# Allergenic α-Methylene-γ-butyrolactones. β-Hydroxy-α-methylene-γ-butyrolactones. 2.[1] Syntheses from Ethyl 2-(Phenylthio)propionate and α-Acetoxy Aldehydes

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β-Hydroxy- and β-acetoxy-α-methylene-γ-butyrolactones were prepared from α-acetoxy aldehydes and ethyl 2-(phenylthio)propionate. Diastereomeric sulfides 8–11 were separated, oxidized, and thermally eliminated, leading to β-acetoxy-*exo*-methylene lactones **23–25** and to butenolides **26–28**, depending on the configuration of the phenylsulfinyl group. β-Hydroxy lactones **19** were prepared by saponification of the β-acetoxy derivatives.

β-Hydroxy-α-alkylidene-γ-butyrolactones are a common feature in many natural compounds from the Lauraceae (e.g., *Litsea japonica*[2]), Magnoliaceae, etc. families. We have described recently[3] the synthesis of $C_1$ and $C_2$ litsenolides isolated by Takeda and co-workers from *Litsea japonica*.[2] Our interest for the skin-sensitizing properties of α-methylene-γ-butyrolactones[4] and in particular of their β-hydroxy analogues (reputedly nonallergenic[5]) led us to devise a general synthesis of β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones and to prepare a derivative of tuliposide B.[1]

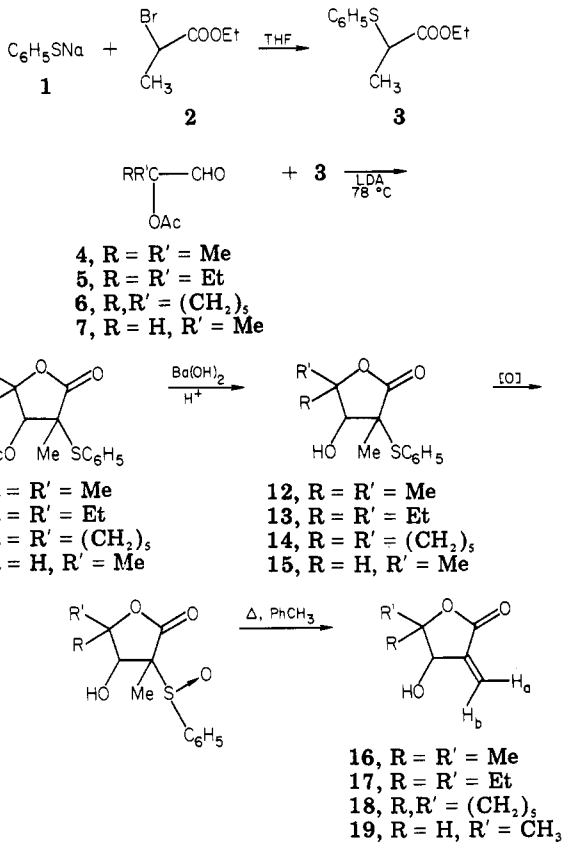
There is a large number of methods available for the synthesis of α-methylene-γ-butyrolactones.[6] Syntheses of β-hydroxy-α-methylene-[7a] and α-alkylidene-β-hydroxy-γ-butyrolactones[7b] have been reported recently. We now describe another method for the preparation of γ- and γ,γ-substituted β-hydroxy-α-methylene-γ-butyrolactones, using sulfoxides to introduce the methylene group.

## Results and Discussion

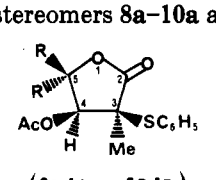
**General Methods.** The general scheme for the synthesis was that shown in Scheme I.

Sulfide **3** was obtained by nucleophilic substitution of ethyl 2-bromopropionate (**2**) with sodium phenyl sulfide (**1**) in 85% yield. The α-acetoxy aldehydes were prepared as described[8] from the corresponding enol acetate which were epoxidized and rearranged either thermally or under acidic conditions. The anion of ethyl 2-(phenylthio)-propionate (**3**) was generated at −78 °C with LDA and reacted in THF with the appropriate α-acetoxy aldehyde. Even when a large excess of aldehyde was used, the reaction was incomplete: an isolated yield of 55–70% was obtained, along with unreacted aldehyde. The β-acetoxy-α-methylene-γ-butyrolactones were obtained directly, the interchange (rearrangement) of the acetyl and hydroxy groups have already been observed in previous work from this laboratory[1] and in the work of others.[9]

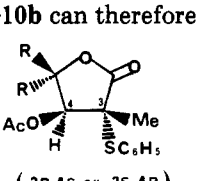
**Scheme I**




When R = R′, there are two chiral centers; two couples of diastereomers **8a–10a** and **8b–10b** can therefore be expected. These were obtained and could be separated by recrystallization; one isomer (the major one, 60%) is a




**8a–10a**




**8b–10b**

(1) Part 1: Corbet, J. P.; Benezra, C. *J. Org. Chem.* **1981**, *46*, 1141–1147.

(2) Takeda, K.; Sakurawi, K.; Ishii, H. *Tetrahedron* **1972**, *28*, 3757–3766.

(3) Barbier, P.; Benezra, C. *Tetrahedron Lett.* **1982**, 3513–3516.

(4) Stampf, J. L.; Schlewer, G.; Ducombs, G. Foussereau, J.; Benezra, C. *Br. J. Dermatol.* **1978**, *99*, 163–169. Schlewer, G.; Stampf, J. L.; Benezra, C. *J. Med. Chem.* **1980**, *23*, 1031–1038. Dupuis, G.; Benezra, C.; Schlewer, G.; Stampf, J. L. *Mol. Immunol.* **1980**, *17*, 1045–1051.

(5) Slob, A. *Phytochemistry* **1975**, *14*, 1997–2005.

(6) Grieco, P. A. *Synthesis* **1975**, 67–82. Gammill, R. B.; Wilson, C. A.; Bryson, T. A.; *Synth. Commun.* **1975**, *5*, 245–268. Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625–694. Newaz, S. S. *Aldrichimica Acta* **1977**, *10*, 64–71. Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133–198.

(7) (a) Nair, V.; Sinhababu, A. K. *J. Org. Chem.* **1980**, *45*, 1893–1897. (b) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, A. *J. Am. Chem. Soc.* **1981**, *103*, 4114–4125.

(8) Bedoukian, P. Z. *J. Am. Chem. Soc.* **1944**, *66*, 1327. Riehl, J. J.; Fougerousse, A. *Bull. Soc. Chim. Fr.* **1968**, 4083–4086 and references therein. Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427–3429.

(9) Welsh, L. H. *J. Org. Chem.* **1967**, *32*, 119–122.

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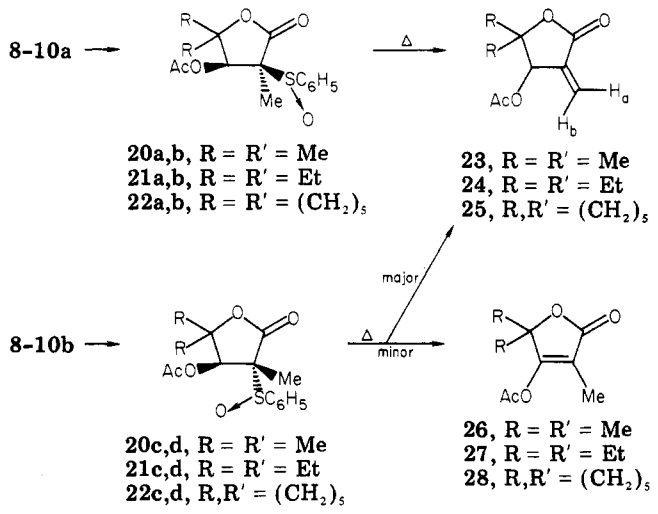
Scheme II




liquid and the other (40%) crystalline. The crystalline isomer was obtained pure, while the liquid one (containing some of the minor crystalline product) could be purified by column chromatography on silica gel.

The two isomers could be distinguished by NMR (for example with R = Me) by looking in particular at the OAc signal ($\delta$ 2.24 from $Me_4Si$ in the crystalline isomer and $\delta$ 2.12 in the liquid one) and the H-4 signal. ($\delta$ 5.27 for the crystalline derivative and $\delta$ 5.32 for the liquid.)

Relative configurations could be assigned when the sulfides **8a–10a** and **8b–10b** were quantitatively oxidized with *m*-chloroperbenzoic acid (MCPBA) and heated. Since the thermal elimination of sulfoxides is syn relative to the hydrogen,[10] one can expect **20a,b–22a,b** (obtained from **8a–10a**) to give exclusively an *exo*-methylene group while **20c,d–22c,d** (obtained from **8b–10b**) could eliminate in both exo and endo directions (Scheme II).

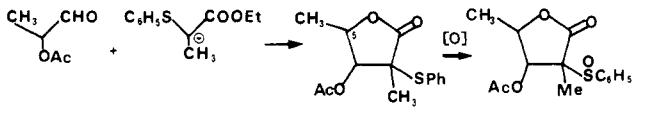
As expected, one isomer (the crystalline one) gave exclusively the *exo*-methylene lactones **23–25** (therefore the relative configurations **8a–10a** are assigned to it) while the liquid isomer gave an inseparable mixture (as shown by NMR) of *exo*-methylene-$\gamma$-lactones **23–25** and butenolides **26–28** where the exo derivative proportion was always superior up to 60%.

Since oxidation of sulfides **8–10** into sulfoxides **20–22** introduces a new chiral center, diastereoisomers were again expected and obtained. All were separated by column chromatography. In each series, a 3:7 proportion of stereoisomers was obtained. The three diastereomeric sulfoxides **20a,b–22a,b** formed from sulfides **8a**, **9a,b**, and **10a,b** (i.e., with PhS and $H_4$ trans) were not separated before heating since only *exo*-methylene derivatives (60% yield from **8a,b**, **9a,b**, and **10a,b**) can be expected.

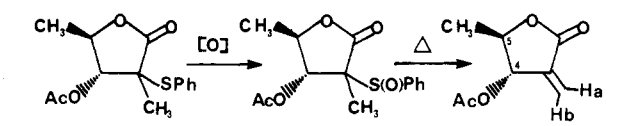
From **8b–10b** (PhS and $H_4$ cis), the two diastereomeric sulfoxides (3:7) formed were heated separately. The major stereomer gave a majority of *exo*-methylene, while for the other, a predominance of the butenolides **26–28** was observed. Under the pyrolysis conditions, compounds **23–25** and **26–28** were stable.

**$\alpha$-Methylene-$\gamma$-lactone from $\alpha$-Acetoxypropionaldehyde.** The same general scheme was used, the situation here being more complicated because of the presence of a third chiral center (C-5) (Scheme III).

Scheme III

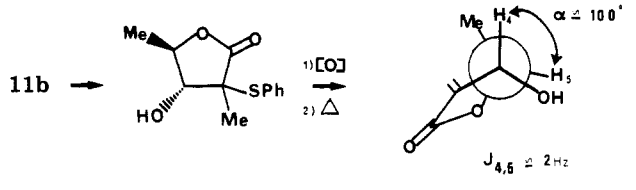


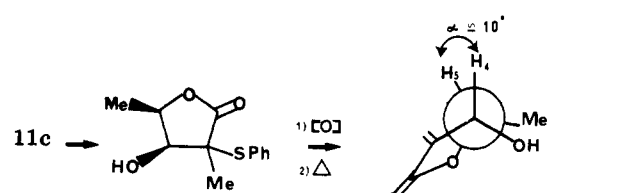

Scheme IV




Among the four possible pairs of stereoisomers, only three were isolated, the fourth one probably being formed in negligible amount. In this series however, the $\gamma$-lactone was not obtained directly, the open-chain compounds were isolated, and they cyclized slowly on standing. Three isomers, **11a–c**, in a 1:5:4 ratio were obtained; the minor (10%) isomer, after oxidation and thermal elimination of sulfoxide **29a**, gave a lactone, **30a**, identical with the one prepared in our laboratory,[1] i.e., with Me and AcO group trans (Scheme IV). The structure of the minor component is thus **11a**.

When the other diastereomers **11b** (50% isomer) and **11c** (40% isomer) where first saponified (AcO → $HO^-$ product **15b,c**), oxidized, and pyrolized, they gave, respectively, the $\beta$-hydroxy-$\gamma$-methyl-$\alpha$-methylene-$\gamma$-butyrolactones **19b** and **19c**. The relative configuration




of these lactones could be assigned by NMR; protons $H_4$ and $H_5$ in isomer **19b** appeared as a complex multiplet at $\delta$ 4.20–4.60 and in isomer **15c** at $\delta$ 4.65–5.00. Double irradiation of the $\gamma$-methyl group resulted in collapse of the multiplet into a singlet for **19b** and a more simplified multiplet in compound **19c**, showing a larger $J_{4,5}$ coupling in the latter case. When making the molecular model, in one of the isomers the $H_4$,$H_5$ dihedral angle is close to 100° (and therefore $J_{4,5}$ is expected to be small), while in the other, this angle is $\simeq$10° (and therefore $J_{4,5}$ should be large). We therefore assign configuration **19b** (Me and OH trans) to the former and **19c** (Me and OH cis) to the latter.

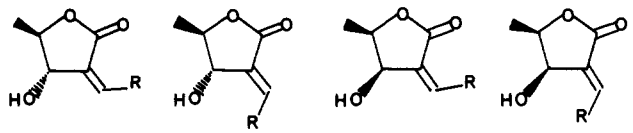
Both **30a** and **19b** have therefore the same relative trans relationship of the methyl and of the hydroxy group while in **19c** these substituants are cis to each other.

These assignments compare well with those described for $\beta$-acetoxy-$\alpha$-methylene-$\gamma$-butyrolactones we prepared recently[1] and with NMR data of litsenolide **31** and mahubanolide **32** derivatives.

(10) Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810–1819. Kwart, H. K.; George, T. J.; Louw, R.; Ultee, W. *Ibid.* **1978**, *100*, 3927–3928.

(11) Barbier, P.; Benezra, C. *Tetrahedron Lett.* **1982**, *23*, 3511–3512.

(12) Latyaeva, V. N.; Razuvaev, G. A. *Tr. Khim.-Tekhnol. Fak., Donetsk. Ind. Inst.* **1962**, *4*, 640–643; *Chem. Abstr.* **1963**, *58*, 1388*d*.



31, R = $C_{13}H_{27}$ 32

The results described here provide a novel entry into β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones. This synthetic scheme was applied with success to the synthesis of natural products, to the synthesis of litsenolides[3] $C_1$ and $C_2$, and to a one-step synthesis of 2-(phenylthio)-2 buten-4-olides.[8]

## Experimental Section

Melting points were determined by using a Tottoli capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Beckman Acculab 1 spectrometer by using $CHCl_3$ solutions; wave numbers ($cm^{-1}$) are given. Proton nuclear magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer R12B (60 MHz); chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard; coupling constants (*J*) are expressed in hertz. Mass spectra were determined (ionization energy 70 eV) on a Thomson-SCF THF 208 apparatus. Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates (silica gel 60F 254, layer thickness 0.25 mm, from Merck, Darmstadt). Silica gel columns for chromatography utilized Merck silica gel 60 (70–230 mesh ASTM). Elemental combustion analyses were performed by the Service de Microanalyse du CNRS (Strasbourg and Lyon). The abbreviations used are as follows: PE, petroleum ether; EE, ethylether; EtOH, ethanol; THF, tetrahydrofuran; s, singlet; m, multiplet; d, doublet; t, triplet; q, quartet, MCPBA, *m*-chloroperbenzoic acid. The "usual workup" means extraction with a solvent ($CH_2Cl_2$ or EE), washing with water, 5% aqueous $NaHCO_3$ or HCl, and water, drying over $MgSO_4$, and removal of solvent.

The preparation of α-acetoxy aldehydes[8] is as shown in Scheme V.

**General Procedure for the Preparation of Enol Acetates RR'C=CHOAc.** An example is as follows. Isobutyraldehyde (36.0 g; 0.500 mol) was dissolved in $Ac_2O$ (76.5 g; 0.750 mol), and anhydrous $K_2CO_3$ (6.00 g; 0.063 mol) was added. The mixture was heated under reflux for 2 h. After the mixture was cooled, washed with water and 5% aqueous $NaHCO_3$, and dried over $MgSO_4$, the crude oil was distilled twice. The known enol acetate was obtained: bp 124 °C (760 mm) (lit.[6] bp 124–126 °C; 20.0 g (0.018 mol, yield, 35%); IR 1675–1740; NMR 1.68 (s, 6 H, $(Me)_2C=C$), 2.11 (s, 3 H, OAc), 6.88 (s, 1 H, $(Me)_2C=CH$).

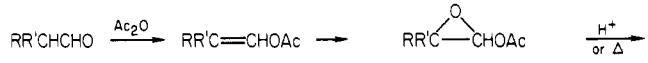
Other enol acetates were $Et_2C=CHOAc$ [bp 165 °C (760 mm); 80% yield], $C_5H_{10}C=CHOAc$ [bp 85 °C (13 mm); 80% yield], $CH_3CH=CHOAc$ [bp 107 °C (760 mm) 40% yield]. All enol acetates had spectral data (IR, NMR) compatible with the proposed structures.

**General Procedure for the Preparation of Enol Epoxy Acetates 32–35.** The enol acetate (20 mmol) in $CH_2Cl_2$ (25 mL) was treated with 1 equiv of MCPBA added in small portions at 0 °C. After completion of the peracid addition, the mixture was stirred 4 h at room temperature. The usual workup of the $CH_2Cl_2$ solution (after filtration) gave pure epoxy acetates in 90% yield.

In this way, the following compounds were prepared. **32**: oil; IR, 1745; NMR 1.30 (s, 6 H, $(CH_3)_2C$), 2.11 (s, 3 H, OAc), 5.30 (s, 1 H, C*H*(OAc)). **33**: oil; IR 1745; NMR 1.00 (m, 6 H, $(CH_3CH_2)_2$), 1.40–2.00 (m, 4 H, $CH_3CH_2)_2$, 2.12 (s, 3 H, OAc), 5.39 (s, 1 H, C*H*(OAc)). **34**: oil; IR 1750; NMR 1.30–1.80 (m, 10 H, $C_5H_{10}C$), 2.04 (s, 3 H, OAc), 5.20 (s, 1 H, C*H*(OAc)). The epoxy acetate with R = H and R' = $CH_3$ was prepared as described.[6]

**General Procedure for the Preparation of α-Acetoxy Aldehydes RR'C(OAc)CHO 4–6.** Treatment with catalytic amounts of $BF_3$/ether of the epoxy acetates in $CH_2Cl_2$ (except for R = H, R' = $CH_3$) gave the corresponding pure α-acetoxy aldehydes (in 100% yield). α-Acetoxypropionaldehyde was prepared as described[6] by heating the epoxy acetate at 120 °C under an argon atmosphere, without solvent, for more than 2 h, and the reaction was followed by NMR.

Scheme V



**32**, R = R' = Me
**33**, R = R' = Et
**34**, R,R' = $(CH_2)_5$
**35**, R = H, R' = Me

RR'C(OAc)CHO

**4**, R = R' = Me
**5**, R = R' = Et
**6**, R,R' = $(CH_2)_5$
**7**, R = H, R' = Me

In this way the following compounds were prepared. **4**: oil (bp 120 °C (760 mm)); IR 1740; NMR 1.40 (s, 6 H, $(CH_3)_2$), 2.10 (s, 3 H, OAc), 9.45 (s, 1 H, CHO). **5**: oil; IR 1730; NMR 0.88 (m, 6 H, $CH_3CH_2$), 1.70–2.20 (m, 4 H, $CH_3CH_2$), 9.48 (s, 1 H, CHO). **6**: oil (bp 107 °C (13 mm)); IR 1735; NMR 1.40–1.90 (m, 10 H, $C_5H_{10}$), 2.10 (s, 3 H, OAc), 9.39 (s, 1 H, CHO).

**Ethyl 2-(Phenylthio)propionate (3).** Sodium (1.15 g, 0.050 mol) was added under argon to 100 mL of EtOH at 0 °C. After formation of EtONa, PhSH (5.51 g, 0.050 mol) was added; 15 min later, EtOH was removed and the crystalline PhSNa suspended in 50 mL of anhydrous THF. Ethyl 2-bromopropionate (9.05 g, 0.050 mol) was rapidly added with a syringe at room temperature, and the mixture was left at room temperature for one night. After removal of the solvent and the usual workup, the crude oil was distilled, and ethyl 2-(phenylthio)propionate (8.92 g, 0.042 mol, 85% yield) was obtained: oil; bp 140 °C (14 mm) [lit.[12] 91 °C (0.6 mm)]; IR 1585, 1730; NMR 1.13 (t, 3 H, $CH_2CH_3$, *J* = 7.2), 1.46 (d, 3 H, $CH_3$, *J* = 7.6), 3.75 (q, 1 H, $CH_3CH$, *J* = 7.6), 4.06 (q, 2 H, $CH_2CH_3$, *J* = 7.2), 7.10–7.60 (m, 5 H, $C_6H_5$).

**General Procedure for the Preparation of β-Acetoxy-α-(phenylthio)-γ-butyrolactones 8–10. From Aldehyde 6 (R,R' = $(CH_2)_5$).** An example is as follows for the synthesis of **10**. To a solution of LDA [0.023 mol; prepared from diisopropylamine (2.33 g, 0.023 mol) and 1.1 equiv of BuLi in 80 mL of dry THF was added drop by drop, under argon at −78 °C, ethyl 2-(phenylthio)propionate (4.77 g, 0.023 mol) in 10 mL of THF; 25 min later, the α-acetoxy aldehyde **6** in 10 mL of dry THF (4.09 g, 0.024 mol) was added slowly, and after usual workup, a crude oil was obtained. Isomer **10a**, with the β-acetoxy and α-phenylthio groups in a cis relationship, crystallized spontaneously. Purification of the two isomers **10a,b** (R,R' = $(CH_2)_5$) was achieved by column chromatography on silica gel (300 g, eluent 75:25 PE/EE). Isomer **10a** (2.00 g, 6.00 mmol) eluted before isomer **10b** (3.00 g, 9.00 mmol); total yield 66%. **10a**: mp 89–90 °C; IR 1765; NMR 1.50 (s, 3 H, $CCH_3$(SPh), 1.40–1.90 (m, 10 H, $C_5H_{10}$), 2.22 (s, 3 H, OAc), 5.19 (s, 1 H, CH(OAc)), 7.20–7.70 (m, 5 H, $SC_6H_5$); mass spectrum (**10a,b** mixture), *m/e* 334 ($M^+$). Anal. (**10a,b** as a mixture) Calcd for $C_{18}H_{22}O_4S$: C, 64.67; H, 6.59; S, 9.58. Found: C, 64.66; H, 6.60; S, 9.46.

**From $Me_2C(OAc)CHO$**; total yield 55%.

**8a**: 33% yield; mp 104 °C; IR 1750, 1765; NMR 1.49–1.52 (2 s, 6 H, $(CH_3)_2C$), 2.24 (s, 3 H, $C(CH_3)$(SPh)), 5.27 (s, 1 H, CH(OAc)), 7.20–7.70 (m, 5 H, $SC_6H_5$).

**8b**: 22% yield; oil; IR 1750, 1765; NMR 1.29, 1.35, 1.47 (3 s, 9 H, $(CH_3)_2C$, $CCH_3$(SPh)), 2.12 (s, 3 H, OAc), 5.32 (s, 1 H, CH(OAc)), 7.20–7.70 (m, 5 H, $SC_6H_5$); mass spectrum (**10a,b** mixture), *m/e* 294 ($M^+$). Anal. (**8a,b** mixture) Calcd for $C_{15}H_{18}O_4S$: C, 61.22; H, 6.12; S, 10.88. Found: C, 61.26; H, 6.08; S, 10.78.

**From $(CH_3CH_2)_2C(OAc)CHO$**; total yield 65%.

**9a**: 39% yield; mp 73–74 °C; IR 1765; NMR 0.80–1.20 (m, 6 H, $(CH_2CH_3)_2$), 1.40–2.00 (m, 4 H, $(CH_2CH_3)_2$), 1.52 (s, 3 H, $CCH_3$(SPh)), 2.21 (s, 3 H, OAc), 5.38 (s, 1 H, CH(OAc)), 7.20–7.80 (m, 5 H, $SC_6H_5$).

**9b**: 26% yield; oil; IR 1765; NMR 0.70–1.20 (m, 6 H, $(CH_2CH_3)_2$), 1.40–2.00 (m, 4 H, $(CH_2CH_3)_2$), 1.49 (s, 3 H, $CCH_3$(SPh)), 2.11 (s, 3 H, OAc), 5.53 (s, 1 H, CH(OAc)), 7.20–7.80 (m, 5 H, $SC_6H_5$); mass spectrum (**9a,b** mixture), *m/e* 322 ($M^+$). Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.35; H, 6.83; S, 9.94. Found: C, 63.40; H, 6.92; S, 9.85.

**Preparation of β-Acetoxy-α-(phenylthio)-γ-butyrolactone 11 from $CH_3CH(OAc)CHO$ Prepared as Above.** **11a**: oil; IR

1740, 1770; NMR 1.45 (d, 3 H, CH($CH_3$), $J$ = 6.3), 1.45 (s, 3 H, CC$H_3$(SPh)), 2.18 (s, 3 H, OAc), 4.28 (dq, 1 H, C$H$($CH_3$), $J$ = 6.3, 4.8), 5.42 (d, 1 H, C$H$(OAc), $J$ = 4.8), 7.20–7.80 (m, 5 H, $SC_6H_5$). **11b**: oil; IR 1740, 1770; NMR 1.36 (d, 3 H, CH($CH_3$), $J$ = 6.0),[16] 1.53 (s, 3 H, CC$H_3$(SPh)), 2.18 (s, 3 H, OAc), 4.38 (dq, 1 H, C$H$($CH_3$), $J$ = 6.0, 8.0), 5.07 (d, 1 H, C$H$(OAc), $J$ = 8.0), 7.20–7.60 (m, 5 H, $SC_6H_5$). **11c**: oil; IR 1745, 1770; NMR 1.40 (d, 3 H, CH($CH_3$), $J$ = 7.1), 1.44 (s, 3 H, CC$H_3$(SPh)), 2.12 (s, 3 H, OAc), 4.32 (dq, 1 H, C$H$($CH_3$), $J$ = 7.1, 4.0), 5.15 (d, 1 H, C$H$(OAc), $J$ = 4.0), 7.30–7.70 (m, 5 H, $SC_6H_5$); mass spectrum (**11a–c** mixture), $m/e$ 280 ($M^+$). Although several elemental analyses of compounds **11a** and **11b** were unsatisfactory, the analyses of the derived sulfoxides and β-hydroxy derivatives were quite acceptable (see below).

**General Procedure for the Preparation of β-Acetoxy-α-methyl-α-(phenylsulfinyl)-γ-butyrolactones 20–22. From Aldehyde 6.** An example is as follows for the synthesis of sulfoxides **22a,b**. To a solution of sulfide **10a** (R,R′ = $(CH_2)_5$; 0.50 g, 1.50 mmol) in 20 mL of $CH_2Cl_2$ was added drop by drop a solution of MCPBA (1.1 equiv) in 5 mL of $CH_2Cl_2$ at −10 °C. The mixture was stirred for 15 min. After the usual workup, the crude sulfoxides were purified by column chromatography (eluent 5:5 EE/PE). The two diastereomers could be separated. **22a** [mp 126 °C; 0.14 g (0.40 mmol)] and **22b** [viscous oil; 0.33 g (0.94 mmol)]: 90% yield; IR (for **22a–d**) 1764; NMR for **22a** (**22b**) 1.71 (1.40) (s, 3 H, CC$H_3$(SPh)), 1.40–2.00 (1.30–1.90) (m, 10 H, $(CH_2)_5$), 2.26 (2.25) (s, 3 H, OAc), 5.50 (5.36) (s, 1 H, C$H$(OAc), 7.40–8.00.

In the same manner, **22c** and **22d** were obtained as viscous oils from **10b**. NMR for **22c** (**22d**) 1.62 (1.38) (s, 3 H, CC$H_3$(S(O)Ph)), 1.30–2.00 (1.40–1.90) (m, 10 H, $C_5H_{10}$), 2.15 (1.78) (s, 3 H, OAc), 5.96 (5.70) (s, 1 H, CH(OAc)), 7.50–8.10 (7.40–7.80) (m, 5 H, S(O)Ph); mass spectrum (for **22a–d**), $m/e$ 290 ($M^+$ − HOAc). Anal. Calcd for $C_{18}H_{22}O_5S$: C, 61.71; H, 6.40; S, 9.14. Found: C, 61.39; H, 6.45; S, 8.93.

**From $Me_2C$(OAc)CHO**; total isolated yield 55%. **20a–c** (R = R′ = Me), viscous oil; **20d** (R = R′ = Me), mp 116 °C; IR (for **20a,b,d**) 1750, 1770; IR (for **20c**) 1745, 1770; NMR **20a** (**20b**) 1.33, 1.53, 1.53, (1.53, 1.49, 1.68) (3 s, 9 H, $(Me)_2C$, C$Me$(S(O)Ph)), 2.29 (2.12) (s, 3 H, OAc), 5.34 (5.42) (s, 1 H, C$H$(OAc)), 7.30–7.70 (7.40–7.70) (m, 5 H, SPh); NMR for **20c** (**20d**) 1.3 0, 1.43, 1.65 (0.78, 1.19, 1.85) (3 s, 9 H, $Me_2C$, C$Me$(SOPh)), 1.69 (2.11) (s, 3 H, OAc), 5.76 (5.36) (s, 1 H, C$H$(OAc)), 7.40–7.80 (7.40–7.70), (m, 5 H, SPh); mass spectrum, $m/e$ 310 ($M^+$). Anal. Calcd for $C_{15}H_{18}O_5S$: C, 64.67; H, 6.59; S, 9.58. Found: C, 64.60; H, 6.60; S, 9.46.

**From $CH_3$CH(OAc)CHO**; total isolated yield 65%. **29a–c** (R = $CH_3$, R′ = H): oils; IR (**29a**) 1740, 1770; IR (**29b**) 1745, 1770; IR (**29c**) 1740, 1770; NMR (**29a**) 0.85 (d, 3 H, CH(C$H_3$), $J$ = 6.7), 1.52 (d, 3 H, CH(C$H_3$), $J$ = 6.0), 1.40, 1.66 (2 s, 3 H, C$Me$(SOPh)), 1.77, 2.09 (s, 3 H, OAc), 4.10–4.40 (m, 1 H, C$H$($CH_3$)), 5.25 (d, 1 H, C$H$(OAc), $J$ = 6.3), 5.67 (d, 1 H, C$H$(OAc), $J$ = 5.0), 7.30–7.80 (m, 5 H, SOPh); NMR (**29b**) 1.35 (d, 3 H, CH(C$H_3$), $J$ = 7.6), 1.53 (s, 3 H, C$Me$(SOPh)), 2.22, 2.30 (s, 3 H, OAc), 4.72 (m, 1 H, C$H$($CH_3$)), 5.32 (d, 1 H, C$H$(OAc), $J$ = 8.2), 5.41 (d, 1 H, C$H$(OAc), $J$ = 8.3), 7.30–7.80 (m, 5 H, S(O)Ph); NMR (**29c**) 1.44 (d, 3 H, CH(C$H_3$), $J$ = 6.3), 1.30 (m, 3 H, CH(C$H_3$)), 1.33 (s, 3 H, CC$H_3$(SOPh)), 2.29, 2.23 (2 s, 3 H, OAc), 4.33 (m, 1 H, C$H$($CH_3$)), 5.58 (d, 1 H, C$H$(OAc), $J$ = 4.0), 5.79 (d, 1 H, CH, (OAc), $J$ = 4.3), 7.40–8.10 (m, 5 H, SOPh). Anal. Calcd C, 56.76; H, 5.41; S, 10.81. Found: C, 56.89; H, 5.40; S, 11.02.

**General Procedure for the Pyrolysis of Sulfoxides 20–22 and 29.** The sulfoxide (0.250 g) was heated to reflux for 30 min in 50 mL of toluene. After removal of the solvent and column chromatography on silica gel (eluent 75:25 EP/E), the following was observed. In each example below pure *exo*-methylene derivatives **23–25** were obtained (60–70% yield) from compounds **20–22a,b** and **29a**. From sulfoxides **20–22c,d** a mixture of *exo*-methylene derivatives **23–25** (in a 36–42% yield) and butenolides **26–28** (in 24–28% yield) was obtained.

**From sulfoxide 22**; 60–70% total yield. **25** (R = R′ = $(CH_2)_5$): IR 1740, 1770; NMR 1.40–1.80 (m, 10 H, $C_5H_{10}$), 2.10 (s, 3 H, OAc), 5.46 (t, 1 H, $H_c$, $J$ = 1.6), 5.93 (br s, 1 H, $H_b$), 6.38 (br s, 1 H, $H_a$). **28**: oil; IR 1680, 1755, 1785; NMR 1.50–1.80 (m, 10 H, $C_5H_{10}$), 1.70 (s, 3 H, $CH_3C$=), 2.30 (s, 3 H, OAc); mass spectrum (**25**), $m/e$ 224 ($M^+$); mass spectrum (**28**), $m/e$ 224 ($M^+$). Anal. (of **25**) Calcd for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.29; H, 7.14. Anal. (of **28**) Calcd for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.11; H, 7.14.

**From sulfoxide 20**; 60–70% total yield. **23** (R = R′ = Me): oil; IR 1740, 1770; NMR 1.39, 1.43 (2 s, 6 H, $Me_2C$), 2.12 (s, 3 H, OAc), 5.55 (t, 1 H, $H_c$, $J$ = 1.5), 6.02 (d, 1 H, $H_b$, $J$ = 2.0), 6.49 (d, 1 H, $H_a$, $J$ = 2.0). **26**: oil; IR 1690, 1765, 1790; NMR 1.38 (s, 6 H, $Me_2C$), 1.70 (s, 3 H, MeC=), 2.30 (s, 3 H, OAc); mass spectrum (for **23**), $m/e$ 185 ($M^+$ + 1); mass spectrum (**26**), $m/e$ 185 ($M^+$ + 1). Although several elemental analyses were unsatisfactory, the analyses of the derived β-hydroxy derivatives were quite acceptable (see below).

**General Procedure for Hydrolysis of Sulfides 8–11.** The β-acetoxy lactone (500 mg) was dissolved in 10 mL of THF and 30 mL of saturated aqueous $Ba(OH)_2$ was added. The mixture was stirred for 4 h at room temperature then the solution was adjusted to pH 4 with aqueous HCl (2 N). After the usual workup, the crude product was purified by column chromatography (eluent 75:25 E/EP) or recrystallization and obtained in a 90% yield.

**From RR′C(OAc)CHO (R,R′ = $(CH_2)_5$; 6). 14a**: 54% yield; viscous oil (hydroxy and phenylthio groups in cis position); IR 3400–3600, 1760; NMR 1.50–1.80 (m, 10 H, $C_5H_{10}$), 1.38 (s, 3 H, C$Me$(SPh)), 3.95 (s, 1 H, C$H$(OH)), 7.20–7.70 (m, 5 H, SPh). **14b**: 36% yield; mp 148–149 °C (hydroxy and phenylthio groups in trans position); IR 3400–3600, 1760; NMR C$H$(OH)), 7.20–7.70 (m, 5 H, SPh); mass spectrum (**14a**), $m/e$ 292 ($M^+$); mass spectrum, (**14b**), $m/e$ 292 ($M^+$). Anal. (**14a,b** mixture) Calcd for $C_{16}H_{20}O_3S$: C, 65.75; H, 6.85; S, 10.96. Found: C, 65.74; H, 6.88; S, 10.91.

**From $(CH_3)_2$C(OAc)CHO (4)**: total yield 90%. **12a,b** (54% **a**, 32% **b**; analyzed as a mixture): mp 114–117 °C; IR 3400–3600, 1765; NMR 1.28, 1.37, 1.48, 1.48, 1.60 (5 s 9 H, $(CH_3)_2C$, CC$H_3$-(SPh)), 4.09, 4.13 (2 s, 1 H, CH(OH)), 7.20–7.70 (m, 5 H, SPh); mass spectrum, $m/e$ 252 ($M^+$). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 60.50; H, 5.88; S, 13.45. Found: C, 60.32; M, 5.83; S, 13.38.

**From $CH_3$CH(OAc)CHO (7)**; total yield 90%. **15b**: 54% yield; oil (γ-methyl and β-hydroxy groups in trans position); IR 3400–3600; NMR 1.46 (s, 3 H, CC$H_3$(SPh)) 1.31 (d, 3 H, CH(C$H_3$), $J$ = 6.0), 7.20–7.70 (m, 5 H, SPh). **15c**: 36% yield; mp 90–92 °C (γ-methyl and β-hydroxy in cis position); IR 3400–3600, 1770; NMR 1.42 (s, 3 H, CC$H_3$(SPh)), 1.52 (d, 3 H,, CH(C$H_3$), $J$ = 6.5), 3.94 (d, 1 H, C$H$(OH), $J$ = 4.0), 4.28 (dq, 1 H, C$H$($CH_3$), $J$ = 6.5, 4.0), 7.20–7.70 (m, 5 H, SPh); mass spectrum, $m/e$ 238 ($M^+$). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.50; H, 5.88; S, 13.45. Found: C, 60.32; H, 5.83; S, 13.38.

**General Procedure for the Preparation of Compounds 16, 18, and 19.** Oxidation of the β-hydroxy phenylthio lactones was conducted in the same way as the β-acetoxy lactones. Pyrolysis of sulfoxides was conducted without further purification and separation of diastereomers. Column chromatography (eluent 75:25 E/EP) afforded pure lactones **16**, **18**, and **19** in 50–65% yield.

**Lactone 18**: 50–65% yield; oil; IR 3400–3600, 1765; NMR 1.40–1.90 (m, 10 H, $C_5H_{10}$), 4.44 (t, 1 H, $H_c$, $J$ = 2.0), 5.88 (d, 1 H, $J$ = 1.8), 6.34 (d, 1 H, $H_a$, $J$ = 2.2); mass spectrum, $m/e$ 182 ($M^+$). Analyses were unsatisfactory although quite acceptable with the derived β-acetoxy derivative (see before).

**Lactone 16**: 50–65% yield; oil; IR 3400–3600, 1770; NMR 1.38, 1.45 (2 s, 6 H, $(Me)_2C$), 4.53 (t, 1 H, $H_c$, $J$ = 2.3), 5.96 (d, 1 H, $H_b$, $J$ = 2.0), 6.36 (d, 1 H, $H_a$, $J$ = 2.3). Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.04. Found: C, 58.93; H, 6.91.

**Lactone 19**; 50–65% total yield. **19b**: 30–42% yield (β-hydroxy and γ-methyl groups in trans position); oil; IR 3200–3400, 1770, 1670; NMR 1.45 (d, 3 H, *MeCH*, $J$ = 6.4), 4.30–4.60 (m, 2 H, C$H$($CH_3$), C$H$(OH)), 6.00 (d, 1 H, $H_b$, $J$ = 1.8), 6.36 (d, 1 H, $H_a$, $J$ = 2.0). **19c** (20–26% yield (β-hydroxy and γ-methyl groups in cis position); oil; IR 3200–3400, 1770, 1670; NMR 1.40 (d, 3 H, CH(C$H_3$), $J$ = 6.0), 4.70–5.00 (m, 2 H, C$H$($CH_3$), C$H$(OH)), 6.00 (d, 1 H, $H_b$, $J$ = 1.8), 6.36 (d, 1 H, $H_a$, $J$ = 2.0); mass spectrum (**19b,c**), $m/e$ 128 ($M^+$).

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76299-72-4; **6**, 56037-77-5; **7**, 22094-23-1; **8a**, 86289-58-9; **8b**, 86289-59-0; **9a**, 86289-60-3; **9b**, 86289-61-4; **10a**, 86289-62-5; **10b**, 86289-63-6; **11**, 86289-64-7; *trans*-**12**, 86289-65-8; *cis*-**12**, 86289-66-9; **14a**, 86289-67-0; **14b**, 86289-68-1; **15**, 86289-69-2; **16**, 86289-70-5; **18**, 86289-71-6; **19b**, 86289-72-7; **19c**, 86289-73-8; **20a**, 86289-74-9; **20b**, 86334-04-5; **20c**, 86334-05-6; **20d**, 86391-04-0; **21a**, 86289-75-0; **21b**, 86334-06-7; **22a**, 86289-76-1; **22b**, 86334-07-8; **22c**, 86334-08-9; **22d**, 86334-09-0; **23**, 86289-77-2; **24**, 86289-78-3; **25**, 86289-79-4; **26**, 86289-80-7; **28**, 86289-81-8; **29**, 86289-82-9; **32**, 86289-83-0; **33**, 86289-84-1; **34**, 86289-85-2; **35**, 86307-80-4; $Me_2C$=CHOAc, 14478-14-9; $Et_2C$=CHOAc, 22014-15-9; $C_5H_{10}C$=CHOAc, 23438-53-1; $CH_3CH$=CHOAc, 3249-50-1; cyclohexylcarboxaldehyde, 2043-61-0; propaldehyde, 123-38-6; thiophenol, 108-98-5; isobutyraldehyde, 78-84-2; 2-ethylbutyraldehyde, 97-96-1.

# Synthesis and Derivitization of 8-Acetylpsoralens. Acetyl Migrations during Claisen Rearrangement

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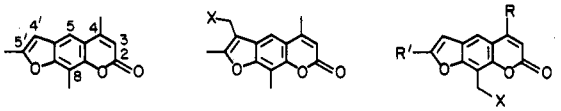
We have synthesized a series of 8-acetylpsoralens in which methyl and hydrogen substitutions were systematically varied at the 4- and 5′-positions. Claisen rearrangement was employed in developing the furano ring, and acetyl migration during the rearrangement was identified as a major side reaction. This migration was circumvented by applying a diethylaluminum chloride catalyzed Claisen rearrangement to the pyrone ring-opened compound. For the 5′-methyl compounds, furano ring formation was most effectively performed in a sulfuric–acetic acid mixture. The 8-acetyl group, through a series of transformations, was then converted to acetic acid and α-hydroxyethyl, β-hydroxyethyl, α-aminoethyl, aminomethyl, hydroxymethyl, and formyl moieties.

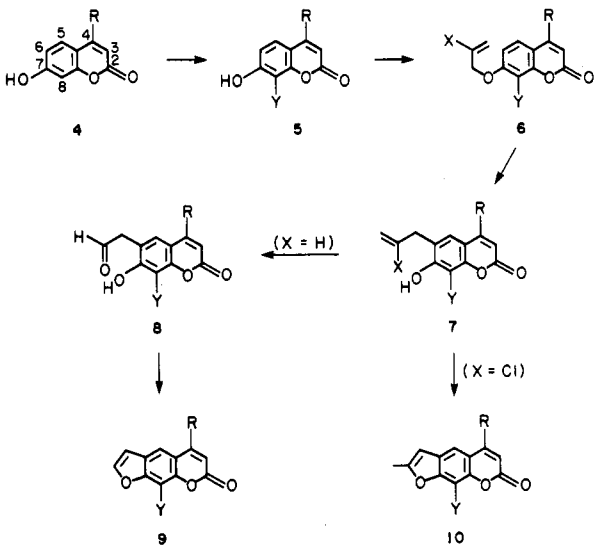
Psoralens **2** in which X = OH or $NH_2$ are superior to 4,5′,8-trimethylpsoralen (**1**) and 8-methoxypsoralen in their abilities to saturate photoreactive sites on DNA and RNA without repeated addition of reagent.[2] In particular, the 4′-aminomethyl derivatives (**2**, X = $NH_2$) is highly soluble in water and binds more strongly to DNA than does **1**. Thus **2** (X = $NH_2$) is a very effective photoreactive cross-linking reagent for both DNA and RNA.[2]



**1** **2** **3**

The effectiveness of **2** (X = $NH_2$) prompted an interest in the dependence of intercalation and photoreactivity on the type and position of substituents on the parent psoralen nucleus.[3] In particular, we wished to examine the extent to which the formation of monoadduct vs. diadduct (cross-link) depends on the substitution pattern on the photoreactive double bonds (C-3, C-4 and C-4′, C-5′).[4] We therefore sought to vary **2** in two ways as depicted in structure **3**. First we wished to move the water-solubilizing group to a nonreacting portion of the psoralen molecule. Placing this group at C-8 instead of C-5 appeared easier in terms of synthetic convenience and also involved the least amount of structural variation with respect to 4,5′,8-trimethylpsoralen (**1**).[5] We then wished to examine the role of the methyl groups at C-4 and C-5′ by making four series of compounds **3**: R = R′ = $CH_3$; R′ = H, R = $CH_3$; R′ = $CH_3$, R = H; R = R′ = H. Characterization of these compounds with respect to DNA and RNA in terms of dark binding constant, ability to saturate photoreactive sites, and ability to cross-link would then establish a basis for a more detailed understanding of the photoreaction of methyl-substituted psoralens with nucleic acids. This understanding could in turn be used as a guide for the

**Scheme I. Generalized Routes for Synthesis of Psoralens 3**




**4** **5** **6** **8** **7** **9** **10**

(1) Fellow of the Jane Coffin Childs Memorial Fund for Medical Research.

(2) Isaacs, S. T.; Shen, C. J.; Hearst, J. E.; Rapoport, H. *Biochemistry* **1977**, *16*, 1058.

(3) Many psoralens substituted with various alkyl groups and a limited number of psoralens substituted with other groups have been prepared and assayed for their ability to photosensitize skin. None of these psoralens contain a water-solubilizing group, a modification first introduced in ref 2. For a discussion of these compounds see: Musajo, L.; Rodighiero, G.; Caporale, G.; Dall'Aqua, F.; Marciani, S.; Bordin, F.; Baccichetti, F.; Bevilacqua, R. In "Sunlight and Man"; University of Tokyo Press: Tokyo, 1974; p 369.

(4) The complete structural characterizations of psoralen–pyrimidine monoadducts and diadducts have recently been reported (Kanne, D.; Straub, K.; Rapoport, H.; Hearst, J. *Biochemistry* **1982**, *21*, 861. Kanne, D.; Straub, K.; Hearst, J.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 6754). These reports also describe a quantitative method for determining the amounts of mono- and diadducts formed in a given psoralen–nucleic acid photoreaction.

(5) Also, models suggested that X in **3** would lie in a hydrophilic region of the double helix.

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