EXPERIMENTS DIRECTED TOWARD THE TOTAL SYNTHESIS OF CHLOROTHRICOLIDE

Thesis By

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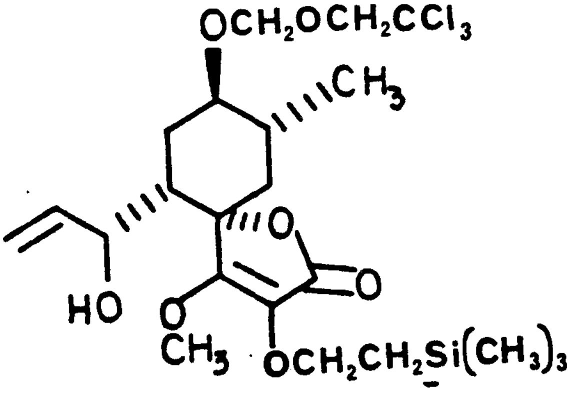
Abstract

The attempted synthesis of a differentially protected "top half" , **i** , of chlorothricolide is described. The key step necessary for this synthesis was the spirocyclization of the anhydride **ii** , to prepare the protected tetronic acid **iii**.



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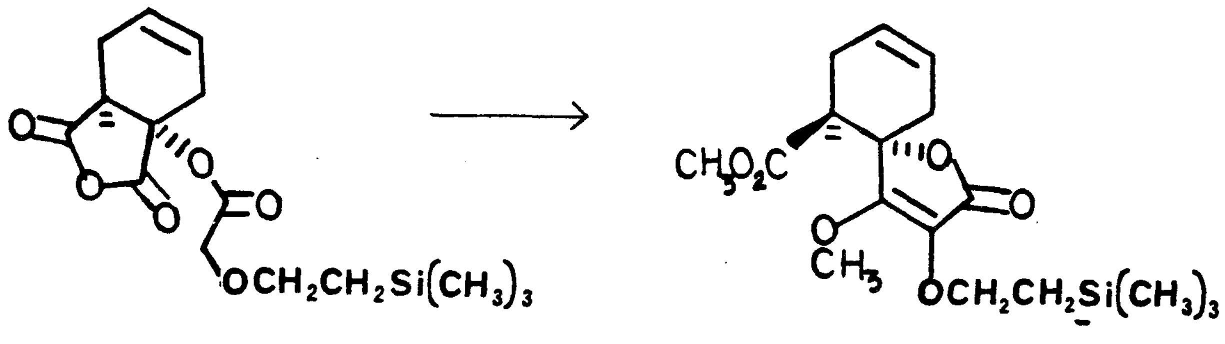

ii

iii

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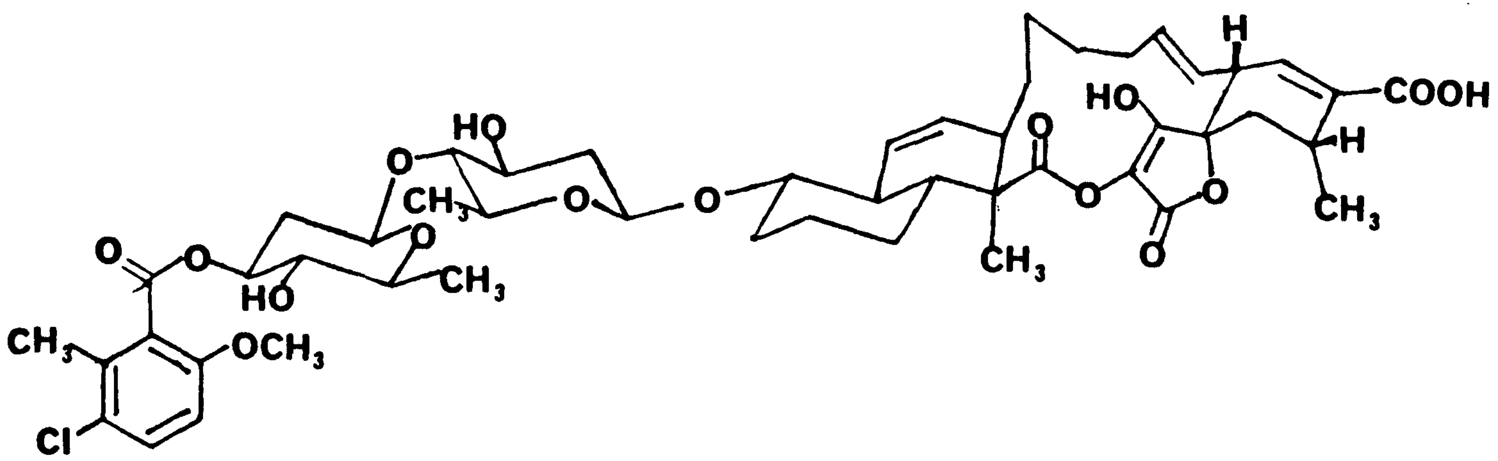
EXPERIMENTS DIRECTED TOWARD THE TOTAL SYNTHESIS OF CHLOROTHRICOLIDE

Introduction

When picromycin was first isolated in 1950[1], it signalled the discovery of a new class of antibiotics, the macrolides. These compounds were orignally classified as containing twelve to eighteen membered macrolactones, containing no more than two double bonds in the ring and one or more glycosidically linked sugars or amino sugar moieties.[2] Now, however, this class has been expanded to include any anti-microbial compound that contains any eight to forty membered carbolactone.[2] By 1972, over 200 macrolides were known.[2a] Several of these compounds, most notably erythromycin and oleandomycin, are clinically important. During the thirty years since their discovery, macrolides have been the subject of extensive research and several reviews[3] have appeared concerning their structural characteristics and their chemistry.

Only recently have attempts at the synthesis of the aglycone portions of the macrolides been successful. The first to yield to total synthesis was methymycin.[4] Since that time, many macrolides have been synthesized, including Erythromycin A.[5]

The difficulty of synthesizing the macrolides arises from two sources; the necessity of controlling the stereochemistry in

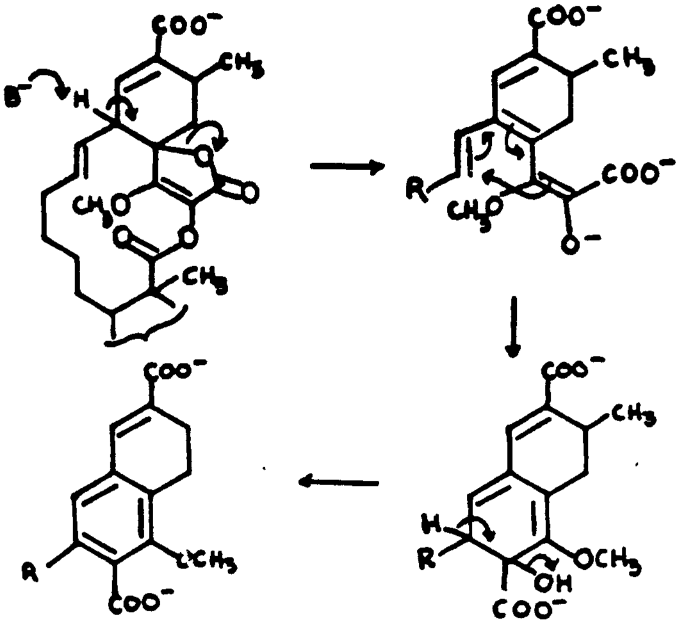


1 , CHLOROTHRICIN

an acylic system, common to many macrolides, and the formation of the macrolactone, found in all macrolides. Several techniques are now available for macrolactonization,[3,5] and recently significant progress has also been made in asymmetric synthesis, making the total synthesis of macrolides a more feasible project.

One macrolide, Chlorothricin, **1** , contains many of the structural complexities common to macrolides. It presents the synthetic chemist with the challenges of both cyclic and acyclic stereochemical control, as well as the problem of creating functionality along a carbon skeleton. Due to these features, the total synthesis of the aglycone of chlorothricin, chlorothricolide, **2** , should not only utilize current knowledge in these areas, but should also contribute significantly to extending this knowledge as well.

In 1969, Keller-Schierlein isolated the unusual macrolide antibiotic, chlorithricin, **1** , from *Streptomyces antibioticus*[7], along with its bromo- and deschloro- analogs. Chlorothricin is active against Gram positive bacteria, such as *Bacillus subtilis* and *Bacillus stearothermophilis*[8]. Biochemical studies [9-13] have shown chlorothricin to act at low concentrations as a non-competitive inhibitor of pyruvate carboxylase, being therefore an antogonist to acetyl CoA. It is not an ionophore, and does not chelate the magnesium necessary for this reaction. This has led Schindler to propose that chlorothricin binds to the hydrophobic portion of pyruvate carboxylase, thereby rendering it inactive.



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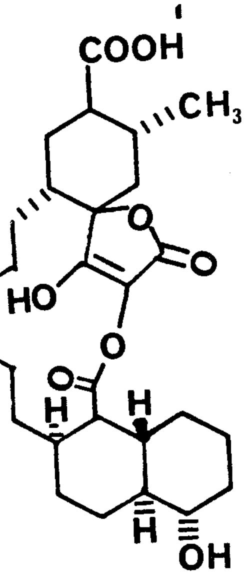


4

At higher concentrations, chlorothricin , **2** , is four to six times less active than the intact macrolide.

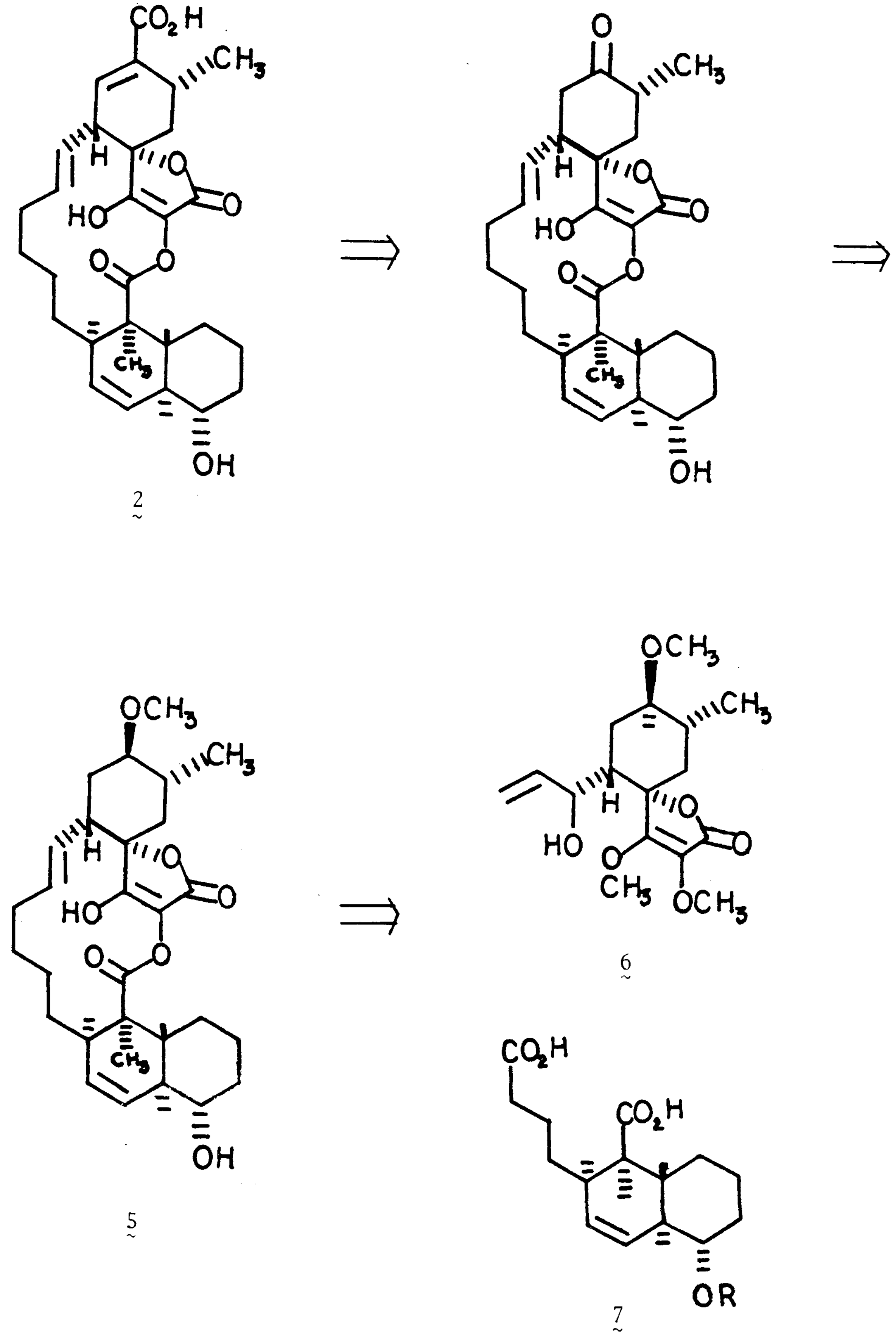
The structure of chlorothricin was elucidated by chemical degradation and by spectroscopy (NMR, IR, UV, and Mass Spectra).[7,14] Methanolysis yields four compounds; chlorothricolide methyl ester, two sugars, both 2-deoxy-D-rhamnose, and an aromatic portion, 5-chloro-6-methylsalicyclic acid. The structure of chlorothricolide was confirmed by an X-Ray analysis of the Cesium salt.[16]

Chlorothricolide has an unusual structure with the macrolactone being closed through the α-hydroxy component of a spirotetronic acid. Although recently several α-acyl tetronic acid containing antibiotics have been discovered[17], the only other known example of a naturally occurring α-hydroxy tetronic acid is to be found in (-)-ascorbic acid (Vitamin C). Other important features include the *trans*-double bond between carbons fifteen and sixteen in the carbon backbone, and the fourteen-membered lactone.

Efforts to obtain the seco-acid by basic hydrolysis, albeit under vigorous conditions, led only to the aromatic compound, **3** , formed by initial removal of the C-17 proton, followed by electrocyclic ring closure and elimination.[15] However, hexahydrochlorothricolide, **4** , was hydrolyzed to the free acid under similar conditions.

With this information in hand, it is now possible to consider the retrosynthetic planning for the synthesis of chlorothricolide. First, it was determined that the C-19, C-20 double bond and the C-20 carboxylic acid should be introduced at a late state, making

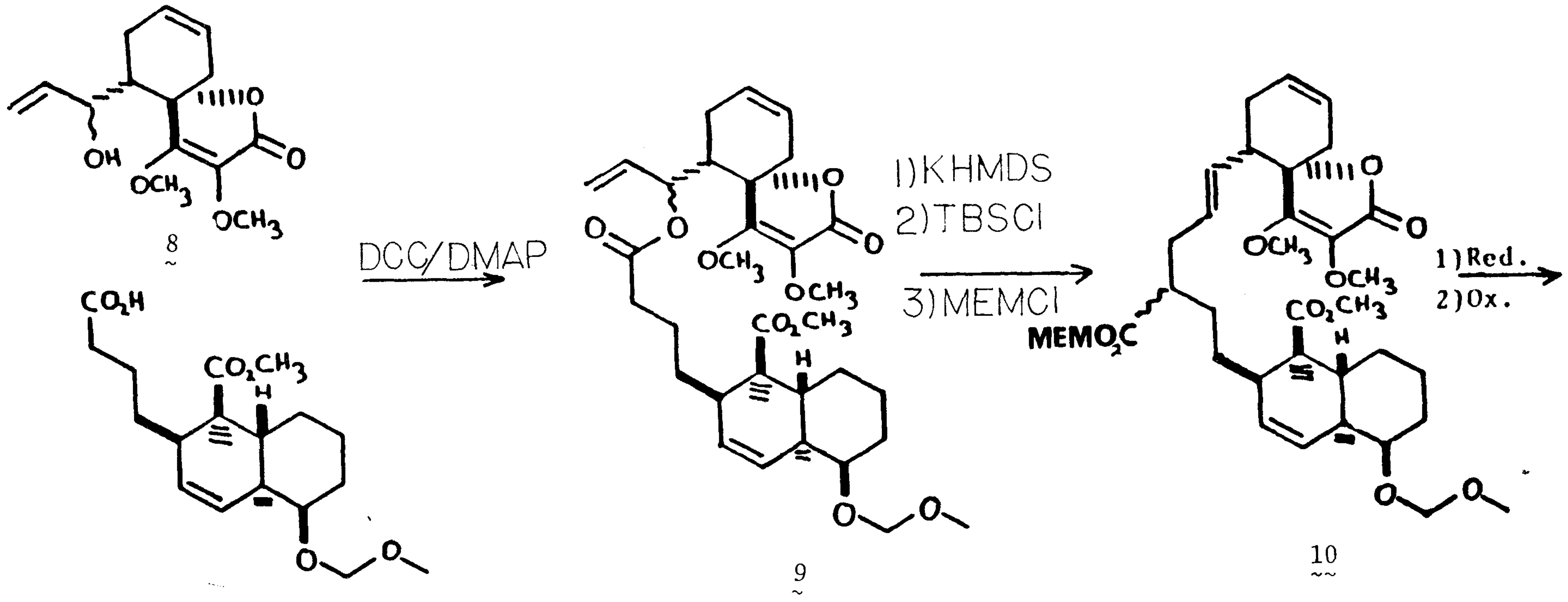
SCHEME II



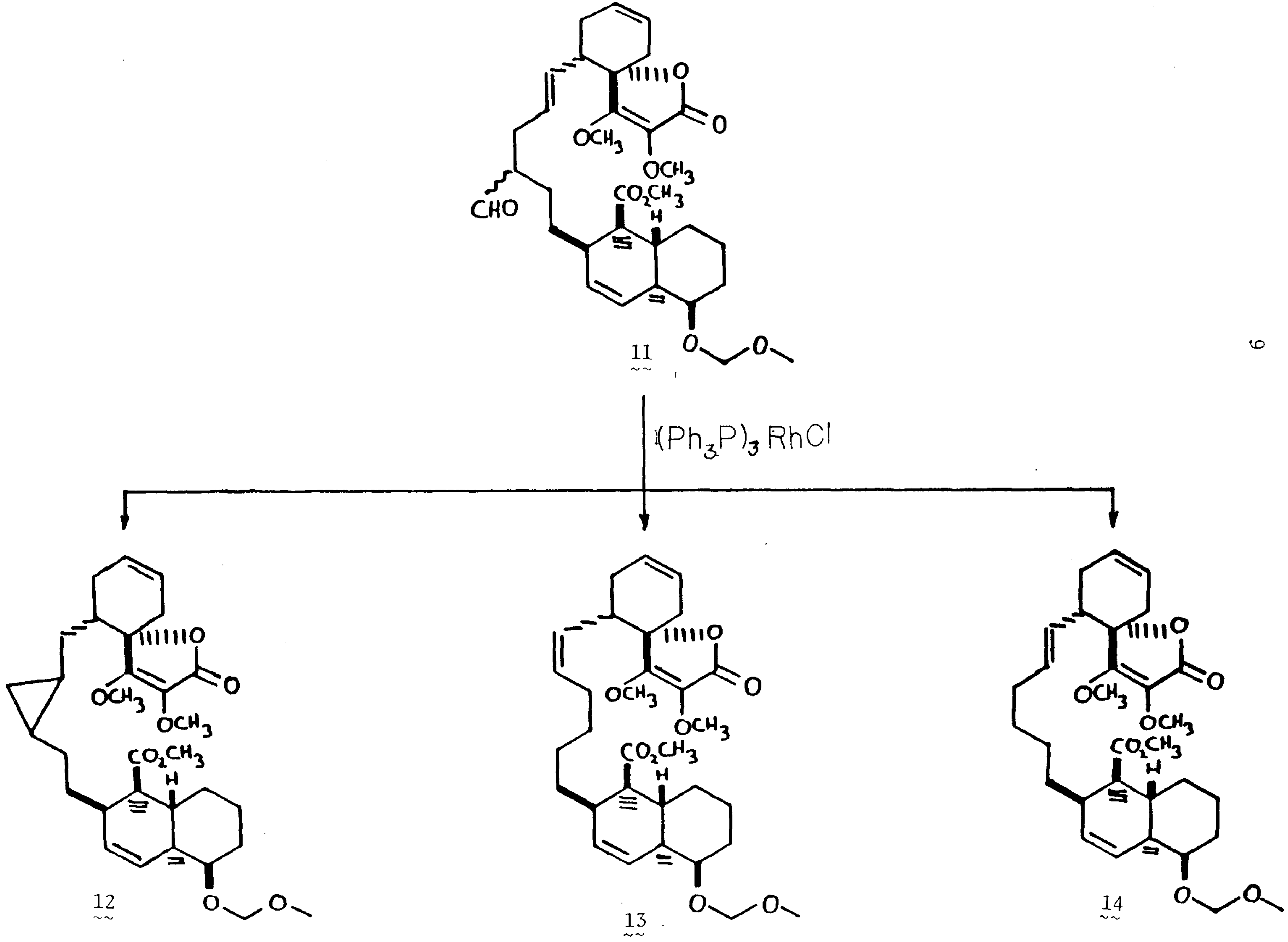
5, the first synthetic target. Examination of **5** shows two functional groups which could be envisioned as facilitating a convergent approach to chlorothricolide; the macrolactone linkage, and the C-16-C-17 *trans* - double bond. Thus the synthesis can now be broken into two approximately equal parts, "top half" **6**, and "bottom half" **7**. These pieces can be joined by esterification, followed by an ester-enolate Claisen rearrangement to form the *trans*- double bond exclusively.[18]

Extensive research in these laboratories has led to the synthesis of a top half [19] and 7-epi-bottom half[20], which could be oxidized and reduced to yield bottom half.

Some preliminary coupling experiments of the two halfs have also been undertaken in Scheme II. The top half model, **8**, and 7-epi-bottom half were joined in 89% yield by allowing them to react in the presence of DCC in dichloromethane and a trace of 4-dimethylaminopyridine [21], to yield the expected 1:1 mixture of diastereoisomers. The ester-enolate Claisen rearrangement was then carried out by treatment of **9**, with potassium hexamethyldisilazane in tetrahydrofuran and hexamethylphosphoramide at -78°C, followed by trapping of the silyl ketene acetal with *tert*-butyldimethylsilyl chloride and thermal rearrangements at room temperature. The crude product was transformed directly to the methoxyethoxymethyl ester, **10**, in 72% overall yield. This ester was reduced to the alcohol with lithium triethylborohydride in 93% yield, and reoxidized with pyridium chlorochromate to yield the aldehyde **11**.


OH
OCH3
OCH3
CO2H
CO2CH3
H
DCC/DMAP
1)KHMDS
2)TBSCl
3)MEMCl
MEMO2C
1)Red.
2)Ox.

8 9 10


11
CHO
OCH_3
OCH_3
CO_2CH_3
H
O
O
O
O
$(Ph_3P)_3$ RhCl
12
13
14

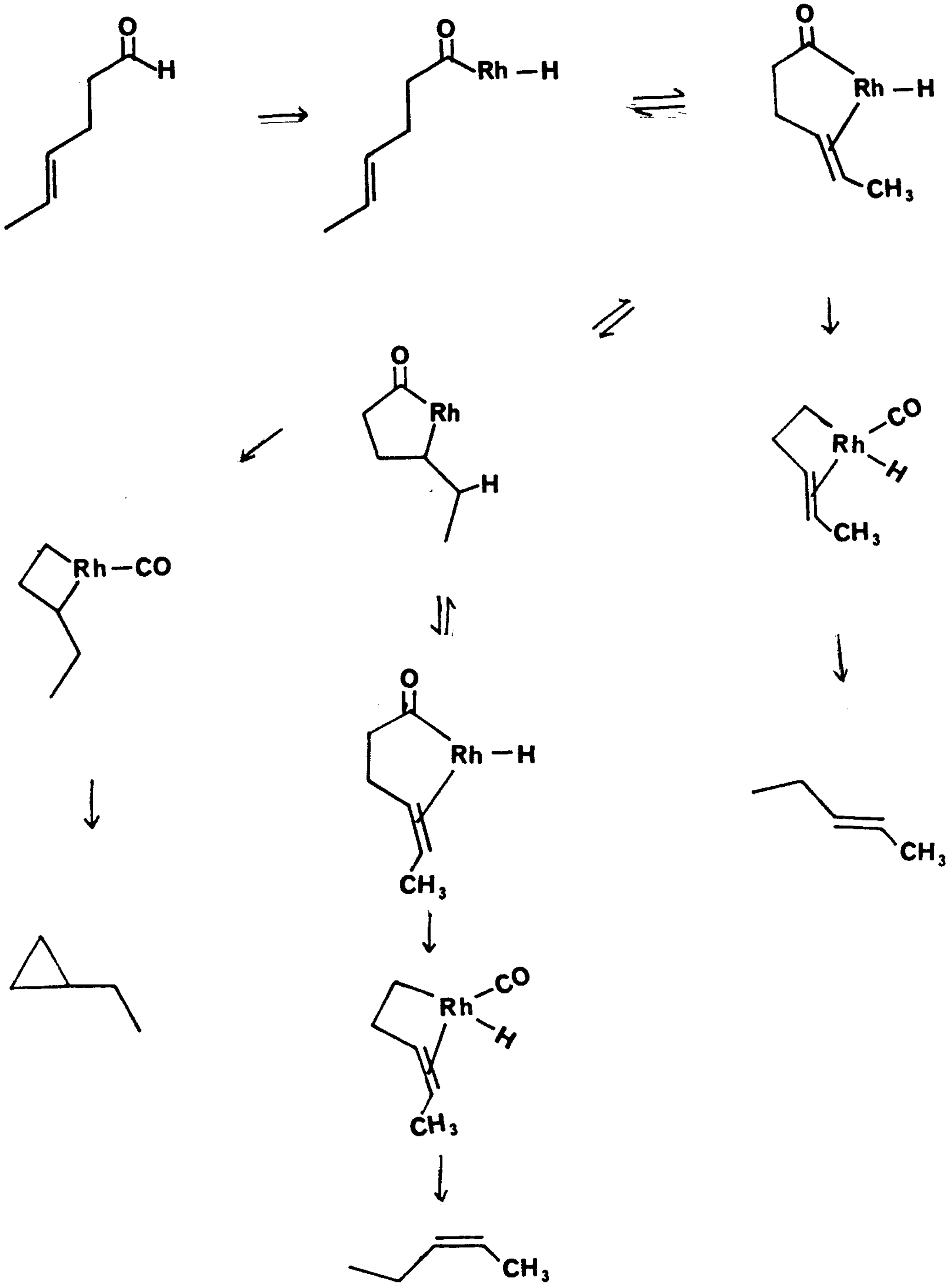
The aldehyde was then treated with Wilkinson's Catalyst ($(\phi_3P)_3RhCl$), in an attempt to effect the decarbonylation. Five hundred Megahertz NMR showed the presence of six compounds, constituting **12**, **13**, and **14**, plus their diastereomers, in a ratio of 38:47:15. Similar results had earlier been observed in these laboratories in a similar system[22] and also in the cyclization of 4-pentenal[23] and in *cis*- and *trans*-4-hexenal.[24] Miller postulates that these products are due to the complexation of the double bond to the rhodium followed by the rearrangements outlined in Scheme III. If this is the case, if may be possible to carry out the decarbonylation following the lactonization, when the molecule may be unable to adopt a conformation wherein coordination of the double bond can occur after rhodium insertion in the aldehyde C-H bond.

Attempts were therefore made to remove the methyl ether from the α-hydroxy tetronic acid by a variety of methods which had been successful on model compounds. None of the conditions attempted resulted in removal of either the methyl ether or the methyl ester.[19] It was therefore, decided to use a more easily removable protective groups for both the α-hydroxy tetronic acid, and the carboxylic acid.

One such protective group would be the trimethylsilylethyl group, $(CH_3)_3SiCH_2CH_2$-,[25] which has been shown to be removed by flouride ions.

The mono-2-(trimethylsilyl)ether ester of the 7-epi-bottom

SCHEME III



half was therefore prepared from the diacid and 2-(trimethylsilyl)-ethanol.[24]

Replacement of the α-hydroxy tetronic acid methyl ether is a more difficult proposition. The protection of this functional group is carried out at an early stage of the synthesis of top half and therefore it is necessary to resynthesize top half to effect this transformation.

The decision was also made to repeat the original top half synthesis as a model system, due to the difficult nature of certain of the reactions in the synthetic pathway.

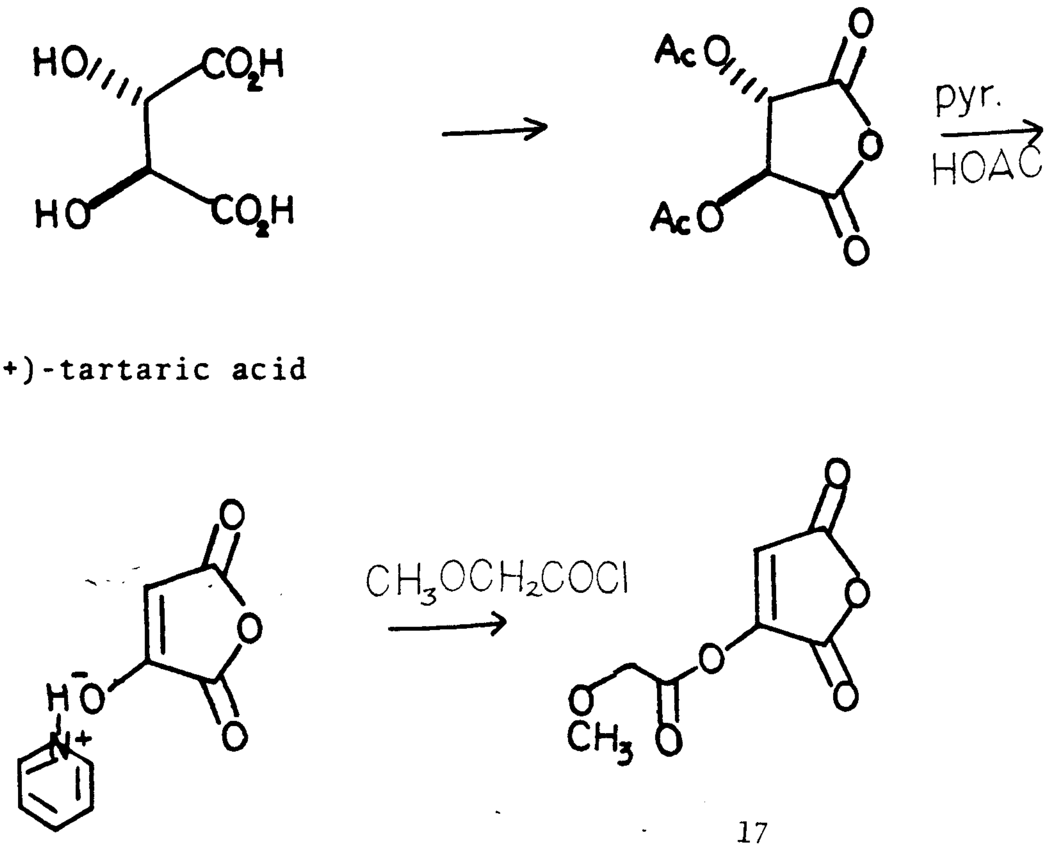
Results and Discussion:

The synthesis of the original top half substrate as developed by W.J. Thompson and repeated herein is outlined in Scheme IV. Acylation of the pyridine salt of hydroxymaleic anhydride **15** with methoxyacetyl chloride **16**, yielded **17** (69%), which was immediately allowed to react with 1,3-butadiene in a sealed tube at 90°C for five days to yield the cyclohexene, **17**, in 82% yield.

The crucial formation of the tetronic acid was the next step to be encountered. Some simple tetronic acid derivatives had previously been synthesized by Haynes and Stanner[26], and a similar transformation had been incorporated in the retrosynthetic planning for the top half of chlorothricolide. Inverse addition of two equivalents of lithium diisopropylamide at -78°C, followed by esterification with methyl fluorosulfonate at 0°C did indeed yield the β-methoxy tetronic acid, **18**, in 43% yield. Epimerization of **18** with a catalytic amoung of sodium methoxide in methanol afforded an 81% yield of the pseudo-equatorial isomer, **19**, and pseudo-axial isomer, **18**, in an 80:20 ratio. These isomers were separated and the pure psuedo-equatorial isomer, **19**, was then reduced with lithium triethylborohydride to the alcohol, **20**. Previous work [19] has shown the tetronic acid moiety to be sensitive to a large number of reducing agents, with lithium triethylborohydride being a notable exception.

The alcohol, **20**, was then protected as the *tert*-butyldimethyl-

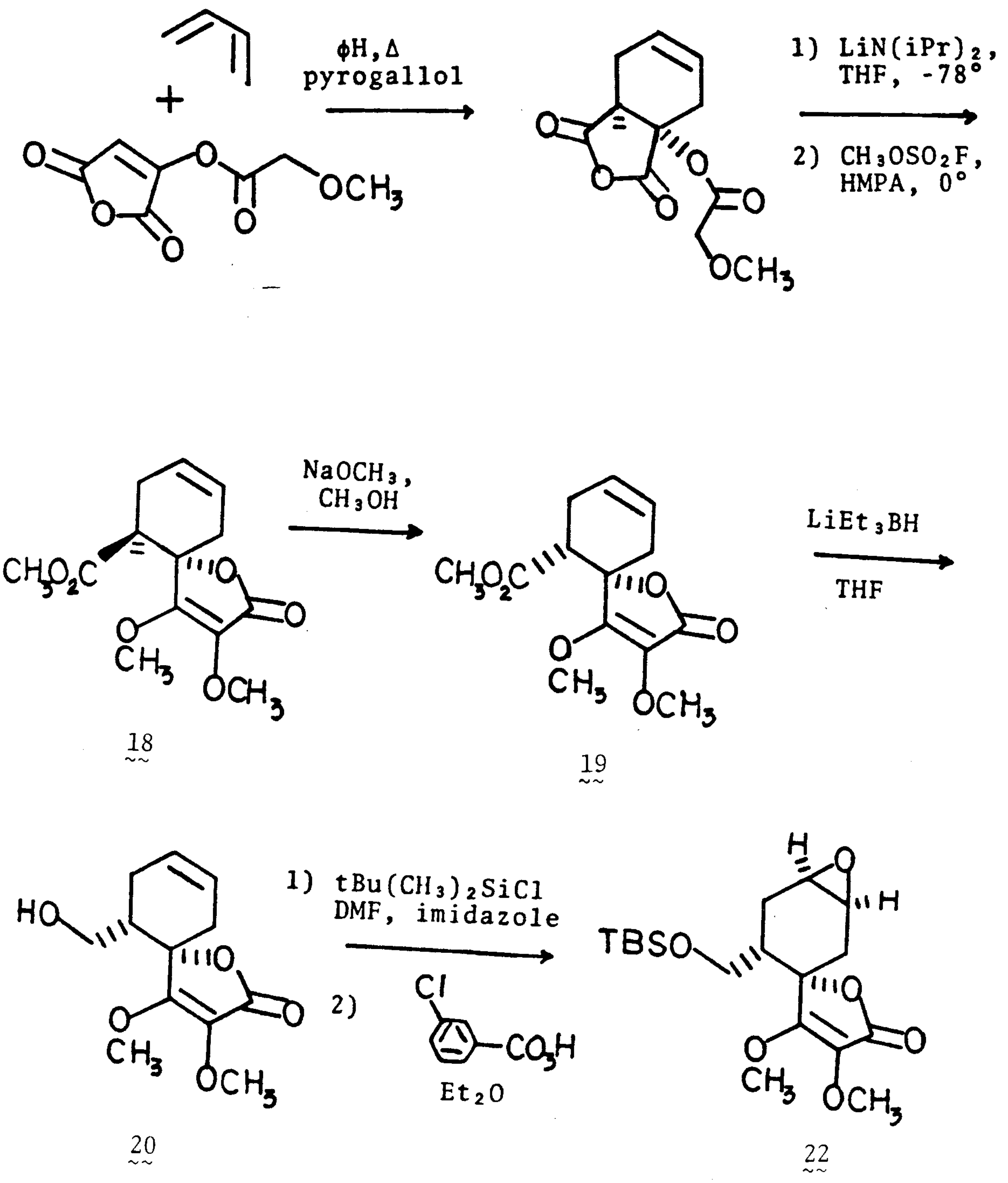
SCHEME IV

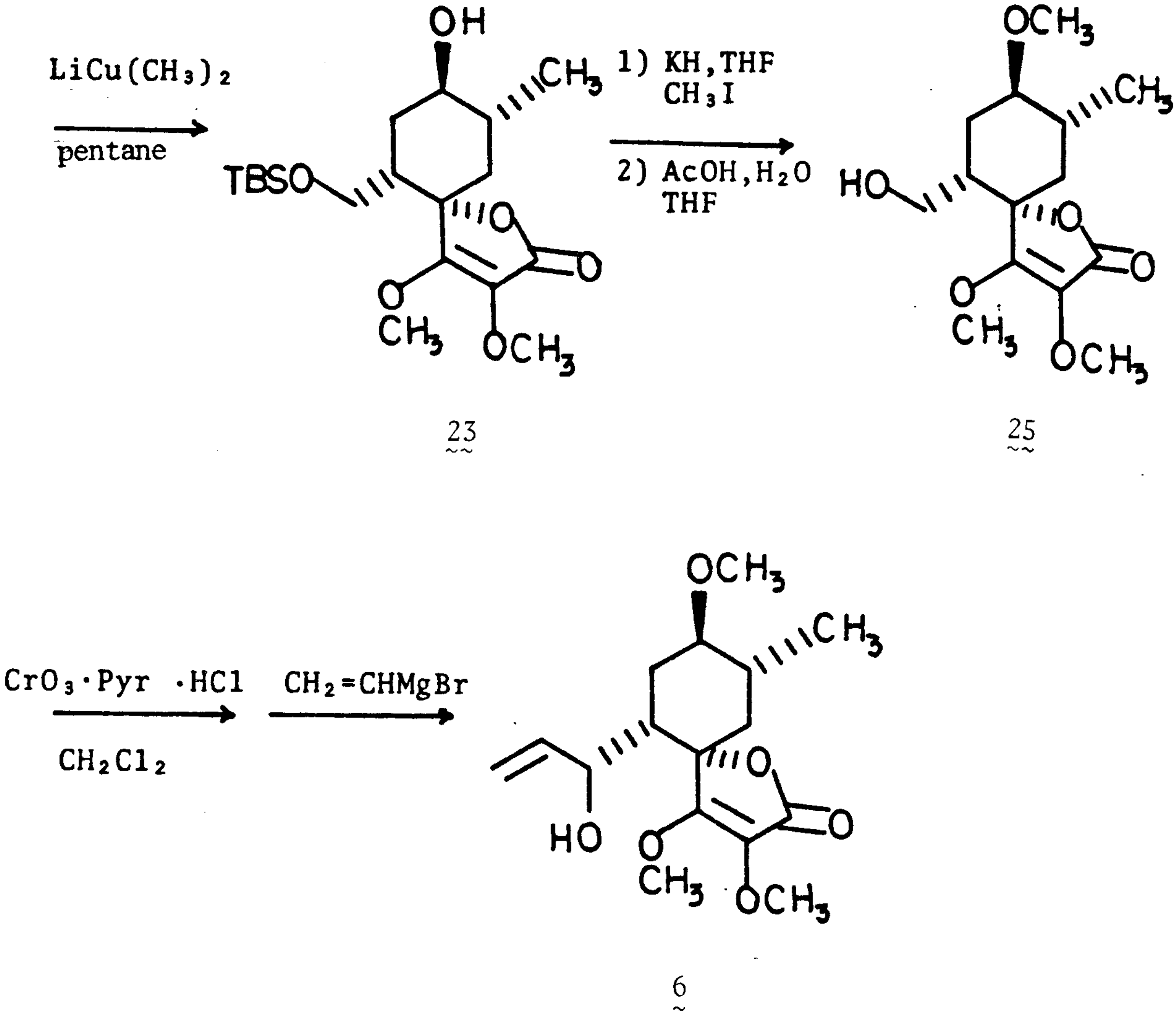


(+)-tartaric acid

15

17


φH, Δ
pyrogallol
1) LiN(iPr)$_2$, THF, -78°
2) CH$_3$OSO$_2$F, HMPA, 0°
NaOCH$_3$, CH$_3$OH
LiEt$_3$BH
THF
1) tBu(CH$_3$)$_2$SiCl DMF, imidazole
2) Et$_2$O
18
19
20
22


LiCu(CH₃)₂
pentane
OH
CH₃
TBSO
O
O
O
CH₃
OCH₃
23
1) KH, THF
CH₃I
2) AcOH, H₂O
THF
OCH₃
CH₃
HO
O
O
O
CH₃
OCH₃
25
CrO₃·Pyr ·HCl
CH₂Cl₂
CH₂=CHMgBr
OCH₃
CH₃
HO
O
O
O
CH₃
OCH₃
6

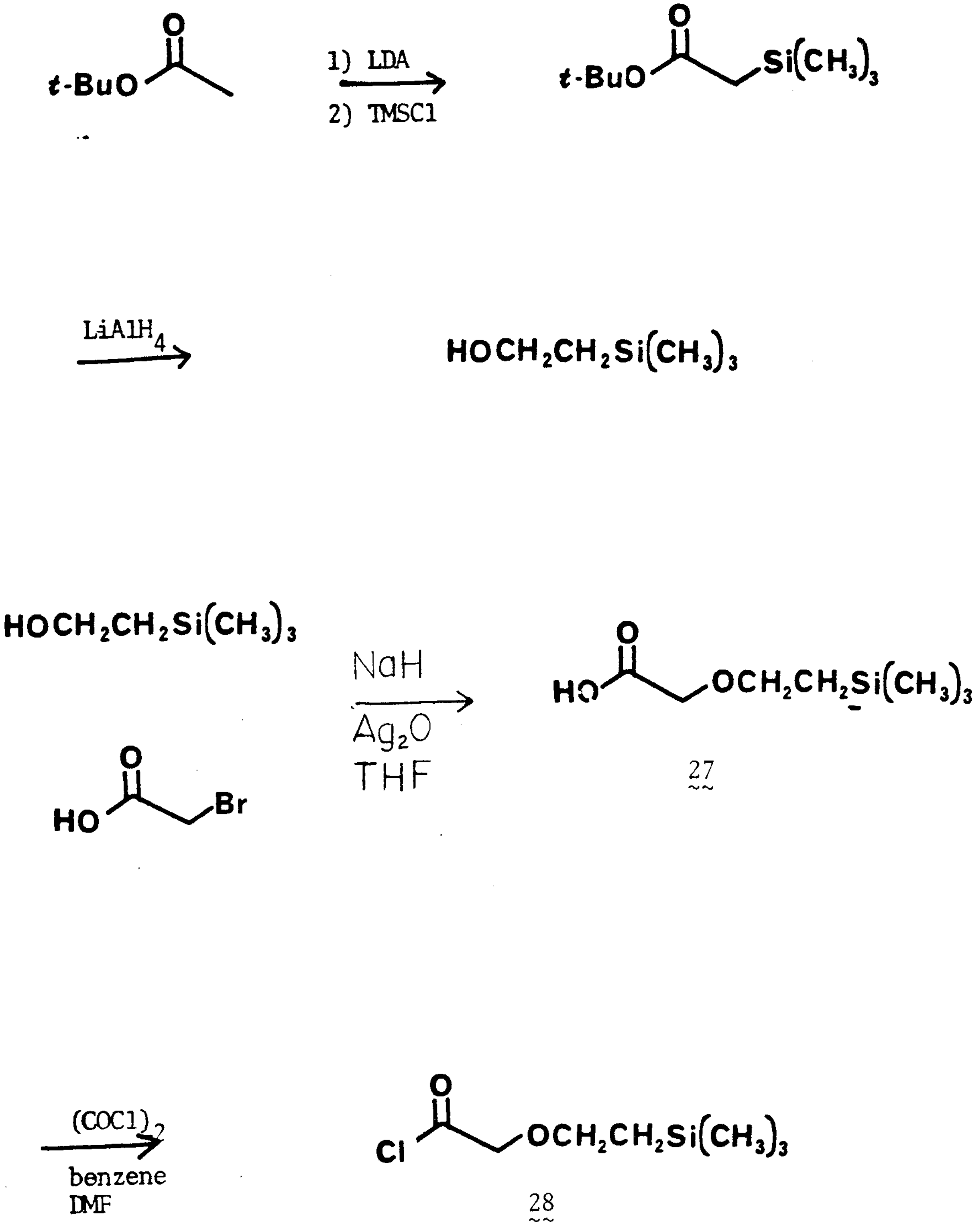
silylether[27] by treatment with tert-butyldimethylsilyl chloride and imidazole in dimethylformamide to produce **21** in 89% yield.

It was now necessary to elaborate the cyclohexene ring by introduction of the axial methyl group at C-21 and functionalization of C-20 suitable for further elaboration after lactonization. Cuprate additions to epoxides have been shown[29] to result in trans-diaxial openings. Careful epoxidation, therefore, with meta-chloroperbenzoic acid in ether containing one equivalent of lithium perchlorate afforded the requisite β-epoxide **22** in 40% yield. Addition of five equivalents of dimethyl cuprate to the epoxide at 10°C in pentane gave the desired alcohol, **23**, 58% along with 11% recovered starting material, **22**. Neither longer reaction times (24 hours), nor a larger excess of cuprate (10 equivalents) were successful in effecting complete transformation of starting material. The alcohol was protected as the methyl ether, using sodium hydride in tetrahydrofuran at 0°C, followed by addition of excess methyl iodide, to afford the methyl ether **24**, in 96% yield. Deprotection of the tert-butyldimethylsilyl ether with acetic acid-water-tetrahydrofuran gave the alcohol, **25**, in 93% yeild. The alcohol **25** was then oxidized to the aldehyde with pyridinium chlorochromate, and vinyl magnesium bromide was added to the unstable aldehyde immediately to give top half, **6**, in 68% yield. This completed the synthesis of the "top half".

The synthesis of the alternative top half, **26**, by this route has been attempted. For this new top half, the methoxy group of the acetyl hydroxymaleic anhydride is replaced with a 2-(trimethylsilyl)ethoxy group, necessitating the use of the previously unknown acid 27. Preparation of this substrate was envisioned as resulting from an S_N2 displacement of bromine ion from bromoacetic acid. Initially, treatment of sodium or lithium bromoacetate with 2-(trimethylsilyl)ethoxide in either tetrahydrofuran or dimethoxyethane gave discouragingly low yields due to the poor nucleophilicity of the 2-(trimethylsilyl)ethoxy anion, but addition of a catalytic amount of silver(I)oxide allowed for obtention of the desired 2-(trimethylsilyl)ethoxyacetic acid, 27, in 88% yield. Treatment of this acid with oxalyl chloride in benzene yielded 98% of the acid chloride, 28. Acylation of the pyridine salt of hydroxymaleic anhydride with this acid chloride in an analogous manner to that previously described gave the unstable enol ether, 29, in 92% yield. This enol ether was used immediately in the Diels-Alder reactions, as decomposition occurred rapidly even at 0°C under argon.

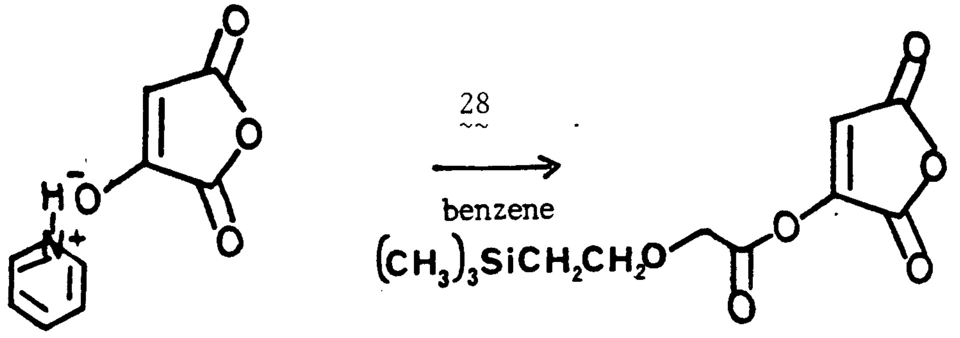
Diels-Alder reaction with this substrate and 1,3-butadiene in benzene in the presence of pyrogallol as a radical inhibitor yielded the anhydride 30, in 55% yield.

Initial small scale reactions on the spirocyclization gave good results. Thus, treatment of anhydride 30 in tetrahydrofuran at -78°C with 2.0 equivalents of lithium diisopropylamide, followed by warming to 0°C, addition of hexamethylphosphoramide and quenching with methyl fluorosulfonate led to the 2-(trimethylsilyl)ethyl protected tetronic acid 31 in 60% yield. However, when larger amounts (more than 0.050 g.) of the anhydride 30 were subjected to these conditions, poor yields, 10-20% resulted. Further invest-

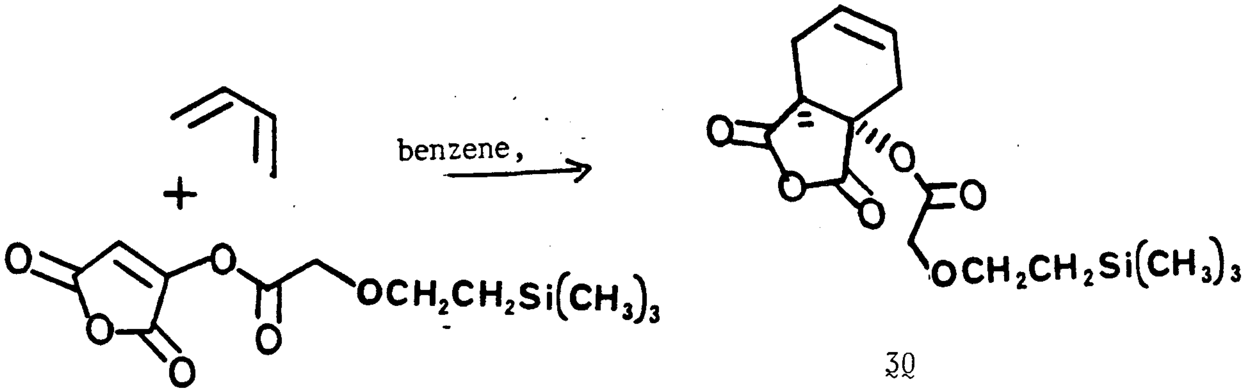

t-BuO
1) LDA
2) TMSCl
t-BuO
Si(CH3)3
LiAlH4
HOCH2CH2Si(CH3)3
HOCH2CH2Si(CH3)3
HO
Br
NaH
Ag2O
THF
HO
OCH2CH2Si(CH3)3
(COCl)2
benzene
DMF
Cl
OCH2CH2Si(CH3)3

27

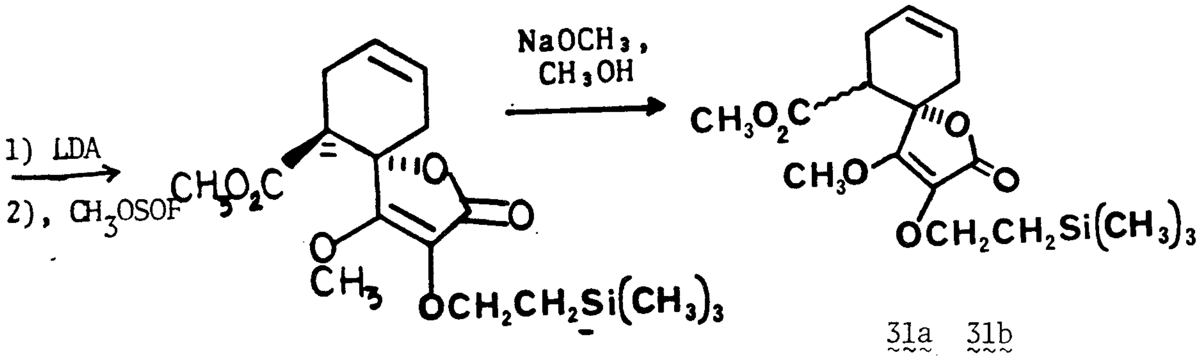
28



29

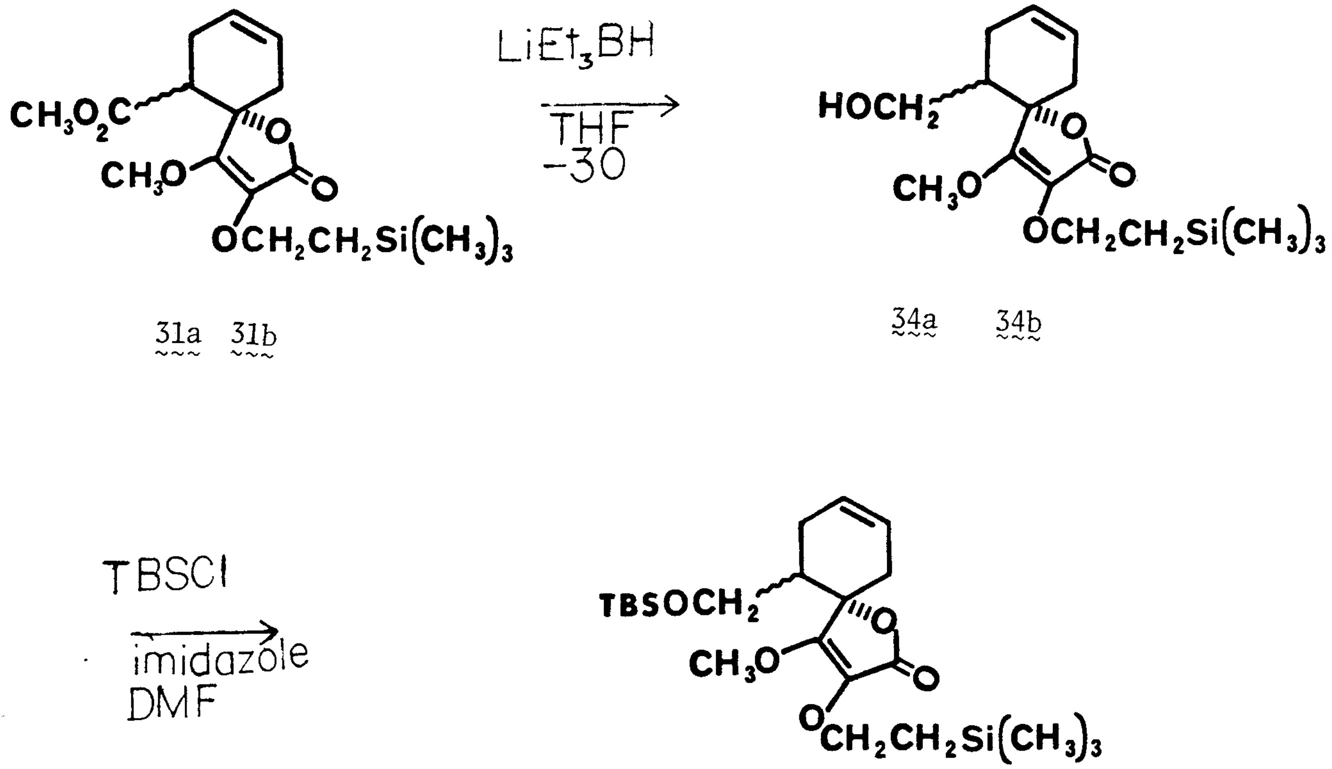


30



31a 31b

31



31a 31b

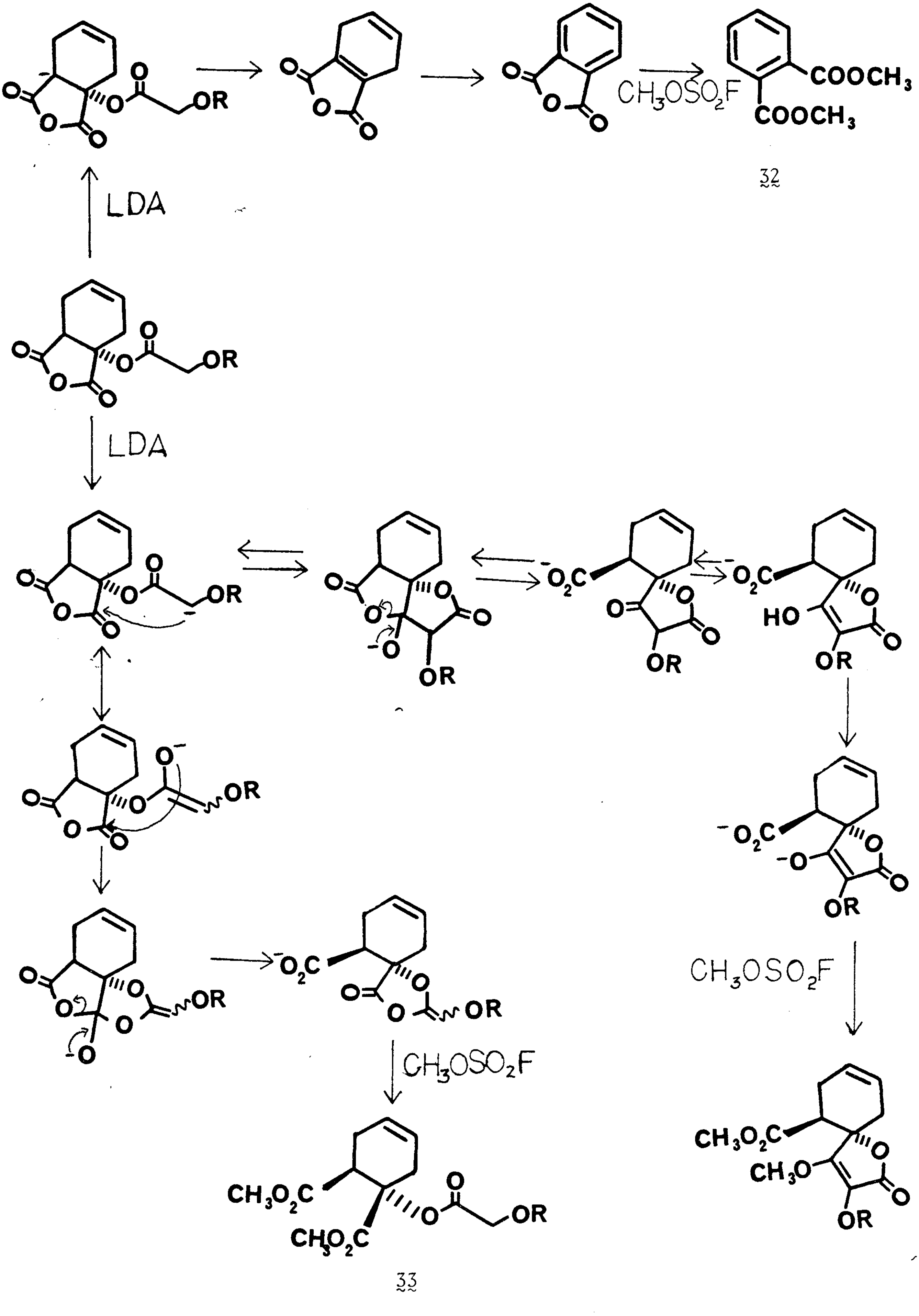
34a 34b

35a 35b

igation of this reaction was then undertaken. Minor modifications of the reaction conditions; change of temperature, or reactions times led to no improvement. The major byproducts were then isolated. These byproducts were mainly the aromatic compound 32, and the diester 33. Possible mechanisms for their formation are shown in Scheme V. To prevent the formation of the aromatic compound 32, it was felt that addition of the anhydride 30 to lithium diisopropylamide would give better results. However, this was not the case. Apparently, the deprotonation on the side chain is due more to less steric crowding in the methoxy case than any large difference in acidity of the protons. It is probable, that in the case of anhydride 30, with the much larger 2-(trimethylsilyl)ethoxy group, the steric crowding at each proton is comparable. Attempts were also made to prevent the formation of 33 which results from attack by the oxygen of the enolate. These attempts were directed toward lowering solvent polarity. However, treatment of the reaction mixture with either methyl fluorosulfonate or methyl trifluoromethylsulfonate without hexamethylphosporamide resulted only in the polymerization of the tetrahydrofuran,[32] and use of less active trapping agents such as dimethyl sulfate gave none of the desired product.

The tetronic acid 31 was next treated with sodium methoxide in methanol to effect the epimerization of the ester. A 65% yield of epimerized yield material resulted, with the two epimers being inseparable, even by HPLC. The ratio of these epimers was 83:17 α:β as determined by 500 MHz NMR. These epimeric

SCHEME V


OR
CH$_3$OSO$_2$F
COOCH$_3$
COOCH$_3$
32
LDA
OR
LDA
OR
OR
$^-$O$_2$C
OR
$^-$O$_2$C
HO
OR
O$^-$
OR
$^-$O$_2$C
$^-$O
OR
OR
$^-$O$_2$C
OR
CH$_3$OSO$_2$F
CH$_3$OSO$_2$F
CH$_3$O$_2$C
CH$_3$O
OR
CH$_3$O$_2$C
CH$_3$O$_2$C
OR
33

esters **31a** and **31b** were then reduced with lithium triethylborohydride at -30°C in tetrahydrofuran to give a 93% yield of the epimeric alcohols **34a** and **34b**. These alcohols were still inseparable and 500 MHz NMR showed that the ratio remained unchanged. The alcohols, **34a** and **34b**, were then treated with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide, to give an 84% yield of the silyl ethers, **35a** and **35b**. These ethers were still inseparable by HPLC, both on silica gel and reverse phase HPLC chromatography.

The combinations of factors described above, led to the conclusion that the 2-(trimethylsilyl)ethyl group is not a suitable protective group for the synthesis of chlorothricolide. Further attempts, therefore, should be directed toward the replacement of the methyl group of the original top half, **6**, with some more suitable protective group.

III. Experimental Section

Melting points were determined by using a Hoover Capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton nuclear magnetic resonance (^1H-NMR) spectra were recorded on a Varian EM-390 spectrometer, except where "500 MHz" denotes spectra recorded on a Bruker WM-500 (Southern California Regional NMR Facility, Caltech, Pasadena, CA). Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ0.00) as an internal standard. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignments). For all spectra, numbering in the assignment employs the numbering system implicit in the name at the heading of each experimental.

Analytical thin layer chromatography (TLC) was conducted on 2.5 x 10 cm. precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm., manufactured by E. Merck and Co., Darmstadt, Germany.

Silica gel columns for chromatography utilized E. Merck "Silica Gel 60", 70-230 mesh ASTM. Flash chromatography was performed on E. Merck "Silica Gel 60", 230-400 mesh ASTM, according to published procedure (Still, W. C., Kahn, M.; Mitra, A.; J. Org. Chem., **1978**, 43, 2923-2925). "Alumina" refers to the grade I neutral variety manufactured by M. Woelm,Eschwege, Germany, which was neutralized to the indicated grade by the addition of water. "Florisil" refers to the 60-100 mesh chromatographic adsorbent manufactured by Matheson, Coleman and Bell, Norwood, Ohio.

Analytical High Performance Chromatrography (HPLC) was performed on a Perkin-Elmer Series 2 Liquid Chromatograph with a LC-75 Spectrophotometric Detecter. Silica gel HPLC was performed on a Perkin-Elmer Analytical Silica 0258-0051(10μm) column, and reverse phase HPLC was performed on a Perkin-Elmer Analytical C-8 0258-1684 (10μm) column.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Benzene and pyridine were distilled from calcium hydride. Diisopropyl amine was distilled under Argon from sodium metal with sodium benzophenone ketyl as indicator. Dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were distilled under reduced pressure from powdered calcium hydride. Tetrahydrofuran (THF), n-pentane, and diethyl ether were distilled under Argon from sodium metal with sodium benzophenone ketyl as indicator. Dichloromethane was distilled from phosphorous pentoxide.

All other reactants and solvents were "Reagent Grade" unless otherwise described. "Ether" refers to anhydrous diethyl ether, which is supplied by Mallinckrodt.

"Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, b.p. 35-60°C, which is supplied by J.T. Baker Co., Phillipsburg, NJ and was not further purified.

Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

Diacetyltartaric Anhydride.

To a mixture of 200g. (1.33 mol) of pulverized d-tartaric acid and 440 mL of acetic anhydride was added 6 mL of concentrated sulfuric acid, and the resulting solution was stirred at room temperature for three hours. After the solution was heated on a steam bath for one hour, the reaction was cooled in an ice bath, and the white crystalline product was collected by vacuum filtration on a medium frit. After the filtrate was washed with 50 mL of benzene and dried in a vacuum desiccator over paraffin for three days, there was obtained 240.0g (93%) of pure crystalline diacetyltartaric anhydride: m.p. 128-129°C; ^{1}H NMR ($CDCl_3$) δ2.23 (s, 6H, $-COCH_3$), 5.73 (s, 2H, -COCHOAc).

Pyridine Salt of Hydroxymaleic Anhydride.

Eighty mL of dry pyridine was added in one portion to a dry, stoppered flask containing 40 g. (0.185 mole) of diacetyltartaric anhydride. The flask was then stoppered, and the mixture was shaken vigorously for 5 seconds. Then 24 mL of glacial acetic acid was added immediately and the resulting mixture was warmed to 45°C until dissolution was complete, approxiamately 20 seconds. The flask was then placed in an ice bath and 90 mL of anhydrous ether was added. The mixture was shaken, and the resulting precipitate was collected by vacuum filtration on a medium frit. The filtercake was thoroughly pressed and washed twice with 10 mL portions of absolute ethanol and then three times with 10 mL portions of ether. After drying the filtrate under reduced pressure for three hours, was obtained 22.0g. (64%) of the pyridine salt of hydroxymaleic anhydride as a slight yellow solid. The crude salt was used directly in the preparation of the acyloxymaleic anhydrides **17** and **29** .

Methoxyacetyl chloride. **16**

1.5g (0.016 mole) of methoxyacetic acid, 3.0 mL (0.034 mole) of oxalyl chloride, and 1 mL of 0.1M dimethylformamide in benzene were stirred rapidly at room temperature for 2 hours. The reaction mixture was then fractionally distilled to yield 1.65 g (95%) of methoxyacetyl chloride. b.p. 113-114°C. The acid chloride was used directly in the preparation of (2-methoxyacetyl)maleic anhydride.

(2-Methoxyacetyl)maleic Anhydride. **17**

To a stirred suspension of 0.67 g. (3.4 mmole) of the pyridine salt of hydroxymaleic anhydride in 10 mL of dry benzene under an argon atmosphere was added 0.48g. (4.4 mmole) of methoxyacetyl chloride. After

stirring the solution for three hours, the benzene solution was decanted and filtered through 5 g. of alumina with 50 mL of benzene. The solvent was removed under reduced pressure to yield a crystalline material which after one recrystallization from benzene in petroleum ether gave 0.314g (50%) of (2-methoxyacetyl)maleic anhydride. m.p. 93-94°C;
IR ($CHCl_3$); 1630 (C=C), 1780 (C=O), 1820 (C=O), 1850 cm^{-1} (C=O). ^1H NMR ($CDCl_3$); δ 3.53 (s, 3H, ether CH_3O-), 4.35 (s, 2H, $COCH_2O$-), 6.90 (s, 1H, vinylic H).

4-Acetoxycyclohexene-*cis*-4,5-dicarboxylic Anhydride.

A thick-walled Pyrex tube was charged with a solution of 0.314g (1.69 mmole) of (2-methoxyacetyl)maleic anhydride and 8.7 mg (0.069 mmole) of pyrogallol in dry benzene and 2.0 mL (24 mmole) of dry 1,3-butadiene. The mixture was cooled in a liquid nitrogen bath under argon and then evacuated and allowed to thaw as a closed system. Freezing, followed by reevacuation, was repeated three times and the tube was then sealed under vacuum while the contents remained frozen. The sealed tube was then heated to 85°C for 5 days. After cooling in a liquid nitrogen bath, the tube was opened, and placed under argon while warming to room temperature. Filtration through celite with 50 mL of anhydrous ether and removal of solvents under reduced pressure, followed by chromatography on 40 g. of silica gel using 45% ethyl acetate in petroleum ether as eluant gave 0.332 g. (82%) of a white crystalline product ( ). m.p. 78-80°C. IR ($CHCl_3$); 1740 (C=O), 1785 and 1855 cm^{-1} (anhydride C=O); ^1H NMR ($CDCl_3$); δ3.47 (s, 3H, ether CH_3O-), 4.12 (s, 2H, $COCH_2O$-), 6.00 (m, 2H, vinylic H's).

2-Oxo-3,4-dimethoxy-10β-carbomethoxy-1α-oxaspiro[4.5] deca-3,7-diene. **18**

A rapidly stirred solution of 0.22 g. (0.935 mmole) of the anhydride ester **17** in 4 mL of dry tetrahydrofuran, was cooled to -78°C under an argon atmosphere. To this solution was added dropwise a solution of 1.8 equivalents (1.5 mmole) of lithium diisopropylamide in 3 mL of dry tetrahydrofuran. The deep red solution was stirred at -78°C for ten minutes, followed by warming to 0°C and addition of 1.6 mL of hexamethylphosphoramide. After stirring the solution at 0°C for ten minutes, 0.2 mL (2.49 mmole) of methyl fluorosulfonate was added. The yellow reaction mixture was quenched with 25 mL of 10% aqueous hydrochloric acid and extracted twice with 25 mL of anhydrous ether. The combined ethereal layers were washed twice with 10 mL portions of 10% aqueous HCl., twice with 10 mL portions of water, then once with saturated aqueous sodium chloride solution. After the solution was dried over magnesium sulfate, the solvents were removed under reduced pressure. Immediate flash chromatography on silica gel using 25% ethyl acetate in petroleum ether afforded 0.1086 g. (43%) of a yellow oil.

IR ($CHCl_3$); 1675 (C=C), 1735 (C=O), and 1760 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$); δ 3.70 3.92, 4.13 (3s, 3x3H, 3xether CH_3O-), 5.73 (broad s, 2H, vinylic H's).

2-Oxo-3,4-dimethoxy-10α-carbomethoxy-1α-oxaspiro[4.5]-deca-3,7-diene. 19

To a stirred solution of 0.38g (1.42 mmole) of spirobutenolide 18) in 30 mL of dry methanol under an argon atmosphere was added 0.40 mL (0.20 mmole) of a freshly prepared 0.54 M. solution of sodium methoxide in dry methanol, and the resulting mixture was heated to reflux for 5 days. The reaction was quenched by addition of 1.0 mL of glacial acetic acid. The solution was then partitioned between 100 mL of dichloromethane and 40 mL of saturated aqueous sodium bicarbonate solution. The organic phase was washed with an additional 50 mL of aqueous sodium bicarbonate and the aqueous phases were combined and extracted twice with 50 mL of dichloromethane. The combined organic phases were washed with saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure and chromatography on 40 g. of silica gel with 25% ethyl acetate in petroleum ether as eluant afforded 0.2468 g (65%) of the αisomer, and 0.0618 g. (16%) of the β isomer.

IR($CHCl_3$); 1675 (C=C), 1735 (C=O), and 1760 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$); δ 3.67, 3.81, 4.13 (3s, 3x3H, 3 x CH_3O-), 5.72 (s, 2H, vinylic H's).

2-Oxo-3.4-dimethoxy-10α-(hydroxymethyl)-1α-oxaspiro-[4.5]deca-3,7-diene. **20**

To a stirred solution of 0.1038 g. (0.387 mmole) of ester **19** , in 10 mL of dry tetrahydrofuran cooled to -15°C under argon, was added 1.4 mL (1.4 mmole) of a 1.0 M solution of lithium triethylborohydride in tetrahydrofuran. The mixture was then allowed to warm to 0°C and stirred for 30 minutes. The reaction was quenched with 5 mL of 10% aqueous hydrochloric acid and extracted three times with 20 mL portions of ether. The combined ethereal extracts were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. The solvents were removed under reduced pressure. Chromatography on 10 g. of silica gel using 50% ethyl acetate in petroleum ether as eluant afforded 0.081 g (87%) of the desired alcohol. m.p.92-93°C IR ($CHCl_3$); 1670 (C=C), 1745 (C=O), 3600 cm^{-1} (-OH); ^1H NMR ($CDCl_3$); δ 3.80 and 4.15 (2s, 2x3H, 2 x CH_3O-), 5.70 (m, 2H, vinylic H's).

2-Oxo-3,4-dimethoxy-10α-[(tert-butyldimethylsiloxy)-methyl]-1α-oxaspiro[4.5]deca-3,7-diene. **21**

To a stirred solution of 0.038 g. (0.156 mmole) of the alcohol **20** in 3.0 mL of dimethylformamide under an argon atmosphere were added 0.048 g. (0.316 mmole) of *tert*-butyldimethylsilylchloride and 0.043 g. (0.636 mmole) of sublimed imidazole. The resulting mixture was stirred for 12 hours at room temperature, then poured into

25 mL of saturated aqueous sodium bicarbonate, and extracted 3 times with 25 mL portions of ether. The ethereal extracts were combined and washed with saturated aqueous sodium chloride and then dried over magnesium sulfate. Removal of solvents followed by chromatography on 10 g. of silica gel using 10% ethyl acetate in petroleum ether as eluant gave 0.049 g. (89%) of the silyl ether.

IR ($CHCl_3$); 1250, 838 ($SiCH_3$), 1670 (C=C), and 1740 cm^{-1} (C=O),

^1H NMR ($CDCl_3$); δ 0.03 (s, 6H, $(CH_3)_3Si-$), 0.87 (s, 9H, $(CH_3)_3C-$), 3.40 (m, 1H, $\underline{CH}CH_2OSi$), 3.76, 4.07 (2xs, 2x3H, CH_3O-), 5.60 (m, 2H, vinylic H's).

2-Oxo-3,4-dimethoxy-7β,8β-epoxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]deca-3-ene. **22**

To a stirred solution of 0.049 g. (0.139 mmole) of the silyl ether **21** in 5 mL of dry ether at 0°C under an argon atmosphere were added 0.077 g. (0.446 mmole) of 85% *m*-chloroperbenzoic acid and 0.041 g. (0.381 mmole) of anhydrous lithium perchlorate. The resulting mixture was then allowed to stir at 0°C for six hours, then quenched with 15 mL of 10% aqueous sodium sulfite solution. The aqueous layer was extracted with three 50 mL portions of dichloromethane. The combined organic layers were washed with 25 mL of saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents under reduced pressure,

followed by chromatography on 10 g. of silica gel, with 25% ethyl acetate in petroleum ether as eluant afforded 0.021 g. (45%) of the desired epoxide. m.p. 90-91°C.
IR ($CHCl_3$); 1680 (C=C), 1765 cm^{-1} (C=O);
^1H NMR ($CDCl_3$); δ 0.03 (s, 6H, $(CH_3)_2Si$-), 0.87 (s, 9H, $(CH_3)_3C$-), 3.73 (s, 3H, CH_3O-), 4.02 (s, 3H, CH_3O-).

2-Oxo-3,4-dimethoxy-7α-methyl-8β-hydroxy-10α-[(*tert*-butyldimethylsiloxy)methyl]-1α-oxaspiro[4.5]dec-3-ene. **23**

To a stirred suspension of 0.40 g. (2.11 mmole) of purified copper(I)iodide in 5 mL of dry pentane, cooled to 0°C under an argon atmosphere was added dropwise 2.2 mL (2.75 mmole) of a 1.25M solution of methyl lithium in pentane. The resulting cuprate (2.75 mmole) was warmed to 10°C, and the epoxide **22** in 2.5 mL of dry ether was added dropwise. The solution was stirred at 10°C for 12 hours. The reaction was then quenched with 25 mL of saturated aqueous ammonium chloride solution and extracted twice with 25 mL portions of ether. The combined organic layers were washed once with 10 mL of saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents under reduced pressure followed by column chromatography on 10 g. of silica gel using 35% ethyl acetate in petroleum ether as eluant gave 0.062 g (58%) of the desired alcohol, along with 0.011 g. (11%) of the recovered epoxide.
IR ($CHCl_3$): 1675 (C=C), 1760 (C=O), and 3600 cm^{-1} (-OH)
^1H NMR ($CDCl_3$

^{1}H NMR ($CDCl_3$): δ 0.03 (s, 6H, $(CH_3)_2Si-$), 0.87 (s, 9H, $(CH_3)_3C-$), 1.10 (d, 3H, J=7Hz, $CH\underline{H}_3$), 3.75 (s, 3H, CH_3O-), 4.07 (s, 3H, CH_3O-).

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy-10α-(hydroxymethyl)-1α-oxaspiro[4.5]dec-3-ene. 25

To a stirred suspension of sodium hydride (0.5 g., 0.02 mmole) in 5 mL of dry tetrahydrofuran at 0°C under an argon atmosphere was added 0.9 mL of methyl iodide (0.014 mmole) freshly distilled from phosphorous pentoxide, followed by a solution of 0.031 g. (0.078 mmole) of the alcohol 23 in 0.5 mL of dry tetrahydrofuran. The mixture was stirred at 0°C for 2 hours, and then quenched with 2 mL of saturated aqueous ammonium chloride solution. The aqueous layer was extracted with 25 mL of ether and the combined ether extracts were washed with 10 mL of 10% aqueous sodium sulfite solution, then dried over magnesium sulfate. Removal of solvents under reduced pressure yielded 0.031 g. (96%) of the methyl ether.

IR ($CHCl_3$): 1675 (C=C), 1760 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ 0.03 (s, 6H, $(CH_3)_2Si-$), 0.87 (s, 9H, $(CH_3)_3C-$), 1.10 (d, 3H, J=7Hz, $CH\underline{H}_3$), 3.23 (s, 3H, CH_3O-), 4.07 (s, 3H, CH_3O-), 3.65 (s, 3H, CH_3O-).

The methyl ether 0.031 g. (0.077 mmole) was taken up in a mixture of 0.6 mL of glacial acetic acid, 0.3 mL of water, and 2.0 mL of tetrahydrofuran. The solution was stirred at room temperature for 48 hours. The reaction mixture was diluted with 10 mL of ether, and the aqueous layer was saturated with sodium chloride and extracted twice with 10 mL portions of ether. The combined organic layers were washed with 10 mL of saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents under reduced pressure followed by chromatography on 10 g. of silica gel with 50% ethyl acetate in petroleum ether as eluant afforded 0.022 g. (93%) of the alcohol.

IR ($CHCl_3$); 1670 (C=C), 1750 (C=O), 3600 cm^{-1} (-OH).

^1H NMR ($CDCl_3$): δ 1.10 (d, 3H, J=7Hz, -CHC$\underline{H}_3$), 3.23 (s, 3H, CH_3O-), 3.75 (s, 3H, CH_3O-), 4.07 (s, 3H, CH_3O-).

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy-10α-carbaldehyde-1α-oxaspiro[4.5]dec-3-ene. 26

To a stirred suspension of 0.031 g. (0.144 mmole) of pyridinium chlorochromate in 1.0 mL of dry dichloromethane was added a solution of 0.022 g. (0.072 mmole) of the alcohol 25 in 1.0 mL of dry dichloromethane. The resulting mixture was allowed to stir at room temperature for three hours, then diluted with 25 mL of anhydrous ether and decanted. The remaining black precipitate was pulverized and washed with three additional 25 mL portions of ether. The combined organic extracts were filtered through a column of 10 g. of silica gel using 200 mL of ether. Removal of the solvents under reduced pressure afforded 0.019 g. (0.066 mmole) of the aldehyde, which was immediately converted to the allylic alcohol 6, as decomposition occurred upon standing.

IR ($CHCl_3$); 1660 (C=C), 1710 (C=O), 1750 (C=O), 2715 cm^{-1} (aldehyde CH).

^1H NMR ($CDCl_3$); δ 1.10 (d, 3H, J=7Hz, $CHC\underline{H}_3$), 3.23 (s, 3H, CH_3O-), 3.75 (s, 3H, CH_3O-), 4.07 (s, 3H, CH_3O-), 9.57 (s, 1H, aldehydic H).

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy- 10α-(1-hydroxy-2-propen-1-yl)-1α-oxaspiro[4.5]dec-3-ene. 6

To a stirred solution of 0.019 g. (0.066 mmole) of the aldehyde 26 in 2.0 mL of dry tetrahydrofuran cooled to -30°C under an argon atmosphere was added dropwise 0.05 mL of a 1.6M solution of vinylmagnesium bromide in tetrahydrofuran. The resulting mixture was allowed to warm to 0°C and stirred for 10 minutes, then quenched with 5.0 mL of saturated aqueous ammonium chloride solution. The aqueous layer was extracted with three 15 mL portions of ether, and the combined ethereal extracts were dried over magnesium sulfate. Removal of solvents under reduced pressure, followed by chromatography on 10 g. of silica gel using 50% ethyl acetate in petroleum ether as eluant afforded 0.014 g. (68% from 25) of the allylic alcohol.

IR ($CHCl_3$); 1680 (C=C), 1765 (C=O), 3600 cm^{-1} (-OH).

^1H NMR ($CDCl_3$); δ 1.09 (d, 3H, J=7Hz, $CHC\underline{H}_3$), 3.26 (s, 3H, Ch_3O-), 3.79 (s, 3H, CH_3O-), 4.10 (s, 3H, CH_3O-), 5.0-6.0 (m, 3H, vinylic H's).

2-(Trimethylsilyl)ethanol.

To a stirred solution of lithium diisopropylamide (0.360 mole) in 200 mL of dry tetrahydrofuran, cooled to -78°C under an argon atmosphere, was added 40.0 g. (0.344 mole) of *tert*-butyl acetate dropwise over one hour. The solution was stirred at -78°C for 30 minutes. 38.0 g. (0.350 mole) of trimethylsilyl chloride was then added dropwise over a period of 30 minutes. The resulting mixture was allowed to warm slowly to 25°C. The reaction was then quenched by addition of 500 mL of 1N aqueous hydrochloric acid, and extraction of the aqueous phase twice with 500 mL of pentane. The organic phases were combined and washed with 250 mL of 1N aqueous hydrochloric acid. The acidic phases were combined and extracted twice with an additional 500 mL of pentane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, and with saturated aqueous sodium chloride solution, then dried over magnesium sulfate. Removal of solvents under reduced pressure afforded 58.0 g. of crude *tert*-butyl-2-(trimethylsilyl) acetate. IR ($CHCl_3$): 1700 cm^{-1} (C=O). ^1H NMR ($CDCl_3$); δ 0.10 (s, 9H, $(CH_3)_3Si$-), 1.40 (s, 9H, $(CH_3)_3C$-), 1.8 (s, 2H, $COCH_2Si$-).

To a suspension of 23.0 g. (0.606 mole) of lithium aluminum hydride in 500 mL of dry ether, cooled to 0°C under an argon atmosphere, was added the crude *tert*-butyl-2-(trimethylsilyl)acetate dropwise. The reaction mixture was then allowed to warm to 25°C and was stirred at room temperature for 12 hours. The reaction mixture was then cooled to 0°C, and the reaction was quenched by the slow addition of 23.0 mL of water, followed by 23.0 mL of

15% aqueous sodium hydroxide solution, followed by 69.0 mL of water. The ethereal layer was decanted and the precipitate was washed with 200 mL of ether. The organic phases were combined and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure followed by fractional distillation afforded 20.0 g. (49% from *tert*-butyl acetate) of the 2-(trimethylsilyl)ethanol;
b.p. (25 mm. Hg) 77-78°C.
IR ($CHCl_3$); 3605 (OH), 3600-3100 cm^{-1} (-OH).
^{1}H NMR ($CDCl_3$); δ 0.00 (s, 9H, $(CH_3)_3Si$-), 0.96 (t, 2H, J=9Hz, $-CH_2Si-$), 1.79 (t, 1H, J=5Hz, -OH), 3.87 (td, 2H, J=9Hz, 5Hz, $-CH_2OH$).

[2-(trimethylsilyl)ethoxy]-acetic acid. **27**

To a rapidly stirred suspension of 2.8 g (0.153 mole) of sodium hydride in 50.0 mL of dry tetrahydrofuran, cooled to -78°C under an argon atmosphere, was added 4.5 g. (0.033 mole) of bromoacetic acid in 25 mL of dry tetrahydrofuran. After addition of the bromoacetic acid was complete, the solution was warmed to 0°C and 4.6 g. (0.039 mole) of 2-(trimethylsilyl)ethanol was added dropwise. The reaction was allowed to warm slowly to room temperature, then 1.5 g (0.0065 mole) of silver oxide was added. The reaction was stirred at room temperature for two days, and then was quenched with 150 mL of 1N aqueous hydrochloric acid. The aqueous phase was extracte- with 150 mL of ether. The organic phase was washed with 100 mL of 1N aqueous hydrochloric acid. The acidic phases were combined and extracted twice with 100 mL of ether. The ethereal extracts were combined and washed with saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate.

Removal of solvents under reduced pressure, followed by fractional distillation afforded 5.1 g. (88%) of as a colorless oil. b.p. (0.01 mm.) 81-82^{o}C.

IR ($CHCl_3$); 3600-2400 (COOH), 1720 cm^{-1} (C=O).

^1H NMR ($CDCl_3$); δ 0.00 (s, 9H, $(CH_3)_3Si$-), 0.98 (t, 2H, J=9Hz, -CH_2Si-), 3.62 (t, 2H, J=9 Hz, -CH_2O-), 4.08 (s, 2H, $COCH_2O$-), 10.64 (s, 1H, COOH).

Anal: Calc: C 47.69, H 9.15%, Found: C 47.74, H 9.21%

[2-(trimethylsilyl)ethoxy]acetyl chloride. 28

To a rapidly stirred solution of 0.73 g (4.15 mmole) of the acid 27 , in 10 mL of dry benzene under an argon atmosphere, was added 2.3 g. (18.3 mmole) of oxalyl chloride, followed by 0.25 mL of a 0.1M solution of dimethylformamide in benzene. The reaction mixture was stirred at room temperature for two hours. The solvents and excess oxalyl chloride were removed under reduced pressure, then 10 mL of dry benzene was added and removed under reduced pressure. The sequence was repeated four times to afford 0.793 g. (98%) of the acid chloride, which was used without further purification.

IR ($CHCl_3$); 1740 cm^{-1} (C=O).

^1H NMR ($CDCl_3$); δ 0.05 (s, 9H, $(CH_3)_3Si$-), 0.99 (t, 2H, J=8Hz, -CH_2Si-), 3.67 (t, 2H, J=8Hz, -CH_2O-), 4.38 (s, 2H, $COCH_2O$-).

[{2-(trimethylsilyl)ethoxy}acetoxy]maleic anhydride. 29

To a rapidly stirred suspension of 0.35 g. (1.82 mmole) of the pyridine salt of hydroxymaleic anhydride in 5 mL of dry benzene, was added 0.375 g. (1.93 mmole) of the acid chloride 28 . The reaction mixture was stirred at room temperature for 35 minutes under an argon atmosphere. The benzene solution was then filtered through 25 g. of Florisil with 50 mL of dry benzene. Removal of solvents under reduced pressure yielded 0.458 g. (92%) of the anhydride , as whitish crystals which were recrystallized once from 20% benzene in petroleum ether.

IR ($CHCl_3$); 1850 (C=O), 1800 (C=O), 1780 (C=O), 1625 cm^{-1} (C=C).

^1H NMR ($CDCl_3$); δ 0.00 (s, 9H, $(CH_3)_3Si$-), 1.01 (t, 2H, J=8Hz, -CH_2Si-), 3.68 (t, 2H, J=8Hz, -CH_2O-), 4.37 (s, 2H, $COCH_2O$-), 6.88 (s, 1H, vinylic H).

4-[2-{2-Trimethylsilyl)ethoxy}acetoxy]-cyclohexene-cis-4,5-dicarboxylic Anhydride. 30

A thick walled Pyrex tube was charged with a solution of 0.255 g (0.937 mmole) of the anhydride 29 , 0.013 g. (0.105 mmole) of pyrogallol in 5.0 mL of dry benzene, and 0.9 g (18.0 mmole) of dry 1,3-butadiene. The mixture was cooled in a liquid nitrogen bath under argon and then evacuated and allowed to thaw as a closed system. Freezing, followed by re-evacuation, was repeated three times and the tube was then sealed under vacuum, while the contents remained frozen. The sealed tube was then heated to 80°C for 5 days. After cooling in a liquid nitrogen bath, the tube was opened and placed under argon while warming to room temperature. Filtration of the contents through celite with 50 mL of anhydrous ether, removal of solvents under reduced pressure, followed by chromatography on 25 g. of silica gel using 25% ethyl acetate in petroleum ether as eluant, afforded 0.171 g. (56%) of the cyclohexene. m.p. 80-82°C.

IR ($CHCl_3$); 1740 (C=O), 1785 and 1855 cm^{-1} (anhydride C=O) ;

^1H NMR ($CDCl_3$); δ 0.00 (s, 9H, $(CH_3)_3Si$-), 0.93 (t, 2H, J=8Hz, $-CH_2Si$-), 3.57 (5, 2H, J=8Hz, $-O\underline{CH_2}CH_2$), 4.10 (s, 2H, $-COCH_2O$-) 5.72-6.15 (m, 2H, vinylic H's).

2-Oxo-3-(2-trimethylsilyl)ethoxy-4-methoxy-10β-carbomethoxy-1α oxaspiro[4.5]deca-3,7-diene. **31**

To a rapidly stirred solution of 0.0984 g. (0.302 mmole) of cyclohexene anhydride **30** in 10 mL of dry tetrahydrofuran, was added dropwise 5.4 mL of 0.10 M hexane-free lithium diisopropylamide. The deep red solution was then stirred at -78°C under an argon atmosphere for 10 minutes, followed by warming to room temperature. The solution was stirred at room temperature for 15 minutes, then was cooled to 0°C and 0.6 mL of dry hexamethylphosphoramide was added. After 10 minutes at 0°C, 1.00 mL (0.012 mmole) of methyl fluorosulfonate was added. The reaction was quenched with 25 mL of a 10% aqueous hydrochloric acid solution, then extracted twice wtih 50 mL portions of ether. The organic phases were combined and washed twice with 25 mL of water and once with 10 mL of saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure followed by flash chromatography on silica gel using 10% ethyl acetate in petroleum ether as eluant afforded 0.0604 g. (61%) of a slightly yellow oil.

IR ($CHCl_3$); 1670 (C=C), 1750, 1755 cm^{-1} (C=O);

^1H NMR ($CDCl_3$); δ 0.03 (s, 9H, $(CH_3)_3Si$-), 1.03 (ddd, 2H, J= 3 Hz, 7 Hz, and 11 Hz, $-CH_2Si$), 3.63 (s, 3H, CH_3O-), 4.08 (s, 3H, CH_3O-), 4.12 (ddd, 2H, J=3, 7, 11 Hz, $-OCH_2$-),

Anal: Calc: C 57.60%, H 7.39%; Found: C 57.65%, H 7.38%.

2-Oxo-3-(2-trimethylsilyl)ethoxy-4-methoxy-10α-carbomethoxy-1α-oxaspiro[4.5)deca-3,7-diene. 31a 31b

To a stirred solution of 0.2337 g. (0.66 mmole) of ester 31 , was added 0.3 mL (0.06 mmole) of a freshly prepared 0.2M solution of sodium methoxide in methanol. The solution was refluxed under argon for 7 days. The solution was cooled to 25°C, and diluted with 100 mL of dichloromethane. The sodium methoxide was quenched by addition of 1.0 mL of glacial acetic acid. The solution was washed twice with 50 mL portions of saturated aqueous sodium bicarbonate. The aqueous phases were combined and extracted twice with 50 mL of dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate. Removal of solvents and chromatography on 30 g. of silica gel with 30% ether in petroleum ether as eluant, afforded 0.1500 g. (64%) of an inseparable mixture of epimers. Ratio 83:17 as determined by 500 MHz NMR.

IR ($CHCl_3$); 1670 (C=C), 1750 (C=O), and 1755 cm^{-1} (C=O).

^1H NMR ($CDCl_3$); δ 0.02 (s, 9H, $(CH_3)_3Si$-), 1.03 (ddd, 2H, J=3Hz, 7Hz, 11 Hz, -CH_2Si-), 3.62 and 3.62 (2s, 3H, 83:17, CH_3O-), 4.1 (ddd, 2H, J=3Hz, 7Hz, 11Hz, -OCH_2-), 4.11 and 4.08 (2s, 3H, 83:17, CH_3O-), 5.57-5.75 (m, 2H, vinylic H's).

Anal: Calc: C 57.60% H 7.39%; Found: C 57.65%, H 7.38%.

2-Oxo-3(2-trimethyl)ethoxy-4-methoxy-10-(hydroxymethyl)-1α-oxaspiro[4.5]deca-3,7diene. 34a 34b

To a rapidly stirred solution of 0.010 g. (0.028 mmole) of the ester 31 in 3.0 mL of dry tetrahydrofuran, cooled to -30°C under an argon atmosphere, was added 0.1 mL (0.1mmole) of 1.0 M lithium triethylborohydride in tetrahydrofuran. The solution was stirred at -30°C for 5 minutes, and then partitioned between 5 mL of 10% aqueous hydrochloric acid, and 10 mL of ether. The acidic phase was extracted twice with 10 mL portions of ether. The organic phases were combined and washed with 15 mL of brine, and dried over anhydrous magnesium sulfate. Removal of solvents under reduced pressure, followed by chromatography on 10 g. of silica gel afforded 8.5 mg. (93%) of the desired alcohol. An analytical sample was prepared by recrystallization from hot ether in pentane.

IR($CHCl_3$); 3600 (OH), 1750 (C=O), 1675 (C=C).

^1H NMR ($CDCl_3$); δ 0.02 (s, 9H, $(CH_3)_3Si$), 1.03 (ddd, 2H, J=3Hz, 7Hz, 11 Hz, $-CH_2Si-$), 3.50 (m, 2H, $HOC\underline{H}_2-$), 4.10 (ddd, 2H, J=3, 7, 11 Hz, $-OCH_2-$), 4.11 and 4.03 (2s, 3H, 83:17, CH_3O).

Anal: Calc: C 58.86%, H 8.03%; Found: C 58.74%, 8.07%.

2-Oxo-3-(2-trimethylsilyl)ethoxy-4-methoxy-10-[(*tert*-butyldimethylsiloxy)-methyl]-1α-oxaspiro[4.5]deca-3,7-diene. **35a** **35b**

To a stirred solution of 0.030 g. (0.092 mmole) of the epimeric alcohols **34a** and **34b** in 0.9 mL of dry dimethylformamide under an argon atmosphere, were added 0.0354 g. (0.235 mmole) of *tert*-butyldimethylsilyl chloride, and 0.0260 g. (0.382 mmole) of sublimed imidazole. The resulting solution was stirred for 12 hours at 25°C, and then partitioned between 25 mL of saturated aqueous sodium bicarbonate and 25 mL of ether. The aqueous phase was extracted twice with 25 mL portions of ether. The combined organic layers were dried over anhydrous magnesium sulfate and the solvents removed under reduced pressure. Chromatography on 10 g. of silica gel afforded

0.0339 g. (84%) of the silyl ether. An analytical sample of the inseparable epimeric mixture was prepared by distillation. b.p. 102-103°C (0.005 mm Hg).

IR ($CHCl_3$); 1750 (C=O), 1675 (C=C),

^{1}H NMR ($CDCl_3$); δ 0.02 (s, 15H, $(CH_3)_3Si$-, and $(CH_3)_2Si$), 0.862 and 0.866 (2s, 9H, 84:16, $(CH_3)_3C$-), 1.06 (ddd, 2H, J=3,7,11 Hz, -CH_2Si-), 4.12 (ddd, 2H, J=3, 7, 11Hz, -$O\underline{CH_2}CH_2$-), 4.11 and 4.08 (2s, 3H, 84:16, CH_3O)

Anal: Calc: C 59.95%, H 9.15%; Found: C 60.07%, H 9.11%.

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