A STEREOSELECTIVE TOTAL SYNTHESIS OF ANTIBIOTIC (±)-LL-Z 1271α

A Thesis

Presented to

the Faculty of the Department of Chemistry

College of Arts and Sciences

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

---

by

William P. Fleming

August 1974

To Sandy

ACKNOWLEDGEMENT

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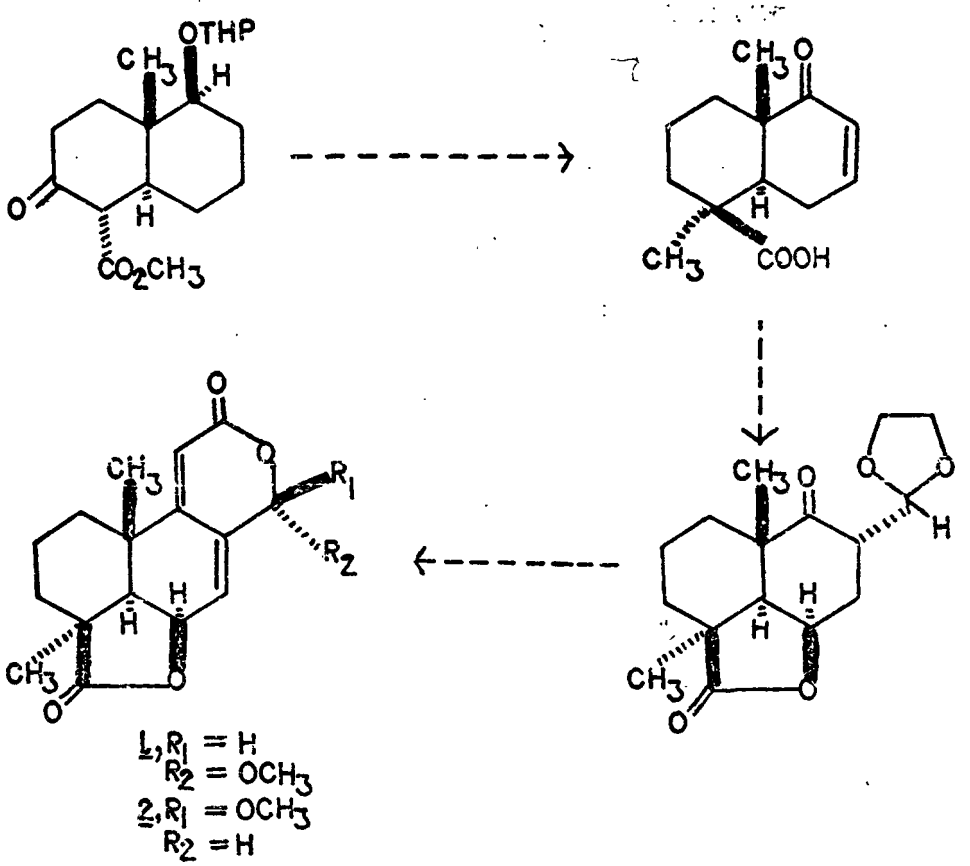
ABSTRACT

The stereoselective total synthesis of (±)-LL-Z 1271α (1) is presented. The general synthetic scheme is shown below.



The synthetic approach presented incorporates a new stereoselective reductive alkylation reaction, a new method of lactonization, and a novel methanolysis reaction to give the title compound (1) and its anomer (2) in a favorable ratio.

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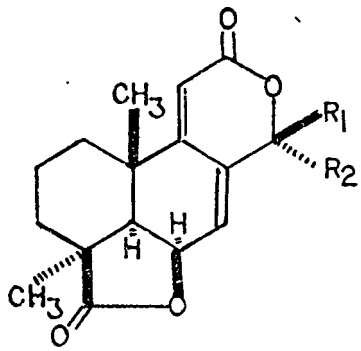
CHAPTER I

INTRODUCTION

INTRODUCTION

The structure of a novel C_{17} terpenoid labeled as (-)-LL-Z 1271α (1) was isolated in 1970 along with a minor amount of lactol (-)-LL-Z 1271γ (3) from the metabolic fermentation products of an Acrostalagmus species. Compound 1 was found to exhibit in vitro and in vivo antifungal activity against several experimental infections. This antifungal antibiotic is noteworthy because it is the first terpene found to have a C_{16} carbon skeleton.[1]



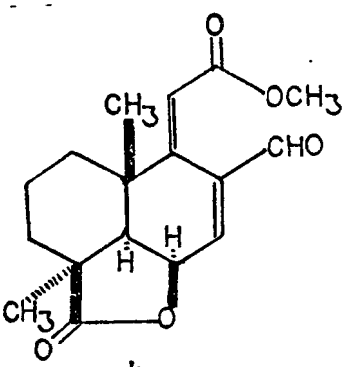
1, $R_1 = H$
$R_2 = OCH_3$

2, $R_1 = OCH_3$
$R_2 = H$

3, $R_1 = H$
$R_2 = OH$

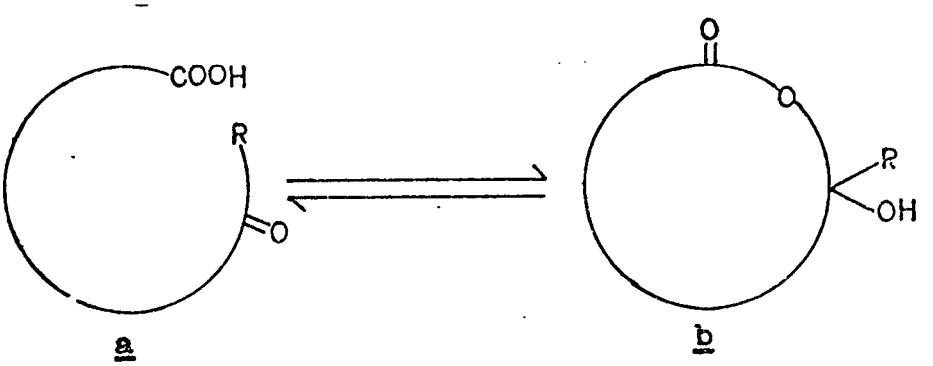
Structural assignments of compound 1 were elucidated on the basis of its elemental composition, $C_{17}H_{20}O_5$, its spectral properties, and other physical methods in conjunction with biogenetic considerations. Several base catalyzed transformations were also found to occur which supported structure 1.[1]

Treatment of compound 3 with ethereal diazomethane in methanol affords compound 4, the ester aldehyde.



4

Such a transformation is characteristic of compounds capable of equilibria of the type a ⟷ b.[1,2]

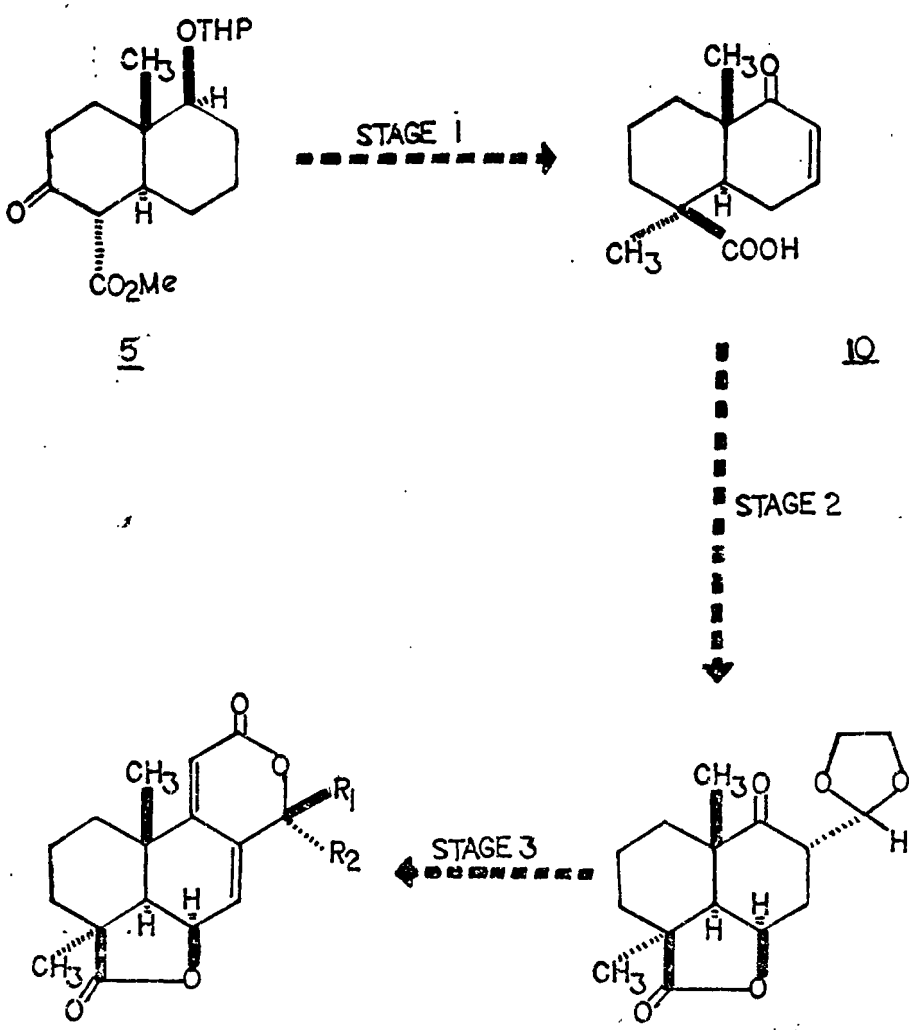


a b

Several factors were considered in devising a route for the construction of (±)-LL-Z 1271α (1). The synthetic scheme focuses on the effective utilization of previously established reactions, but more importantly on the creation of new synthetic methods and ideas to effect the synthetic goal. Factors such as functionality, presence of chiral centers, and stability of intermediates were taken into account. The economy of such a synthetic scheme dictated that the starting materials be readily available, the stereoselectivity of the reactions be high, and that the synthesis consist of a limited number of specific steps in a proper sequence.

The general synthetic pathway is illustrated on Chart I. The starting material chosen was ketoester 5 which can be prepared from the Wieland-Miescher ketone[6] by the method of Spencer and coworkers.[3,4] The first stage involves the conversion of compound 5 to bicyclic intermediate 10 by a new reductive alkylation procedure to give the proper stereochemistry in ring A.[5] The second stage creates the lactone by a novel reaction from compound 10. A protected α-formyl group is then introduced to give compound 14. The third stage employs a double bond insertion reaction followed by a methanolysis reaction based on the previously mentioned transformation a ⟷ b,[2] to give (±)-LL-Z 1271α (1) and its anomer (2).

CHART I



5

10

11

1, $R_1 = H$
$R_2 = OCH_3$

2, $R_1 = OCH_3$
$R_2 = H$

CHAPTER II

RESULTS AND DISCUSSION

Stage 1

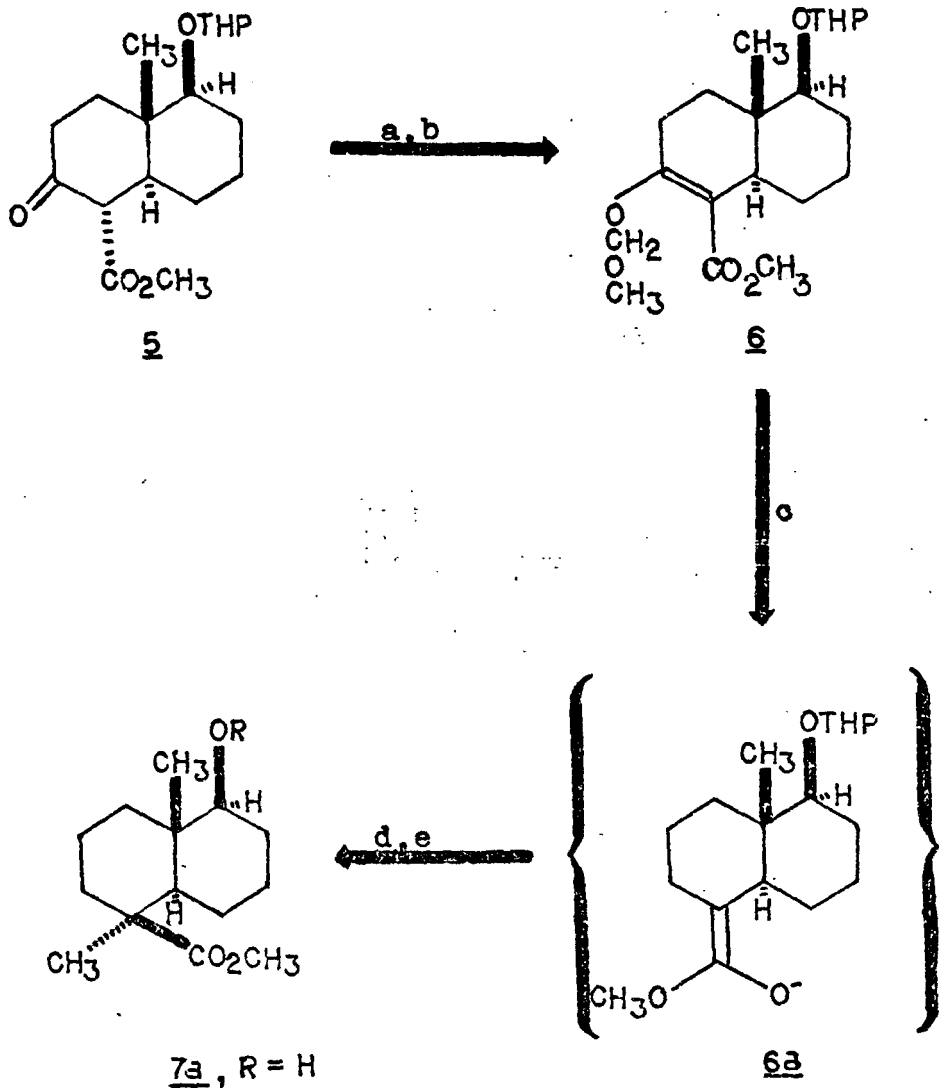
Starting material 5 was prepared from the well known and readily available Wieland-Miescher ketone[6] by the method of of Spencer and coworkers using the Stork reductive carbomethoxylation procedure.[3,4]

Conversion of compound 5 to an important intermediate 7b was performed in two steps as revealed on Chart II. The basis of this conversion follows from the fact that exocyclic enolates 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 usually produces equitorially alkylated products. Exocyclic enolate 6a may stereoselectively methylate to give the desired ester 7b. The best and most efficient method of generating enolate 6 is via the reductive elimination reaction developed by Coates and Shaw.[7] Ketoester 5 was treated with sodium hydride in hexamethylphosphoramide (HMPA) at room temperature for two hours, then O-alkylated with chloromethyl methyl ether for three hours to give methoxymethyleneoxyvinyl ether ester 6 in 91% yield. Treatment of compound 6 with lithium in anhydrous liquid ammonia and 1,2-dimethoxyethane (DME) followed by methyl iodide and acid hydrolysis gave ester 7a in 64% yield. The melting point and spectral characteristics (ir and nmr) of compound 7a were identical to that reported by Spencer and coworkers.[4]

This sequence of reactions represents a new type of

CHART II

Stage 1



7a , R = H

7b , R = THP

a) NaH, HMPA; b) $ClCH_2OCH_3$; c) Li, NH_3, DME; d) CH_3I; e) H_3O^+, CH_3OH.

reductive alkylation reaction. The procedure is unique in that it effects deoxygenation and stereoselective methylation of ring A in one step. Moreover, the important and versatile intermediate 7b is obtained in a considerably better overall yield (32%) by this method than by that previously reported.[4]

Axial C_4 esters of the type found in structure 7 are extremely resistant to saponification under ordinary conditions.[4] Compound 7b could, however, be quantitatively cleaved to the acid by the method of Bartlett and Johnson.[8] Treatment of ester 7b with a previously prepared solution of lithium n-propyl mercaptide in hexamethylphosphoramide (HMPA) at room temperature overnight followed by removal of the tetrahydropyranyl (THP) ether in a usual manner gives compound 8.

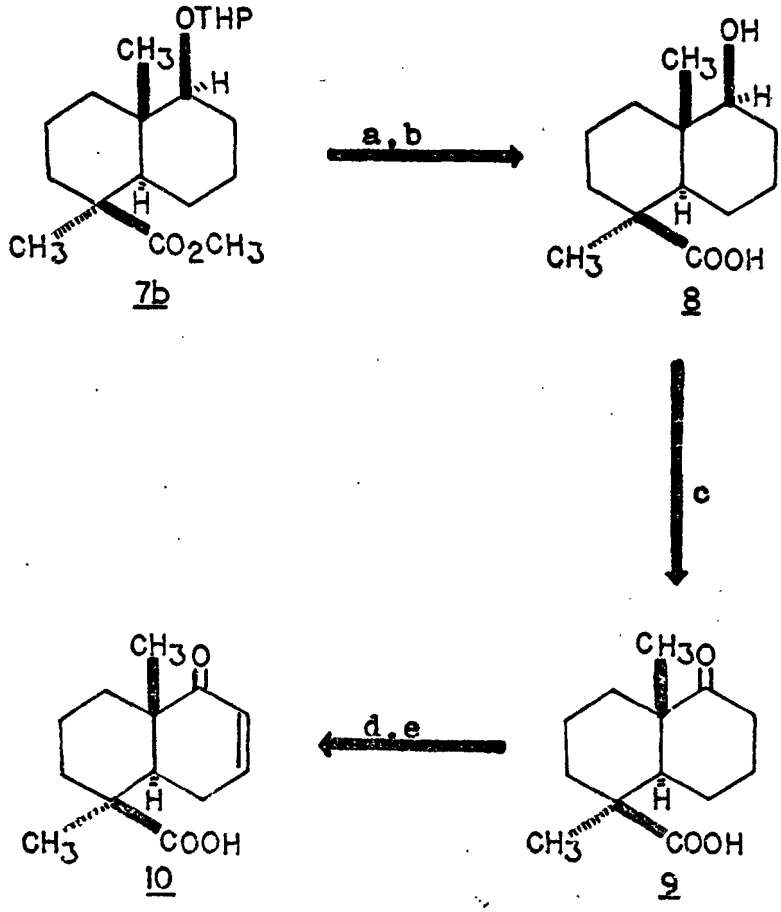
Alcohol 8 was smoothly converted to the crystalline keto-acid 9 by a standard Jones' oxidation[9] in 85% yield. The resulting keto-acid 9 was then brominated with a solution of bromine and acetic acid in dichloromethane to produce a mixture of the two diastereomeric bromoketones which were dehydrohalogenated by heating at reflux with calcium carbonate in N,N-dimethylacetamide (DMA) for 30 minutes to afford crystalline enone-acid 10 in 91% overall yield.[10]

Stage 2

The next goal of the synthesis was to effect closure of the acid to give lactone 11. All attempts to functionalize C_6 of enone-acid 9 or the corresponding enone-methyl ester by oxidative procedures were unsuccessful. Another

CHART III

Stage 1 (cont'd)



a) $LiSCH_2CH_2CH_3$, HMPA; b) H_3O^+, CH_3OH; c) Jones' Reagent d) $Br_2/HOAc/CH_2Cl_2$; e) $CaCO_3$, DMA, Δ.

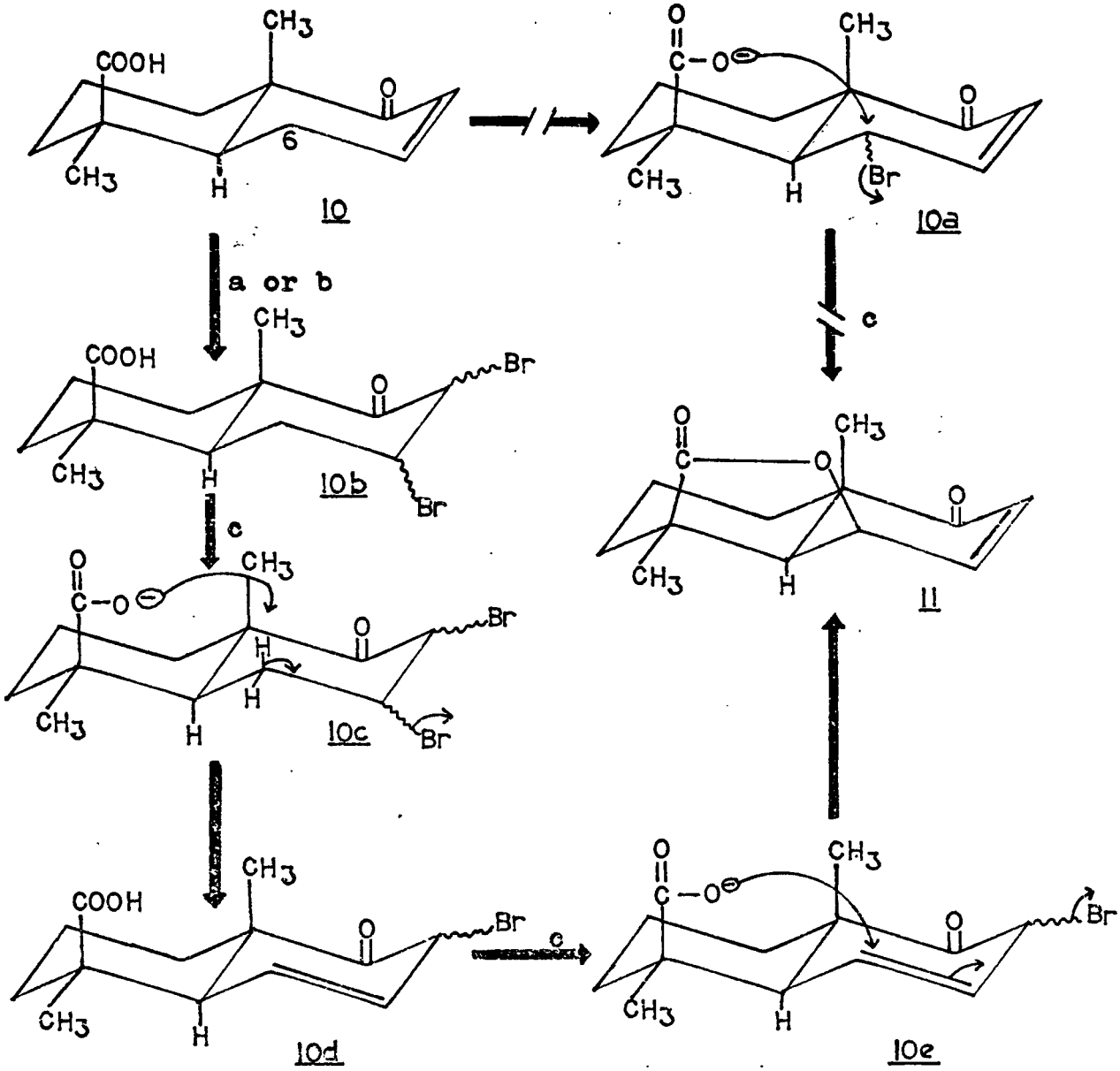
unsuccessful attempt was to prepare the ethylene ketal of the α,β-unsaturated ketone 10 which would presumably deconjugate the double bond to the more stable $\Delta^{6,7}$ position thus providing a suitable precursor for ring closure of the acid. The ethylene ketal could readily be prepared but resulted in a mixture of the two olefinic compounds. Attempts to shift the double bond via formation of the corresponding enamines or vinyl ethers proved futile since the enamines and vinyl ethers could not be prepared by standard procedures.

Lactonization was finally realized by the route shown on Chart IV. The original plan was an allylic bromination of C_6 to give compound 10a followed by treatment with base to bring about ring closure by intramolecular substitution of the bromine atom. The absence of vinyl protons in the nmr of the bromide intermediate indicated that compound 10b was the precursor to compound 11 when enone 10 was treated with excess phenyltrimethylammonium tribromide (PTAB) in tetrahydrofuran (THF) followed by potassium carbonate in N,N-dimethylformamide (DMF) at room temperature for one hour. Thereafter, bromine in carbon tetrachloride solution followed by potassium carbonate in dimethylformamide was used to effect the conversion to lactone 11 in 69% yield after chromatography.

The proposed mechanism for this new method lactonization is illustrated on Chart IV. The axial position of the carboxylate anion restricts attack on C_6 from the top side of the molecule as shown in structure 10e to give the desired

CHART IV

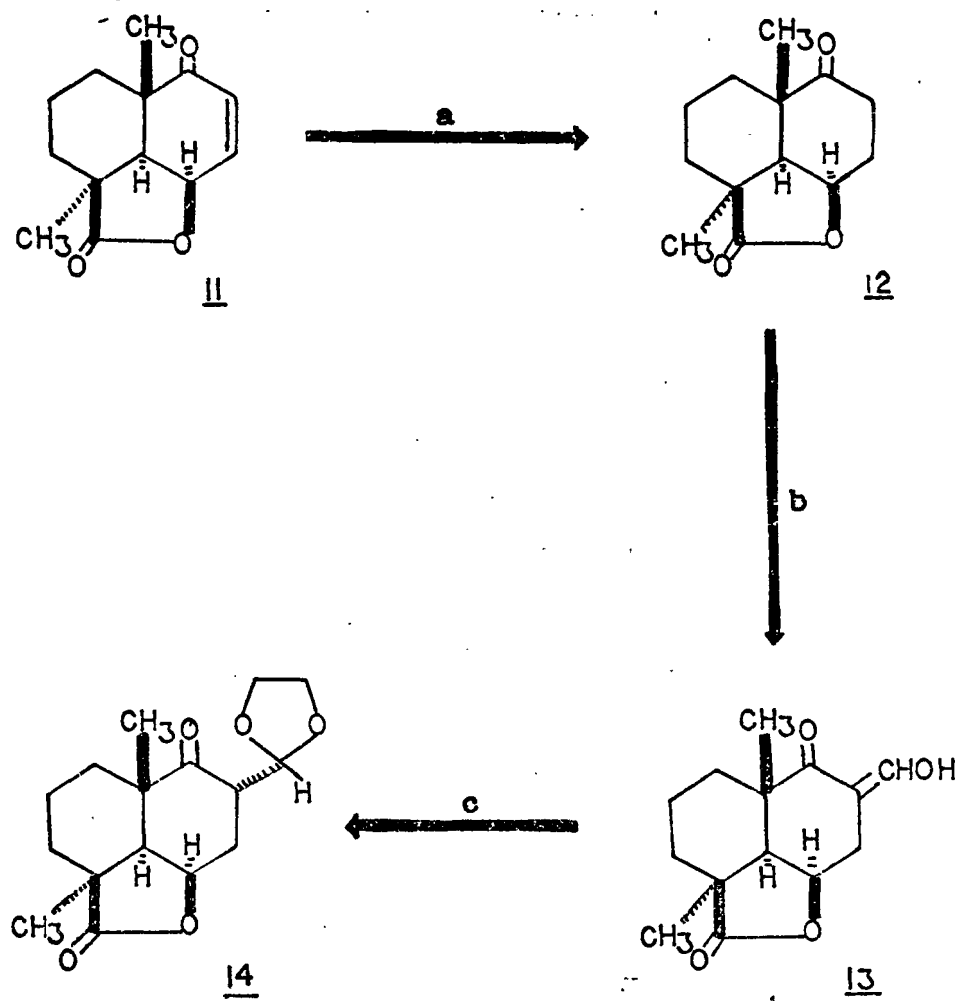
Stage 2



a) PTAB, THF or DMF; b) Br_2/CCl_4; c) K_2CO_3, DMF.

CHART V

Stage 2 (cont'd)



a) H_2, Wilkinson's Catalyst; b) NaH, ethyl formate, MeOH, DME; c) ethylene glycol, benzene, p-tsOH.

stereochemistry.

Attempted hydrogenation of olefin 11 using 5% palladium-on-charcoal resulted in hydrogenolysis of the lactone as well as hydrogenation of the carbon-carbon double bond to afford compound 9. The homogeneous catalyst tris-(triphenylphosphine)chloro rhodium (Wilkinson's Catalyst) was then tried successfully.[11] Compound 11 was dissolved in a freshly distilled benzene solution with a catalytic amount of Wilkinson's catalyst and stirred for three hours under hydrogen at low pressure to give compound 12 in 95% yield after filtration through alumina. The saturated ketone 12 was then stirred with sodium hydride in ethyl formate with a catalytic amount of methanol at 0° for one hour then overnight after the addition of 1,2-dimethoxyethane (DME) to produce hydroxymethylene derivative 13 in 96% overall yield.[4]

Ethylene acetal 14 was easily prepared by a standard procedure. The stereochemistry of chiral atom C_8 thus formed may be assigned on the basis of precedent as the more stable equitorial isomer. A model examination reveals that a severe 1,3-diaxial interaction occurs between the acetal group and the axial C_{10} methyl group in the axially substituted diastereomer.

Stage 3

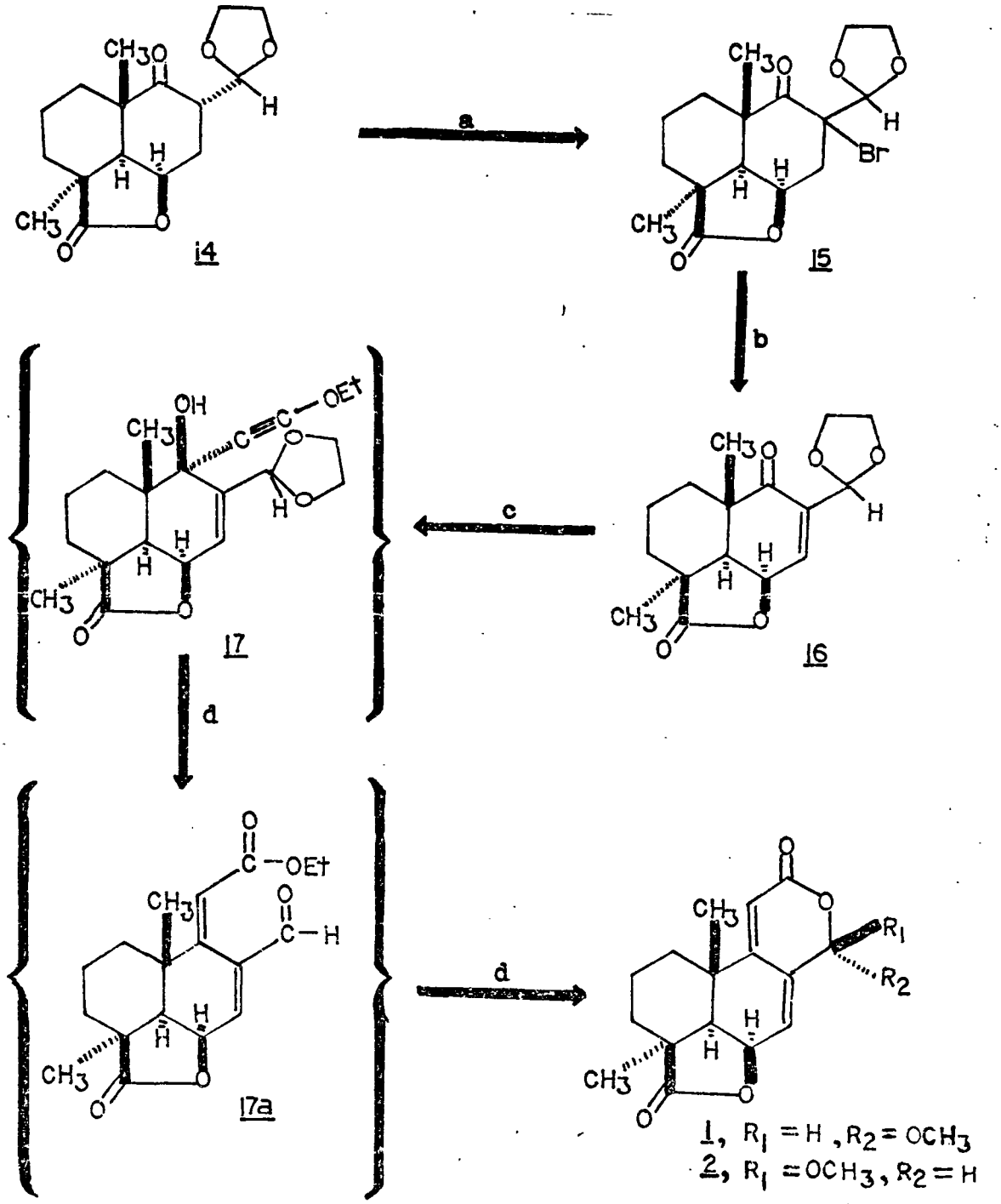
The next stage of the synthetic scheme called for reinsertion of the double bond to form α,β-unsaturated ketone 16. This step proved to be the most challenging of the entire sequence. Compound 15 was easily obtained in quantitative

yield by bromination of compound 14 with phenyltrimethylammonium tribromide (PTAB) in tetrahydrofuran (THF).[12] Several dehydrohalogenations of the bromide were tried under a wide variety of condtions. It was found that calcium carbonate in N,N-dimethylformamide (DMA) at 180° provided the best results. Olefin 16 could be obtained utilizing this procedure in 31% yield after purification by preparative thin layer chromatography.

Intermediate 16 dissolved in tetrahydrofuran was treated with freshly prepared lithium ethoxyacetylide at -78° for one hour followed by stirring for one hour at room temperature to furnish the final precursor 17.[13] The stereochemistry of this compound be assigned as shown on structure 17 due to the preferred α-side attack of the nucleophile. Due to the suspected fragile nature of compound 17 it was not purified but directly subjected to methanolysis by stirring in a methanol solution containing a catalytic amount of 5% sulfuric acid for three hours at room temperature to complete the synthesis. The final reaction proceeds through the ester aldehyde 17a as shown in Chart VI. Compound 17a undergoes ring closure to give a mixture of compounds 1 and 2.[14] A careful separation by thin layer chromatography gave the two diastereomers in 42% overall yield from compound 16. Racemic LL-Z 1271α (1) and its anomer 2 were found to be formed in a 70 : 30 ratio, respectively. The spectral data (ir, nmr, uv) of compound (1) corresponded directly with the literature values for the natural product.[1] No detectable amount of lactol 2 could be found.

CHART VI

Stage 3



a) PTAB, THF; b) $CaCO_3$, DMA, 180°; c) LiC≡COEt, THF; d) MeOH, 5% H_2SO_4.

CHAPTER III

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

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

Infrared (ir) spectra were recorded on a Perkin-Elmer 700 spectrophotometer. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10 mm sodium chloride cells. Liquid samples were 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.

For all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120° for several hours, then allowed to cool in a dessicator. All liquid transfers were made with nitrogen filled syringes.

The term "pet-ether" refers to Baker "Analyzed Reagent" bp 30-60°. 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 anhydrous conditions. "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 (6)^{5,7}-Sodium hydride (1.20 g, 28.5 mg-at, 57% dispersion) was washed with dry ether (3 x 10 ml) under dry nitrogen. The residual ether was evaporated with an infrared heat lamp under a stream of dry nitrogen. Dry hexamethylphosphoramide (HMPA, 50 ml, stored over molecular sieves 13x) was added followed by β-ketoester (5, 8.31 g, 25.6 mmole) in HMPA (3 x 15 ml). After stirring at room temperature for 3.5 hours, chloromethyl methyl ether (2.20 ml, 29 mmole) was added. The reaction mixture was allowed to stir for an additional 2 hours 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 x 50 ml). The combined ethereal layers were washed with water (4 x 25 ml), saturated sodium chloride solution (50 ml), 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 6. Compound 6 was purified by column chromtography on silica gel 60 using 40% ether : 60% pet-ether. Fractions 9-16 were combined to give 8.59 g (91%) of pure vinyl ether 6 as a colorless liquid: bp 150° (external

temperature, 0.5 mm), ir (film) 1725 (CO), 1685 cm^{-1} (C=C); nmr (CCl_4) δ 0.85 (s, 3, CH_3), 3.35 (s, 3, OCH_3), 3.60 (s, 3, $-COCH_3$), 4.69 ppm (AB, 2, J_{AB}=6 Hz, $-OCH_2O-$).

Anal. Calcd. for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75.

Found: C, 65.22; H, 8.71.

4α, 10β-Dimethyl-4β-carbomethoxy-9β-hydroxy-trans-decalin (7a)[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-at) cut in ten small pieces was added. After stirring at -33° for 20 minutes vinyl ether 6,(3.30 g, 8.96 mmole) dissolved in 1,2-dimethoxyethane (DME, 3 x 15 ml) was added. The mixture remained blue and after 15 minutes methyl iodide (3.0 ml, 48.2 mmole) was added rapidly. The resulting white slurry was allowed to stir at -33° for one hour, 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 x 50 ml). The combined ether extracts were washed with 10% sodium sulfite solution (50 ml), water (4 x 50 ml), saturated sodium chloride solution (50 ml), 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 7b as a colorless oil.

The crude product was dissolved in methanol (150 ml)

containing para-toluenesulfonic acid (p-tsOH, 0.5 g) and stirred at reflux for 5 hours. 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 x 50 ml). The combined ethereal extracts were washed with water (4 x 50 ml), saturated sodium bicarbonate solution (50 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 2.03 g (97%) of crude ester-alcohol 7a. The crude product was chromatographed on silica gel 60 (200 g) using 60%ether : 40% pet-ether eluant in a column 3 cm x 110 cm. Fractions 8-16 gave 1.38 g (64%) of compound 7a: mp 71-72° [lit.[4] mp 72.5-73.5°]; 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 (s, 3, CO_2CH_3). These spectral data were identical to those reported by Spencer and coworkers.[4]

Compound 7b (2.85 g crude) from a similar experiment was chromatographed on silica gel 60 (300 g) using 15% : 85% pet-ether as the eluant. Fractions 3-6 gave 2.09 g (72%) of pure compound 7b 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 (m, 1, -OCHO-). This material was carried on to the next experiment without further purification.

4α,10β-Dimethyl-4β-carboxy-9β-hydroxy-trans-decalin-(8)[4,8]-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 (7, 0.7505 g, 2.31 mmoles) was added to the reagent in dry HMPA (20 ml). After stirring for 5 hours 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 then extracted with ether (5 x 20 ml). The combined ethereal extracts were separated and evaporated <u>in vacuo</u>. The crude acid-tetrahydropyranyl ether was then dissolved in methanol (150 ml) containing para-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), extracted with ether (10 x 50 ml). The combined ethereal extracts were washed with water (3 x 50 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated <u>in vacuo</u> to give 0.5172 g (99%) of crystalline acid-alcohol 8: mp 139-142°; [lit.[4] mp 142-144.5°]; ir (CCl_4) 3300-2550 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 (s, 1, COOH). These spectral data were in agreement with those reported by Spencer and coworkers.[4]

<u>4α,10β-Dimethyl-4β-carboxy-trans-decalone-9 (9)</u>[4,9]-To a

solution of crude hydroxy acid (1.24 g, 5.48 mmole) in acetone (50 ml) was added excess Jones' reagent (2.67 M) dropwise until the stirred solution remained orange. After stirring for 2 hours at room temperature, the mixture was poured into a separatory funnel containing water (700 ml). The aqueous layer was extracted with ether (5 x 90 ml). The ethereal extracts were combined and washed with water (3 x 50 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated <u>in vacuo</u> to give 1.035 g (85%) of crystalline keto acid: mp 155-156°; [lit.[4] mp 156-157°]; ir ($CHCl_3$) 2500-3300 (broad, COOH), 1690 cm^{-1} (CO); nmr ($CDCl_3$) δ1.10 (s, 3, CH_3), 1.28 (s, 3, CH_3), 11.15 (s, broad, 1, OH). These spectral data were in agreement with those reported by Spencer and coworkers.[4]

<u>4α,10β-Dimethyl-4β-carboxy-trans-$\Delta^{6,7}$-decalone-9 (10)</u>[10]-

To a solution of keto-acid (9, 1.07 g, 4.77mmole) in dichloromethane (30 ml) was added bromine (0.834 g, 1.1 equivalent) in glacial acetic acid (8 ml) dropwise over 30 minutes. The reaction was stirred at ambient temperature for an additional 15 minutes then poured into a separatory funnel containing water (200 ml). The water layer was extracted with ether (5 x 70 ml). The combined ethereal extracts were washed with water (5 x 100 ml), saturated sodium chloride solution (100 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated <u>in vacuo</u> to give 1.466 g of crude bromide. NMR data showed that no starting material remained. The crude α-bromoketone

was dissolved in N,N-dimethylacetamide (DMA, 50 ml) along with calcium carbonate (1.43 g, 14.3 mmole). The mixture was heated at reflux under nitrogen for 30 minutes then poured into a separatory funnel containing 10% hydrochloric acid (100 ml) and water (200 ml). The aqueous mixture was extracted with ether (3 x 70 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.970 g (91%) of unsaturated ketone 10. The analytical sample was prepared by column chromatography on silica gel 60 (75 g) using 40% : 60% pet-ether to elute the column. The chromatographed sample was then recrystallized from ether-pentane four times: mp 165-166°; ir ($CHCl_3$) 2500-3500 (COOH), 1690 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.02 (s, 3, CH_3), 1.30 (s, 3, CH_3), 5.86 (broad d, J=10 Hz, 1, -CO-CH=), 6.93 ppm (m, 1, -C=CH).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16.

Found: C, 70.12; H, 8.08.

3,4,5,5a,8aα,8bα-Hexahydro-2aα,5aβ-dimethyl-2H-naptho [1,8-bc] furan-2,6-(2aH)-7-en-dione (11)-Method A: To a solution of acid enone 10 (0.586 g, 2.6 mmole) in dichloromethane (15 ml) was added bromine in carbon tetrachloride (7.8 ml of 0.34 M) over 30 minutes. After stirring for an additional 30 minutes, 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), saturated sodium chloride solution (20 ml), 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) with a small amount of anhydrous potassium carbonate (50 mg). Monitoring by gas phase chromatography using a 3% SE-30 on Varaport 30, 100/120 mesh (Varian) 5-foot, stainless steel column, and flow rate of 15 ml/min at 200° (column temperature), revealed that the reaction had gone almost to completion. 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 x 25 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated *in vacuo* to give 0.400 g (69%) of crystalline lactone 10 after preparative thin layer chromatography on silica gel using 90% ether : 10% pet-ether to elute the plate.

Method B: A solution of acid enone 10 (0.138 g, 0.625 mmole) in N,N-dimethylformamide (DMF, 4 ml, distilled from calcium hydride onto molecular sieves type 4A) was stirred at 0° (ice-bath) under nitrogen while a solution of phenyltrimethylammonium tribromide in DMF (6.83 ml, 0.095 M solution) was added slowly. After 30 minutes at 0° the ice-bath was removed. Then after 2 hours at room temperature an additional amount of phenyltrimethylammonium tribromide (20 ml, 0.364 M solution in DMF) was added. After stirring for a total of 24 hours anhydrous potassium carbonate (0.5 g) was

was added. After stirring at room temperature for 6 hours, 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), water (8 x 25 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.100 g (73%) of lactone 10.

An analytical sample of lactone 10 was prepared by preparative thin layer chromatography followed by recrystallization from ether-hexane (4x): mp 114-115°; UV(EtOH) 209 nm (ε 5040); ir ($CHCl_3$) 1780 (lactone), 1700 cm^{-1} (α,βunsaturated ketone); nmr ($CDCl_3$) δ 1.20 (s, 3, CH_3), 1.33 (s, 3, CH_3), 2.13 (d, J=4,8 Hz, 1, bridgehead proton), 4.92 (t, J=4,8 Hz, 1, oxymethine), 6.09 (d, J=10 Hz, 1, -CO-CH=C-), 6.88 ppm (q, J=4 Hz, 1, -CO-C=CH).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32.
Found: C, 70.83; H, 7.21.

3,4,5,5a,7,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-2H-naptho [1,8-b,c] furan-2,6-(2aH)-dione (11)[11]-Into a 250-ml Parr hydrogenation bottle was placed enone lactone 10, 1.457 g, 6.61 mmole) and tris-(triphenylphosphine)chloro rhodium (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 then evacuated and filled with hydrogen (3x). The sample was stirred for 3 hours at room temperature

under 4 psi of hydrogen. The mixture was then filtered through an alumina column (Woelm neutral, Activity III, 10 g) with dichloromethane (3 x 50 ml) to remove the catalyst and to give 1.39 g (95%) of saturated lactone 11. The analytical sample was prepared by recrystallization four times from ether-pentane: mp 121-122°, ir ($CHCl_3$) 1770 (lactone), 1715 cm^{-1} (ketone); nmr ($CDCl_3$)δ1.18 (s, 3, CH_3), 1.36 (s, 3, CH_3), 1.95 (d, J=6 Hz, 1, bridgehead CH), 5.03 (m, 1, oxymethine).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16.

Found: C, 70.26; H, 8.13.

3,4,5a,7β,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-7α-formyl-2H-naptho[1,8-bc] furan-2,6-(2aH)-dione (13)[4]-Into a flask fitted with a nitrogen gas inlet and a septum was placed sodium hydride (0.284 g, 6.67 mg-at, 57% oil dispersion). The sodium hydride was washed with anhydrous ether (3 x 1 ml) and dried under vacuum. A solution of ketone 12 (0.500 g, 2.2 mmole) and anhydrous methyl alcohol (1 drop) in ethyl formate (5 ml) was added at 0° (ice-bath) followed by an additional quantity of ethyl formate (2 ml) needed to complete the transfer. After the mixture had stirred for 1 hour at 0°, 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 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 x 50 ml). The combined ether extracts were washed with water (3 x 50 ml) and saturated

sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated <u>in vacuo</u> to give 0.5365 g (95.6%) of crystalline hydroxy methylene derivative (<u>13</u>). An analytical sample was prepared by recrystallization from a dichloromethane, ether, pet-ether mixture, followed by sublimation (130°, 50μ): mp 192-193°: ir ($CHCl_3$) 1765 (lactone), 1750 (ketone), 1585 cm^{-1} (HC(OH)⇌HC(=O)-): nmr ($CDCl_3$) δ 1.19 (s, 3, CH_3), 1.31 (s, 3, CH_3), 2.95 (d, J=8 Hz, 2, CH_2), 5.00 (q, J=8 Hz, 1, oxymethine), 7.35 ppm (s, 1, -C=C<u>H</u>-OH).

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25.

Found: C, 67.20; H, 7.11.

<u>3,4,5,5a,7β,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-7α-formylethylenedixoyacetal-2H-naptho[1,8-bc] furan-2,6—(2aH)-dione (14)</u>-Into a flask fitted with a Dean-Stark trap filled with calcium sulfate (Drierite, 8 mesh) and fitted with a reflux condenser, was added hydroxy methylene compound <u>13</u> (0.517 g, 2.07 mmole), para-toluenesulfonic acid (p-tsOH, 0.20 g), dry benzene (40 ml), and ethylene glycol (1 ml). The reaction mixture was stirred at reflux under dry nitrogen for 40 hours during which time the trap was drained at irregular intervals (10 x 2 ml). After cooling, the mixture was poured into a separatory funnel containing ether (200 ml). The ether was washed with water (3 x 50 ml), and saturated sodium chloride solution (50 ml). After drying (Na_2SO_4), the solvent was removed <u>in vacuo</u> to give 0.5982 g (98%) of acetal <u>14</u>. The analytical sample was prepared by recrystallization from

ether-pentane (5x): mp 178-180°; ir ($CDCl_3$) 1765 (lactone), 1715 cm^{-1} (ketone); nmr ($CDCl_3$) δ1.16 (s, 3, CH_3), 1.35 (s, 3, CH_3), 3.95 (s, 4, $(-O-CH_2-)_2$), 5.04 (m, 1, oxymethine), 5.46 ppm (d, J=2 Hz, 1, -OCHO-).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53.
Found: C, 65.31; H, 7.57.

3,4,5,5a,7,8,8aα,8bα-Octahydro-2aα,5aβ-dimethyl-7-bromo-7-formylethylenedioxyacetal-2H-naptho [1,8-bc] furan-2,6-(2aH)-dione (15)[12]-A solution of phenyltrimethylammonium tribromide (PTAB, 0.255 g, 0.92 mmole) in dry tetrahydrofuran (THF, 12 ml, freshly distilled from $LiAlH_4$) was added to acetal 14 (0.189 g, 0.65 mmole) under a dry nitrogen atmosphere. The reaction was stirred for 5 hours 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 x 25 ml), saturated sodium chloride solution (1 x 25 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.238 g (99%) of the highly crystalline bromo acetal 15. The analytical sample was prepared by preparative thin layer chromatography using silica gel and 50% ether: 50% pet-ether as eluant followed by two recrystallizations from dichloromethane, ether, pentane: mp 218-219°, ir ($CHCl_3$) 1770 (lactone), 1720 cm^{-1} (ketone); nmr ($CDCl_3$) δ1.17 (s, 3, CH_3), 1.38 (s, 3, CH_3), 2.53 (d, J=6 Hz, 1, bridgehead CH), 2.90 (t, J=8 Hz, 2, $-CH_2-C-Br$), 4.02 (s, 3, CH_3), 5.04 (m, 1, oxymethine), 5.56 ppm (s, 1,

-OCHO-).

Anal. calcd. for $C_{16}H_{21}O_5Br$: C, 51.49; H, 5.67; Br, 21.41.
Found: C, 51.51; H, 5.69; Br. 21.39.

3,4,5,5a,8aα,8bα-Hexahydro-2aα,5aβ-dimethyl-7-formyl-ethylenedioxyacetal-2H-naphtho [1,8-bc] furan-2,6-(2aH)-dione (16)[10]-To a solution of bromoacetal (15, 0.067 g, 0.180 mmole) in N,N-dimethylacetamide (DMA, 2 ml) was added calcium carbonate (0.054 g, 0.54 mmole). The sample was degassed and filled with nitrogen (3x). The flask was fitted with a condenser and immersed in an oil bath preheated to 190°, then stirred at reflux for 30 minutes. The flask was allowed to air cool for a few minutes then cooled to 0° in an ice bath. The reaction mixture was poured into water (100 ml) and extracted with ether (3 x 50 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and evaporated *in vacuo* to give 0.0407 g of a mixture. Compound 16 was isolated in 31% yield by preparative thin layer chromatography on silica gel using 75% ether : 25% pet-ether to elute the plate. An analytical sample was prepared by recrystallization four times from dichloromethane, ether, pentane: mp 144-145°; uv (CH_3OH) 212 nm (ε6390), 263 nm (ε718); ir ($CHCl_3$) 1770 (lactone), 1695 cm^{-1} (ketone); nmr ($CDCl_3$) δ1.22 (s, 3, CH_3), 1.35 (s, 3, CH_3), 2.14 (d, J=5 Hz, 2, bridgehead CH), 3.99 (s, 4, $-OCH_2-$), 5.02 (t, J=5 Hz, 1, oxymethine), 5.70 (s, 1, -OCHO- , 6.97 ppm (d, J=5 Hz, 1, -C=CH-).

Anal. calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90.

Found: C, 65.76; H, 6.99.

(±)-LL-Z 1271α (1) and anomer (2)[1,13,14]-To a flask containing ethoxyacetylene (0.0450 g, 0.56 mmole) in dry tetrahydrofuran (THF, 2 ml) cooled to -78° (dry-ice, acetone) under nitrogen atmosphere, was added n-butyl lithium in hexane (1.9M, 0.33 ml). After the solution of lithium ethoxyacetylide had stirred for 15 minutes, a solution of ketone 16 (0.0609 g, 0.208 mmole) in THF (2 ml) was added followed by an additional amount of THF (1 ml) needed to complete the transfer. The resulting reaction mixture was stirred under dry nitrogen for 1 hour at -78°. 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 x 25 ml). The combined ethereal extracts were washed with water (3 x 25 ml), saturated sodium chloride solution (20 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.0636 g of crude ethoxyacetylide derivative 17: ir ($CHCl_3$) 3550 (OH), 1772 cm^{-1} (lactone); nmr ($CDCl_3$) 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°. Three drops of 5% sulfuric acid were added and the mixture stirred at ambient temperature for 2.5 hours. The mixture was then dissolved in ether (100 ml), washed with water (20 ml), sodium

chloride solution (20 ml), 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 and eluted with 60% ether : 40% pet-ether. Compounds 1 (0.0186 g) and 2 (0.0081 g) were isolated in a combined yield of 42% (ratio 70:30, respectively).

The analytical sample of anomer 2 was prepared by recrystallization from dichloromethane, ether, pentane (3x): mp 151-153°; uv (CH_3OH) 258 nm (ε16,000); ir ($CHCl_3$) 1770 (lactone), 1720 cm^{-1} (α,β unsaturated lactone); nmr ($CDCl_3$) δ1.18 (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 (d, J=1.8 Hz, J=5 Hz, 1, C-C-H). These spectral data correspond to those previously reported.[14]

Anal. calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62.
Found: C, 67.14; H, 6.77.

The analytical sample of racemic LL-Z 1271α was prepared by several recrystallizations from ether, pentane followed by sublimation (115°, 0.1 mm): mp 195-196°, uv (CH_3OH) 257 nm (ε13,250); ir ($CHCl_3$) 1770 (lactone), 1715 cm^{-1} (α,β unsaturated lactone); nmr ($CDCl_3$), δ1.17 (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, -OCHOMe, -CH-CO_2-), 6.52 ppm (m, 1, -O-C-CH=). These spectral data are identical to those reported for the natural product.[1]

Anal. calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62.

Found: C, 66.87; H, 6.79.

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