The solution was steam-distilled until no more volatile base was distilling. The residue was adjusted to pH 3 with 18 N H_2SO_4, and the precipitate was removed and washed by centrifugation. The total supernatants were combined and filtered through celite, and the filtrate was steam-distilled until no more acid was distilling. Titration of the distillate to pH 8.5 with 1 N NaOH required 36.4 ml. The titrated solution was evaporated to dryness under reduced pressure. The residue was dissolved in water, adjusted to pH 2, and again steam-distilled until the volatile acid had distilled over. The distillate was adjusted to pH 8.1 with 1 N NaOH and again evaporated to dryness under reduced pressure, yield 2.47 g, ^{1}H NMR (D_2O) δ 2.0 (s) and 8.57 (s) in addition to a DOH signal.

The sodium salts (2.26 g) were converted to the *p*-bromophenacyl ester by the procedure of Shriner and Fuson,[26] yield 3.82 g; ^{1}H NMR ($CDCl_3$) δ 2.08 (s) and 8.07 (s). Vapor-phase chromatography showed the presence of materials having the elution times of *p*-bromophenacyl formate, *p*-bromophenacyl acetate, and ω-hydroxyacetophenone.

Rate of Base Hydrolysis of Nogalamycin (1). A solution of 1 g of **1** in 40 ml of 0.5 N NaOH was boiled under reflux for 0.5 h. The cooled reaction mixture was extracted with three 20-ml portions of $CHCl_3$. The aqueous layer was acidified to pH 3 with 1 N HCl. The precipitate was collected and washed by centrifugation. The product was dried at 60 °C under reduced pressure, weight 233 mg. Its ^{1}H NMR (D_2O–NaOD) showed no signal for CH_3O.

Supplementary Material Available: UV, visible, and ^{1}H NMR spectral data (Tables I.S and II.S) (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) A preliminary account of a portion of this work has been published: see P. F. Wiley, F. A. MacKellar, E. L. Caron, and R. B. Kelly, *Tetrahedron Lett.*, 663 (1968). We wish to express our appreciation for the assistance of Dr. Lubomir Baczynskyj with the mass spectra and to Mr. David W. Elrod for experimental results. This study was supported in part by Contract NO1-CM-43753 and previous contracts with the Division of Cancer Treatment, National Institutes of Health, Education, and Welfare.
(2) (a) B. K. Bhuyan and A. Dietz, *Antimicrob. Agents Chemother.*, 836 (1965); (b) B. K. Bhuyan, R. B. Kelly, and R. M. Smith, U.S. Patent 3 183 157 (1965); (c) B. K. Bhuyan and F. Reusser, *Cancer Res.*, **30**, 984 (1970).
(3) P. F. Wiley, D. J. Duchamp, V. Hsiung, and C. G. Chidester, *J. Org. Chem.*, **36**, 2670 (1971).
(4) A. DiMarco, M. Gaetani, P. Orezzi, B. M. Scarpinato, R. Silvestrini, M. Soldati, T. Dasdia, and L. Valentini, *Nature (London)*, **201**, 706 (1964).
(5) J. J. Gordon, L. M. Jackman, W. D. Ollis, and I. O. Sutherland, *Tetrahedron Lett.*, 28 (1960).
(6) H. Bloom, L. H. Briggs, and B. Cleverley, *J. Chem. Soc.*, 178 (1959).
(7) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Organic Compounds", Macmillan, New York, N.Y., 1964, pp 127, 286.
(8) C. J. P. Spruitt, *Recl. Trav. Chim. Pays-Bas*, **68**, 325 (1949).
(9) H. Brockmann and W. Müller, *Chem. Ber.*, **92**, 1164 (1959).
(10) H. Brockmann, *Fortschr. Chem. Org. Naturst.*, **21**, 121 (1963).
(11) R. A. Morton and W. T. Earlam, *J. Chem. Soc.*, 159 (1941).
(12) (a) D. L. Fitzell, D. P. H. Hsieh, R. C. Yao, and G. N. LaMar, *J. Agric. Food Chem.*, **23**, 442 (1975); (b) P. F. Wiley, unpublished results based on ^{13}C NMR spectra of steffimycin and its degradation products; (c) R. C. Paulick, M. L. Casey, and H. W. Whitlock, *J. Am. Chem. Soc.*, **98**, 3370 (1976).
(13) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(14) W. D. Ollis, I. O. Sutherland, and J. J. Gordon, *Tetrahedron Lett.*, 17 (1959).
(15) J. R. Hegyi and N. N. Gerber, *Tetrahedron Lett.*, 1587 (1968).
(16) (a) J. S. E. Holker, S. A. Kagal, L. J. Mulhern, and P. M. White, *Chem. Commun.*, 911 (1966); (b) P. Raffey and M. V. Sargent, *ibid.*, 913 (1966).
(17) R. J. Reed and W. K. Reid, *Tetrahedron*, **19**, 1817 (1963).
(18) H. Brockmann Jr., H. Budzikiewicz, C. Djerassi, H. Brockmann, and J. Niemeyer, *Chem. Ber.*, **98**, 1260 (1965).
(19) J. Tax, P. Sedmera, J. Vakoum, K. Eckardt, I. Komersová, and Z. Vaněk, *Collect. Czech. Chem. Commun.*, **38**, 2661 (1973).
(20) J. H. Bowie and A. W. Johnson, *J. Chem. Soc.*, 3927 (1964).
(21) D. Tresselt, K. Eckardt, and J. Tax, *Tetrahedron*, **31**, 613 (1975).
(22) H. Brockmann and J. Niemeyer, *Chem. Ber.*, **100**, 3578 (1967).
(23) H. Brockmann, H. Brockmann Jr., and J. Niemeyer, *Tetrahedron Lett.*, 4719 (1968).
(24) F. Arcamone, G. Cassinelli, G. Franceschi, R. Mondelli, P. Orezzi, and S. Penco, *Gazz. Chim. Ital.*, **100**, 949 (1970).
(25) H. Brockmann and H. Brockmann Jr., *Chem. Ber.*, **94**, 2681 (1961).
(26) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1935, p 144.

A Stereoselective Total Synthesis of the Antifungal Mold Metabolite 7α-Methoxy-3a,10b-dimethyl-1,2,3,3aα,5aα,7,10bβ,10cα-octahydro-4*H*,9*H*-furo[2′,3′,4′:4,5]naptho[2,1-*c*]pyran-4,10-dione

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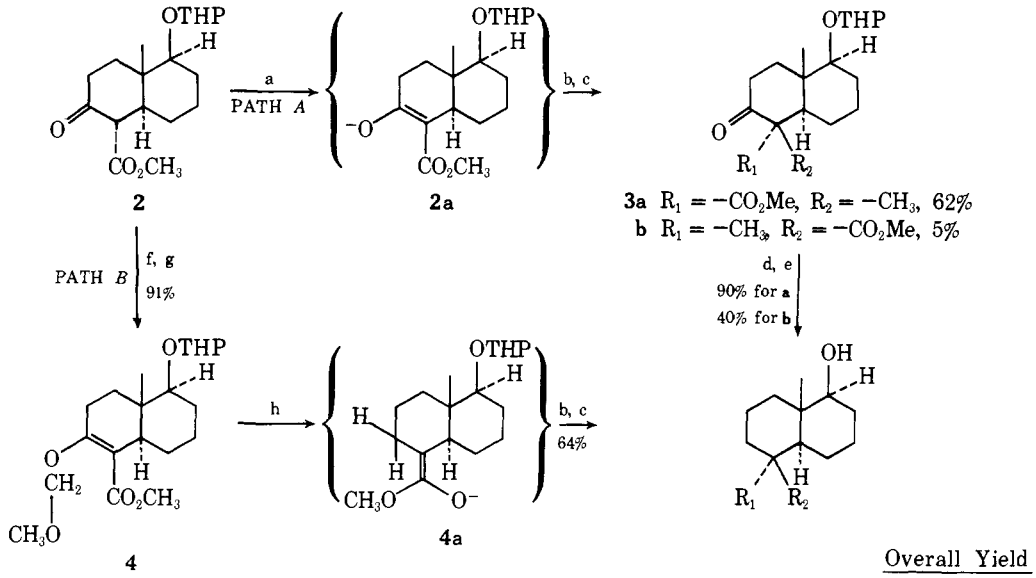
Abstract: A stereoselective total synthesis of the antifungal mold metabolite **1a** [(±)-LL-Z1271α] from the Wieland–Miescher diketone is reported. The synthetic approach utilizes a highly stereoselective reductive-elimination–alkylation reaction for establishing the axial stereochemistry of the carbomethoxy functional group at position 4 in esters **5b** and **5c**. The synthetic approach also includes a novel bromolactonization reaction in the construction of γ-lactone **8**. Finally **1a** and anomer **1b** were produced in a favorable anomeric ratio of 70:30, respectively, by employing the Meyer–Schuster rearrangement of the Arens–van Dorp synthesis on enone acetal **13**.

The mold metabolite 7α-methoxy-3a,10b-dimethyl-1,2,3,3aα,5aα,7,10bβ,10cα-octahydro-4*H*,9*H*-furo[2′,3′,-4′:4,5]naptho[2,1-*c*]pyran-4,10-dione [(±)-LL-Z1271α] (**1a**) (Scheme II) was isolated from the fermentation products of an *Acrostalagmus* species and was found to exhibit in vitro and in vivo antifungal activity against several pathogenic fungi.[1] The structure and stereochemistry of the novel terpenoid antifungal agent **1a** were determined by degradation and spectroscopy in conjunction with biogenetic considerations.[1] A previously reported synthesis of (−)-LL-Z1271α (**1a**) from a degradation product of marrubin also establishes the structure and absolute stereochemistry of antibiotic **1a**.[2] We wish to report herein a highly stereoselective total synthesis of (±)-LL-Z1271α (**1a**) from the readily available Wieland–Miescher diketone.[3,4]

Preparation of the Starting Material, Ester 5b

β-Keto ester **2** (Scheme I) was prepared from the Wieland–Miescher diketone in approximately 50% overall yield in three synthetic stages as reported by Spencer and coworkers.[5] Alkylation of β-keto ester **2** using sodium hydride in 1,2-dimethoxyethane (DME) followed by methyl iodide

Scheme I



	Overall Yield	
	PATH *A*	*B*
5a $R_1 = -CO_2Me$, $R_2 = -CH_3$,	56%	0
b $R_1 = -CH_3$, $R_2 = -CO_2Me$,	2%	58%

a) NaH DME; b) CH_3I; c) CH_3OH, p-TsOH; d) $(CH_2SH)_2$, $BF_3 \cdot OET_2$; e) Ra-Ni, EtOH; f) NaH, HMPA; g) CH_3OCH_2Cl; h) Li, NH_3, DME.

affords (after hydrolysis of the tetrahydropyranyl protecting group) keto esters **3a** and **3b** in 62 and 5% yield, respectively.[5] This alkylation presumably takes place via endocyclic enolate anion **2a**. Raney nickel desulfurization of the intermediate thioketals affords esters **5a** and **5b** in approximately 90 and 40% yield, respectively. Ester **5a**, produced in 56% overall yield from compound **2**, proved to be a useful synthetic intermediate for abietic acid-type resin acids.[5] However, ester **5b**, an extremely attractive synthetic intermediate for a variety of podocarpic acid-type resin acids was formed in only 2% overall yield from compound **2** via path A.[5] Obviously if ester **5b** (or **5c**) is to be a realistic synthetic precursor in a total synthesis of (±)-LL-Z 1271α (**1a**) then an alternate route for construction of ester **5b** (or **5c**) must be designed. Such an alternative synthetic route was devised and recently reported.[4] This new method was conceived knowing that exocyclic enolate anions in cyclohexane rings have a decided preference for alkylation in which the alkylating agent approaches the cyclohexane ring from the less hindered side. Methylation of these types of enolates, such as anion **4a**, generally produces equatorially alkylated products.[6-8] One of the most efficient methods for generating enolate anion **4a** is via the reductive-elimination reaction developed by Coates and Shaw.[9] Keto ester **2** when allowed to react with sodium hydride in hexamethylphosphoramide (HMPA) at room temperature under nitrogen for 2 h, followed by the addition of chloromethyl methyl ether and stirring for 3 h affords methoxymethyleneoxy ether ester **4** in 91% yield. Treatment of ether ester **4** with lithium metal (6.14 equiv) in anhydrous liquid ammonia/1,2-dimethoxyethane followed by quenching with methyl iodide[10] produces, after acid methanolysis, ester **5b** in 64% yield. No other isomeric material was observed (GLC) or isolated (LC). The overall yield of ester **5b** from β-keto ester **2** via path B is 58%. The melting point (mp 71-72 °C) and spectral data (IR and NMR) of this product were identical with that reported by Spencer and co-workers for ester **5b**.[5] This sequence of reactions (**4** → **4a** → **5b**) represents a new type of reductive-elimination-alkylation reaction. This reaction sequence is unique because it effects deoxygenation and concomitant stereoselective methylation in a single step.

Attempts to Functionalize Position 6 of Enones 15a, 15b, and 7b

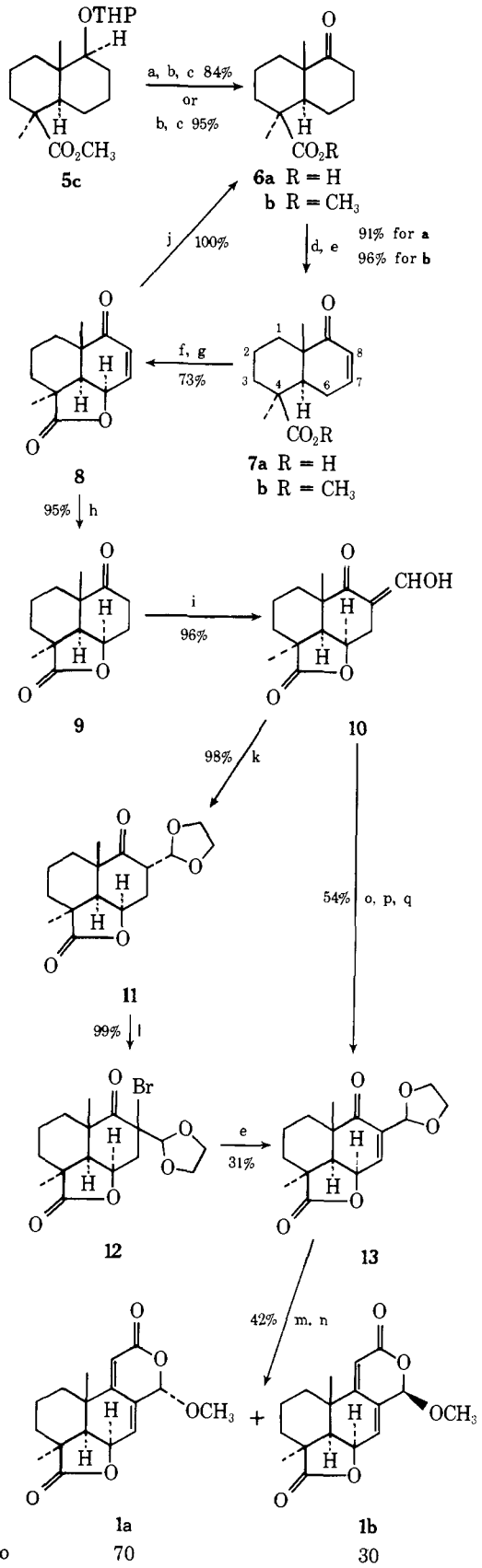
Removal of the tetrahydropyranyl protecting ether on compound **5c** by acid-catalyzed methanolysis followed by oxidation of the resulting alcohol using Jones' reagent[11] in acetone gives keto ester **6b**[5] in 95% yield (Scheme II). Treatment of keto ester **6b** with sodium hydride in ethyl formate/1,2-dimethoxyethane affords hydroxymethylene ketone **14**[5] in 97% yield (Scheme III). Oxidation of compound **14** using 2,3-dichloro-5,6-dicyano-1,4-benzonquinone (DDQ) in *p*-dioxane at room temperature for 4 h produces an α,β-unsaturated keto aldehyde in 68% yield.[12] This unstable keto aldehyde was then converted to stable acetals **15a** and **15b** (in 56 and 60% overall yield, respectively from compound **14**) by treatment with methanolic hydrogen chloride in the presence of Drierite (8 mesh) or ethylene glycol, sulfuric acid (catalytic amount), in tetrahydrofuran (THF) in the presence of Drierite (8 mesh), respectively. All attempts to functionalize position 6 ($CrO_3 \cdot Pyr_2/CH_2Cl_2$;[13] CH_3CO_3-*t*-Bu/$CuBr_2$[14]) of enone acetal **15a** and **15b** were unsuccessful. It was then decided to explore the possibility functionalization of position 6 in enone ester **7b** (Scheme II).

Bromination of keto ester **6b** (Scheme II) with bromine in glacial acetic acid followed by dehydrohalogenation of the crude bromoketone using anhydrous calcium carbonate in refluxing *N,N*-dimethylacetamide (DMA) for 25 min gives enone ester **7b** in 96% yield.[15] Again all attempts to functionalize position 6 ($CrO_3 \cdot Pyr_2/CH_2Cl_2$;[13] CH_3CO_3-*t*-Bu/$CuBr_2$[14]) of enone ester **7b** were unsuccessful. We then turned our attention toward the possibility of forming γ-lactone **8** by allylic bromination of enone acid **7a** followed by allylic displacement of the resulting bromide (at position 6) with the carboxylic acid anion at close proximity (at position 4).

Discussion and Results of the Synthesis of (±)-LL-Z1271α

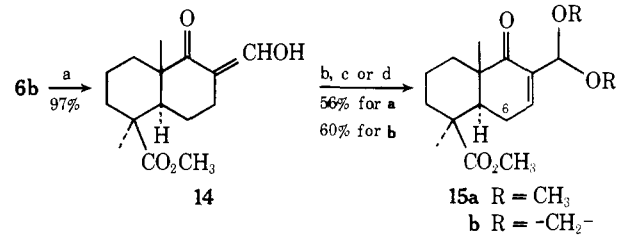
Ester ether **5c** (Scheme II) was obtained in 72% overall yield from vinyl ether ester **4** by reductive-elimination-alkylation. Cleavage of ether ester **5c** using lithium *n*-propyl mercaptide in HMPA[16] followed by acidification and then treatment with

Scheme II



a) *n*-PrSLi, HMPA; b) H_3O^+, CH_3OH; c) CrO_3, H_2SO_4, H_2O, acetone; d) Br_2, HOAc; e) $CaCO_3$, DMA, Δ; f) Br_2, CH_2Cl_2; g) K_2CO_3, DMF; h) H_2, $(Ph_3P)_3RhCl$, PhH; i) NaH, HCO_2Et, DME; j) H_2, EtOH, 10% Pd/C; k) $(CH_2OH)_2$, *p*-TsOH, PhH; l) PTAB, THF; m) LiC≡C—OEt, THF; n) 5% H_2SO_4, CH_3OH; o) Et_3N, PhSeCl, THF; p) MCPBA, THF; q) $(CH_2OH)_2$, H_2SO_4(cat.), THF, $CaSO_4$, 5°.

Scheme III

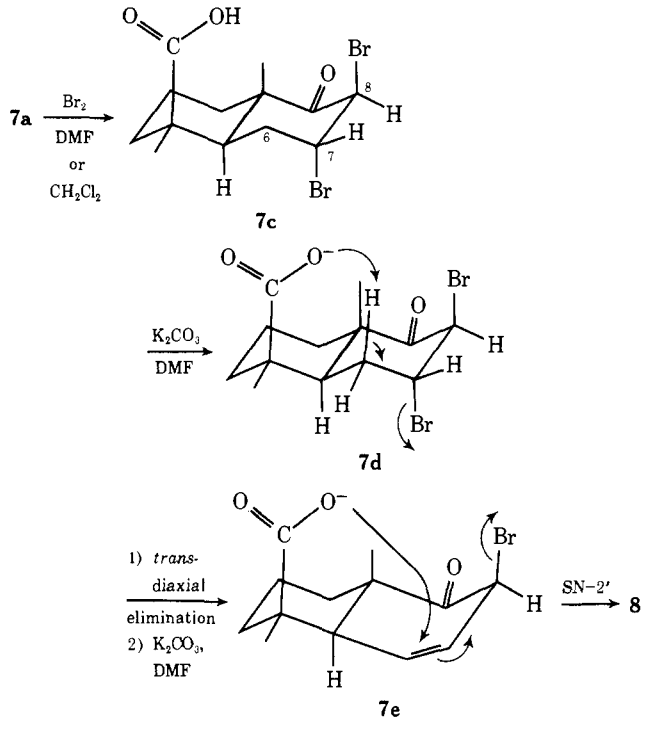


a) NaH, HCO_2Et, DME; b) DDQ, dioxane; c) CH_3OH, $HCl_{(g)}$ (cat.), $CaSO_4$; d) $(CH_2OH)_2$, H_2SO_4 (cat.), THF, $CaSO_4$.

p-toluenesulfonic acid in methanol affords crystalline carboxylic acid alcohol **5d**. Finally, oxidation of alcohol **5d** with Jones' reagent in acetone produces crystalline keto carboxylic acid **6a**[5] in 84% overall yield from ether ester **5c**. Bromination of keto acid **6a** in glacial acetic acid followed by dehydrohalogenation of the crude bromo ketone with anhydrous calcium carbonate in refluxing *N,N*-dimethylacetamide[15] for 30 min gives enone acid **7a** in 91% yield. The initial plan was to effect allylic bromination at position 6 with either *N*-bromosuccinimide or phenyltrimethylammonium perbromide (PTAB) and then to generate the carboxylic acid anion with potassium carbonate in a polar aprotic solvent such as *N,N*-dimethylformamide (DMF, which is known to facilitate substitution reactions). Hopefully, the carboxylic acid anion, being in close proximity to the allylic bromide, would intramolecularly displace the bromide ion to form the desired γ-lactone **8**. Treatment of enone acid **7a** with PTAB[17] in DMF for 24 h followed by the addition of anhydrous potassium carbonate and stirring at room temperature for 6 h affords γ-lactone **8** (mp 114–115 °C) in 73% yield. This reaction also works when *N*-bromosuccinimide is used in place of PTAB; however, the yield of lactone **8** is only 25%. Lactone **8** displays two intense carbonyl absorptions in the IR [(CCl_4) 1695 and 1780 cm^{-1}; ($CHCl_3$) 1710 and 1760 cm^{-1}] and an ultraviolet absorption [(ethanol) 209 nm, ε 5040]. The NMR spectrum ($CDCl_3$) is completely consistent with structure **8** [ABX system: four lines centered at δ 6.88, two lines centered at δ 6.09, and three lines centered at δ 4.99 for the vinylic protons at positions 8 and 7 as well as the oxymethine proton at position 6, respectively; doublet, J = 5 Hz, centered at δ 2.15 for the bridgehead proton at position 5; singlet at δ 1.36 for the methyl group at position 4; and a singlet at δ 1.23 for the methyl group at position 10].

Isolation of intermediate bromo compound **7c** (Scheme IV) and examination by infrared and NMR spectra indicated that allylic bromination had not taken place. The infrared spectrum ($CHCl_3$) shows the presence of a saturated six-membered ring ketone (1695 cm^{-1}) and a carboxylic acid functional group (1710 cm^{-1}). The NMR spectrum ($CDCl_3$) clearly shows the absence of vinylic protons; however, there are two absorptions indicative of bromomethine protons (δ 4.81 and 4.51) as well as two methyl singlets (δ 1.60 and 1.30). From these spectral data and knowledge of the bromination of alkenes in steroids we postulate that this crude bromo compound can be represented by structure **7c**. Attack of the alkene function of enone acid **7a** from the more accessable side by bromine should form an α-bromonium ion. Attack of bromide ion on this α-bromonium ion in a trans-diaxial ring opening should result in the formation of dibromide **7c**.[18] Treatment of dibromo acid **7c** with anhydrous potassium carbonate will then generate carboxylic acid anion **7d** which presumably facilitates the dehydrohalogenation via a trans-diaxial elimination of the bromide substituent at position 7. A second equivalent of anhydrous potassium carbonate once again generates the carboxylic acid anion **7e**, which because of close proximity and proper stereochemistry, undergoes a facile intramolecular S_N2' reaction

Scheme IV



with the simultaneous elimination of the bromide substituent at position 8. The cis relationship between the entering nucleophile ($-CO_2^-$) and the leaving group ($-Br^-$) in a S_N2' reaction appears to be general.[19] Once dibromide **7c** was discovered as the actual intermediate in this bromolactonization reaction, then treatment of enone acid **7a** with bromine in dichloromethane was used to produce the dibromide. Treatment of dibromide **7c** (generated in this manner) with anhydrous potassium carbonate in *N,N*-dimethylformamide results in the formation of lactone **8** in 69% overall yield from enone acid **7a.**

Catalytic hydrogenation of unsaturated lactone **8** over 10% palladium on carbon in anhydrous ethanol affords saturated keto acid **6a** in quantitative yield. The results of this hydrogenolysis, although unexpected, did prove that no rearrangement had occurred in the formation of γ-lactone **8.** The cleavage of this very labile carbon–oxygen bond at position 8 was circumvented by catalytic hydrogenation using Wilkinson's catalyst,[20] tris(triphenylphosphine)rhodium(I) chloride, in benzene to give saturated lactone **9** [mp 121–122 °C, IR ($CHCl_3$) 1710 and 1760 cm^{-1}]. Lactone **9** when allowed to react with sodium hydride in the presence of ethyl formate in 1,2-dimethoxyethane produces hydroxymethylene ketone **10** in 96% yield.[21] All attempts to oxidize hydroxymethylene ketone **10** to an α,β-unsaturated keto aldehyde using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane,[12] similar to that employed in the oxidation of compound **14,** failed completely. Hydroxymethylene ketone **10** when treated with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene with a Dean–Stark water separator (and monitoring the reaction by gas chromatography) produces formylethylenedioxyacetal **11** in 98% yield.[22] Bromination of ketone **11** with phenyltrimethylammonium perbromide in anhydrous tetrahydrofuran affords bromide **12** in 99% yield.[17] Dehydrohalogenation of bromide **12** using anhydrous calcium carbonate in refluxing *N,N*-dimethylacetamide[15] (DMA) for 30 min gives enone acetal **13** [UV (CH_3OH) 212 nm (ε 6390), 263 cm (ε 718)] in 31% yield after preparative thin layer chromatography on silica gel. Other methods of dehydrohalogenation (Li_2CO_3, LiBr, DMF, or DMA; collidine/Δ; DBN/Δ; or DBU/Δ) proved to be much less efficient. A better method for preparing enone **13** from hydroxymethylene ketone **10** was devised using phenylselenyl reagents.[23] Treatment of ketone **10** with phenylselenyl chloride (1.1 equiv) in anhydrous tetrahydrofuran in the presence of triethylamine (1.1 equiv) affords a crude α-phenylselenyl ketone. Oxidation of this crude α-phenylselenyl ketone with *m*-chloroperbenzoic acid (2 equiv) affords an intermediate enone aldehyde which when dissolved in dry tetrahydrofuran containing anhydrous ethylene glycol and a catalytic amount of sulfuric acid over Drierite (8 mesh) and allowed to stand at 5 °C overnight produces enone **13** in 54% overall yield from ketone **10.** Finally, the synthesis was completed by employing the Meyer–Schuster rearrangement of the Aren–van Dorp synthesis on enone acetal **13.** Treatment of enone acetal **13** with lithium ethoxyacetylide[24] in THF gives an unstable tertiary allylic-propargylic alcohol which when dissolved in methanol containing a catalytic amount of 5% sulfuric acid solution[25] produces (±)-LL-Z1271α (**1a**) and anomer **1b** in 42% overall yield in a favorable anomeric ratio of 70:30, respectively. The UV, IR, NMR, and TLC data for synthetic antifungal agent **1a** were identical with that displayed by an authentic sample of (−)-LL-Z1271α (**1a**).

Experimental Section

Melting points were determined on a Fisher–Johns and/or Büchi melting point apparatus and are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Silica gel PF 254-366 (E. Merck No. 7748) and silica gel 60 (E. Merck No. 7734, 70–230 mesh) available from Brinkmann Instruments were used for thin layer and column chromatography, respectively.

Analytical gas phase chromatography (GLC) was performed using the following types of columns and flow rates: (A) 5-ft, stainless steel, 0.125-in. column, packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian), flow rate 15 ml/min at ambient temperature; (B) 6-ft, stainless steel, 0.125-in. column, packed with 5% FFAP on Varaport-30, 80/100 mesh (Varian), flow rate 15 ml/min at ambient temperature; (C) 6-ft, stainless steel, 0.125-in. column, packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian), flow rate 15 ml/min at ambient temperature.

Infrared (IR) spectra were recorded on a Perkin-Elmer 237B and/or 700 spectrophotometer. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10-mm sodium chloride cells. Liquid samples were sometimes taken as thin films between sodium chloride plates.

Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer. The following abbreviations are used to describe NMR spectral bands reported herein: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and δ (parts per million, ppm, downfield from tetramethylsilane).

Ultraviolet spectra were recorded on a Cary Model 14 UV spectrometer in 95% ethanol or absolute methanol as indicated.

For all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[26] All liquid transfers were made with nitrogen filled syringes.

The term "pet-ether" refers to Baker "Analyzed Reagent" bp 30–60 °C. The terms "dry tetrahydrofuran", "dry 1,2-dimethoxyethane", and "dry diethyl ether" refer to purification of the commercial materials by distillation from lithium aluminum hydride under nitrogen. "Dry benzene" and "dry hexamethylphosphoramide" were obtained by distillation of the commercial materials from calcium hydride. "Dry dichloromethane" was obtained by distillation of the solvent from phosphorus pentoxide.

3-Methoxymethyleneoxy-4-carbomethoxy-9β-tetrahydropyranyloxy-10β-methyl-$\Delta^{3,4}$-*trans*-decalin (4).[5,9] Sodium hydride (1.20 g, 28.5 mmol, 57% dispersion) was washed with dry ether (3 × 10 ml) under dry nitrogen. The residual ether was evaporated with an infrared heat lamp under a stream of dry nitrogen. Dry hexamethylphosphoramide[27] (HMPA, 50 ml, stored over molecular sieves 13X) was added, followed by β-keto ester **2** (8.31 g, 25.6 mmol) in HMPA (3 × 15 ml). After stirring at room temperature for 3.5 h, chloromethyl methyl ether[27] (2.20 ml, 29 mmol) was added. The reaction mixture

was allowed to stir for an additional 2 h under dry nitrogen. The mixture was then poured into a separatory funnel containing ice–water (500 ml). The aqueous layer was extracted with ether (4 × 50 ml). The combined ethereal layers were washed with water (4 × 25 ml) and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and evaporated in vacuo with a drop of pyridine to give 9.43 g (100%) of vinyl ether **4.** Compound **4** was purified by column chromatography on silica gel 60 (750 g) using 40% ether:60% pet-ether eluent (450-ml fractions). Fractions 9–16 were combined to give 8.59 g (91%) of pure vinyl ether **4** as a colorless liquid: bp 150 °C (0.5 mm, external temperature); IR (film) 1725 (CO), 1675 cm^{-1} (C=C); NMR (CCl_4) δ 0.85 (s, 3, CH_3), 3.35 (s, 3, OCH_3), 3.60 (s, 3, $-CO_2CH_3$), 4.77 ppm (AB, 2, J_{AB} = 6 Hz, $-OCH_2O-$. Anal. ($C_{20}H_{32}O_6$) C, H.

4α,10β-Dimethyl-4β-carbomethoxy-9β-hydroxy-*trans*-decalin (5b).[4,5] Anhydrous liquid ammonia (250 ml, distilled through two potassium hydroxide towers, then from sodium metal) was collected in a flask fitted with a dry ice condenser. The condenser was fitted with a soda-lime drying tube to protect the ammonia from moisture. Lithium ribbon (0.349 g, 55 mg-atom) cut in ten small pieces was added. After stirring at −33 °C for 20 min vinyl ether **4** (3.30 g, 8.96 mmol) dissolved in 1,2-dimethoxyethane (DME, 3 × 15 ml) was added. The mixture remained blue, and after 15 min methyl iodide (3.0 ml, 48.2 mmol) was added rapidly. The resulting white slurry was allowed to stir at −33 °C for 1 h, then the ammonia was removed by distillation (hot water bath). The crude reaction mixture was taken up in water (100 ml) and 10% hydrochloric acid solution (500 ml) and extracted with ether (5 × 50 ml). The combined ether extracts were washed with 10% sodium sulfite solution (50 ml), water (4 × 50 ml), and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), ethereal diazomethane added (enough to give a slight yellow color), and concentrated in vacuo to give 2.85 g (98%) of crude ester **5c** as a colorless oil.

The crude product was dissolved in methanol (150 ml) containing *p*-toluenesulfonic acid (*p*-tsOH, 0.5 g) and stirred at reflux for 5 h. The reaction mixture after cooling was poured into ice–water (100 ml) and saturated sodium chloride solution (50 ml). The mixture was extracted with ether (5 × 50 ml). The combined ethereal extracts were washed with water (4 × 50 ml), saturated sodium bicarbonate solution (50 ml), and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 2.03 g (97%) of crude ester alcohol **5b.** The crude product was chromatographed on silica gel 60 (200 g) using 60% ether:40% pet-ether eluent in a column 3 × 110 cm. Fractions 8–16 gave 1.38 g (64%) of compound **5b:** mp 71–72 °C (lit.[4] mp 72.5–73.5 °C); IR (CS_2) 1730 (CO), 3500–3600 cm^{-1} (OH); IR ($CHCl_3$) 1720 (CO), 3500–3630 cm^{-1} (OH); IR (CCl_4) 1730 (CO), 3500–3600 cm^{-1} (OH); NMR (CS_2) δ 0.58 (s, 3, CH_3), 1.10 (s, 3, CH_3), 3.53 ppm (s, 3, CO_2CH_3); NMR (CCl_4) δ 0.64 (s, 3, CH_3), 1.12 (s, 3, CH_3), 3.57 ppm (s, 3, CO_2CH_3). These spectral data were identical with those reported by Spencer and co-workers.[5]

Compound **5c** (2.85 g crude) from a similar experiment was chromatographed on silica gel 60 (300 g) using 15% ether:85% pet-ether as the eluent. Fractions 3–6 gave 2.09 g (72%) of pure compound **5c** as a colorless oil: IR (CCl_4) 1725 cm^{-1} (CO); NMR (CCl_4) δ 0.67 (s, 3, CH_3), 1.10 (s, 3, CH_3), 3.57 (s, 3, OCH_3), 4.53 ppm (m, 1, $-OCHO-$). This material was carried on to the next experiment without further purification.

4α,10β-Dimethyl-9β-hydroxy-*trans*-decalin-4β-carboxylic Acid (5d).[5,16] The mercaptide reagent was prepared by adding freshly distilled *n*-propyl mercaptan (4 ml) to a suspension of powdered lithium hydride (0.92 g) in dry hexamethylphosphoramide (HMPA, 20 ml). The mixture was stirred under dry nitrogen at room temperature overnight.

The ester tetrahydropyranyl ether **5c** (0.7505 g, 2.31 mmol) was added to the reagent in dry HMPA (20 ml). After stirring for 5 h at room temperature, the mixture was poured into a separatory funnel containing 5% sodium hydroxide solution (100 ml) and ether (100 ml). The base layer was separated and washed with ether (20 ml) and acidified with 10% hydrochloric acid and then extracted again with ether (5 × 20 ml). The combined latter ethereal extracts were separated and evaporated in vacuo. The crude acid tetrahydropyranyl ether was then dissolved in methanol (150 ml) containing *p*-toluenesulfonic acid (0.5 g) and stirred for several hours at room temperature to completely remove the tetrahydropyranyl ether. The mixture was diluted with a large volume of water (300 ml) and extracted with ether (10 × 50 ml). The combined ethereal extracts were washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.5172 g (99%) of crystalline acid alcohol (**5d**): mp 139–142 °C (lit.[5] mp 142–144.5 °C; IR (CCl_4) 3300–2550 cm^{-1} (OH), 1690 cm^{-1} (CO); NMR ($CDCl_3$) δ 0.85 (s, 3, CH_3), 1.24 (s, 3, CH_3), 3.75 (s, broad, 1, OH), 7.10 ppm (s, 1, COOH). These spectral data were in agreement with those reported by Spencer and co-workers.[5]

4α,10β-Dimethyl-*trans*-9-decalone-4β-carboxylic Acid (6a).[5,11] To a solution of crude hydroxy acid **5d** (1.24 g, 5.48 mmol) in acetone (50 ml) was added excess Jones' reagent (2.67 M) dropwise until the stirred solution remained orange. After stirring for 2 h at room temperature, the mixture was poured into a separatory funnel containing water (700 ml). The aqueous layer was extracted with ether (5 × 90 ml). The ethereal extracts were combined and washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 1.035 g (85%) of crystalline keto acid **6a:** mp 155–156 °C (lit.[5] mp 156–157 °C); IR ($CHCl_3$) 2500–3300 (broad, COOH), 1690 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.10 (s, 3, CH_3) 1.28 (s, 3, CH_3), 11.15 ppm (s, broad, 1, OH). These spectral data are in agreement with those reported by Spencer and co-workers.[5]

4α,10β-Dimethyl-Δ^{7,8}-ene-*trans*-9-decalone-4β-carboxylic Acid[15] **(7a).** To a solution of keto acid **6a** (1.07 g, 4.7 mmol) in dichloromethane (30 ml) was added bromine (0.834 g, 5.22 mmol, 1.1 equiv) in glacial acetic acid (8 ml) dropwise over 30 min. The reaction was stirred at ambient temperature for an additional 15 min, then poured into a separatory funnel containing water (200 ml). The water layer was extracted with ether (5 × 70 ml). The combined ethereal extracts were washed with water (5 × 100 ml) and saturated sodium chloride solution (100 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 1.466 g of crude bromide. The NMR data showed that no starting material remained. The crude α-bromo ketone was dissolved in *N,N*-dimethylacetamide (DMA, 50 ml) along with calcium carbonate (1.43 g, 14.3 mmol). The mixture was heated to reflux under nitrogen for 30 min, cooled, and then poured into a separatory funnel containing 10% hydrochloric acid (100 ml) and water (200 ml). The aqueous mixture was extracted with ether (3 × 70 ml). The combined ethereal extracts were washed with saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.970 g (91%) of unsaturated ketone acid **7a.** The analytical sample was prepared by column chromatography on silica gel 60 (75 g) using 40:60% ether: pet-ether to elute the column. The chromatographed sample was then recrystallized from ether–pentane four times: mp 165–166 °C; IR ($CHCl_3$) 2500–3500 (COOH), 1690 cm^{-1} (CO) 1665 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.02 (s, 3, CH_3), 1.33 (s, 3, CH_3), 5.90 (broad dofd, J = 10 and 1 Hz, 1, $-CO-CH=$), 6.97 (8 line m, $w_{1/2}$ = 20 Hz, 1, $-C=CH$), 10.7 ppm (s, 1, CO_2H). Anal. ($C_{13}H_{18}O_3$) C, H.

Methyl 4α,10β-Dimethyl-*trans*-9-decalone-4β-carboxylate (6b).[5] To a solution of hydroxy ester **5b** (4.95 g, 20.5 mmol) in reagent acetone (300 ml) was slowly added Jones' reagent (5.2 ml, 2.67 M), maintaining the internal temperature between 10–20 °C (ice bath). After the addition the resulting orange mixture was allowed to stir for an additional 30 min and then quenched with isopropyl alcohol, followed by the addition of water (900 ml). Saturated sodium chloride solution (100 ml) was added, and the mixture was extracted with ether (5 × 100 ml). The ethereal extracts were washed with saturated sodium chloride solution, then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 4.77 g (98%) of keto ester **6b:** mp 84–89 °C (lit.[5] 87.5–88.5 °C); IR (CCl_4) 1710 (CO), 1735 cm^{-1} ($-CO_2CH_3$); NMR (CCl_4) δ 0.91 (s, 3, CH_3), 1.16 (s, 3, CH_3), and 3.60 ppm (s, 3, CH_3O). These spectral data are in agreement with those reported by Spencer and co-workers.[5]

Methyl 4α,10β-Dimethyl-Δ^{7,8}-ene-*trans*-9-decalone-4β-carboxylate (7b).[5,15] To a solution of keto ester **6b** (1.89 g, 7.94 mmol) in glacial acetic acid (13 ml) was added a solution of bromine in glacial acetic acid (4.9 ml, 1.63 M, 7.98 mmol) over a period of 10 min. After an additional 10 min, the reaction mixture was poured into water (50 ml) and ether (150 ml). The ether layer was separated. The aqueous layer was extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with water (3 × 50 ml), saturated sodium bicarbonate solution (3 × 25 ml), water (50 ml), and saturated sodium chloride solution (25 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 2.58 g (100%) of crude bromo ketone. The crude bromo ketone was dissolved in *N,N*-dimethylacetamide (32 ml)

containing anhydrous calcium carbonate (1.56 g). This mixture was then placed into a preheated oil bath (180 °C) and allowed to reflux under nitrogen for 25 min. After cooling to room temperature, the mixture was poured into water (60 ml) and ether (120 ml). The ether layer was separated, and the aqueous layer was extracted with ether (3 × 25 ml). The combined ethereal extracts were washed with water (4 × 60 ml) and saturated sodium chloride solution (60 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 1.80 g (96%) of enone ester **7b**: mp 86–87 °C (hexane); IR ($CHCl_3$) 1665 (CO), 1720 cm^{-1} ($-CO_2CH_3$); NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.24 (s, 3, CH_3), 3.69 (s, 3, OCH_3), 5.86 (two m, 1, COC*H*=CH), 5.91 ppm (m, 1, COCH=C*H*). Anal. ($C_{14}H_{20}O_3$) C, H.

3,4,5,5a,8aα,8bα-Hexahydro-2aα,5aβ-dimethyl-2*H*-naphtho-[1,8-*b*,*c*]furan-2,6-(2a*H*)-7-enedione (8). Method A. To a solution of acid enone **7a** (0.586 g, 2.6 mmol) in dichloromethane (15 ml) was added bromine in carbon tetrachloride (7.8 ml of 0.34 M, 2.65 mmol) over 30 min. After stirring for an additional 30 min, the reaction was poured into a mixture of ether (200 ml) and water (100 ml). The ether layer was washed with 5% sodium sulfite solution (20 ml), water (20 ml), and saturated sodium chloride solution (20 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and evaporated in vacuo to give 1.109 g of the crude dibromide. The dibromide was dissolved in *N*,*N*-dimethylformamide (DMF, 10 ml) containing anhydrous potassium carbonate (50 mg). Monitoring by gas phase chromatography using column A (column temperature 200 °C) revealed that the reaction had gone almost to completion within 2 h. After stirring at ambient temperature overnight, the mixture was poured into a separatory funnel containing water (50 ml) and ether (100 ml). The ether layer was separated and washed with water (10 × 25 ml) and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.400 g (69%) of crystalline lactone **8** after preparative thin layer chromatography on silica gel using 90% ether:10% pet-ether to elute the 20 × 20 cm × 1.5 mm plate.

Method B. A solution of acid enone **7a** (0.138 g, 0.654 mmol) in *N*,*N*-dimethylformamide (DMF, 4 ml, distilled from calcium hydride onto molecular sieves type 4A) was stirred at 0 °C (ice bath) under nitrogen while a solution of phenyltrimethylammonium perbromide in DMF (6.83 ml, 0.095 M solution, 0.649 mmol) was added slowly. After 30 min at 0 °C the ice bath was removed. Then after 2 h at room temperature an additional amount of phenyltrimethylammonium perbromide (20 ml, 0.364 M solution in DMF, 7.28 mmol) was added. After stirring for a total of 24 h, anhydrous potassium carbonate (0.5 g) was added. After stirring at room temperature for 6 h, the reaction mixture was diluted with 10% hydrochloric acid solution (25 ml) and ether (100 ml). The ether layer was separated. The ether layer was washed with saturated sodium bicarbonate solution (25 ml), 5% sodium sulfite solution (25 ml), and water (8 × 25 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.100 g (73%) of lactone **8**.

An analytical sample of lactone **8** was prepared by preparative thin layer chromatography followed by recrystallization from ether–hexane (4×): mp 114–115 °C; UV (EtOH) 209 nm (ε 5040); IR (CCl_4) 1780 (lactone), 1695 cm^{-1} (α,β-unsaturated ketone); IR ($CHCl_3$) 1760 (lactone), 1710 cm^{-1}(α,β-unsaturated ketone); NMR ($CDCl_3$) δ 1.23 (s, 3, CH_3), 1.36 (s, 3, CH_3), 2.15 (d, J = 4.8 Hz, 1, bridgehead proton), 4.99 (t, J = 4.8 Hz, 1, oxymethine), 6.09 (d, J = 10 Hz, 1, -CO-CH=C-), 6.88 ppm (4 line m, J = 10 and 4 Hz, 1, -CO-C=CH). Anal. ($C_{13}H_{16}O_3$) C, H.

3,4,5,5a,7,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-2*H*-naphtho-[1,8-*bc*]furan-2,6-(2a*H*)-dione (9).[20] Into a 250-ml Parr hydrogenation bottle was placed enone lactone **8** (1.457 g, 6.55 mmol) and tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's Catalyst, 0.100 g). Dry nanograde benzene (25 ml) was distilled under nitrogen from calcium hydride into the hydrogenation bottle which was then quickly transferred to the hydrogenation apparatus and then evacuated and filled with hydrogen (3×). The sample was stirred for 3 h at room temperature under 1–3 atm of hydrogen. The mixture was then filtered through an alumina column (Woelm neutral, Activity III, 10 g) with dichloromethane (3 × 50 ml) to remove the catalyst and to give 1.39 g (95%) of saturated lactone **9**. The analytical sample was prepared by recrystallization four times from ether–pentane: mp 121–122 °C; IR ($CHCl_3$) 1760 (lactone), 1710 cm^{-1} (ketone); NMR ($CDCl_3$) δ 1.18 (s, 3, CH_3), 1.36 (s, 3, CH_3), 1.95 (d, J = 6 Hz, 1, bridgehead CH), 5.03 ppm (m, 1, oxymethine). Anal. ($C_{13}H_{18}O_3$) C, H.

3,4,5a,7β,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-7α-formyl-2*H*-naphtho[1,8-*bc*]furan-2,6-(2a*H*)-dione (10).[5] Into a flask fitted with a nitrogen gas inlet and a septum was placed sodium hydride (0.284 g, 6.67 mmol, 57% oil dispersion). The sodium hydride was washed with anhydrous ether (3 × 1 ml) and dried under vacuum. A solution of ketone **9** (0.500 g, 2.2 mmol) and anhydrous methyl alcohol (1 drop) in ethyl formate (5 ml) was added at 0 °C (ice bath), followed by an additional quantity of ethyl formate (2 ml) needed to complete the transfer. After the mixture had stirred for 1 h at 0 °C, dry 1,2-dimethoxyethane (DME, 10 ml) was added to facilitate the dissolution. The resulting mixture was allowed to stir overnight under an atmosphere of dry nitrogen and then poured into a separatory funnel containing 10% hydrochloric acid solution (50 ml) and water (150 ml). The aqueous mixture was extracted with ether (4 × 50 ml). The combined ether extracts were washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.537 g (96%) of crystalline hydroxymethylene derivative (**10**). An analytical sample was prepared by recrystallization from a dichloromethane–ether–pet-ether mixture, followed by sublimation [130 °C, (0.05 mm)]: mp 192–193 °C; IR ($CHCl_3$) 1765 (lactone), 1650 (ketone), 1585 cm^{-1} [HC(OH) = HC(=O)]; NMR ($CDCl_3$) δ 1.18 (s, 3, CH_3), 1.31 (s, 3, CH_3), 2.90 (d, J = 8 Hz, 2, CH_2), 4.99 (m, J = 8 and 16, Hz, 1, oxymethine), 7.34 ppm (s, 1, -C=C*H*-OH). Anal. ($C_{14}H_{18}O_4$) C, H.

3,4,5,5a,7β,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-7α-formylethylenedioxyacetal-2*H*-naphtho[1,8-*bc*]furan-2,6-(2a*H*)-dione (11).[22] Into a flask fitted with a Dean–Stark trap filled with calcium sulfate (Drierite, 8 mesh) and fitted with a reflux condenser, was added hydroxymethylene ketone **10** (0.5165 g, 2.07 mmol), *p*-toluenesulfonic acid (0.20 g), dry benzene (40 ml), and ethylene glycol (1 ml). The reaction mixture was stirred at reflux under dry nitrogen for 40 h during which time the trap was drained at irregular intervals (10 × 2 ml). The reaction was monitored by gas chromatography using column A. After cooling, the mixture was poured into a separatory funnel containing ether (200 ml). The ether was washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml). After drying (Na_2SO_4), the solvent was removed in vacuo to give 0.5982 g (98%) of acetal **11**. The analytical sample was prepared by recrystallization from ether–pentane (5×): mp 178–180 °C; IR ($CHCl_3$) 1765 (lactone), 1715 cm^{-1} (ketone); NMR ($CDCl_3$) δ 1.16 (s, 3, CH_3), 1.35 (s, 3, CH_3), 3.95 (s, 4, $(-O-CH_2-)_2$), 5.08 (m, J = 7 and 16 Hz, 1, oxymethine), 5.48 ppm (d, J = 2 Hz, 1, -OCHO-). Anal. ($C_{16}H_{22}O_5$) C, H.

3,4,5,5a,7,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-7-bromo-7-formylethylenedioxyacetal-2*H*-naphth[1,8-*bc*]furan-2,6-(2a*H*)-dione (12).[17] A solution of phenyltrimethylammonium perbromide (0.255 g, 0.92 mmol) in dry tetrahydrofuran (THF, 12 ml, freshly distilled from $LiAlH_4$) was added to acetal **11** (0.189 g, 0.65 mmol) under a dry nitrogen atmosphere. The reaction was stirred for 5 h, during which time a heavy yellow precipitate formed. The mixture was poured into a separatory funnel containing ether (150 ml). The ether layer was washed with water (10 × 25 ml) and saturated sodium chloride solution (1 × 25 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.238 g (99%) of the highly crystalline bromo acetal **12**. The analytical sample was prepared by preparative thin layer chromatography using silica gel (20 × 20 cm × 1.5 mm) and 50% ether:50% pet-ether as eluent, followed by two recrystallizations from dichloromethane–ether–pentane: mp 218–219 °C; IR ($CHCl_3$) 1770 (lactone), 1720 cm^{-1} (ketone); NMR ($CDCl_3$) δ 1.17 (s, 3, CH_3), 1.38 (s, 3, CH_3), 2.53 (d, J = 6 Hz, 1, bridgehead CH), 2.89 (t, J = 8 Hz, 2, $-CH_2-C-Br$), 4.02 (s, 4, OCH_2CH_2O), 5.06 (m, J = 16 and 7 Hz, 1, oxymethine), 5.56 ppm (s, 1, -OCHO-1). Anal. ($C_{16}H_{21}O_5Br$) C, H, Br.

3,4,5,5a,8aα,8bα-Hexahydro-2aα,5aβ-dimethyl-7-formylethylenedioxyacetal-2*H*-naphtho[1,8-*bc*]furan-2,6-(2a*H*)-dione (13).[15] **Method A.** To a solution of bromo acetal **12** (0.067 g, 0.180 mmol) in *N*,*N*-dimethylacetamide (2 ml) was added calcium carbonate (0.054 g, 0.54 mmol). The solution was degassed and sealed under nitrogen (3×).[26] The flask was immersed in an oil bath preheated to 190 °C and then allowed to stir at reflux for 30 min. The flask was then allowed to air cool for a few minutes and then cooled to 0 °C in an ice bath. The reaction mixture was poured into water (100 ml) and extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and evaporated in

vacuo to give 0.0407 g of a mixture. Compound **12** was isolated in 31% yield by preparative thin layer chromatography on silica gel (20 × 20 cm × 1.5 mm) using 75% ether:25% pet-ether to elute the plate. An analytical sample was prepared by recrystallization four times from dichloromethane–ether–pentane: mp 134–135 °C; UV (CH_3OH) 212 nm (ε 6390), 263 nm (ε 718); IR ($CHCl_3$) 1770 (lactone), 1695 cm^{-1} (ketone); NMR ($CDCl_3$) δ 1.22 (s, 3, CH_3), 1.35 (s, 3, CH_3), 2.14 (d, J = 5 Hz, 2, bridgehead CH), 4.00 (s, 4, $-OCH_2-$), 5.03 (t, J = 5 Hz, 1, oxymethine), 5.70 (s, 1, -OCHO-), 6.97 ppm (d, J = 5 Hz, 1, -C=CH-).

Method B. Sodium hydride (50 mg, 50% in mineral oil, 1.04 mmol) was washed with 1,2-dimethoxyethane (2 × 2 ml) to remove the mineral oil. Keto lactone **9** (50 mg, 0.225 mmol) was dissolved in ethyl formate (2 ml, distilled from P_2O_5) and added to the sodium hydride at 0 °C. Additional ethyl formate (2 ml) was used to complete the transfer. This mixture was stirred at 0 °C for 1 h. Dimethoxyethane (6 ml, distilled from $LiAlH_4$) was added, and the mixture was allowed to stir overnight at room temperature. The solution was poured into ether and washed with 5% HCl (50 ml), followed by water (25 ml) and saturated sodium chloride solution (25 ml). The aqueous portions were extracted with ether, and the combined ether extracts were dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo. The resulting material was dissolved in THF (20 ml). Triethylamine (25.0 mg, 0.248 mmol, distilled from CaH_2) was added to the solution, followed by phenylselenyl chloride (47.7 mg, 0.249 mmol). A white precipitate formed. The mixture was stirred for 10 min, and *m*-chloroperbenzoic acid (85%, 100.6 mg, 0.496 mmol) was added. This was allowed to stir for an additional 5 min. The mixture was poured into ether (50 ml) and washed with water (25 ml) and saturated sodium chloride solution (25 ml). The aqueous portions were extracted with ether, and the combined ether extracts were dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated. The crude material was immediately dissolved in THF (20 ml) and ethylene gylcol (1 ml). A small drop of concentrated sulfuric acid was added, and the solution was stored over Drierite (8 mesh) overnight at 5 °C. The solution was allowed to warm to room temperature, and ~1 g of anhydrous potassium carbonate was added. The solution was filtered and poured into ether (50 ml). The ether was washed with a dilute potassium carbonate solution (~25 ml) and saturated sodium chloride solution (25 ml). The aqueous portions were extracted with ether, and the combined ether extracts were dried (K_2CO_3), filtered, and concentrated in vacuo to yield 90 mg of crude material. This was chromatographed on a 10 × 20 cm silica gel preparative thin layer plate (~1.5 mm thick) using ether as the eluent. This gave 35.3 mg (54%) of compound **13:** R_f 0.3; mp 134–136 °C; IR ($CHCl_3$) 1770, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.35 (s, 3 H), 1.4–2.2 (M, 6 H), 4.0 (broad singlet, 4 H), 5.03 (t, J = 5 Hz, 1 H), 5.70 (broad singlet, 1 H), and 6.97 ppm (d, J = 5 Hz, 1 H). Anal. ($C_{16}H_{20}O_5$) C, H.

(±)-LL-Z1271 (1a and Anomer 1b).[1,2,24,25] To a flask containing freshly distilled ethoxyacetylene (0.0450 g, 0.56 mmol) in dry tetrahydrofuran (THF, 2 ml) cooled to −78 °C (dry ice, acetone) under a nitrogen atmosphere was added *n*-butyllithium in hexane (0.331 ml, 1.88 m, 0.625 mmol). This solution was stirred at −78 °C under nitrogen for 15 min. A solution of compound **13** (0.0609 g, 0.208 mmol) in tetrahydrofuran (2 ml) was added, followed by an additional amount of tetrahydrofuran (1 ml) needed to complete the transfer. The resulting reaction mixture was stirred under dry nitrogen for 1 h at −78 °C. The flask was then allowed to warm up to room temperature and stir for an additional hour. The resulting red solution was poured into a flask containing water (50 ml), then extracted with ether (4 × 25 ml). The combined ethereal extracts were washed with water (3 × 25 ml) and saturated sodium chloride solution (20 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.0636 g of crude unstable ethoxyacetylide derivative: IR ($CHCl_3$) 3550 (OH) 2270 (C≡C), 1765 cm^{-1} (lactone); NMR ($CDCl_3$) δ 1.38 (t, J = 7 Hz), 4.1 ppm (q, J = 7 Hz). Because of the sensitive nature of this compound it was carried on to the next step without purification.

The crude ethoxyacetylene derivative (0.0636 g) was dissolved in anhydrous methanol (2.5 ml) and cooled to 0 °C (ice bath). Three drops of 5% sulfuric acid solution were then added. The mixture was stirred at room temperature for 2.5 h then transferred into a separatory funnel with ether (100 ml). The ether layer was washed with water (20 ml) and saturated sodium chloride solution (20 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to yield a crude mixture of products. The mixture was separated by preparative thin layer chromatography on silica gel (20 × 20 cm × 1.5 mm) and eluted with 60% ether:40% pet-ether. Compounds **1a** (0.0186 g) and **1b** (0.0081 g) were isolated in a combined yield of 42.2% (ratio 70:30, respectively).

The analytical sample of anomer **1b** was prepared by recrystallization from dichloromethane–ether–pentane (3×): mp 151–153 °C; UV (CH_3OH) 258 nm (ε 16 000); IR ($CHCl_3$) 1770 (lactone), 1720 cm^{-1} (α,β-unsaturated lactone); NMR ($CDCl_3$) δ 1.18 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.92 (d, J = 5 Hz, 1, bridgehead proton), 3.56 (s, 3, OCH_3), 5.02 (t, J = 5 Hz, 1, oxymethine), 5.55 (s, 1, =CH-CO-) 5.74 (d, J = 1.8 Hz, 1, *HC*-OMe), 6.34 ppm (dofd, J = 1.8 and 5 Hz, J = 5 Hz, 1, C-C-H). These spectral data correspond to those previously reported.[14] Anal. ($C_{17}H_{20}O_5$) C, H.

The analytical sample of racemic LL-Z1271α (**1a**) was prepared by several recrystallizations from ether–pentane followed by sublimation [115 °C (0.1 mm)]: mp 195–196 °C; UV (CH_3OH) 257 nm (ε 13 250); IR ($CHCl_3$) 1770 (lactone), 1715 cm^{-1} (α,β-unsaturated lactone); NMR ($CDCl_3$), δ 1.17 (s, 3, CH_3), 1.34 (s, 3, CH_3), 1.92 (d, J = 5 Hz, 1, bridgehead CH), 3.71 (s, 3, OCH_3), 5.00 (t, J = 5 Hz, 1, oxymethine), 5.73 (m, 2, -*OCH*OMe, -CH-CO_2-), 6.52 ppm (m, 1, -O-C-CH=). These spectral data are identical with those reported for the natural product.[1] Anal. ($C_{17}H_{20}O_5$) C, H.

Methyl 4α,10β-Dimethyl-8-hydroxymethylene-*trans*-9-decalone-4β-carboxylate (14).[5] To a solution of keto ester **6b** (2.95 g, 12.4 mmol) in ethyl formate (25 ml, freshly distilled from anhydrous calcium chloride) was added sodium hydride (2.61 g of a 57% dispersion in mineral oil, 62 mmol) and anhydrous methanol (2 drops) under nitrogen at 0 °C (ice bath). The mixture was stirred at 0 °C for 1 h, then dry ether (40 ml) was added. The resulting slurry was allowed to stir at room temperature for 5 h. Cold water (25 ml) was added, and the ether layer was separated. The aqueous layer was extracted with ether (3 × 25 ml). The combined ethereal extracts were washed with 2% sodium hydroxide solution. The combined basic aqueous layers were cooled to 0 °C (ice bath) and carefully acidified with concentrated hydrochloric acid. The mixture was extracted with ether (4 × 25 ml). The combined latter ethereal extracts were washed with saturated sodium chloride, then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 2.84 g (97%) of hydroxymethylene ketone **14:** mp 135–136 °C (lit. 135–137.5 °C); IR ($CHCl_3$) 1720 ($-CO_2CH_3$), 1630, and 1575 cm^{-1} (COC=CHOH); NMR ($CDCl_3$) δ 1.03 (s, 3, CH_3), 1.12 (s, 3, CH_3), 3.66 (s, 3, OCH_3), 8.67 ppm (bs, 1, OH). These spectral data are in agreement with those reported by Spencer and co-workers.[5]

Methyl 4α,10β-Dimethyl-8-formyldimethoxyacetal-*trans*-decal-$\Delta^{7,8}$-en-9-one-4β-carboxylate (15a) and Methyl 4α,10β-Dimethyl-8-formylethylenedioxyacetal-*trans*-decal-$\Delta^{7,8}$-en-9-one-4β-carboxylate (15b).[12] To the hydroxymethylene ketone **14** (0.537 g, 2.02 mmol) dissolved in dry dioxane (5.0 ml, freshly distilled from lithium aluminum hydride) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.04 g, 3.76 mmol) dissolved in dry dioxane (5 ml). A yellow precipitate formed within 2 min; however, the reaction was allowed to stir at room temperature for 4 h and then quenched by adding dichloromethane (100 ml). The reaction mixture was washed with 2% sodium hydroxide solution (3 × 25 ml), water (4 × 50 ml), and saturated sodium chloride solution (25 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.360 g (67.5%) of unstable α,β-unsaturated keto aldehyde: IR ($CHCl_3$) 1720 ($-CO_2CH_3$), 1695 (CHO), 1675 (CO), and 1620 cm^{-1} (C=CH); NMR ($CDCl_3$) δ 0.93 (s, 3, CH_3), 1.25 (s, 3, CH_3), 3.70 (s, 3, OCH_3), 7.76 (dofd, J = 3 and 6 Hz, 1, C=CH), 9.67 (s, 1, -CHO). This substance was carried on to the following two acetal derivatives which were more stable: The unsaturated keto aldehyde (0.0479 g, 0.178 mmol) was dissolved in anhydrous methanol (20 ml) containing a trace amount of hydrogen chloride gas and a few crystals of anhydrous calcium sulfate (Drierite, 8 mesh). This mixture was allowed to stand in a refrigerator at 5 °C for 72 h and then quenched with solid sodium bicarbonate. The mixture was added to a saturated sodium bicarbonate solution (20 ml) and extracted with ether (4 × 75 ml). The combined ethereal extracts were washed with water (4 × 25 ml) and saturated sodium chloride solution (40 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.0462 g (83.5%) of keto acetal **15a:** bp 95–97 °C (external temperature, 0.05 mm); IR ($CHCl_3$) 1720 ($-CO_2CH_3$), 1670 cm^{-1} (CO); NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.26 (s, 3, CH_3), 3.30 (s, 3, OCH_3); 3.36 (s, 3, OCH_3), 3.62 (s, 3, CO_2CH_3), 5.14 (s, 1, $CH(OCH_3)_2$), 7.13 ppm (dofd, J = 2 and 6 Hz, 1, C=CH). Anal. ($C_{17}H_{26}O_5$) C, H.

The unsaturated keto aldehyde (0.0494 g, 0.185 mmol) was dissolved in dry tetrahydrofuran (1.0 ml) and ethylene glycol (0.0115 g, 0.185 mmol), dried over $CaSO_4$, and distilled from sodium metal onto activated molecular sieves type 13X). A few crystals of calcium sulfate (Drierite, 8 mesh) were added along with 2 μl of concentrated sulfuric acid. The mixture was then allowed to stand in a refrigerator at 5 °C overnight. The reaction was then quenched with solid sodium bicarbonate. The mixture was poured into saturated sodium bicarbonate solution (10 ml) and ether (50 ml). The ether layer was separated, and the aqueous layer was extracted with ether (3 × 10 ml). The combined ethereal extracts were washed with water (4 × 5 ml) and saturated sodium chloride solution (10 ml), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo. The crude keto acetal was chromatographed on silica gel-60 (20 g) using 60% ether:40% pet-ether (bp 30–60 °C) eluent collecting 12-ml fractions. Fractions 10–13 were combined to give 0.0513 g (89.5%) of keto acetal **15b:** bp 93–95 °C (external temperature, 0.05 mm); IR ($CHCl_3$) 1720 (CO_2CH_3), 1670 cm^{-1} (CO); NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.23 (s, 3, CH_3), 3.67 (s, 3, OCH_3), 3.96 (bs, 4, OCH_2CH_2O), 5.55 (s, 1, CHO_2), 7.20 ppm (dofd, J = 2 and 6 Hz, 1, C=CH). Anal. ($C_{17}H_{24}O_5$) C, H.

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References and Notes

(1) G. A. Ellestad, R. H. Evans, M. P. Kunstmann, J. E. Lancaster, and G. O. Morton, *J. Am. Chem. Soc.*, **92**, 5483 (1970).
(2) M. Adinolfi, L. Mangoni, G. Barone, and G. Laonigro, *Tetrahedron Lett.*, 695 (1972); *Gazz. Chim. Ital.*, **103**, 1271 (1973); L. Mangoni, M. Adinolfi, G. Laonigro, and R. Caputo, *Tetrahedron*, **28**, 611 (1972).
(3) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950); S. Ramachandran and M. S. Newman, *Org. Synth.*, **41**, 38 (1961).
(4) For preliminary reports see: S. C. Welch, C. P. Hagan, D. H. White, and W. P. Fleming, *Synth. Commun.*, **4**, 373 (1974), Abstracts, 30th Southwest Regional Meeting of the American Chemical Society, Houston, Texas, Dec 1974, ORGN No. 303; S. C. Welch and C. P. Hagan, *ibid.*, **2**, 221 (1972).
(5) T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); T. A. Spencer, R. J. Friary, W. W. Schmiegal, J. F. Simeone, and D. S. Watter, *ibid.*, **33**, 719 (1968).
(6) H. O. House, J. Lubinkowski, and J. J. Good, *J. Org. Chem.*, **40**, 86 (1975); H. O. House and T. M. Bare, *ibid.*, **33**, 943 (1968).
(7) R. E. Ireland and L. N. Mander, *Tetrahedron Lett.*, 3453 (1964); *J. Org. Chem.*, **32**, 689 (1967).
(8) F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 315 (1974).
(9) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597, 2601 (1970).
(10) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).
(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(12) J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. C. Rivera, R. Urquiza, L. Cardona, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **29**, 3481 (1964); P. Morand, S. Stavric, and D. Godin, *Tetrahedron Lett.*, 49 (1966).
(13) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).
(14) D. Z. Denney, A. Appelbaum, and D. B. Denney, *J. Am. Chem. Soc.*, **84**, 4969 (1962).
(15) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).
(16) P. A. Bartlett and W. S Johnson, *Tetrahedron Lett.*, 4459 (1970).
(17) J. Jacques and A. Marquet, *Org. Synth.*, **53**, 111 (1973).
(18) H. O. House, "Modern Synthetic Methods", W. A. Benjamin, New York, N.Y., 1972, pp 422–426, and references cited therein.
(19) R. Breslow, "Organic Reaction Mechanisms", W. A. Benjamin, New York, N.Y., 1966, pp 69–72; R. H. DeWolfe and W. G. Young, *Chem. Rev.* **56**, 769 (1956); G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4609 (1956).
(20) C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.*, **88**, 4537 (1966).
(21) C. Ainsworth, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, N.Y., 1963, p 536.
(22) S. R. Wilson and R. B. Turner, *J. Org. Chem.*, **38**, 2870 (1973).
(23) H. J. Reich and J. M. Renga, *J. Org. Chem.* **40**, 3313 (1975).
(24) J. F. Arens in R. A. Raphael, E. C. Taylor, and H. Wynberg, *Adv. Org. Chem.*, **2**, 117–212 (1960); J. F. Arens, D. A. van Dorp, and W. Graham, *Recl. Trav. Chim. Pays-Bas*, **68**, 604, 609 (1949).
(25) H. Saunders, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, N.Y., 1955, p 22; B. C. L. Weedon, *Prog. Org. Chem.*, **1**, 160 (1952); I. Heilbron, E. R. H. Jones, M. Julia, and B. C. L. Weedon, *J. Chem. Soc.*, 1823 (1949); K. H. Meyer and K. Schuster, *Chem. Ber.*, **55**, 819 (1922).
(26) W. S. Johnson and W. P. Schneider, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, N.Y., 1963, p 132.
(27) This reaction must be conducted in a well-ventilated hood; the chemist should wear rubber gloves during the workup because both hexamethylphosphoramide and chloromethyl methyl ether are carcinogens.

Asymmetric Syntheses via Enantiotopically Selective Horse Liver Alcohol Dehydrogenase Catalyzed Oxidations of Diols Containing a Prochiral Center[1a,b]

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Abstract: The practicality of exploiting the enantiotopic specificity of horse liver alcohol dehydrogenase (HLADH) has been demonstrated using substituted pentane-1,5-diol substrates in which C-3 is a prochiral center. The catalysis was stereoselective for the pro-*S* hydroxyl group in each case. HLADH catalyzed oxidation of 3-methylpentane-1,5-diol gave (3*S*)-3-methylvalerolactone of >90% optical purity. The corresponding 3*S* lactones obtained with 3-isopropyl- and 3-phenylpentane-1,5-diols as substrates were of 25 and 21% optical purities, respectively. From the more highly C-3 substituted substrate, 3-hydroxy-3-methylpentane-1,5-diol, the product was (3*S*)-mevalonic lactone (14% optical purity). The methyl and isopropyl lactones were formed in situ by HLADH catalyzed oxidation of the cyclic hemiacetal form of the initial hydroxyaldehyde product. The 3-isopropyl and 3-hydroxy-3-methyl hemiacetals were poor HLADH substrates and were oxidized to their lactones chemically. When enzyme-catalyzed oxidation of the hemiacetal intermediate could occur, its stereospecificity influenced the optical yield to a significant degree. The stereospecificities of the oxidations, which are very sensitive to the nature of the C-3 substituent, are all interpretable in terms of a diamond lattice section of the enzyme's active site. All reactions were performed on a preparative (up to 2 g) scale and good (up to 75%) yields of hemiacetal or lactone products were isolated.

The ability to effect stereoselective transformations of enantiotopic groups attached to a prochiral center is an important aspect of asymmetric synthesis for which the current techniques are woefully inadequate.[2] The capacity of enzymes to distinguish such groups is well documented,[3-5] but their potential as practical catalysts for this purpose remains largely untapped.[5b] During the course of our overall evaluation of the synthetic utility of enzymes in this regard, we have initiated