pressure to give a brown viscous oil. This oil was purified by preparative TLC [chloroform–acetone (10:1 v/v)] to yield 3,15-bis(3,4-dimethyl-2-pentenoyl)bruceolide (**3**, $[\alpha]^{25}_D$ −25° (*c* 0.45, pyridine), yield 47%] and 3-(3,4-dimethyl-2-pentenoyl)bruceolide (**4**, white crystals, 79.91 mg, yield 31%). Compound **4** could be converted to **3** in 77% yield by further esterification using **9** in an extract procedure described above. The relevant NMR and mass spectral data of **3** and **4** have been described in Table I.

Acid Hydrolysis of 3 to Bruceantin (5). A solution of compound **3** (78.3 mg, 0.119 mmol) in methanol (16 mL) was added to *p*-toluenesulfonic acid (240 mg, 1.26 mmol). The mixture was refluxed and examined by TLC (chloroform–acetone, 1:1). After 92 h, it was purified by preparative TLC (chloroform–acetone, 1:1) to yield **5** (26.9 mg, 41.3%) as white crystals. Further purification of these white crystals by high-performance LC [chloroform–ethyl acetate (1:1), Whatman partisil M 9 10/50] gave 98% pure **5**: mp 220–223 °C (lit.[1] mp 225–226 °C); $[\alpha]^{25}_D$ −31.6° (*c* 0.5, pyridine) [lit.[1] $[\alpha]^{25}_D$ −43° (*c* 0.31, pyridine)]. The identity of **5** was confirmed by a direct comparison (mixture melting point, TLC, IR, NMR, and mass spectra) with an authentic sample of bruceantin. In addition to **5**, unreacted triester (10.9 mg, 14%) and bruceolide (**2**, 6.5 mg, 13%) were also isolated from this reaction product by preparative TLC (chloroform–acetone, 1:1).

An alternate hydrolysis of **3** to **5** resulted in only 15% yield. This procedure was carried out by use of a solution of **3** (59.2 mg, 0.09 mmol) in 3 N H_2SO_4–MeOH (1:2, 6 mL) which was heated at reflux for 46 h. The reaction product was purified by preparative TLC (chloroform–acetone, 1:1) to afford pure **5** (7.2 mg) as white crystals.

15-Desenecioyl Bruceoside-A (6). A mixture of **1** (692.3 mg, 1.16 mmol) and 1 N KOH–MeOH (21 mL) was stirred at room temperature for 6 h. The mixture was neutralized with cation-exchange resin (Dowex 50 W-X2) and filtered. The filtrate was methylated with diazomethane[14] in the usual manner. The methylated product was evaporated in vacuo and purified by preparative TLC (chloroform–methanol–water, 50:14:3) to yield **6** (184.2 mg, 57% yield) as an amorphous substance which decomposed at ca. 200 °C. The relevant IR, ^{13}C NMR, and mass spectral data of **6** have been described in the text.

(14) Further methylation of the C-13 $COOCH_3$ was needed as it had been partially hydrolyzed.

Acid Hydrolysis of 6. A solution of **6** (306 mg) in 3 N H_2SO_4–MeOH (1:1, 40 mL) was refluxed for 7 h and then extracted with chloroform. The chloroform extract was dried ($MgSO_4$), filtered, and evaporated in vacuo to give a product which was subjected to preparative TLC (chloroform–acetone, 1:1) to yield pure **2** (43.5 mg).

The aqueous layer was neutralized with cation-exchange resin (Amberlite IR-45), filtered, dried, and evaporated to give a residue which was identified as the trimethylsilyl derivative of D-glucose by GLC [3% OV-17 on Chromosorb (80–100 mesh), 3 mm × 2 m, 170 °C, N_2, 15 mL/min, injection temperature 180 °C, detector temperature 180 °C].

Esterification of 6 and Hydrolysis of 3,5-Dimethyl-2-pentenoyl Ester of 6. A solution of **6** (89.9 mg, 0.15 mmol) in dry pyridine (2 mL) was added dropwise to a solution of **9** (330 mg, 2.25 mmol) in dry chloroform (2 mL). The mixture was stirred at room temperature for 20 h until the TLC (chloroform–methanol–water, 50:14:3) showed the disappearance of **6** and then water was added to decompose the unreacted acid chloride. The reaction product (**7**, proposed[15]), without further purification and isolation, was dissolved in dichloromethane (10 mL) and then 6 drops of BF_3 etherate was added. The reaction mixture was stirred at room temperature and examined by TLC (chloroform–acetone, 1:1). After 4 days, the product was subjected to preparative TLC (chloroform–acetone, 10:1) to yield pure **5** (47.7 mg, 58% yield).

Acknowledgment. This investigation was supported by a grant from the National Cancer Institute (CA 22929). We thank Dr. Matthew Suffness of the National Cancer Institute for an authentic sample of bruceantin, Dr. David L. Harris, Department of Chemistry, University of North Carolina at Chapel Hill for NMR spectra, and Dr. David Rosenthal and Mr. Fred Williams, Research Triangle Center for Mass Spectrometry, for mass spectral data.

Registry No. **1**, 63306-30-9; **2**, 25514-28-7; **3**, 76215-40-2; **4**, 76215-41-3; **5**, 41451-75-6; **6**, 76215-42-4; **7**, 76232-15-0; (*E*)-**9**, 76215-43-5; (*E*)-**10**, 38972-59-7; (*E*)-**11**, 21016-44-4; **12**, 563-80-4.

(15) Structure **7** was proposed for this reaction product based upon the fact that in an analogous study of the esterification of brusatol (**8**), bruceantin (**5**), and bruceoside-A (**1**), both hydroxyl groups at C-11 and C-12 of these compounds were resistant to this kind of esterification.

Allergenic α-Methylene-γ-lactones. General Method for the Preparation of β-Acetoxy- and β-Hydroxy-α-methylene-γ-butyrolactones from Sulfoxides. Application to the Synthesis of a Tuliposide B Derivative

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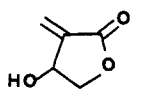
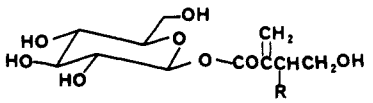
A general synthesis of β-hydroxy-α-methylene-γ-butyrolactones, which is based on the sulfoxide–sulfenate rearrangement, is presented. Several β-acetoxy-α-methylene-γ-butyrolactones have been prepared and transformed into the β-hydroxy derivatives through base hydrolysis. This synthesis has been applied to the first preparation of (tetraacetoxybenzyl)tuliposide B (**22**).

Many natural compounds contain the β-hydroxy-α-methylene-γ-butyrolactone unit **1**.[1] Several of these



1



2

substances show bactericidal or fungicidal activity. Among them are β-hydroxy-α-methylene-γ-butyrolactone precursors such as tuliposide B (**2**, R = OH), which is found in tulip bulbs,[2] along with tuliposide A (**2**, R = H), re-

(1) C. J. Cavallito and J. H. Haskell, *J. Am. Chem. Soc.*, **68**, 2332–2334 (1946); M. Niwa, M. Iguchi, and S. Yamamura, *Chem. Lett.*, 655–658 (1975); K. Takeda, K. Sakwawi, H. Ishū, *Tetrahedron*, **28**, 3757–3766 (1972); J. C. Martinez, V. M. Yoshida, and O. R. Gottlieb, *Tetrahedron Lett.*, 1021–1024 (1979).

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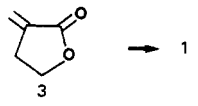
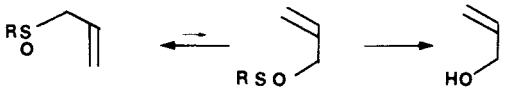
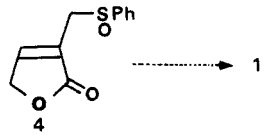
Scheme I



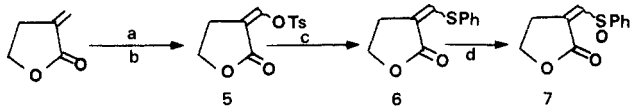
Scheme II



Scheme III



Scheme IV[a]



[a] (a) HCOOEt, NaH; (b) TsCl; (c) PhSNa; (d) *m*-CPBA.

sponsible for "tulip fingers",[3] an allergic contact dermatitis (ACD) to tulip bulbs. Interestingly, the presence of a hydroxy group β to the lactone function seems to *inhibit* ACD to this compound.

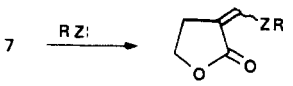
Our involvement in the study of the molecular mechanisms of ACD[4] led us to study these compounds in relation with α-methylene-γ-butyrolactones, which are potent sensitizers.[5] At the beginning of this research, no general method for the preparation of β-hydroxy-α-methylene-γ-butyrolactones was available. This paper reports a general synthesis of β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones (a short account on part of this work has appeared[6]) and the first synthesis of a derivative of tuliposide B.

Results and Discussion

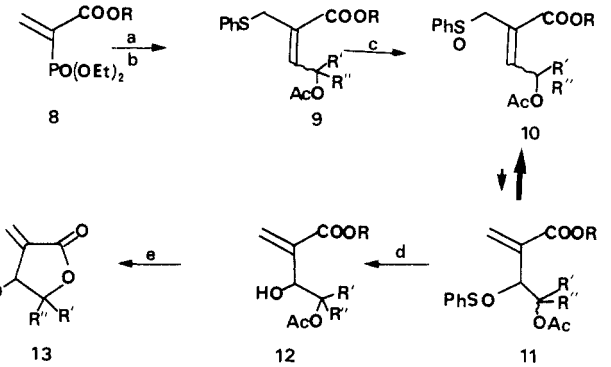
Synthesis of β-Hydroxy-α-methylene-γ-butyrolactones. When this work was started, only one preparation of tulipalin B (1, β-hydroxy-α-methylene-γ-butyrolactone) was in the literature,[7] and it consisted of the allylic oxidation of α-methylene-γ-butyrolactone (3) with SeO_2 and gave poor yields (Scheme I). Recently[8] this compound was prepared by another route.

Since 1 and its derivatives are allylic alcohols, it seemed natural to use the Mislow–Evans rearrangement[9] of sulfoxides into sulfenates, the latter yielding allylic alcohols through the use of a thiophile reagent (Scheme II).

Scheme V

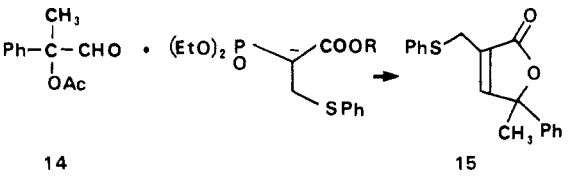


Scheme VI[a]



[a] (a) PhSNa; (b) R'R''C(OAc)CHO; (c) *m*-CPBA; (d) $P(OMe)_3$; (e) *p*-TsOH.

Scheme VII



We first attempted to isomerize phenyl sulfoxide 4 into compound 1 (Scheme III). We reasoned that compound 4, a β-unsaturated sulfoxide, could be obtained through the known isomerization of vinyl into allyl sulfoxide.[10] Treatment of vinyl tosylate 5 with phenyl sulfide gave sulfide 6 which was oxidized to vinyl sulfoxide 7 by the sequence outlined in Scheme IV. However, numerous attempts to isomerize vinyl sulfoxide 7 were unsuccessful.

Base treatment of sulfoxide 7 always resulted in an addition–elimination reaction leading to substituted vinyl ethers or enamines (Scheme V). We have taken advantage of these latter results to realize a short and convenient one-carbon degradation of a natural sesquiterpene lactone, isoalantolactone.[11]

Finally, we succeeded in preparing β-acetoxy-α-methylene-γ-butyrolactones, including the acetoxy derivative of tulipalin B, by using the sequence outlined in Scheme VI which starts from the α-methylene phosphonate 8. This compound has been used previously by McIntosh and Sieler[12] in the synthesis of dihydrothiophenes and by Heathcock[13] and Semmelhack[13] in the preparation of 2-[(alkylthio)methyl]acrylates. Michael addition of phenyl sulfide to phosphonate 8 led to an intermediate of a Horner–Emmons-type reaction, giving an allylic sulfide 9 with a properly chosen α-acetoxy aldehyde. The latter compounds were prepared from the corresponding epoxy acetates by thermal or acidic treatment.[14]

(2) R. Tschesche, F. J. Kammerer, and G. Wulff, *Chem. Ber.*, 102, 2057–2071 (1969); R. Tschesche, F. J. Kammerer, G. Wulff, and F. Schonbeck, *Tetrahedron Lett.*, 701–706 (1968); A. Slob, *Phytochemistry*, 12, 811–815 (1972); A Slob, B. Jekel, B. de Jong and E. Schlatmann, *ibid.*, 14, 1997–2008 (1975).

(3) G. A. W. Verspyck Mijnssen, *Br. J. Dermatol.*, 81, 737–745 (1969).

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

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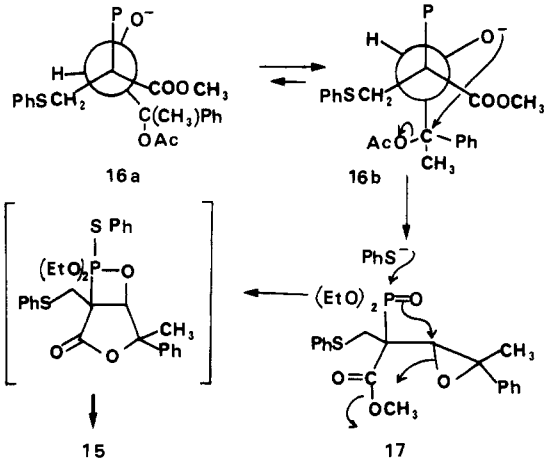
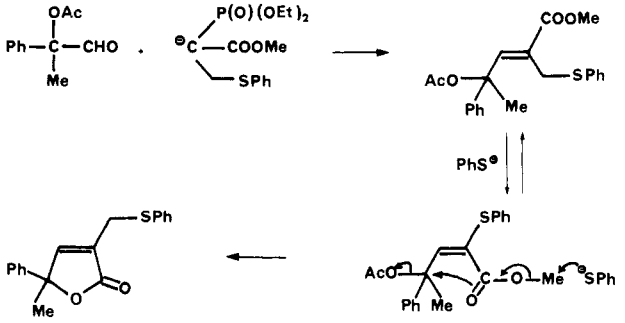
Scheme VIII



Scheme IX



Two stereoisomeric sulfides were obtained. The major one (>95%) had the *Z* configuration as deduced from its NMR spectrum: the vinyl protons had a signal at δ 6.9–7.0 (relative to internal Me_4Si), characteristic of such systems.[15] This result is consistent with findings in the literature showing that the major stereoisomer obtained with stabilized phosphonates corresponds to the intermediate betaine with the COOR group and the bulky group [here CRR(OAc)] trans.[16]

Interestingly, with sterically hindered aldehydes such as compound **14**, the expected sulfide **9** was not obtained. Instead, another compound, butenolide **15**, was formed (Scheme VII). A tentative explanation can be offered. In the Horner–Emmons reaction, the initially formed betaine **16** must adopt an eclipsed conformation, **16a**, in order to eliminate the phosphate ion. When the aldehyde has bulky groups, eclipsed conformation **16a** is certainly not as populated as the staggered conformation **16b** (Scheme VIII), so that another reaction can occur, such as, for instance, an S_N2 reaction on the C–OAc carbon. This would lead to epoxide **17** which can be transformed through PhS^- attack on phosphorus to an oxaphosphetane and finally to compound **15**. [A referee has suggested another possible mechanism (Scheme IX).]

Oxidation of sulfides **9** led to a 1:1 mixture of diastereomers **10A** and **10B**. While each isomer could be isolated, they epimerized slowly, through sulfenate formation. After being allowed to stand 180 h neat, either one of them gave again a 1:1 mixture of **10A** and **10B**. Treatment of sulfoxide **10** with trimethyl phosphite at room temperature for 72 h gave allylic alcohol **12**; the latter could finally be cyclized through TsOH treatment. Not unexpectedly, the β-acetoxy derivative **13** rather than the β-hydroxy one was obtained. This vicinal rearrangement is a common finding in carbohydrate chemistry (Scheme X).

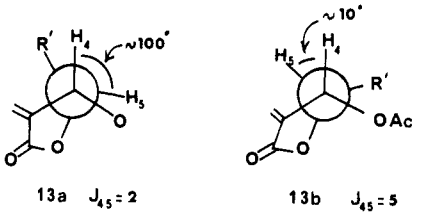
Table I. Preparation of β-Acetoxy-α-methylene-γ-butyrolactones 13

R′	yield,[a] %	R′	yield,[a] %
H (13a)	22 (42)	i-C_3H_7 (13d)	20
CH_3 (13b)	30 (33)	n-C_5H_{11} (13e)	19
C_2H_5 (13c)	37 (40)		

[a] After purification, on the basis of the starting α-acetoxy aldehydes, and five steps, **8** → **13** (in parentheses is the yield after three steps, with the direct **10** → **13** transformation).

Trimethyl phosphite treatment of sulfoxide **10** was time consuming and required final *p*-TsOH treatment for ring closure. We discovered incidentally that β-acetoxy lactone **13** could be obtained directly from sulfoxide **10** in one step by *p*-TsOH treatment. This interesting shortcut should prove invaluable in the synthesis of other similar lactone derivatives.

The series of reactions described above gave a number of β-acetoxy-α-methylene-γ-butyrolactones in fair to good yields (Table I). The β-substituted derivatives were obtained as a 1:1 mixture of separable diastereomers. Rearrangement of the AcO group can be depicted as in Scheme X. Because the OH and OAc groups must be cis to each other, the configuration of lactones **13** at C_4 and C_5 must be the same as that in the allylic alcohols **12** and can be deduced from the value of $J_{4,5}$ = 2 Hz in isomer **13a** whereas it is 5 Hz in isomer **13b**. Molecular models show dihedral angles ~100° and ~10°, respectively.



Tulipalin B (**1**) could be obtained in 45% yield from hydroxy ester **18** by $Ba(OH)_2$ treatment followed by acidification to pH 4. The hydroxy acid **19** crystallized slowly and changed spontaneously at room temperature into β-hydroxy-α-methylene-γ-butyrolactone (**1**, Scheme XI).

The reactions described above were used to synthesize a derivative of tuliposide B.

Synthesis of a Benzyltetraacetyl Derivative of Tuliposide B. Several attempts using 2,3,4,6-tetrabenzylglucose **23** (X = OH, R′ = $CH_2C_6H_5$) and acyl chloride derivatives, as well as 1-bromo- or 1-chloro-2,3,4,6-tetrabenzylglucose with β-hydroxy-α-methylenecarboxylate silver salts were unsuccessful.

Finally, the benzyltetraacetoxy derivative of tuliposide B was prepared from tetraacetobromoglucose **23** (R′ = Ac, X = Br) and the silver salt **24**, prepared as shown in Scheme XII.

Tuliposide B derivative **22** was a 80/20 mixture of diastereomers, since the silver carboxylate derivative **24** was not resolved. This was shown clearly by the vinyl proton signals which appear as two broad singlets at δ 6.11 and 6.50 for the major isomer and at δ 6.03 and 6.44 for the minor isomer, as well as by the presence of two unequal broad singlets for the benzylic protons at δ 4.59 (major isomer) and δ 4.57 (minor isomer). The β configuration at the anomeric C_1 carbon was demonstrated by a H_1H_6 coupling of 7.0 Hz. For an α-configuration, one would have

(15) A. Saeffer, R. J. Pratt, H. P. Ruesch, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 383–403 (1970).
(16) J. Boutagy, and R. Thomas, *Chem. Rev.*, **74**, 87–99 (1974).
(17) L. H. Welsh, *J. Org. Chem.*, **32**, 119–122 (1967).

expected a value of ~3 Hz.[18]

The mass spectrum of compound **22** was also in agreement with the proposed structure: in particular, there were peaks at m/e 534 ($M^{+\cdot}$ - 18) and 331 (breaking of the C_1OCO bond). The IR showed the expected absorption bands at 1755 (OAc) and 1745 cm^{-1} ($OCO{=}CH_2$).

Conclusion

The results described here provide an entry into β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones. This synthetic scheme can be applied to the synthesis of various natural products with the β-hydroxy-α-methylene-γ-butyrolactone moiety. Preliminary results on experimental sensitization of guinea pigs confirmed earlier findings of the literature: β-hydroxy-α-methylene-γ-butyrolactones are much less sensitizing than the corresponding unsubstituted derivatives.

Although tuliposide B itself (**2**) could not be prepared, a derivative, **22**, was prepared for the first time.

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 $CHCl_3$ or CCl_4 solutions; wave numbers (cm^{-1}) are given. Proton nuclear magnetic resonance (NMR) spectra were recorded on Perkin-Elmer R24 B, R12 B (60 MHz), or R 32 (90 MHz), Bruker WH 90 (90 MHz), or Cameca (250 MHz) spectrometer; chemical shifts are reported as δ values in part per millions 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 60 F 254, layer thickness 0.25 mm, from Merck, Darmstadt). Preparative TLC was conducted on 20 × 20 cm glass precoated plates (2-mm thickness) with silica gel 60 F 254 from Merck.

Silica gel columns for chromatography utilized Merck silica gel 60, 70–230-mesh ASTM. Vapor-phase chromatography (VPC) analyses were performed on a Girdel 300 equipped with a flame-ionization detector.

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, ethyl ether; AcOEt, ethyl acetate; EtOH, ethanol; THF, tetrahydrofuran; s, singlet; m, multiplet; d, doublet; t, triplet; q, quartet; *m*-CPBA, *m*-chloroperbenzoic acid.

"Usual workup" means extraction with a solvent (CH_2Cl_2 or EE), washings with water, 5% aqueous $NaHCO_3$ or HCl, and water, drying over Na_2SO_4, and removal of solvent.

3-(Hydroxymethylene)-γ-butyrolactone-3-*p*-toluenesulfonate (**5**), 3-[(phenylthio)methylene]-γ-butyrolactone (**6**), and 3-[(phenylsulfinyl)methylene]-γ-butyrolactone (**7**) were prepared according to standard procedures. All analytical data: combustion analyses, IR, NMR and mass spectra were consistent with the proposed structures.

General Procedure for the Preparation of Enol Acetates, R′R″C=CHOAc. An example is as follows. 2-Phenylpropionaldehyde (67.0 g, 0.50 mmol) was dissolved in Ac_2O (500 mL), and anhydrous K_2CO_3 (1.0 mol) and KOAc (0.50 g) were added; the mixture was heated for 2 h at 130 °C. The precipitate was filtered off, excess Ac_2O was evaporated on a Rotavapor (Büchi), and the residue was distilled. The known enol acetate was obtained: bp 65–66 °C (0.1 mm); 51 g (0.29 mmol, yield 58%); IR 1760, 1655, 1580; NMR 1.98 (d, 3 H, J = 1.5, E or Z isomer), 2.06 (d, 3 H, J = 1.5, Z or E isomer), 2.13 (s, 3 H, OAc), 7.26 (s, 5 H, Ph), 7.46 (q, 1 H, = CHOAc, J = 1.5).

Other enol acetates were MeCH=CHOAc [bp 107 °C (760 mm), 40% yield] and *i*-PrCH=CHOAc [bp 60–65 °C (15 mm), 60%]. All enol acetates had spectral data (IR, NMR) compatible with the proposed structures.

General Procedure for the Preparation of Enol Epoxy Acetates, R′R″C–CH(OAc)–O. The enol acetate (20 mmol) in CH_2Cl_2 (25 mL) was treated with 1 equiv of *m*-CPBA added in small portions at 0 °C. After completion of peracid addition, the mixture was stirred 4 h at room temperature. The usual workup of the CH_2Cl_2 solution gave in ~90% yield pure epoxy acetates.

In this way were prepared (with 100% yield from the enol acetate) MeCHCH(OAc)O [a mixture of E and Z isomers): oil; IR 1760; NMR 1.33 (d, 3 H, Me, J = 5.3, E isomer), 1.40 (d, 3 H, Me, J = 5.3, Z isomer), 2.10 (s, 3 H, OAc, E isomer), 2.13 (s, 3 H, OAc, Z isomer), 2.9–3.3 (m, CH_3CH), 5.30 (d, CHOAc, J = 2.3, E isomer), 5.53 (d, CHOAc, Z isomer)] and *i*-PrCHCH(OAc)O.

The epoxy acetate with R′ = CH_3 and R″ = C_6H_5 could not be isolated and led directly to an α-acetoxy aldehyde. Epoxy acetate with R′ = H and R″ = C_5H_{11} was prepared as described.[14]

General Procedure for the Preparation of α-Acetoxy Aldehydes R′R″C(OAc)CHO. Treatment with catalytic amounts of BF_3/ether of epoxy acetates R′R″CC(OAc)O (R′ = R″ = Et; R′ $C_2H_5CH(OAc)CHO$ Ph, R″ = Me) gave the corresponding α-acetoxy aldehydes in satisfactory yields. The other aldehydes were prepared by heating the epoxy acetates at 120 °C under an argon atmosphere, without solvent, for more than 4 h. When necessary (as shown by NMR), the aldehyde was distilled; the α-acetoxy aldehyde with R′ = C_5H_{11} and R″ = H was prepared as described.[14]

All α-acetoxy aldehydes had IR (1750, 1740 cm^{-1}) and NMR spectral data in agreement with the proposed structures. Thus were prepared $CH_3CH(OAc)CHO$ [bp 60 °C (14 mm), lit. bp 63–64 °C (16 mm)], $C_2H_5CH(OAc)CHO$ [bp 65 °C (13 mm), lit. bp 65–66 °C (13 mm)], $(CH_3)_2CHC(OAc)CHO$ [bp 60–65 °C (15 mm)], and $C_6H_5(CH_3)C(OAc)CHO$ (viscous oil).

Preparation of α-Acetoxy Acetaldehyde (R′ = R″ = H). 1,2-Diacetoxy-1-ethoxyethane was prepared as described in the literature[19] in 70% yield from ethyl vinyl ether and $Pb(OAc)_4$; bp 110 °C (14 mm) [lit. bp 103–105 °C (12 mm)]. To a solution of the above compound (60.0 g, 315 mmol) in water (5.7 mL) was added 1 drop of concentrated HCl. After vigorous stirring at room temperature for 24 h, the homogeneous mixture was distilled: bp 77 °C (50 mm) [lit. bp 75 °C (50 mm)]; 8.0 g (0.78 mmol, yield 25%).

General Procedure for the Preparation of Allylic Sulfides 9. An example is as follows. To a solution of NaSPh in 20 mL of anhydrous THF [prepared from NaH (0.938 g, 21.5 mmol) and PhSH (2.36 g, 21.5 mmol) at 0 °C] was added with a syringe, under argon, 1 equiv of phosphonate **8** (R = Me). When the addition was completed, a clear solution was obtained. After 2 min, α-acetoxyacetaldehyde (R′ = CH_3, R″ = H) was added (2.5 g, 21.5 mmol) with a syringe. After some minutes a voluminous precipitate of phosphate was obtained. The mixture was left at room temperature for 2 h, diluted with ether, washed with water (3 × 50 mL), and dried, and the solvent was removed. After column chromatography (eluent PE/EE, 75:25), allylic sulfide **9a** (3.53 g, 12.0 mmol, 60% yield) was obtained: oil; IR 1745, 1733, 1645; NMR 1.95 (s, 3 H, OAc), 3.69 (s, 3 H, $COOCH_3$), 3.75 (s, 2 H, CH_2SPh), 4.28 (d, 2 H, CH_2OAc, J = 6.2), 6.71 (t, 1 H, CH=C($COOCH_3$), J = 6.2), 7.1–7.6 (m, 5 H, Ph); mass spectrum, m/e 280 ($M^{+\cdot}$).

Anal. Calcd for $C_{13}H_{16}O_4S$: C, 60.18; H, 5.82; S, 11.70. Found: C, 60.0; H, 5.71; S, 11.42.

Other allylic sulfides prepared were $CH_3CH(OAc)CH{=}C(COOCH_3)CH_2SPh$ (**9b** 56% yield), $C_2H_5CH(OAc)CH{=}C(COOCH_3)CH_2SPh$ (**9c**, 60% yield), $(CH_3)_2CHCH(OAc)CH{=}C(COOC_2H_5)CH_2SPh$ (**9d**, 44% yield), and $C_5H_{11}CH(OAc)CH{=}C(COOC_2H_5)CH_2SPh$ (**9e**, 50% yield).

All of them had satisfactory combustion analyses (except **9b**, for which all other data, including mass spectral data, supported

(18) L. D. Hall, *Tetrahedron Lett.*, 1457–1460 (1964); V. S. Rao and J. F. Foster, *J. Phys. Chem.*, **67**, 951–954 (1963).

(19) R. Criegee, P. Dimroth, K. Noll, R. Simon, and C. Weis, *Chem. Ber.*, **90**, 1070–1081 (1957).

the structure) and spectral data compatible with the proposed structures.

Preparation of Lactone 15. The procedure was as above, using phenacyl chloride as the carbonyl compound. No reaction occurred after 2 h at room temperature. The mixture was then refluxed for 2 h. After the usual workup and column chromatography on silica gel (eluent EtOAc), a 10% yield of lactone **15** was obtained. The structure was deduced from mass spectrometry [296 (M^+)], IR (C=O absorption at 1770 cm^{-1}, a γ-lactone) and NMR: oil; IR 1770, 1655, 1585; NMR 1.61 (s, 3 H, CH_3), 3.62 (d, 2 H, H_6, $J_{6,4}$ = 1.0), 6.98 (t, 1 H, H_4, $J_{4,6}$ = 1.0), 6.9–7.4 (m, 5 H, C_6H_5).

General Procedure for the Preparation of Allylic Sulfoxides 10. An example is as follows for the synthesis of sulfoxide **10b**, $CH_3CH(OAc)CH{=}C(COOCH_3)CH_2S(O)Ph$. To a solution of sulfide **9b** [$CH_3CH(OAc)CH{=}C(COOCH_3)CH_2SPh$); 1.51 g, 5.14 mmol, in 10-mL of CH_2Cl_2] was added a solution of *m*-CPBA (0.97 g, 5.65 mmol) at −10 °C. After the usual workup, the crude sulfoxide was purified by column chromatography (eluent PE/EE, 1:1); sulfoxide **10b** (1.55 g, 5.0 mmol, 97% yield) was obtained as a mixture of diastereomers: oil; IR 1735, 1725, 1645; NMR (isomer 1) 1.45 (d, 3 H, CH_3CH, J = 6.0), 1.99 (s, 3 H, OAc), 3.35 (s, 3 H, $COOCH_3$), 4.31 (AB q, δ_A 4.30, δ_B 3.93, J = 13.3, 2 H, $CH_2S(O)Ph$), 5.41 (dq, CH(OAc), J = 6.0, 8.9), 6.83 (dd, CH=, J = 8.9, 0.5), 7.6 (s, 5 H, Ph); NMR (isomer 2) 1.47 (d, 3 H, CH_3CH), 1.98 (s, 3 H, OAc), 3.74 (s, $COOCH_3$), 3.96 (d, $CH_2S(O)Ph$), 5.53 (dq, 1 H, CH(OAc), J = 6.0, 9.2), 6.91 (d, CH=, J = 9.2), 7.3–7.8 (m, 5 H, Ph); mass spectrum, m/e 311 (M^+ + 1). The two diastereomers could be separated by thick-layer chromatography. They both had the *Z* configuration (see text). Although several elemental analyses were unsatisfactory, the above data fully support the proposed structures.

The other sulfoxides gave satisfactory elemental analyses and spectral (IR, NMR, and mass spectra) data. They included the following: **10a**, $AcOCH_2CH{=}C(COOCH_3)CH_2S(O)Ph$ (97% yield from sulfide **9a**); **10c**, $C_2H_5CH(OAc)CH{=}C(COOCH_3)CH_2S(O)Ph$ (84% yield); **10d**, $(CH_3)_2CHCH(OAc)CH{=}C(COOC_2H_5)CH_2S(O)Ph$ (65% yield); **10e**, $C_5H_{11}CH(OAc)CH{=}C(COOC_2H_5)CH_2S(O)Ph$ (50% yield).

General Procedure for the Preparation of Allylic Alcohols 12. An example is as follows. A diastereomeric mixture of sulfoxides **10e** (0.580 g, 1.51 mmol) was dissolved in MeOH (2 mL), and freshly distilled $(MeO)_3P$ was added (0.189 g, 1.52 mmol). The mixture, under an argon atmosphere, was left 3 days at room temperature, and MeOH was removed under vacuum. The residue was column chromatographed (eluent PE/EE, 4:6). A 1:1 mixture of diastereoisomers, A and B, was isolated: 0.362 g (1.33 mmol, yield 87%); oil; IR 3500, 1745, 1720, 1635; NMR (isomer A) 0.86 (t, $CH_3CH_2CH_2$, J = 7.0), 1.1 (m, 8 H), 1.31 (t, $COOCH_2CH_3$, J = 7.3), 1.99 (s, CH_3CO), 4.4–4.6 (m, CH(OH)), 5.0–5.3 (m, CH(OAc), 5.81 (s, $=CH_b$), 6.26 (s, $=CH_a$); NMR (isomer B) 0.86 (t, $CH_3CH_2CH_2$, J = 7.0), 1.1–1.9 (m, 8 H), 4.17 (q, $COOCH_2CH_3$), 4.1–4.5 (m, CH(OH)), 4.9–5.2 (m, CH(OAc), 5.75 (s, $=CH_b$), 6.30 (s, $=CH_a$).

Other allylic alcohols prepared were as follows: **12a**, $CH_3COOCH_2CH(OH)C(COOCH_3){=}CH_aH_b$ (40% yield); **12b**, $CH_3CH(OAc)CH(OH)C(COOCH_3){=}CH_aH_b$ (62% yield); **12c**, $C_2H_5CH(OAc)CH(OH)C(COOCH_3){=}CH_aH_b$ (80% yield); **12d**, $(CH_3)_2CHCH(OAc)CH(OH)C(COOC_2H_5){=}CH_aH_b$ (81% yield). All had spectral data (IR and NMR) compatible with the proposed structures.

General Procedure for the Preparation of β-Acetoxy-α-methylene-γ-butyrolactones 13 from Allylic Alcohols 12. The corresponding allylic alcohols were refluxed for 45 min under an argon atmosphere, in the presence of a catalytic amount of TsOH. The resulting lactones (obtained quantitatively from the alcohols) were purified by column chromatography. Analytical and spectral data are recorded in Table II.

Direct Preparation of β-Acetoxy-α-methylene-γ-butyrolactones 13 from Allylic Sulfoxides 10. An example is as follows. Sulfoxides **10** (R′ = Me, R″ = H; 0.100 g, 0.322 mmol) in CCl_4 (5 mL) were refluxed under argon for 2 h in the presence of a catalytic amount of TsOH. After removal of the solvent and column chromatography (eluent PE/EE, 1:1), lactone **13** (R′ = Me, R″ = H; 0.035 g, 0.203 mmol, 63% yield) was obtained.

Tulipalin B: β-Hydroxy-α-methylene-γ-butyrolactone (1). The ester **18** (0.550 g, mmol) was dissolved in $Ba(OH)_2$ (0.5 N, 20 mL) for 1 day at room temperature. The pH was then adjusted to 4.0 with an aqueous 2 N HCl solution. The resulting aqueous solution was partially lyophilized (to 10 mL of solution), NaCl was added, and the usual workup with ether gave a residue which was hydroxy acid **19**, partially lactonized into γ-lactone **1** (as shown by IR). Ring closure was achieved by heating the compound for 2 h at 40 °C. The residue was then chromatographed on a silica gel column (elution with $CHCl_3$/MeOH, 9:1) to give 0.139 mg (1.22 mmol) of a tulipalin B (**1**, yield 45%), whose IR and NMR spectra were identical with those described in the literature.[7]

β-Hydroxy-α-methylene-γ-pentyl-γ-butyrolactone. It was prepared as described above for tulipalin B in 32% yield (after purification): oil; IR 3350, 1765, 1665; NMR 0.89 (br t, $C_4H_8CH_3$, J = 6), 1.0–2.0 (m, 8 H), 2.0–2.5 (m, OH, removed with D_2O), 4.1–4.4 (m, 1 H, H_5), 4.4–4.6 (m, H_4 isomer 4*R*,5*S* plus 4*S*,5*R*), 4.84 (dt, 1 H, H_4, isomers 4*R*,5*R* and 4*S*,5*S*, $J_{4a} = J_{4b}$ = 2.0, $J_{4,5}$ = 5.6), 5.97 (d, 1 H, H_b, J_{4b} = 2.0), 6.39 and 6.41 (2 d, 1 H, H_a, 2 isomers, J_{4a} = 2.0); mass spectrum, m/e 185 (M^+ + 1), 167 (M^+ + 1 − H_2O), 166 (M^+ − H_2O).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.69. Found: C, 65.39; H, 8.85.

Synthesis of Silver 4-(Benzyloxy)-3-hydroxy-2-methylenebutanoate (24, R = CH_2Ph). α-(Benzyloxy)acetaldehyde was prepared as follows. To benzyl alcohol (750 mL) was added ground NaOH (40 g), and the mixture was heated for 1 h at 140 °C. After the mixture cooled to 90–110 °C, ethylene chlorohydrin (110 g, 1 mol) was added, and then the temperature was raised to and maintained at 140 °C for an additional hour. After the mixture cooled at room temperature, the organic phase was washed with water and distilled. The benzylic ether distilled at 150 °C (0.2 torr) [lit. 164–166 °C (2 torr)]; yield 55%.

The above distilled ether (60.7 g, 0.330 mol) was treated with sodium bismuthate (1 equiv) as described. Then was obtained, after distillation, 23.0 g (0.153 mol) of α-(benzyloxy)acetaldehyde: bp 119 °C (13 mm); 46% yield.

Allylic sulfide $(PhCH_2O)CH_2CH{=}C(COOC_2H_5)CH_2SPh$ was prepared as described above in 88% yield from the aldehyde: oil; IR 1715, 1640, 1580; NMR 1.25 (t, 3 H, CH_2CH_3, J = 7.0), 3.71 (br s, 2 H, H_5), 3.78 (d, 2 H, H_4, $J_{4,3}$ = 5.7), 4.18 (q, 2 H, CH_2CH_3, J = 7.0), 4.35 (s, 2 H, OCH_2Ph), 6.85 (t, 1 H, H_3, $J_{3,4}$ = 5.7), 7.26 (br s, 10 H, C_6H_5); mass spectrum, m/e 342 (M^+), 232 (M^+ − PhSH).

Anal. Calcd for $C_{20}H_{22}O_3S$: C, 70.17; H, 6.43; S, 9.35. Found: C, 70.21; H, 6.48; S, 9.45.

The corresponding sulfoxide was obtained quantitatively as described above: oil; IR 1710, 1645, 1045; NMR 1.20 (br t, 2 H, CH_2CH_3, J = 7.0), 3.85 (br s, 2 H, H_5), 4.05 (q, 3 H, CH_2CH_3, J = 7.0), 4.0–4.2 (m, 2 H, H_4), 7.17 (t, 1 H, H_3, $J_{3,4}$ = 6.0), 7.25 (s, 5 H, $CH_2C_6H_5$), 7.2–7.7 (m, 5 H, SC_6H_5); mass spectrum, m/e 250 (M^+ − $PhCH_2OH$), 232 (M^+ − PhSOH).

Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.04; H, 6.14; S, 8.93. Found: C, 66.91; H, 6.21; S, 8.66.

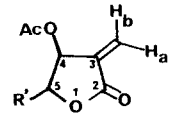
The corresponding allylic alcohol was obtained as described above by using $(MeO)_3P$ in a 45% yield: oil; IR 3600, 1715, 1630; NMR 1.25 (t, 3 H, CH_2CH_3, J = 7.5), 3.15 (m, 1 H, OH, removed with D_2O), 3.60 (AB part of an ABX, δ_A 3.75, δ_B 3.44, J = 4.61, s, 2 H, CH_2Ph), 4.61–4.93 (m, 1 H, H_3), 6.03 (br s, 1 H, H_b), 6.40 (br s, 1 H, H_a), 7.35 (br s, 5 H, C_6H_5); mass spectrum, m/e 251 (M^+ + 1).

Ester $PhCH_2OCH_2CH(OH)C(COOEt){=}CH_aH_b$ (0.890 g, 3.6 mmol) was treated at room temperature with a 0.5 N $Ba(OH)_2$ aqueous solution (16 mL) for 24 h. After this time, the pH was adjusted to 4.0 (with 2 N HCl), and the usual workup with ether gave a crystalline residue acid, $PhCH_2OCH_2CH(OH)C(COOH){=}CH_aH_b$, which was recrystallized in CH_3Cl_3: 0.560 g (2.5 mmol, yield 69%); mp 96 °C dec; IR 1690, 1625; NMR 3.55 (AB part of an ABX, 2 H, H_4, δ_A 3.71, δ_B 3.39, J_{AB} = 9.3, J_{AX} = 3.2, J_{BX} = 7.4), 4.55 (s, 2 H, CH_2Ph), 4.5–4.9 (m, 1 H, H_3), 6.06 (br s, 1 H, H_b), 6.45 (br s, 1 H, H_a), mass spectrum, m/e 223 (M^+ + 1), 205 (M^+ + 1 − H_2O).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30. Found: C, 64.73; H, 6.44.

The silver salt of the above acid was prepared by dissolving the acid (0.340 g, 1.53 mmol) in acetone (10 mL) and water (2

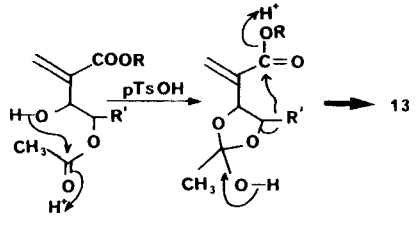
Table II. β-Acetoxy-α-methylene-γ-butyrolactones 13



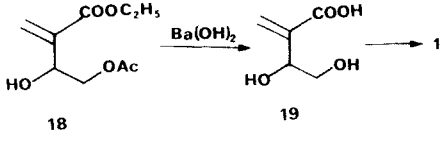
R′	yield,[a] %	NMR, δ (J, Hz) R′	OAc	H_5	H_4	H_b	H_a	IR, cm^{-1}	MS,[b] m/e	microanalyses,[c] found (calcd) C	H
H (13a)	95 (72)		2.11 s	4.43 [AB(X), δ_A 4.57, δ_B 4.28, J_{AB} 10.8, = J_{AX} = 6.7, J_{BX} = 3.1]	5.7–6.0 m	6.13 d (1.3)	6.53 d (1.5)	1780, 1745, 1670	157, 96	54.2 (53.8)	5.30 (5.13)
CH_3 (13b)	90 (61)	1.41 d[d] (6.6)	2.10 s	4.53 dq (6.6, 2.2)	5.38 ddd (2.2, 1.5, 1.6)	6.06 d (1.5)	6.50 d (1.6)	1775, 1745, 1670	138[e]		
		1.36 d[f] (5.9)	2.10 s	4.73 (5.5)	5.80 ddd (5.3, 1.7, 1.7)	6.03 d (1.7)	6.45 d (1.7)				
C_2H_5 (13c)	92 (58)	1.01 t (7.0, CH_2CH_3), 1.70 q (7.0, CH_2CH_3)	2.10 s	4.38 dt (6.0, 2.2)	5.52 ddd (2.2, 1.7, 1.7)	6.09 d (1.7)	6.49 d (1.7)	1775, 1745, 1670	185, 124	58.7 (58.7)	6.46 (6.52)
		1.01 t (7.0), 1.70 q (7.0, CH_2CH_3)	2.10 s	4.43 dt	5.86 dt	6.06 d	6.42 d				
$CH(CH_3)_2$ (13d)	88	0.97 d (6.5), 0.99 d (6.5), 1.7–2.5 m	2.10 s	4.23 dd (6.0, 2.6)	5.63 ddd (2.5, 1.6, 1.6)	6.08 s	6.46 d (1.6)	1780, 1750, 1670	199, 138[g]	59.0 (60.1)	7.07 (7.07)
		0.93 d, 1.10 d (6.5), 1.7–2.5 m	2.10 s	4.13 dd (8.6, 4.8)	5.88 ddd (4.8, 1.2, 1.2)	6.08 s	6.40 d (1.2)				
C_5H_{11} (13e)	82	0.87 t (7.0), 1.0–1.8 m	2.08 s	4.3–4.7 m	5.46 ddd (2.1, 1.8, 1.8)	6.03 s	6.46 d (1.8)	1780, 1745, 1670	166	63.9 (63.7)	7.78 (7.69)
		0.87 t, 1.0–1.8 m	2.08 s	4.3–4.7 m	5.80 ddd (5.6, 1.7, 1.7)	6.01 d (1.7)	6.40 d (1.7)				

[a] Based on the starting allylic alcohol (yield calculated from the allylic sulfoxide by direct cyclization). [b] m/e given for $M^+ + 1$ and $M^+ - 60$. [c] All microanalyses were satisfactory (±0.4%), except for the compounds with R′ = $CH(CH_3)_2$ and R′ = CH_3; all other analytical data were, however, consistent with the proposed structures. [d] Diastereomer 4S,5R (or 4R,5S), i.e., with H_4 and H_5 trans (small J). [e] m/e for $M^+ - 60$ (loss of AcOH); no molecular peak obtained. [f] Diastereoisomer 4S,5S (or 4R,5R), i.e., with H_4 and H_5 cis (large J). [g] High-resolution mass spectrum calcd m/e 198.089, found m/e 198.088.

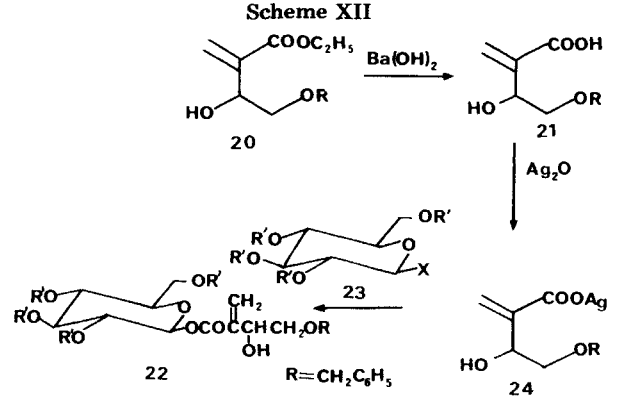
Scheme X



Scheme XI



Scheme XII



mL). NaOH (2 N) was added to adjust pH to ~7, and then $AgNO_3$ (0.172 g, 1.01 mmol) in water (4 mL) was added. The mixture was stirred in the dark for 3 h at 2 °C, and the precipitate was filtered off, washed with ethanol and ether, and dried: 0.400 g (1.22 mmol, yield 80%); mp 150 °C dec; IR (Nujol) 1530, 1340 COO^-.

Preparation of Glucoside 22. The above silver salt (0.400 g, 1.22 mmol) was suspended in anhydrous benzene (20 mL) and (bromoacetoxy)-β-D-glucose. The mixture was stirred for 24 h in the dark. The precipitate was filtered off and the solvent removed. The residue was chromatographed on preparative TLC plates (eluent PE/EE, 25:75): two main bands (R_f ~0.4 and R_f ~0.2) were isolated. The less polar product (R_f ~0.4) was a mixture of acetylglucose and glucoside **22**. The more polar product (R_f ~0.2) was a 4:1 mixture of diastereomeric glucosides **22** which was recrystallized in ether–hexane: 0.065 g (0.18 mmol, yield 15%); mp 158–159 °C; IR 1755, 1745; NMR 2.02 (m, 12 H, OAc), 4.57 (s, 2 H, OCH_2Ph, minor isomer), 4.59 (s, 2 H, OCH_2Ph, major isomer), 3.3–5.5 (m, 10 H, CHO and OH), 5.74 (d, 1 H, H_α, J = 7.0), 6.11 and 6.50 (2 br s, 2 H, $C{=}CH_2$, major isomer), 6.03 and 6.44 (2 br s, 2 H, minor isomer); mass spectrum, m/e 354 (M^+ – 18), 331 (M^+ – aglycon part).

Anal. Calcd for $C_{26}H_{32}O_{13}$: C, 56.52; H, 5.79. Found: C, 56.53; H, 5.67.

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Registry No. **1**, 38965-80-9; **5**, 76299-53-1; **6**, 76299-54-2; **7**, 76299-55-3; **8** (R = Me), 993-88-4; **8** (R = Me), 20345-61-3; **9a**, 73756-09-9; **9b**, 73738-48-4; **9c**, 76299-56-4; **9d**, 73738-53-1; **9e**, 73738-55-3; **10a**, 73738-58-6; **10b** (isomer 1), 76319-65-8; **10b** (isomer 2), 76299-57-5; **10c**, 73738-84-8; **10d**, 73738-62-2; **10e**, 73738-64-4; **12a**, 73738-67-7; **12b**, 73738-65-5; **12c**, 76299-58-6; **12d**, 73738-71-3; **12e** (isomer 1), 76299-59-7; **12e** (isomer 2), 76299-60-0; **13a**, 73738-80-4; **13b** (isomer 1), 73738-74-6; **13b** (isomer 2), 73738-75-7; **13c**, 76299-61-1; **13d**, 76299-62-2; **13e**, 76299-63-3; **15**, 76299-64-4; **18**, 73738-72-4; **19**, 24923-78-2; **20** (R = CH_2Ph), 76299-65-5; **21** (R = CH_2Ph), 76299-66-6; **22** (isomer 1), 76299-67-7; **22** (isomer 2), 76299-68-8; **23**, 6919-96-6; **24** (R = CH_2Ph), 76299-69-9; 2-phenylpropionaldehyde, 93-53-8; $Ph(CH_3)C{=}CH(OAc)$ (isomer 1), 37973-51-6; $Ph(CH_3)C{=}CH(OAc)$ (isomer 2), 37973-52-7; $MeCH{=}CHOAc$, 3249-50-1; i-$PrCH{=}CHOAc$, 54779-59-8; MeCHCH(OAc)O (isomer 1), 76299-70-2; MeCHCH(OAc)O (isomer 2), 76319-66-9; i-PrCHCH(OAc)O, 76299-71-3; $C_5H_{11}CHCH(OAc)O$, 53662-41-2; $(CH_3)_2CHC(OAc)CHO$, 73738-47-3; $CH_3CH(OAc)CHO$, 22094-23-1; $C_2H_5CH(OAc)CHO$, 5921-90-4; $C_6H_5(CH_3)C(OAc)CHO$, 60860-35-7; $C_2H_5(C_2H_5)C(OAc)CHO$, 76299-72-4; $C_5H_{11}CH(OAc)CHO$, 22094-22-0; $CH_2(OAc)CHO$, 5371-49-3; 1,2-diacetoxy-1-ethoxyethane, 3100-09-2; ethyl vinyl ether, 109-92-2; phenacyl chloride, 98-88-4; β-hydroxy-α-methylene-γ-pentyl-γ-butyrolactone, 76299-73-5; α-(benzyloxy)acetaldehyde, 60656-87-3; $ClCH_2CH_2OCH_2Ph$, 17229-17-3; $(PhCH_2O)CH_2CH{=}C(COOC_2H_5)CH_2SPh$, 76299-74-6; $(PhCH_2O)CH_2CH{=}C(COOC_2H_5)CH_2OSPh$, 76299-75-7.

Microbial Stereodifferentiating Reduction of 1,6-Spiro[4.4]nonanedione, a Gyrochiral Diketone with Two Homotopic Carbonyl Groups

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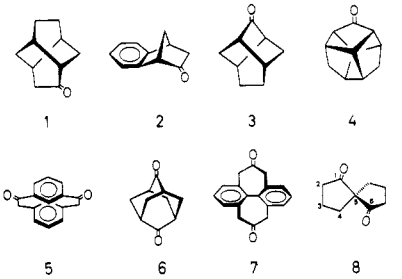
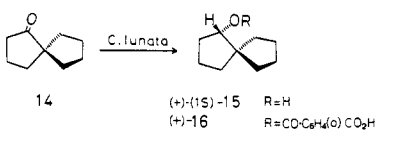
After a preliminary incubation of 1-spiro[4.4]nonanone (**14**) with *Curvularia lunata*, affording (+)-(1*S*)-alcohol **15** with 100% optical purity, (±)-1,6-spiro[4.4]nonanedione (**8**) was incubated with *C. lunata* for 8 h at 30 °C to yield a 34:30:36 mixture of (−)-(5*S*)-**8**, (+)-*trans*-(5*R*,6*S*)-ketol **9**, and (−)-*cis*-(5*R*,6*R*)-ketol **10** with respective 82%, 76%, and 6% optical purities. Incubation of (±)-*trans*-6-hydroxyspiro[4.4]nonan-1-one (**9**) furnished a metabolite mixture containing (−)-*trans*-(5*S*,6*R*)-**9**, (+)-*trans*,*trans*-(1*S*,5*R*,6*S*)-diol **11**, and (+)-*cis*,*trans*-(1*R*,5*S*,6*S*)-diol **12** with respective 56%, 80%, and 73% optical purities. Although a modified quadrant rule for C_1 ketones could explain these microbial stereoselectivities, serious perturbing effects from the unique spirane framework and the neighboring functional groups were observed.

Summarizing the stereodifferentiating aptitude of *Curvularia lunata* and *Rhodotorula rubra* in the microbial reduction of various cage-shaped ketones (e.g., **1** and **2**, Chart I) with C_1 symmetry, we have proposed a "quadrant rule" whose application in predicting the stereochemical course of the microbial reduction as well as in assigning the absolute configuration of the metabolites has been demonstrated in a wide variety of substrate ketones.[1] Prompted by this accomplishment, we then explored the stereochemistry of the microbial reduction of C_2 ketones[2] (e.g., **3** and **4**); accumulated stereochemical information in this field led us to propose a "C_2-ketone rule".[3]

Chart I



Scheme I



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