# The Total Synthesis of Chlorotricolide; The Top Half

Thesis by

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To my parents, my sister Carol

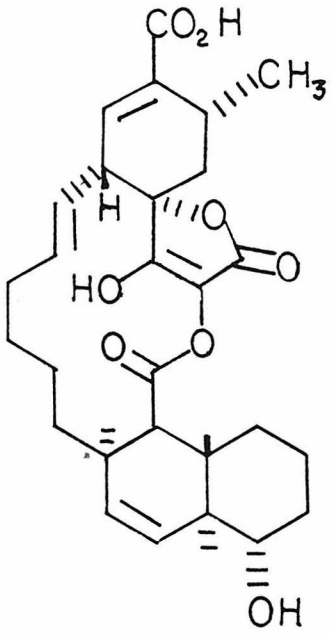
and my brothers

# ACKNOWLEDGEMENTS

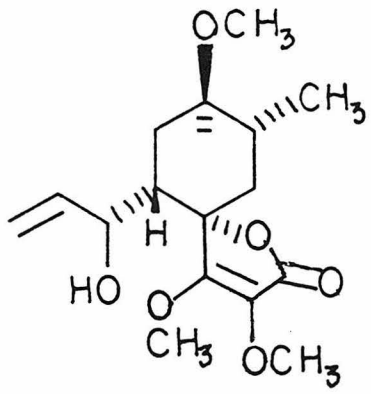
I wish to thank Professor Robert E. Ireland for his scientific guidance and moral support. His enthusiasm and eternal youthfulness are a constant inspiration. I also thank the group for providing a stimulating environment in which to learn, and Beth Cooper for her time, patience, and skill in preparing this thesis. Finally, I thank the National Institute of Health and the California Institute of Technology for financial support.

# ABSTRACT

The total synthesis of the top half of chlorotricolide 2, is described. The top half 65 was prepared in 14 steps (10% overall yield) from tartaric acid. The potential usefulness of this top half in the total synthesis of chlorotricolide was demonstrated by connection to bottom half models. Successful deprotection of the α-hydroxy-tetronic acid dimethyl ether moiety is also described.




chlorotricolide, 2

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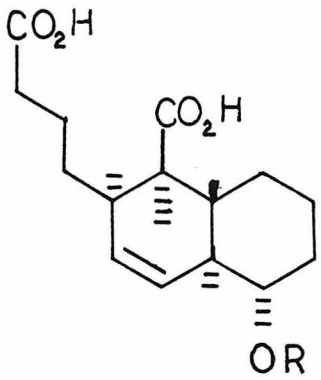



bottom half

# TABLE OF CONTENTS

# INTRODUCTION

With the isolation of pikromycin in 1950 by Brockmann and Henkel, a new facet in the chemistry of antibiotics was uncovered; the macrolides.[1] Aided by the advance of modern spectroscopy and x-ray crystallography over the past two decades, new structures appeared faster than chemists could classify them. By 1972, of the estimated 4000 known antibiotics, approximately 200 were macrolides, and of these, only about 50 still met the criteria set forth by Woodward in 1957.[2,3] The 14-membered macrolides erythromycin A and B, and oleandomycin are three medicinally important antibiotics which have become commercially competitive with the penicillins, due to modern fermentation technology.[1]

Concomitant with the surge of chemical and biological research in this area of antibiotics,[4] is the proliferation of chemical literature associated with their structure, conformation, activity, biosynthesis, degradation, modification and more recently synthesis. Fortunately, several reviews have appeared covering the literature through 1977.[5]

It has only been in recent years that the synthetic organic chemist has begun a major assault on the

macrolides. Synthetic methodology was aimed for a large part on obtaining solutions to the important classes of compounds:the steroids, terpenes, vitamins, alkaloids and prostaglandins. There have been major advances in these areas, and as a result of the synthetic expertise that developed, the first entries into the total synthesis of macrolide antibiotics have appeared. In order of appearance they are methymycin,[6] pyrenophorin,[7] vermiculine,[8] nonactin[9] and brefeldin A.[10]

Why have the macrolides been reluctant to yield to the skillful hands of the synthetic chemist? Total syntheses of the other antibiotics,the penicillins, cephalosporins and tetracyclines,were already accomplished by the end of the sixties.[11] The two major problems, as pointed out by Masamune, who was responsible for the total synthesis of methymycin, are macrocyclic lactonization and control of stereochemistry in an acyclic system. While the first of these two problems has seen some initial solutions,[5] the latter one has been met with only limited success. Some elegant approaches to this problem have appeared which involve the use of stereochemical control in the transition state of facile thermal rearrangements,[12,13] but by far the most common approach is the exploitation of stereochemical

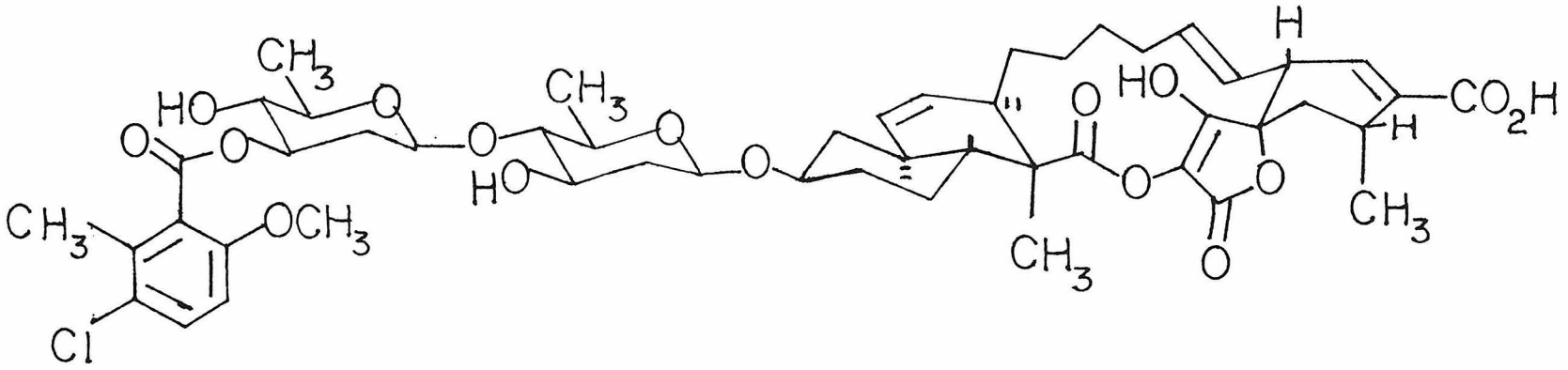
control in a rigid acyclic system, followed by ring cleavage to generate the desired acyclic system.

Having attempted an explanation or perhaps rationalization for total synthesis of macrolide antibiotics, attention is now turned to one macrolide antibiotic, chlorothricin 1, whose skeletal complexity and diverse functionality challenge the synthetic organic chemist with problems common to many types of natural products. A project directed toward the total synthesis of chlorothricin should draw chemical expertise together from many areas of natural products, and as a result of the synthetic effort, contribute chemical knowledge valuable to these same areas.

Isolated by W. Keller-Schierlein in 1969 from Streptomyces antibioticus,[14] the unusual structure of chlorothricin was elucidated by spectral data (NMR, IR, UV, Mass. Spec.) of the natural product and its methanolysis products.[15] X-ray analysis of the aglycone portions confirmed its structure.[16] Thus, chlorothricin consists of an aglycone portion, chlorotricolide 2; two sugars, both 2-deoxy-D-rhamnose; and an aromatic portion, 5-chloro-6-methyl salicyclic acid.

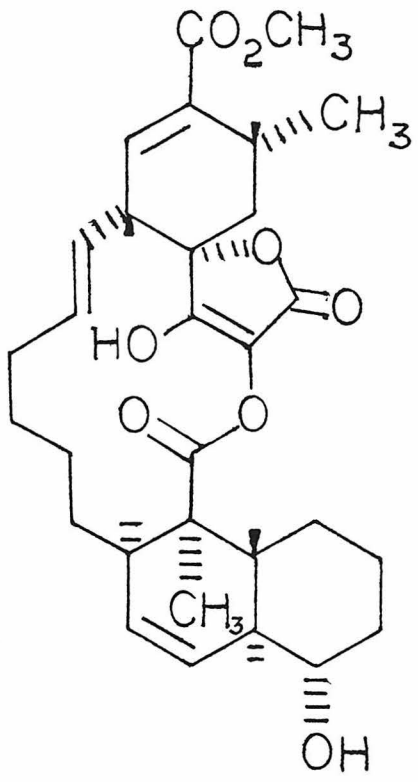
Chlorothricin was found to be active against Gram positive bacteria such as Bacillus subtilis and Bacillus

Figure 1




1 , CHLOROTHRICIN

Figure 2



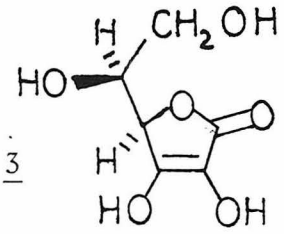

2

CHLOROTRICOLIDE

METHYL ESTER

Stearothermophilis.[17] Studies on the mode of action of chlorothricin[18-22] reveal that it is a non-competitive inhibitor of the reaction catalyzed by pyruvate carboxylase at low concentration, but does not act like an ionophore, chelating magnesium ion necessary for the reaction. At higher concentrations chlorothricin has been found to lyse bacteria.[18] Schindler proposes that the macrolide interacts with the hydrophobic area of the enzyme, thus rendering it inactive.[17,18,20] The aglycone portion chlorotricolide, has been found to be 4 to 6 times less active than the intact antibiotic, while the sugar and aromatic portions show no activity.[18] Thus, unlike a majority of the macrolides which generally function by inhibiting protein biosynthesis, chlorothricin acts as an antagonist to acetyl CoA.

Central to the chemistry of chlorotricolide is the α-hydroxytetronic acid moiety, which is the link necessary for the closure of the macrolactone. While a large number of natural products containing a tetronic acid nucleus have been isolated,[23-25] only one other example of one with an α-oxy substitutent is known;[26] the nutritionally important (−)-ascorbic acid (vitamin C) 3. Tetronic acid itself is β-Keto butyrolactone 4, which exists predominantly in the enolic form, and has a pKa of 3.76.[27]



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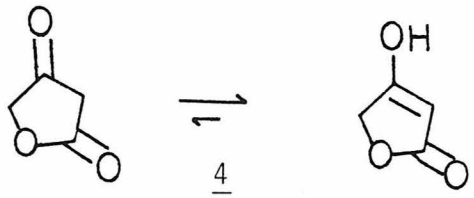
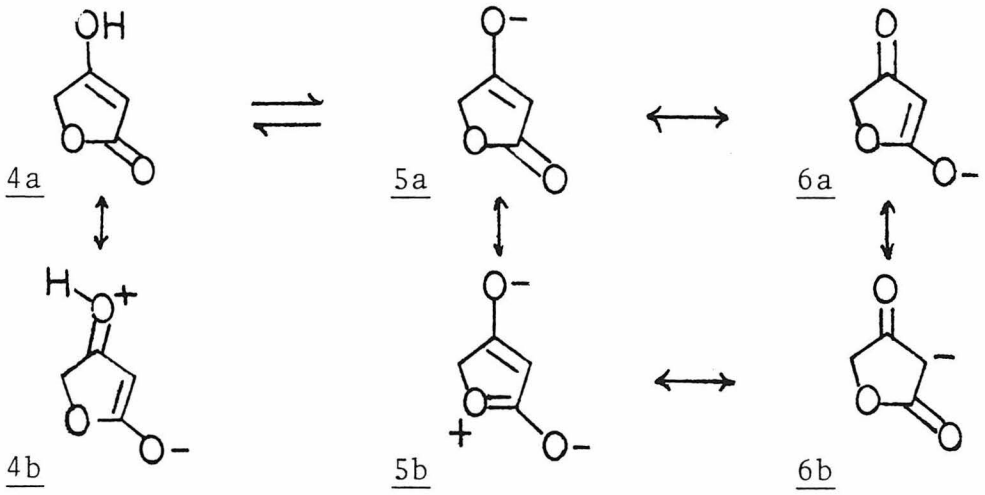


4

The strongly acid tetronic nucleus is characterized by its stability toward acid and base, and like phenols, its susceptibility toward substitution in the α-position.

Depending on their substitution, tetronic acids show a wide range of pK's from 1.68 (α-nitro) to 5.00 for chlorotricolide.[15,27] The high acidity of tetronic acids as compared to their linear counterparts, acetoacetic esters, has been suggested to result from increased resonance stabilization in the trans-coplanar arrangement, and to decreased repulsion between the oxygen atoms in a rigid cyclic system which exists in the enolic form.[27]



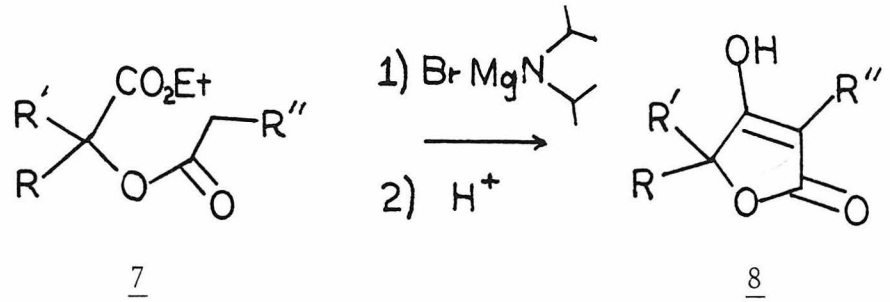
4a 5a 6a

4b 5b 6b

Due to the fact that resonance form 5b has 3 formal charges and 2 double bonds in the 5-membered ring, it is expected to contribute very little to the resonance stabilization. In the case of acetoacetic ester, however, the ester oxygen does exert an inductive effect to destabilize the anion, thus making it a weaker acid than the corresponding pentane-1,3-dione. As a result, tetronic acid is similar in pKa to cyclopentane-1,3-dione, but with a slightly lower pKa due to the additional inductive effect of the ring oxygen through the γ-carbon.

A convergent approach to construction of the tetronic acid nucleus which allows introduction of a variety of substituents on the ring, is the intramolecular Claisen ester condensation, as described by Haynes and Stanners[28] (Scheme 1). Using ethereal diisopropyl magnesium bromide at 0° C, or sodium metal in xylene at 140° C, they obtained various simple tetronic acid derivatives in moderate to good yields. However, in an attempt to extend this method to more complex mold tetronic acids, Svendson and Boll were unable to induce cyclization of the 3-ethoxycarbonylacetyl derivative of diethyl maleate 9.[29]

Scheme 1

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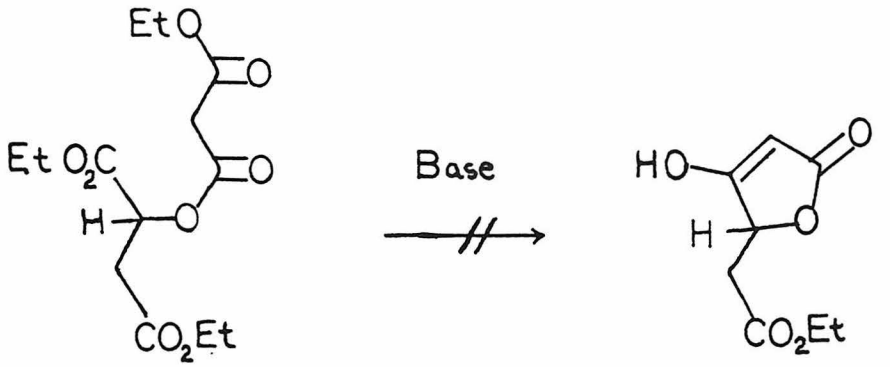


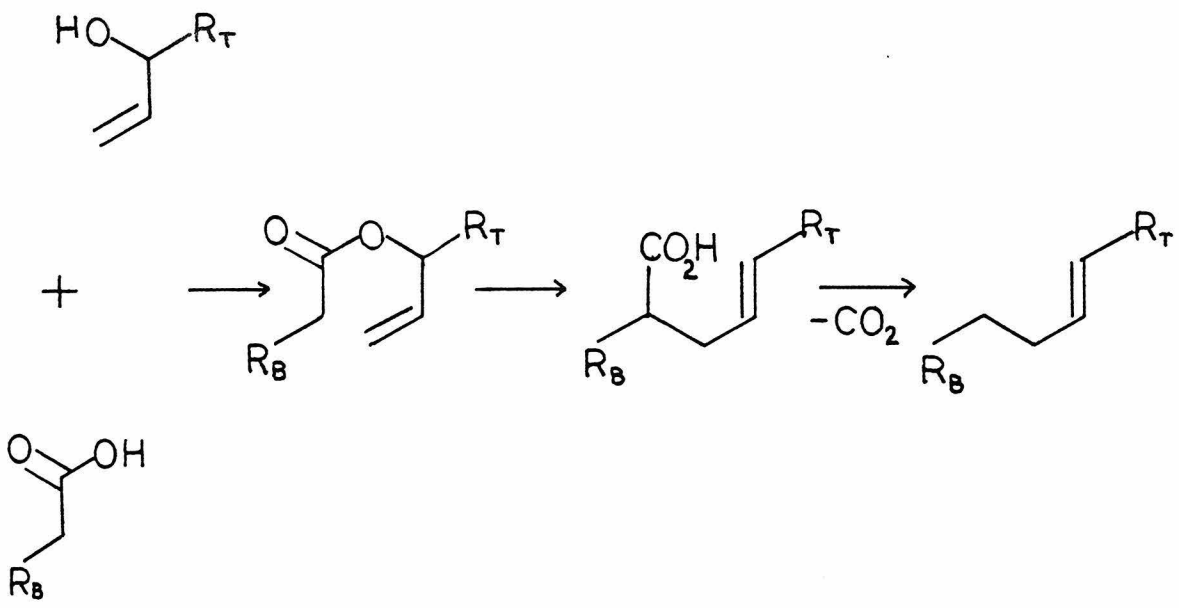

9 10

It was hoped that this intramolecular cyclization could be used to generate the spiro-α-oxy-tetronic acid moiety (10, R=-OH) as found in chlorotricolide.

The overall plan chosen for the total synthesis of chlorotricolide takes advantage of the increased efficiency inherent to a convergent approach.[30]

The molecule was visualized in a retrosynthetic sense as being constructed from two halves, which were appropriately named "top half" and "bottom half".

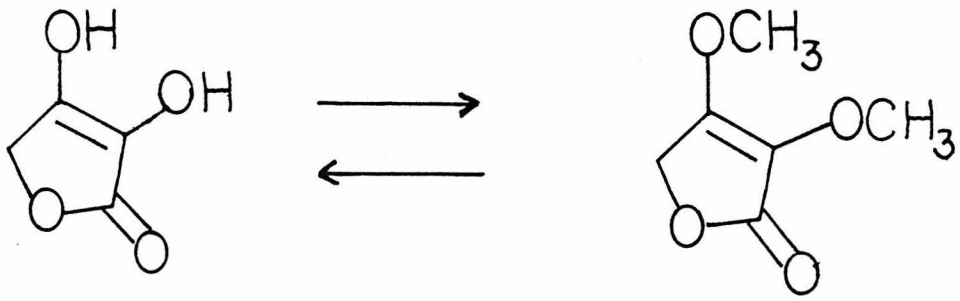
Scheme 2




Since both halves would be valuable synthetic intermediates, it would be advantageous to make the initial bond connection via a facile esterification process, and then exploit the mild basic conditions of the ester enolate Claisen reaction[31] to form the carbon-carbon bond in an intramolecular rearrangement. Furthermore, the Claisen rearrangement proceeds through a chair-like transition state

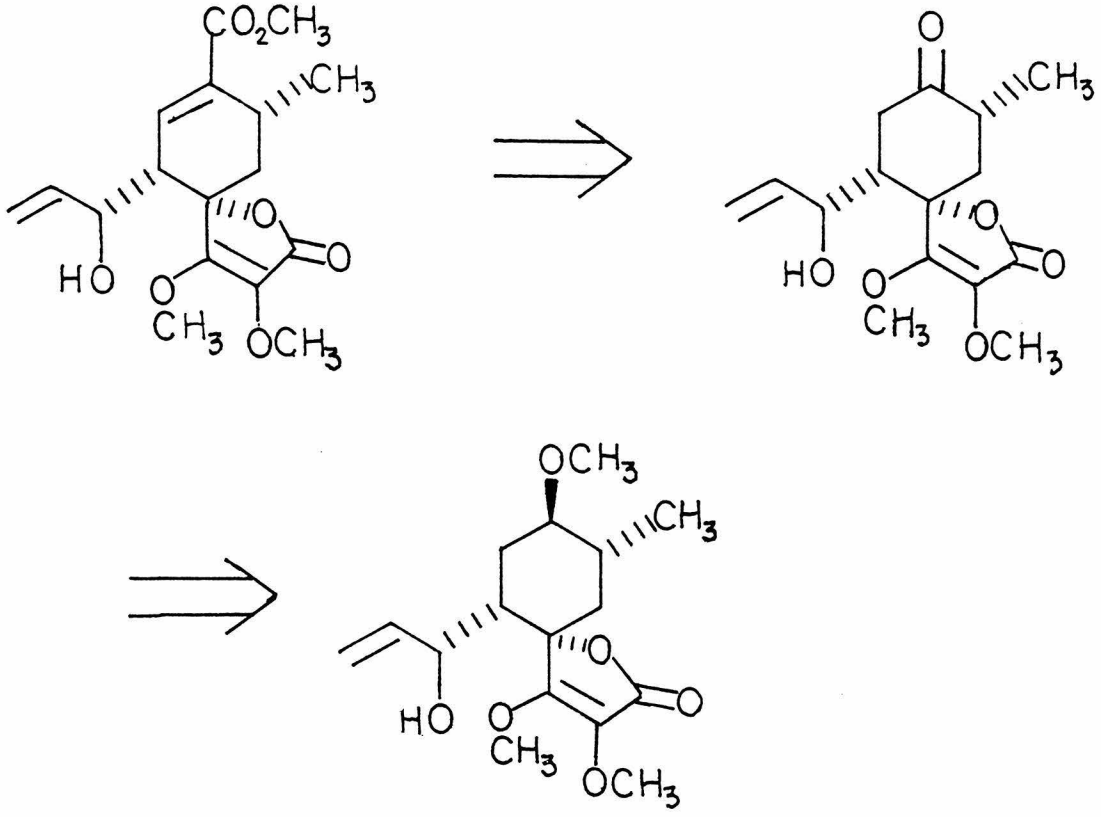
and would serve a dual purpose by controlling the trans-geometry of the double bond. Such control has been recently shown by Confalone and coworkers, in a synthesis of biotin, to be quite difficult using the more conventional Wittig reaction.[32] The resulting carboxyl group, which was employed as a lynch pin to connect the halves, would have to be removed without concomitant isomerization of the double bond.

The free α-hydroxy tetronic acid is highly sensitive to oxidation, and since it was desired to introduce it early in the synthetic scheme, it would be necessary to protect it in a form which would survive a variety of reaction conditions. Furthermore, it would have to be liberated cleanly to the free α-hydroxy tetronic acid, so that lactonization could be achieved. It was hoped that the phenolic nature of the enediol system in the α-hydroxy tetronic acid would allow for its facile protection and deprotection as a simple dimethyl ether.



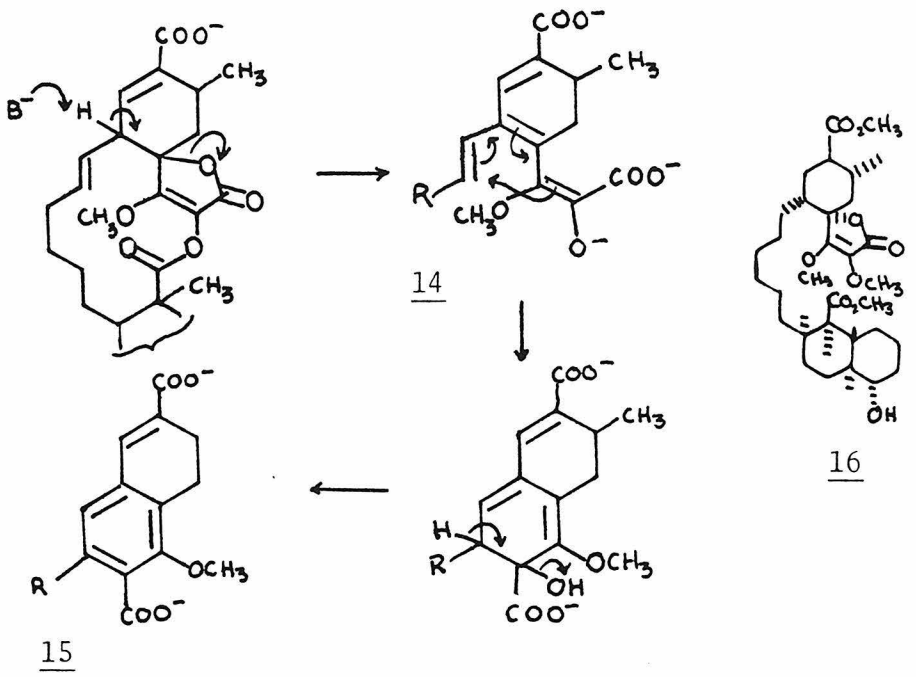
In addition, due to the basic nature of the enolate Claisen reaction, it was felt that the γ-proton to the α,β-unsaturated carboxylic ester would be susceptible to deprotonation, resulting in β-elimination and destruction of the spiro-butenolide ring. The problem of top half was now reduced to 11, where the α,β-unsaturated ester would be introduced in the final steps of the synthesis.

Scheme 3



It was later reported that in an attempt to open the lactone ring by saponification, chlorotricolide O-methyl ether does in fact undergo deprotonation of the γ-proton followed by β-elimination and rearrangement to afford dihydronapthalene derivative 15 (Scheme 4). The conditions employed for this rearrangement, however, were quite rigorous. (0.75 M NaOH under refluxing ethanol.)[33]

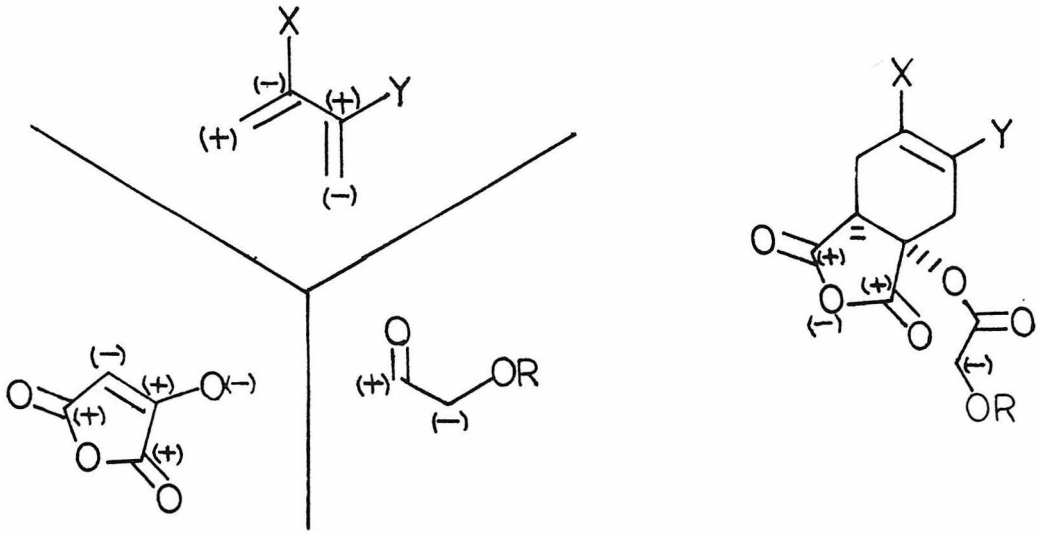
Scheme 4




It is interesting to note that hexahydro-chlorotricolide methyl ether , obtained by catalytic hydrogenation, could be saponified in good yield to give 16, after treatment with diazomethane.[33] There are, however, no reports in the literature of attempts to induce lactonization of this material.

The proposed synthesis of the top half of chlorotricolide takes advantage of the convergent Diels-Alder reaction to construct the cyclohexane ring.

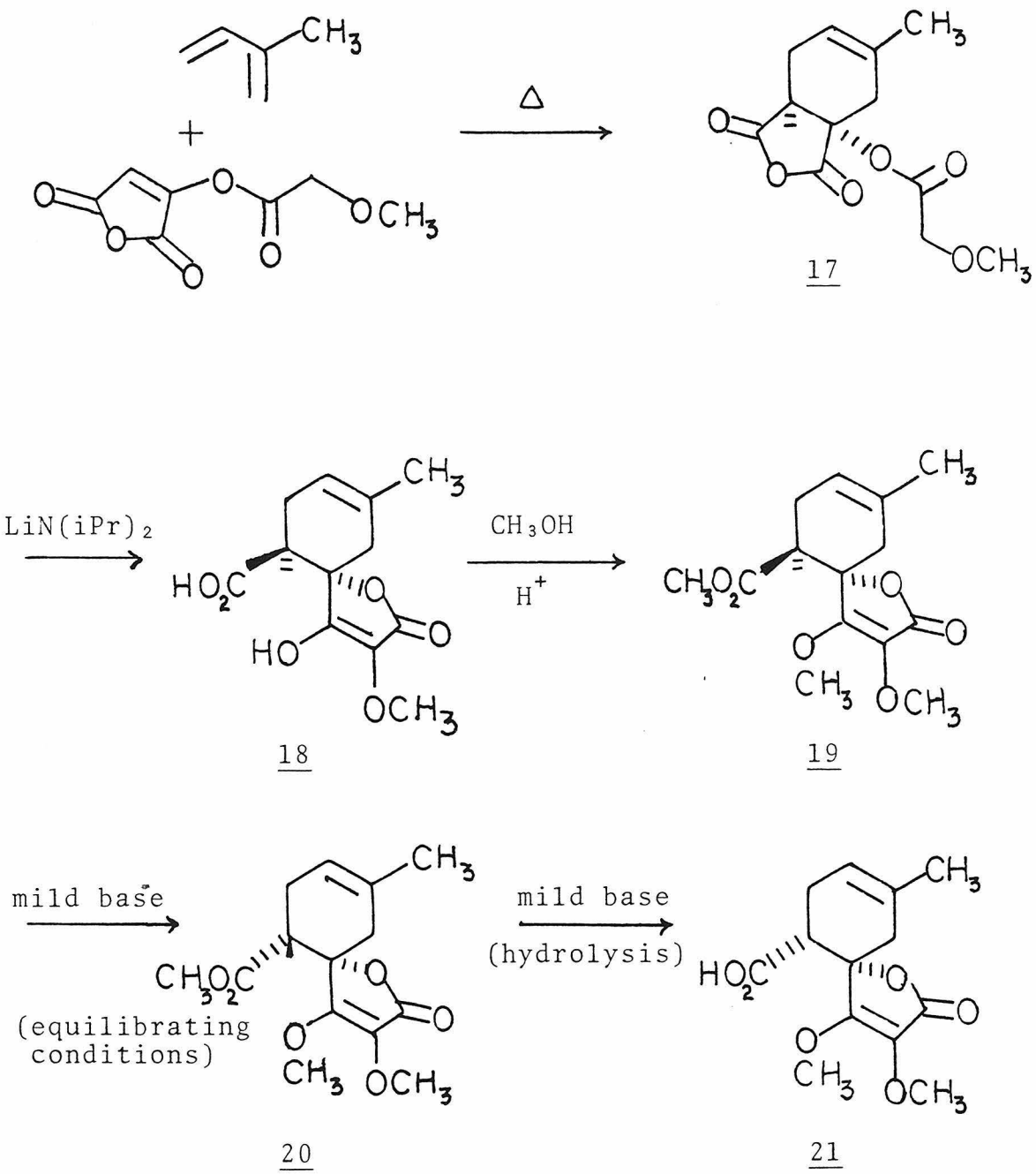
Scheme 5



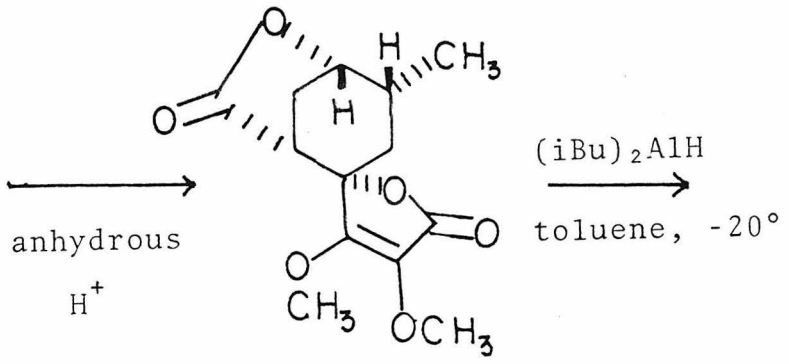
The versatility of this approach, which results from the high degree of experimental modification made possible, allows considerable structural modification of the antibiotic. The initially proposed synthetic plan is shown in Scheme 6.

Ultimately, the two halves, upon completion, would be connected and transformed into desoxychlorotricolide as outlined in Scheme 7. The bottom half is the subject of another dissertation, and will not be discussed here.[34] After enolate Claisen rearrangement, the resulting γ,δ-unsaturated acid would be reduced to an aldehyde and then

Scheme 6: Proposed Synthesis of the Top Half



Scheme 6, cont.

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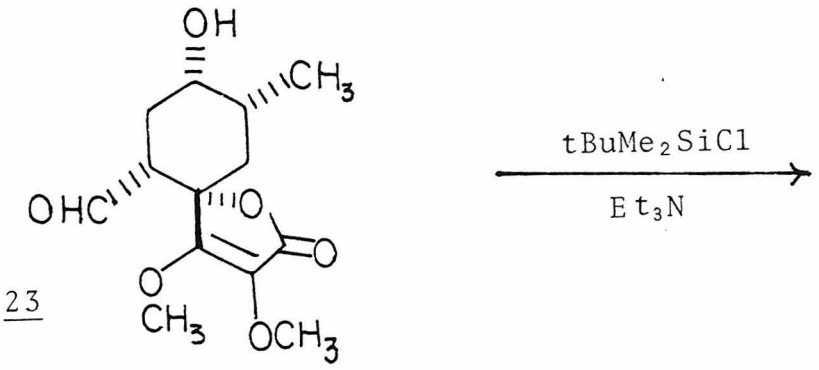


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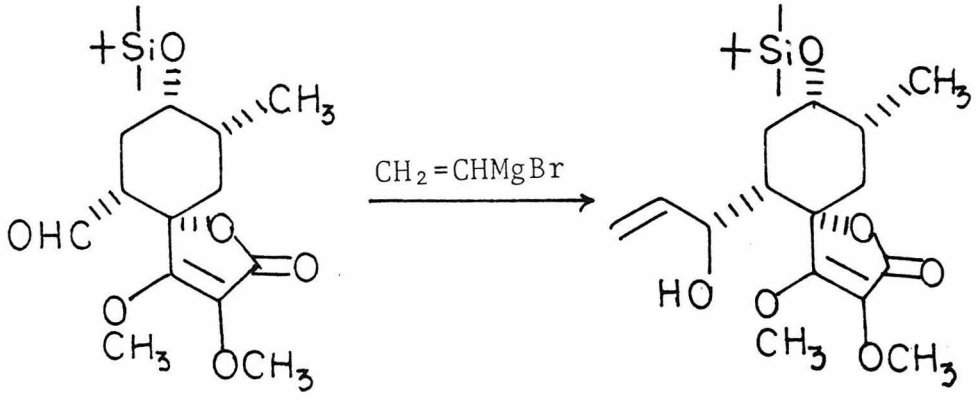


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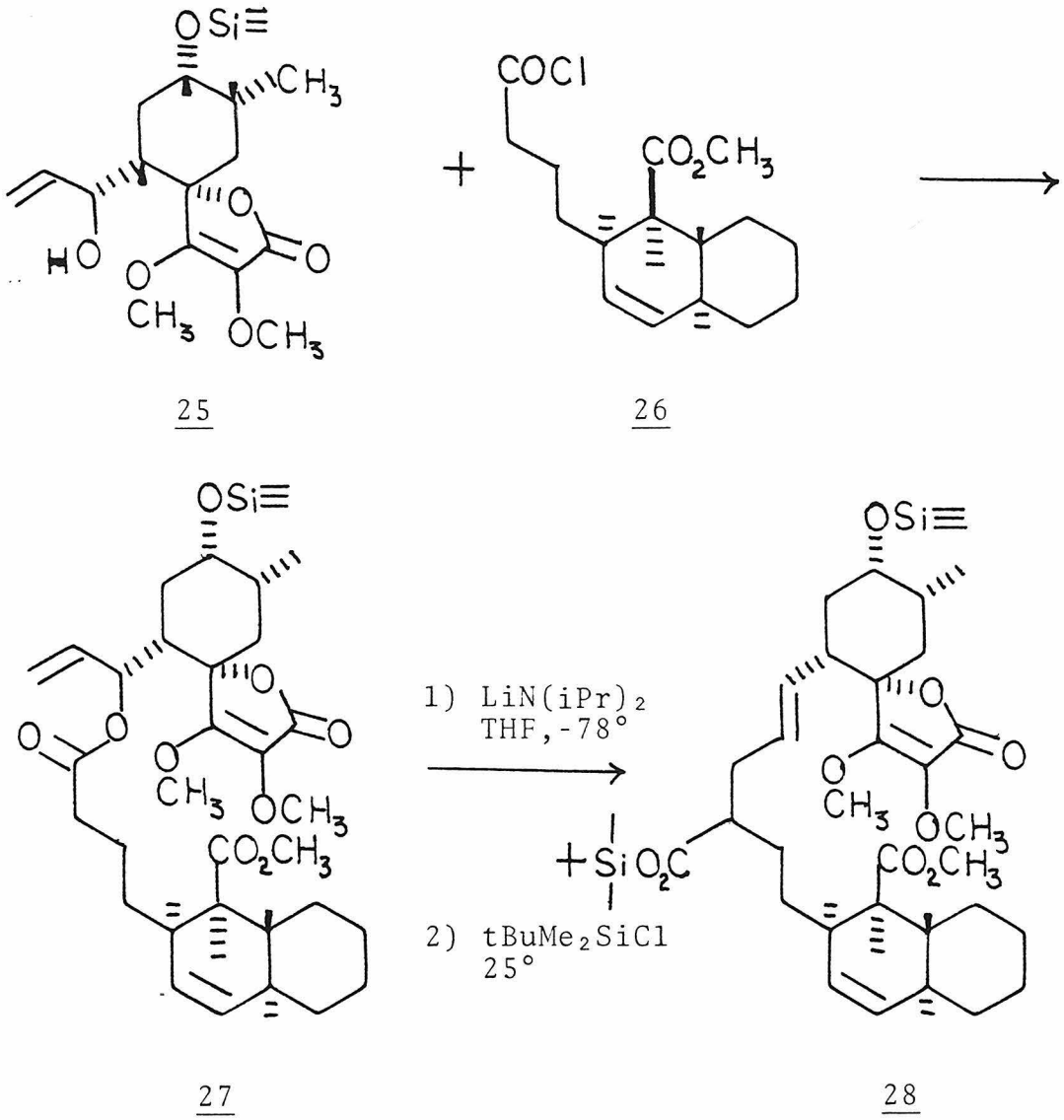
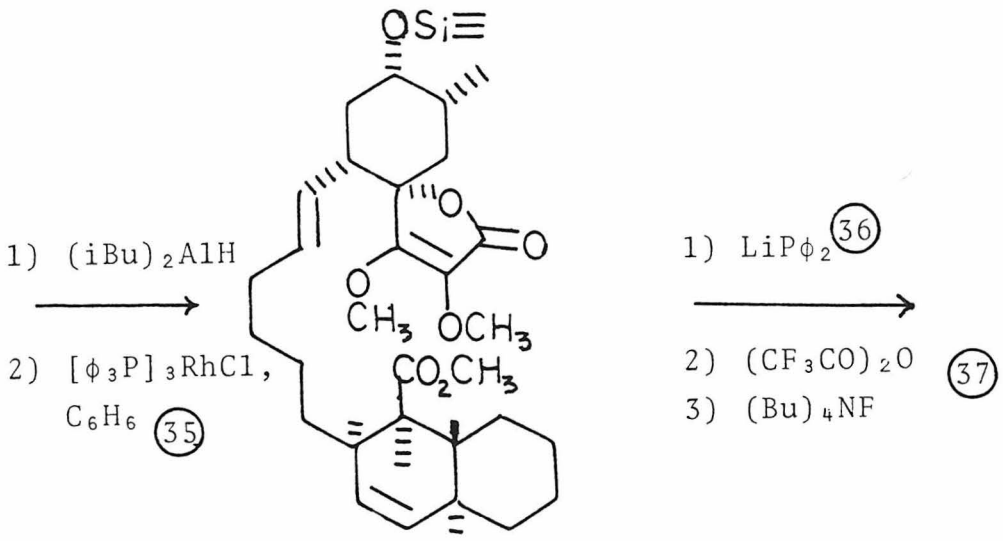
25

Scheme 7: Proposed Synthesis of Desoxychlorotricolide

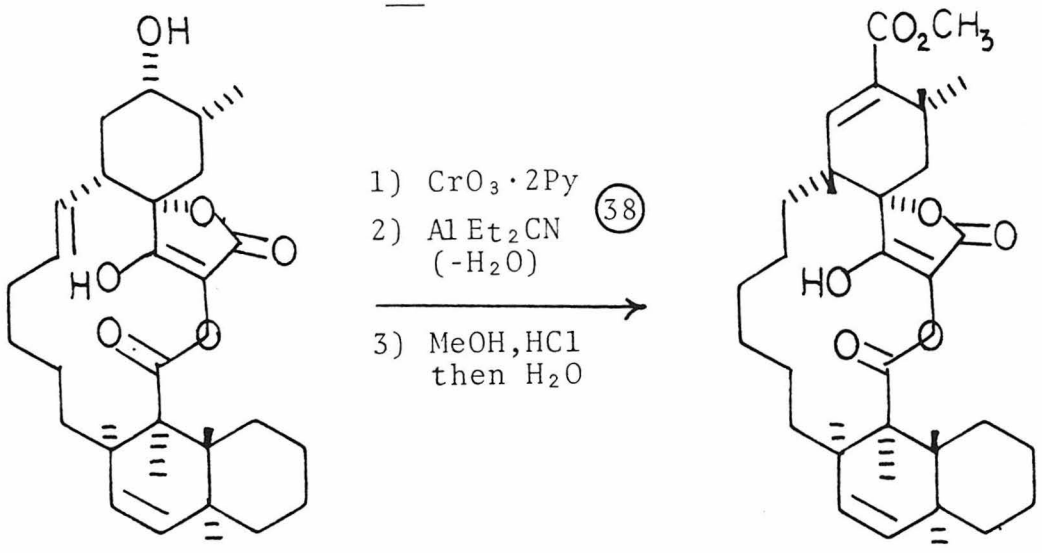



25 26

27 28


1) (iBu)2AlH
2) [φ3P]3RhCl, C6H6 (35)
1) LiPφ2 (36)
2) (CF3CO)2O (37)
3) (Bu)4NF
OSi≡
CH3 OCH3
CO2CH3

29

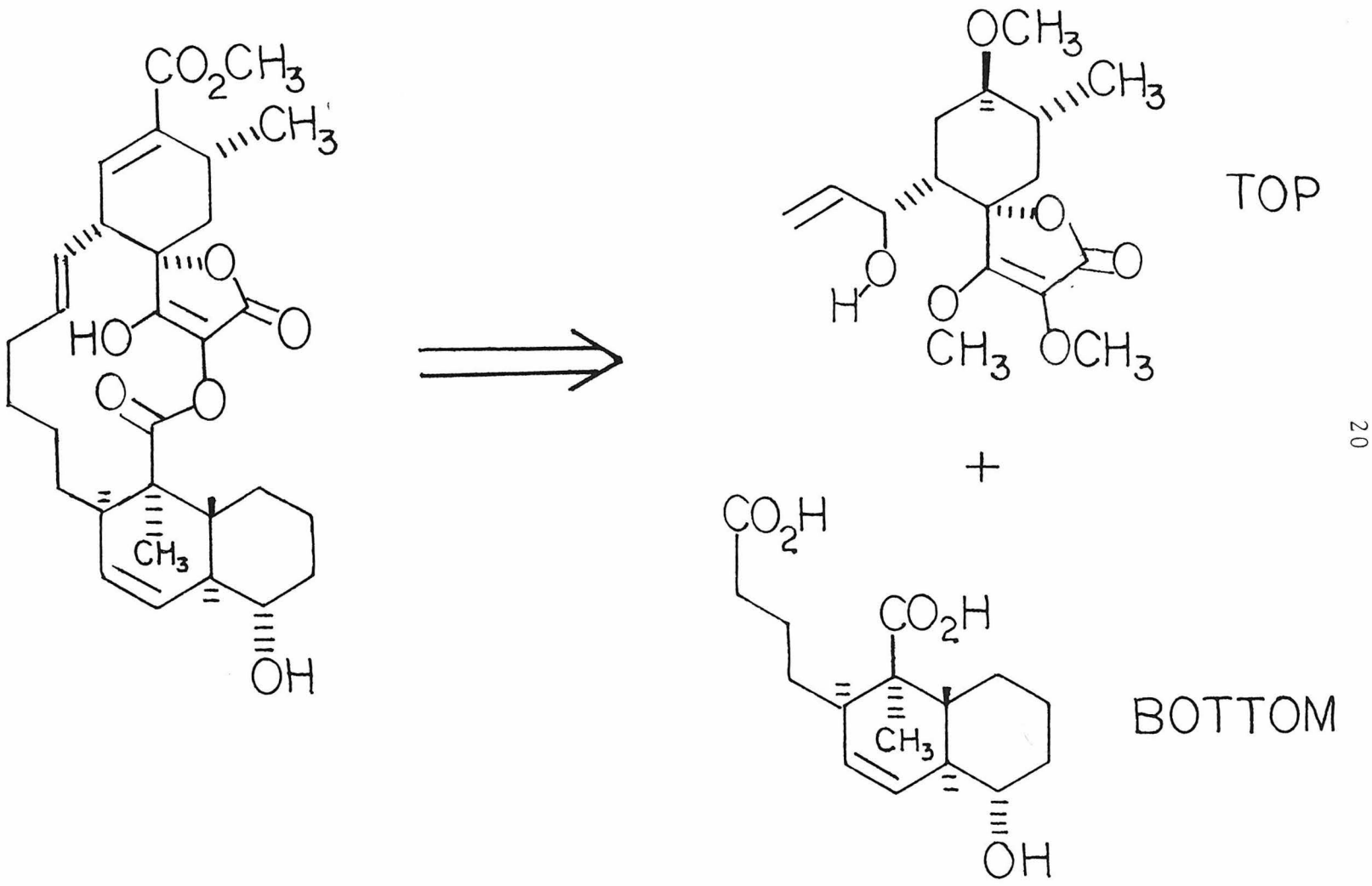

OH
1) CrO3·2Py
2) AlEt2CN (-H2O) (38)
3) MeOH,HCl then H2O
CO2CH3
HO

30

31

removed via a rhodium assisted decarbonylation process. Deprotection, and lactonization, followed by elaboration of the top half by a cyanide addition process should afford desoxychlorotricolide 31. Introduction of a suitably protected hydroxyl functionality should not interfere with any of the reactions in the sequence, and was omitted for purposes of simplifying the synthesis of the bottom half.

With these concepts in mind, we now turn to the realization of our goals.


TOP
+
BOTTOM

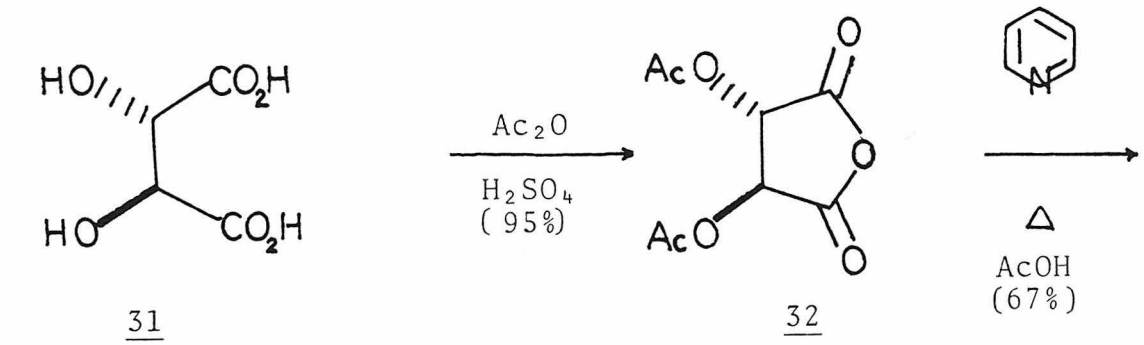
# DISCUSSION

## A. Diels-Alder Experiments

To test the feasibility of using the Diels-Alder reaction for the construction of the substituted cyclohexane ring of top half, 1,3-butadiene and acetoxymaleic anhydride were chosen as models. The most efficient preparation of acetoxymaleic anhydride was found to be the modified procedure of Wohl and Oesterlin as described by Roberts[40-41] (Chart 1). The readily available (+)-tartaric acid 31 was converted quantitatively to (+)-diacetyl tartaric anhydride 32, which upon treatment with pyridine followed by acetic acid gave the pyridine salt of hydroxymaleic anhydride 33 (67% crude yield) as an air sensitive solid. After drying *in vacuo*, the pyridine salt was treated with acetyl chloride (R = H) in benzene and gave acetoxymaleic anhydride 34a (80% recrystallized yield). Alternatively, treatment with methoxyacetyl chloride afforded the α-methoxyacetoxymaleic anhydride derivative 34b in 70% yield after filtration thru alumina.

After several attempts, it was found that heating acetoxymaleic anhydride in dry benzene containing pyrogallol as an inhibitor with 15 equivalents of 1,3-butadiene in a sealed tube (90°, 5 days) afforded the

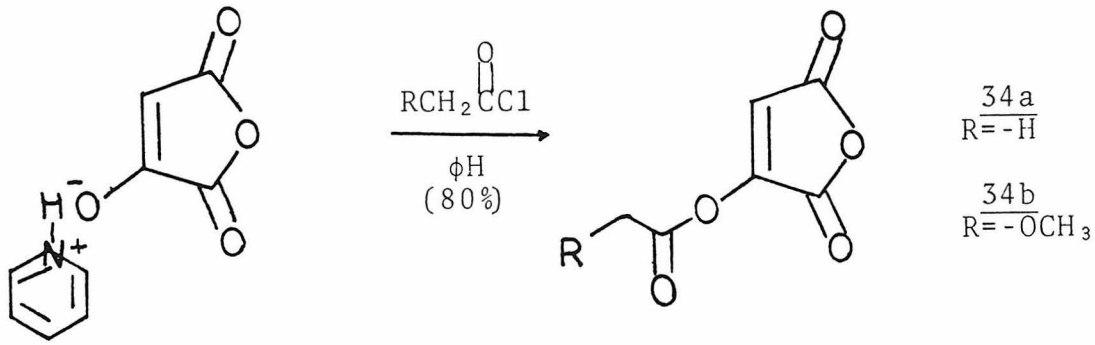
Chart 1




31

(+)-tartaric acid

32

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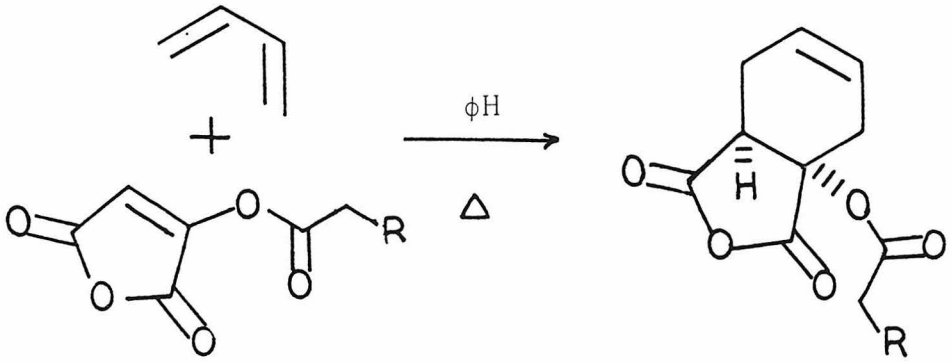



34a,b

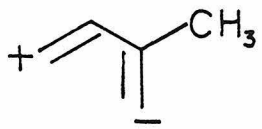
35a, 93%

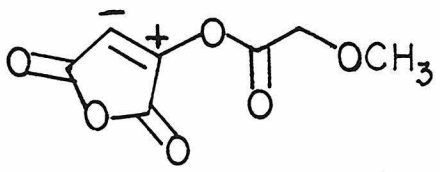
35b, 89%

desired adduct 35a in 93% chromatographed yield. The α-methoxy analogue 34b, under similar conditions, gave a crystalline adduct 35b in 89% chromatographed yield.

Having been rewarded in our initial studies, we were lured further to exploit the regioselectivity reported for the Diels-Alder reaction, so that the ring could be completely functionalized in the same step.

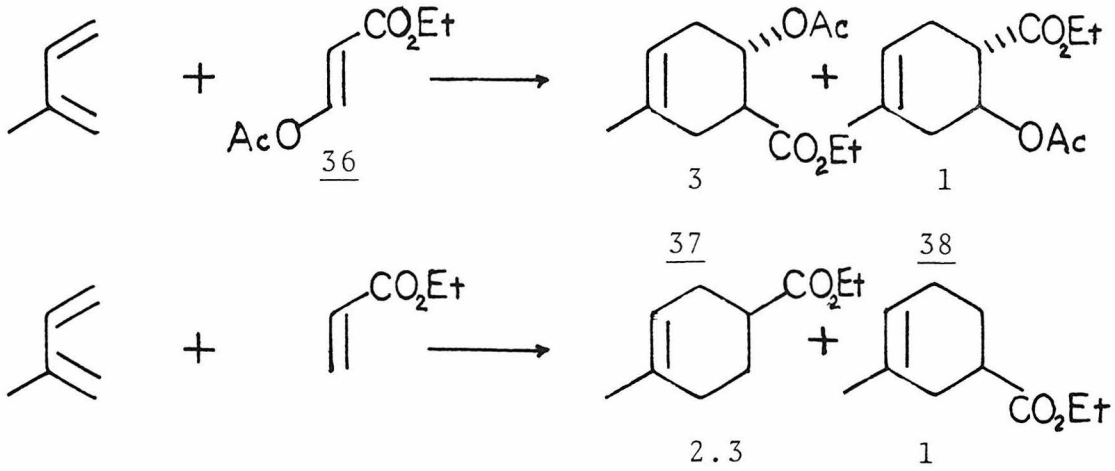
Isoprene was investigated first. Assuming the diene and dienophile would orient according to their polarization, one might predict a predominance of meta product.[42,43]



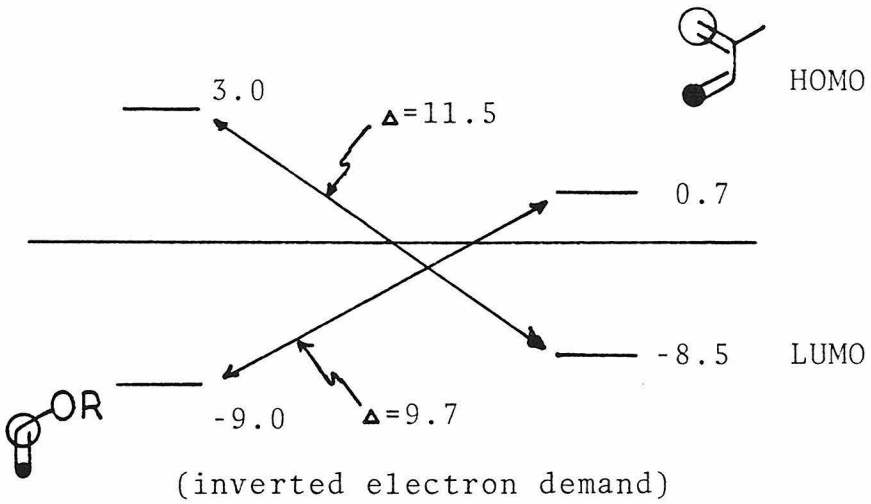

Literature examples for the selectivity of isoprene are usually dated and unreliable. Clifford[44] and Putmann[45] reported in 1946 that isoprene gave entirely

meta -adduct with chloromaleic anhydride. Onischenko[42] references the above authors, claiming they obtained mixtures, with para predominating. The classical Diels-Alder reaction of isoprene and ethyl acrylate is known to give mixtures (uncatalyzed) of para/meta ratios of 2.3/1.[46] Minato and coworkers reported a 3/1 mixture of 37:38 with ethyl β-acetoxy acrylate 36 and isoprene.[47]




An examination of the model put forth by Houk[48] and Sustmann[49] predicts meta product between isoprene and a vinyl ether. They suggest that the principal stabilization in the transition state arises from the interaction fo the HOMO-LUMO pairs of addend frontier orbitals which are closest in energy. Secondly, the model predicts that the larger terminal coefficients of

the respective addends will become bonded preferentially in the transition state. Thus, for isoprene and vinyl ether ,inverse electron demand is predicted. The LUMO of isoprene will interact with the HOMO of vinyl ether to give overlap of the larger coefficients, leading to meta adduct. Obviously, one can not simply extend this prediction to the case of acetoxymaleic anhydride without first obtaining actual values for the frontier orbitals (from the IP and EA of the components). It is entirely possible that the two carboxyl groups will change the HOMO and LUMO to such an extent that normal para addition will occur.

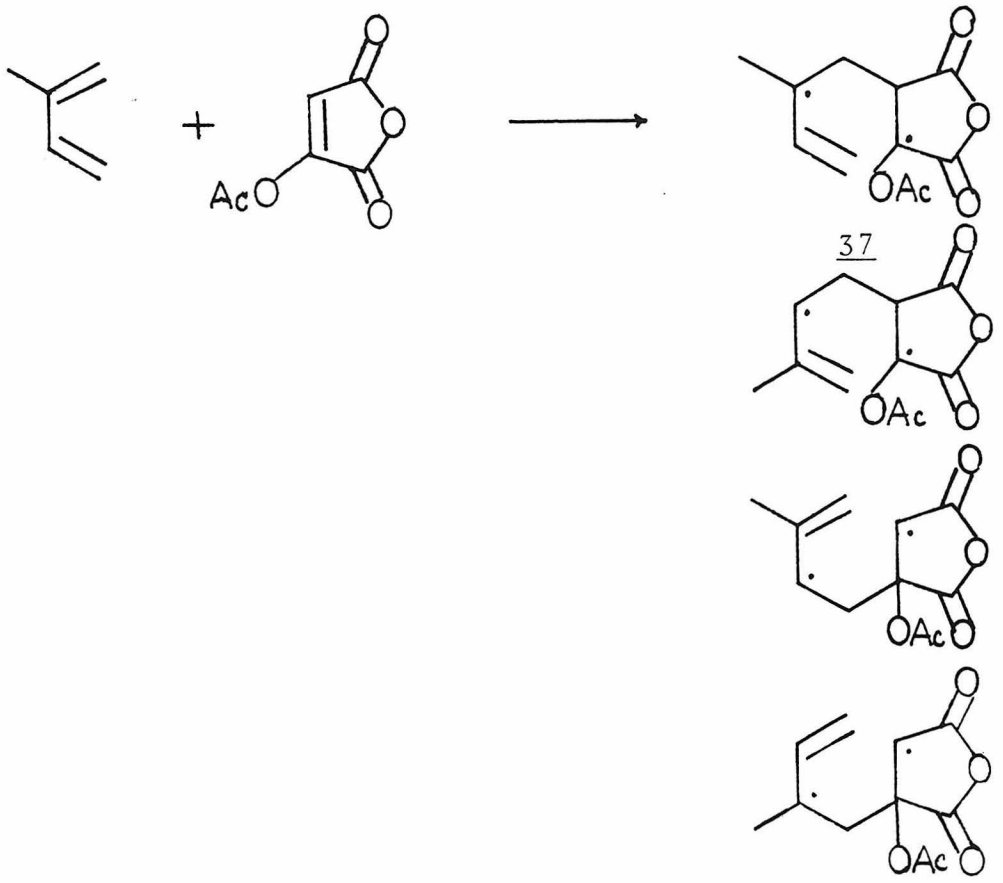



(inverted electron demand)

A radical or radicaloid type mechanism would predict para product on the basis that 37 is the most stabilized

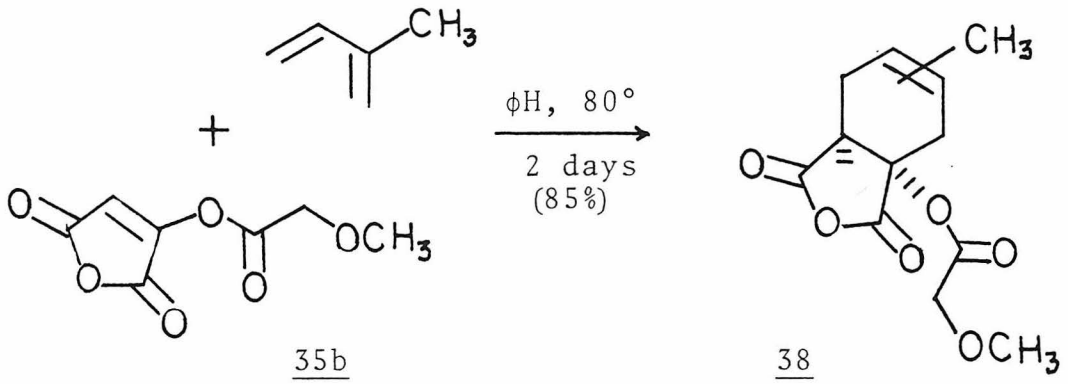
transition state (Scheme 7).[50,51] The kinetic path should be via the lowest energy transition state.

Scheme 7




37

When in fact isoprene and α-methoxyacetoxymaleic anhydride were allowed to react, a 1:1 mixture of adducts 38 was isolated in good yield.



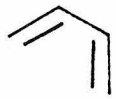
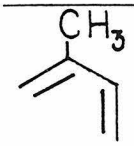
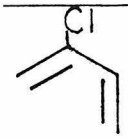
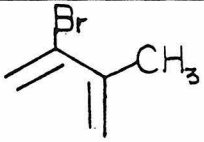
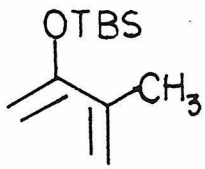

35b 38

High resolution $^1$H -NMR (220 mHz) spectra of this material revealed two vinyl signals of approximately equal intensity separated by 15 Hz, and two AB quartets due to the proton α to the anhydride carbonyl.

At this point more selective dienes were investigated. The 2-halogenated butadienes are known to be regio-selective, giving almost entirely para products.[52] The commercially available chloroprene failed to react with α-methoxyacetoxy maleic anhydride under any conditions tried (Table 1). This dienophile is known to decompose at temperatures greater than 100° to carbon suboxide.[54] Bromoprene is more reactive but is difficult to prepare (from vinyl acetylene)[55]. Iodoprene is to reactive to isolate easily. The 2-bromo-3-methyl butadiene is easier to make, and is reported to be more reactive than bromoprene towards maleic anhydride.[56]

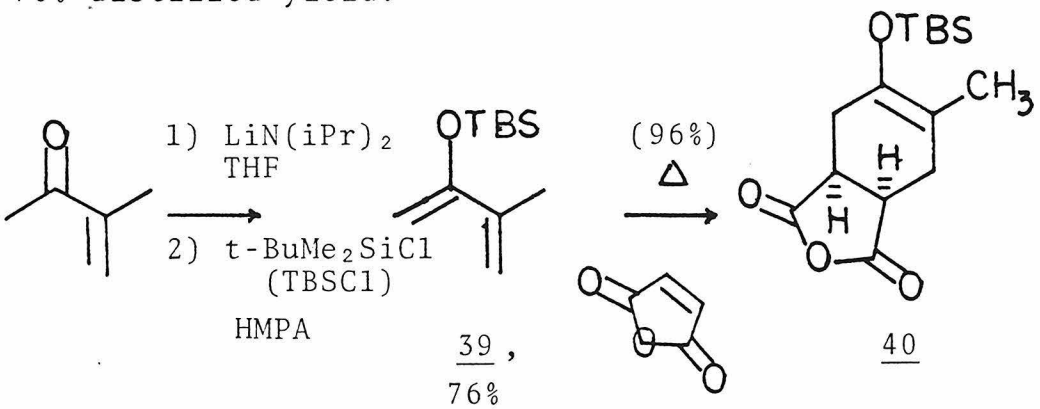
TABLE 1

Diels-Alder Reactions with
α-methoxyacetoxymaleic Anhydride

| Diene | Conditions | eq.diene dienophile | % | Products |
|---|---|---|---|---|
|  | 1) reflux ØH, 5 hrs. (bubbled butadiene through) | -- | 0 | adduct |
| | 2) sealed tube, 85°, 5 days | 15 | 89 | |
|  | 1) reflux ØH, 2 days | 15 | 0 | inseparable |
| | 2) reflux ØH, 2 days | 0.5 | 0 | mixture of |
| | 3) sealed tube, 85°, 3 days | 15 | 97 | isomers |
|  | 1) neat, 50°, 20 hrs. | 16 | 0 | starting |
| | 2) reflux ØH, 2 days | 10 | 0 | material |
| | 3) sealed tube, 80°, 3 days | 17 | 0 | recovered |
|  | 1) reflux ØH, 3 days | 3 | 0 | starting |
| | 2) sealed tube, 80°, 2 days | 15 | 0 | material recovered |
| | 3) reflux ØH, 3 days | 1 | 0 | |
|  | 1) 35°, NMR tube, neat | 4 | 0 | |
| | 2) reflux ØH, 6 days | 1 | 7 | starting |
| | 3) R.T., ØH, 3 days | 1 | 0 | material not |
| | 4) reflux ØH, 24 hrs | 4.8 | <5 | recovered. |
| | 5) reflux ØH, 6 days (pyrogallol) | 0.5 | 0 | copolymer only |
| | 6) reflux ØH, 6 days | 0.5 | 0 | |
| | 7) sealed tube, 85°, ØH,3 days | 10 | 0 | |
| | 8) 50 KBar, (W.G.Dauben) | | 67 | inseparable mixture of isomers |

Although 2-chloro-3-methyl butadiene is less reactive than the 2-bromo derivative, it is reported to give entirely para product (chloride para) with either methyl acrylate,[57] or chloromaleic anhydride.[58] Unfortunately, 2-bromo-3-methyl butadiene also refused to react with α-methoxy acetoxy maleic anhydride.

It was apparent that a more reactive, selective diene was necessary. The 2-alkoxy and acyloxy butadienes are selective, and are known to undergo adduct formation with TCNE 40 times faster than isoprene.[59-61] It was also necessary to have the resulting adduct stable to survive the cyclization, so that it could be used to put in the methyl group. Alternatively, a diene with the methyl in the 3-position would allow for a more convergent approach. One such diene would be a 2-siloxy-3-methyl butadiene (after Danishefsky and Kitihara[62,63]). Thus 2-t-butyl-dimethylsiloxy-3-methyl-butadiene 39 was prepared in 76% distilled yield.



Under normal reaction conditions, the maximum yield obtained was 7% (Table 1). When the reaction was run at high pressure (50 KBar, room temperature) by W.G.Dauben, a 67% yield of a 50:50 mixture of regioisomers was obtained.

Having ascertained the low reactivity of acetoxymaleic anhydride toward various substituted dienes, we turned our attention toward modification of the dienophile.

The corresponding α-acyloxy butenolide 41 was prepared from D-erythronolactone[64] in 83% overall yield. Unfortunately, unlike the parent butenolide which undergoes Diels-Alder reaction at 200° in xylene with butadiene, the butenolide 41 would not react with either of two dienes (1,3 butadiene or the 2-siloxydiene 39).

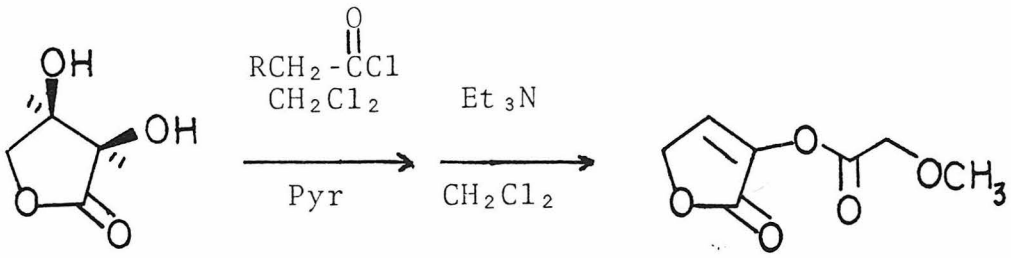
The α,β-unsaturated ester 42, prepared in an analogous fashion in 97% overall yield from 2,4-O-ethylidene-D-erythronic acid ,[64] also failed to undergo the Diels-Alder reaction with 1,3-butadiene (Chart 2).

Our initial enthusiasm with the Diels-Alder reaction was rapidly waning, so with the butadiene adducts 35a and 35b in hand, we proceeded to the crucial cyclization experiments, with the hope that the double bond could be used to introduce the methyl group later in the sequence.

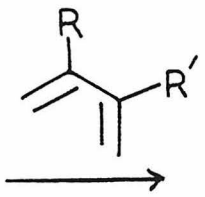
## B. Cyclization and Epimerization Studies

Cyclization of the acetoxy anhydride 35a with two

Chart 2




41, 83% overall

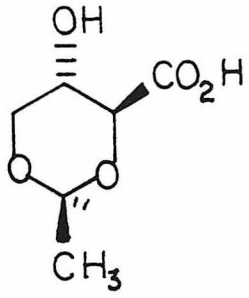


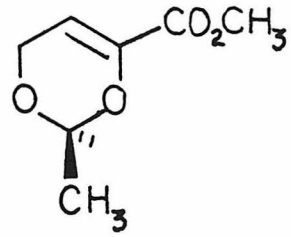
R,R´ = H.H

= -$CH_3$,-$OSi(tBu)(CH_3)_2$

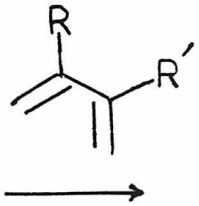
Δ

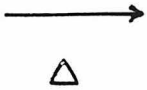
no reaction



42, 97% overall





Δ

no reaction

equivalents lithium diisopropylamide in THF at -78°, followed by methylation of the resulting dianion with methyl fluorosulfonate (2 equivalents, 0°, HMPA) afforded the spiro compound 43 in 70% overall chromatographed yield (Chart 3).

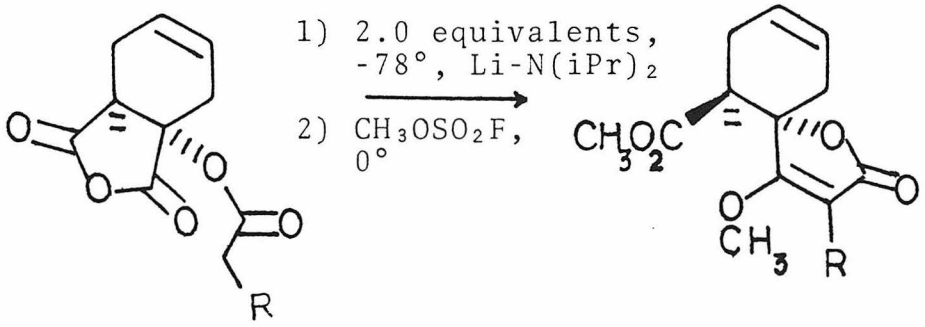
Epimerization proceeded smoothly with 0.15 equivalents of sodium methoxide in dry methanol (5 days, reflux) affording an 80:20 mixture of pseudo-equatorial and pseudo-axial epimers, 44 and 43 in 98% yield. In one experiment, a sample of the pseudo-axial epimer 43 was subjected to the epimerization conditions (8 days), and gave an 87:13 mixture( by $^{1}$H -NMR). A sample of the pseudo-equatorial epimer, when subjected to equilibrating conditions (4 days),gave the same 87:13 mixture, thus establishing the equilibrium mixture at 65° (Keq = 6.7, $\Delta G°$ = -1.13 kcal).

Application of these conditions to the α-methoxy-acetoxy anhydride 35b, afforded spiro-butenolide 45 in 65% overall chromatographed yield and the epimerized spiro-butenolide 46 in 97% yield (based on recovered starting material).

## C. Reduction of the Ester

Having proceeded smoothly thus far, we anticipated little difficulty with the ester to aldehyde conversion. Unfortunately, this transformation was not achieved as easily as we had hoped.

Chart 3

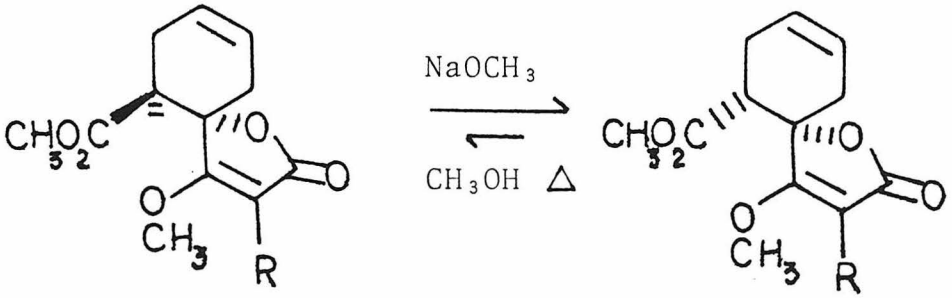



35a, R = H

35b, R = -$OCH_3$

43, R = H, 70%

45, R = -$OCH_3$, 65%




| | | | | |
|---|---|---|---|---|
| R = H | (13) | 98% | (87) | 44 |
| R = -$OCH_3$ | (20) | 98% | (80) | 46 |

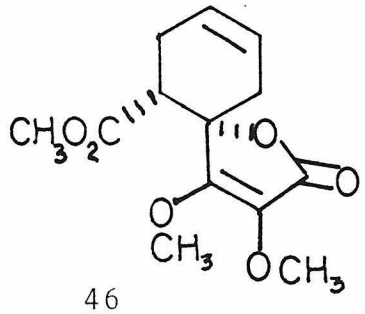
Initially a direct ester to aldehyde conversion was attempted (Chart 4). Following the procedure of Zakhavkin and Khorlina ,[65] the ester 46 was treated with 1.5 equivalents of diisobutyl aluminum hydride (DIBAL) in toluene at-78°. Only starting material could be isolated under these conditions. Use of three or more equivalents of DIBAL gave a complex mixture of products, with loss of all carbonyls (IR). The α-methoxy tetronic acid methyl ether was apparently highly susceptible to reduction, possibly via a mechanism involving complexation by the α-methoxy substituent.[66]

As early as 1952, Petuely and Bauer had shown that ascorbic acid could not be reduced by lithium aluminum hydride in refluxing ether for 15 hours.[67] It was thought that if selective deprotection of the tetronic acid could be achieved, a selective reduction could then be performed.

Treatment of the ester 46 with lithium n-propyl mercaptide (1.1 equivalents, HMPA, room temperature),as described by Bartlett and Johnson,[68]afforded ester acid 47 in 79% crude yield. This material could be reduced with DIBAL and NaH in ether to afford the alcohol 48 , after treatment with diazomethane, in 35% overall yield.

Unsatisfied with this low yield, we examined the literature [69] and found a report that esters could be reduced to alcohols with lithium borohydride in good yields. On the expectation that some selectivity might occur,

Chart 4



46

$(i\text{-}Bu)_2AlH$

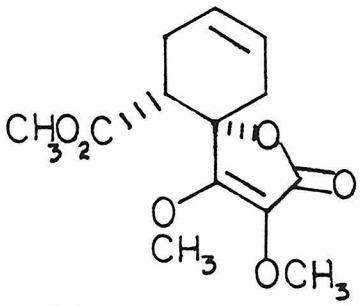
1 equivalent

starting material

$(i\text{-}Bu)_2AlH$

2-10 equivalents

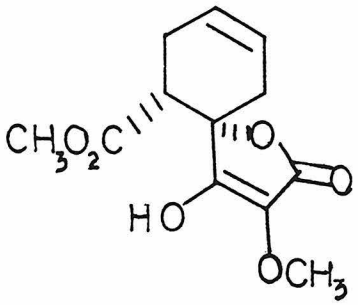
loss of all carbonyls



46

1.1 equivalent
$Li\text{-}S(n\text{-}C_3H_7)$

HMPA

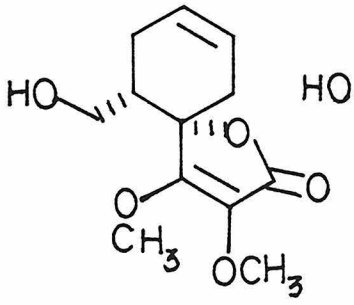


47, 79%

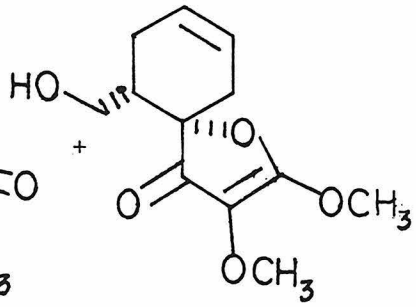
1) $NaH$, $(i\text{-}Bu)_2AlH$
$Et_2O$

2) $H_3O^+$

3) $CH_2N_2$



48, 30%



4%

the ester-butenolide 46 was treated with lithium borohydride in tetrahydrofuran (14 equivalents, room temperature) . We were rewarded when the alcohol 48 was isolated in 52% yield after chromatography, along with 43% of starting material (91% based on recovered starting material) (Chart 5).

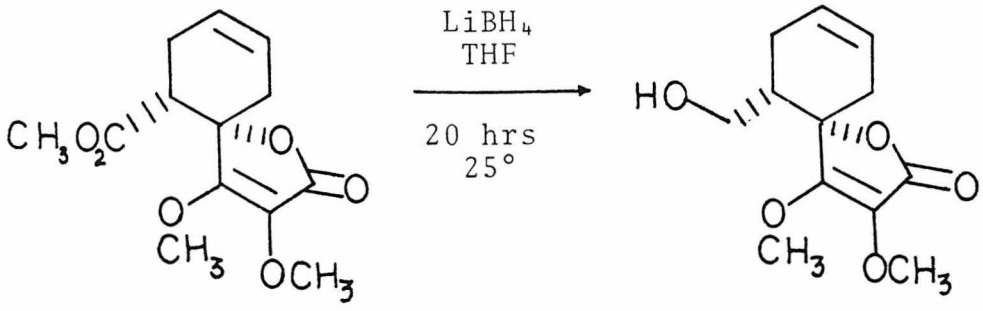
With this dramatic discovery, some other complex reducing agents were later examined with the hope of increasing the rate of reaction. While aluminum reagents lacked selectivity, it was found that lithium triethyl borohydride, reported by Brown and Krishnamurthy to be 10,000 times more nucleophilic than lithium borohydride,[71] afforded the alcohol 48 in quantitative chromatographed yield (30 min, 0° C, using three equivalents hydride). This does not appear to be general , since treatment of methyl cyclohexane carboxylate with three equivalents of lithium triethyl borohydride afforded only 8% of alcohol and 92% of recovered starting material (Chart 5).

Perplexed by the chemistry of the tetronic acid methyl ether, we decided to synthesize a simpler model system and determine its reactivity with various reagents.

## D. Chemistry of the Tetronic Acid Moiety: Model Studies

Treatment of methyl α-acetoxy isobutyrate with lithium diisopropylamide (2 equivalents) at -78°, followed

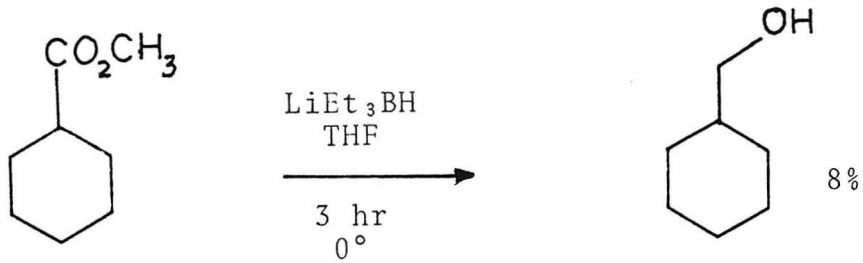
Chart 5




46

48, 92%


48, 100%



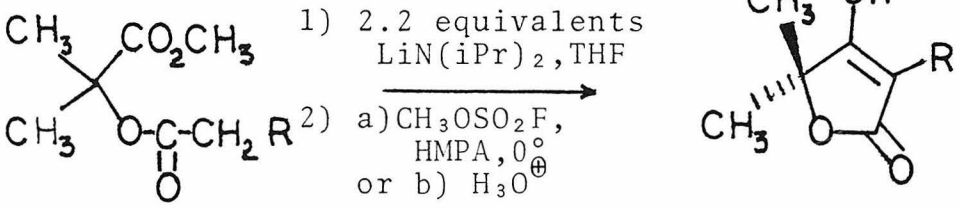

8%

by quenching at 0° with aqueous acid afforded the tetronic acid 49a in 95% yield, an improvement over the earlier reported yield of 64% (using diisopropyl magnesium bromide in ether). By quenching with methyl fluorosulfonate in HMPA at 0° , the methyl ether 49b was isolated directly in 90% overall yield (Chart 6). Application of these conditions to α-methoxy ester 50 afforded the tetronic acids 51a and 51b in 95% overall yields.

An investigation into the chemistry of these tetronic acid derivatives is summarized in Chart 6. While the parent γ,γ-dimethyl tetronic acid methyl ether 49b was found to be quite resistant to oxidation or reduction, the α-methoxy substituted analog was susceptible to both. Interestingly, the α-methoxy derivative 51b was more resistant to oxidation in ether than dichloromethane. Perhaps oxygenated solvents compete with the α-methoxy ether oxygen with respect to hydrogen bonding with the peracid, but results with allylic ethers[72] would tend to cast doubt on such an explanation.

The dimethyl ether 51b was then used as a model to test conditions for deprotection. While it was found that selective demethylation of the β-methoxy was quite facile, no conditions were found which gave the totally deprotected α-hydroxy tetronic acid in one step. It was found, however, that acetylation of the 3-position, followed by treatment with boron tribromide in dichloromethane at -78°, gave cleanly the α-hydroxy tetronic acid 53 (Chart 6).

Chart 6




49a, R′=-H, R=-H, 95%

49b, R′=-CH3, R=-H, 90%

51a, R′=-H, R=-OCH3, 95%

51b, R′=-CH3, R=-OCH3, 95%

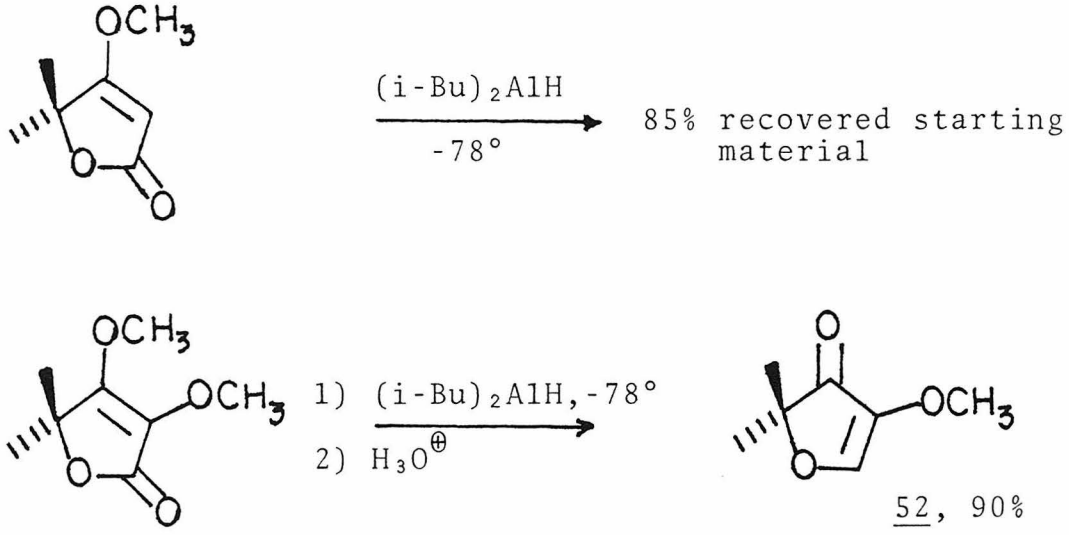
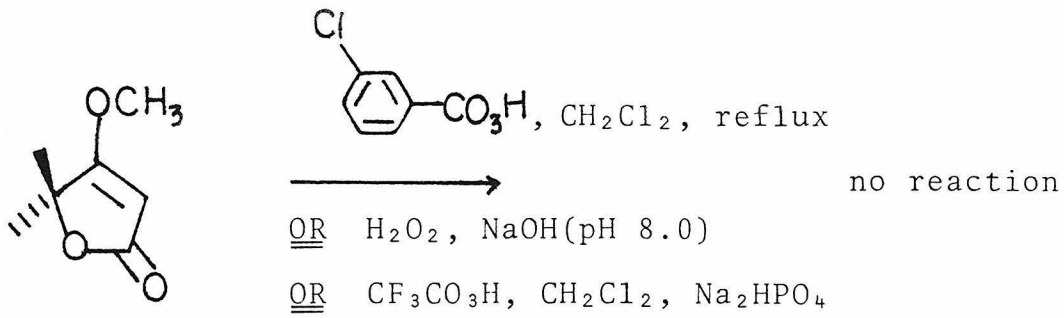
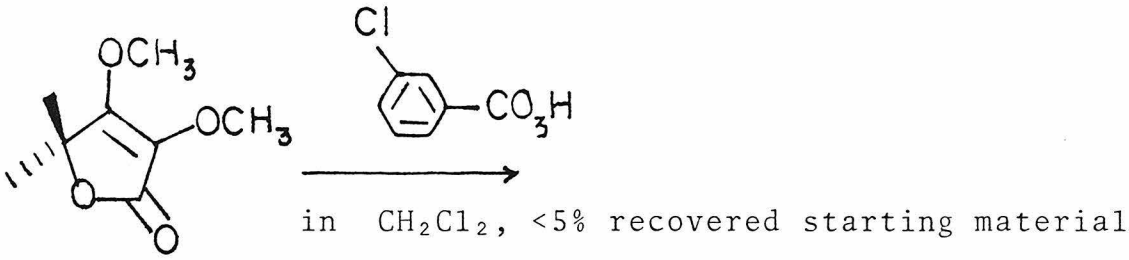
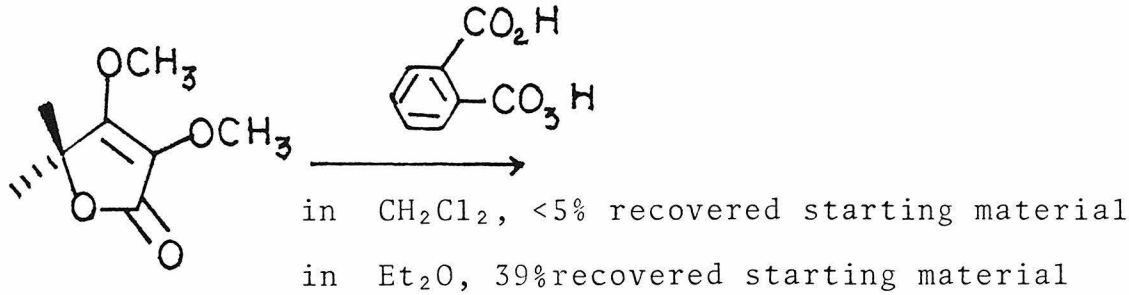


Chart 6, cont.


Cl
CO3H, CH2Cl2, reflux
no reaction
OR H2O2, NaOH(pH 8.0)
OR CF3CO3H, CH2Cl2, Na2HPO4


Cl
CO3H
in CH2Cl2, <5% recovered starting material
in Et2O, >95% recovered starting material


CO2H
CO3H
in CH2Cl2, <5% recovered starting material
in Et2O, 39%recovered starting material

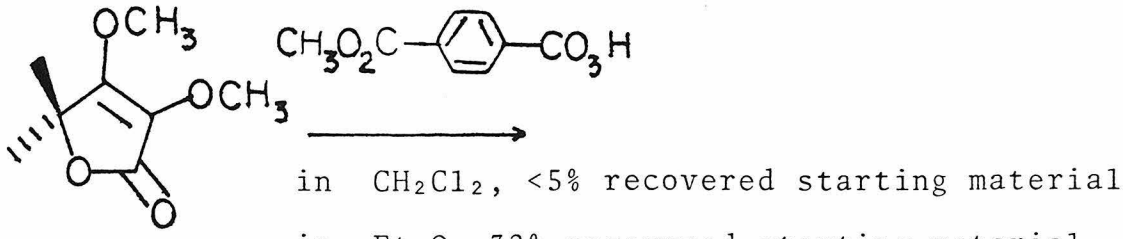
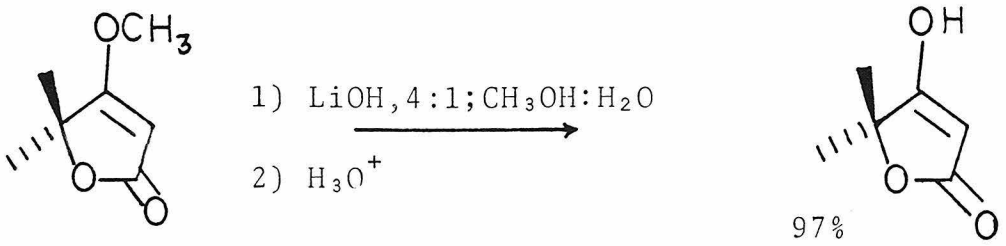
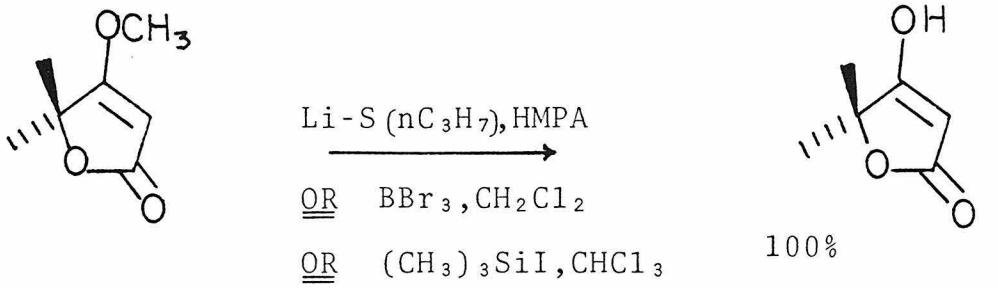
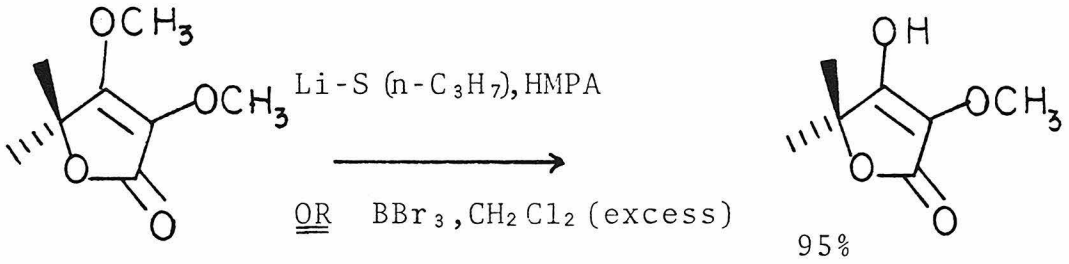
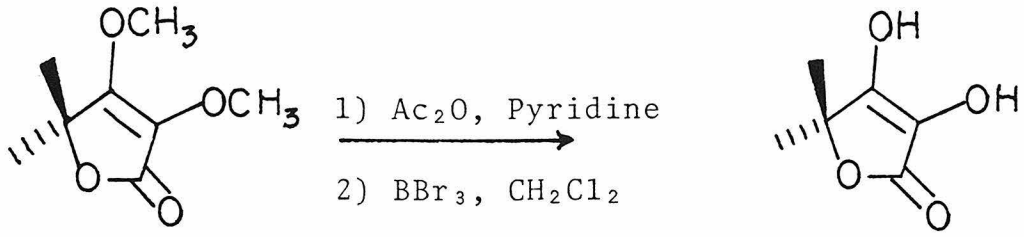

CH3O2C
CO3H
in CH2Cl2, <5% recovered starting material
in Et2O, 32% recovered starting material

Chart 6, cont.



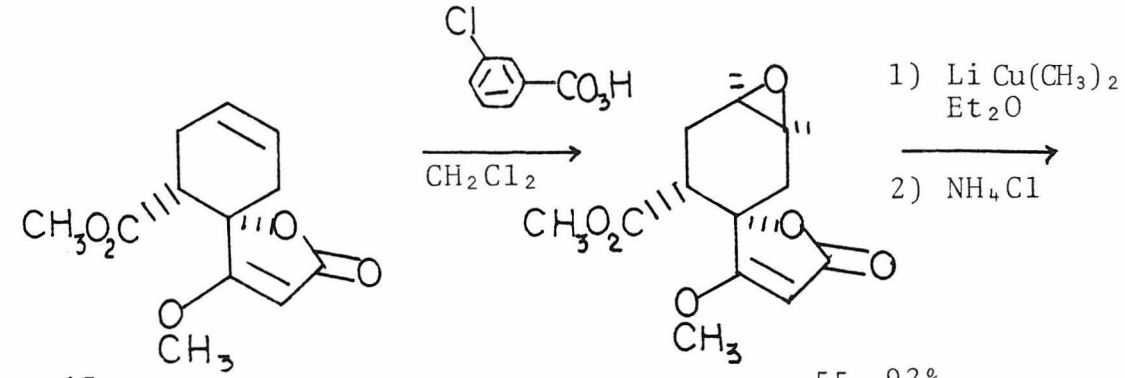

53. 95%

E. Solution to Functionalization of the Ring via the Double Band.

Trans diaxial ring opening of epoxides with lithium dimethyl cuprate is well documented in the literature.[74-80] It was hoped that the resistance of esters to cuprate reagents would allow selective attack at an epoxide.[75,80] To test this possibility, the ester 46 was epoxidized with m-chloro perbenzoic acid in $CH_2Cl_2$ to afford the β-epoxide 54 in 41% yield, accompanied by about 7% of the α-isomer and 31% over oxidation products (Chart 7). The $H^1$-NMR of the predominant crystalline β-isomer was consistent with a spectrum calculated from coupling constants derived from the Karplus equation,[81] using a Nicolet NMRCAL program for 6 spins, and overlapping data (Figure 2).

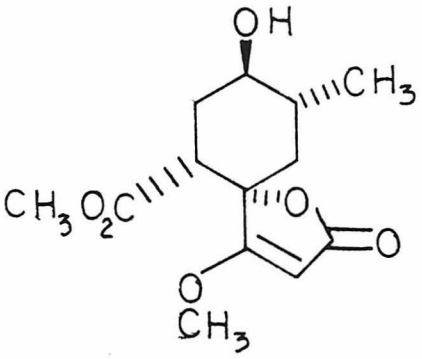
Epoxidations with most peracids are sensitive to polar influences, and in the absence of hydroxyl groups, anti-attack is favored in non-polar solvents.[72] In particular, Cerefice and Fields recently studied the effect of -OAc and $-CO_2CH_3$ on the stereospecificity of epoxidations, and found that in general an anti-directing effect was observed.[82] The rigidity of the spiro-butenolide ester 46, together with the pseudo-axial orientation of the ring oxygen, shield the α-face of the molecule, resulting in a predominance of β-epoxidation.

Chart 7

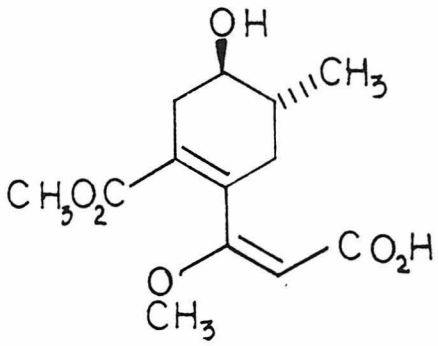



43

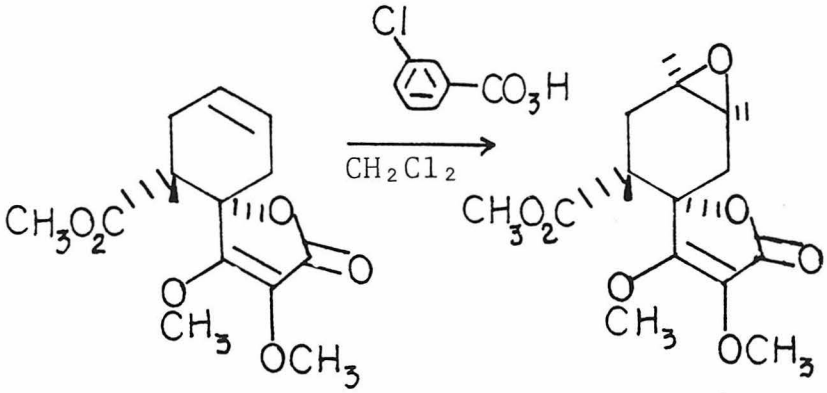
55 , 92%




56 , 12%




57 , 42%

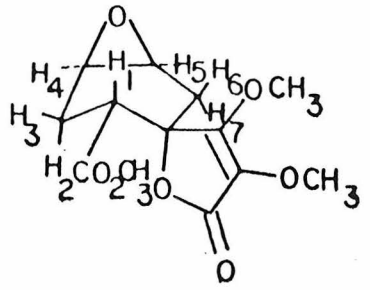


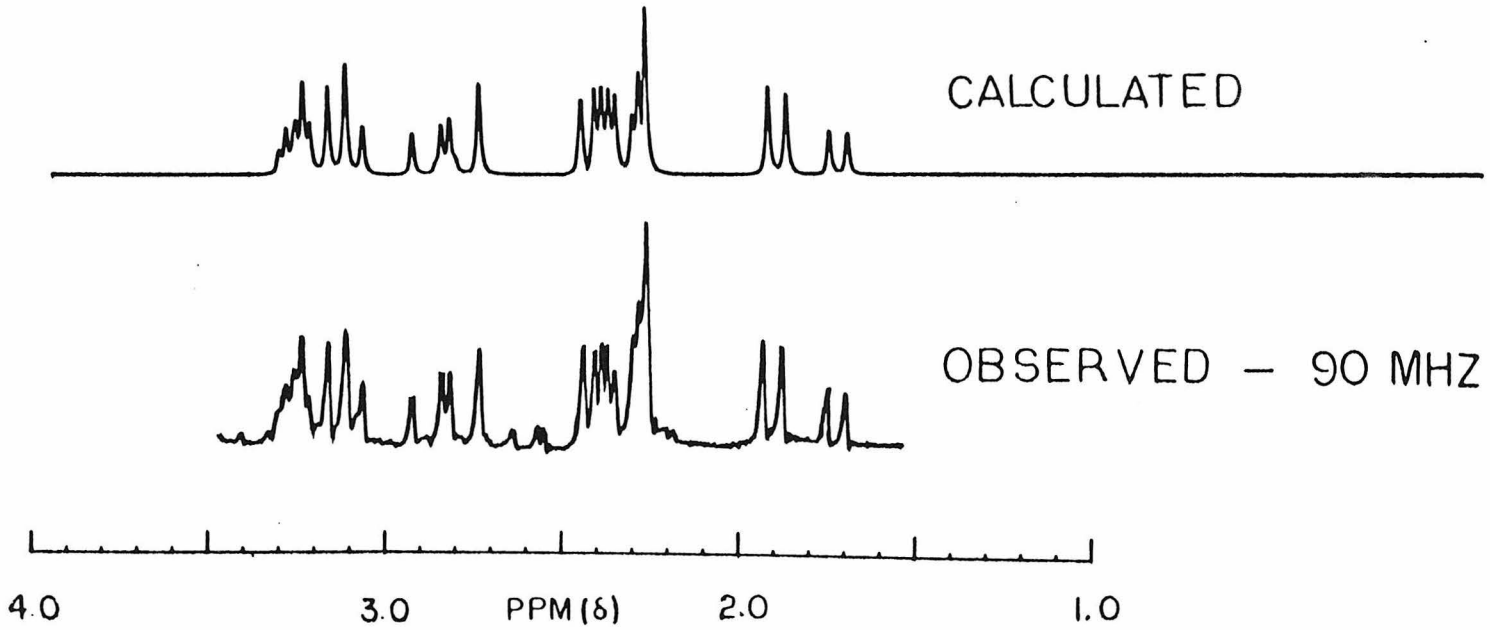

54, 41%

(31% over oxidation products)

Figure 2

| (x,y) | J(x,y) | (x) | v(x) |
|---|---|---|---|
| 1,2 | 7.5 Hz | 1 | 258.70 Hz |
| 1,3 | 9.6 | 2 | 216.60 |
| 2,3 | 0.0 | 3 | 217.25 |
| 2,4 | 1.8 | 4 | 297.25 |
| 3,4 | 1.8 | 5 | 285.50 |
| 4,5 | 4.2 | 6 | 170.00 |
| 5,6 | 4.6 | 7 | 216.30 |
| 5,7 | 0.0 | | |
| 6,7 | 15.5 | | |



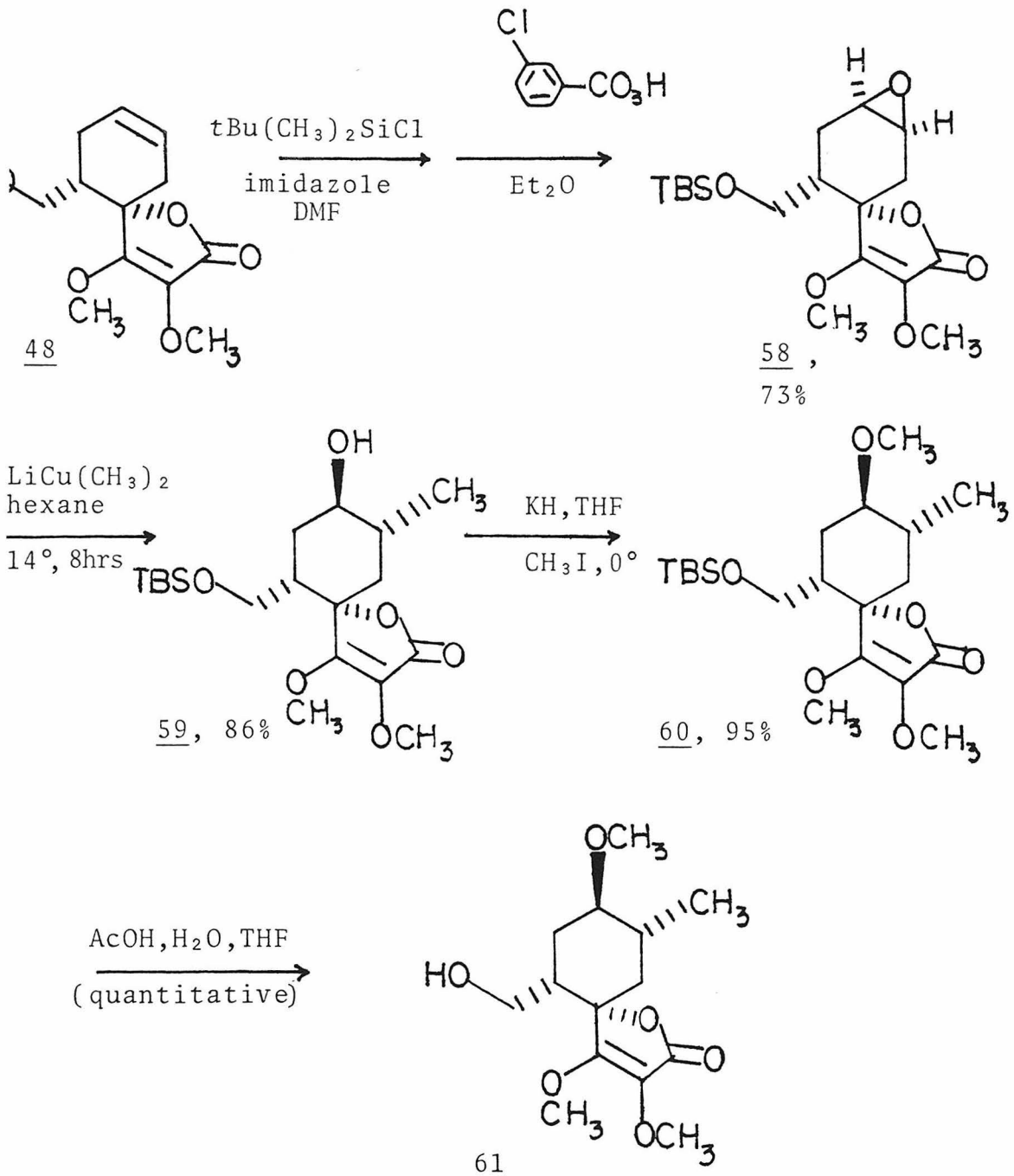



When the epoxy ester 55, used as a model, was treated with lithium dimethyl cuprate under conditions employed previously (0° , ether)[73], the desired alcohol 56 was formed in 12% yield, together with elimination product 57 (42%), which arises from base catalyzed deprotonation of the ester group. Conjugate addition to the α,β- unsaturated lactone, a process known to occur via electron transfer, is not expected due to the high reduction potential ($E_{redn}$ ~2.6 eV) of the β-methoxy butenolide system relative to the reduction potential of lithium dimethyl cuprate ($E_{ox}$ ~1.9 V and $E_{red}$-$E_{ox}$ should be greater than -0.4 V).[83]

To avoid the base catalyzed elimination process, the epoxide opening was delayed until after the reduction of the ester 46 to alcohol 48. Protection of alcohol 48 as the t-butyl-dimethylsilyl ether using imidazole and DMF,[84] followed by epoxidation with m-chloroperbenzoic acid in ether, gave the desired β-epoxide 58 in 73% overall chromatographed yield (Chart 8). The $^1$H -NMR of 58, while more complicated, contained 4-multiplets identical with the ester epoxide 54 (magnetic environment unchanged for 4 protons). Treatment of epoxide 58 with 5 equivalents of lithium dimethyl cuprate in hexane ( 14° for 8 hrs ) gave the desired alcohol 59 in 86% chromatographed yield.

The alcohol 59 was protected as the methyl ether 60 using potassium hydride in tetrahydrofuran with methyl

Chart 8

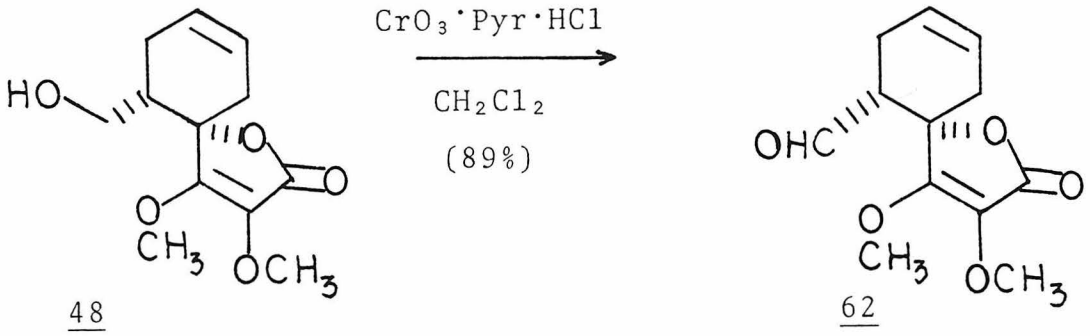

Cl
CO3H
tBu(CH3)2SiCl
imidazole
DMF
Et2O
H
O
H
TBSO
O
O
CH3
OCH3
48
58, 73%
LiCu(CH3)2
hexane
14°, 8hrs
OH
CH3
TBSO
O
O
CH3
OCH3
59, 86%
KH, THF
CH3I, 0°
OCH3
CH3
TBSO
60, 95%
AcOH, H2O, THF
(quantitative)
HO
61

iodide at 0° in 95% yield. Deprotection of the silyl ether using acetic acid and water in tetrahydrofuran[84] gave the desired alcohol 61 in nearly quantitative yield. Having solved the problem of functionalizing the ring, all that remained to complete the synthesis of the top half was elaboration of the side chain to the allylic alcohol.

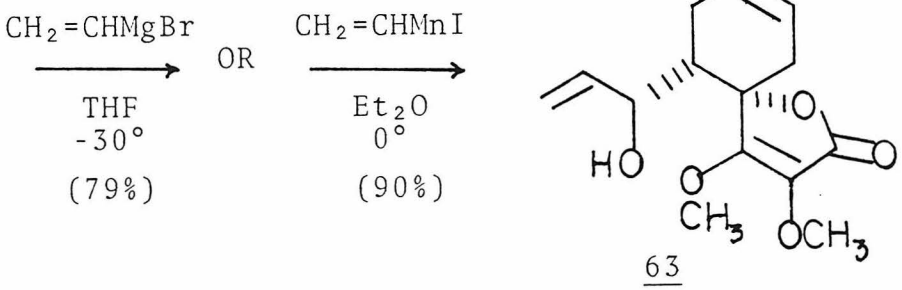
## F. Completion of the Top Half

After the difficulty encountered in the simple ester to alcohol conversion, it was only after considerable contemplation that one doubting Thompson could bring himself to attempt an oxidation of the alcohol 48 to aldehyde 62, especially considering the precarious β-position of the tetronic ring oxygen. With Grignard reagent close at hand, the alcohol 48 was treated with pyridinium chlorochromate[85] ( $CH_2Cl_2$, room temperature, 2 hrs ) and after filtration through silica gel, the aldehyde 61 was isolated in 89% yield. Treatment with vinyl-magnesium bromide in tetrahydrofuran (1.1 equivalent, -30°) afforded the desired allylic alcohol in 79% chromatographed yield. It was later found that vinylmanganese iodide, prepared as recently described by Cahiez and Normant was more selective, affording the desired allylic alcohol 63 in 90% yield (diethyl ether, 0°, 1 hr) (Chart 9).

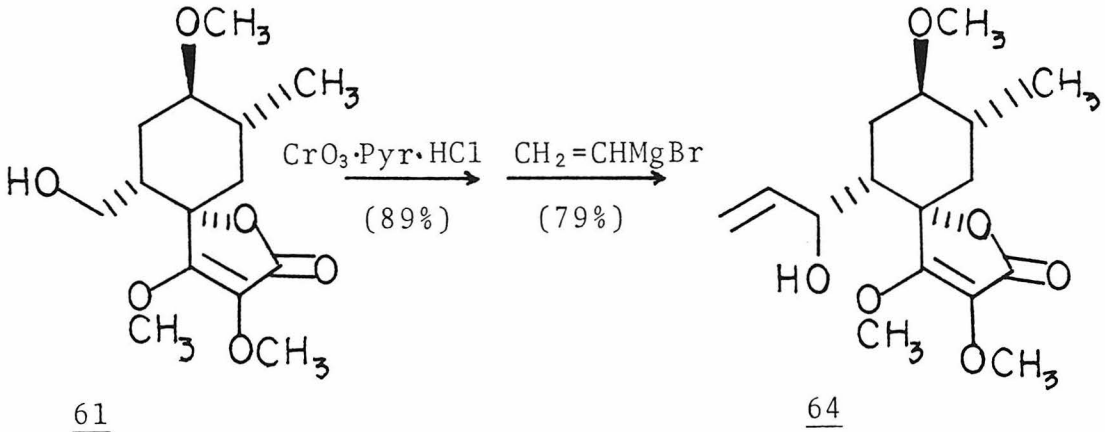
Chart 9




48 62




63




61 64

Chart 10: Synthesis of the Top Half

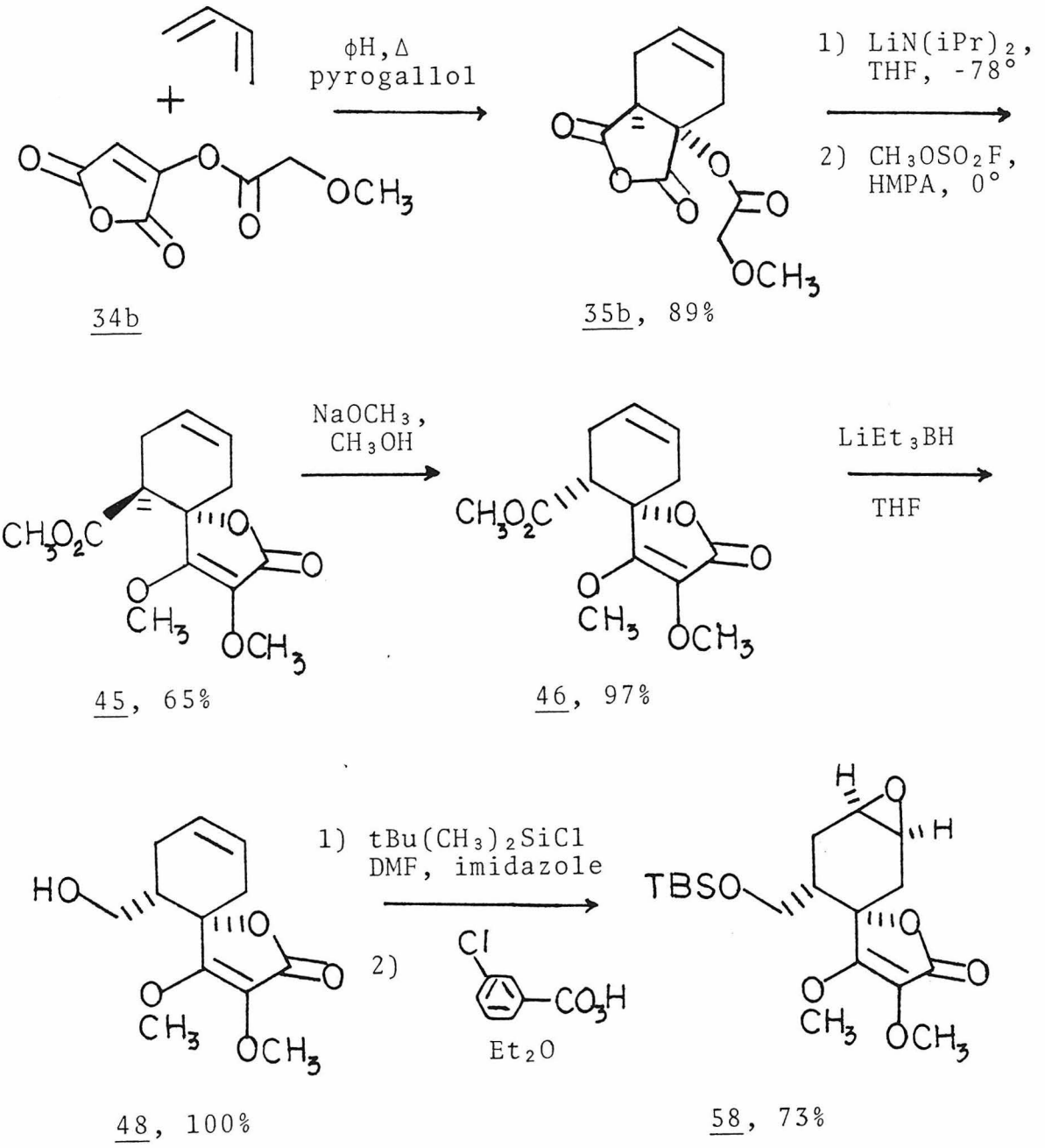
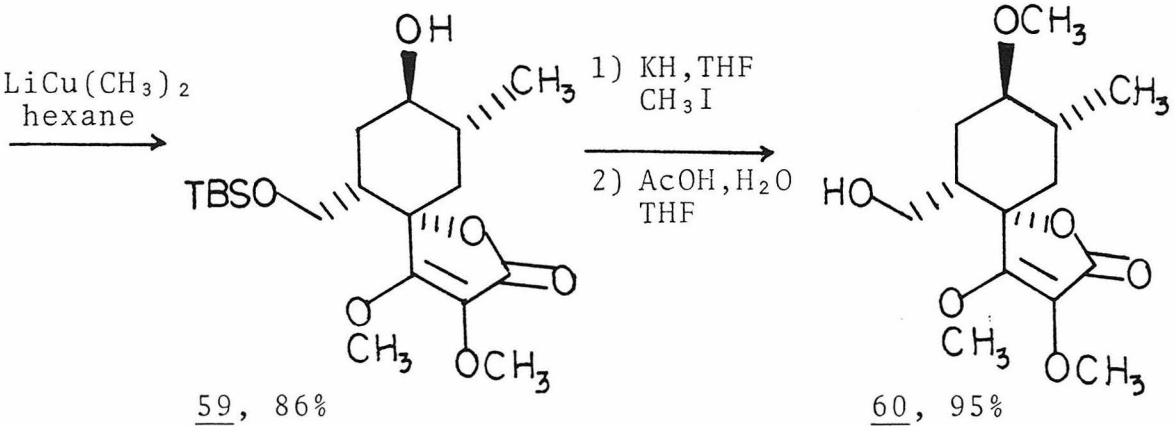
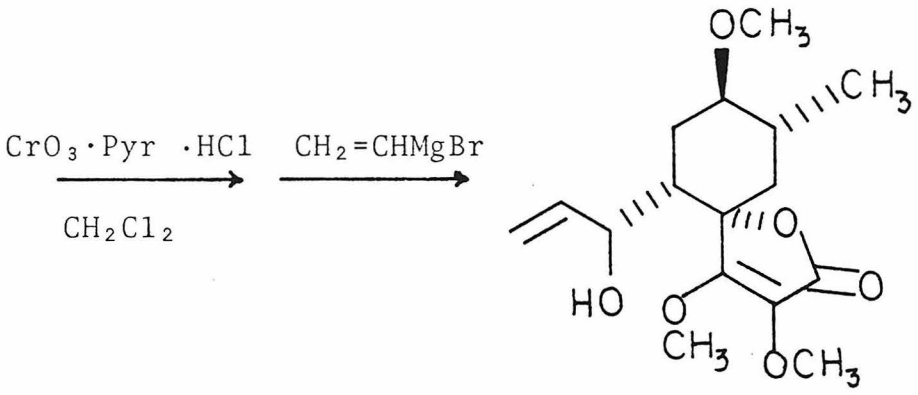


Chart 10, cont.




59, 86%

60, 95%




64, 70%

The more functionalized alcohol 61 gave aldehyde 64 and allylic alcohol 65 in identical yields, thus completing the synthesis of the proposed top half of chlorotricolide (Chart 10).

## G. Connection and Rearrangement of Bottom Half Models

With a potential top half in hand, it was necessary to test whether the enolate Claisen rearrangement was a viable route to the connection of top and bottom halves. Initially, the propionate was made as a model to see if the butenolide ring would be stable to the conditions necessary for enolization and rearrangement. The allylic alcohol 63, on treatment with 10 equivalents of propionyl chloride (in $CH_2Cl_2$ containing 10 equivalents of pyridine) afforded propionate 65, in 76% chromatographed yield, accompanied by large amounts of ketene polymer. Enolization ,using the conditions reported by Ireland and Willard,[87] proved to be very difficult. Only starting material was isolated upon treatment with up to 10 equivalents of lithium diisopropylamide.

This result led to the hypothesis that lithium was coordinating with the ether oxygen on the tetronic ring in a manner preventing further approach by base on the propionate side chain. It was then found that substituting potassium hexamethyldisilylamide (2 equivalents) for

lithium diisopropylamide led to the desired rearranged ester 66, after treatment with diazomethane, in 88% overall chromatographed yield (Chart 11).

At this juncture, a model closer to the actual bottom half was needed. The rigidity inherent in the bicyclic cis-anti-trans ring fusion of bottom half results in the most stable conformation, as shown in Figure 3, with the carboxyl group in a pseudo-equatorial position. In a monocyclic system such as 67 or 68 (Figure 3), it would be expected that the trans isomer 67 would lead to equatorial orientation of carboxyl, whereas the cis isomer 68 would result in a predominance of axial carboxyl. Since the axial is more hindered to attack, for purposes of lactonization, an equatorial carboxyl group would be preferred. However, since the natural product has cis geometry, and since in a monocyclic system inversion could occur more readily, the cis isomer was prepared as shown in Chart 12.

The readily available bicyclic ketone 69[88] was converted to the enolacetate[89] and cleaved with ozone (oxidative work-up) to afford the cis diacid 70 in 63% overall yield. The cis diacid 70 was converted to ester-acid chloride 71 as described by Bachmann and Drieding.[90]

Esterification with the top half allylic alcohol 63, using the same conditions as the propionate case, gave the ester 72 in 62% yield. Treatment of this ester with

Chart 11

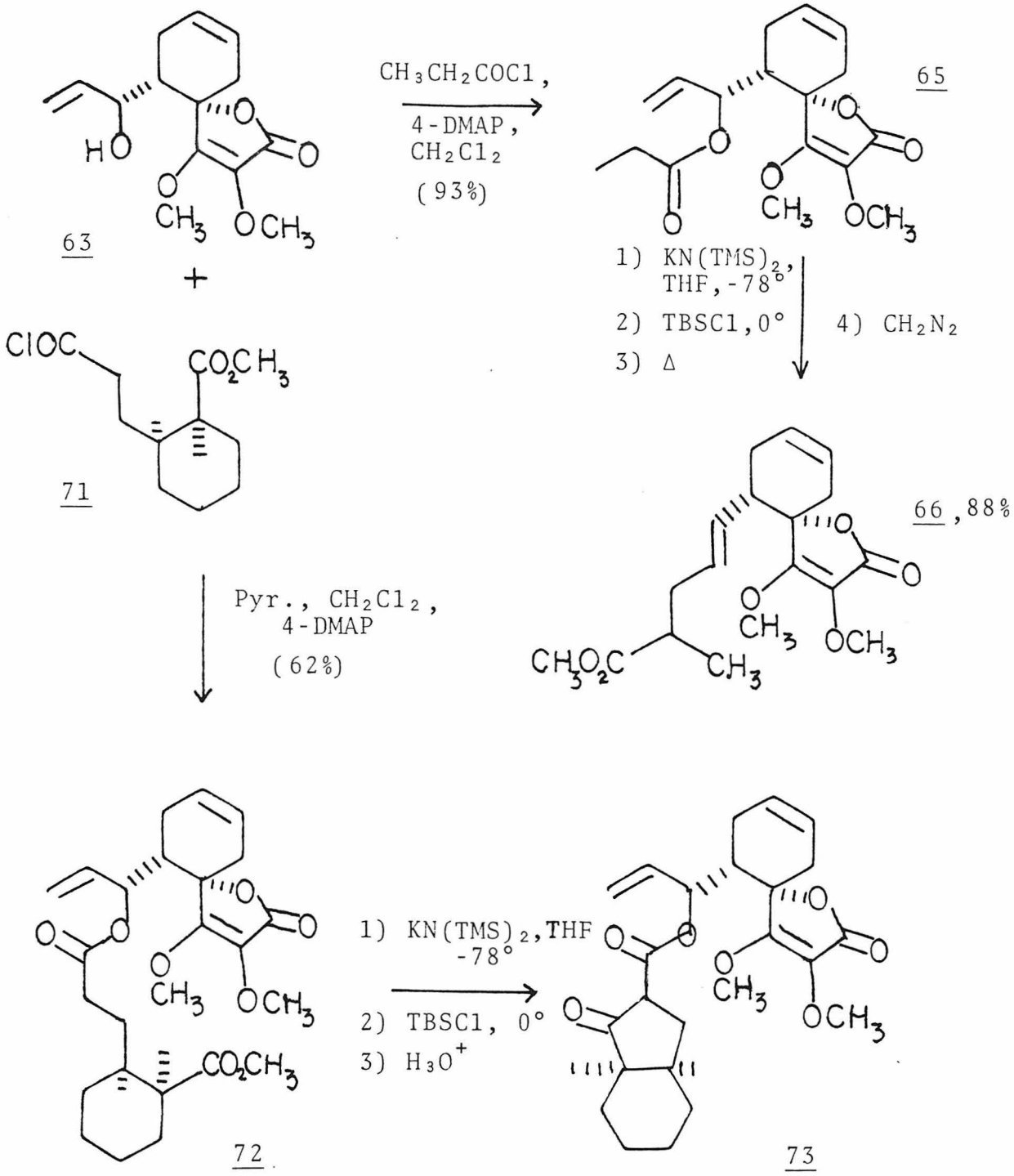
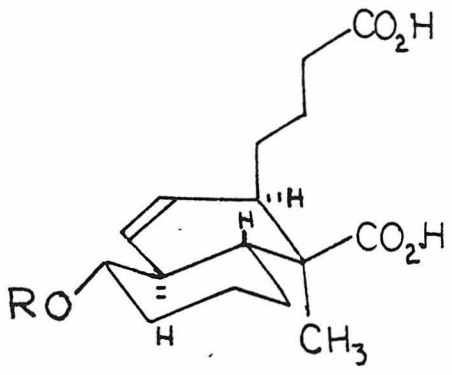
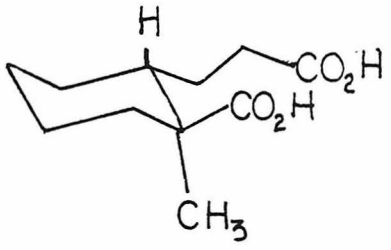

63
+
ClOC
CO2CH3
71
CH3CH2COCl,
4-DMAP,
CH2Cl2
(93%)
65
1) KN(TMS)2,
THF, -78°
2) TBSCl, 0°
3) Δ
4) CH2N2
66, 88%
Pyr., CH2Cl2,
4-DMAP
(62%)
72
1) KN(TMS)2, THF
-78°
2) TBSCl, 0°
3) H3O+
73

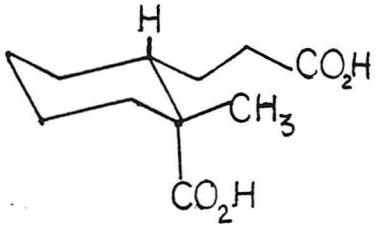
Figure 3




Bottom Half

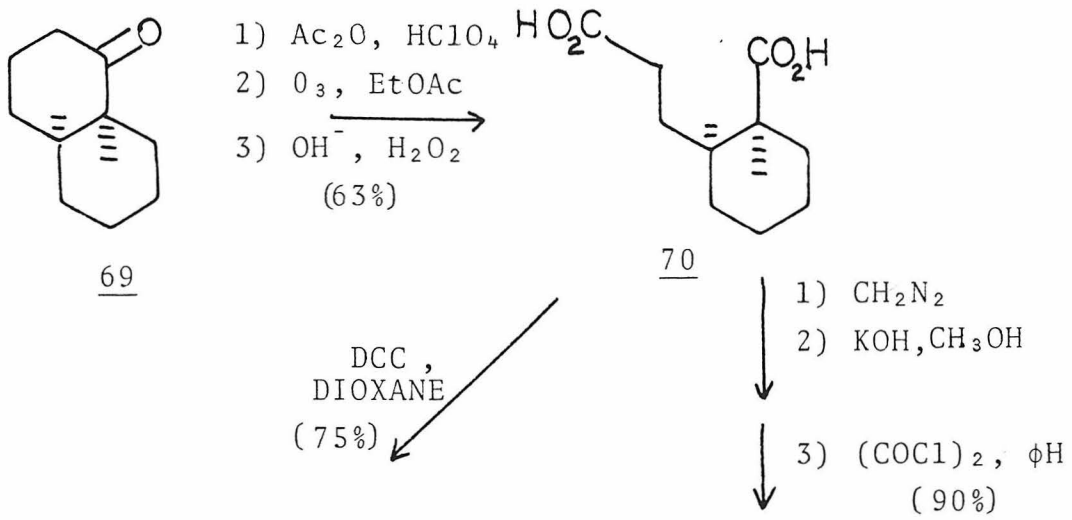



67

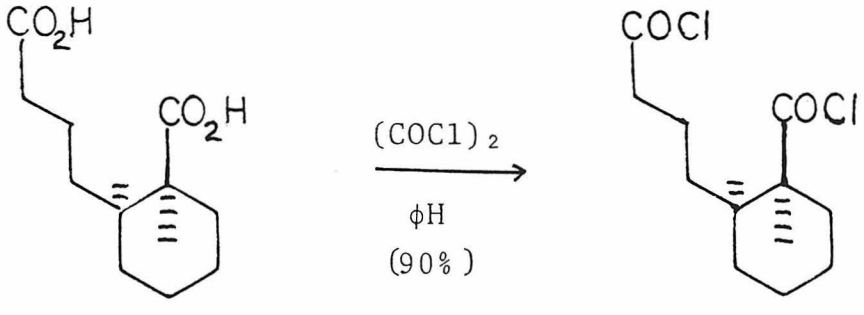



68

Chart 12




69 70 74 71




75 76

potassium hexamethyldisilylamide did not,however,lead to the desired Claisen rearrangement product. Instead, Dieckmann cyclization occurred, resulting in a 90% yield of hydrindanone 73 (Chart 11).

This undesirable side reaction was prevented by protection of the carboxyl group with the easily removable pair of electrons. The seven-membered anhydride 74, prepared in 75% yield using N,N'-dicyclohexylcarbodiimide,[91] reacted with the allylic alcohol 63 to give acid-ester 77 in 85% yield (4-dimethylaminopyridine, $CH_2Cl_2$,$\Delta$).[92] Enolate Claisen rearrangement, using trimethylsilyl chloride to quench the enolate, afforded diester 78 in 80% overall yield.

Conversion of the diester 18 to the corresponding aldehydo-ester with diisobutyl aluminum hydride in ether (2 equivalents, $-78^{o}$), followed by decarbonylation with $[\emptyset_3P]_3RhCl$ in benzene[93-96] effected the removal of the carboxyl group in 48% overall yield.

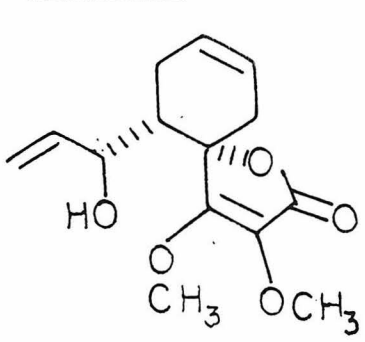
With these results, the utility of the ester-enolate Claisen rearrangement in connecting the two halves was demonstrated. The esterification of the two halves, however, still warranted further investigation. While the 7-membered anhydride was ideally suited for the model with a propionate side chain, the "real" bottom half would require a butyrate side chain, and 8-membered anhydrides are nearly

inaccessible. Thus, an alternative method of carboxyl activation was necessary. Since the two carboxyl groups are still in very different steric environments, it was thought that activation of both carboxyls in the same manner should present no problems with regioselectivity.

To test these possibilities, cis-diacid 75, prepared as described by Bachmann and Dreiding,[90] was converted to the diacid chloride 76 in 90% crude yield (oxalyl chloride, benzene). The esterification of this diacid chloride with allylic alcohol 80, using various amine bases, led to the discovery that 2,6-lutidine gave optimum yields, with maximum selectivity (Table 2). Application of these conditions to the top half allylic alcohol 63, afforded an 83% yield of acid-ester 81, with virtually no esters resulting from acylation at the more hindered acid chloride (Chart 14).

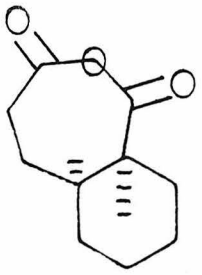
The completion of chlorotricolide now awaits the completion of the "real" bottom half (Charts 15 and 16).

Chart 13



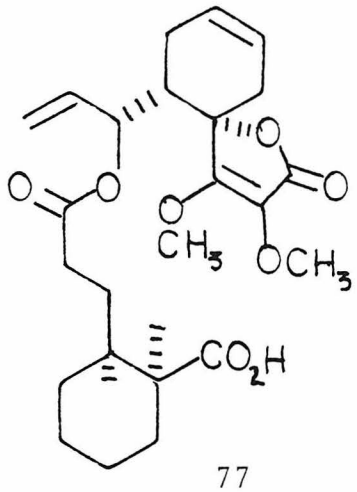
63

+



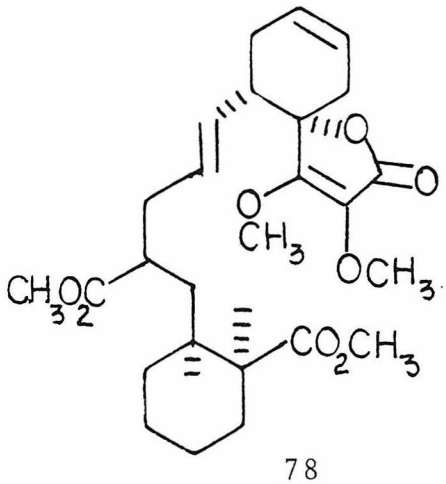
74

4-DMAP,
$CH_2Cl_2$, Δ
85%



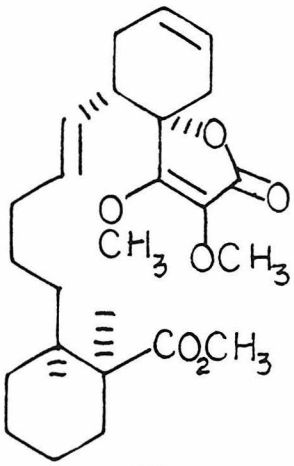
77

1) $KN(TMS)_2$
THF, -78°
2) TMSCl, -78°
3) Δ
4) $CH_2N_2$
80%



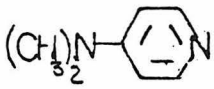
78

1) DIBAL, $Et_2O$
-78°
2) $(\phi_3P)_3RhCl$
$\phi H$, Δ
48%

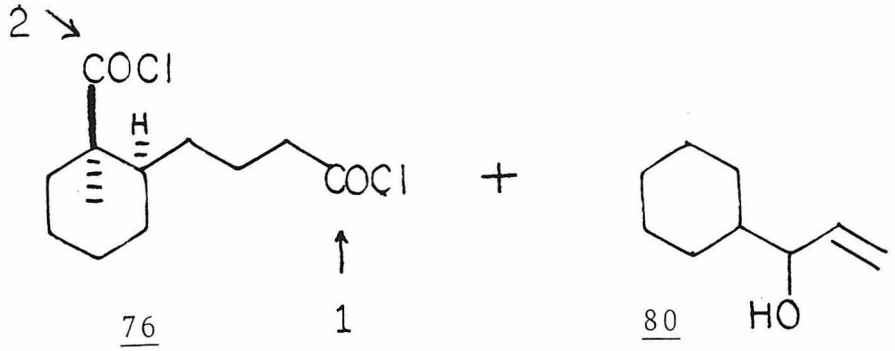


79

Table 2

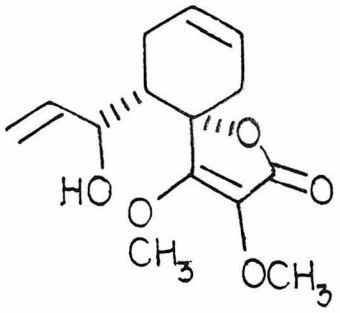
| Base | Time (hrs) | % Yield* | 1 | 2 | 1+2 |
|---|---|---|---|---|---|
| $Et_3N$ | >48 | 9 | 9 | -- | -- |
| $\phi$-$N(CH_3)_2$ | >48 | 11 | 11 | -- | -- |
|  | 12 | 80 | 46 | 16 | 18 |
|  | 8 | 95 | 86 | 4 | 5 |
|  | 4 | 86 | 36 | 14 | 20 |

* (isolated yields based on alcohol)



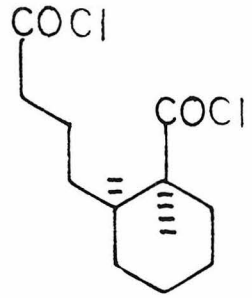

76 1 80

Chart 14

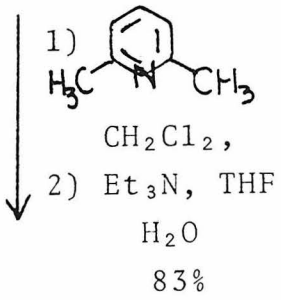


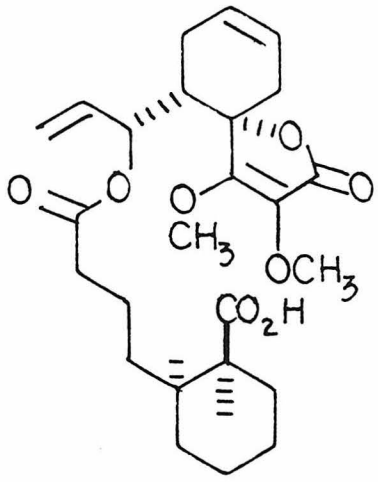
63

+



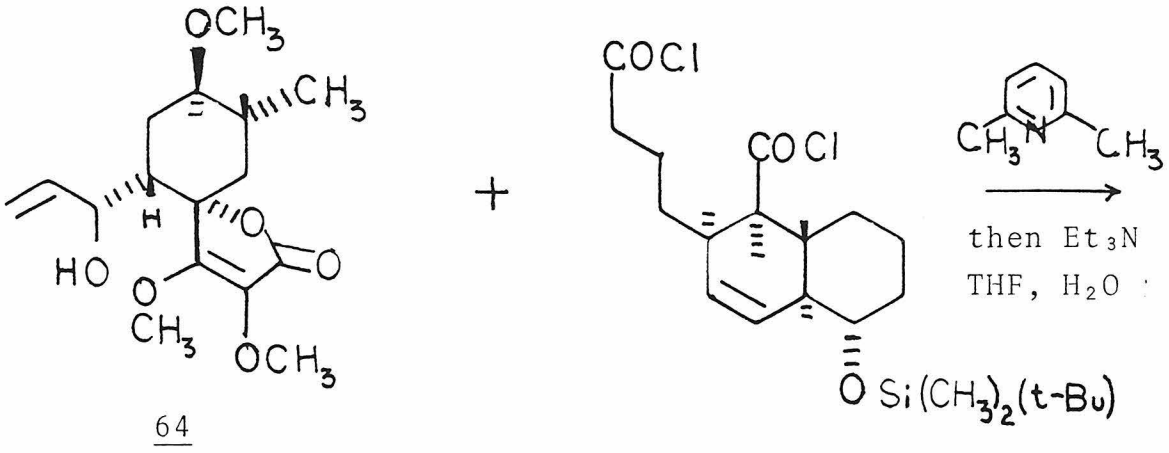
76



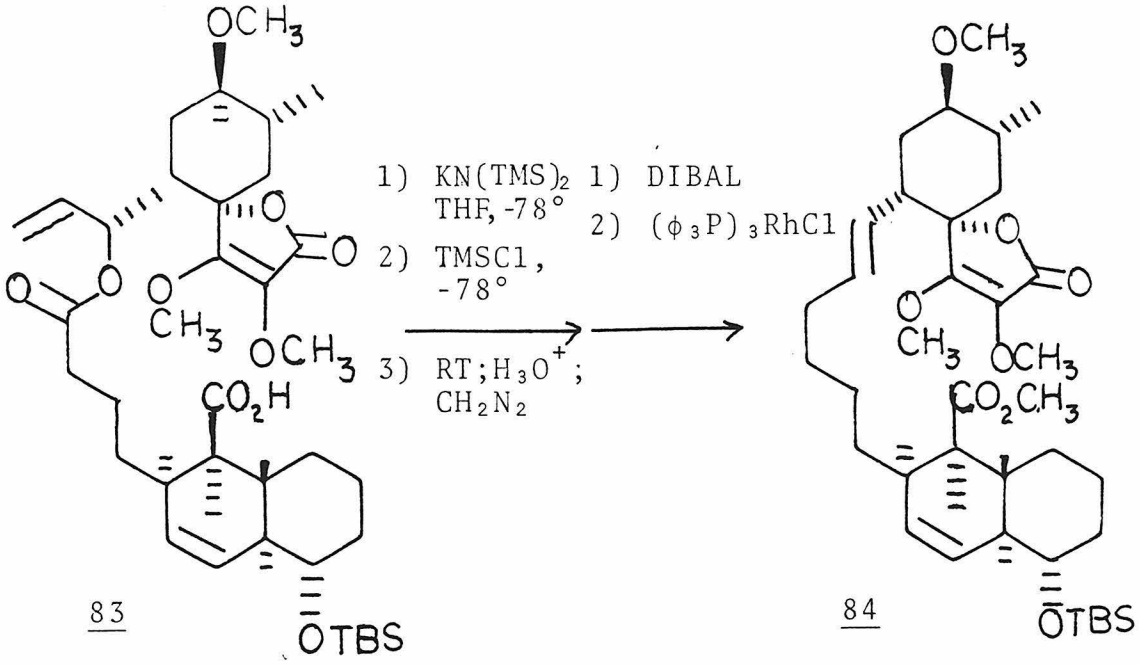



81

Chart 15; Completion of Chlorotricolide (proposed)

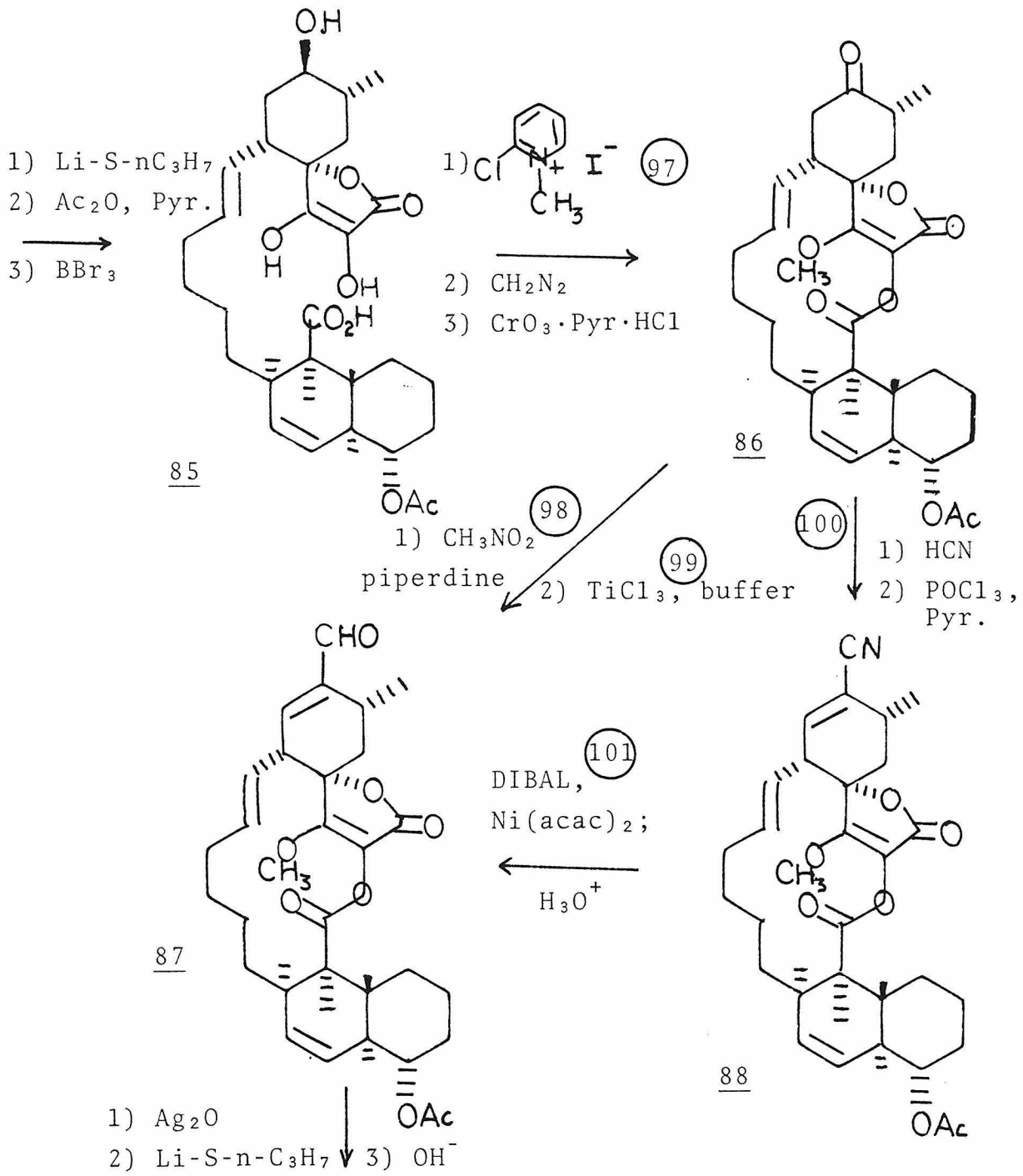



64 82



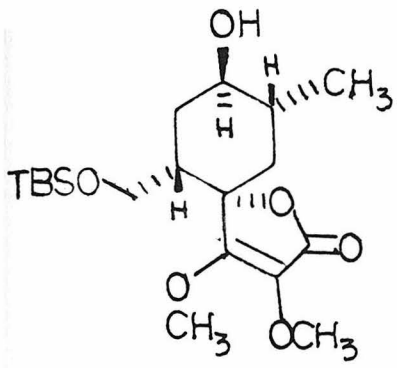

83 84

Chart 15; cont.




Chlorotricolide, 2

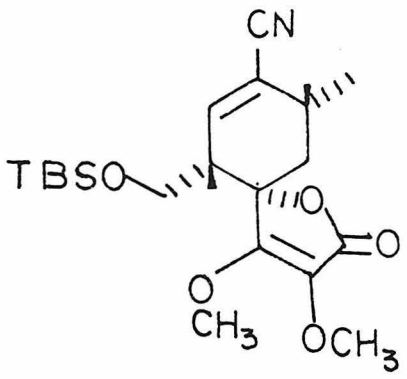
Chart 16; An Alternate, More Convergent Route



59

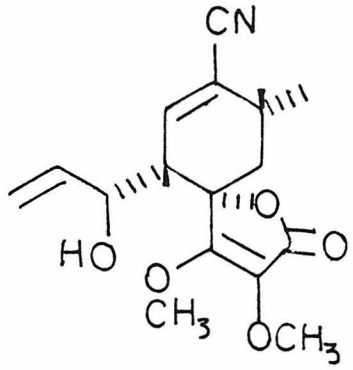
1) $CrO_3 \cdot Py \cdot HCl$
2) HCN
3) $POCl_3$, Pyr.

(100)



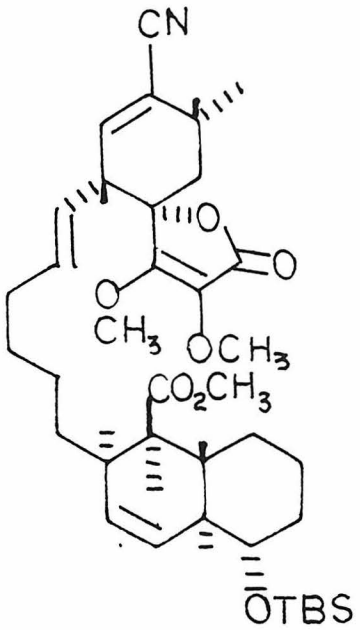
89

1) $(nBu)_4NF$, THF
2) $CrO_3 \cdot Pyr \cdot HCl$
3) $CH_2=CHMgBr$



90

1) bottom half
2) ester-enolate Claisen
3) $CH_2N_2$
4) DIBAL
5) $(\phi_3P)_3RhCl$

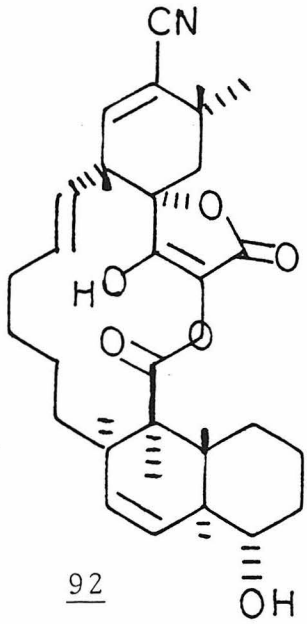


91

1) Li-S-n-$C_3H_7$
2) $Ac_2O$; $BBr_3$
3) lactonize

$H_3O^+$ or $Pd^{II}$, $H_2O$

(101)



92

Chlorotricolide, 2

## EXPERIMENTAL

Melting points were taken using a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on either a Perkin-Elmer 237B, 727B, or Beckman 4210 infrared spectrometer, and nuclear magnetic resonance (nmr) spectra were recorded using either a Varian T-60, EM-390 or A-60 spectrometer. Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ($\delta_{TMS}$ = 0.0 PPM) as an internal standard.

Gas-liquid chromatographic (vpc) analyses were determined on a Hewlett-Packard 5750 gas chromatograph using helium carrier gas at a flow rate of 60 ml/min. All analytical vpc was conducted on a 5 ft x 0.125 in. column packed with 4% SE-30 on 60-80 mesh chromosorb WAW DMCS.

Preparative layer chromatography was carried out on pre-coated PLC plates with a 20 x 20 x 2 mm layer of silica gel 60F-254 on glass plates manufactured by E. Merck, Darmstadt, Germany. Thin layer chromatography was performed on E. Merck TLC plates 60F-254, 0.25 mm. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany. All silica gel was E. Merck "Silica Gel 60", 70-230 mesh ASTM. Preparative medium pressure chromatography was

performed using glass columns and fittings supplied by Chromatronix, Inc., Berkeley, Ca., and an instrument mini-pump made by Milton Roy Co., St. Petersburg, Fla. The columns were packed with silica gel H "for tlc acc. to Stahl" (10-40 mesh) from E. Merck and Co., Darmstadt, Germany.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether, tetrahydrofuran, and dimethoxyethane were distilled under dry argon from sodium metal using benzophenone ketyl as an indicator. Benzene and toluene were distilled from calcium hydride. Hexane and dichloromethane were distilled from phosphorous pentoxide. Methanol was distilled from magnesium methoxide. HMPA was distilled at 0.5 mm from pulverized calcium hydride.

"Dry" amines, whether used as solvents or reagents, were distilled as follows; triethylamine immediately before use under argon from sodium-benzophenone ketyl; pyridine immediately before use from calcium hydride; 2,6-lutidine from calcium hydride; diisopropylamine from calcium hydride under argon; dimethylaniline from calcium hydride under argon; hexamethyldisilazane (supplied by Petrarch Systems Inc.) from calcium hydride under argon. (b.p. 126-6°).

All other solvents were "Reagent Grade" unless described otherwise. "Anhydrous ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, b.p. 35-60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not purified further. Drying agents such as magnesium sulfate, or potassium carbonate are anhydrous reagent grade.

All water used in the reactions was distilled water. "Brine" refers to a saturated aqueous solution of sodium chloride. "Concentration of solvents in vacuo" refers to first solvent removal under reduced pressure (water aspirator) using a rotary evaporator at or below 40°, then drying the residue in vacuo at 1 mm for several hours at room temperature.

Syringes and "oven-dried" reaction flasks were dried at least twelve hours in an oven (at 120-140°) and cooled in a desiccator over anhydrous calcium sulfate prior to use. All reactions (except oxidations) were run under argon which was dried by passing thru a calcium chloride drying tower.

Mass spectral analyses were run by Dr. Kai Fang, UCLA, Los Angeles, Ca. Microanalyses were performed by

Spang Microanalytical Laboratory, Ann Arbor, Michigan, or Susan Rottschaefer here at Caltech.

Analytical samples were obtained by bulb to bulb distillation at 0.01 mm, unless otherwise indicated.

Diacetyltartaric anhydride, (32)

To a mixture of 100 g (0.67 mole) of pulverized d-tartaric acid and 220 ml acetic anhydride was added 3 ml of concentrated sulfuric acid, and the resulting solution stirred magnetically at room temperature for 3 hours, then heated on a steam bath for a few minutes and cooled in an ice bath. The white crystalline product was collected on a medium frit, by vacuum filtration, washed with 50 ml of benzene, then dried in a vacuum desiccator over paraffin for 3 days to afford 141.0 g (98%) of pure crystalline diacetyl tartaric anhydride. m.p. 128-130° (lit 128-130°). nmr ($CDCL_3$) δ2.23 (s,6,-$COCH_3$), 5.73 (s,2,ring-H).

Pyridine salt of hydroxy maleic anhydride, (33)

In a dry stoppered flask containing 40 g (0.185 mole) of diacetyl tartaric anhydride 32, was added in one portion 80 ml of dry pyridine, the flask quickly stoppered, the mixture vigorously shaken for 5 seconds (pale green

color develops), 12 ml glacial acetic acid immediately added, the resulting mixture agitated at 45° (water bath) until dissolution was complete, the flask placed in an ice bath and 45 ml anhydrous ether added. The mixture was shaken, then collected by vacuum filtration on a medium frit (60 ml) thoroughly pressed, washed twice with 10 ml portions of absolute ethanol, three times with 10 ml portions of ether, then dried in vacuo 3 hours to give 23 g of a slightly yellow, microcrystalline solid (67%). The crude salt was used directly in the next step. (lit. yield 80%)[40]

(2-Methoxyacetoxy) maleic anhydride, (34b)

To a stirred suspension of 16 g (0.083 mole) of the pyridine salt of hydroxymaleic anhydride 33 in 160 ml of dry benzene under argon, was added 8.2 ml (0.090 mole) of methoxyacetyl chloride[102] in one portion. The resulting mixture was stirred 30 minutes at room temperature. The clear supernatant was decanted off and filtered through 120 ml of alumina with 800 ml of benzene. The eluate was concentrated in vacuo to about 75 ml, and 200 ml of petroleum ether added. The product was collected by vacuum filtration on a medium frit then dried in a vacuum desiccator over $P_2O_5$ to give 11.2 g (73%) of

pure colorless crystalline anhydride 34b. m.p. 93-94°, ir ($CHCl_3$) 1630 $cm^{-1}$ (C=C), 1780 $cm^{-1}$ (C=O), 1820 $cm^{-1}$ (C=O), 1850 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ3.53 (s,3,-$OCH_3$), 4.35 (s,2,α-$CH_2$), 6.90 (s,1,vinyl).

Acetoxymaleic anhydride, (34a)

Prepared as above using acetyl chloride (17.7 ml, 0.25 mole) to give pure crystalline anhydride 34a (12.4 g, 96%) m.p. 89-90°. (lit 89-90°) ir ($CHCl_3$) 1630 $cm^{-1}$ (C=C), 1780 $cm^{-1}$ (C=O), 1820 $cm^{-1}$ (C=O), 1850 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 2.41 (s,3,CO-$CH_3$), 6.81 (s,1,vinyl).

4-Acetoxycyclohexene-cis-4,5-dicarboxylic anhydride, (34a)

Sealed tube procedure:

The following procedure is typical for all sealed tube reactions involving substituted butadienes and butenolides or maleic anhydride type dienophiles.

To a solution of 2.0 g (0.013 mole) of acetoxymaleic anhydride in 40 ml of dry benzene in a thick wall tube of pyrex was added 9.3 g (0.18 mole) of dry 1,3-butadiene. The mixture was cooled via liquid nitrogen under argon, then evacuated and allowed to thaw as a closed system. Freezing followed by re-evacuation was repeated twice more, then the tube sealed under vacuum with the contents

frozen. The sealed tube was then heated to 85 to 90° for 5 days, then cooled via liquid $N_2$ until frozen, opened and placed under argon while warming. Removal of solvents in vacuo gave a resin which was taken up in ether, and filtered thru celite to remove polymers. Removal of solvent in vacuo, followed by column chromatography thru silica gel using 45% ethyl acetate benzene gave 2.5 g (93%) of white crystalline adduct 34a. m.p. 78-90° ; ir ($CHCl_3$) 1740 $cm^{-1}$ (C=O), 1785 and 1855 $cm^{-1}$ (anhydride C=O); nmr ($CDCl_3$) δ 2.16 (s,3,CO-$CH_3$), 3.46 (m,1,α-H to C=O), 6.00 (m,2,vinyl).

An analytical sample was prepared by recrystallization from ether.

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.79. Found C, 57.00; H, 4.77.

4-(2-Methoxyacetoxy)-cyclohexene-cis-4,5 dicarboxylic anhydride, (34b)

A Parr series 4500 pressure reaction apparatus equipped with a glass liner was charged with 25 g (0.134 mole) of methoxyacetoxymaleic anhydride 34b, 800 ml of dry benzene and 0.5 g of pyrogallol as a radical inhibitor. To this solution was added 109 g (2.0 mole) of 1,3-butadiene which was purified by passage thru a drying

column charged with 8 mesh calcium chloride, and condensed into an evacuated flask cooled *via* a dry ice-acetone bath. The reaction vessel was then sealed off, and stirred 5 days at 80°. The crude reaction product was filtered through celite, then concentrated *in vacuo* to give an oil which crystallized on standing. Chromatography on silica gel using 35% ethyl acetate benzene gave the desired adduct 35b, as an oil which crystallized on standing. (27.4 g, 85%) m.p. 60-62°. ir ($CHCl_3$) 1765 $cm^{-1}$ (C=O), 1790 $cm^{-1}$ and 1860 $cm^{-1}$ (anhydride C=O); nmr ($CDCl_3$) δ 3.47 (s,3,-$OCH_3$), 4.13 (s,2,α-$CH_2$ to carbonyl), 6.00 (m,2,vinyl).

An analytical sample was recrystallized from ether.

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 55.03; H, 5.07.

1-Methyl-4-(2-methoxyacetoxy)cyclohexene-*cis*-4,5-dicarboxylic anhydride, and 2-methyl-4-(α-methoxyacetoxy)-cyclohexene-*cis*-4,5-dicarboxylic anhydride, (38).

From isoprene (7.8 ml, 78 mmoles) and α-methoxyacetoxy maleic anhydride (sealed tube) (0.971 g, 5.2 mmoles), 3 days, 85°. Chromatography afforded 1.1 g (85%) of pure adduct. ir ($CHCl_3$) 1765 $cm^{-1}$ (C=O), 1790 and 1860 $cm^{-1}$

(anhydride C=O); nmr ($CDCl_3$) δ 1.80 (s,3,-$CH_3$), 3.47 (s,3-$OCH_3$) 4.13 (s,2,α-$CH_2$), 5.5 (m,1,vinyl).

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.60; H, 5.55. Found: C, 56.64; H, 5.54.

2-t-Butyldimethylsiloxy-3-methyl-butadiene (39)

To a stirred solution of 0.142 moles of lithium diisopropyl amide in 200 ml of dry tetrahydrofuran at -70° (dry ice-acetone) under argon, was added 2-methyl-3-oxo-1-butene in 15 ml of dry tetrahydrofuran dropwise over 10 min. After stirring 10 min at -70°, 28.5 ml dry hexamethylphosphoramide was added followed by a solution of 19.9 g (0.132 mole) t-butyldimethylsilyl chloride in 25 ml tetrahydrofuran. After warming to room temperature over 30 min, the reaction was quenched with 200 ml water and extracted into 500 ml of pentane. The aqueous layer was extracted one more time with pentane, then the organic layers combined,washed with water, saturated sodium chloride, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by distillation at reduced pressure (b.p. 87-90° at 15 mm) gave 18.1 g (76%) of colorless pure diene 39. ir ($CHCl_3$) 1600 $cm^{-1}$(C=C), 1250 $cm^{-1}$(Si-C); nmr ($CDCl_3$) 80.17 (s,9,Si-$(CH_3)_2$), 1.0 (s,9,t-butyl), 1.90 (s,3,-$CH_3$) 4.40 (s,1,vinyl), 4.50 (s,1,vinyl), 5.0 (s,1,vinyl) 5.50 (s,1,vinyl).

Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18. Found: C, 66.22; H, 11.25.

1-t-Butyldimethylsilyloxy-2-methyl-cyclohexene 4,5-dicarboxylic anhydride (40)

The diene 39 (0.243 g, 1.2 mmoles) and maleic anhydride (0.1 g, 1.0 mmoles) in refluxing benzene (6 ml) gave adduct 40 (0.284 g, 96%) after chromatography. (45% ethyl acetate-benzene on silica gel) ir ($CHCl_3$) 1675 (C=C), 1775 and 1850 $cm^{-1}$ (anhydride C=O); nmr ($CDCl_3$) δ, 0.13 (s,3,Si-$CH_3$) 0.17 (s,3,Si-$CH_3$) 1.0 (s,9,t-butyl) 1.67 (s,3,-$CH_3$), 3.40 (m,2,α-CH to carbonyl).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 60.78; H, 8.16. Found: C, 60.79; H, 8.01.

3-(2-Methoxyacetoxy)-2-oxo-2,5-dihydrofuran (41)

To a stirred solution of 3.18 g (0.027 mole) of D-erythronolactone [64] in 10 ml of dry pyridine at 0° under argon was added 4.9 ml (0.055 mole) of methoxyacetylchloride dropwise over 5 min. After standing 1 hour at room temperature, the mixture was taken up in 50 ml dichloromethane, and washed with 100 ml saturated sodium bicarbonate, then 50 ml saturated sodium chloride

The organic layer was dried over magnesium sulfate, and the solvents removed *in vacuo* to give 7.7 g of crude diester lactone. The lactone was then taken up in 12 ml dry dichloromethane, and cooled to 0° with stirring under argon. Triethylamine (4.1 ml, 0.029 mole) was added and the resulting mixture allowed to stir at room temperature for 2.5 hours. The mixture was then diluted with 100 ml dichloromethane, and washed twice with 50 ml portions of 1 N hydrochloric acid, twice with water, once with saturated sodium chloride, then dried over magnesium sulfate. After decolorizing with activated charcoal, the solvents were removed *in vacuo* to afford crude butenolide *41* as a yellow oil. (3.84 g, 83%) ir ($CHCl_3$) 1625 $cm^{-1}$ (C=C), 1775 $cm^{-1}$ (C=O) nmr ($CDCl_3$) $\delta$ 3.50 (s,3,-$OCH_3$), 4.32 (s,2,CO-$CH_2$-OR), 4.95 (d,2,J = 2 hz), 7.42 (t,1,J = 2 hz). Mass measured molecular ion; calcd for $C_7H_8O_5$; 172.0372; found 172.0370.

2-Methyl-6-carbomethoxy-2,4-dihydro-1,3-dioxine (*42*)

To a stirred solution of (0.402 g, 0.0023 mole) methyl 2,4-O-ethylidene-D-erythronate (made by diazomethane treatment of 2,4-O-ethylidene-D-erythronic acid)[64] in 4 ml of dry pyridine at 0° under argon, was added 0.19 ml (0.0025 mole) of methanesulfonyl chloride.

The mixture was then allowed to stir 4 hours at room temperature. The mixture was then diluted with dichloromethane then extracted twice with water, twice with 5% sodium bicarbonate, and then dried over magnesium sulfate. Removal of solvents *in vacuo* gave 0.565 g of crude mesylate. The mesylate was treated with 1.5 equivalents sodium methoxide in methanol (from 0.086 g, 0.0037 mole of sodium metal and 10 ml of methanol) for 1 hour at room temperature. The mixture was diluted with dichloromethane then washed with two portions of water, and dried over potassium carbonate. Removal of solvents *in vacuo*, followed by evaporative distillation (50-60° at 0.25 mm) afforded 0.352 g of ester *41*. ir ($CHCl_3$) 1650 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 1.45 (d,J=6 Hz,3,$-CH_3$), 3.80 (s,3,$-OCH_3$), 4.40 (d,J = 2.5 Hz,2), 4.9 (q,J = 6 Hz,1), 6.1 (t,J = 2.5 Hz,1).

*Anal*. Calcd for $C_7H_{10}O_4$: C, 53.16; H 6.37. Found: C, 53.05; H, 6.41.

*2-Oxo-3,4-dimethoxy-10β-carbomethoxy-1-α-oxaspiro[4.5] deca-3,7-diene (45)*.

To a rapidly stirred solution of 6.6 g (0.027 mole) of the anhydride-ester *35b*, in 390 ml of dry tetrahydrofuran cooled to -78° (dry ice-acetone) under argon was

added dropwise 1.8 equivalents (0.055 mole) of lithium diisopropylamide (from 0.055 mole n-butyllithium and 9.31 ml, (0.066 mole) of diisopropylamine) in 230 ml of dry tetrahydrofuran, over a period of 40 minutes. The deep red solution was then allowed to warm to 0° (ice bath) over 30 min, then 75 ml of dry hexamethylphosphorictriamide was added, followed by 7.0 ml (0.0825 mole) of methyl fluorosulfonate (95%, Aldrich) and the resulting mixture allowed to stir for 10 min at 0°. The resulting slightly yellow mixture was quenched with 75 ml of 10% hydrochloric acid and extracted with two 200 ml portions of ether. The combined ethereal layers were washed two times with 10% hydrochloric acid, (100 ml), three times with water (100 ml) then once with saturated sodium chloride solution, and dried over magnesium sulfate. Removal of solvent *in vacuo*, followed by column chromatography over silica gel (15% ethyl acetate-benzene),afforded 4.4 g (61%) of the spiro butenolide **45** as an oil. ir ($CHCl_3$) 1675 $cm^{-1}$ (C=C), 1735 $cm^{-1}$ (C=O), and 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.70, 3.92, 4.13 (3s,3,3-$OCH_3$), 5.72 (s,2,vinyl).

*Anal*. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.28; H, 6.11.

2-Oxo-4-methoxy-10β-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene, (43)

Procedure as above. 1.03 g (0.005 mole) of anhydride afforded 0.83 g (70%) of spiro butenolide 43, after silica gel chromatography using 20% ethyl acetate-benzene. ir ($CHCl_3$) 1625 $cm^{-1}$ (C=C), 1740 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.70, and 3.90 (2s,3,2-$OCH_3$), 5.0 (s,1,vinyl) 5.70 (s,2,vinyl).

Anal. Cacld for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.67; H, 5.85.

2-Oxo-3,4-dimethoxy-10α-carbomethoxy-1α-oxaspiro[4.5]-deca-3,7-diene, (46)

To a stirred solution of 4.3 g (16 mmole) of spiro-butenolide 45, in 500 ml of dry methanol, under argon was added 3.0 ml (1.6 mmole) of freshly prepared 0.54 M sodium methoxide in dry methanol, and the resulting mixture warmed to 70-80° for 4 days. The reaction was quenched with 0.5 ml of glacial acetic acid, and the solvents removed in vacuo. The residual 0.7 was taken up in dichloromethane, and washed with saturated sodium bicarbonate solution, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by careful chromatography over silica gel (15% ethyl acetate benzene),gave 3.36 g (78.3%) of the epimerized

46 and 0.841 g (19.6%) of starting material 45. Overall yield of 46 based on recovered starting material, 97%. ir ($CHCl_3$) 1675 $cm^{-1}$ (C=C), 1735 $cm^{-1}$ (C=O), and 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.67, 3.81, 4.13 (3s,3,3-$OCH_3$) 5.72 (s,2,vinyl).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.18; H, 5.93.

2-Oxo-4-methoxy-10α-carbomethoxy-1α-oxaspiro[4.5]deca-3,7-diene, (43)

Procedure as above. From 0.182 g (0.87 mmole)of spiro butenolide 43, 0.140 g epimerized 44 (78%), m.p. 119-120°, and 0.035 g (19%) of starting material 43, m.p. 99-102°. ir ($CHCl_3$) 1635 $cm^{-1}$ (C=C), and 1750 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.65 and 3.92 (2s,3,2x-$OCH_3$), 5.1 (s,1,vinyl) 5.70 (m,2,vinyl).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.73; H, 6.01.

2-Oxo-3-methoxy-4-hydroxy-10 -(hydroxymethyl) -1 -oxaspiro-[4.5]deca-3,7-diene, (47)

To a stirred solution of 0.150 g (0.56 mmole) of ester 46 in 1 ml of dry hexamethylphosphoramide under argon, was added 1.34 ml (0.67 mmole) of a freshly

prepared 0.5 M solution of lithium n-propylmercaptide in dry hexamethylphosphoramide. (From 6.1 mmoles n-butyllithium, 0.65 ml (7.2 mmoles) n-propylmercaptan (distilled from magnesium under argon) in 5 ml dry hexane, followed by evacuation and addition of 12 ml dry hexamethyl phosphoramide). The resulting mixture was allowed to stir 20 hours at room temperature, then 25 ml of 10% hydrochloric acid was added and the mixture extracted with 50 ml of ether. The ether layer was washed twice with 5 ml of 10% hydrochloric acid, and the combined aqueous layers extracted twice with 25 ml of ether. The combined organic layers were washed once with saturated sodium chloride, then dried over magnesium sulfate. Removal of solvents in vacuo gave 0.142 g crude 47. (70% pure by nmr integration of the $-OCH_3$ peaks.) This material was used directly in the next step, due to its instability. ir ($CHCl_3$) 1685 $cm^{-1}$ (C=C), 1725 $cm^{-1}$ (C=O) and 1780 (C=O); nmr ($CDCl_3$) $\delta$ 3.64 and 3.80 (2s, 3,2-$OCH_3$), 5.75 (m,2,vinyl).

Treatment of this material with diazomethane gave back starting material 46 (nmr, ir).

2-Oxo-3,4-dimethoxy-10α-(hydroxymethyl)-1α-oxaspiro[4.5]-deca-3,7-diene (48)

A. By reduction of 47 with sodium diisobutyl aluminum dihydride.

To a stirred solution of 0.14 g (5.9 mole) of sodium hydride (from 47% oil dispersion, washed three times with dry hexane) in 5 ml of dry ether was added 4.5 ml of a 1.3 M solution of diisobutyl aluminum hydride in hexane, and the mixture cooled to -70° via cry ice-acetone bath. Next, 0.150 g (0.59 mmole) of 47 in 2 ml of dry ether was added dropwise, and the resulting mixture stirred 3 hours at -70°, then allowed to warm to 0° (ice bath) and quenched with methanol. The resulting mixture was poured into 10 ml 10% aqueous hydrochloric acid, and extracted with three 25 ml portions of ether. The ethereal extracts were dried over magnesium sulfate, then the solvents removed in vacuo. Treatment with diazomethane, followed by column chromatography over silica gel using 45% ethyl acetate-benzene gave 0.042 g (30%) of alcohol 48, which crystallized on standing m.p. 91-4°. ir ($CHCl_3$) 1670 $cm^{-1}$ (C=C), 1745 $cm^{-1}$(C=O), 3600 $cm^{-1}$ (-OH); nmr ($CDCl_3$) 3.80 and 4.15 (2s,3,2-$OCH_3$), 5.70 (m,2,vinyl).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.05; H, 6.71.

B. By reduction of ester 45 with lithium borohydride.

To a stirred solution of 2.0 g (7.5 mmole) of the ester 45 in 10 ml of dry tetrahydrofuran, was added 25.2 ml (26.26 mmole) of a freshly prepared, 1.03 M solution of lithium borohydride in tetrahydrofuran. The resulting solution was allowed to stir at room temperature for 20 hours, then cooled to 0° and quenched by careful addition of 20 ml of glacial acetic acid. The mixture was then diluted with 250 ml dichloromethane and washed with 20 ml of 10% hydrochloric acid, then saturated sodium chloride solution. The organic layer was dried over magnesium sulfate, and the solvents removed in vacuo. Boronate impurities were removed by addition of methanol containing a drop of 10% hydrochloric acid and removing the solvent in vacuo until constant weight. Column chromatography on silica gel (45% ethyl acetate-benzene) afforded 0.885 (44%) of starting material and 0.937 (52%) of the desired alcohol 48. (92% based on recovered starting material.)

C. By reduction of ester 45 with lithium triethylborohydride.

To a stirred solution of 0.480 g (1.8 mmole) of ester 45, in 4.0 ml dry tetrahydrofuran cooled to -15° under argon was added 5.36 ml (5.4 mmole) of a 1.0 M solution of lithium triethylborohydride in tetrahydrofuran, dropwise over 10 min. The mixture was then allowed to warm to 0° and stir for 1 hr. The reaction was quenched with 5 ml 10% hydrochloric acid, and extracted three times with 20 ml portions of ether. The ethereal extracts were combined and dried over magnesium sulfate, and solvents removed in vacuo. Chromatography over silica gel using 45% ethyl acetate-benzene gave 0.430 g (99.5%) of the desired alcohol 48.

2-Oxo-2,5-dihydro-3-methoxy-4-methoxyfuran (51a)

To a stirred solution of lithium diisopropylamide (0.079 moles, from 0.079 moles n-butyl lithium and 13.4 ml, 0.095 mole of diisopropylamine) in 100 ml dry tetrahydrofuran, cooled to -78° (via dry ice-acetone bath) under argon, was added a solution of the methyl-2-methoxyacetoxy-2-methyl propanoate 50 (from methoxyacetyl chloride and methyl 2-hydroxy isobutyrate in pyridine) in 20 ml of dry tetrahydrofuran dropwise, and

and the resulting mixture allowed to stir at -78° for 15 min, then warmed to room temperature and quenched with 60 ml of 10% hydrochloric acid. The aqueous layer was saturated with sodium chloride and extracted three times with ether (100 ml) and the combined organic layers dried over magnesium sulfate. Removal of solvents *in vacuo*, followed by recrystallization from ether-petroleum ether afforded 5.7 g (95%) of crystalline 51a. m.p. 134-135°. ir ($CHCl_3$) 1650 $cm^{-1}$ (C=C), 1730 $cm^{-1}$ (C=O) and 3520 $cm^{-1}$ (-OH); nmr ($CDCl_3$) 1.40 (s,6,-$CH_3$), 3.80 (s,3,-$OCH_3$).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.98; H, 6.20.

2-Oxo-2,5-dihydro-3,4-dimethoxy-furan (51b)

From 1.2 g (6.3 mmole) 50, same procedure as 51a, except quenching at -78° with 1.5 equivalents of methyl fluorosulfonate and hexamethylphosphoramide. Silica gel chromatography (25% ethyl acetate-benzene) gave 1.03 g (95%) of 51b, identical to the material obtained by treating 51a with diazomethane. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 1.40 (s,6,-$CH_3$), 3.84 (s,3,-$OCH_3$) and 4.18 (s,3,-$OCH_3$).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.90; H, 7.08.

2-Oxo-2,5-dihydro-3-hydroxyfuran, (49a)

From methyl-2-acetoxy-2-methyl-propanoate (3.14 g, 0.018 mole), using the same procedure as for 51a. 1.92 g (95%) of 49a was obtained. m.p. 140-142° (lit m.p. 140-142°). ir ($CHCl_3$) 1740 $cm^{-1}$ and 1755 $cm^{-1}$ (C=O) (mainly keto form).

2-Oxo-2,5-dihydro-3-methoxyfuran, (49b)

From 1.1 g (6.3 mmole) of methyl-2-acetoxy-2-methyl-propanoate, using the same procedure as described for 51b, afforded 0.72 g (90%) of the methyl ether 49b. m.p. 71-2°. ir ($CHCl_3$) 1625 $cm^{-1}$ (C=C) and 1730 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.42 (s,6,-$CH_3$), 3.85 (s,3,-$OCH_3$), 4.94 (s,1,vinyl).

Attempted oxidation of 49b or 51b

The following procedure is typical. The butenolide (1.0 mmole) was taken up in 1 ml of solvent (dichloromethane or ether and treated with 1-2 equivalents of the oxidizing agent (peracid). The reaction was quenched with aqueous sodium bisulfite solution, and the products isolated by ether extraction, then preparative thin layer chromatography. Yields are shown in Chart 6.

Attempted reduction of 49b or 51b.

The following procedure is typical.

3-Oxo-2,3-dihydro-2,2-dimethyl-4-methoxyfuran, (52)

To a stirred solution of 0.405 g (2.35 mmole) of the butenolide 51b in 35 ml dry ether, cooled to -78° under argon, was added 4.7 ml of a 1.0 M solution of diisobutyl aluminum hydride in hexane (4.7 mmole). The resulting mixture was allowed to stir for 2 hrs at -78°, then quenched with 4 ml methanol, and warmed to room temperature. The mixture was diluted with 100 ml ether and washed with 20 ml of 10% hydrochloric acid. The ethereal extract was washed with water, then saturated sodium chloride solution, and then dried over magnesium sulfate. Removal of solvents in vacuo gave 0.330 g (90%) of crude 52, which decomposed on standing. ir ($CHCl_3$) 1690 $cm^{-1}$ (C=C) and 1740 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.40 (s,6,-$CH_3$), 3.75 (s,3,-$OCH_3$), 7.90 (s,1,vinyl).

2-Oxo-2,5-dihydro-3,4-dihydroxyfuran, 53 (from 51b)

To a stirred solution of 0.003 mole of lithium n-propylmercaptide in dry hexamethylphosphoric triamide (0.5 M, 6 ml) prepared as in the procedure for 47, was added 0.25 g (0.00145 mole) of methyl ether 51b.

After 6 hrs at room temperature, it was worked up as described for 47, to give a nearly quantitative yield of 51a (0.225 g).

To a stirred solution of 0.50 g (3.16 mmole) of 51a in 5.0 ml dry dichloromethane containing 0.54 ml (6.6 mmole) of pyridine at 0°, was added 0.60 ml (6.3 mmole) of acetic anhydride and the resulting mixture stirred for 12 hrs at room temperature. Concentration of solvents in vacuo, followed by filtration through silica gel using 30% ethylacetate-chloroform, gave 0.60 g (95%) of crystalline acetate. The acetate was taken up in 5 ml of dry dichloromethane, and cooled to -78° (dry ice-acetone), under argon with stirring. To this solution was added 8.3 ml (15.8 mmole) of a 1.9 M solution of boron tribromide in dichloromethane. After stirring 1 hr at -78°, it was allowed to warm to 0° over 2 hrs, then stirred at 0° for 3 hrs. The reaction was quenched by careful addition of 10 ml of water. The aqueous layer was saturated with sodium chloride, then extracted twice with 50 ml portions of ethyl acetate. The organic layer was dried over magnesium sulfate, then solvents removed in vacuo. Methanol (100 ml) and a drop of dilute aqueous acid were added, and concentrated in vacuo. This procedure was repeated until at constant weight. (0.465 g, 102%). ir (nujol

mull) 1625 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (C=O), 3300 $cm^{-1}$ (broad, -OH) nmr ($d_6$-acetone) δ 1.40 (s,-$CH_3$). Mass measured molecular ion: calcd for $C_6H_8O_4$; 144.0423; found 144.0421.

2-Oxo-3,4-dimethoxy-7β,8β-epoxy-10 -carbomethoxy-1α-oxaspiro[4.5]deca-3-ene, (54)

To a stirred solution of 0.55 g (0.58 mmole) of 46 in 10 ml dry dichloromethane was added 0.141 g (0.70 mmole) of 85% m-chloroperbenzoic acid. The resulting mixture was stirred for 5 days at 20°. Excess peracid was destroyed with 15 ml of 10% sodium sulfite, and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with 20 ml 5% aqueous sodium bicarbonate, 30 ml water, and 30 ml saturated sodium chloride, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by column chromatography over silica gel (20% ethyl acetate-benzene) afforded 0.015 (9.7%) starting material 46, 0.054 g of an unidentified oxidation product (loss of spiro-ring), and 0.068 g (41%) of the desired β-epoxide 54. m.p. 91-3° (from ether) ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1735 $cm^{-1}$ (C=O), 1765 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.63, 3.77, 4.10 (3s ,3,3 -$OCH_3$), See also Figure 2.

Anal. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 55.03; H, 5.74.

2-Oxo-4-methoxy-7β,8β-epoxy-10α-carbomethoxy-1α-oxaspiro-[4.5]deca-3-ene, (55)

Using the procedure described above for 54, 0.087 g (0.365 mmole) of 43 gave after chromatography on silica gel (45% ethyl acetate-benzene), 0.085 g (92%) of crystalline epoxide 55. m.p. 105-106.5° (from ether) ir ($CHCl_3$) 1635 $cm^{-1}$ (C=C) and 1750 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 3.77, 4.05 (2s,3,2 $-OCH_3$), 5.18 (s,1,vinyl).

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.69; H, 5.60.

Attempted epoxide opening of 55 with lithium dimethyl cuprate

To a stirred solution of lithium dimethyl cuprate (0.16 mmole, from 0.030 g (0.16 mmole copper(I) iodide, 0.28 mmoles methyl lithium in ether) in 1.0 ml of dry ether at 0° was added 0.010 g (0.040 mmole) of the epoxide 55 in 0.5 ml dry benzene. After stirring 4 hrs. at 0°, the reaction was quenched with 10 ml saturated ammonium chloride solution, and extracted into 50 ml of ether. The organic layer was dried over magnesium sulfate, and the solvents removed in vacuo

to give 9 mg of crude oil. After preparative thin layer chromatography, 1.3 mg (12%) of a UV active material whose spectral properties were consistent with the desired product 56, and 5 mg (~42%) of a highly polar material, presumably 57 was isolated. ir ($CHCl_3$) 1635 $cm^{-1}$ (C=C), 1750 $cm^{-1}$ (C=O), 3600 $cm^{-1}$ (-OH); nmr ($CDCl_3$) δ 1.20 (d,J-6Hz,-$CH_3$), 3.60 (s,3,-$OCH_3$), 3.90 (s,3,-$OCH_3$).

2-Oxo-3,4-dimethoxy-10α-(t-butyldimethylsiloxymethyl)-1α-oxaspiro[4.5]deca-3,7-diene.

To a stirred solution of 1.3 g (0.0055 mmole) of alcohol 48 in 3.0 ml of dry dimethylformamide (distilled from silica gel) under argon was added 1.5 g (0.021 mole) sublimed imidazole and 1.65 g (0.011 mole) t-butyldimethylsilyl chloride (Petrarch), and the resulting mixture stirred 12 hours at 35°. The reaction was then poured into 25 ml saturated sodium bicarbonate, and extracted three times with 25 ml portions of ether. The ethereal extracts were washed once with saturated sodium chloride then dried over anhydrous magnesium sulfate. Removal of solvents in vacuo followed by chromatography over silica gel with 5% ethyl acetate-benzene gave 1.93 g (99%) of the silyl ether as a colorless oil. nmr ($CDCl_3$) δ 0.03 (s,6,Si-$(CH_3)_2$),

0.87 (s,9,Si-C($CH_3$)$_3$), 3.76, 4.07 (2s,3,2-$OCH_3$), 3.40 (m,1,methine), 5.60 (m,2,vinyl).

2-Oxo-3,4-dimethoxy-7β,8β-epoxy-10α-(t-butyldimethyl-siloxymethyl)-1α-oxaspiro[4,5]deca-3-ene, (58)

To a stirred solution of 0.430 g (1.21 mmoles) of the above silylether in 5 ml of dry ether was added 0.74 g (3.64 mmole) of m-chloroperbenzoic acid (85%), and the resulting mixture allowed to stir at 0° for 6 hrs., then quenched with 15 ml of 10% sodium sulfite, and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography over silica gel (15% ethyl acetate-benzene) gave 0.327 g (73%) of the desired epoxide 58. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1765 (C=O); nmr ($CDCl_3$) δ 0.03 (s,6,Si-($CH_3$)$_2$), 0.87 (s,9,Si-C($CH_3$)$_3$), 3.73 (s,3,-$OCH_3$), 4.02 (s,3,-$OCH_3$).

Anal. Calcd for $C_{18}H_{30}O_6Si$: C, 58.35; H, 8.16. Found: C, 58.47; H, 8.12.

2-Oxo-3,4-dimethoxy-7α-methyl-8β-hydroxy-10α-(t-butyl-dimethylsiloxymethyl)-1α-oxaspiro[4.5]deca-3-ene, (59)

To a stirred suspension of 1.34 mmoles of lithium dimethyl cuprate in 4.0 ml dry hexane under argon

(prepared in hexane by adding 1.64 ml (2.65 mmole) of low halide methyl lithium (Alfa) in ether (1.61 M) to a suspension of copper(I) iodide in 4.0 ml dry hexane at 0°) was added 0.100 g (0.27 mmole) of epoxide 58 in 0.5 ml dry ether. The mixture was allowed to warm to 15°, and stir at that temperature for 3 hrs. It was quenched with 50 ml saturated ammonium chloride, and extracted twice into 30 ml portions of ether. The combined organic layers were washed once with saturated sodium bicarbonate, then dried over magnesium sulfate. Removal of solvents in vacuo, followed by column chromatography (25% ethyl acetate-benzene) gave 0.043 g (43%) of starting material, 0.007 g (7%) of a ketone (ir ($CHCl_3$) 1670 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (C=O, ketone) and 1760 $cm^{-1}$ (C=O, butenolide) , and 0.051 g (49%) of the desired alcohol 59 (86% based on recovered starting material). ir ($CHCl_3$) 1675 $cm^{-1}$ (C=C), 1760 $cm^{-1}$ (C=O), 3600 $cm^{-1}$ (-OH); nmr ($CDCl_3$) δ 0.03 (s,3,-$Si(CH_3)_2$), 0.87 (s,0,-Si-$C(CH_3)_3$), 1.10 (d(J-7hz),3,CH-$CH_3$) , 3.75 (s,3,-$OCH_3$), 4.07 (s,3,-$OCH_3$).

Anal. Calcd for $C_{19}H_{34}O_6Si$: C, 59.04; H, 8.87. Found: C, 59.08; H, 8.98.

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy-10α-(hydroxymethyl)-1α-oxaspiro[4.5]deca-3-ene, (61)

To a stirred suspension of 0.0095 g (0.24 mmole) of potassium hydride (from 0.040 g of the 24% oil

dispersion supplied by Alfa, washed three times with dry pentane under argon and dried under vacuum) in 2 ml of dry tetrahydrofuran at 0° under argon was added 0.120 ml (1.91 mmole) of methyl iodide (freshly distilled from $P_2O_5$) followed by a solution of 0.074 g (0.191 mmole) of alcohol 59 in 0.5 ml of dry tetrahydrofuran. After stirring 15 min. at 0°, the mixture was allowed to warm to room temperature then stirred for 30 min. The reaction mixture was then cooled to 0° and quenched with 2 ml saturated ammonium chloride solution. The aqueous layer was extracted with 30 ml of ether, and the combined ether extracts washed with 20 ml of 10% sodium sulfite then dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography over silica gel (15% ethyl acetate-benzene) afforded 0.073 g (95%) of the methyl ether 60. ir ($CHCl_3$) 1675 $cm^{-1}$ (C=C), 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 0.03 (s,3,-$Si(CH_3)_2$), 0.87 (s,9,-Si-$C(CH_3)_3$), 1.10 (d,J=7hz),3,-CH-$CH_3$) 3.23 (s,3,-$OCH_3$), 3.75 (s,3,-$OCH_3$), 4.07 (s,3,-$OCH_3$). The methyl ether 60 (0.073 g, 0.182 mmole) was taken up in a mixture of 1.4 ml glacial acetic acid, 0.4 ml water and 2.4 ml tetrahydrofuran, and kept at room temperature for 24 hrs. Ether (10 ml) was added, the aqueous layer saturated with sodium chloride and extracted two more times with ether. The combined

organic layers were washed with saturated sodium bicarbonate (10 ml) then dried over magnesium sulfate. Removal of solvents in vacuo, followed by chromatography on silica gel (45% ethyl acetate-benzene), afforded 0.052 g (100%) of the alcohol 61. ir ($CHCl_3$) 1670 $cm^{-1}$ (C=C), 1750 $cm^{-1}$ (C=O), 3600 $cm^{-1}$ (-OH); nmr ($CDCl_3$) 1.10 (d(J-7Hz),3,-CH-$CH_3$), 3.23 (s,3,-$OCH_3$), 3.75 (s,3,-$OCH_3$) 4.07 (s,3,-$OCH_3$). Mass measured molecular ion calcd for $C_{14}H_{22}O_6$; 286.1416; found 286.1415.

2-Oxo-3,4-dimethoxy-10α-carbaldehyde-1α-oxaspiro[4.5]-deca-3,7-diene, (62).

To a stirred suspension of 0.318 g (1.48 mmole) of pyridinium chlorochromate[85] in 2 ml of dry dichloromethane was added 0.178 g (0.741 mmole) of alcohol 48 in 2 ml of dry dichloromethane, and the resulting mixture allowed to stir at room temperature for 3 hrs, then diluted with 25 ml of anhydrous ether and decanted. The black ppt. was washed with three additional portions of ether then the combined organic extracts filtered through silica gel using ether. Removal of solvent in vacuo afforded 0.157 g (89%) of aldehyde 62, which was not purified further but used directly in the next step (decomposes on standing at room temperature).

ir ($CHCl_3$) 1660 $cm^{-1}$ (C=C), 1710 $cm^{-1}$ (C=O), 1750 $cm^{-1}$ (C=O), 2720 $cm^{-1}$ (aldehyde C-H); nmr ($CDCl_3$) δ 3.83 (s,3,-$OCH_3$), 4.16 (s,3,-$OCH_3$), 5.70 (m,2,vinyl), 9.53 (d(J-1hz),1,aldehydic proton).

2-Oxo-3,4-dimethoxy-10α-(1-hydroxy-2-propen-1-yl)-1α-oxaspiro[4.5]deca-3,7-diene, (63)

A. Using vinylmagnesium bromide.

The aldehyde 62 (0.157 g, 0.66 mmole) was taken up in dry tetrahydrofuran and cooled to -78° (dry ice-acetone) under argon with stirring. To this solution was added 0.72 ml (0.72 mmole) 1.0 M vinylmagnesium bromide[103] (from vinyl bromide and magnesium turnings) in tetrahydrofuran, and the resulting mixture kept at -78° for 15 min, allowed to warm to -30° for 15 min, then quenched with 2.0 ml of saturated ammonium chloride solution. The aqueous layer was extracted three times with 20 ml of ether, and the ethereal extracts dried over magnesium sulfate. Removal of solvents in vacuo, followed by column chromatography over silica gel using 45% ethyl acetate-benzene gave 0.137 g (79%) of the allyic alcohol 63, which was immediately acylated with an appropriate active ester. ir ($CHCl_3$) 1665 $cm^{-1}$ (C=C), 1740 $cm^{-1}$ (C=O), 3590 $cm^{-1}$ (-OH); nmr ($CDCl_3$) δ 3.87 (s,3,-$OCH_3$), 4.16 (s,3,-$OCH_3$), 5.0-6.0 (m,5H,vinyls).

B. Using vinylmanganese iodide.[86]

To a stirred suspension of 0.107 g (0.346 mmole) of anhydrous manganese iodide (ROC/RIC) in 2 ml of dry ether cooled to -20° (isopropanol-water-dry ice bath) was added 0.32 ml (0.317 mmole) of 1.0 M vinylmagnesium bromide in tetrahydrofuran dropwise over 5 min. After stirring for 5 min at -20°, it was allowed to warm to room temperature and stir 30 min, then cooled to -10° and 0.050 g (0.210 mmole) of the aldehyde 62 was added dropwise. The resulting cream colored suspension was stirred for 45 min at -10°, then quenched with 5 ml of saturated ammonium chloride soltuion and extracted with 50 ml of ether. The ether extract was washed with 50 ml 10% sodium sulfite, then twice with saturated sodium bicarbonate, and dried over magnesium sulfate. Removal of solvents in vacuo, followed by silica gel column chromatography (45% ethyl acetate-benzene) gave 0.049 g (92%) of the desired vinyl alcohol 63.

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

Using an identical procedure as for aldehyde 62, from 0.048 g (0.17 mmole) of alcohol 61, 0.043 g (89%) of aldehyde 64 was obtained. ir ($CHCl_3$) 1660 $cm^{-1}$ (C=C), 1710 $cm^{-1}$ (C=O), 1750 $cm^{-1}$ (C=O), 2715 $cm^{-1}$ (H-C=O);

nmr ($CDCl_3$) δ 1.10 (d(J=7 hz),3,CH-$CH_3$), 3.23 (s,3,-$OCH_3$), 3.75 (s,3,-$OCH_3$), 4.07 (s,3,-$OCH_3$), 9.57 (s,1,H-C=O).

2-Oxo-3,4-dimethoxy-7α-methyl-8β-methoxy-10α-(1-hydroxy-2-propen-1-yl)-1 -oxaspiro[4.5]deca-3-ene, (64).

Treatment of the aldehyde 62 (0.040 g, 0.14 mmole) with 0.17 ml of 1.0 M vinylmagnesium bromide in tetrahydrofuran (0.17 mmole) as described for the allylic alcohol 63, afforded 0.034 g (79%) of allylic alcohol 65. ir ($CHCl_3$) 1665 $cm^{-1}$ (C=C), 1740 $cm^{-1}$ (C=O), 3600 $cm^{-1}$ (-OH); nmr ($CDCl_3$) δ 3.25 ( ,3,-$OCH_3$) 3.76 (3s,3-$OCH_3$) 4.06 (s,3,-$OCH_3$), 5.0-6.0 (m,3,vinyl).

Anal. Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.76. Found: C, 61.50; H, 7.68.

(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl-propionate, (65).

A. Using pyridine as a base.

To a stirred solution of 0.090 g (0.354 mmole) of allylic alcohol 63 in 2.0 ml of dry dichloromethane at 0° (ice bath) under argon was added 0.032 ml (0.39 mmole) dry pyridine followed by 0.034 ml (0.39 mmole) propionyl chloride. After warming to room temperature, the mixture was stirred 1.5 hr, then dichloromethane added and washed with saturated sodium bicarbonate. The organic

layer was dried over magnesium sulfate, then the solvents removed *in vacuo*. Column chromatography on silica gel (30% ethyl acetate-benzene) gave 0.083 g (76%) of the propionate *65*. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1730 $cm^{-1}$ (C=O) and 1750 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 1.10 (t(J=7.5hz),3,--$CH_2$-$CH_3$), 3.82 (s,3,-$OCH_3$), 4.12 (s,3,-$OCH_3$). Mass measured molecular ion; calcd for $C_{17}H_{22}O_6$; 322.1416; found 322.1412 .

B. Using 4-dimethylaminopyridine as a base.[92]

To a stirred solution of 0.015 g (0.059 mmole) of the allylic alcohol *63* in 1.0 ml dry dichloromethane was added 0.0085 g (0.078 mmole) 4-dimethylaminopyridine followed by 0.0056 ml (0.065 mmole) of propionyl chloride. After 2 hrs. at room temperature, the mixture was concentrated to dryness *in vacuo*, then purified by preparative thin layer chromatography (45% ethyl acetate-benzene), to afford 0.017 g (92%) of the desired propionate *65*.

*2-Oxo-3,4-dimethoxy-10α-(4-carbomethoxy-(Z)-1-penten-1-yl)-1α-oxaspiro[4.5]deca-3,7-diene, (66)*.

A. Attempted enolization of *65* with lithium diisopropylamide in tetrahydrofuran.

To a stirred solution of 1.35 mmoles of lithium diisopropylamide (from 1.35 mmoles of n-butyl lithium in

hexane and 0.23 ml (1.65 mmoles) dry diisopropylamine, removal of hexane *in vacuo* and replacement with dry tetrahydrofuran under argon) in 2.0 ml of dry tetrahydrofuran cooled to -78° under argon was added dropwise 0.083 g (0.27 mmole) of propionate *65* in 0.5 ml dry tetrahydrofuran. After stirring for 10 min. at -78°, 0.90 ml (1.35 mmole) of 1.50 M t-butyldimethylsilyl-chloride in hexamethylphosphorictriamide was added and the resulting mixture allowed to warm to room temperature and stir for 2 hrs. The resulting mixture was diluted with ether and washed with 5% sodium bicarbonate solution, then water, saturated sodium chloride, and dried over magnesium sulfate. Removal of solvent *in vacuo* followed by chromatography over silica gel (25% ethyl acetate-benzene) gave back 0.070 g (85%) of the starting material.

B. Enolization with potassium hexamethyl disilylamide (*PHD*)[104]

To a stirred solution of 0.225 mmole potassium hexamethyl disilylamide in 1.0 ml dry tetrahydrofuran (prepared as described by C.A. Brown ) cooled to -78° under argon was added 0.035 g (0.113 mmole) of propionate *65* in 0.5 ml tetrahydrofuran. Stirred 5 mm at -78°, then 0.16 ml (0.242 mmole) of 1.5 M t-butyldimethylsilyl-

chloride in hexamethylphosphorictriamide was added and the resulting mixture allowed to warm to room temperature and stir 3 hrs. The reaction was quenched with 10% hydrochloric acid and extracted into ether. The ethereal extracts concentrated in vacuo, the residue was taken up in tetrahydrofuran and 10% hydrochloric acid added. After 20 min.TLC indicates no silyl ester remaining, and the mixture diluted with ether, aqueous layer washed twice with 10 ml portions of ether and the combined ether layers dried over magnesium sulfate. Treatment with diazomethane followed by removal of solvents in vacuo and chromatography over silica gel (25% ethyl acetate-benzene) gave 0.0064 g (18%) starting material and 0.025 g (68%) of the desired methylester 66.
ir ($CHCl_3$) 1675 $cm^{-1}$ (C=C), 1725 $cm^{-1}$ (C=O), 1750 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 1.10 (m,3,-$CH_3CH_3$), 3.63 (s,3,-$OCH_3$) 3.77 (s,3,-$OCH_3$), 4.04 (s,3,-$OCH_3$), 5.21 (m,2,vinyl), 560 (m,2,vinyl).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.23.

[(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl]-cis-2-carboxy-trans-2-methyl-cyclohexanepropionate, (72)

Prepared as described for the propionate 65, except addition of 4-dimethylamino-pyridine as a catalyst.

From 0.110 g (0.416 mmole) of allylic alcohol 63, and 0.110 g (0.457 mmole) of the acid chloride 71,[90] in 2 ml dry dichloromethane containing 0.040 ml (0.457 mmole) dry pyridine and 0.010 g (0.04 mmole) 4-dimethylaminopyridine was obtained 0.120 g (62%) of ester 72. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1730 $cm^{-1}$ (C=O) and 1750 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 1.20 (s,3,-$CH_3$), 3.64, 3.77, 4.04 (3s,3,3 -$OCH_3$), 5.0-6.0 (m,5,vinyls).

Attempted rearrangement of allylic ester 72

The allylic ester 72 (0.100g, 0.285 mmole) was subjected to the conditions used to rearrange ester 65 (potassium hexamethyldisilylamide in tetrahydrofuran, trapping with t-butyldimethylchlorosilane in hexamethylphosphoramide). No rearranged product was detected (TLC). Instead 90 mg of the 2-carboxy hydrindanone 73 was isolated (preparative thin layer chromatography) ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (C=O) 1740 $cm^{-1}$ (C=O) and 1750 $cm^{-1}$ (C=O); nmr 1.16 (s,3,-$CH_3$), 3.77, 4.04 (2s,3,2-$OCH_3$) 5.0-6.0 (m,5,vinyls).

1α- Methyl-7αH-2-oxabicyclo[5.4.0]undeca-2,5-dione (74)

To a stirred solution of 0.200 g (0.934 mmole) of dicyclohexyl-carbodiimide, and the resulting mixture allowed to stir at room temperature for 22 hrs. The

resulting white precipitate was filtered off, and the solvent removed in vacuo. The crude product was then evaporatively distilled (0.01 mm, 95-100°) to give 0.138 (75%) of the anhydride 74. ir ($CHCl_3$) 1750 $cm^{-1}$ and 1800 $cm^{-1}$ (anhydride C=O); nmr ($CDCl_3$) δ 1.25 (s,3,-$CH_3$).

[(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-dien-10α-yl)-2-propen-1-yl]cis-2-carboxy-trans-2-methyl-cyclohexane propionate (77)

To a stirred solution of 0.130 g (0.662 mmole) of anhydride 74 and 0.062 g (0.233 mmole) of allylic alcohol 63 in 3 ml of dry dichloromethane was added 0.054 g (0.42 mmole) of 4-dimethylaminopyridine and the mixture stirred at room temperature for 30 min, then refluxed for 15 min and cooled to room temperature. Ether was added and the organic layer washed once with 10% hydrochloric acid, twice with saturated copper II sulfate solution, then saturated sodium chloride and dried over magnesium sulfate. Removal of solvents in vacuo followed by chromatography over silica gel using 45% ethyl acetate-benzene gave 0.092 g (85%) of the acid-ester 77. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1700 $cm^{-1}$ (carboxyl C=O), 1735 $cm^{-1}$ (C=O), 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) δ 1.22 (s,3,$CH_3$), 3.76, 4.13 (2s,3,2-$OCH_3$), 5.0-6.0 (complex

multiplets, 5, vinyl), 8.8 (s,1-$CO_2H$). Mass measured molecular ion: calcd for $C_{25}H_{34}O_8$; 462.2253; found 462.2261.

2-Oxo-3,4-dimethoxy-10α-(4-carbomethoxy-5-(cis-2-carbomethoxy-trans-2-methyl cyclohexane)-(Z)-1-penten-1-yl)-1α-oxaspiro[4.5]deca-3,7-diene (78)

Using the procedure described for 66; from 0.092 g (0.199 mmole) of acid ester 77, 0.80 mmole potassium hexamethyldisilylamide, 5 ml dry tetrahydrofuran, quenching at -78° with 0.210 ml (1.28 mmole) of 75% trimethylsilylchloride in dry triethylamine (centrifuged under argon to remove triethylamine hydrochloride), and stirring 12 hrs at room temperature, gave after workup a crude diacid which was treated with diazomethane in ether to give the diester 78. Chromatography over silica gel (15% ethyl acetate-benzene) afforded 0.078 g (80%) of diester 78. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (ester C=O), 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 1.22 (s,3,-$CH_3$), 3.64 (s,6,2-$OCH_3$), 3.77, 4.04 (2s,3,2-$OCH_3$), 5.21 (m,2,vinyl), 5.60 (m,2, vinyl). Mass measured molecular ion: calcd for $C_{27}H_{38}O_8$; 490.2566; found 490.2580.

2-Oxo-3,4-dimethoxy-10α-(5-(cis-2-carbomethoxy-trans-2-methylcyclohexane)-(Z)-1-penten-1-yl)-1α-oxaspiro[4.5]-deca-3,7-diene (79).

To a stirred solution of 0.045 g (0.0917 mmoles) of diester 78 in dry ether cooled to -78° under argon was added 0.13 ml (0.183 mmole) of 1.40 M diisobutylaluminumhydride in hexane, and the resulting mixture allowed to stir at -78° for 1 hr, 1.0 ml of methanol added, and after stirring for 10 min at -78°, was allowed to warm to room temperature over 10 min. Ether was added and washed four times with saturated sodium potassium tartrate, and dried over magnesium sulfate. Removal of solvents in vacuo gave 0.042 g crude aldehyde-ester. ir ($CHCl_3$) 1640 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (aldehyde C=O), 1735 (ester C=O), 1760 $cm^{-1}$ (butenolide C=O), 2780 (aldehyde C-H). The aldehyde was taken up in 3 ml of dry benzene and 0.100 g (0.110 mmole) of tris-(triphenylphosphine)-rhodium chloride was added and the mixture degassed twice (freeze-pump-thaw cycles). After refluxing for 48 hrs under argon, the mixture was concentrated in vacuo, and taken up in ether (10 ml) filtered and concentrated in vacuo. Preparative thin layer chromatography (15% ethyl acetate-benzene) afforded 0.020 g (48%) of the ester 79. ir ($CHCl_3$) 1640 $cm^{-1}$ (C=C), 1720 $cm^{-1}$ (ester C=O), 1760 $cm^{-1}$ (C=O). nmr ($CDCl_3$) 1.22 (s,3,-$CH_3$), 3.64, 3.77, 4.04 (3s,3,3-$OCH_3$),

5.20 (m,2,vinyl), 5.60 (m,2,vinyl). Mass measured molecular ion: calcd for $C_{25}H_{36}O_6$; 432.2512; found 432.2517.

cis-2-Chloroformyl-trans-2-methyl-cyclohexane butyryl chloride (76)

To a stirred solution of 0.710 g (3.1 mmoles) of diacid 75 in 15 ml of dry benzene was added 0.95 ml (11.0 mmoles) of oxalylchloride, and the mixture allowed to stir 24 hrs at room temperature. Removal of solvents in vacuo, gave 0.639 g (90%) of diacid chloride 76, which was used without further purification in the esterification step. ir ($CHCl_3$) 1975 $cm^{-1}$ (acyl chloride C=O); nmr ($CDCl_3$) $\delta$ 1.20 (s,3,$-CH_3$).

[(2-Oxo-3,4-dimethoxy-1α-oxaspiro[4.5]deca-3,7-diene-10α-yl)-2-propenyl-1-yl]cis-2-carboxy-trans-2-methyl-cyclohexane butyrate (81)

To a stirred solution of 0.085 g (0.318 mmole) of the alcohol 63 in 5 ml of dry dichloromethane was added 0.044 ml (0.382 mmole) of dry 2,6-lutidine and 0.085 g (0.32 mmole) of the diacid chloride 76. The resulting mixture was allowed to stir overnight, then diluted with dichloromethane and washed with 10% hydrochloric acid and saturated copper (II)sulfate solution. The products

were isolated by column chromatography over silica gel using 45% ethyl acetate-benzene to give 0.122 g (83%) of the desired acid-ester 81. ir ($CHCl_3$) 1680 $cm^{-1}$ (C=C), 1700 $cm^{-1}$ (carboxyl C=O), 1735 $cm^{-1}$ (C=O), 1760 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 1.23 (s,3,-$CH_3$), 3.76, 4.10 (2s,3,2-$OCH_3$), 5.0-6.0 (complex multiplets, 5,vinyl), 9.0 (s,1,-$CO_2H$) mass measured molecular ion: calcd for $C_{26}H_{36}O_8$; 476.2410; found 476.2413.

## REFERENCES AND NOTES


1. J. Berdy, Adv. Appl. Microbiology, 18, 309-406 (1974).
2. R. B. Woodward, Angew Chem., 69, 50 (1957).
3. J. S. Glasby, "Encyclopedia of Antibiotics", Wiley-Interscience, New York, N. Y., 1976.
4. For a provocative introduction to the aspects of antibiotics research, and a definition of the biochemical problems associated with them, see H. Zahner, Angew. Chem. Int. Ed. Engl., 16, 687-694 (1974).
5. a) M. Berry, Quart. Rev., 17, 343 (1963);
   b) W. D. Clemer, Pure Appl. Chem., 28, 413 (1971);
   c) W. Keller-Schierlem, Fortschr. Chem. Org. Naturstoffe, 30, 313 (1973);
   d) S. Masamune, G. S. Bates, J. W. Corcoran, Angew. Chem. Int. Ed. Engl., 16, 585-607 (1977).
   e) K. C. Nicolau, Tet. Lett., 33, 683-710 (1977).
   f) T. G. Back, Tet., 33, 3041-3059 (1977).
6. a) S. Masumune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, G. S. Bates, J. Amer. Chem. Soc., 97, 3512 (1975);
   b) S. Masamune, H. Yamamoto, S. Kamata, A. Fukuzawa, ibid., 97, 3513 (1975).
7. E. W. Colvin, T. A. Purcell, and R. A. Raphael, J. Chem. Soc. Chem. Comm., 1031 (1972); J. Chem. Soc. Perkin I, 1718 (1976).

8. E. J. Corey, K. C. Nicolaou, and T. Toru, J. Amer. Chem. Soc., 97, 2287 (1975).

9. a) J. Gombos, E. Haslinger, H. Zak, and U. Schmidt, Tet. Lett., 3591 (1975);

b) U. Schmidt, J. Gombos, E. Haslinger, and H. Zak, Chem. Ber., 109, 2628 (1976);

c) H. Gerlach, K. Oetle, A. Thalmann, and S. Servi, Helv. Chim. Acta, 58, 2036 (1975).

10. E. J. Corey and R. H. Wollenberg, Tet. Lett., 4705 (1976).

11. F. Johnson, in "The Total Synthesis of Natural Products", J. ApSimon, ed., Wiley-Interscience, New York, N.Y., 1973, pp. 331-465.

12. R. E. Ireland and C. S. Wilcox, Tet. Lett., 2839 (1977).

13. D. A. Evans, D. J. Baillargeon, and J. V. Nelson, J. Amer. Chem. Soc., 100, 2242 (1978).

14. W. Keller-Schierlein, R. Muntwyler, W. Pache, and H. Zähner, Helv. Chim. Acta, 52, 127 (1969).

15. a) R. Muntwyler, J. Widmer, and W. Keller-Schierlein, Helv. Chim. Acta, 53, 1544 (1970);

b) R. Muntwyler and W. Keller-Schierlein, Helv. Chim. Acta, 55, 2071 (1972).

16. M. Brufani, S. Cerrini, W. Fedeli, F. Mazza, and R. Muntwyler, Helv. Chim. Acta, 55, 2094 (1972).

17. P. W. Schindler and H. Zaehner, Eur. J. Biochem., 55, 543 (1975).

18. a) P. W. Schindler, Eur. J. Biochem., 51, 579 (1975);
b) P. W. Schindler and M. C. Crutton, Eur. J. Biochem., 55, 543 (1975).

19. B. D. Sawal, P. Maeba, and R. A. Cook, J. Biol. Chem., 241, 5177 (1966).

20. P. W. Schindler and H. Zaehner, Arch. Microbiol., 82, 66 (1972).

21. W. Pache and D. Chapman, Biochem. Biophys. Acta, 255, 348 (1972).

22. A. Tomasz and S. Waks, P.N.A.S., 72, 4162 (1975).

23. T. K. Devon and A. I. Scott, "Handbook of Naturally occurring Organic Compounds", Vol. I, Academic Press, New York, N.Y., 1975, pp. 403-407; see also Reference 27.

24. For recent marine natural products containing tetronic acids see W. Hofheinz and P. Schönhdzer, Helv. Chim. Acta, 60, 1367 (1977) and references cited therein.

25. Phytotoxic tetronic acid derivatives; K. Kobayashi and T. Ui, Tet. Lett., 4119 (1972) and references cited therein.

26. With the exception of ascorbic acid, the literature pertaining to these compounds is sparse. They have

been prepared in an impure state by L. J. Haynes, and J. R. Plimmer, J. Chem. Soc., 4665 (1956); for a review on ascorbic acid see E. L. Hirst, Fortschr. Chem. Org. Naturstoffe., 132 (1939).

27. For good reviews on tetronic acids see a) L. J. Haynes, J. R. Plimmer, Quarterly Reviews, 14, 292-315 (1960);
b) Y. S. Rao, Chem. Rev., 76, 625-694 (1976).

28. L. J. Haynes, A. H. Stanners, J. Chem. Soc., 4103 (1956).

29. A. Svendson and P. M. Boll, J. Org. Chem., 40, 1927 (1975).

30. R. E. Ireland, "Organic Synthesis", Prentice-Hall, Englewood Cliffs, N.J., 1969, P. 29.

31. R. E. Ireland, R. H. Mueller and A. K. Willard, J. Org. Chem., 41, 986 (1976).

32. P. N. Confalone, G. Pizzolato, E. C. Baggiolini, D. Lollar, and M. R. Uskokovic, J. Amer. Chem. Soc., 99, 7020 (1977).

33. A. Gerhard, R. Muntwyler, and W. Keller-Schierlein, Helv. Chim. Acta, 58 (1975).

34. T. H. O'Neil, Ph. D. Dissertation, California Institute of Technology, in preparation.

35. D. J. Dawson and R. E. Ireland, Tet. Lett., 689 (1973). For reviews on decarbonylation see references 93-95.

36. F. G. Mann and M. J. Pragnell, Chem. Ind. (London), 1389 (1964); R. E. Ireland and D. M. Walba, Org. Syn., 56, 44 (1977).

37. G. Stork and P. F. Hudrlik, J. Amer. Chem. Soc., 90, 4463, 4464 (1968); E. J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1972).

38. W. Nagata, M. Yoshioka, and S. Hirai, J. Amer. Chem. Soc., 94, 4635-4672 (1972); W. Nagata and M. Yoshioka, Org. Syn., 52, 90, 100 (1972).

39. R. P. Linstead and A. F. Millidge, J. Chem. Soc., 478 (1936).

40. A. Wohl and C. Oesterlin, Ber., 34, 1144 (1901).

41. J. C. Roberts, J. Chem. Soc., 3315 (1952).

42. A. S. Onischenko, "Diene Synthesis", Israel Program for Scientific Translations, Jerusalem, 1964, p. 144.

43. M. C. Kloetzel, Org. Reactions, 4, 8 (1945).

44. A. M. Clifford, Chem. Abstracts, 40, 3196 (1946).

45. S. Putmann, Ind. Eng. Chem. Analyt. Ed., 18, 628 (1946).

46. A. S. Onishchenko, ref. 42, p. 136.

47. H. Minato and I. Horibe, J. Chem. Soc. (C), 2131 (1968).

48. K. N. Houk, J. Amer. Chem. Soc., 95, 4092 (1973).

49. R. Sustmann, Tet. Lett., 2721 (1971); I. Fleming, F. L. Gianni, T. Mah, Tet. Lett., 881 (1976).

50. R. A. Firestone, J. Org. Chem., 2181 (1972); T. Kametani, Y. Kato, T. Houda, K. Fukumoto, J. Chem. Soc. Perkin I, 2001 (1975).

51. J. Klein, E. Dunkelblum, D. Avrahami, J. Org. Chem., 32, 935 (1967).

52. Carbon-13 nmr spectra later confirmed this result.

53. A. S. Onischenko, ref. 42, p. 203.

54. L. Crombie, P. A. Gilbert, R. P. Houghton, J. Chem. Soc. (C), 135 (1968).

55. W. H. Carothers, A. M. Collins, and J. E. Kirby, J. Amer. Chem. Soc., 55, 786 (1933).

56. A. A. Petrov, Zhurnal Obshei Khimii, 13, 741 (1943).

57. K. Alder, Ann., 586, 138 (1954).

58. E. D. Bergmann, J. Appl. Chem., 3, 145 (1953).

59. R. Sustmann, Tet. Lett., 2721 (1971).

60. B. Lythgoe, R. S. Davidson, P. S. Littlewood, T. Medcalfe, S. M. Waddinton-Feather, and P. H. Williams, Tet. Lett., 1413 (1963).

61. M. S. Newman and H. A. Lloyd, J. Org. Chem., 17, 577 (1952); I. N. Nazavov, Izv. An. SSSR Okhn., 1462 (1956).

62. S. Danishefsky and T. Kitahara, J. Amer. Chem. Soc., 96, 7807 (1974).

63. S. Danishefsky and T. Kitahara, J. Org. Chem., 40, 538 (1975).

64. R. Barker and D. L. MacDonald, J. Amer. Chem. Soc., 82, 2301 (1960).

65. L. I. Zakhavkin and I. M. Khorlina, Tet. Lett., 619 (1962).

66. M. J. Begley, D. W. Knight, and G. Pattendon, Tet. Lett., 4279 (1975).

67. P. Petuely and H. F. Bauer, Monatsh., 83, 758 (1952).

68. P. A. Bartlett and W. S. Johnson, Tet. Lett., 4459 (1970).

69. For a review on the selectivity of hydride reducing agents see E. R. H. Walker, Chem. Society Reviews, 5, 23-50 (1976).

70. R. W. Jeanloz and E. Walker, Carbohydrate Res., 4, 504 (1967).

71. H. C. Brown and S. Krishnamurthy, J. Amer. Chem. Soc., 95, 1669 (1973).

72. For a good review of directive effects in epoxidation, see G. Berti, Topics in Stereochemistry, 7, 93-252 (1973).

73. J. F. W. McOmie, M. L. Watts, and D. E. West, Tetrahedron, 24, 2289 (1968).

74. R. D. Acker, Tet. Lett., 3407 (1977).

75. R. W. Herr, D. M. Wieland, and C. R. Johnson, J. Amer. Chem. Soc., 92, 3813 (1972).

76. T. Livinghouse and B. Rickborn, J. Org. Chem., 38, 4263 (1973).

77. E. J. Corey and M. G. Bock, Tet. Lett., 2643 (1975).

78. D. R. Hicks and B. Fraser-Reid, Can. J. Chem., 53, 2017 (1975).

79. R. A. Amos and J. A. Katzenellenbogen, J. Org. Chem., 42, 2537 (1977).

80. G. H. Posner, Org. Reactions, 22, 287-90, 389-93 (1975).

81. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Ed. K. L. Rinehart, Jr., Prentice-Hall, Englewood Cliffs, N.J., 1965, pp. 116-117.

82. S. A. Cerefice and E. K. Fields, J. Org. Chem., 41, 355 (1976).

83. H. O. House, Acc. Chem. Res., 9, 59 (1976).

84. E. J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1972).

85. E. J. Corey and J. W. Suggs, Tet. Lett., 2647 (1975).

86. G. Cahiez and J. F. Normant, Tet. Lett., 3383 (1977).

87. R. E. Ireland and A. K. Willard, Tet. Lett., 3975 (1975).

88. R. F. Church, R. E. Ireland, and D. R. Shridhar, J. Org. Chem., 27, 707 (1962).

89. B. E. Edwards and P. N. Rao, J. Org. Chem., 31, 324 (1966).

90. W. E. Bachmann and A. S. Dreiding, J. Org. Chem., 13, 317 (1948).

91. N. J. Doorenbos and M. T. Wu, Chem. and Ind. 648 (1965).

92. G. Höfle and W. Steiglich, Synthesis, 619 (1972) and references cited therein.

93. For reviews on decarbonylation see J. Tsuji, in "Organic Synthesis via Metal Carbonyls", Vol II.,

I. Wender and P. Pino, Eds., Wiley-Interscience, 1977, pp. 595-654.

94. K. Sakai, O. Oda, and N. Nakamura, Tet. Lett., 1287 (1972).

95. B. M. Trost and M. Preckel, J. Amer. Chem. Soc., 7862 (1973).

96. C. W. Bird, "Transition Metals in Organic Synthesis", Chapter 9, New York, N.Y., 1967, pp. 239-247.

97. T. Mukaiyama, M. Usui and K. Saigo, Chem. Lett., 49 (1976).

98. Z. Eckstein, A. Sachen, and T. Urbanski, Bull. Acad. Polon. Sci. Classe III, 5, 213 (1957).

99. J. E. McMurray, Accts. Chem. Res., 7, 281 (1974) and references cited therein.

100. K. Mori and M. Matsui, Tet., 24, 3127 (1968); see also reference 39.

101. For the use of transition metal assisted nucleophilic attack at nitriles see L. Bagnell, E. A. Jeffery, A. Meisters, and T. Mole, Aust. J. Chem., 27, 2577 (1974); T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, Tetrahedron Lett., 4555 (1969); C. Paraskewas, Synthesis, 574 (1974); M. S. Kharasch, R. C. Seyler, and F. R. Mayo, J. Amer. Chem. Soc., 60, 882 (1958).

102. F. Benington and R. D. Morin, J. Org. Chem., 26, 194 (1961).

103. For a review of the use and preparation of alkenyl magnesium halides see: H. Normant, Adv. Org. Chem., 2, 1-65 (1960).

104. C. A. Brown, J. Org. Chem., 39, 3913 (1974).