has been utilized in the synthesis of all synthetic cannabinoids reported here to insure the most stringent test for the need of phenolic functionality [6].

In the synthetic strategy chosen, we envisioned that a tricyclic C-1 hydroxymethyl derivative (*e.g.* **16**) would provide intermediates useful for conversion to other targeted C-1 substitution (*e.g.* COOH). The synthesis of C-1 hydroxymethyl derivatives was accomplished as outlined in Scheme I

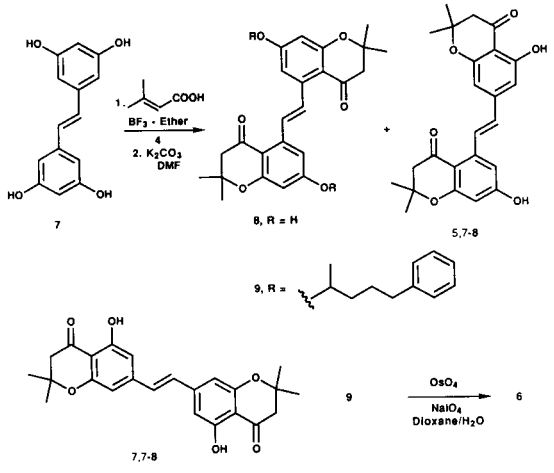


Schemes I-III. A crucial synthetic intermediate, chromanone aldehyde **6**, was efficiently obtained from either of two different stilbene precursors. In the first case (Scheme I), chromanone **2** was prepared by a boron trifluoride etherate catalyzed Pechmann condensation at 25° between 3,3-dimethylacrylic acid and pinosylvine **1** [7] yielding a 2.8:1 ratio of the *trans* isomers **2**:**3** (78%). The bulk of the desired isomer **2** was obtained by crystallization of the crude reaction product. Higher reaction temperatures reverse this ratio in favor of the undesired positional isomer **3**. Attachment of the 1-methyl-4-phenylbutoxy side chain was completed at this point by alkylation of 7-hydroxychromanone **2** with mesylate **4** [8] and potassium carbon-

ate as base to give chromanone ether **5** in quantitative yield. The stilbene double bond of **5** underwent a ready oxidative cleavage using osmium tetroxide-sodium periodate to give in 96% yield the aldehyde **6** and benzaldehyde as a side product.

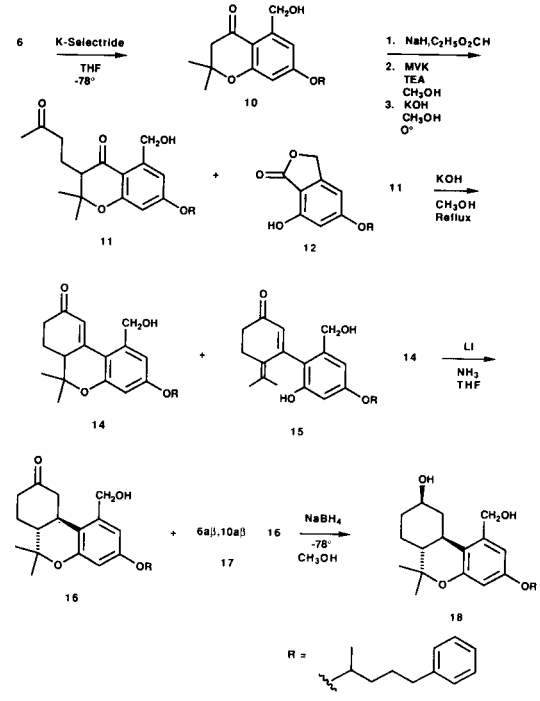
In an alternative and more convergent approach to the preparation of aldehyde **6** (Scheme II), 3,3′,5,5′-tetrahydroxystilbene (**7**) [9] was condensed under the above conditions with 3,3-dimethylacrylic acid to give a mixture of *trans* condensation products. The desired bis-chromanone isomer **8** was isolated in 59% yield by direct crystallization of this mixture. Column chromatography of the mother liquor provided lesser amounts of the asymmetric 5,7-**8** isomer (17%) and symmetrical 7,7-**8** isomer (1.1%). The 5,7-**8**

Scheme II

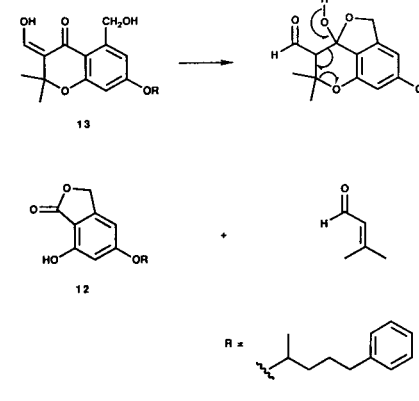


isomer was readily assigned by the nonequivalency of nmr proton resonances. Isomer 5,7-**8** also exhibited both a sharp intramolecular hydrogen bonded (δ 11.72) and broad non-intramolecular hydrogen bonded (δ 10.58) resonance characteristic of the C-5 and C-7 phenolic OH respectively. Isomer 7,7-**8** exhibits one set of nmr proton resonances with one sharp phenolic OH resonance at δ 11.84. The symmetrical isomer **8** also has one set of nmr proton resonances and a single broad phenolic OH resonance at δ 10.56. The vinyl protons of **8** experience a deshielding effect (δ 7.89) relative to isomer 7,7-**8** (δ 7.44) due to the proximate C-4 carbonyl. Alkylation of **8** with mesylate **4** gave the dialkylated derivative **9** in moderate 45% yield. A 10% yield of monoalkylated product was also isolated. It is assumed that the low yield in this reaction was a result of poor solubility of starting material **8** and the observation that under these alkylating conditions the reaction proceeds with a large increase in viscosity. Using the catalytic osmium conditions compound **9** underwent quantitative oxidative cleavage yielding aldehyde **6**. This route was noteworthy since oxidation of **9** released two molecules of aldehyde **6** thus, conserving all the carbon atoms of **9** as compared to the formation of benzaldehyde by oxidation of **5** → **6**.

Scheme III



The third ring of the hexahydro-6*H*-dibenzo[*b*,*d*]pyran ring system was constructed using the Robinson annelation route as outlined in Scheme III. Aldehyde **6** was selectively reduced in high yield with potassium tri-sec-butylborohydride to give the required C-1 hydroxymethyl group in **10**. Methylene activation of chromanone **10** by formylation with ethyl formate (**13**) followed by Michael addition to methyl vinyl ketone and basic hydrolysis of the spent formyl group gave a moderate yield for three steps as a mixture of ketone **11** (34%) and the unexpected phthalide **12** (40%). Formation of the phthalide product **12** was probably a result of base catalyzed fragmentation of the 3-formyl intermediate **13** as shown. Supporting this explanation the yields of diketone products such as **11** could be



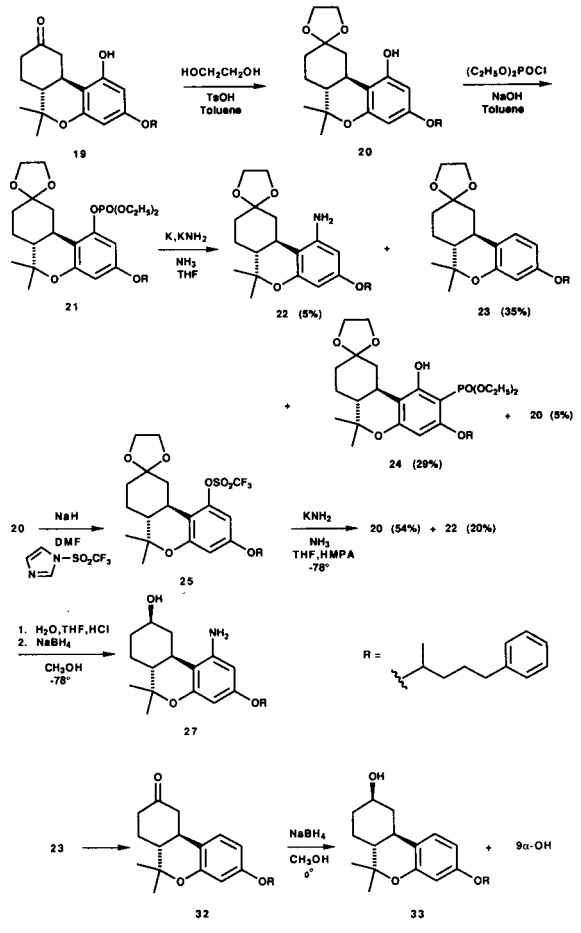
approximately doubled if a protected form of the hydroxymethyl group on **10** was utilized. However, this solution invariably led to unfavorable product ratios in the subsequent aldol dehydration step and it remained most efficient to proceed with **11**. A separate step for cold basic hydrolysis of the formyl activating group was precautionary because of the tendency in these systems for formation of a spiro ring derivative during subsequent cyclization to the enone **14** [8]. Ketone **11** could be cyclized with methanolic potassium hydroxide to provide a mixture of the desired enone **14** (35%) and the ring opened dienone **15** (18%). Under these basic aldol conditions enones such as **14** do show a slight tendency to be oxidized to phenols. Otherwise, enone **14** is relatively stable to the reaction conditions which suggests dienone **15** arises from initial pyran ring fragmentation in **11**. The dienone **15** could be cyclized to **14** by treatment with *p*-toluenesulfonic acid in toluene at 80°. As noted, when protected hydroxymethyl groups on **11** were employed, the dienone products became predominate.

The *trans* 6aβ,10aα stereochemistry, present in HHC, was introduced by lithium liquid ammonia reduction of enone **14** leading to predominantly [10] the desired saturated *trans* ketone **16** (61%) and a lesser amount of its 6aα,10aβ-isomer **17** (15%). Stereochemistry of the *trans* (**16**) and *cis* (**17**) ketones was assigned by pmr chemical shift differences of the C-6 methyls (**16**: δ 1.12 and 1.50 ppm; **17**: δ 1.33 and 1.38) as previously reported for 6,6-dimethyl-9*H*-dibenzo[*b*,*d*]pyran-9-ones [11] and derivatives [10]. Ketone **16** is the first intermediate in which non-equilibratable diastereomers exist. The final products reported here were synthesized for preliminary biological evaluation and it was desirable not to routinely separate diastereomers. However, for one case (Scheme V), compound **39** → **39A** and **39B**, diastereomers of the final product were separated. An alternative solution to this issue is use of the requisite optically active mesylates **4** to remove one racemic center as we have previously used for the synthesis of levonantradol [8]. The diastereomeric centers in these compounds are sufficiently well insulated to make simple separations problematical. Care was taken to insure final products were 1:1 mixtures of diastereomers as was shown for **39** (*vide infra*).

Reduction of ketone **16** with sodium borohydride at −78° in methanol gave a quantitative yield of the expected [3] equatorial alcohol final product **18**. Higher reaction temperatures (for example 0° in the case of **32** → **33**) do lead to small amounts of axial alcohols. The stereochemistry of C-9 alcohols was confirmed by correlation with pmr chemical shift differences and couplings expected for equatorial versus axial cyclohexanols [3, 12].

The 1-amino derivative **27** was prepared from ketone **19** (see Scheme V) as outlined in Scheme IV. Ketone **19** was

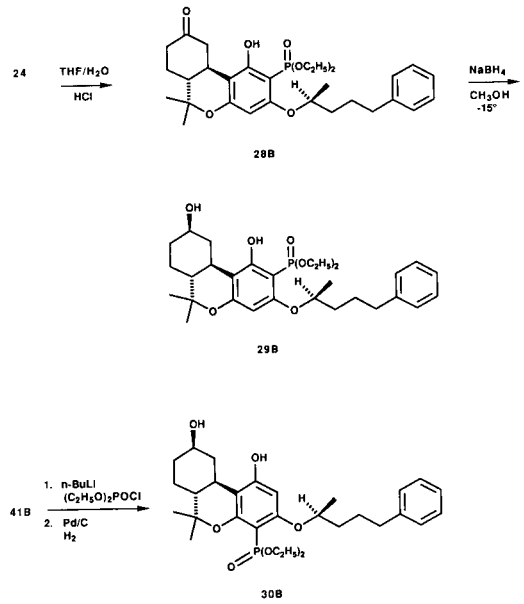
Scheme IV



first protected as the ethylene ketal **20** (100%) and the phenol then converted to the diethyl phosphate ester **21** (100%) using diethylchlorophosphate in a biphasic basic system. The reduction of aryl phosphate esters with potassium amide and potassium metal has been reported as a mild method for conversion of phenols to anilines and is assumed to proceed *via* trapping of an intermediate aryl radical by amide anion [13]. Whereas reaction of **21** with lithium liquid ammonia led as expected to only reductive cleavage of the phosphate ester to give **23** (91%), reaction of **21** with potassium amide and potassium metal led predominately to **23** (35%), phosphonate ester **24** (29%) and a low yield (5%) of desired amine **22**.

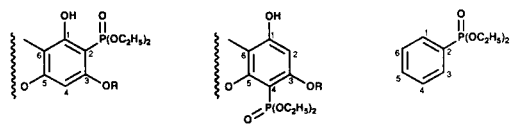
The formationof phosphonate **24** was unusual and the scope of this reaction has been reported elsewhere [14] and investigated further [15]. The *ortho* phenolic phosphonate structure of **24** was first assigned by nmr comparison of **29B** and **30B**. The ketal of **24** was hydrolyzed with aqueous acid to yield ketone **28** (100%). For these structure assignments single diasteromers were prepared thus **28B** was obtained by fractional crystallization of **28**. (In this paper **A** and **B** denote relative configurations with respect to the C-3 sidechain methyl and the hexahydro-6*H*-

dibenzo[*b,d*]pyran nucleus.) Sodium borohydride reduction of **28B** gave crystalline **29B** (89%). The para phosphonate isomer **30B** was one diastereomer as a result of synthesis from **41B** of known structure (*vide infra*). Metallation of **41B** with n-butyllithium and phosphonylation with diethyl chlorophosphate gave an intermediate dibenzyl ether (67%). Deprotection by catalytic hydrogenolysis provided crystalline **30B** (62%).



The ^{13}C nmr analysis of **29B** and **30B** and comparison to a standard, diethyl phenyl phosphonate **31** [16] was used to define the positions of the phosphonate groups in these compounds. Carbon-phosphorus coupling constant correlations are listed in Table I. The phenolic carbons were assigned by hydroxyl deuterium oxide exchange and

Table I
Carbon-13 J_{CP} Correlations for Structure Assignment of 29B



	29B		30B		31	
Position [a]	Line (Hz)	J_{CP} (Hz)	Line (Hz)	J_{CP} (Hz)	Line (Hz)	J_{CP} (Hz)
1	163.7	7.3	161.9	1.3	131.0	10.1
2	88.7	184.3	93.8	10.2	127.7	187.5
3	159.6	21.2	159.07	18.4	131.0	10.1
4	92.0	15.7	94.2	197.9	127.8	15.4
5	159.5	19.2	159.14	18.4	134.6	2.9
6	104.5	12.4	104.3	9.3	127.8	15.4

[a] Deuteriochloroform, deuterium oxide exchanged.

induced chemical shift differences [17]. The relative magnitude of J_{CP}s measured for **29B** and **30B** are consistent with those expected [17] and with the standard **31**. Finally, the structure assignment of **24** was verified *via* single crystal X-ray analysis of **28B**. An ORTEP drawing of the crystal structure for **28B** is presented in Figure 1.

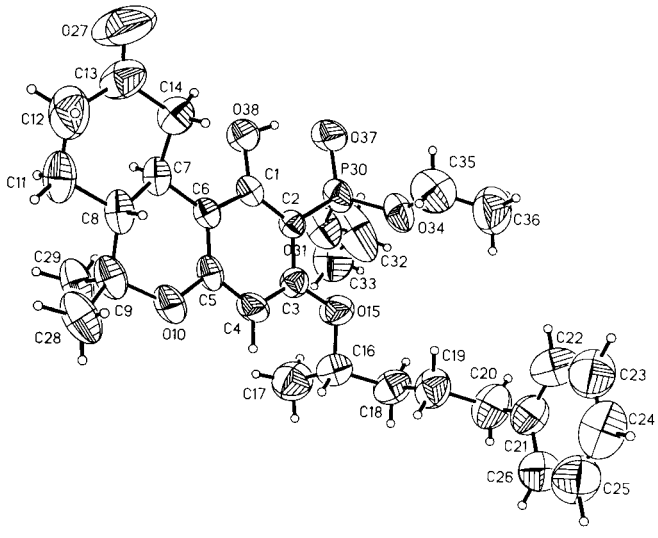


Figure 1. X-Ray crystal structure of phosphonic acid ester **28B**.

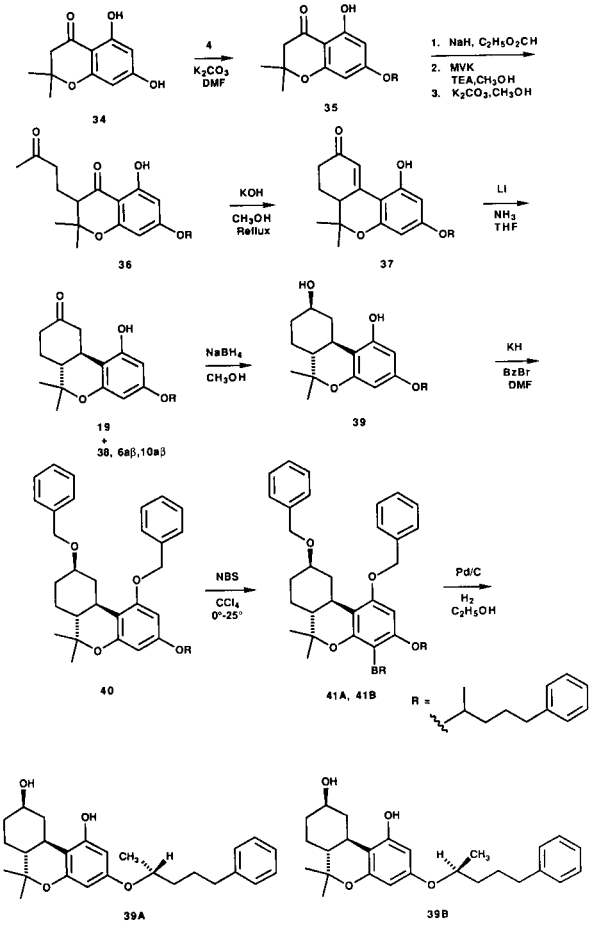
Considering the formation of phosphonate **24**, which likely occurred by metallation at C-2 ortho to the phosphate followed by intramolecular phosphonylation, the low yield of amine **22** above was potentially the result of amide anion addition to a benzyne formed by elimination of diethylphosphate. Proceeding with this premise we attempted to enhance benzyne formation from a derivative of **20**. The methyl sulfonate, *p*-tolylsulfonate and mesitylsulfonate esters of **20** were prepared. Treatment of these sulfonates with potassium amide in liquid ammonia led exclusively to cleavage at sulfur and regeneration of phenol **20**. However, the more reactive trifluoromethylsulfonate **25**, prepared from **20** with trifluoromethylsulfonyl imidazole, when reacted with potassium amide at $-78°$ in liquid ammonia-THF did give a low yield (8%) of the amine **22** along with phenol **20** (84%). To increase the basicity of potassium amide the reaction of triflate **25** was conducted in a mixed solvent system of liquid ammonia-THF-HMPA which gave an optimized 20% yield of the amine **22** and 54% of cleaved phenol **20**. The exact mechanism whereby amine **22** was generated from triflate **25** is not certain. Evident attack at sulfur of the less reactive and more hindered sulfonates (*e.g.* mesitylsulfonate) suggests mechanisms other than benzyne formation may be operative with the triflate. The reactive triflate case may be an example of a direct nucleophilic aromatic substitution. Alternatively, an electron transfer process, especially in the presence of HMPA and as originally proposed (*vide supra*) for reaction with potassium metal, may be considered.

The ethylene ketal of **22** was removed with acid hydrolysis and the intermediate amino ketone **26** obtained directly reduced with methanolic sodium borohydride at $-78°$. The desired amino alcohol **27** was obtained in 54% yield as a somewhat air-sensitive substance.

A sample of the C-1 hydrogen derivative, **33**, was prepared from **23**. Acidic hydrolysis of **23** gave ketone **32** (87%) which was reduced at 0° with sodium borohydride to yield a mixture of the equatorial alcohol **33** (87%) and the C-9 epimeric axial alcohol (9%).

The parent phenol **39** was synthesized (Scheme V) in a manner analogous to Scheme III. The relative stereochemistry at C-6a, 9 and 10a of **39** was set during the synthesis but the C-3 sidechain asymmetric center was not. Phenol **39** was obtained as a solid foam that was a 1:1 mixture

Scheme V



of diastereomers. Fractional crystallization of this material readily yields only the high melting diastereomer **39A**. However, a three step synthetic procedure allowed chromatographic separation of diasteromers. Thus, **39** was alkylated to give the dibenzyl ether **40** (76%). Selective C-4 bromination of **40** with *N*-bromosuccinimide provided the diasteromers, **41A** and **41B**, (95% combined) which were separable by normal phase silica gel chromatography. Removal of the benzyl ethers and reduction of the bromides by catalytic hydrogenolysis furnished the pure crystalline diasteromers **39A** (55%) and **39B** (44%). The relative configuration of bromide **41B** was determined by single crystal X-ray analysis. By analogy **39A** and **39B** have the relative configurations shown. An ORTEP drawing of **41B** as determined by X-ray analysis is presented in Figure 2.

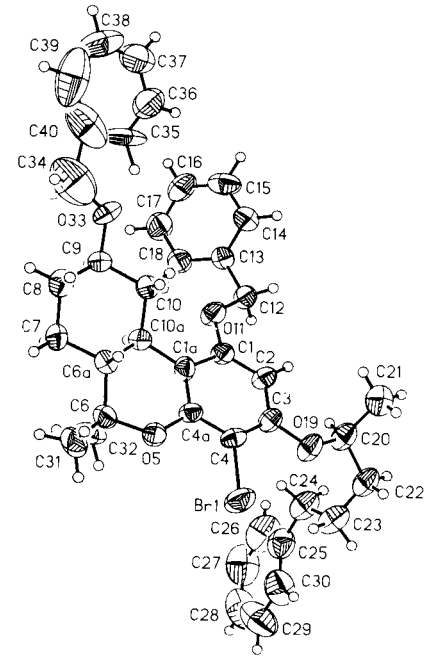


Figure 2. X-Ray crystal structure of bromide **41B**.

Biological activity of the synthetic cannabinoids presented here has been reported elsewhere and confirms that the phenol is required for potent analgetic activity [18].

EXPERIMENTAL

Melting points were determined with open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. The ^{1}H-nmr spectra (pmr), obtained on a Varian T-60, XL-100 or XL-300 spectrometer, were recorded in deuteriochloroform, unless otherwise noted, and data are reported as δ (ppm) values with respect to tetramethylsilane. The ^{13}C-nmr spectra (cmr) were obtained on a Varian XL-100 or XL-300 in deuteriochloroform and are recorded in ppm. Infrared spectra (ir), obtained on a Perkin-Elmer 237B spectrophotometer, were recorded in chloroform, unless otherwise noted, and data are reported in reciprocal centimeters. High-resolution mass spectra (hrms and ms) were obtained on an AEI-MS 30 coupled with a DS-50 system. Single crystal X-ray analysis was conducted on a Nicolet R3m/μ diffractometer. Elemental analyses were performed by the Pfizer Central Research Analytical Department. Elemental analyses on noncrystalline compounds were obtained on material that was chromatographically pure.

2,3-Dihydro-2,2-dimethyl-7-hydroxy-5-(2-phenylethenyl)-4*H*-1-benzopyran-4-one (**2**) and 2,3-Dihydro-2,2-dimethyl-5-hydroxy-7-(2-phenylethenyl)-4*H*-1-benzopyran-4-one (**3**).

A 25° mixture of 30.0 g (0.142 mole) of 3,5-dihydroxystilbene (**1**, pinosylvine) [7] and 18.4 g (0.184 mole) of 3,3-dimethylacrylic acid in 75 ml (0.609 mmole) of borontrifluoride etherate was stirred for 40 hours. The reaction was slowly diluted with 150 ml

of water and then with 330 ml of 6*N* sodium hydroxide. The resultant mixture was heated on a steam bath for 10 minutes followed by cooling in ice and acidification with 150 ml of concentrated hydrochloric acid. The reaction mixture was extracted twice with 550 ml portions of ethyl acetate. The extracts were combined, washed twice with 500 ml portions of saturated sodium bicarbonate and dried over magnesium sulfate. The extract was concentrated under reduced pressure to 300 ml volume and the concentrate allowed to crystallize yielding 21.8 g (52%) of **2**, mp 221° (from ether-ethyl acetate); ir: (potassium bromide) 1642, 1623, 1597 and 1575 cm^{-1}; pmr (D_6-DMSO): δ 1.33 (s, C-2 methyls), 2.66 (s, methylene), 6.25 (d, J = 2 Hz, C-8 ArH), 6.68 (d, J = 2 Hz, C-6 ArH), 6.93 (d, J = 16 Hz, vinyl proton), 7.17-7.57 (m, PhH) and 8.12 (d, J = 16 Hz, vinyl proton); ms: (m/e) 294 (M+), 279, 239 and 238.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.09; H, 6.15.

The mother liquor was purified *via* column chromatography on silica gel eluted with 50% ether-hexane to yield another 3.85 g (9.2%) of **2** and 9.2 (22%) of **3**, mp 116° (from hexane); ir: 3675, 1642 and 1628 cm^{-1}; pmr: δ 1.48 (s, C-2 methyls), 2.75 (s, methylene), 6.55 (d, J = 2 Hz, C-8 ArH), 6.62 (d, J = 2 Hz, C-6 ArH) and 7.0-7.6 (m, vinyl and PhH); ms: (m/e) 294 (M+), 279, 261, 239 and 221.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.39; H, 6.15.

2,3-Dihydro-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-5-(2-phenylethenyl)-4*H*-1-benzopyran-4-one (**5**).

A mixture of 21.8 g (74.1 mmoles) of **2**, 21.8 g (90.0 mmoles) of 1-methyl-4-phenylbutyl methanesulfonate (**4**) and 21.8 g (158 mmoles) of anhydrous potassium carbonate in 150 ml of dimethylformamide was heated at 85° for 20 hours. The reaction mixture was then cooled and added to a mixture of one liter of ether and one liter of cold water. The ether extract was washed with two 500 ml portions of water. The total aqueous extract was extracted again with 500 ml of ether and the ether extract washed with two 250 ml portions of water. The total combined extract was dried over magnesium sulfate and evaporated to an oil which was purified *via* column chromatography on 750 g of silica gel eluted with 50% ether-hexane to yield 33 g (100%) of **5** as an oil; ir: 1667, 1631, 1595 and 1563 cm^{-1}; pmr: δ 1.33 (d, J = 6 Hz, side chain methyl), 1.45 (s, C-2 methyls), 1.77 (m, two side chain methylenes), 2.67 (m, benzylic side chain methylene), 2.70 (s, C-3 methylene), 4.45 (m, side chain methine), 6.32 (d, J = 2 Hz, C-8 ArH), 6.73 (d, J = 2 Hz, C-6 ArH), 6.93 (d, J = 16 Hz, vinyl proton), 7.22 (s, PhH), 7.1-7.8 (m, PhH) and 0.97 (d, J = 16 Hz, vinyl proton); ms: (m/e) 440 (M+), 294 and 279.

Anal. Calcd. for $C_{30}H_{32}O_3$: C, 81.79; H, 7.32. Found: C, 81.80; H, 7.28.

2,3-Dihydro-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-4-oxo-2*H*-1-benzopyran-5-carboxaldehyde (**6**).

A.

A mixture of 30.0 g (68.1 mmoles) of **5**, 43.8 g (204 mmoles) of sodium periodate and 169 mg (0.67 mmole) of osmium tetroxide in 272 ml of dioxane and 68 ml of water was stirred at 25° for 15 hours. The reaction mixture was then added to a mixture of one liter of ether and 500 ml of 15% sodium sulfite solution. The ether extract was washed with 500 ml of saturated sodium bicarbonate and evaporated to an oil which was purified *via* column chromatography on 750 g of silica gel eluted with 40% ether-petroleum ether to yield 24 g (96%) of **6** as an oil; ir: 1678, 1600 and 1587 cm^{-1}; pmr: δ 1.31 (d, J = 6 Hz, side chain methyl); 1.50 (s, C-2 methyls), 1.75 (m, two side chain methylenes), 2.63 (m, benzylic side chain methylene), 2.78 (s, C-3 methylene), 4.5 (m, side chain methine), 6.60 (d, J = 2 Hz, C-8 ArH), 6.98 (d, J = 2 Hz, C-6 ArH), 7.28 (s, PhH), and 10.78 (s, CHO); ms: (m/e) 366 (M^+), 338, 192 and 177.

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.39; H, 7.15. Found: C, 75.02; H, 7.18.

B.

A mixture of 1.0 g (1.42 mmoles) of **9**, 2 mg (0.008 mmoles) of osmium tetroxide and 942 mg (4.40 mmoles) sodium periodate in 8 ml of dioxane and 2 ml of water was stirred at 25° for 24 hours. The reaction mixture was added to 200 ml of ether-150 ml of water. The organic phase was separated and washed successively with 100 ml of 10% sodium sulfite and 100 ml of saturated sodium bicarbonate. It was then dried over magnesium sulfate and evaporated to give 1.09 g (100%) of **6** as an oil.

5,5'-(1,2-Ethenediyl)bis[2,3-dihydro-7-hydroxy-2,2-dimethyl-4*H*-1-benzopyran-4-one] (**8**).

A mixture of 10.0 g (40.98 mmoles) of 3,3',5,5'-tetrahydroxystilbene (**7**) [9] and 12.3 g (0.123 mole) of 3,3-dimethylacrylic acid in 51 ml of borontrifluoride etherate complex was stirred at 25° for 39 hours. The reaction mixture was then diluted with 41 ml of water and then 276 ml of cold 5*N* sodium hydroxide. The resultant mixture was acidified with 124 ml of concentrated hydrochloric acid forming a light yellow precipitate. The precipitate was filtered, washed with water and air dried. The dried precipitate was slurried in ethyl acetate, boiled gently, cooled and filtered to yield 9.80 g (59%) of **8** as a light yellow solid, mp 335-336°; ir (potassium bromide): 1648, 1598 and 1565 cm^{-1}; pmr (300 MHz, D_6-DMSO): δ 1.36 (s, C-2 methyls), 2.68 (s, CH_2), 6.23 (d, J = 2 Hz, ArH), 6.69 (d, J = 2 Hz, ArH), 7.89 (s, vinyl H) and 10.56 (bs, OH); ms: (m/e) 408 (M+), 393, 353, 270, 268, 217 and 203.

Anal. Calcd. for $C_{24}H_{24}O_6 \cdot \frac{1}{2}H_2O$: C, 69.05; H, 6.04. Found: C, 69.14; H, 5.94.

Concentration of the mother liquor and crystallization from ethyl acetate gave a yellow powder. Recrystallization from ethyl acetate gave 1.59 g (9.5%) of the 5,7 isomer of **8**, mp 270-273°; ir (potassium bromide): 1666, 1627 and 1575 cm^{-1}; pmr (300 MHz, D_6-DMSO): δ 1.36 and 1.41 (s, C-2 methyls), 2.69 and 2.88 (s, methylenes), 6.27 (d, J = 2 Hz, ArH), 6.63 (m, 3 ArH), 6.86 (d, J = 16 Hz, vinyl H), 8.20 (d, J = 16 Hz, vinyl H), 10.58 (bs, C-7 OH) and 11.72 (s, C-5 OH); ms: (m/e) 408 (M+), 390, 389, 373, 353, 335, 334, 324, 309, 295, 229, 217, 189 and 169.

Anal. Calcd. for $C_{24}H_{24}O_6$: C, 70.58; H, 5.92. Found: C, 70.21; H, 5.85.

The remaining mother liquor was purified *via* column chromatography on 500 g of silica gel eluted with 50% ethyl acetate-hexane to give in order of elution: 182 mg (1.1%), crystallized from ether, of the 7,7 isomer of **8**, 1.26 g (7.5%), from ethyl acetate, of the 5,7 isomer of **8** and 250 mg (1.5%), from ethyl acetate, of **8**. The 7,7 isomer of **8** had mp 232-235°; ir (potassium bromide): 1629, 1560 and 1526 cm^{-1}; pmr (300 MHz, D_6-DMSO-D_5-pyridine): δ 1.42 (s, C-2 methyls), 2.91 (s, methylenes), 6.83 (s, ArH), 7.44 (s, vinyl H) and 11.84 (s, OH); ms: (m/e) 408 (M+), 393, 375 and 353.

Anal. Calcd. for $C_{24}H_{24}O_6$: C, 70.58; H, 5.92. Found: C, 70.21; H, 5.85.

5,5'-(1,2-Ethenediyl)bis[2,3-dihydro-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-4*H*-1-benzopyran-4-one] (**9**).

A mixture of 3.00 g (7.30 mmoles) of **8**, 4.60 g (18.9 mmoles) of 1-methyl-4-phenylbutyl methanesulfonate and 3.94 g (28.6 mmoles) of anhydrous potassium carbonate in 25 ml of dimethylformamide was heated at 85° for 16 hours. The reaction mixture was then cooled and added to 250 ml of ether-250 ml of water. The organic phase was separated and washed twice with 200 ml of water, dried over magnesium sulfate and evaporated to an oil. Crystallization of the oil in ether gave 1.3 g (25%) of **9**, mp 109° (from ether); ir: 1658, 1587 and 1570 cm^{-1}; pmr: δ 1.35 (d, J = 6 Hz, side chain methyl), 1.48 (s, C-2 methyls), 1.78 (m, two methylenes of side chain), 2.72 (s, C-3 methylene), 2.7 (m, side chain benzylic methylene), 4.53 (m, side chain methine), 6.35 (d, J = 2 Hz, C-8 ArH), 7.00 (d, J = 2 Hz, C-6 ArH), 7.28 (s, PhH) and 8.10 (s, vinyl proton); ms: (m/e) 700 (M+) and 408 (100%).

Anal. Calcd. for $C_{46}H_{52}O_6$: C, 78.82; H, 7.48. Found: C, 78.72; H, 7.49.

Column chromatography of the mother liquor on 250 g of silica gel eluted with 50% ether-petroleum ether gave from a less polar fraction another 1.01 g (20%) of **9** after crystallization from ether. A more polar fraction gave 0.42 g (10%) of the monoalkylated derivative of **8**, mp 172-173° (from ether); ir: 3125, 1656 and 1590 cm^{-1}; pmr: δ 1.32 (d, J = 6 Hz, side chain methyl), 1.42 (s, C-2 methyls), 1.72 (m, two methylenes of side chain), 2.70 (s, C-3 methylenes), 2.7 (m, side chain benzylic methylene), 4.5 (m, side chain methine), 6.3 (d, J = 2 Hz, C-8 ArH), 6.37 (d, J = 2 Hz, C-8 ArH), 6.95 (m, C-6 ArH), 7.26 (s, PhH), 7.81 (s, OH) and 8.03 (s, vinyl protons); ms: (m/e) 554 (M+), 539, 524 and 4.08.

Anal. Calcd. for $C_{35}H_{38}O_6 \cdot \frac{1}{4}H_2O$: C, 75.18; H, 6.94. Found: C, 75.18; H, 6.94.

2,3-Dihydro-5-(hydroxymethyl)-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-4*H*-1-benzopyran-4-one (**10**).

To a −78° solution of 20.0 g (54.6 mmoles) of **6** in 400 ml of tetrahydrofuran was added dropwise (45 minutes) 109.3 ml (54.6 mmoles) of a 0.5 *M* tetrahydrofuran solution of potassium tri-sec-butylborohydride. After 30 minutes the reaction mixture was added to a mixture of one liter each of ether and saturated sodium chloride. The ether extract was washed with 500 ml of saturated sodium chloride, dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* column chromatography on 750 g of silica gel eluted with 50% ether-petroleum ether to yield 19.3 g (96%) of **10** as an oil; ir: 3436, 1667, 1608 and 1587 cm^{-1}; pmr: δ 1.30 (d, J = 6 Hz, side chain methyl), 1.45 (s, C-2 methyl), 1.73 (m, two side chain methylenes), 2.66 (m, benzylic side chain methylene), 2.71 (s, C-3 methylene), 4.46 (m, side chain methine), 4.68 (bs, hydroxymethylene), 6.31 (d, J = 2 Hz, C-8 ArH), 6.51 (d, J = 2 Hz, C-6 ArH) and 7.25 (s, PhH); ms: (m/e) 368 (M+), 353, 340 and 222.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.89; H, 7.83.

2,3-Dihydro-5-(hydroxymethyl)-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-3-(3-oxobutyl)-4*H*-1-benzopyran-4-one (**11**).

A solution of 16.0 g (43.4 mmoles) of **10** in 50 ml of ethyl formate and 40 ml of ether was added, over a 15 minute period, to 5.2 g (0.217 mole) of sodium hydride in a 10° bath. After stirring one hour at 15° the reaction mixture was added to a mixture of 500 ml of ethyl acetate-300 ml of saturated sodium chloride-25 ml of concentrated hydrochloric acid. The organic extract was separated, dried over magnesium sulfate and evaporated to yield 2,3-dihydro-5-(hydroxymethyl)-(3-hydroxymethylene)-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-4*H*-1-benzopyran-4-one (**13**) as an oil. This crude product was dissolved in 130 ml of methanol-10 ml of ether and 6.07 ml (43.4 mmoles) of triethylamine and 10.5 ml (0.130 mole) of methyl vinyl ketone added. The reaction mixture was stirred for 18 hours at 25° and then deformylated by cooling to 0° followed by addition of 30 ml of 2*N* potassium hydroxide in methanol. The reaction mixture was stirred for 15 minutes at 0° and was then evaporated under reduced pressure to a thick oil (temperature <25°). The residue was dissolved in 200 ml of water-500 ml of ether. The ether extract was separated and washed once each with 200 ml of concentrated potassium carbonate and 200 ml of saturated sodium chloride. The ether extract was dried over magnesium sulfate and evaporated to an oil. The oil was purified *via* column chromatography on 700 g silica gel eluted with ether to yield 6.5 g (34%) of **11** as an oil; ir: 3401, 1718, 1656, 1603 and 1575 cm^{-1}; pmr: δ 1.33 (d, J = 6 Hz, side chain CH_3), 1.43, 1.48 (s, C-6 CH_3), 2.18 (s, CH_3CO), 4.65 (s, CH_2OH), 4.6 (m, OH, side chain methine), 6.33 (d, J = 2 Hz, ArH), 6.55 (d, J = 2 Hz, ArH), and 7.30 (s, PhH); ms: (m/e) 438 (M+), 423, 420, 277 and 274.

Anal. Calcd. for $C_{27}H_{34}O_5$: C, 73.95; H, 7.81. Found: C, 73.68; H, 8.10.

The total aqueous extract was cooled to 0° and acidified with concentrated hydrochloric acid. Extraction with ether followed by drying of the extract over magnesium sulfate and evaporation gave 5.4 g (40%) of 7-hydroxy-5-(1-methyl-4-phenylbutoxy)phthalide, **12**, as a solid. Column chromatography of this product on silica gel eluted with 50% ether-dichloromethane yielded an analytical sample of **12** as a hydrated solid with a poorly defined mp and that liquifies if made anhydrous by vacuum drying; ir: 3425, 1733 and 1626 cm^{-1}; pmr: δ 1.35 (d, J = 6 Hz, side chain CH_3), 1.80 (m, side chain CH_2CH_2), 2.70 (m, CH_2Ph), 4.50 (m, side chain methine), 5.30 (s, OCH_2Ar), 6.50 (s, ArH), and 7.32 (s, PhH); ms: (m/e) 312 (M+), 167 and 166.

Anal. Calcd. for $C_{19}H_{20}O_4 \cdot \frac{3}{4}H_2O$: C, 70.03; H, 6.65. Found: C, 69.77; H, 6.35.

6,6a,7,8-Tetrahydro-1-(hydroxymethyl)-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-9*H*-dibenzo[*b*,*d*]pyran-9-one (**14**).

A solution of 6.0 g (13.7 mmoles) of **11** in 400 ml of 1*N* potassium hydroxide in methanol was heated 3.5 hours at reflux and then stirred for 15 hours at 25°. The reaction mixture was evaporated to a small volume under reduced pressure (temperature <25°) and diluted with 500 ml of ether, 500 ml of water and 65 ml of concentrated hydrochloric acid. The ether extract was separated, washed twice with 300 ml portions of saturated sodium chloride, dried over magnesium sulfate and evaporated to an oil. The crude oil was purified *via* column chromatography on 500 g of silica gel eluted with 2:1 ethyl acetate:cyclohexane to yield, in order of elution, 2.0 g (35%) of **14** as an oil; ir: 3571, 3390, 1656, 1613 and 1587 cm^{-1}; pmr: δ 1.20 (s, C-6 CH_3), 1.32 (d, J = 6 Hz, side chain CH_3), 1.53 (s, C-6 CH_3), 4.4 (m, side chain methine), 4.82 (s, CH_2OH), 6.40 (d, J = 3 Hz, ArH), 6.58 (d, J = 2 Hz, C-10 vinyl proton), 6.85 (d, J = 3 Hz, ArH) and 7.32 (s, PhH); ms: (m/e) 420 (M+), 405, 274, 259 and 256.

Anal. Calcd. for $C_{27}H_{32}O_4 \cdot \frac{1}{4}H_2O$: C, 76.30; H, 7.71. Found: C, 76.33; H, 7.59.

One g (18%) of 3-[2-hydroxy-6-(hydroxymethyl)-4-(1-methyl-4-phenylbutoxy)phenyl]-4-(1-methylethylidene)-2-cyclohexen-1-one

(**15**) was obtained, mp 125-128°; ir: 3484, 3125, 1667, 1647, 1613 and 1597 cm^{-1}; pmr: δ 1.30 (d, J = 6 Hz, side chain CH_3), 1.33, 1.48 (s, vinyl CH_3), 1.5-3.0 (m), 4.34 (m, side chain methine), 4.50, 4.90 (AB, J = 16 Hz, CH_2OH), 6.25 (d, J = 2 Hz, ArH), 6.48 (d, J = 2 Hz, ArH), 6.98 (s, vinyl proton), 7.23 (s, PhH), and 7.9 (bs, OH); ms: (m/e) 420 (M+), 405, 274 and 259.

Anal. Calcd. for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 76.92; H, 7.67.

(±)-6,6aβ,7,8,10,10aα-Hexahydro-1-(hydroxymethyl)-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-9*H*-dibenzo[*b,d*]pyran-9-one (**16**) and the 6aβ,10aβ-isomer **17**.

To a −78° solution of 88 mg (12.6 mmoles) of lithium metal in 200 ml of liquid ammonia and 75 ml of tetrahydrofuran was added a solution of 2.0 g (4.76 mmoles) of **14** in 75 ml of tetrahydrofuran. An additional 44 mg (6.3 mmoles) and 11 mg (1.6 mmoles) of lithium was added to keep the reaction blue during addition of the enone. After the addition was complete (5 minutes), the reaction mixture was stirred for 15 minutes and then quenched with excess solid ammonium chloride. The ammonia was allowed to evaporate and the residue added to 250 ml of ether-50 ml of saturated ammonium chloride. The organic phase was separated, dried over magnesium sulfate and evaporated to an oil. This oil was purified *via* column chromatography on 200 g of silica gel eluted in 10 ml fractions with ether to yield in order of elution 1.21 g (61%) of **16** as an oil; ir: 3571, 3390, 1718, 1618 and 1582 cm^{-1}; pmr: δ 1.12 (s, C-6 methyl), 1.28 (d, J = 6 Hz, side chain methyl), 1.50 (s, C-6 methyl), 4.40 (m, side chain methine), 4.68 (s, hydroxymethylene), 6.35 (d, J = 2 Hz, C-4 ArH), 6.61 (d, J = 2 Hz, C-2 ArH), and 7.26 (s, PhH); ms: (m/e) 422 (M+), 408, 394, 276, 261 and 258.

Anal. Calcd. for $C_{27}H_{34}O_4 \cdot \frac{1}{4}H_2O$: C, 75.94; H, 8.14. Found: C, 76.27; H, 8.28.

Compound **17** (0.29 g, 15%) was obtained as an oil; ir: 3546, 3390, 1715, 1613 and 1580 cm^{-1}; pmr: δ 1.28 (d, J = 6 Hz, side chain methyl), 1.33 and 1.38 (s, C-6 methyls), 4.30 (m, side chain methine), 4.67 (bs, hydroxymethylene), 6.38 (d, J = 2 Hz, C-4 ArH), 6.63 (d, J = 2 Hz, C-2 ArH) and 7.23 (s, PhH); ms: (m/e) 422 (M+), 407, 276 and 261.

Anal. Calcd. for $C_{27}H_{34}O_4 \cdot \frac{1}{4}H_2O$: C, 75.94; H, 8.14. Found: C, 75.95; H, 8.33.

(±)-6aβ,7,8,9,10,10aα-Hexahydro-9-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b,d*]pyran-1-methanol (**18**).

To a −78° solution of 50 mg (0.118 mmole) of **16** in 1 ml of methanol was added 10 mg (0.26 mmole) of sodium borohydride. The reaction mixture was stirred for 40 minutes and was then added to 100 ml of ether and 100 ml of saturated sodium chloride solution. The organic extract was separated, dried over magnesium sulfate and evaporated to give a quantitative yield of **18** as an oil; ir: 3661, 3588, 3445, 1609 and 1575 cm^{-1}; pmr: δ 1.05 (s, C-6 methyl), 1.28 (d, J = 6 Hz, side chain methyl), 1.40 (s, C-6 methyl), 3.9 (m, C*H*OH), 4.40 (m, side chain methine), 4.70 (s, C-1′ methylene), 6.30 (d, J = 2 Hz, C-4 ArH), 6.58 (d, J = 2 Hz, C-2 ArH) and 7.23 (s, PhH); ms: (m/e) 424 (M+), 278, 260, 245, 227, 217 and 91.

Anal. Calcd. for $C_{27}H_{36}O_4 \cdot \frac{1}{4}H_2O$: C, 75.58; H, 8.57. Found: C, 75.83; H, 8.63.

(±)-6,6aβ,7,8,10,10aα-Hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)spiro[9*H*-dibenzo[*b,d*]pyran-9,2′-[1,3]dioxolan]-1-ol (**20**).

A mixture of 6.6 g (16.1 mmoles) of **19**, 8.99 ml (0.161 mole) of ethylene glycol and 500 mg of *p*-toluenesulfonic acid monohydrate in 100 ml of benzene was heated under reflux with a Dean-Stark trap for 1 hour. The reaction mixture was cooled and added to 100 ml of ether and 100 ml of saturated sodium bicarbonate. The organic phase was separated, washed once with 100 ml of saturated sodium bicarbonate, dried over magnesium sulfate and evaporated to yield 7.26 g (100%) of **20** as an oil; ir: 3571, 3300, 1623 and 1587 cm^{-1}; pmr: δ 1.03 (s, C-6 methyl), 1.24 (d, J = 6 Hz, side chain methyl), 1.35 (s, C-6 methyl), 4.00 (s, ethylene ketal), 5.52 (s, OH), 5.78 and 5.90 (d, J = 2 Hz, C-2 and C-4 ArH) and 7.18 (s, PhH); ms: (m/e) 452 (M+), 437, 407, 391 and 306.

Anal. Calcd. for $C_{28}H_{36}O_5$: C, 74.31; H, 8.02. Found: C, 73.97; H, 7.85.

Phosphoric Acid Diethyl (±)-6,6aα,7,8,10,10aβ-hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)spiro[9*H*-dibenzo[*b,d*]pyran-9,2′-[1,3]dioxolan]-1-yl Ester (**21**).

To a 0° solution of 3.0 g (6.64 mmoles) of **20** in 12 ml of toluene was added over a 3 minute period 1.32 ml (6.64 mmoles) of 20% sodium hydroxide and 1.15 g (6.64 mmoles) of diethyl chlorophosphate. After stirring for 15-30 minutes, the above portions of reagents were again added to the reaction mixture and the addition procedure repeated twice more after that. The reaction mixture was then added to 150 ml of ether-150 ml of 10% sodium hydroxide, the organic phase separated and washed once each with 150 ml of water and 150 ml of saturated sodium chloride. The organic extract was dried over magnesium sulfate and evaporated to yield 3.9 g (100%) of **21** as an oil; ir: 1626, 1580, 1269, 1142, 1095 and 1015 cm^{-1}; pmr: δ 1.0-2.1 (m), 2.3-3.4 (m), 4.02 (m, ethylene ketal), 3.9-4.6 (m, $P(O)OCH_2$ and side chain methine), 6.20 (d, J = 2 Hz, C-4 ArH), 6.52 (dd, J_H = 2 Hz, J_P = 1 Hz, C-2 ArH) and 7.21 (s, PhH); ms: (m/e) 588 (M+).

Anal. Calcd. for $C_{32}H_{45}O_8P$: C, 65.29; H, 7.70. Found: C, 65.16; H, 7.70.

(±)-6,6aβ,7,8,10,10aα-Hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)spiro[9*H*-dibenzo[*b,d*]pyran-9,2′-[1,3]dioxolan]-1-amine (**22**).

Method A.

To a −78° mixture of 25 mmoles of potassium amide [from 975 mg (25 mmoles) of potassium and 50 mg of ferric nitrate nonanhydrate in 50 ml of liquid ammonia at −33°] in 50 ml of liquid ammonia was simultaneously added a solution of 2.9 g (4.93 mmoles) of **21** in 10 ml of tetrahydrofuran and a total of 200 mg of potassium (5.12 mmoles) in three portions. The resultant blue solution was stirred 10 minutes longer and quenched with excess ammonium chloride. The reaction mixture was allowed to warm, ether added, and the ammonia allowed to evaporate. The residue was added to 200 ml of ether and 100 ml of water, the organic phase separated, washed once with 100 ml of saturated sodium bicarbonate, dried (magnesium sulfate) and evaporated to an oil. This oil was purified *via* column chromatography on 200 g of silica gel eluted with 2:1 ether:cyclohexane to yield the following fractions in order of elution:

Fraction 1.

Compound **23** (756 mg, 35%) was obtained as an oil; see preparation of **23** for data.

Fraction 2.

Compound **20** (116 mg 5%) was obtained as an oil.

Fraction 3.

This was a mixture of fractions 1 and 2 (52 mg, 2%).

Fraction 4.

This fraction was (±)-[6,6aβ,7,8,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)spiro[9*H*-dibenzo[*b,d*]-pyran-9,2'-[1,3]dioxolan]-2-yl]-phosphonic acid diethyl ester (**24**) (848 mg, 29%) obtained as an oil; ir: 1626, 1587, 1149, 1127, 1105, 1020 and 976 cm^{-1}; pmr: 1.12 (s, C-6 methyl), 1.40 (s, C-6 methyl), 4.02 (s, ethylene ketal), 5.82 (d, J_{H-P} = 6 Hz, C-4 ArH), 7.23 (s, PhH) and 13.73 (d, J_{H-P} = 1 Hz, phenol); hrms: (m/e) 588.2965 (M+ 588.2852 Calcd. for $C_{32}H_{45}O_8P$).

Anal. Calcd. for $C_{32}H_{45}O_8P$: C, 65.29; H, 7.70. Found: C, 65.64; H, 7.96.

Fraction **5**.

Compound **22** (104 mg, 5%) was obtained as an oil; ir: 3425, 1626 and 1587 cm^{-1}; pmr: δ 1.08 (s, C-6 methyl), 1.25 (d, J = 6 Hz, side chain methyl), 1.40 (s, C-6 methyl), 4.03 (s, ethylene ketal), 4.20 (m, side chain methine), 5.85 and 5.92 (d, J = 2 Hz, C-2 and C-4 ArH), and 7.27 (s, PhH); ms: (m/e) 451 (M+), 436 and 305.

Anal. Calcd. for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.42; H, 7.93; N, 2.73.

Method B.

A mixture of 1.0 g (2.21 mmoles) of **20** and 441 mg (2.56 mmoles) of trifluoromethanesulfonylimidazole was heated to 80°. After the mixture became fluid, 3 mg of 50% sodium hydride in mineral oil was added. Additional 44 mg (0.25 mmole) portions of trifluoromethanesulfonylimidazole were added 70 and 85 minutes after the first addition. After 2 hours the reaction mixture was cooled and diluted with 50 ml of ether. The resulting mixture was poured into 250 ml of water-150 ml of ether and the ether extract was washed once with 100 ml of saturated sodium bicarbonate solution, once with 100 ml of saturated sodium chloride solution, dried over magnesium sulfate and evaporated to yield 1.20 g (93%) of (±)-6,6aβ,7,8,10,10aα-hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)spiro[9*H*-dibenzo[*b,d*]pyran-9,2'-[1,3]-dioxolan]-1-yl trifluoromethanesulfonic acid ester (**25**) as an oil; pmr: δ 1.20 and 1.23 (d, J = 6 Hz, side chain methyls), 1.10, 1.40 (s, gem dimethyl), 3.96 (bs, ethylene ketal), 4.23 (m, side chain methine), 6.30 (s, two ArH) and 7.10 (s, Ph). This reactive material was used without further purification or identification.

Potassium amide was prepared from 28.5 g (0.73 mole) of potassium and 802 mg of ferric nitrate nonanhydrate in 570 ml of liquid ammonia at −33°. The ammonia was allowed to evaporate to 230 ml followed by addition of 70 ml of tetrahydrofuran and 230 ml of hexamethylphosphoramide. A solution of 42.9 g (73.5 mmoles) of **25** in 70 ml of tetrahydrofuran was rapidly added to the −33° potassium amide solution. The reaction was stirred 20 minutes and then slowly added to 2 liters of ice water. The quenched reaction was extracted three times with ether (500 ml). The combined ether extract was washed three times with water (1 liter) and once with 1 liter of saturated sodium chloride, dried over magnesium sulfate and evaporated to an oil. The crude product was purified *via* column chromatography on 400 g of silica gel eluted with 1:1 ether:hexane to yield in order of elution, 18.9 g (54%) of **20** as an oil and 6.77 g (20%) of **22**.

(±)-6,6aβ,7,8,10,10aα-Hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)spiro[9*H*-dibenzo[*b,d*]pyran-9,2'-[1,3]dioxolane] (**23**).

To 25 ml of liquid ammonia cooled to −78° was added a solution of 1.00 g (1.70 mmoles) of **21** in 15 ml of tetrahydrofuran. To this solution was added a total of 51 mg (7.28 mmoles) of lithium (wire) in three portions yielding a blue solution. After stirring 15 minutes longer the reaction was quenched with excess ammonium chloride and then allowed to evaporate. The residue was added to 150 ml of ether-100 ml of water. The ether extract was washed once with water, once with saturated sodium chloride and dried over magnesium sulfate to yield 675 mg (91%) of **23** as an oil; ir: 1623 and 1585 cm^{-1}; pmr: δ 1.18 (s, C-6 methyl), 1.28 (d, J = 6 Hz, side chain methyl), 1.43 (s, C-6 methyl), 4.03 (s, ethylene ketal), 4.33 (m, side chain methine), 6.33 (s, overlapping 6.42, C-4 ArH), 6.42 (d,d J = 8 and 2 Hz C-2 ArH), 7.03 (d, J = 8 Hz, C-1 ArH) and 7.23 (s, PhH); ms: (m/e) 436 (M+) and 290.

Anal. Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.06; H, 8.35.

(±)-1-Amino-6aβ,7,8,9,10,10aα-hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b,d*]pyran-9β-ol (**27**).

A solution of 229 mg (0.508 mmole) of **22** in 15 ml of tetrahydrofuran and 7 ml of 1*N* hydrochloric acid was heated at reflux for 45 minutes. The cooled reaction was added to 150 ml of ether-100 ml of saturated sodium bicarbonate. The ether extract was dried over magnesium sulfate and evaporated to give a quantitative yield of ketone **26** as an oil; pmr: δ 1.13 (s, C-6 methyl), 1.27 (d, J = 6 Hz, side chain methyl), 1.48 (s, C-6 methyl), 3.5 (bm, NH_2), 4.2 (m, side chain methine), 5.80 and 5.90 (d, J = 3 Hz, ArH) and 7.20 (s, PhH). This material was used without further purification.

To a −78° solution of 207 mg (0.508 mmole) of the above ketone in 15 ml of ethanol and 4 ml of tetrahydrofuran was added 115 mg (3.0 mmoles) of sodium borohydride. The reaction mixture was stirred for 30 minutes at −78° and for 10 minutes at 0° followed by quenching with 1*N* hydrochloric acid and addition of 150 ml of ether and 50 ml of saturated sodium bicarbonate. The ether extract was dried over magnesium sulfate and evaporated to an oil. The crude oil was purified *via* column chromatography on 6 g of silica gel eluted with 20% ethyl acetate-ether to yield 112 mg (54%) of **27** as a solid foam; ir: 3662, 3594, 3387, 1621, 1580 and 1491 cm^{-1}; pmr: δ 1.06 (s, CH_3), 1.26 (d, J = 6 Hz), 1.40 (s, CH_3), 6.06 (s, 2 ArH) and 7.23 (s, ArH); hrms: (m/e) 409.2617 (M+; 409.2718 Calcd. for $C_{26}H_{35}NO_3$), 394, 351, 318, 304, 290, 263, 248, 230 and 205.

Anal. Calcd. for $C_{26}H_{35}NO_3 \cdot \frac{1}{4}H_2O$: C, 75.42; H, 8.64; N, 3.38. Found: C, 75.38; H, 8.38; N, 3.23.

(±)-[6aβ,7,8,10,10aα-Hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-9-oxo-6*H*-dibenzo[*b,d*]pyran-2-yl]-phosphonic Acid Diethyl Ester (**28**).

To a solution of 2.90 g (4.93 mmoles) of ketal **24** in 75 ml of tetrahydrofuran was added 50 ml of 1*N* hydrochloric acid. The reaction mixture was heated at reflux for 1 hour. The cooled reaction was added to 200 ml of ether and 200 ml of saturated sodium bicarbonate. The organic extract was washed with 200 ml of saturated sodium chloride, dried over magnesium sulfate and evaporated to an oil. The crude oil was purified *via* column chromatography on 300 g of silica gel eluted with 2:1 ether:cyclohexane to give 2.7 g (100%) of **28**. Fractional crystallization of this material from ether-petroleum ether provided one diastereomer in pure form **28B**, mp 117-119°; ir: 3671, 1708, 1617 and 1577 cm^{-1}; pmr: (300 MHz) δ 1.07 (s, CH_3), 1.41 (s, CH_3), 2.35 (m, 1H), 2.55 (m, 2H), 2.73 (m, 1H), 3.79-4.1 (m, P-OCH_2),

4.29 (m, CH), 5.75 (d, J_{HP} = 6 Hz, ArH), 7.04-7.3 (m, PhH) and 11.81 (d, J_{HP} = 1.5 Hz, OH); ms: (m/e) 544 (M+), 398, 383, 341 and 91.

Anal. Calcd. for $C_{30}H_{41}O_7P$: C, 66.16; H, 7.59. Found: C, 65.90; H, 7.54.

(±)-[6aβ,7,8,9,10,10aα-Hexahydro-1,9β-dihydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b,d*]pyran-2-yl]-phosphonic Acid Diethyl Ester (**29B**).

To a −15° solution of 750 mg (1.38 mmoles) of ketone **28B** in 25 ml of methanol was added 52 mg (1.38 mmoles) of sodium borohydride. After 15 minutes the reaction was added to 200 ml of ether-200 ml of saturated sodium chloride. The organic extract was washed with 150 ml of saturated sodium chloride, dried over magnesium sulfate and evaporated to an oil. Crystallization of this oil from 1:1 ether-pentane gave a total of 516 mg (69%) of **29B**, mp 129-131°; ir: 3636, 3448, 3000, 1631 and 1585 cm^{-1}; pmr: (100 MHz) δ 1.08 (s, CH_3), 1.39 (s, CH_3), 3.49 (m, CH), 3.7-4.7 (m, P-OCH_2), 4.36 (m, CH), 5.76 (d, J_{HP} = 6 Hz, ArH), 7.1-7.5 (m, PhH) and 11.81 (d, J_{HP} = 1.5 Hz, OH); cmr: 164.0, 160.3, 159.6, 142.1, 128.3 (4C), 125.8, 104.7, 92.5, 89.0; 78.2, 73.2, 70.5, 62.2 (2C), 48.4, 39.1, 35.9, 35.7, 35.4, 33.1, 27.7, 27.0, 26.0, 19.4, 19.2 and 16.2 (2C); ms: (m/e) 546 (M+), 531, 528, 400, 385 and 382.

Anal. Calcd. for $C_{30}H_{43}O_7P$: C, 65.91; H, 7.93; P, 5.67. Found: C, 65.93; H, 7.81; P, 5.68.

(±)-[6aβ,7,8,9,10,10aα-Hexahydro-1,9β-dihydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b,d*]pyran-4-yl]-phosphonic Acid Diethyl Ester (**30B**).

To a −78° solution of 800 mg (1.2 mmoles) of bromide **41B** in 4 ml of tetrahydrofuran was added dropwise 0.52 ml (1.2 mmoles) of 2.3 M *n*-butyllithium in hexane. The reaction solution was stirred 1 hour longer at −78°. To this anion solution was added dropwise 217 mg (1.26 mmoles) of diethyl chlorophosphate. The reaction was stirred 5 minutes at −78° and then allowed to warm to 25°. The reaction was added to 150 ml of ether-150 ml of saturated sodium chloride. The ether extract was dried over magnesium sulfate and evaporated to a crude product. The product was purified *via* column chromatography on 30 g of silica gel eluted with 4% methanol-dichloromethane to yield 581 mg (67%) of *O,O*-dibenzyl **30B**; pmr: δ 1.05 (s, CH_3), 1.42 (s, CH_3), 3.9-4.4 (m, P-OCH_2), 4.40 (m, OCH_2Ph), 5.00 (s, OCH_2Ph), 6.00 (d, J_{HP} = 6 Hz, ArH) and 7.1-7.5 (m, PhH).

A solution of the above dibenzyl ether (540 mg, 0.744 mmoles) in 10 ml of methanol and 270 mg of 5% palladium on carbon (50% water) was stirred under 1 atmosphere of hydrogen for 4.5 hours. The reaction was filtered and the crude product, after evaporation, was purified *via* column chromatography on 12 g of silica gel eluted with 5% methanol-dichloromethane to give 250 mg (62%) of **30B**, mp 106-109° (chloroform); ir: 3030 (broad), 1579 and 1475 cm^{-1}; pmr: (100 MHz) δ 1.01 (s, CH_3), 3.4-3.9 (m, 3H), 3.9-4.4 (m, $POCH_2$ and CH), 5.90 (d, J_{HP} = 6 Hz, ArH), 7.1-7.4 (m, PhH) and 10.48 (s, OH); cmr: 162.1, 159.8, 159.1, 142.2, 128.3 (4C), 125.7, 104.5, 94.5, 94.0, 78.1, 73.3, 70.7, 61.7, 61.4, 47.4, 38.6 35.9 (2C), 35.0, 33.4, 27.2, 26.8, 26.1, 19.8, 18.8 and 16.4 (2C); hrms: (m/e) 546.2813 (M^+, 546.2748 Calcd. for $C_{30}H_{43}O_7P$), 427, 400, 385 and 91.

Anal. Calcd. for $C_{30}H_{43}O_7P$: C, 65.92; H, 7.93. Found: C, 65.96; H, 8.08.

(±)-6,6aα,7,8,10,10aα-Hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-9*H*-dibenzo[*b,d*]pyran-9-one (**32**).

A solution of 1.3 g (2.98 mmoles) of **23** in 50 ml of tetrahydrofuran and 25 ml of 1*N* hydrochloric acid was heated at reflux for 1 hour. The reaction was cooled and added to 200 ml of ether-100 ml of saturated sodium chloride. The ether extract was washed once with 100 ml of saturated sodium bicarbonate, dried over magnesium sulfate and evaporated to an oil. The crude oil was purified by column chromatography on 100 g of silica gel eluted with 2:1 ether; cyclohexane to yield 1.01 g (87%) of **32** as an oil; ir: 1718, 1626 and 1585 cm^{-1}; pmr: δ 1.25 (d, J = 6 Hz, side chain methyl), 1.47 and 1.67 (s, C-6 methyls), 4.30 (m, side chain methine), 6.30 (bs, C-4 ArH), 6.38 (dd, J = 8 and 2 Hz, C-2 ArH), 6.88 (d, J = 8 Hz, C-1 ArH) and 7.15 (s, PhH); hrms: (m/e) 392.2384 (M+, 392.2351 Calcd. for $C_{26}H_{32}O_3$), 247 and 231.

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22. Found: C, 79.37; H, 8.39.

(±)-6aβ,7,8,9,10,10aα-Hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b,d*]pyran-9β-ol (**33**) and the 9α Isomer.

To a 0° solution of 479 mg (1.22 mmoles) of **32** in 10 ml of ethanol was added 464 mg (12.2 mmoles) of sodium borohydride. The reaction mixture was stirred for 25 minutes and was then added to 200 ml of ether-100 ml of saturated sodium chloride solution. The ether extract was separated, washed twice with 200 ml portions of saturated sodium chloride solution, dried over magnesium sulfate and evaporated to an oil. The oil was purified *via* column chromatography on 100 g of silica gel eluted with 2:1 ether:cyclohexane to yield in order of elution 9α-**33** (45 mg (9%), as an oil); ir: 3668, 3583, 3433, 1615 and 1576 cm^{-1}; pmr: δ 1.20 (s, C-6 methyl), 1.28 (d, J = 6 Hz, side chain methyl), 4.35 (m, C-9 methyl), 4.35 (m, C-9 methine and side chain methine), 6.38 (bs, C-4 ArH), 6.48 (dd, J = 8 and 2 Hz, C-2 ArH), 7.10 (d, J = 8 Hz, C-1 methyl) and 7.28 (s, PhH); hrms: (m/e) 394.2435 (M+, 394.2508 Calcd. for $C_{26}H_{34}O_3$), 248, 230, 215 and 187.

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 78.77; H, 8.57.

Fifteen mg (3%) of mixed fractions and **33** (417 mg (37%) was obtained as an oil); ir: 3559, 3413, 1623 and 1580 cm^{-1}; pmr: δ 1.15 (s, C-6 methyl), 1.28 (d, J = 6 Hz, side chain methyl), 1.42 (s, C-6 methyl), 3.85 (bm, C-9 methine), 4.35 (m, side chain methine), 6.42 (bs, C-4 ArH), 6.50 (dd, J = 8 and 2 Hz, C-2 ArH), 7.13 (d, J = 8 Hz, C-1 ArH) and 7.28 (s, PhH); hrms: (m/e) 394.2484 (M+, 394.2508 Calcd. for $C_{26}H_{34}O_3$), 379, 248, 288 and 230.

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 79.22; H, 8.79.

2,3-Dihydro-2,2-dimethyl-5-hydroxy-7-(1-methyl-4-phenylbutoxy)-4*H*-1-benzopyran-4-one (**35**).

A mixture of 308 g (1.48 moles) of 2,3-dihydro-2,2-dimethyl-5,7-dihydroxy-4*H*-1-benzopyran-4-one (**34**) [19], 394 g (1.63 moles) of 1-methyl-4-phenylbutyl methanesulfonate (**4**) and 409 g (2.96 moles) of anhydrous potassium carbonate in 1.5 liters of dimethylformamide was heated at 80° for 4 hours. An additional 100 g (0.724 moles) of anhydrous potassium carbonate and 100 g (0.413 mole) of **4** were added and heating at 80° continued for 4 hours. Another 50 g (0.362 mole) portion of anhydrous potassium carbonate was added and heating continued for 15 hours. The reaction mixture was cooled in ice and added to 8 liters cold water. The quenched reaction was extracted with three 1 liter portions of ether. The combined ether extract was washed four times with 300 ml portions of water, washed once with 1 liter of saturated sodium chloride, dried over magnesium sulfate and evaporated

to an oil. Crystallization of this oil from hexane gave 216 g (41%) of **35**. Column chromatography of the mother liquor on 1.3 kilograms of silica gel eluted with 33% dichloromethane-hexane and crystallization from hexane gave another 116 g (22%) of **35**, mp 84-86°; ir: 1624 and 1566 cm^{-1}; pmr: δ 1.3 (d, J = 7 H_2, CH_3), 1.3-2.0 (m, 2 CH_2), 1.5 (s, diCH_3), 2.7 (s, CH_2), 2.5-2.9 (m, CH_2), 4.1-4.7 (m, CH), 5.9-6.1 (m, 2 ArH), 7.1-7.5 (m, 5 ArH) and 12.2 (s, OH); ms: (m/e) 354 (M+).

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.68; H, 7.46.

2,3-Dihydro-2,2-dimethyl-5-hydroxy-3-(3-oxobutyl)-7-(1-methyl-4-phenylbutoxy)-4*H*-1-benzopyran-4-one (**36**).

A solution of 332 g (0.937 mole) of **35** and 1.16 liters (11.7 moles) of ethyl formate in 900 ml of ether was added dropwise (to control hydrogen evolution) over 2.25 hours to a slurry of 112 g (4.67 moles) of sodium hydride in 1.8 liters of ether. The reaction mixture was stirred 18 hours longer and then added to ice water while being acidified with concentrated hydrochloric acid. The quenched reaction was extracted twice with ether. The combined ether extract was washed with water, saturated sodium chloride, dried over magnesium sulfate and evaporated to 362 g (101%) of 2,3-dihydro-5-hydroxy-3-(hydroxymethylene)-2,2-dimethyl-7-(1-methyl-4-phenylbutoxy)-4*H*-1-benzopyran-4-one as a viscous oil. This oil was used without further purification; pmr: δ 1.3 (d, J = 7 Hz, CH_3), 1.3-2.0 (m, 2 CH_2), 1.4 (s, 2CH_3), 2.3-2.8 (m, CH_2), 4.1-4.7 (m, CH), 5.8-6.0 (m, 2 Ar), 7.0-7.4 (m, 5 ArH and vinyl H), 10.0 (s, OH) and 13.3 (s, OH).

A solution of 358 g (0.937 mole) of the above viscous oil, 229 ml (2.80 moles) of methyl vinyl ketone and 35.7 ml (0.255 mole) of triethylamine in 1.5 liters of methanol was stirred at 25° for 20 hours. The reaction was cooled in ice and 1 liter of 10% potassium carbonate added followed by stirring at 0° for 2 hours. The reaction was added to 5 liters of water and acidified with concentrated hydrochloric acid. The quenched reaction was extracted twice with ether. The combined ether extract was washed with saturated sodium chloride, dried over magnesium sulfate and evaporated to give a quantitative yield of **36** as an oil. The oil was used without further purification; pmr: δ 1.35 (d, J = 7 Hz, CH_3), 1.47 (s, CH_3), 1.52 (s, CH_3), 2.20 (s, CH_3), 1.5-2.9 (series of m, 5 CH_2, CH), 4.42 (m, CH), 5.96 (d, J = 2 Hz, ArH), 6.02 (d, J = 2 Hz, ArH), 7.30 (s, 5 ArH) and 10.27 (2, OH).

Anal. Calcd. for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.59; H, 7.49.

(±)-6,6a,7,8-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-9*H*-dibenzo[*b,d*]pyran-9-one (**37**).

To a solution of 397 g (0.937 moles) of **36** in 1 liter of ethanol was added a warm solution of 112 g (2.0 mole) of potassium hydroxide in 1 liter of ethanol. The reaction was heated at reflux for 18 hours. (Note: methanol as the solvent in this cyclization gave poor results). The reaction was cooled, added to 6 liters of ice water and acidified with concentrated hydrochloric acid. The quenched reaction was extracted twice with ethyl acetate. The combined ethyl acetate extract was washed with saturated sodium chloride, dried over magnesium sulfate and evaporated to an oil. Crystallization from ether-pentane gave 204 g (54%) of **37**, mp 160-168°; ir: 1578 cm^{-1}; pmr: δ 1.3 (d, J = 7 Hz, CH_3), 1.1-2.3 (m, 15H), 2.3-3.0 (m, CH_2), 4.1-4.7 (m, CH), 5.95 (d, J = 2 Hz, ArH), 6.3 (d, J = 2 Hz, ArH), 7.2-7.4 (m, 5 ArH) and 8.0 (d, J = 2 Hz, vinyl H); ms: (m/e) 406 (M+).

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.74; H, 7.48.

(±)-6,6aβ,7,8,10,10aα-Hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-9*H*-dibenzo[*b,d*]pyran-9-one (**19**) and the 6aβ,10aβ Isomer (**38**).

A solution of 101 g (0.25 mole) of **37** in 900 ml of tetrahydrofuran was added dropwise to a −78° solution of 500 mg of lithium wire (0.02% sodium) in 1.5 liters of ammonia and 250 ml of tetrahydrofuran. Additional lithium wire was added during the addition to maintain a blue color [total lithium wire used was 4.28 g (0.638 mole)]. The reaction was quenched by addition of excess solid ammonium chloride and the ammonia then allowed to evaporate overnight. The resulting reaction mixture was added to 4 liters of ice water and extracted twice with 1.5 liter portions of ether. The combined ether extract was washed with saturated sodium chloride, dried over magnesium sulfate and evaporated. Crystallization in ethyl acetate-hexane gave 65.5 g (65%) of **19**. The mother liquor was purified *via* column chromatography on 750 g of silica gel eluting with 50% ether-hexane to give in order of elution 11.3 g (11%) of **19**, 8.2 g (8%) of the 6aβ,10aβ isomer **38** and 3.18 g (3%) of the over-reduced alcohol **39**. Compound **19** had mp 122-125°; ir (potassium bromide): 1709 cm^{-1}; pmr: δ 1.11 (s, CH_3), 1.24 (m, side chain CH_3), 1.45 (s, CH_3), 1.3-2.2 (m), 2.22 (m, 1H), 2.6 (m, 3H), 2.82 (m, 1H), 4.11 (bd, J = 14 Hz, C-10 H), 4.27 (m, side chain CH), 5.94 (d, J = 2 Hz, ArH), 6.06 (d, J = 2 Hz, ArH), 7.1-7.3 (m, 5 ArH), 7.98 and 8.00 (s, OHs, diasteromer ratio = 1:1).

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.22; H, 7.79.

6aβ,10aβ Isomer **38**.

This isomer had mp 141-142°; ir (potassium bromide): 1707 cm^{-1}; pmr: (300 MHz) δ 1.20 (d, J = 6 Hz, side chain CH_3), 1.31 (s, CH_3), 1.37 (s, CH_3), 1.4-1.9 (m, 5H), 2.1 (m, 2H), 2.3-2.5 (m, 2H), 2.6 (m, 2H), 2.85 (m, 1H), 3.45 (m, 2H), 4.2 (m, side chain CH), 5.89 (d, J = 2 Hz, ArH), 5.94 (d, J = 2 Hz, ArH), 7.1-7.2 (m, 5 ArH) and 7.28 (s, OH).

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.58; H, 7.92.

(±)-6aβ,7,8,9,10,10aα-Hexahydro-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b,d*]pyran-1,9β-diol (**39**) and Pure Diasteromers **39A** and **39B**.

Compound **39**.

To a −78° solution of 5.0 g (12.3 mmoles) of **19** in 150 ml of methanol and 25 ml of tetrahydrofuran was added 3.75 g (99.1 mmoles) of sodium borohydride. The mixture was then stirred for 18 hours at −78°. The reaction was warmed to 0-25° and concentration *in vacuo*. The residue was dissolved in ether and saturated sodium chloride. The ether layer was removed and washed with water, saturated sodium chloride, dried over magnesium sulfate and evaporated to give 4.70 g (94%) of **39** as a foam; ir: 3574, 3286, 1613 and 1580 cm^{-1}; pmr: (300 MHz, deuteriochloroform + D_6-DMSO): δ 1.21 (d, J = 7 Hz, CH_3), 1.22 (d, J = 7 Hz, CH_3), 1.31 (s, CH_3), 1.38 (s, CH_3), 1.5-1.95 (m, 3 CH_2), 2-2.22 (m, CH_2), 2.3-2.5 (m, CH_2), 2.60 (d, J = 7 Hz, CH_2), 2.94 (dd, J = 12 & 5 Hz, CH), 3.4-3.6 (m, 2 CH), 4.2 (m, CH), 5.89 (d, J = 2 Hz, ArH), 5.97 (d, J = 2 Hz, ArH), 7.14 (m, 3 ArH), 7.23 (m, 2 ArH) and 7.59 (d, J = 7 Hz, OH); ms: (m/e) 410 (M+).

Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 75.96; H, 8.50.

Compound **39A**.

A mixture of 1.00 g (1.49 mmoles) of **41A** and 1.0 g of 5% palladium on carbon (50% water) in 20 ml of tetrahydrofuran and 20 ml of methanol was stirred under hydrogen (1 atmosphere) for 4 hours. The reaction mixture was filtered through magnesium sulfate and evaporated to an oil. Crystallization of this oil from dichloromethane-ether gave 399 mg (55%) of **39A**, mp 210-212°; ir: (potassium bromide) 1626, 1595, 1520 and 1502 cm^{-1}; pmr (deuteriochloroform + D_6-DMSO): δ 1.03 (s, CH_3), 1.25 (d, J = 6 Hz, CH_3), 1.37 (s, CH_3), 4.18 (bm, CH), 5.76 (d, J = 2 Hz, ArH), 5.90 (d, J = 2 Hz, ArH) and 7.12 (s, 5 ArH); hrms: (m/e) 410.2503 (M+; 410.2457 Calcd. for $C_{26}H_{34}O_4$), 264, 246, 223, 139 and 91.

Anal. Calcd. for $C_{26}H_{34}O_4 \cdot \frac{1}{4}H_2O$: C 74.43; H, 8.41. Found: C, 74.51; H, 8.11.

Compound **39B**.

This procedure was performed as above for **41A** using 1.00 g (1.49 mmoles) of **41B** to give after crystallization from dichloromethane-pentane 270 mg (44%) of **39B**, mp 85-88°; ir: (potassium bromide): 1613, 1580 and 1502 cm^{-1}; pmr: δ 1.02 (s, CH_3), 1.20 (d, J = 7 Hz, CH_3), 1.32 (s, CH_3), 4.2 (m, CH), 5.78 (d, J = 2 Hz, ArH), 5.87 (d, J = 2 Hz, ArH) and 7.15 (bs, 5 ArH); hrms: (m/e) 410.2495 (M+; 410.2457 Calcd. for $C_{26}H_{34}O_4$), 264, 246, 223, 139 and 91.

Anal. Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.35. Found: C, 75.86; H, 8.26.

(±)-6aβ,7,8,9,10,10aα-Hexahydro-6,6-dimethyl-1,9-di-(phenylmethoxy)-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo[*b*,*d*]pyran (**40**).

To a slurry of 1.13 g (28.2 mmoles) of potassium hydride in 10 ml of dimethylformamide was added dropwise a solution of 4.60 g (11.2 mmoles) of **39** (mixture of diastereomers). After the addition was complete the reaction was allowed to stir at 25° for 30 minutes. The reaction was again cooled to 0° and 3.84 g (22.5 mmoles) of benzyl bromide was slowly added. The reaction was then stirred 9 hours at 25°. The reaction was added to saturated sodium chloride and the quench extacted twice with ether. The

Table II. Single Crystal X-Ray Crystallographic Analysis of **28B** and **41B**

A. Crystal Parameters	**28B**	**41B**
formula	$C_{30}H_{41}O_7P$ (544.7)	$C_{40}H_{45}O_4Br$ (669.7)
crystallization medium	acetone and heptane	acetone
crystal, size, mm	0.14 x 0.15 x 0.19	0.20 x 0.20 x 0.23
cell dimensions	a = 9.962 (3) Å	a = 15.598 (3) Å
	b = 12.037 (3) Å	b = 14.771 (3) Å
	c = 12.999 (3) Å	c = 16.252 (3) Å
	α = 86.54 (2) °	α = 90.0 °
	β = 77.83 (2) °	β = 110.65 (1) °
	γ = 85.04 (2) °	γ = 90.0 °
	V = 1516.6 (7) $Å^3$	V = 3503 (1) $Å^3$
space group	$P\bar{1}$	$P2_1/n$
molecules/unit cell	2	4
density obsd, g/cm^3	1.19	1.25
density calcd, g/cm^3	1.19	1.27
linear absorption factor, cm^{-1}	11.31	18.89
B. Refinement Parameters		
number of reflections	3066	3594
nonzero reflections ($I > 3.0\sigma$)	2302	3285
R-index = $\Sigma\|\|Fo\|-\|Fc\|\|/\Sigma\|Fo\|$	0.072	0.066
GOF = $[\Sigma w(Fo^2-Fc^2)^2/(m-s)]^{\frac{1}{2}}$	1.65	2.34
scale factor	1.729 (4)	1.523 (3)
secondary extinction factor	30 (8) x 10^{-4}	33 (6) x 10^{-4}

combined ether extract was dried over magnesium sulfate and evaporated to an oil. Purification by column chromatography on 300 g of silica gel eluted with 10% ether-hexane gave 5.0 g (76%) of **40** as an oil; pmr: δ 1.02 (s, CH_3), 1.16 (d, J = 7 Hz, CH_3), 1.32 (s, CH_3), ~1-2.9 (series of m), 3.4 (m, 2H), 4.18 and 4.40 (AB-d, J = 12 Hz, CH_2), 4.98 (s, CH_2), 6.0 (d, J = 2 Hz, ArH), 6.11 (d, J = 2 Hz, ArH) and 7.1-7.6 (m, 15 ArH).

Anal. Calcd. for $C_{40}H_{46}O_4$: C, 81.32; H, 7.85. Found: C, 81.47; H, 7.83.

(±)-6aβ,7,8,9,10,10aα-Hexahydro-4-bromo-6,6-dimethyl-1,9-di(phenylmethoxy)-3-(1-methyl-4-phenylbutoxy)-6*H*-dibenzo-[*b*,*d*]pyran (**41**) and Pure Diasteromers **41A** and **41B**.

To a 0° solution of 39.3 g (66.6 mmoles) of **40** in 240 ml of carbon tetrachloride was added 11.9 g (66.6 mmoles) of *N*-bromosuccinimide. The reaction mixture was then stirred 2 hours at 0° and allowed to warm to 25° while stirring overnight. The reaction was filtered and the filtrate evaporated to an oil. The crude product was purified *via* column chromatography on 1.35 kilograms of silica gel eluted with 20-55% dichloromethane-hexane to yield, in order of elution, after crystallization from hexane, 7.3 g (16%) of pure diasteromer **41A** and 7.47 g (17%) of pure diasteromer **41B**. In addition 27.4 g (62%) of a 1:1 mixture of diastereomers **A** and **B** was obtained and this mixture could be rechromatographed to again obtain pure **A** and **B**. Diastereomer **41A**, mp 129-132°; ir: 1600 and 1567 cm^{-1}; pmr: (100 MHz) δ 1.03 (s, CH_3), 1.30 (d, J = 6 Hz, CH_3), 1.46 (s, CH_3), 2.18 (bd, CH), 2.39 (dt, J = 11 & 3 Hz, CH), 2.63 (bt, J = 7 Hz, CH_2), 3.41 (m, CH), 3.52 (m, CH), 4.3 and 4.43 (AB-d, J = 12 Hz, CH_2), 5.00 (s, CH_2), 6.14 (s, ArH) and 7.1-7.5 (m, 15 ArH); ms: (m/e), 670, 668 (M+), 524 and 91.

Anal. Calcd. for $C_{40}H_{45}BrO_4$: C, 71.74; H, 6.78. Found: C, 71.74; H, 6.86.

Diastereomer **41B**.

This diastereoisomer had mp 132-133°; ir: 1597 and 1563 cm^{-1}; pmr: (100 MHz) δ 1.03 (s, CH_3), 1.26 (d, J = 6 Hz, CH_3), 1.46 (s, CH_3), 2.18 (bd, CH), 2.39 (dt, J = 11 & 3 Hz, CH), 2.66 (bt, J = 7 Hz, CH_2), 3.41 (m, CH), 3.52 (m, CH), 4.3 and 4.43 (AB-d, J = 12 Hz, CH_2), 4.99 (s, CH_2), 6.14 (s, ArH) and 7.1-7.5 (m, 15 ArH); ms: (m/e) 670, 668 (M+), 524 and 91.

Anal. Calcd. for $C_{40}H_{45}BrO_4$: C, 71.74; H, 6.78. Found: C, 71.57; H, 6.45.

Single Crystal X-Ray Analysis of **28B** and **41B**.

A representative crystal was surveyed and a 1 Å data set (maximum sin θ/λ = 0.5) was collected on a Nicolet R3m/μ diffractomer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography [20]. All crystallographic calculations were facilitated by the SHELXTL system [21]. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table II.

Trial structures were obtained by direct methods and they refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens, and in the case of **28B** the hydrogen on oxygen, were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-indices are summarized in Table II. Final difference Fourier revealed no missing or misplaced electron density.

The refined structures were plotted using the SHELXTL plotting package. Coordinates, distances and angles will be submitted to The Cambridge Crystallographic Data Center, Lensfield Road, Cambridge, CB2-1EW, England.

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