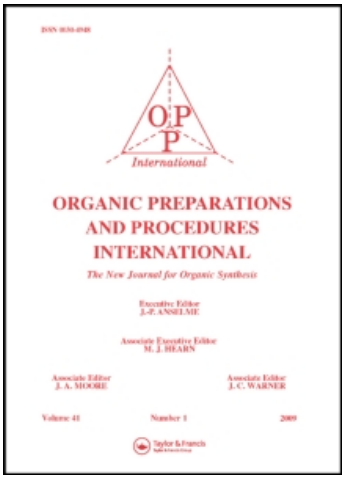


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF METHYL (*E*)-4-[2-(2,3-DIHYDRO-3-METHYL-3-HYDROXYMETHYLBENZO[*b*]THIEN-5-YL)-1-PROPENYL]BENZOATE [(*E*)-3], METHYL (E)-4-[2-(2,3-DIHYDRO-3-METHYL-3-HYDROXYMETHYL-5-BENZOFURANYL)-1-PROPENYL] BENZOATE [(*E*)-4], AND METHYL (*E*)-4-[2-(2,3-DIHYDRO-3,3-DIMETHYL-5-BENZOFURANYL)-3-HYDROXY-1-PROPENYL]BENZOATE [(*E*)-7] AS POTENTIAL METABOLITES OF SELECTED HETEROAROTINOIDS WITH FUSED FIVE-MEMBERED RINGS

Jonathan B. Gale[a]; Jozef Klucik[a]; Shankar Subramanian[a]; K. Darrell Berlin[a]
[a] Department of Chemistry, Oklahoma State University, Stillwater, OK

To cite this Article Gale, Jonathan B. , Klucik, Jozef , Subramanian, Shankar and Berlin, K. Darrell(2001) 'SYNTHESIS OF METHYL (*E*)-4-[2-(2,3-DIHYDRO-3-METHYL-3-HYDROXYMETHYLBENZO[*b*]THIEN-5-YL)-1-PROPENYL]BENZOATE [(*E*)-3], METHYL (E)-4-[2-(2,3-DIHYDRO-3-METHYL-3-HYDROXYMETHYL-5-BENZOFURANYL)-1-PROPENYL] BENZOATE [(*E*)-4], AND METHYL (*E*)-4-[2-(2,3-DIHYDRO-3,3-DIMETHYL-5-BENZOFURANYL)-3-HYDROXY-1-PROPENYL]BENZOATE [(*E*)-7] AS POTENTIAL METABOLITES OF SELECTED HETEROAROTINOIDS WITH FUSED FIVE-MEMBERED RINGS', Organic Preparations and Procedures International, 33: 5, 487 — 499
To link to this Article: DOI: 10.1080/00304940109356616
URL: http://dx.doi.org/10.1080/00304940109356616

SYNTHESIS OF METHYL (*E*)-4-[2-(2,3-DIHYDRO-3-METHYL-3-HYDROXYMETHYL-BENZO[*b*]THIEN-5-YL)-1-PROPENYL]BENZOATE [(*E*)-3], METHYL (*E*)-4-[2-(2,3-DIHYDRO-3-METHYL-3-HYDROXYMETHYL-5-BENZOFURANYL)-1-PROPENYL] BENZOATE [(*E*)-4], AND METHYL (*E*)-4-[2-(2,3-DIHYDRO-3,3-DIMETHYL-5-BENZOFURANYL)-3-HYDROXY-1-PROPENYL]BENZOATE [(*E*)-7] AS POTENTIAL METABOLITES OF SELECTED HETEROAROTINOIDS WITH FUSED FIVE-MEMBERED RINGS

Jonathan B. Gale, Jozef Klucik, Shankar Subramanian, and K. Darrell Berlin*

Department of Chemistry, Oklahoma State University, Stillwater, OK 74078

The chemistry and biology of natural retinoids such as, **I** and **II**, are highly active areas for cancer research.[1] Heteroarotinoids **1-5** are a family of synthetic heterocycles which contain at least one aryl ring commonly fused to a five- or six-membered ring which possess a heteroatom and are structurally-related to endogenous retinoids, usually *trans*-retinoic acid (*t*-RA, **I**) or a derivative thereof such as 13-*cis*-retinoic acid (13-*c*-RA, **II**).[2] Heteroarotinoids[3] with fused five-membered and

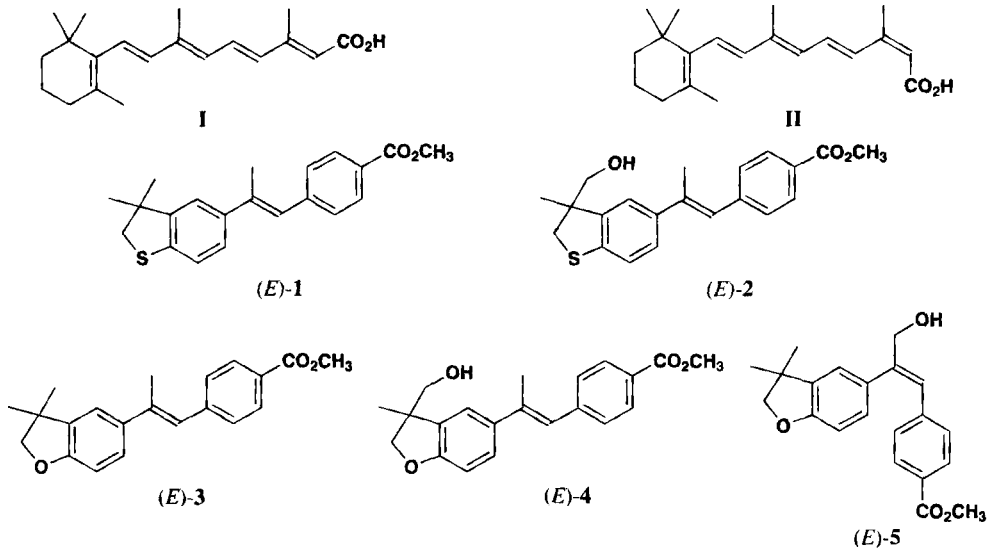
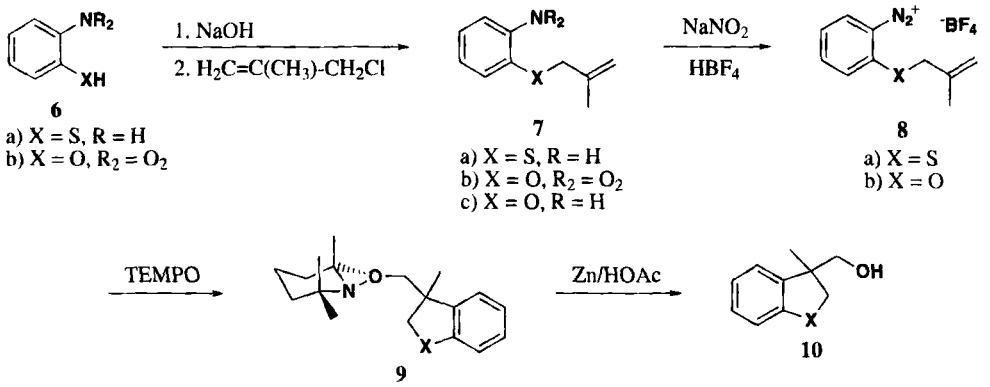


Figure 1

six-membered ring systems[2,3] have exhibited strong biological activity. Heterocycles with a second aryl ring (like **1-4**) closely resemble 13-*c*-RA (**II**) since they possess a *cisoid* arrangement of the double bonds in the second aryl ring at the end of the side chain. Because of our need for standards for examining metabolic mixtures from animals for the title compounds and in view of the finding that the metabolism of *t*-RA (**I**) in humans and rats produced a variety of oxygenated derivatives of **I**,[4] including the hydroxylation product resulting from oxidation of one of the geminal dimethyl groups, we report herein the first syntheses of possible metabolites (*E*)-**2** and (*E*)-**4** as potentially derivable from (*E*)-**1** and (*E*)-**3**, respectively. Compound (*E*)-**5**, related to (*E*)-**4**, was also prepared since **1** has been reported to undergo isomerization[5] *in vivo* to derivatives (including **II**), a situation conceivable for (*E*)-**5** *via* conversion *in vivo* of (*E*)-**3** to (*Z*)-**5**. Epoxidation of **I** also occurs *in vivo* at the ring double bond,[1] but the process is blocked in (*E*)-**1**, (*E*)-**2**, (*E*)-**3**, (*E*)-**4**, and (*E*)-**5**.

To the sodium salt of **6a** (*Scheme 1*), prepared in situ, was added a small excess of freshly distilled α-methallyl chloride. After heating (100°, 2 h), the mixture was cooled, decomposed, and evaporated to an oil which, upon distillation, afforded **7a** as a colorless oil. Immediate diazotization of

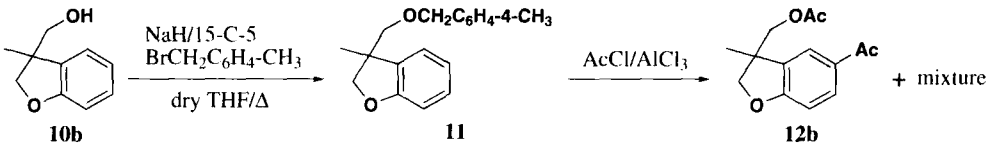


Scheme 1

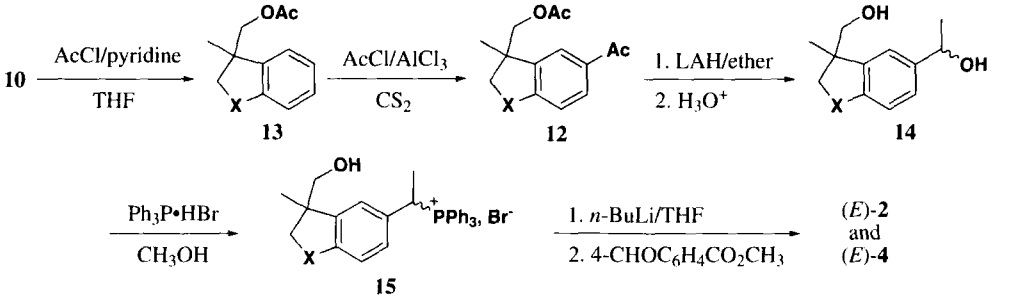
7a with HBF_4 gave salt **8a** as yellow crystals. Cycloalkylation of **8a** with 2.4 equivalents of TEMPO [2,2,6,6-tetramethyl-1-piperidinyoxy free radical] in freshly distilled and deoxygenated acetone gave **9a** (purified by chromatography) as a yellow oil. Reductive cleavage of **9a** with Zn/HOAc at 70° gave **10a** (61%).

o-Nitrophenol (**6b**, X = O) was converted to **7b** as above. The ether **7b** was reduced to **7c** by $SnCl_2$/HCl. The remaining procedure for **7c** to **8b** partially paralleled that used for **7a** to **8a**. Diazotization of **8b**, followed by treatment with TEMPO, gave **9b** as an oil. Reductive cleavage of **9b** with Zn/HOAc produced **10b** as a low melting solid.

Since multiacetylations of **10a** and **10b** were possible, **10b** was converted to the protected ether **11**. Acetylation of **11** with AcCl/$AlCl_3$ resulted in the generation of a mixture (which included the diacetylated **12b**) which could not be purified by chromatography. Subsequently, **10a** and **10b** were esterified to **13a** (92%) and **13b** (86%), respectively, which were in turn acetylated with acetyl



chloride in $CS_2/AlCl_3$ to give **12a** and **12b** (*Scheme 2*). Reduction of **12a** and **12b** with $LiAlH_4$ gave the diols **14a** and **14b** in essentially quantitative yields (the ratio of diastereomeric isomers in each case was near unity *via* proton NMR analysis). Treatment of **14a** and **14b** with Ph_3P•HBr proceeded regiospecifically and in near quantitative fashion to provide salts **15a** and **15b**, respectively. Addition of methyl 4-formylbenzoate to the ylids obtained from **15a** and/or **15b** (by treatment with *n*-butyllithium (THF/hexane, –84°) gave a mixture of (*E*)-**2** and (*Z*)-**2** and/or (*E*)-**4** and (*Z*)-**4**. Purification of these products required repeated chromatography.



Scheme 2

Since isomerization of retinoids is known to occur *in vivo*,[5] the preparation of (*E*)-**5** was initiated from (*E*)-**3**. Oxidation of the allylic methyl group in (*E*)-**3** with SeO_2 in hot ethanol gave a mixture of (*E*)-**5** and (*Z*)-**5** from which (*E*)-**5** could be purified *via* repeated chromatography. The structure of (*E*)-**5** (note the configurational arrangement is an *E* assignment in spite of the larger groups being in a *cis* relationship around the double bond) was confirmed by spectral analysis and elemental analyses. All oxidative methods employed with the sulfur analog (*E*)-**1** were unsuccessful in providing a sulfur-containing counterpart of (*E*)-**5**, with only very complex mixtures being formed. The sensitivity of sulfur to oxidants is also reflected in a lower yield of **9a** compared to **9b**.

Heteroarotinoids (*E*)-**2**, (*E*)-**4**, and (*E*)-**5** are the first examples of potential metabolites conceivable and reasonable from the metabolism of the five-membered ring systems (*E*)-**1** and (*E*)-**3**. One report[6] of the synthesis of potential metabolites from certain fused six-membered heteroarotinoids has appeared, and some structures have been verified as being formed in rats.[7]

EXPERIMENTAL SECTION

IR spectra were recorded on a Perkin-Elmer 681 unit. All NMR spectra were recorded and registered as δ or ppm values from TMS using either a Varian 300 MHz or Varian 400 MHz spectrometer with ^1H spectra taken at 299.94 MHz or 399.95 MHz, respectively. All ^{13}C NMR spectra were taken at

75.43 MHz or 100.6 MHz, respectively. All elemental analyses were obtained by Atlantic Microlab, Inc, Norcross, GA. Compounds (*E*)-**1**[3c] and (*E*)-**3**[3a] have been reported. All chromatographic separations employed silica gel (Baker, 40μ, 60 Å, flash). Storage of all compounds in the cold/dark minimized decomposition.

2-[(2-Methyl-2-propenyl)thio]benzamine (7a).- To a warm (~40°) mixture of 2-aminothiophenol (**6a**, 19.00 g, 0.152 mol) and aqueous NaOH (6.33 g, 0.158 mol) in water (17 mL) was added dropwise distilled α-methallyl chloride (15.20 g, 0.168 mol) under N_2. After the mixture was heated (100°, 2 h) and allowed to cool to RT, water (50 mL) and ether (100 mL) were added to generate two layers. Extracts (ether, 3 x 50 mL) of the aqueous layer were combined with the original ether layer and were washed with 9% aqueous NaOH and saturated brine and then dried (Na_2SO_4). Evaporation of the solvent and vacuum distillation of the oil gave **7a** (22.7 g, 83.4%) as an oil, bp 91-93°/0.5 mm. IR (neat) 3457, 3360 (N-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.85 [m, 3 H], 3.33 [d, J = 0.9 Hz, 2 H], 4.33 [s, 2 H], 4.62 [m, 1 H], 4.72 [m, 1 H], 6.66 [m, 1 H], 6.71 [m, 1 H], 7.10 [m, 1 H], 7.31 [m, 1 H]; ^{13}C NMR ($DCCl_3$): δ 21.0, 42.3, 113.9, 114.8, 117.8, 118.3, 129.7, 136.2, 141.1, 148.2. The oil **7a** was air sensitive and was used immediately to prepare **8a**.

2-[(2-Methyl-2-propenyl)oxy]nitrobenzene (7b).- To a slightly warmed solution of 2-nitrophenol (**6b**, 30.00 g, 0.216 mol) and aqueous NaOH (8.65, g, 0.216 mol) in water (60 mL) was slowly added freshly distilled α-methylallyl chloride (25.50 g, 0.282 mol), the system being heated such that the reaction mixture began to boil at the end of the addition. After being heated (~84°, 4 h), the mixture was allowed to cool to RT. Extracts (ether, 4 x 50 mL) of the aqueous mixture were combined, washed with 10% NaOH (2 x 50 mL), and saturated brine (50 mL) and then were dried (Na_2SO_4). Filtration of the solution, evaporation of the solvent, and distillation of the residual oil gave **7b** (23.2 g, 56%), bp 106-111°/0.18 mm. IR (neat) 1525, 1353 (NO_2) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.83 [m, 3 H], 4.55 [s, 2 H], 5.01 [m, 1 H], 5.15 [m, 1 H], 7.00 [m, 1 H], 7.07 [m, 1 H], 7.50 [m, 1 H], 7.81 [m, 1 H]; ^{13}C NMR ($DCCl_3$): δ 19.2, 72.7, 113.4, 114.7, 120.4, 125.5, 134.1, 139.5, 139.9, 151.9. The oil **7b** was air sensitive and was used immediately to prepare **7c**.

2-[(2-Methyl-2-propenyl)oxy]benzamine (7c).- A chilled (ice-water bath) solution of **6b** (30.00 g, 0.155 mol) in absolute ethanol (75 mL) and chilled (ice) conc HCl (145 mL) were mixed. To this chilled solution was added dropwise a solution of $SnCl_2$•2 H_2O (108.0 g, 0.479 mol) in absolute ethanol (145 mL) with stirring over 0.5 h. The resulting mixture was stirred at RT (18 h), with the temperature being maintained below 30° during the first 0.75 h at which time the reaction was exothermic. The reaction mixture was partitioned between H_2O (500 mL) and $HCCl_3$ (300 mL) and resulted in two layers. Extracts (water, 2 x 100 mL) of the organic layer and the original water layer were combined, and $HCCl_3$ (300 mL) was added. The resulting mixture was cooled (0°) and then treated dropwise with 58% aqueous H_4NOH (~200 mL) which produced an emulsion. The two layers were separated as much as possible, and the aqueous layer was again treated with 58% H_4NOH (~20 mL). Brine was added to the aqueous emulsion, and the resulting solution was extracted ($HCCl_3$, 2 x 150 mL). These extracts were combined with the original organic layer, dried (Na_2SO_4), filtered, and

evaporated to an oil. Distillation afforded **7c** (15.27 g, 60%) as a pale yellow oil, bp 80.7-90.1°/0.17 mm [*lit.*[10] bp 105-110°/0.5 mm]. Reported[10] spectral data were modest. IR (neat) 3468, 3376 (N-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.81 [m, 3 H], 3.75 [s, 2 H], 4.41 [s, 2 H], 4.96 [m, 1 H], 5.07 [s, 1 H], 6.63-6.80 [m, 4 H]; ^{13}C NMR ($DCCl_3$): δ 19.4, 71.9, 111.9, 112.5, 115.1, 118.3, 121.3, 136.4, 141.0, 146.3. The oil **7c** was air sensitive and was used immediately to prepare **8b**.

2-[(2-Methyl-2-propenyl)thio]benzenediazonium Fluoroborate (8a).- To a stirred, cooled (ice bath) solution of amine **7a** (1.74 g, 9.70 mmol) in 21% HBF_4 [48% HBF_4 (3.1 g) in H_2O (5.3 mL)] was added a chilled (0°) solution of $NaNO_2$ (0.67 g, 9.7 mmol) in H_2O (1.7 mL). After stirring at 0° (5 min), the mixture was cooled in a dry ice-CCl_4 bath (~ -20°) for 5 min. Filtration of the mixture through a chilled sintered glass funnel gave a yellow solid. The solid was washed with 5% HBF_4 (15 mL, chilled) and water (2 x 10 mL, chilled), dried, and recrystallized as follows. To a solution of the solid in dry acetone (35 mL) was slowly added dry ether (100 mL). Crystals formed, were filtered, washed (dry ether), and recrystallized again in the same manner. The final solid **8a** (2.05 g, 76%) was dried and had a mp of 91°. IR (KBr) 2260 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.92 [s, 3 H], 3.81 [m, 2 H], 4.96 [m, 1 H], 5.05 [m, 1 H], 7.67-7.79 [m, 2 H], 7.99-8.06 [m, 1 H], 8.83-8.89 [m, 1 H]. The sample of **8a** appeared to be air sensitive and was used without further purification to prepare **9a**.

2-[(2-Methyl-2-propenyl)oxy]benzenediazonium Fluoroborate (8b).- Amine **7c** (8.45 g, 51.8 mmol) and a solution of HBF_4 (21%, 47 mL) were individually chilled (0°) and mixed. To the new chilled (0°) solution was added dropwise a cold solution of $NaNO_2$ (3.58 g, 51.9 mmol) in H_2O (7.6 mL) over 5 min. The resulting mixture contained a solid, and the entire mixture was cooled (dry ice-CCl_4, ~-20°) for 2 min and then filtered through a chilled, sintered glass funnel. The solid was washed with cold, aqueous 5% HBF_4 and finally with cold distilled water. The slightly colored (grey) solid was dried at RT (0.15-1 mm) for 5 h. A solution of the dried solid in acetone (42 mL) was treated slowly with dry ether (175 mL) which induced precipitation. The solid was collected, and the purification process was repeated. Drying the final solid under vacuum for 0.25 h gave **8b** (9.15 g, 67%) as a very light tan, crystalline solid, mp 99.0-100.2° (sl dec). IR (KBr) 2275 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.89 [s, 3 H], 4.85 [s, 2 H], 5.18 [s, 2 H], 7.30 [m, 1 H], 7.36 [m, 1 H], 8.05 [m, 1 H], 8.64 [m, 1 H]. Salt **8b** appeared air sensitive and used immediately to prepare **9b**.

1-[2,3-Dihydro-3-methylbenzo[*b*]thien-3-yl)methoxy]-2,2,6,6-tetramethylpiperidine (9a).- To a solution of TEMPO (2.70 g, 17.3 mmol) in dry, deoxygenated acetone (145 mL) was added **8a** (2.00 g, 7.19 mmol) all at once. The resulting reddish-brown mixture was heated at reflux (0.75 h), and then the warm mixture was evaporated to near dryness. Extracts (hexanes:ether, 1:1, 3 x 30 mL; this was followed by hexanes:acetone, 4;1, 50 mL) of the mixture were combined, filtered,and concentrated (~ 30 mL). Dilution (hexanes, 50 mL) of this solution induced a very small amount of precipitation, and thus the solution was filtered and evaporated to an oil. Two separate chromatographic separations (hexanes:ether, 40:1) led to **9a** (0.44 g, 19%) as a light yellow oil. IR (neat) 1374, 1361 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.0-1.6 [m, 21 H], 3.14 [d, J = 11.1 Hz, 1 H], 3.47 [d, J = 11.1 Hz, 1 h], 3.73 [d, J = 8.2 Hz, 1 H], 3.83 [d, J = 8.2 Hz, 1 H], 7.0-7.32 [m, 2 H]. This oil **9a** appeared somewhat air sensitive and

used immediately to prepare **10a**.

1-[(2,3-Dihydro-3-methyl-3-benzofuranyl)methoxy]-2,2,6,6-tetramethylpiperidine (9b).-To a solution of TEMPO (11.35 g, 72.6 mmol) in dry, freshly distilled and degassed acetone (600 mL) was added over 0.25 h a solution of **8b** (9.10 g, 34.7 mmol) in degassed acetone (45 mL). The solution was boiled (1.5 h), and then the solvent was removed immediately while hot to yield a residue. Dry ether (65 mL) and hexanes (130 mL) were added to the residue, and the resulting mixture was swirled for several minutes after which time the supernatant liquid was decanted from the solid residue and filtered. The new residue was extracted (hexanes 2 x 25 mL), and the extracts were filtered, combined with the previous filtrate, and concentrated to a brown oil. Chromatography of a solution of the oil in minimum hexanes, followed by elution with hexanes:ethyl acetate (10:1, 750 ml, and 5:1, 60 mL), gave solutions which, when evaporated, gave an oil. Repeated chromatography using the same conditions as outlined above led to an oil **9b** (6.61 g, 63%), $n^{22.3}$ = 1.5148. IR (neat) 1376, 1362 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.0-1.6 [m, 21 H], 3.81 [s, 2 H], 4.15 [d, *J* = 8.7 Hz, 1 H], 4.54 [d, *J* = 8.7 Hz, 1 H], 6.78 [m, 1 H], 6.82-6.89 [m, 1 H], 7.08-7.19 [m, 2 H]; ^{13}C NMR ($DCCl_3$): δ 17.0, 20.1, 20.2, 22.7, 32.9, 33.2, 39.7, 46.4, 60.0, 60.1, 80.7, 81.5, 109.5, 120.2, 123.6, 128.3, 132.9, 159.7. Oil **9b** was air sensitive and was used at once to prepare **10b**.

2,3-Dihydro-3-methyl-3-benzo[*b*]thienmethanol (10a).- A mixture of **9a** (5.64 g, 17.7 mmol), acetic acid:water (1:2, 52 mL), and zinc powder (4.90 g, 0.074 g atom) was heated and stirred under N_2 at 68-70° for 18 h. Additional zinc powder was added after 6 h and after 12 h [4.90 g (0.074 g atom) added each time]. Additional acetic acid:water (1:2, 10 mL each time) was added at the same times as was the zinc powder. After 12 h, the mixture was allowed to cool, was filtered, and was then transferred to a stirred, two-phase mixture of ether (150 mL) and 20% aqueous Na_2CO_3 (150 mL). Upon termination of the evolution of CO_2, the mixture was extracted (ether, 3 x 75 mL). The combined organic phases were washed with brine, 2% HCl, and 5% $NaHCO_3$. After drying (Na_2SO_4), the solvent was evaporated to an oil which was treated with hexanes (10 mL). Upon standing in a freezer overnight, crystals formed and were filtered off and washed with cold hexanes. Removal of traces of the solvent gave pale yellow crystals of **10a** (1.93 g, 60%), mp 63.9-66.0° [*lit.*[9] 62-64.5°]. Although reported,[9] the spectral analyses were very modest. IR (KBr) 3600-3100 (O-H) cm^{-1}. ^1H NMR ($DCCl_3$): δ 1.40 [s, 3 H], 1.58 [m, 1 H], 3.15 [d, *J* = 11.2 Hz, 1 H], 3.44 [d, *J* = 11.2 Hz, 1 H], 3.55 [d, *J* = 11.2 Hz, 1 H], 3.72 [d, *J* = 11.2 Hz, 1 H], 7.03-7.25 [m, 4 H]; ^{13}C NMR ($DCCl_3$): δ 22.4, 41.7, 52.7, 67.7, 122.6, 123.7, 124.4, 128.1, 142.0, 143.4.

2,3-Dihydro-3-methyl-3-benzofuranmethanol (10b).- In a like manner as for **10a**, a mixture of **9b** (6.20 g, 20.4 mmol), acetic acid:water (1:2, 60 mL), and zinc powder (5.65 g, 86.4 g atom) was heated at 68-70° (12 h). The remainder of the procedure was identical to that for **10a**. Recrystallization (hexanes), followed by two washes with cold hexanes, of the solid obtained and drying under vacuum gave **10b** as a creamy-white solid (2.25 g, 67%), mp 59.6-60.6° [*lit.*[9] 58°]. Reported[9] spectral analyses were modest. IR (KBr) 3600-3000 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.36 [s, 3 H], 1.62 [bs, 1 H], 3.55 [d, *J* = 10.7 Hz, 1 H], 3.65 [d, *J* = 10.7 Hz, 1 H], 4.17 [d, *J* = 8.8 Hz, 1 H], 4.56 [d, *J* = 8.8 Hz, 1 H],

6.81 [m, 1 H], 6.89 [m, 1 H], 7.11 [m, 1 H], 7.16 [m, 1 H]; ^{13}C NMR ($DCCl_3$): δ 21.9, 47.6, 69.0, 80.1, 109.0, 120.6, 123.1, 128.8, 131.8, 160.2.

2,3-Dihydro-3-methyl-3-[(4-xylyloxy)methyl]benzofuran (11).- A solution of **10b** (0.55 g, 3.3 mmol) and 15-C-5 (0.18 g, 0.82 mmol) in dry THF (8 mL) was added to solid NaH (0.12 g, 5.0 mmol), and the mixture was stirred (0.25 h, RT). To this mixture was added dropwise α-bromo-*p*-xylene (0.75 g, 4.0 mmol) in dry THF (7 mL), and the resulting mixture was heated at reflux (6 h) and then allowed to cool to RT. Dilution (dry ether, 25 mL) of the reaction mixture and filtering gave a new solution which was evaporated to an oil. Dissolving the oil in hexanes:ether (4:1, 100 mL) gave a solution which was washed (H_2O, 3 x 50 mL), dried (Na_2SO_4), filtered, and evaporated to a new oil. Chromatography of this oil (hexanes:ether, 20:1 and 10:1) produced a large fraction containing **11** (0.52 g, 58%) as a colorless oil. IR (neat) 1099 (C-O) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.40 [s, 3 H], 2.32 [s, 3 H], 3.41 [s, 2 H], 4.13 [d, *J* = 8.8 Hz, 1 H], 4.45 [s, 2 H], 4.54 [d, *J* = 8.8 Hz, 1 H], 6.75-6.87 [m, 2 H], 7.05-7.19 [m, 6 H]; ^{13}C NMR ($DCCl_3$): δ 21.1, 22.6, 46.5, 73.2, 76.0, 80.7, 109.6, 120.3, 123.3,127.6, 128.4, 129.0, 132.8, 135.2, 137.2, 159.8. The oil **11** appeared unstable and was used at once to prepare **12b**.

Attempted Acetylation of 11.- To a stirred suspension of $AlCl_3$ (0.30 g, 2.25 mmol) in cooled (ice-water, 0°), freshly distilled CS_2 (2 mL) was added dropwise a solution of **11** (0.40 g, 1.49 mmol) in CS_2 (2 mL). The mixture was stirred (1 h), diluted (ether, 10 mL), and quenched cautiously (0°) with water (10 mL). Extracts (ether, 5 x 10 mL) of the aqueous phase were combined with the original organic layer, and the solution was dried (Na_2SO_4), filtered, and evaporated to an oil. Chromatography (hexanes:ether, 6:1, 4:1, 3:1, 2:1, and 3:2) led to the major components residing in the 2:1 and 3:2 fractions. Spectral analyses (IR and ^{1}H NMR) indicated the presence of considerable **12b** but heavily contaminated with many side products. All attempts to separate and purify **12b** by chromatography and/or recrystallizations were unsuccessful.

1-(3-Acetoxymethyl-2,3-dihydro-3-methylbenzo[*b*]thien-5-yl)ethanone (12a).- To a stirred and cooled (ice-water bath) suspension of $AlCl_3$ (2.25 g, 16.9 mmol) in distilled CS_2 (10 mL) was added slowly **13a** (1.40 g, 6.30 mmol), distilled acetyl chloride (1.2 g, 1.1 mL, 15 mmol), and CS_2 (9 mL) over 8 min. Stirring was continued at 0-8° (0.75 h) and at RT for an additional 40 min. During the latter time, additional $AlCl_3$ (0.5 g, 4 mmol) was added after 15 min and after 35 min along with acetyl chloride (0.44 g, 0.40 mL, 5.6 mmol after 0.25 h and 0.99 g, 0.90 mL, 13 mmol after 0.75 h, 1 h, and 1.25 h, respectively) being added also. Clumps of $AlCl_3$ formed in the reaction mixture and were fragmented by mechanical means. After 1.5 h, the reaction mixture was cooled (0°), diluted (ether, 25 mL), and quenched carefully with 5% HCl (~ 20 mL). Extracts (ether, 4 x 25 mL) of the aqueous layer were combined with the original organic layer and were washed with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL). After drying (Na_2SO_4), the solution was evaporated to an oil which was chromatographed (hexanes:ether, 4:1, 3:1, and 2:1). Keto-ester **12a** (1.42 g, 86%) was obtained as a light yellow oil in the 2:1 fractions. IR (neat) 1743 (C=O), 1682 (C=O) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.47 [s, 3 H], 2.06 [s, 3 H], 2.56 [s, 3 H], 3.22 [d, *J* =11.4 Hz, 1 H], 3.43 [d,

J = 11.4 Hz, 1 H], 4.12 [d, J = 11.1 Hz, 1 H], 4.16 [d, J = 11.1 Hz, 1 H], 7.26 [d, J = 8.1 Hz, 1 H], 7.68 [d, J = 1.6 Hz, 1 H], 7.77 [dd, J = 8.1 Hz, J = 1.6 Hz, 1 H]; ^{13}C NMR ($DCCl_3$): δ 20.9, 22.8, 26.5, 42.4, 50.4, 67.9, 122.2, 123.4, 129.2, 134.1, 143.7, 148.9, 170.8, 196.9. The keto-ester **12a** was used immediately to prepare **14a**.

Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. Found: C, 63.46; H, 6.45

1-(3-Acetoxymethyl-2,3-dihydro-3-methyl-5-benzofuranyl)ethanone (12b).- To a stirred and cooled (ice-water bath) suspension of $AlCl_3$ (2.25g, 16.9 mmol) in freshly distilled CS_2 (10 mL) was added dropwise **13b** (1.30 g, 6.30 mmol), distilled acetyl chloride (1.2 g, 1.1 mL, 15 mmol), and CS_2 (10 mL) over 0.25 h. The mixture was stirred at 0° for 1 h during which time additional quantities of $AlCl_3$ [0.8 g (6 mmol) after 0.25 h] and acetyl chloride [0.22 g (2.8 mmol) after 0.25 h and 0.5 h] were added. Fragmentation of the clumping $AlCl_3$ was done at various intervals during the reaction. After the 1 h, the mixture was diluted (ether, 40 mL) and quenched slowly with water (25 mL) at 0°. Extracts (ether, 4 x 25 mL) of the aqueous layer were combined with the original organic layer and were washed (5% $NaHCO_3$, 2 x 50 mL), dried (Na_2SO_4), and evaporated to an oil. Chromatography (hexanes:ether, 1:0, 4:1, 3:1, 2:1, 3:2) of the oil gave fractions containing **12b** which were combined and evaporated to give the keto-ester **12b** (1.37 g, 88%) as a colorless oil. IR (neat) 1745 (C=O), 1677 (C=O) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.44 [s, 3 H], 2.05 [s, 3 H], 2.56 [s, 3 H], 4.09 [d, J = 11.0 Hz, 1 H], 4.13 [d, J = 11.0 Hz, 1 H], 4.28 [d, J = 9 Hz, 1 H], 4.59 [d, J = 9 Hz, 1 H], 6.83 [m, 1 H], 7.81 [m, 1 H], 7,85 [m, 1 H]; ^{13}C NMR ($DCCl_3$): δ 20.8, 22.3, 26.4, 45.2, 69.4, 81.23, 109.5, 124.0, 131.0, 131.3, 132.4, 164.1 170.9, 196.4. Keto-ester **12b** was used at once to prepare **14b**.

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.63; H, 6.74

3-Acetoxymethyl-2,3-dihydro-3-methylbenzo[*b*]thiophene (13a).- To a stirred solution of acetyl chloride (1.60 g, 20.4 mmol) in dry ether (25 mL) cooled to (~ –45°, dry ice-CCl_4) was added dry pyridine (1.9 mL, 1.9 g, 24 mmol) all at once. After stirring for 0.25 h, a solution of **10a** (1.80 g, 9.99 mmol) in dry THF (15 mL) was added quickly. The cold bath was removed, and the resulting mixture was stirred at RT (14 h). The system was cooled (ice-water bath) again, and the mixture was diluted (ether, 35 mL) and stirred for 5 min. Water (25 mL) was added slowly, and two clear, colorless layers separated. Extracts (ether, 4 x 25 mL) of the aqueous layer were combined with the original organic layer, and the new solution was washed with 2% HCl (2 x 50 mL) and saturated $NaHCO_3$ (2 x 50 mL) and was then dried (Na_2SO_4). Filtration and evaporation of the solvent gave an oil which was chromatographed (hexanes:ether, 9:1, 8:1, 7:1, and 6:1). Fractions containing **13a** (2.0 g, 92%) were combined, and evaporated to a colorless oil. IR (neat) 1743 (C=O) cm^{-1}; ^{1}H NMR ($DCCl_3$): δ 1.42 [s, 3 H], 2.07 [s, 3 H], 3.15 [d, J = 11.3 Hz, 1 H], 3.37 [d, J = 11.3 Hz, 1 H], 4.10 [d, J = 11.0, 1 H], 4.14 [d, J = 11.0 Hz, 1 H], 7.05-7.25 [m, 4 H]; ^{13}C NMR ($DCCl_3$): δ 20.9, 22.5, 42.1, 50.7, 68.0, 122.6, 123.8, 124.5, 128.3, 141.4, 142.8, 171.0. Ester **13a** was used at once to obtain **12a**.

Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35. Found: C, 64.56; H, 6.43

3-Acetoxymethyl-2,3-dihydro-3-methylbenzofuran (13b).- To a cooled (dry ice-CCl_4, ~ -35°) solution of distilled acetyl chloride (2.0 mL, 2.8 g, 28 mmol) in dry ether (35 mL) was added dry pyridine

(2.6 mL, 2.5 g, 32 mmol). To this mixture (-30°) was added in one bolus **10b** (2.25 g, 13.7 mmol) dissolved in freshly distilled THF (15 mL). The cold bath was removed, and the mixture was stirred at RT for 8 h after which time the mixture was cooled (ice bath) and quenched with ether (25 mL) and water (25 mL). Stirring was initiated and continued until two layers clearly separated after which the organic layer was washed with water (3 x 25 mL). The organic solution was dried (Na_2SO_4), filtered, and concentrated to an oil. Chromatography of the oil (hexanes:ether, 9:10 followed by 6:1 and then 4:1) gave **13b** (2.43 g, 86%) as a colorless oil, n^{22} = 1.5149. IR (neat) 1749 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.40 [s, 3 H], 2.05 [s, 3 H], 4.09 [d, *J* = 11 Hz, 1 H], 4.13 [d, *J* = 11 Hz, 1 H], 4.17 [d, *J* = 9 Hz, 1 H], 4.49 [d, *J* = 9 Hz], 6.81 [m, 1 H], 6.89 [m, 1 H], 7.10-7.20 [m, 2 H]; ^{13}C NMR ($DCCl_3$): δ 20.8, 22.3, 45.6, 69.4, 80.2, 109.9, 120.7, 123.3, 128.9, 131.4, 159.8, 170.9. Ester **13b** was converted to **12b** at once.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.74

1-(2,3-Dihydro-3-methyl-3-hydroxymethylbenzo[*b*]thien-5-yl)ethanol (14a).- To a stirred suspension of $LiAlH_4$ (0.09 g, 2.4 mmol) in dry ether (2 mL) was added dropwise a solution of **12a** (0.21 g, 0.79 mmol) in dry ether (2 mL) over 2 min. The resulting mixture was stirred at mild reflux for 8 h and then was cooled to 0°. After dilution (ether, 2 mL), the reaction was quenched carefully with water (2 mL) and then with 5% HCl (4 mL, pH~4). The addition of ether (8 mL) caused two layers to form, and these were separated. Extracts (ether, 10 x 10mL) of the aqueous layer were combined with the original organic layer, washed with saturated $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered, and evaporated to an oil. The oil was stirred overnight with dry pentane which was then decanted to remove traces of ether. To remove traces of solvent, the resulting oil was subjected to high vacuum distillation (50-60°/0.3 mm) which gave **14a** (0.16 g, 90%; diastereomeric ratio was 1:1 by ^1H NMR-CH_3) as a yellow paste. IR (neat) 3700-3050 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.34 [s, 3 H], 1.42 [d, *J* = 6.4 Hz, 3 H], 1.43 [d, *J* = 6.4 Hz, 3 H], 2.6-3.1 [m, 2 H], 3.08 [d, *J* = 11.2 Hz, 1 H], 3.10 [d, *J* = 11.2 Hz, 1 H], 3.36 [d, *J* = 11.2 Hz, 1 H], 3.37 [d, *J* = 11.2 Hz, 1 H], 3.47 [d, *J* = 10.9 Hz, 1 H], 3.60 [d, *J* = 10.9 Hz, 1 H], 4.7-4.8 [m, 1 H], 7.0-7.2 [m, 3 H]; ^{13}C NMR ($DCCl_3$): δ 22.40, 22.40, 24.7, 25.1, 42.0, 52.5, 52.6, 67.3, 70.0, 70.1, 120.7, 11.6, 122.2, 122.4, 125.2, 125.8, 140.8, 140.9, 141.9, 142.0, 143.8, 144.0. This diastereomeric mixture of diols appeared air sensitive and was used at once to prepare **15a**.

1-(2,3-Dihydro-3-methyl-3-hydroxymethyl-5-benzofuranyl)ethanol (14b).- To a stirred suspension of $LiAlH_4$ (0.60 g, 16 mmol) in dry ether (20 mL) was added slowly a solution of **12b** (1.25 g, 5.03 mmol) in dry ether (8 mL) over about 5 min. After stirring at RT for 38 h, the mixture was diluted (ether, 20 mL) and cooled (ice bath). Decomposition of the mixture was cautiously effected with 5% HCl (25 mL, pH~8), and two layers separated. Extracts (ether, 10 x 25 mL) of the aqueous layer and the original organic layer were combined, dried (Na_2SO_4), filtered, and evaporated (warming to 50-65°, ~ 10 min) to a thick, pale yellow oil **14b** (~0.9 g, 95%). IR (neat) 3700-3050 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.33 and 1.34 [2s, 3 H], 1.45 and 1.46 [2 d, *J* = 9 Hz, *J* = 9 Hz, 1 H], 2.32 and 2.45 [2 s, 2 H], 4.16 [d, *J* = 9 Hz, 1 H], 4.52 and 4.53 [2d, *J* = 9 Hz, *J* = 9 Hz, 1 H], 4.78 and 4.80 [2q, *J* = 6

Hz, J = 6 Hz, 1 H], 6.75 [m, 1 H], 7.05-7.20 [m, 2 H]; ^{13}C NMR ($DCCl_3$): δ 21.9, 24.9, 25.1, 47.6, 68.7, 68.8, 70.1, 70.3, 80.4, 109.3, 109.5, 120.3, 120.8, 126.0, 126.5, 132.2, 132.4, 138.0, 159.7. This diastereomeric mixture appeared sir sensitive and was used at once to prepare **15b**.

[1-(2,3-Dihydro-3-methyl-3-hydroxymethylbenzo[*b*]thien-5-yl)ethyl]triphenylphosphonium Bromide (15a).- A solution of diol **14a** (0.59 g, 2.4 mmol) and $Ph_3P.Br$ (0.81, g, 2.4 mmol) in absolute methanol (18 mL) was stirred at RT for 15 h. Evaporation of the solvent with slight warming (~50-60°) produced a foam which solidified and was fragmented when suspended in ether with rapid stirring under N_2. Filtration of the suspension and drying the solid at RT/0.1 mm (followed by 77° for 1 h) gave the diastereomeric mixture (1:1 by ^1H NMR-CH_3) of **15a** as a creamy-white powder (1.31 g, qt), mp 128-138°. IR (KBr) 3700-3100 cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.07 [s, 3 H], 1.14 [s, 3 H], 1.68-1.85 [m, 3 H], 2.92 and 2.98 [2d, J = 11 Hz, 1 H], 3.34 and 3.44 [m, 1 H], 3.53 and 3.59 [m, 1 H], 3.68 [m, 1 H], 6.0-6.2 [m, 1 H], 6.70 and 6.82 [m, 1 H], 6.94 [2d, 1 H], 7.00 and 7.09 [2m, 1 H], 7.6-7.9 [m, 15 H]. Salt **15a** appeared air sensitive and was used at once to prepare (*E*)-**2**.

[1-(2,3-Dihydro-3-methyl-3-hydroxymethylbenzo[*b*]furan-5-yl)ethyl]triphenyphosphonium Bromide (15b).- A solution of **12b** (1.03 g, 4.55 mmol) and $Ph_3P.HBr$ (1.52 g, 4.46 mmol) in absolute methanol (35 mL) was stirred at RT for 15 h. Evaporation of the solvent with gentle warming generated a foam which was fragmented *via* rapid stirring in dry ether (25 mL) for 9 h under N_2. The mixture was filtered, the solid was washed with dry cold ether, and the new solid was dried under vacuum (77°/~0.1 mm) for 1 h. Salt **15b** (2.28 g, 96%) was obtained as a white powder (diastereomeric ratio was 1:1 *via* ^1H NMR-CH_3), mp 212.2-215.0°. IR 3650-3100 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.11 and 1.15 [2s, 3 H], 1.77 and 1.78 [m, 3 H], 3.35-3.55 [m, 2 H], 4.08 and 4.10 [m, 1 H], 4.61 and 4.63 [m, 1 H], 5.85-6.10 [m, 1 H], 6.51 [m, 1 h], 6.70-6.95 [m, 2 H], 7.60-7.9 [m, 15 H]. Salt **15b** was used immediately without further purification to prepare (*E*)-**4**.

Methyl (*E*)-4-[2-(2,3-Dihydro-3-methyl-3-hydroxymethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoate [(*E*)-2].- A solution of *n*-butyllithium (3.2 mL, 5.1 mmol, 1.6 *M*) in hexane was added slowly to a stirred mixture of salt **15a** (2.30 g, 4.19 mmol) in dry THF (30 mL). The mixture was stirred (~ 1 h) after which time additional *n*-butyllithium (0.5 mL, 0.8 mmol, 1.6 *M*) in hexane was added. After stirring for another 0.75 h at RT, the Wittig reagent was cooled (-84°, N_2/EtOAc bath). Methyl 4-formylbenzoate (0.72 g, 4.40 mmol) in dry THF (15 mL) was added over 5 min. The cold bath was removed, and the resulting mixture was stirred (11 h). The mixture was diluted (ether, 20 mL) and quenched with saturated brine (25 mL) followed by 5% HCl (1.7 mL to pH~5). The organic layer was separated, washed with brine, and dried (Na_2SO_4). Filtration of the solution and evaporation of the solvent gave a solid (~5.0 g). TLC analysis of this solid revealed several spots with the (*E*)-**2**:(*Z*)-**2** being approximately 1:1 *via* proton NMR analysis. Repeated chromatography of the solid (hexanes:ether, 1:1) and several recrystallizations (ethyl acetate:hexanes, 2:1) of each product from each chromatographic separation removed minor products and gave (*E*)-**2** containing a very small amount of (*Z*)-**2**. Dissolving this mixture in EtOAc (2 mL/0.2 g), followed by the addition of *n*-pentane (~6 mL/0.2 g), gave a solution which, when exposed to an atmosphere of *n*-pentane in a

closed system, provided crystalline (*E*)-**2**. Recrystallization (boiling hexanes, 10 mL/0.1 g) gave pure (*E*)-**2** (0.107 g, 7%), mp 115.1-116.1°. IR (KBr) 3650-3150 (O-H), 1716 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.45 [s, 3 H], 2.28 [m, 3 H], 3.21 [d, *J* = 11.2 Hz, 1 H], 3.49 [d, *J* = 11.2 Hz, 1 H], 3.64 [dd, *J* = 10.9 Hz, *J* = 5.6 Hz, 1 H], 3.77 [dd, *J* = 10.9 Hz, *J* = 5.8 Hz, 1 H], 3.93 [s, 3 H], 6.80 [bs, 1 H, H(12)], 7.21 [d, *J* = 2 Hz, 1 H], 7.22 [d, *J* = 8 Hz, 1 H], 7.34 [dd, *J* = 8 Hz, *J* = 2 Hz, 1 H], 7.42 [d, *J* = 8.2 Hz, 2 H], 8.04 [d, *J* = 8.2 Hz, 2 H]; ^{13}C NMR ($DCCl_3$): δ 17.8, 22.5, 42.1, 52.1, 52.7, 67.8, 121.3, 122.4, 126.1, 127.9, 129.0, 129.5, 139.2, 140.1, 141.6, 143.0, 143.7, 167.0.

Anal. Calcd for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.26. Found: C, 71.45; H, 6.32

Although (*Z*)-**2** could not be freed of (*E*)-**2**, the presence of (*Z*)-**2** was noted in the ^1H NMR spectrum from the signal for vinyl H(12) which appeared at δ 6.46 in contrast to the same signal in (*E*)-**2** appearing at δ 6.80. The pattern is the same as found for (*E*)-**3** and (*Z*)-**3**,[8] that is, the H(12) signal is at higher field with *cisoid* aryl groups than with *transoid* aryl groups.

Methyl (*E*)-4-[2-(2,3-Dihydro-3-methyl-3-hydroxymethyl-5-benzofuranyl)-1-propenyl]benzoate [(*E*)-4].-A solution of *n*-butyllithium (3.2 mL, 5.1 mmol, 1.6 *M*) in hexane was added slowly to a stirred solution of salt **15b** (2.25 g, 4.22 mmol) in dry THF (30 mL). The mixture was stirred (~ 1 h) after which time additional *n*-butyllithium (0.5 mL, 0.8 mmol, 1.6 *M*) in hexane was added slowly. After stirring for another 0.5 h at RT, the Wittig reagent was cooled (–84°, N_2/EtOAc bath). Methyl 4-formylbenzoate (0.71 g, 4.30 mmol) in dry THF (15 mL) was added over 5 min. The cold bath was removed, and the resulting mixture was stirred (12 h). The mixture was diluted (ether, 100 mL) and quenched with saturated brine (50 mL) and 5% HCl (2.5 mL, to pH~5). Two layers separated, but salt had to be added to destroy an emulsion which formed. The aqueous layer was extracted (ether, 50 mL), and the remaining emulsion and aqueous layer were separated and extracted separately (ether, 2 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. Evaporation of solvent gave a solid (~ 5.0 g) the TLC of which showed several spots with the (*E*)-**4b**:(*Z*)-**4b** being appoximately 7:3 with six other impurities. Repeated chromatography (hexanes:ether, 1:1) of this mixture, followed by repeated recrystallizations (ethyl acetate:*n*-pentane, ~1:4), gave a final product which was mostly (*E*)-**4b** with a trace of (*Z*)-**4b**. Treating this mixture with boiling hexanes gave pure (*E*)-**4b** as a white crystalline solid (0.060 g, 6%), mp 106-108°. IR 3650-3050 (O-H), 1722 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.42 [s, 3 H], 2.28 [d, *J* = 1 Hz, 3 H], 3.63 [d, *J* = 10.7 Hz, 1 H], 3.72 [d, *J* = 10.7 Hz, 1 H], 3.93 [s, 3 h], 4.24 [d, *J* = 8.9 Hz, 1 H], 4.62 [d, *J* = 8.9 Hz, 1 H], 6.77 [bs, 1 H, H(12)], 6.82 [d, *J* = 8.3 Hz, 1 H], 7.29 [d, *J* = 2 Hz, 1 H], 7.35 [dd, *J* = 8.3 Hz, *J* = 2 Hz, 1 H], 7.41 [d, *J* = 8.3 Hz, 2 H], 8.03 [d, *J* = 8.3 Hz, 2 H]; ^{13}C NMR ($DCCl_3$): δ 17.9, 21.9, 47.7, 52.1, 69.0, 80.6, 109.6, 120.7, 125.4, 127.0, 127.7, 129.0, 129.5, 132.1, 136.5, 139.3, 143.4, 161.1, 167.0.

Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.56; H, 6.66

Although (*Z*)-**4b** could not be isolated free of (*E*)-**4b**, isomer (*Z*)-**4b** could be seen in the proton NMR spectrum with the signal for vinyl H(12) at δ 6.43 in contrast to the signal for the same proton in (*E*)-**4b** which appeared at δ 6.77.

Methyl (*E*)-4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-3-hydroxy-1-propenyl]benzoate [(*E*)-5].- A mixture of (*E*)-**3** (0.200 g, 0.620 mmol), SeO_2 (0.208 g, 1.87 mmol), and 95% ethanol (15 mL) was stirred at reflux (22 h). After cooling to RT (1 h), the mixture was filtered, concentrated (to ~ 0.5 mL), diluted with ether (30 mL), and filtered again. Solvent evaporation gave a solid residue which was chromatographed (hexanes:ether, 1:1). Starting material was removed in the early fractions while an oil comprised the majority of middle fractions. Trituration of the oil [0.043 g; (*E*)-**5** vs (*Z*)-**5** was 10:1 for vinyl H(12)] from combined fractions with cold hexanes induced crystallization, and recrystallization (boiling hexanes) of the product led to pure (*E*)-**5** as a light yellow solid (0.025 g, 12%), mp 125.1-125.7°. IR (KBr) 3600-3150 (O-H), 1717 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$): δ 1.23 [s, 6 H], 1.60 [s, 1 H, OH], 3.87 [s, 3 H], 4.25 [s, 2 H], 4.49 [m, 2 H], 6.68 [s, 1 H], 6.76 [m, 1 H], 6.89 [m, 1 H], 6.99 [m, 1 H], 7.07 [m, 2 H], 7.79 [m, 2 H]; ^{13}C NMR ($DCCl_3$): δ 27.5, 41.8, 68.1, 84.8, 110.0, 123.2, 124.8, 128.0, 128.1, 129.1, 129.2, 129.8, 137.4, 141.8, 144.2, 159.1, 166.9.

Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.58; H, 6.57

Acknowledgments.-We gratefully acknowledge the National Science Foundation for a departmental grant (DMB-860-3864) for funds to upgrade the XL-300 NMR spectrometer and a separate grant (CHE-8718150) to purchase the XL-400 NMR spectrometer. We are also pleased to acknowledge funding for the Varian Gemini 2000 (300 MHz), the Varian Unity Inova-400 MHz NMR, and the Varian Unity Inova-600 MHz spctrometers in the Oklahoma Statewide Shared NMR facility by the National Science Foudnation (BIR-95`2269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foudnation, and Conoco, Inc. Thanks are extended (KDB) to the College of Arts & Sciences for partial salary support. The NIH is also thanked for partial support of the research through the National Cancer Institute (CA 73639). We thank the late Dr. Kurt Leoning, Director Emeritus of Nomenclature of Chemical Abstracts, for naming the compounds.

REFERENCES

1. D. S. Alberts, O. M. Colvin, A. H. Conney,V. L. Ernster, J. E. Garber, P. Greenwald, L. Gudas, K. W. Hong, G. J. Kelloff, R. A. Kramer, C. E. Lerman, D. J. Mangelsdorf, A.Matter, J. D. Minna, W. G. Nelson, J. M. Pezzuot, F. Prendergast, V. W. Rusch, M. B. Sporn, L. W. Wattenberg, and I. B. Weinstein, *Cancer Res.*, **59**, 4743 (1999).

2. (a) M. I. Dawson and P. D. Hobbs, "The Synthetic Chemistry of Retinoids", In *The Retinoids-Biology, Chemistry, and Medicine*, 2nd Edition, M. B. Sporn, A. B. Roberts, and D. S. Goodman, Editors, Raven Press, New York, 1994, Ch 1, pp 5-178. (b) M. I. Dawson, "Retinoids", In Burger's *Medicinal Chemistry and Drug Discovery*, Fifth Edition, Volume 3, Chp 44, Wiley, New York, 1996, pp 575-628.

3. (a) L. W. Spruce, S. N. Rajadhyaksha, K. D. Berlin, J. B. Gale, E. T. Miranda, W. T. Ford, E. C. Blossey, A. K. Verma, M. B. Hossain, D. van der Helm, and T. R. Breitman, *J. Med. Chem.*, **30**, 1474 (1987). (b) J. B. Gale, S. N. Rajadhyaksha, L. W. Spruce, K. D. Berlin, X. Ji, A. Slagle, and D. van der Helm, *J. Org. Chem.*, **55**, 3984 (1990). (c) L. W. Spruce, J. B. Gale, K. D. Berlin, A. K. Verma, T. R. Breitman, X. Ji, and D. van der Helm, *J. Med. Chem.*, **34**, 430 (1991). (d) R. A. S. Chandraratna, *Br. J. Dermatol.*, **135**, 18 (1996). (e) D. M. Benbrook, M. M. Madler, L. W.

Spruce, P. J. Birckbichler, E. C. Nelson, S. Subramanian, G. M. Weerasekare, J. B. Gale, M. K. Patterson, Jr., B. Wang, W. Wang, S. Lu, T. C. Rowland, P. DiSivestro, C. Lindamood, D. L. Hill, and K. D. Berlin, *J. Med. Chem.*, **40**, 3567 (1997). (f) D. M. Benbrook, S. Subramanian, J. B. Gale, S. Liu, C. W. Brown, M. F. Boehm, and K. D. Berlin, *J. Med. Chem.*, **41**, 3753 (1998).

4. (a) R. Hanni, F. Bigler, W. Mesiter, and G. Englert, *Helv. Chim. Acta*, **59**, 2221 (1976). (b) R. Hanni and F. Bigler, *Helv. Chim. Acta*, **60**, 881 (1977). (c) R. Hanni, F. Bigler, W. Vetter, G. Englert, and P. Loeliger, *Helv. Chim. Acta*, **60**, 2309 (1977).

5. For a review; see C. A. Frolik, "Metabolism Of Retinoids", In *The Retinoids*, Volume 2, M. B. Sporn, A. B. Roberts, and D. S. Goodman, Editors, Academic Press, New York, 1984, pp 177-208.

6. P. S. Sunthankar, K. D. Berlin, E. C. Nelson, R. L. Horne, P.W. Geno, J. C. Archer, L. L. Rolf, Jr., and K. E. Bartels, *J. Pharmaceutical Sciences*, **82**, 543 (1993).

7. (a) M. Simms-Kelley "Growth Promoting Activity and Metabolism of Selected Heteroarotinoids in Vitamin A-Deficient Rats", Ph.D. Dissertation, Oklahoma State University, May, 2000. (b) R. L. Z. Thorne, "Biological Activity and Metabolism of Selected Heteroarotinoids", Ph.D. Dissertation, Oklahoma State University, May, 1993; *Dissertation Abstr.*, **54**, 2490-B (1993).

8. K. D. Berlin, E. M. Holt, W. T. Ford, and M. D. Thompson, U.S. Patent 4,826,984, May 2, 1989; *Chem. Abstr.*, **111**, 173986 (1989).

9. H. Wolf, H.-U. Gonzenbach, K. Muller, and K. Schaffner, *Helv. Chim. Acta*, **55**, 2919 (1972).

10. R. Fusco, L. Garanti, and G. Zeechi, *J. Org. Chem.*, **40**, 1906 (1975).

(Received January 2001; in final form July 2001)