PROGRESS TOWARDS THE TOTAL SYNTHESIS
OF CHLOROTHRICOLIDE

by

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ABSTRACT

The intramolecular Diels-Alder reactions of a series of methyl
undeca-2,8,10-trienoates have been examined in connection with a
planned synthesis of the bottom-half 54 of chlorothricolide 3. The
intramolecular Diels-Alder reactions of these substrates preferen-
tially afford products possessing cis-ring fusions rather than the
desired trans-fused cycloadducts. In each case, the product dis-
tribution is independent of dienophile stereochemistry. Product
ratios range from 62:28 to 81:19 (cis:trans). Trienes 84 and 85
afford essentially equal mixtures of cis- and trans-fused products.
The intramolecular Diels-Alder reaction of trienone 91 shows re-
versed selectivity for the trans-fused product (65:35 trans:cis),
but 142 isomerizes to 143 under the reaction conditions.

The intramolecular Diels-Alder reactions of diene acetylenes
90, 190, and 201 were examined in connection with a modified syn-
thetic approach to 54. Dissolving metal reduction of α,β-unsaturated
acid 206 afforded almost exclusively a mixture of trans-fused acids
207 and 208. The stereochemistry of the enolate protonation step
in the work-up of the dissolving metal reduction was dependent on
the functionality present within the C(6)-side chain of acids 193
and 206. Alkylation of ester 209 provided a 4:1 mixture of 213:
214. Alkylation of lactone 216 afforded exclusively the desired
α-methylated product, 219, a synthetic equivalent of the bottom-
half of chlorothricolide.

The overall yield of 219 from the starting material, 4-benzylxy-
butyraldehyde, was 15% for the fourteen step sequence.

Thesis Supervisor: Dr. William R. Roush

Title: Rodger and Georges Firmenich Career Development
Assistant Professor of Natural Products Chemistry
To my loving wife

Jane
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ABBREVIATIONS

THF - tetrahydrofuran
DMF - dimethylformamide
DMSO - dimethylsulfoxide
DMAP - 4-dimethylaminopyridine
PCC - pyridinium chlorochromate
PDC - pyridinium dichromate
HMPA - hexamethylphosphoric triamide
DCC - dicyclohexylcarbodiimide
DME - dimethoxyethane
MCPBA - m-chloroperbenzoic acid
DIBAL - diisobutylaluminum hydride
LDA - lithium diisopropylamide
TMSCl - trimethylsilylchloride
TBDMSCl - t-butyldimethylsilylchloride
p-TsOH - p-toluenesulfonic acid
NMO - N-methylmorpholine-N-oxide
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CHAPTER 1
INTRODUCTION

Chlorothricin (1) was first isolated from the fermentation broths of *Streptomyces antibioticus* by Keller-Schierlein and coworkers in 1969. This metabolite was not obtained in a purified form, but rather was isolated as an inseparable mixture with the corresponding dechloro compound (approximately 4:1, 1: dechloro-1). Keller-Schierlein et al. were able to induce the organism to synthesize the related bromo analog by the addition of 0.5% potassium bromide to the fermentation medium.

(1) Chlorothricin

\[ R^1 = \quad R^2 = H \]

(2) Chlorothricin methyl ester \( R^1 = H, \quad R^2 = CH_3 \)

(3) Chlorothricolide \( R^1 = H, \quad R^2 = H \)


The structure of chlorothricin was reported three years later\(^3,4\). The structure determination relied heavily on an x-ray crystal structure analysis of the aglycone, chlorothricilide methyl ester \(^2\). This work revealed that chlorothricin \(_1\) was a novel macroclide antibiotic. The 14-membered macrocyclic lactone of chlorothricilide \(_3\) incorporates a trans-decalin system and a tetronic acid moiety spiro-linked to a cyclohexenyl ring\(^6\). The disaccharide residue, linked to the trans-decalin nucleus, consists of two molecules of 2,6-dideoxy-D-arabino-hexose (2-deoxy-D-rhamnose)\(^7\).


7. This sugar has been the subject of intense synthetic interest. For recent syntheses of this hexose see:

(a) Roush, W.R.; Brown, R.J. J. Org. Chem. 1982, 47, 1371;


(c) Thiem, J.; Sievers, A. Chem. Ber. 1980, 113, 3505;

(d) Ref. 3 and 5 cited in ref. 7a. For other recent syntheses of carbohydrates from non-carbohydrate precursors see

This dideoxyhexose is only occasionally encountered in antibiotics, e.g., in the venturicidins\(^8\), avilamycin\(^9\), curamycin\(^10\), olivomycin\(^11\), and the chromomycins\(^12\). The aromatic side chain which is esterified to the 3"'-hydroxyl group of the disaccharide was identified as 5-chloro-6-methyl salicylic acid methyl ether by independent synthesis\(^3\).

At the time of its isolation and identification, chlorothricin was the only natural product known to possess this unique ring system or carbon skeleton. Recently, however, the structures of tetrocarin (4)\(^13\) and kijanimicin (5)\(^14\) were reported by groups in Japan and the U.S., respectively (Scheme I). Each of these antibiotics consists of an aglycone portion and five sugars. Although the type and connection points of the sugars differ substantially, the aglycones of tetrocarin A (4) and kijanimicin (5) are very similar. These compounds, especially kijanolide (7), bear a structural resemblance to chlorothricolide (2).

(f) Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Viti, S.M. \textit{ibid} 1982, 47, 1378.

SCHEME I

tetronolide (6) \[ R^1 = R^2 = H \]
tetrocarin A (4) (The complete structure has not yet been determined, however, hydrolysis of 4 gave 6 plus a novel nitro-sugar and 2 moles each of L-digitoxose and L-amicetose)

kijanolide (7) \[ R^1 = R^2 = H \]
kijanimycin (5)
Tetronolide (6) and kijanolide (7) possess additional functionality (mainly methyl groups) in both the trans-decalin nucleus and the side chain linking the top and bottom halves. The major difference between these aglycones and chlorothricolide, however, is that tetronolide 6 and kijanolide 7 possess 13-membered carbocyclic rings, whereas chlorothricolide 3 contains a 14-membered lactone. It is possible that the 14-membered ring of 3 is derived biosynthetically from a precursor analogous to 6 or 7 by a Baeyer-Villiger reaction (vide infra).

The uniqueness of chlorothricin resides not only in its novel structure but also in its biological activity. In contrast to a variety of other macrolide antibiotics which generally function by inhibiting

(b) Tomita, F.; Tamaoki, T. J. Antibiot. 1980, 33, 940;
(e) Tetrocarcin A was shown to be identical with antlermicin A; Kobinata, K.; Uramoto, K.; Mizuno, T.; Inono, K. J. Antibiot. 1980, 33, 244.

protein biosynthesis\textsuperscript{15} chlorothricin was shown to act as an antagonist to CH\textsubscript{3}COSCoA, inhibiting the anaplerotic CO\textsubscript{2}-fixation catalyzed by pyruvate carboxylase (equation 1)\textsuperscript{16}.

\[
\text{Pyruvate + ATP + HCO}_3^- \rightleftharpoons \frac{\text{Mg}^{2+}, K^+}{\text{CoA}^{2+}} \xrightarrow{\text{CoASAc}} \text{Oxaloacetate + ADP + Pi}
\]  
(Equation 1)

Pache and Chapman observed that chlorothricin lyses bacteria at concentrations only slightly higher than the minimum inhibitory concentration (m.i.c.)\textsuperscript{17}. They suggested that the lytic action of chlorothricin on bacteria could be explained by the interaction of the antibiotic with the hydrocarbon chains of phospholipids in the cell membrane/wall. Lipid chain fluidity seems to be an important condition for a functioning membrane; thus, a reduction in the fluidity of the lipid chains caused by interaction with chlorothricin would account well for the observed permeability changes and distortion of the bilayer structure. In addition, these authors suggested that chlorothricin may interact with lipids bound to proteins, resulting in a change in tertiary structure of the lipoprotein. Since the action of some membrane enzymes are known to depend on the presence of phospholipids\textsuperscript{18}, a change in lipopro-


tein structure caused by the antibiotic could have a lethal effect on the cell. In any event, they concluded that the molecular details of the interaction of chlorothricin with the lipid bilayer are likely to be relevant to its in vivo antibiotic action.

Although Schindler and Zahner first reported that chlorothricin acted as a competitive inhibitor of pyruvate carboxylase with respect to CoASAc\textsuperscript{19}, additional kinetic studies contradicted these results. In fact, inhibition by chlorothricin appeared to be non-competitive when measured as a function of the concentration of the reaction substrates as well as of Mg\textsuperscript{2+} and CoASAc\textsuperscript{20}. This pattern of inhibition suggested that chlorothricin interacts at unique sites on the pyruvate carboxylases\textsuperscript{21} which are distinct from both the catalytic and activator (Acetyl-CoA) sites. Inhibition in this case may then be the result of significant distortion of both the catalytic and activator sites caused by occupancy of the multiple interacting sites. That different inhibition characteristics were observed for pyruvate carboxylases isolated from different organisms\textsuperscript{21} suggest that chlorothricin may operate by different mechanisms.

21. These authors examined the interaction of chlorothricin with three pyruvate carboxylases which exhibited different requirements for activation by CoASAc; \textit{A. vinelandii} (activity is independent of CoASAc activation), rat liver (activity is partially dependent on CoASAc activation), and chicken liver (inactive without CoASAc activation).
in the various enzyme preparations.

The inhibitory nature of 1 is not limited to pyruvate carboxylase; chlorothricin also inhibited the mitochondrial and cytoplasmic forms of pig heart malate dehydrogenase\textsuperscript{22}, which catalyzes the reduction of oxaloacetate to L-malate (equation 2).

\[
\text{Oxaloacetate} + \text{NADH} + \text{H}^+ \rightarrow \text{L-malate} + \text{NAD}^+ \quad \text{(Equation 2)}
\]

Chlorothricicolide methyl ester 2, produced on methanalysis of the antibiotic, retains 10-25\% of the original activity of the antibiotic itself. The other methanalysis product, \(\alpha\)-methyl-2-deoxy-3-O-(5'-chloro-2'-methoxy-6'-methylbenzoyl)-D-rhamnoside, however, showed a lack of activity\textsuperscript{20}.

The unique structural features present within chlorothricin raises the question of how this antibiotic is formed in nature. Floss and his associates have studied the biosynthesis of chlorothricin by a series of feeding experiments with radiolabeled precursors (Scheme II)\textsuperscript{6,23}. These workers established a polyketide mode of biosynthesis for this antibiotic. The substituted 6-methylsalicylic acid residue is derived from four acetate units with the 0-methyl group originating from methionine. The two 2-deoxy-D-rhamose units are derived from glucose with retention of the

SCHEME II

Labeling Pattern of the Acyl and Aglycon Moieties of Chlorothricin\(^{23}\)

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{COOH} & \quad \text{CH}_3\text{COOH} \quad \text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCOOH} \\
\text{NH}_2
\end{align*}
\]

hydrogens at C(1), C(2), and C(6) with the loss of C(3)-H and C(5)-H. The C(4)-H of glucose was shown to be transferred intramolecularly to C(6) of the hexose, replacing the hydroxyl group at C(6) in an inversion mode, a result which implicates the thymidine 5'-diphosphate-glucose oxidoreductase reaction in this transformation\(^{23}\).

The aglycone portion of the molecule is comprised of ten acetate and two propionate units; the origins of three carbons, C(22), C(23), and C(24) could not be determined unambiguously. The results obtained in
additional feeding experiments suggested that the formation of the tetrionic acid moiety may parallel that of other, more simple tetrionic acids such as carolic and carlosic acids (Scheme III)\(^\text{24}\).

**SCHEME III**

\[
\begin{align*}
\text{HOOC} & \quad \text{COOH} \\
\text{OH} & \\
\rightarrow & \\
\text{HOOC} & \quad \text{CO}_{2}\text{H} \\
\text{O} & \quad \text{S}
\end{align*}
\]

\[
\begin{align*}
\text{Acetyl-CoA} & \\
\rightarrow & \\
\text{carlosic acid} & \quad \text{hydroxylate}
\end{align*}
\]

\[
\begin{align*}
\text{HOOC} & \quad \text{CO}_{2}\text{H} \\
\text{O} & \\
\rightarrow & \\
\text{HOOC} & \quad \text{CO}_{2}\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{HOOC} & \quad \text{CO}_{2}\text{H} \\
\text{O} & \\
\rightarrow & \\
\text{HOOC} & \quad \text{CO}_{2}\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{HOOC} & \quad \text{CO}_{2}\text{H} \\
\text{O} & \\
\rightarrow & \\
\text{HOOC} & \quad \text{CO}_{2}\text{H}
\end{align*}
\]


SCHEME IV

Possible Pathways for the Biosynthesis of Chlorothricolide
By analogy to the biosynthesis of carolic acid, a precursor unit possessing all of the requisite functionality could be formed by condensation of oxaloacetate and malonyl-CoA (Scheme IV). This compound (9) would undergo functionalization at C(3) of the lactone or, again by analogy to carlosic acid formation, may be acylated in that position by the carboxy-terminus of the polyketide chain 11 to form intermediate 13. Subsequent Baeyer-Villiger oxidation of 13 would provide the basic skeleton of the aglycone, chlorothricolide. The latter possibility seems plausible since the closely-related aglycones, tetronolide 6 and kijanolide 7, have structures containing a 13-membered carbocycle possessed by precursor 13. An alternate hypothesis is that the main polyketide chain does not terminate with propionate at C(1), but rather with an acetate unit which gives rise to C(25) and C(26) as outlined in Scheme IV (12 → 13). Additional feeding experiments designed to test this possibility did not, however, provide a definite answer to the question of whether carbons 22-24 are derived from a C$_4$ acid.

Although the origins of many of the carbon atoms of chlorothricolide have been identified, none of the actual steps of construction of the aglycone have been determined. It is reasonable to assume that the top half is assembled by a route closely related to those described in Scheme IV. No proposals for the biosynthesis of the bottom half, however, have been published.

We originally speculated that an intramolecular Diels-Alder reaction, 14 → 15, was a viable possibility for the construction of
the bottom half. This type intramolecular cyclization has been suggested in the biosynthesis of other natural products\textsuperscript{25,26}.

Joshi et al. proposed that the piperaceae alkaloids, cyclostachine A(16) and cyclostachine B(17), are derived biosynthetically from precursor \textsuperscript{18}\textsuperscript{26}. These workers also isolated cyclopiperstachine 19 and its

proposed biosynthetic precursor piperstachine 20. The fact that all three alkaloids 16, 17, and 19 were isolated as racemic mixtures supports their assumption that these compounds are formed by an intramolecular cyclization of an achiral precursor. The intramolecular Diels-Alder reaction has also been implicated in the biosynthesis of iboga and aspidosperma alkaloids\(^{25a,b,27}\). Although dehydromescodine 21 has not yet

   For specific examples see:

been isolated nor synthesized, it seems reasonable that cantharantine 22 and tabersonine 23 are formed by the cyclization of ester 21. In support of this proposition is the in vivo incorporation of secodine 24 into the aspidosperma skeleton27a,b. Whether the cyclization 14 → 15 is actually involved in the biosynthesis of chlorothricolide remains for determination. The results reported in Chapter 2, however, suggest that this hypothesis may be unwarranted.


(b) Kutney, J.P. Heterocycles 1976, 4, 169, 429;

For recent reports in this area see:


(g) Raucher, S.; MacDonald, J.E.; Lawrence, R.F. Tetrahedron Lett. 1980, 4335;


Synthetic Considerations

Although chlorothricin exhibits some interesting and novel biological activity, Schindler and Scrutton suggested that this antibiotic would not be useful in a clinical context\textsuperscript{20}. This conclusion derives from chlorothricin's lack of specificity in the inhibition of pyruvate carboxylases purified from vertebrate and microbial sources, and also because of its specific inhibitory effects on other enzymes\textsuperscript{16,19-20,22}. Thus, our interest in the synthesis of chlorothricolide stemmed from its complex and unique structure.

Central to the chemistry of chlorothricolide is the spiro $\alpha$-hydroxy tetronic acid nucleus, which contains the hydroxyl group necessary for closure of the 14-membered lactone. Unlike other macrolides, chlorothricolide methyl ester \textsuperscript{2} could not be opened under basic conditions without concomitant $\beta$-elimination of the tetronic acid ring system.
and subsequent condensation to give the aromatic derivative 2528.

\[
\begin{align*}
\text{CO}_2\text{CH}_3 & \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{Me} & \quad \text{Me} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Ireland and Thompson have performed degradation studies on chlorothricin in connection with their studies on the synthesis of the aglycone29. As mentioned previously, chlorothricolide methyl ester 2 could be isolated in good yield by acidic methanolysis of chlorothricin20. Subsequent degradation of the aglycone, as outlined in Scheme V afforded the bottom-half 27 of chlorothricolide.


SCHEME V

OXIDATIVE CLEAVAGE OF O-METHYL CHLOROTHRICOLIDE METHYL ESTER

CHLOROTHRICIN 1

\[
\text{CHLOROTHRICIN 1} \xrightarrow{a,b,c} \quad 78\% \quad \text{CHLOROTHRICOLIDE METHYL ESTER}
\]

\[
\text{CHLOROTHRICOLIDE METHYL ESTER} \xrightarrow{d} \quad 81\% \quad (\text{based on recovered starting material})
\]

\[
\text{CHLOROTHRICOLIDE METHYL ESTER} \xrightarrow{e,f,g,h} \quad 42\% \quad \text{CHLOROTHRICOLIDE METHYL ESTER}
\]

Key: (a) CH\(_3\)OH, H\(_2\)SO\(_4\), \(\Delta\); (b) CH\(_2\)N\(_2\), Et\(_2\)O; (c) CH\(_3\)OCH\(_2\)Cl, (i-C\(_3\)H\(_7\))\(_2\)C\(_2\)H\(_5\)N, CH\(_2\)Cl\(_2\); (d) OsO\(_4\), NMO, THF, H\(_2\)O, t-BuOH; (e) NaIO\(_4\), dioxane, H\(_2\)O; (f) Py\(_2\)Cr\(_2\)O\(_7\), DMF; (g) NaOH, EtOH, \(\Delta\); (h) CH\(_2\)N\(_2\), Et\(_2\)O.
Ireland et al. have recognized that chlorothricolide could be assembled by a convergent pathway which would involve the connection of two nearly equal-sized halves at a stage late in the synthesis. These workers have observed that once the macrocyclic lactone of 3 had been opened, it could be reclosed by treatment with trifluoroacetic anhydride\textsuperscript{30}. The next to the last stage of the synthesis, therefore, would involve construction of the carbon-carbon bond connecting the two halves. A Claisen rearrangement was selected for this purpose.

30. Ireland, R.E.; unpublished results presented at a seminar at M.I.T. in the Fall of 1978.

Ireland's synthesis of spiro-lactone 28, his synthetic equivalent of the top half of chlorothricolide, is outlined in Scheme VI. The key steps of this synthesis are the Diels-Alder reaction of butadiene with 2-acetoxymaleic anhydride 29 to afford cyclohexene 30 followed by the intramolecular cyclization of 30 to give the spiro tetronic acid nucleus 31. Intermediate 31 was elaborated to the target, synthetic top-half 28, by the sequence outlined in Scheme VI.

With the top half synthon in hand, the viability of the proposed connection scheme was examined using synthetic top-half 32 with a bottom-half model 33. Although this scheme is successful for accom-
SCHEME VI \textsuperscript{31} IRELAND'S SYNTHESIS OF THE TOP-HALF

\[
\begin{align*}
\text{OAc} & \xrightarrow{a} \text{H}^+ \xrightarrow{b} \text{OCH}_3 \\
\text{O} & \xrightarrow{c} \text{H}^+ \xrightarrow{d,e} \text{H}_2\text{COOC} \xrightarrow{f} \text{H}_2\text{COOC} \\
\text{OAc} & \xrightarrow{g} \text{HO} \xrightarrow{h,i} \text{R}^0 \xrightarrow{j} \text{R}^0 \\
\text{O} & \xrightarrow{k} \text{R}^0 \xrightarrow{l,m} \text{OHC} \xrightarrow{n} \text{HO} \\
\end{align*}
\]

Key: (a) C\textsubscript{5}H\textsubscript{5}N, $\Delta$, AcOH; (b) CH\textsubscript{2}OCH\textsubscript{2}COCl, PhH; (c) CH\textsubscript{2}=CH=CH=CH\textsubscript{2}, PhH, pyrogallol, $\Delta$; (d) LDA, THF, -78°C; (e) HMPA, CH\textsubscript{3}OSO\textsubscript{2}F, 0°C; (f) NaOCH\textsubscript{3} (catalytic), CH\textsubscript{3}OH, $\Delta$; (g) LiEt\textsubscript{3}BH, THF, 0°C; (h) TBDMSCl, imidazole, DMF; (i) MCPBA, LiClO\textsubscript{4}, Et\textsubscript{2}O; (j) LiMe\textsubscript{2}Cu, hexane; (k) KH, MeI, THF, 0°C; (l) AcOH, THF, H\textsubscript{2}O, 50°C, 24h; (m) C\textsubscript{5}H\textsubscript{5}N-HCl-CrO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}; (n) CH\textsubscript{2}=CHMgBr, THF, -30°C.
plishing the desired connection, it is complicated by the need to effect the reductive-decarboxylation of the ester group in their Claisen product 34.

Workers in Ireland's laboratory have investigated several approaches for the synthesis of the bottom-half of chlorothricolide. An initial approach involved the Diels-Alder reaction of 2-methylcyclopentenone and silyl enol ether 35\textsuperscript{32}. The mixture of cycloadducts 36 was converted quantitatively to dione 37 by treatment with tetra-n-butylammonium fluoride in tetrahydrofuran. An x-ray crystal analysis

![Chemical Reaction Diagram]


of dione 37, however, showed it to possess the undesired cis-syn-trans structure rather than the desired cis-anti-trans isomer. The Diels-Alder reaction of 2-methylcyclopentenone and 35 must therefore, have proceeded to give almost exclusively the endo adduct 36, in line with the general preference for the endo transition state in bimolecular Diels-Alder reactions33.

Ireland has recently published a synthesis of the epi-bottom half by a route which avoided the stereochemical problems associated with the previous approach. Their entire sequence is outlined in Scheme VII, and afforded the 7-epi-bottom half 38 of chlorothricolide in 9.5% overall yield for eighteen steps starting from 2-methyl-cyclohept-2-enone 3929.

Central to the success of this scheme is the stereoselective conjugate addition of 4-(benzyloxy) butyl magnesium bromide to enedione 40. This copper-catalyzed reaction proceeded selectively via psuedoaxial attack of the organometallic reagent on the less-hindered convex face of the bicyclic system and afforded the desired anti relationship at C(3). Oxidation of alcohol 41 followed by an acid-catalyzed aldol condensation gave enone 42, epoxidation of which afforded 43 as the major product. Direct reduction of ketoepoxide 43 with lithium-ammonia led to a mixture of products in which the undesired cis-anti-cis epimer 44 predominated. Fortunately, sodium-ammonia reduction of the related acetonide 46 afforded a 7:1 mixture of the desired cis-anti-trans epimer 47 and the cis-anti-cis epimer 48. Alcohol 47 was elaborated to 38 by an uneventful series of transformations. Comparison of the 'H NMR spectroscopic data for syn-
SCHEME VII IRELAND'S SYNTHESIS OF THE 7-EPI BOTTOM-HALF

Key: (a) 200°C; (b) H_3O^+; (c) BnO(CH_2)_4MgBr, Cu(OAc)_2, THF; (d) (CH_2OH)_2, PhH, p-TsOH; (e) LDA, THF, ClPO(NMe)_2; (f) Li, NH_3, THF, t-BuOH; (g) Py_2Cr_2O_7, CH_2Cl_2; (h) PhH, p-TsOH; (i) 30% H_2O_2, 10% aqueous NaOH, CH_3OH; (j) Li, NH_3, THF; NH_4Cl; (k) OsO_4, NMO, THF, H_2O, t-BuOH; (l) CH_3C(OCH_3)_2CH_3, p-TsOH; (m) Na, NH_3, THF; NH_4Cl; (n) CH_3OCH_2Cl, (i-C,H_7)_2C_2H_5N, CH_2Cl_2; (o) LDA, THF; ClPO(NMe)_2; (p) Li, EtNH_2, THF, t-BuOH; (q) CH_3OH, H_2O, PyOTs; (r) NaIO_4, CH_3OH, H_2O; (s) Py_2Cr_2O_7, DMF.
SCHEME VIII IRELAND'S STUDIES ON THE UNION OF THE
"TOP HALF" WITH 7-EPI-BOTTOM HALF

Key: (a) DCC, DMAP, CH₂Cl₂; (b) KN(TMS)₂, THF, HMPA; t-BuMe₂SiCl, THF, CH₃OC₂H₅OCH₂Cl, (i-C₃H₇)₂C₂H₅N, CH₂Cl₂; (c) LiEt₃BH, THF; (d) C₅H₅N·HCl·CrO₃, CH₂Cl₂; (e) (Ph₃P)₃RhCl, ClCH₂CH₂Cl, Δ.
thetic diester 49 with that of authentic bottom-half 27 (prepared by degradation of chlorothricin, vide supra) revealed that 49 possessed the unnatural configuration of the C(7)-alkoxy group. Thus, the initial epoxidation of enone 42 must have occurred preferentially from the undesired $\beta$-face.

In contrast to their original model studies, the connection of the top (32) and 7-epi-bottom (50) halves did not proceed smoothly (Scheme VIII). In particular, attempts to effect the reductive decarbonylation of intermediate 51 led mainly to cyclopropane 52 and cis-olefin 53b rather than the desired olefin 53a. No additional progress towards the total synthesis of chlorothricolide has been reported from the Cal Tech laboratories.

Our retro-synthetic analysis of chlorothricolide also suggested that this antibiotic should be prepared by a convergent pathway. In contrast to Ireland's approach, our connection scheme would involve the formation of the "left-hand" bridge by a direct carbon-carbon bond forming reaction between $C_x$ and $C_y$. There are several choices available for the functionality present within X and Y. One example would be the alkylation of a stabilized carbanion (X=ArSO$_2$) of 54 (or a suitably protected derivative) with an allylic alkylating agent 55 (X = Cl, Br, OTs). This particular approach would require reductive cleavage of the activating group (ArSO$_2$) following the connection of the top and bottom halves.
Initially our efforts were directed to the development of an efficient synthesis of the bottom half of chlorothricolide\textsuperscript{34}. We envisioned that the desired trans-octahydropnaphthalene 54 might be assembled readily by an intramolecular Diels-Alder reaction of a triene ester such as 56. This strategy was particularly appealing since the cyclization 56 $\rightarrow$ 54, an endo Diels-Alder reaction, would introduce each of the stereo-centers in the cyclohexene ring in a single step. Of course, the success

\begin{itemize}
\item 54
\item \textsuperscript{34} We have initiated synthetic studies on the top-half of chlorothricolide. Our results, however, are of a preliminary nature and will therefore not be discussed in this thesis.
\end{itemize}
of such a route would depend heavily on the degree to which the cyclization of trienes such as 56 follow the "endo rule".

The intramolecular Diels-Alder reaction has become a powerful tool in the construction of complex, multicyclic natural products\textsuperscript{25c,35}. When our work was initiated, the majority of published examples dealing with the construction of perhydronaphthalenes involved the cyclization of o-quinodimethane intermediates. A number of authors had shown that compounds of this type cyclize to afford, almost exclusively, trans-

![Diagram](image)

fused products\textsuperscript{36}. The overwhelming preference for the trans-octalins in the cyclizations of unactivated decatrienes (such as 57 and 58) suggested that the intramolecular Diels-Alder reaction of activated undeca-

trienes, such as 56, should occur with high selectivity to afford the desired trans-fused ring system. In contrast to this expectation, however, Joshi et al. had reported that triene 59 cyclized to afford a 2:1 mixture of cis (exo) and trans (endo)-fused products. This report prompted us to undertake a preliminary model study to test the viability of our approach. The results of this and related stereochemical studies are presented in Chapter II.

36. For leading references see:

(a) Oppolzer, W. Synthesis 1978, 793;

37. The majority of the work discussed in Chapter II has been published: Roush, W.R.; Hall, S.E. J. Am. Chem. Soc. 1981, 103, 5200. The structures in Chapters II and III are represented as only one enantiomer, however, all compounds were prepared as racemic mixtures.
CHAPTER 2
SYNTHESIS AND CYCLIZATION OF MODEL TRIENE 74

As a test of our strategy we chose to synthesize and study the Diels-Alder reaction of model triene 61. We anticipated that 61 would be a valid model for cyclization of 56 since the steric bulk of the C(11)-methyl group of 61 is not significantly different from the methylene group at C(11) of 56. We envisioned that ester 51 could be assembled readily from sorbaldehyde 62. In this manner we would be able to rapidly evaluate the potential of our synthetic strategy.

We anticipated that diene aldehyde 63 would be prepared by the condensation of sorbaldehyde with a suitably protected 4-metallated butyraldehyde, i.e., the Grignard reagent prepared from 4-bromobutyrl-
aldehyde diethyl acetal. The requisite bromoaldehyde 65\textsuperscript{38} was prepared by cleavage of tetrahydrofuran with HBr followed by oxidation of alcohol 66 with pyridinium chlorochromate (PCC)\textsuperscript{39}. Treatment of

\[
\begin{align*}
\text{Br} & \xrightarrow{\text{48\% HBr}} \text{BrOH} \\
\Delta & \quad 39\% 
\end{align*}
\]

\[
\begin{align*}
\text{BrOH} & \xrightarrow{\text{PCC, CH}_2\text{Cl}_2} \text{OC} & \xrightarrow{\text{72\%}} \text{OC}
\end{align*}
\]

the resultant aldehyde with absolute EtOH, triethyl orthoformate, and a catalytic amount of NH\textsubscript{4}Cl afforded acetal 67 in 67\% yield.

Condensation of sorbaldehyde\textsuperscript{40} with Grignard reagent 68, which


was prepared from acetal 67 and magnesium in refluxing THF, proceeded rapidly at 0°C to afford hydroxy acetal 69 in 93% yield. Although we anticipated that the new hydroxyl group would have to be protected prior to the Diels-Alder cyclization, we postponed this task and proceeded with the liberation of the carboxaldehyde functional group.

Hydrolysis of acetal 69 with a mixture of 5% aqueous oxalic acid in THF provided the expected product 70, which exists exclusively in

40. Commercial sorbaldehyde 56 is a mixture of diene isomers of which the (E,E)-isomer is the major component (~85%). The sorbaldehyde used in this study was prepared from isomerically pure sorbic acid (mp 134.5-135°C; recrystallized two times from H₂O) by LiAlH₄ reduction (60%; Nystrom, R.F.; Brown, W.G. J. Am. Chem. Soc. 1947, 69, 2548) to the alcohol which was oxidized to 56 with the reagent prepared from DMSO and oxaly chloride (Mancuso, A.J.; Huang, S.-L.; Swern, D. J. Org. Chem. 1978, 43, 2480). The crude aldehyde (>95% isomerically pure, 84% yield) obtained from this oxidation was used directly in the Grignard reaction.
the hemi-acetal form$^{41}$, along with smaller amounts of mixed acetal $^{71}$. Careful control of the hydrolysis reaction conditions was necessary, however, since stronger acidic conditions or prolonged reaction times led to varying amounts of rearrangement products. One of the rearrangement products was alcohol $^{72}$. This structure was assigned principally on the basis of its $^1$H NMR spectrum. Most noteworthy was an upfield shift of the signal for the C(9)-methyl group which appears as a doublet centered at $\delta$ 1.27. Although a pure sample of hemi-acetal $^{70}$

was obtained in 61% yield by preparative TLC of the aforementioned reaction mixture, in practice the crude product was used in the next step without purification.

As anticipated, hemi-acetal $^{70}$ proved to be an excellent precursor to undecatriene $^{64}$. Treatment of $^{70}$ with $\alpha$-(carbomethoxy)-ethylidenetriphenylphosphorane$^{42}$ in refluxing benzene provided a mixture of products in which (E,E,E)-$^{64}$ predominated. Separation of

$^{41}$. This was clear from the spectroscopic properties of $^{70}$. The $^1$H NMR spectrum of $^{70}$ showed a multiplet at $\delta$4.46 for C(1)-H with the absence of any signals downfield from $\delta$ 7.00. In addition, the IR spectrum of $^{70}$ did not show any absorptions in the carbonyl region.
this mixture by flash chromatography\textsuperscript{43} afforded 61\% of 64 (from acetal 69), 3\% of a mixture of 64 and a compound tentatively assigned structure 73, and 12\% of mixed acetal 71\textsuperscript{44}.

The $^1$H NMR spectrum of major isomer 64 has a one proton triplet of quartets, $J_{3,4} = 7$Hz and $J_{3,13} = 1.3$Hz, centered at $\delta$ 6.71 and a two-proton multiplet at $\delta$2.16 for the allylic protons at C(4). Taken together, these data fully support the assignment of an (E)-configuration.


\textsuperscript{44} Acetal 71 could be recycled by hydrolysis to 70 under conditions similar to those used for the hydrolysis of 69 in 78\% yield.
to the \(\alpha,\beta\)-unsaturated ester\(^{45}\). Minor isomer \(73\) was not rigorously purified and characterized. Its \(^1\)H NMR spectrum, however, showed no olefinic signals downfield from \(\delta 6.2\). In addition, the resonance for the allylic protons at C(4) of \(73\) was centered at \(\delta 2.64\) which suggested that this isomer possesses a (Z)-configuration at the newly-formed double bond\(^{45}\).

The stage was now set for the crucial intramolecular Diels-Alder reaction. Alcohol \(64\) was first transformed into its t-butyldimethylsilyl ether \(74\) in 83\% yield by treatment with t-butyldimethylsilyl chloride and imidazole in dimethylformamide (DMF)\(^{46}\); protection of the hydroxyl group at this point was deemed necessary to avoid the possibility of a competing intramolecular Michael addition to \(75\). Silyl ether \(74\) cyclized smoothly at 150\(^\circ\)C as a 2M solution in tetrachloroethylene over a period of five hours. Analysis of the crude reaction mixture by gas-liquid chromatography (GLC) showed the presence of four cyclization products in a ratio of 15:13:23:49 plus uncyclized triene\(^{47}\). Initial flash chromatography\(^{43}\) afforded three

45. Jackman, L.M.; Wiley, R.H.  

46. Corey, E.J.; Venkateswarlu, A.  
   J. Am. Chem. Soc. 1972,  
   94, 6190.

47. GC conditions: 20 ft. 4\% DC-QF-1, 165\(^\circ\)C, flow = 15 mL/min  
   retention times, 112+136 min.
mixed fractions of cycloadducts in 90% yield, along with a 10% yield of un cyclized triene. The mixtures of cycloadducts were separated, following deprotection, by repeated careful chromatography to afford pure samples of 60 (7%), 76 (3%), 77 (6%) and a 60:40 mixture of 77:78 (35%). Repeated chromatography of a small sample of the latter mixture provided a pure sample of 78.

Although we anticipated that trans-fused alcohols 60 and 76, the products of an endo Diels-Alder reaction, would be the major products of the cyclization of triene 74, double-irradiation experiments showed

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{CO}_2\text{CH}_3 & \quad \text{OH} \\
(1) \quad 150^\circ\text{C}, 5 \text{ h} & \quad 60 (7\%) \\
(2) \quad 1\text{N HCl}, \text{MeOH} & \\
\text{H}_3\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{OH} & \quad \text{H} \\
74 & \\
\text{H}_3\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{Me} & \quad \text{OH} \\
77 (27\%) & \\
\text{H}_3\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{Me} & \quad \text{OH} \\
78 (14\%) & \\
\end{align*}
\]

unambiguously that both 77 and 78 possessed cis-ring fusions. This was clear from the coupling constants observed for the ring junction protons in 77 \(J_{4a,8a} = 6\text{Hz}\) and 78 \(J_{4a,8a} = 4\text{Hz}\). Therefore, the
major products, 77 and 78, arose from an exo rather than the expected endo Diels-Alder cyclization. Minor isomer 76 was assigned a trans-ring fusion by 'H NMR methods: double-irradiation experiments showed the coupling constant between C(4a)-H and C(8a)-H to be 11.4 Hz. The remaining cycloadduct, 60, was assigned a trans-ring fusion by comparison of its 'H NMR spectrum to the NMR spectrum of 27, a degradation product of natural chlorothricolide kindly provided by Professor R.E. Ireland.

The stereochemistry at C(1) of these compounds was also assigned by 'H NMR analyses. These assignments are straightforward for the conformationally-rigid trans-fused isomers 60 and 76. The signal for C(1)-H of 60 appears as a doublet of triplets, J=4 and 10Hz, centered at 3.35. The multiplicity of this signal requires that C(1)-H is in an axial position and is flanked by axial hydrogens at C(2) and C(8a) and an equatorial hydrogen at C(2). In trans-fused 76, however, the signal for C(1)-H appears downfield at 4.09 as a broad singlet (W = 7Hz). The multiplicity and the dramatic downfield shift of this resonance is evidence that this proton occupies an equatorial position on the cyclohexenyl ring 48.

The assignment of C(1)-stereochemistry is somewhat more complicated for the cis-fused products, 77 and 78, due to the potential conformational flexibility in these systems. Intuitively, one


49. This ratio was determined by GLC analysis of the crude reaction mixture. The ratio of endo/exo products determined by product isolation was 20:80.
would expect 78 to adopt conformation 78a since conformer 78b should be significantly destabilized by the severe steric interaction between the C(1)-hydroxyl group and the C(5)-methyl group. Double irradiation experiments supported this assumption. The signal for C(4a)-H appeared as a multiplet which included one large coupling constant (12Hz); the resonance for C(8a)-H appeared as a narrow multiplet ($W_J = 10$Hz) without any large coupling constants; and the complex signal for C(1)-H possessed one large (10Hz) coupling constant. Taken together these data are consistent only with structure 78a.

The major product 77 was determined to exist as conformer 77a by similar considerations. The signal observed for C(1)-H of 77 appears as a doublet of triplets ($J = 3, 6$Hz). The multiplicity of this signal is consistent only with structures in which C(1)-H occupies an equatorial position. The multiplicities observed for the resonance of C(4a)-H and C(8a)-H in 77 are very similar to those observed for alcohol 78,
a result which suggests that these protons occupy similar stereochemical environments in both isomers. Thus, C(1)-H and C(8a)-H of 77 occupy equatorial positions and C(4a)-H occupies an axial position with respect to the right-hand cyclohexyl ring.

Clearly, model compound 60 is a minor product of the cyclization of 74. Moreover, the endo-exo or trans-cis ratio of products from this experiment was 28:72. This ratio is clearly out of line with the results of previous studies of unactivated dienophile-o-diquinomethane intramolecular cyclizations which are usually highly selective for the trans-fused products. On the other hand, the product distribution realized with 74 resembled the results obtained by Joshi et al. in the cyclization of 59 (2:1, cis-trans). It was clear to us at this stage that 56 appeared to be an unpromising precursor to the bottom-half of chlorothricolide. As a consequence of the variation in the results with 59 and 74 versus the o-diquinomethane series, we decided to study a number of additional trienes related to 74 (and 59) in an attempt to define the stereochemical parameters of these Diels-Alder reactions. We hoped, of course, that our efforts in this regard would lead to the development of a useful route to the bottom-half of chlorothricolide.
SYNTHESIS OF SUBSTITUTED UNDECA-2,8,10-TRIENOATES

In our attempt to elucidate the parameters responsible for the stereoselectivity observed in the cyclization of model triene 74, we briefly examined three variables. These consisted of dienophile substitution, dienophile stereochemistry, and diene substitution at C(11) and C(7). The trienes chosen for this study are listed in Scheme IX.

SCHEME IX
Triene 79 was prepared by a simple modification of the route used for model triene 74. Treatment of crude hemiacetal 70 with α-carbomethoxymethyleneetriphenylphosphorane\(^{50}\) in refluxing benzene gave, after purification by column chromatography, the desired ester 79a in 63% yield (from acetal 69), along with smaller amounts of 80a (6%) and 71 (20%).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{Ph}_2\text{P}=\text{CHCO}_2\text{CH}_3 \\
\text{H}_2\text{C} & \quad \text{H}_2\text{C} \\
\text{OH} & \quad \text{OH} \\
\text{70} & \quad \text{79a (63% from 69)} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{H}_2\text{C} & \quad \text{H}_2\text{C} \\
\text{OH} & \quad \text{OC}_2\text{H}_5 \\
\text{80a (6% from 69)} & \quad \text{71 (20% from 69)} \\
\end{align*}
\]

The stereochemistry of the newly formed double bond was clearly evident from the 'H NMR spectra of 79a and 80a. The (E)-configuration of the major product 79a was confirmed by the large coupling constant between the vinylic protons \(J_{2,3} = 15.7\text{Hz}\). The 'H NMR spectrum of minor isomer 80a showed no olefinic signals downfield from δ6.5 and has a two-proton multiplet centered at δ2.7 for the C(4)-allylic protons.

again consistent with a (Z)-α,β-unsaturated ester\(^{45}\). Although this reaction provided small amounts of (Z,E,E)-triene \(^{80a}\), our need for larger quantities of appropriate (Z,E,E)-triens such as \(^{80}\) prompted us to develop a stereoselective route to triens of this stereochemical series.

We envisioned that triene \(^{80}\) might be prepared by Lindlar hydrogenation\(^{51}\) of an acetylenic precursor \(^{86}\). This compound might, in turn, be prepared by the addition of a suitably protected 5-metallated-1-pentyne \(^{87}\) to sorbaldehyde followed by appropriate functional group manipulations.

51. (a) Review: Marvell, E.N.; Thomas, L.I. *Synthesis* 1973, 457;
Thus, addition of sorbaldhyde\textsuperscript{40} to the Grignard reagent prepared from 1-(5-bromo-1-pentynyl)-trimethylsilane\textsuperscript{88,52,53} resulted in a rapid condensation to afford the expected adduct in nearly quantitative yield.

\[
\begin{array}{c}
\text{H}_3\text{C} \quad \text{H} \\
\text{\textsuperscript{62}}
\end{array}
\quad \xrightarrow{(1) \text{BrMg}}
\quad \text{H}_3\text{C} \quad \text{H}
\begin{array}{c}
\text{\textsuperscript{89}}
\end{array}
\]

\[
\text{THF, 0°C}
\]

\[
\text{KF, DMF, H}_2\text{O}
\]

\[
84\% \text{ overall}
\]

The crude product was treated directly with KF in aqueous dimethylformamide\textsuperscript{55} to afford acetylenic alcohol\textsuperscript{89}. Purification of this intermediate was effected by bulb-to-bulb distillation, providing the


53. Bromide\textsuperscript{88} was prepared by the following sequence:

\[
\begin{array}{c}
\text{Cl} \quad \text{H} \\
\text{i}
\end{array}
\quad \xrightarrow{a} \quad \text{Cl} \quad \text{TMS}
\begin{array}{c}
\text{ii}
\end{array}
\quad \xrightarrow{b} \quad \text{TMS}
\begin{array}{c}
\text{iii}
\end{array}
\quad \xrightarrow{c} \quad \text{TMS}
\begin{array}{c}
\text{iv}
\end{array}
\]

\[
d (94\%)
\]

Key: (a) MeLi, THF; TMS\textsubscript{Cl}; (b) NaI, acetone,\textdegree; (c) LiBr, DMF \textdegree{50} C; (d) LiBr, cat. NaI, 2-butane,\textdegree.

The corresponding chloride ii and iodide iii were not useful intermediates for Grignard reagent formation.
desired alcohol in 84% overall yield from sorbaldehyde. Alcohol 89 was converted into its t-butyldimethylsilyl ether derivative\textsuperscript{46}, which without purification was treated with n-butyllithium followed by excess methyl chloroformate. Purification of the crude product by silica gel chromatography afforded acetylenic ester 90 in 84% overall yield from alcohol 89.

\begin{align*}
\text{H}_2, \text{Lindlar} & \xrightarrow{83\%} \text{H}_2\text{C} \quad \text{CO}_2\text{CH}_3 \\
\text{83b} & \quad \text{OTBDMS}
\end{align*}

Hydrogenation of acetylene 90 with Lindlar catalyst\textsuperscript{51} proceeded selectively to afford the desired \((Z)\)-\(\alpha,\beta\)-unsaturated ester 80b in 83% yield, along with recovered starting material (8%) and an unidentified over-reduction product (5%)\textsuperscript{56}. The amount of over-reduction could be mini-


mized by careful control of reaction conditions\textsuperscript{57}. That the new double bond possessed the desired Z-stereochemistry was clearly evident from its 'H NMR spectrum (J\textsubscript{2,3} = 12.5 Hz).

Ketals 81, 82, and 83 were prepared from the corresponding alcohols 64, 79\text{a} and 80\text{a}. Attempts to effect the oxidation of alcohol 64 with either PCC\textsuperscript{34} (22%) or activated-DMSO based reagents\textsuperscript{58} (22%) led to low yields of the expected dienone 91. Oxidation with Ag\textsubscript{2}CO\textsubscript{3}/Celite\textsuperscript{59}, however, proceeded smoothly in refluxing benzene to afford ketone 91 in greater than 98\% yield. The crude product was routinely used in the next step without purification. On one occasion, however, further purification was effected by bulb-to-bulb distillation to afford pure 91 in 85\% yield.

57. The progress of this reaction was monitored by analytical TLC. When no starting material could be detected (UV analysis), the reaction was terminated.

Ketone 91 was converted into its corresponding ethylene glycol ketal 81 by treatment with ethylene glycol, 2-methoxy-1,3-dioxolane \textsuperscript{60}, and a catalytic amount of p-TsOH. This reaction was monitored carefully by TLC since prolonged reaction times led to lower yields of the desired ketal \textsuperscript{61}. For this reason the reaction was routinely terminated before all of the starting ketone 91 had been consumed. Purification of the crude product by preparative TLC gave ketal 81 in 70\% overall yield from alcohol 64.

In a similar fashion ketals 82 and 83 were prepared in 72\% and 64\% overall yield, respectively, from alcohols 79a and 80a.

\[ \text{H}_3\text{C} \quad \text{CO}_2\text{CH}_3 \quad (1) \text{Ag}_2\text{CO}_3/\text{Celite} \quad \text{H}_3\text{C} \quad \text{CO}_2\text{CH}_3 \\
\text{OH} \quad (2) \text{MeO} \quad \text{HOCH}_2\text{CH}_2\text{OH}, \text{p-TsOH(cat.)} \]

72\%


61. Ketal 81 apparently decomposes slowly under the reaction conditions. The ratio of ketal 81: ketone 91 reaches a maximum and then slowly decreases. When the ratio of 81:91 did not increase (TLC analysis) the reaction was terminated.
Since we did not anticipate a need for large quantities of either triene \(84\) or \(85\), we decided to pursue a synthetic sequence which would provide \(84\) and \(85\) from a common set of precursors. We envisioned that these two trienes could be assembled by a non-selective Wittig reaction of aldehyde \(92\), which would be prepared by a coupling reaction between a pentadienol derivative and a suitably functionalized and protected organometallic reagent. Thus, addition of a THF solution of the Grignard reagent prepared from 4-bromobutyraldehyde diethyl acetal to
a cooled solution of 2,4-pentadienyl acetate\textsuperscript{62} and Li\textsubscript{2}CuCl\textsubscript{4}\textsuperscript{63} gave a mixture of the desired coupling product \textsuperscript{93} in 43\% yield along with a 38\% yield of a mixture of reductive coupling products of 2,4-pentadienyl acetate. Hydrolysis of acetal \textsuperscript{93} with 5\% aqueous oxalic acid in THF provided aldehyde \textsuperscript{92}, which without purification was allowed to react with α-(carbomethoxy)methyleneetriphenylphosphorane\textsuperscript{50} in methanol to afford a 5:3 mixture of triene esters, \textsuperscript{84} and \textsuperscript{85}, in 95\% combined yield. These

63. (a) Samain, D.; Descoins, C.; Commeron, A. Synthesis 1978, 388;
    (c) Preparation of Li\textsubscript{2}CuCl\textsubscript{4}; Tamura, M.; Kochi, J. Synthesis 1971, 303.
isomers were readily separated by flash chromatography\textsuperscript{43} to give (E,E)-triene ester \textsuperscript{84} in 52\% yield and (Z,E)-triene \textsuperscript{85} in 30\% yield.

**STEREOCHEMISTRY OF THE INTRAMOLECULAR DIELS-ALDER REACTION**

We assumed from the outset that both trienes \textsuperscript{79b} and \textsuperscript{80b} might be useful precursors to the model bottom-half (\textsuperscript{60}) of chlorothricolide. If the cyclization of \textsuperscript{79b} or \textsuperscript{80b} was selective for the trans-fused adduct, then the missing C(5)-methyl group might be introduced by an alkylation reaction. Trienes \textsuperscript{79b} and \textsuperscript{80b} cyclized smoothly by heating a dilute toluene solution of these esters in an 150\textdegree{}C oil bath for 19h and 17h, respectively. Unfortunately, the major products from the intramolecular Diels-Alder reaction of both \textsuperscript{79b} and \textsuperscript{80b} possessed cis-ring fusions (Scheme X). Stereochemistry was assigned to the individual cycloadducts by a combination of spectroscopic and chemical methods, as discussed below.
SCHEME X

\[
\begin{align*}
79a & \xrightarrow{150^\circ C, 19 \text{ h}} & 94 (29\%) \\
79a & \xrightarrow{150^\circ C, 17 \text{ h}} & 99 (42\%) \\
\text{(1) bis(trimethylsilyl)acetamide} & \quad & \text{(a) } R=\text{TBDMS} \\
\text{(2) } 150^\circ C, 19 \text{ h} & \quad & \text{(b) } R=\text{H} \\
\end{align*}
\]
SCHEME XI

95 \[\text{PCC} \rightarrow 95\text{ (81\%)}\]

95 \[\text{PCC} \leftarrow 95\text{ (95\%)}\]

(1) LDA
(2) HOAc
58\%

95 \[\text{p-TsOH} \rightarrow 103\text{ (91\%)}\]

100a R=TBDMS
b R=H

99a R=TBDMS
b R=H

102a R=TBDMS
b R=H

101a R=TBDMS
b R=H

98 \[\text{PCC} \rightarrow 107\text{ (90\%)}\]

107 \[\text{PCC} \leftarrow 97\text{ (95\%)}\]

(1) NaOCH₃
(2) H₂O⁺
79\%
The major products, 94 and 95, of the Diels-Alder reaction of 79b were initially assumed to be hydroxyl epimers (at C(1)) as a consequence of the similarities of the 'H NMR signals for C(5)-H, the proton alpha to the carbomethoxy group. In both isomers, this resonance appears as a doublet of doublets, J=10 and 12Hz. These data require that the hydrogens at C(4a), C(5), and C(6) occupy axial positions on the cyclohexenyl ring. The epimeric nature of these compounds was subsequently established by oxidation of either with pyridinium chlorochromate (PCC)\(^\text{39}\) to give ketone 96 in excellent yield (Scheme XI). The ring fusions of 94 and 95 were shown to be cis by double irradiation experiments \((J_{4a,8a} = 3.5\text{Hz for each isomer})\). It is clear from the multiplicities observed for C(5)-H of 94 and 95 that B must be the most stable conformation for each isomer.

The structure of the major products (99 and 100) of the intramolecular Diels-Alder reaction of 80b were assigned by correlation with 94 and 95 respectively. Treatment of 99a with NaOCH\(_3\) in CH\(_3\)OH at 80°C
followed by acid hydrolysis effected complete epimerization and deprotection to 94 in 79% yield. Contrathermodynamic epimerization of 95 was effected by treatment of 95 with four equivalents of lithium diisopropylamide, followed by quenching of the enolate solutions with glacial acetic acid in THF. This procedure afforded epimer 100b in 58% yield along with a 31% yield of recovered ester 95. Alcohol 100b was also prepared from Diels-Alder adduct 100a by mild acid hydrolysis. The multiplicity of the resonances observed for C(5)-H (dd, J = 7.2, 2.7 Hz) and C(1)-H(m, W2 = 16Hz) in 100b and C(1)-H(br s, W2 = 9Hz) in 99b suggested that conformer A is more stable than B in each of these epimers.

![Diagram](image)

Treatment of 100b with a catalytic amount of p-TsOH in refluxing benzene resulted in smooth cyclization to lactone 103 in 91% yield\(^6\). The facile lactonization of 100b thus provides unequivocal evidence that the ring fusions of 94, 95, 99, and 100 are cis.
The structure of the minor products of the Diels-Alder reactions of 79 and 80 were assigned by analogous methods. Oxidation of either 101b or 102b, prepared from the corresponding silyl ethers 101a and 102a by acid hydrolysis, with PCC\textsuperscript{39} afforded ketone 104 in greater than 95\% yield. The ring fusion stereochemistry of both 101b and 102b was shown to be \textit{trans} by double irradiation experiments, J\textsubscript{4a,8a} = 9.5Hz for each isomer. The remaining stereocenters at C(5) and C(6) were assigned by analysis of the 'H NMR resonances for C(5)-H which appear as doublets, J = 3.5-4 Hz, for each isomer. The multiplicity of this signal is consistent only with structures in which an axial carbomethoxyl group is flanked by a pseudoaxial alkyl group at C(6). It is interesting to note that the signal for C(5)-H of these compounds is very similar to the signal for C(4)-H of stereochemically related perhydroindene intramolecular cycloaducts, such as 105\textsuperscript{65a,d} and 106\textsuperscript{65e,f}.

\[ \text{CO}_2\text{CH}_3 \]
\[ \text{C(4)-H} \]
\[ \text{OH} \]
\[ \text{105} \]

\[ \text{CO}_2\text{CH}_3 \]
\[ \text{C(4)-H} \]
\[ \text{OH} \]
\[ \text{106} \]

64. The lactone structure assigned for product 103 was supported by its spectroscopic properties. The 'H NMR spectrum of 103 showed the loss of the methoxyl signal and the characteristic acylation shift of C(1)-H (from δ3.74 in 100b to δ4.45 in 103). The IR spectrum of 103 showed an absorption at 1725 cm\textsuperscript{-1} which is consistent with the six-membered lactone.
The structure of cycloadducts 97 and 98 were assigned on the basis of 'H NMR spectroscopy and by their smooth PCC\textsuperscript{39} oxidation to trans-fused ketone 107, J\textsubscript{4a,8a} = 12.5Hz. The resonance for C(5)-H of these compounds appears as a doublet of doublets, J = 10 and 5Hz. These data leave little doubt about the stereochemical environment of C(5)-H, since these coupling constants are characteristic of trans-fused cycloadducts possessing equatorial carbomethoxyl groups flanked by a pseudoaxial alkyl group at C(6)\textsuperscript{26,65}.

Quantitation of these product mixtures was complicated by the difficult task of separating the four diastereomeric reaction products obtained in each case. Pure samples of all four cycloadducts from triene 80 could be obtained by repeated, careful flash chromatography\textsuperscript{43}. The mixture of cycloadducts from triene 79 were separated with the assistance of a novel, selective hydrolysis of the respective trimethylsilyl ethers. Thus, silica gel column chromatography of the crude mixture of cycloadducts from 79 resulted in the selective hydrolysis (on the column) of the two equatorial silyl ethers.

(b) Roush, W.R.; Gills, H.R. J. Org. Chem. 1980, 45, 4283;
(c) Roush, W.R.; Gills, H.R. ibid 1980, 45, 4267;
(d) Roush, W.R.; Gills, H.R.; Ko, A.I. ibid 1980, 45, 4264;
(e) Roush, W.R. J. Amer. Chem. Soc. 1980, 102, 1390;
These isomers eluted from the column as the free alcohols 94b and 97b. The axial silyl ethers 95a and 98a eluted from the column relatively unscathed. The resulting binary mixtures of 94b and 97b, and 95a and 98a were separable by standard chromatographic methods.
It is evident that the stereochemical outcome of an intramolecular Diels-Alder reaction (i.e., cis-trans product ratio) may be affected by stereocenters or functionality on the chain connecting the diene and dienophile (vide infra). The results summarized above for 74, 79 and 80 show that the stereocenter at C(7) does indeed affect the stabilities of the diastereomeric transition states leading to the epimeric pairs of trans-fused and cis-fused products (i.e., ratios of 94:95 and 97:98 are not 1:1). Whether this stereocenter effected the ratio of cis and trans fused products, however, is not easily deduced from the data. In an attempt to resolve this question, we decided to investigate the cyclizations of ketals 81, 82, and 83 (Scheme XII). Results in this series might be more easily interpreted since there would be only two, and not four, transition states to consider. Moreover, it is clear that ketals 81, 82, and 83 also possess the requisite functionality for use in a synthesis of the bottom-half model 60.

66. This is not surprising since there are several examples of significant rate differences in the reactivity of axial vs. equatorial substituents are well known. An example of this is shown below; Eliehl, E.L.; Haubenstock, H.; Acharya, R.V. J. Am. Chem. Soc. 1961, 83, 2351.
The results of these cyclizations are summarized in Scheme XII. Unfortunately, all three ketals, 81, 82, and 83 cyclized preferentially to afford cis-fused products. The stereochemistry of the cycloadducts

**SCHEME XII**

![Chemical structures](image)

81: 19

76: 24

79: 21
tabulated in Scheme XII was assigned by analysis of their 'H NMR spectra. The major product 108 from the cyclization of 81 was shown to possess a cis-ring fusion on the basis of double irradiation experiments, J\textsubscript{4a,8a} = 4 Hz. The stereochemistry of the minor cycloadduct 109 could not be assigned directly because of the complexity of the 'H NMR spectrum. It was, therefore, assigned a trans-ring fusion by comparison with the spectroscopic data for trans-fused alcohols 60 and 76. In particular, the resonances observed for C(5)-methyl and C(6)-methyl groups in 109, centered at δ 1.13 and δ 0.86, are in good agreement with the signals for C(5)-methyl, δ1.17 and δ1.16, and C(6)-methyl, δ0.86 and δ0.90, in cycloadducts 60 and 76, respectively.

The stereochemistry of the major products from the cyclization of 82 and 83 were assigned by analogous considerations. Double irradiation experiments showed unambiguously that 110 and 112 possessed cis-ring fusions, J\textsubscript{4a,8a} = 4.5 Hz in 110 and J\textsubscript{4a,8a} = 4 Hz in 112.

The multiplicity of C(5)-H of both 110 and 112 were very similar to those of cis-fused alcohols, 94-95 and 99-100, respectively. This result is not surprising since one would expect that ketals 110 and 112 would assume the conformations adopted by alcohols 94-95 and 99-100. In 110, the major product from the cyclization of 82, C(5)-H appears as a doublet of doublets, J = 11.6 and 9.4 Hz. This compares favorably with the observed coupling constants for C(5)-H in alcohols 94 and 95, J=12 and 10 Hz in both isomers. The magnitude of these coupling constants leaves little doubt that C(5)-H of 110 occupies an axial position and is flanked by an axial hydrogen at C(4a) and a pseudoaxial hydrogen at C(6).
In contrast, C(5)-H of 112 (the major product from the cyclization
of 83) appears as a doublet of doublets, J=3 and 7Hz. This is in good
agreement with the multiplicity of C(5)-H in alcohol 100b (J= 2.5 and
7Hz) and is consistent only with structures in which an axial C(5)-H
is flanked by an equatorial C(4a)-H and a psuedoequatorial C(6)-H.

The minor product, 111, from the cyclization of 82 was assigned
a trans-ring fusion on the basis of double irradiation experiments,
J_{4a,8a} = 10.7 Hz. In addition, the 'H NMR spectrum of 111 showed the
characteristic doublet of doublets for C(5)-H (J= 11.6 Hz), the multi-
plicity of which is diagnostic for trans-fused cycloadducts of this
type. The stereochemistry of the minor product, 113, from the cycli-
zation of 83 could not be determined directly, but was assigned a trans
ring fusion based on the epimerization of trans-fused 111 to 113. Thus,
treatment of ester 111 with a solution of sodium methoxide in methanol (100°C, 25h) afforded a 70:30 mixture of 111 and 113.

Although the stereochemical outcome of the cyclization of ketals 81-83 follows the same general trend previously established for alcohols 64, 79, and 80, it is interesting to note that the ketal cyclizations are somewhat more selective for the cis-fused products than are the corresponding alcohol derivatives.

In an attempt to elucidate the factors responsible for the observed selectivity for cis-fused products, we examined the cyclizations of unsubstituted trienes 84 and 85. Unfortunately, these two trienes
cyclized non-selectively to afford essentially 1:1 mixtures of the endo and exo cycloadducts. Although the mixture of 114 and 115 was not separable by preparative TLC, these cycloadducts could be separated by careful, preparative gas-liquid chromatography (12 ft 15% SE-30 on Chromasorb A). The mixture of 116 and 117 was, however, inseparable by either preparative TLC or gas-liquid chromatography.

The stereochemistry of adduct 114 was assigned by hydrogenation to the known compound 118. The $^{13}$C NMR spectrum of the hydrogenation product (118) was in good agreement with the published values for this compound. The structure of 117 was assigned by correlation with 115. Thus, epimerization of 115 with sodium methoxide in methanol afforded a 1:1 mixture of 115 and 117.

67. The ratio of cycloadducts was determined by integration of the carbomethoxyl signals in the 250 MHz NMR spectra of the crude reaction products.

On the basis of the results summarized above and in Schemes X and XII we conclude the following:

1) The unexpected product selectivity realized with 74 is general for trienes of this type, as cis-fused cycloadducts are the major products for each of the Diels-Alder reactions of 79-83.

2) Product selectivity is independent of dienophile stereochemistry.

3) Secondary, orbital interactions do not control the stereochemical course of these Diels-Alder reactions.

In the case of trienes 74, and 79-83 the major products arise via transition state A. Clearly, the endo rule is violated by (E,E,E)-triienes 74, 79, 81 and 82. Although the major products of the Diels-Alder reactions of (Z,E,E)-triienes, 80 and 83, are endo adducts, it is apparent that secondary orbital interactions are not the controlling factor for these cyclizations. To the extent that an endo transition state is stabilized by secondary orbital interactions, one expects to observe relatively more cis-fused product from the (Z,E,E,)-triienes and relatively more trans-fused product from the (E,E,E)-triienes. This tendency is not apparent in the data. In fact, (E,E,E)-triienes 79 and 82 afford slightly more cis-fused (exo) product than is obtained from the corresponding (Z)-dienophile isomers.
Control experiments established that each of the cyclizations reported above is kinetically controlled. In these experiments, the individual cycloadducts were resubjected to the Diels-Alder reaction conditions and were recovered unchanged (GLC analysis). It therefore follows that cis-fused transition state A is somewhat lower in energy than trans-fused transition state B (1.0-1.2 Kcal mol\(^{-1}\) for 79-83). The results obtained with 84 and 85 imply that the greater selectivity realized with the more highly functionalized trienes, such as 64, 79, and 80, is related to the presence of substituents at C(7) and possibly C(11). The latter possibility may now be ruled out since other workers in this laboratory have observed that trienes 119 and 120 cyclize to afford mixtures of products in a ratio of approximately 1:1\(^6\)9. The fact that these ratios are very similar to the product ratios obtained in the cyclization of unsubstituted trienes 84 and 85 show

\[\text{119} \quad \text{180}^\circ\text{C, 36 h, 72%} \quad 55:45\]

\[\text{120} \quad \text{160}^\circ\text{C, 48 h, 70%} \quad \sim 50:50\]

that substitution at C(11) is not a critical factor in determining the stereochemical outcome of these cyclizations.

Examination of the results summarized in Table 1 raises a fundamental question regarding these studies: why are the substituted trienes 74, 79, and 80 more selective for cis-fused products than the corresponding "parent" trienes, 84 and 85, both of which cyclize in a stereorandom fashion? In addition, why are ketal s 81-83 more selective for cis-fused products than their corresponding protected alcohol counterparts?

It is apparent, that the increased selectivity of 79 and 80 for cis-fused products must be associated with the alkoxy substituent at C(7). Examination of molecular models of these trienes suggests a possible explanation. Whereas cis-fused transition states A or A' and trans-fused transition state B' show no noticeable steric interactions between the C(7)-hydroxyl functionality and C(9)-H, trans-fused tran-
<table>
<thead>
<tr>
<th>Entry</th>
<th>Triene</th>
<th>Ratio of cis:trans-fused products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Triene 1" /></td>
<td>84 ........................ 49:51</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Triene 2" /></td>
<td>120 ........................ 50:50</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Triene 3" /></td>
<td>79a ........................ 70:30</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Triene 4" /></td>
<td>64 ........................ 72:28</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Triene 5" /></td>
<td>82 ........................ 79:21</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Triene 6" /></td>
<td>81 ........................ 81:19</td>
</tr>
</tbody>
</table>
TABLE 1 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Triene</th>
<th>Ratio of cis:trans-fused products</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image" alt="Triene 7" /></td>
<td>85 .......... 51:49</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Triene 8" /></td>
<td>119 .......... 45:55</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Triene 9" /></td>
<td>80a .......... 62:38</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Triene 10" /></td>
<td>83 .......... 76:24</td>
</tr>
</tbody>
</table>

Transition state B appears to be destabilized by allylic 1,3-strain between C(9)-H and C(7)-OR. If this argument is valid, one would expect ketals 82 and 83 to be more cis-selective. This conclusion derives from the fact that 74, 79, and 80 can cyclize to trans-fused products via transition state B' (void of the allylic strain present in B), but ketals 82 and 83 can cyclize to trans-fused products only through transition state A" in which this steric interaction between C(9)-H and C(7)-OR must be present. This, indeed, is the trend which is observed.
It is, of course, dangerous to overinterpret such small changes in product ratios since the difference in transition state energies associated with these changes is quite small (<1.5 Kcal mole\(^{-1}\)). Based on the above model one would predict that the ratio of the two cis-fused products (99:100 and 77:78) would be close to one. In each case this ratio is nearly two. Thus, other more subtle steric and/or conformational factors may play an important role in determining the stereochemical outcome of these cyclizations.

It is now apparent that intramolecular Diels-Alder reactions which occur at temperatures in excess of 100°C are not governed by secondary orbital interactions. This conclusion is not surprising since bimolecular Diels-Alder reactions of open-chain dienes and dienophiles obey the endo rule only at low temperatures. For example, 2,4-pentadienoic acid undergoes cyclization with acrylic acid at 75°C to afford only the endo adduct. When, however, the reaction

    (b) Onishenko, A.S.; "Diene Synthesis" (English translation), 1964, Israel Program for Scientific Translation, Jerusalem;
temperature is increased to 130°C, a 1:1 mixture of the endo and exo products is obtained. Unlike the bimolecular reaction, the intramolecular Diels-Alder reaction may not show a dramatic change in product ratios with respect to reaction temperatures since these cyclizations are often dominated by conformational and/or steric interactions.

\[
\begin{align*}
\text{COOH} + \text{COOH} & \xrightarrow{\Delta} \text{COOH} \\text{COOH} \\
\text{121} & \text{122}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>75</th>
<th>90</th>
<th>100</th>
<th>110</th>
<th>130</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Ratio</td>
<td>121:122 121 only 7:1 4.5:1 2:1 1:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous studies from these laboratories have shown that the intramolecular Diels-Alder reactions of a series of methyl (E,E,E)- and (Z,E,E)-deca-2,7,9-trienoates preferentially afford trans-perhydroindene cycloadducts. It is interesting to note that the stereo-

\[
\begin{align*}
\text{R}^1 & \text{R}^2 \xrightarrow{\Delta} \text{R}^1 \text{R}^2
\end{align*}
\]

chemical parameters of these cyclizations parallel the results presented in Schemes X and XII in many respects. In both series, product selectivity is independent of dienophile stereochemistry; in
both series, product selectivity seems to be dominated by subtle steric and/or conformational factors; and the parent unsubstituted trienes are the least selective examples in each series. The principle difference between the two sets of reactions is that decatrienoates afford primarily trans-fused products, whereas the undecatrienoates afford predominantly cis-fused products.

At the outset of our studies, we were uncertain why trienes 59, 74, and 79-83 cyclize selectively to afford predominantly cis-fused products, whereas 57, 58 and other unactivated 1,7,9-trienes cyclize with pronounced trans-selectivity. Since the initiation of this work, however, several publications have appeared which may explain this range of results.

Wilson and coworkers observed that triene 123 cyclized to afford a 55:45 mixture of trans- and cis-fused products which were analyzed following oxidation of the epimeric alcohols. In contrast triene 124, which differs from 123 only in the replacement of C(8)-H with a methyl group, cyclized with high selectivity to give a mixture of the trans-fused epimeric alcohols 125 in greater than 95% yield.

\[ \text{123} \xrightarrow{(1) \Delta} \xrightarrow{(2) \text{oxidation}} \]

Wilson suggested that the pronounced \textit{trans}-selectivity observed in the cyclization of 124 may derive in part from steric interactions between substituents at C(8) of the diene and an axial C(5)-H in the \textit{cis}-fused transition state 126\textsuperscript{71,73}.

Several related trienes, all of which possess alkyl substituents at C(8) of the diene, also cyclize preferentially to afford \textit{trans}-fused cycloadducts.

It is likely that this steric interaction is responsible for the high stereoselectivity observed in the cyclizations of o-quinodimethane intermediates such as 131-133; all of these substrates possess a carbon substituent at this key position. Whether or not substituents at the corresponding position of trienes 74 and 79-83 will alter the stereochemical course of these cyclizations remains for determination.


The addition of Lewis acids has been employed to improve both the regio- and stereoselectivity in intermolecular Diels-Alder reactions (see, for example, equations 3 and 4).

Regioselectivity

\[
\text{toluene, } 120^\circ\text{C, no catalyst} \quad 59 : 41
\]
\[
\text{benzene, } 25^\circ\text{C, SnCl}_4 \cdot 5\text{H}_2\text{O} \quad 96 : 4
\]

Stereoselectivity

\[
0^\circ\text{C, no catalyst} \quad 84 : 16
\]
\[
-70^\circ\text{C, } +47\% \text{ AlCl}_3 \cdot \text{Et}_2\text{O} \quad 97 : 3
\]

Lewis acids have also been employed in intramolecular Diels-Alder reactions as a method to improve the stereoselectivity of the cyclization. Several recent examples are recorded below in which a marked increase in the rates of these cyclizations was coupled with increased stereoselectivity. Thus, we hoped that trienes and might show an increased preference for the endo adduct (trans-fused in these cases) under the influence of Lewis acid catalysis.

79. For several recent examples directed toward natural product syntheses see:
134

\[ \text{CO}_2\text{CH}_3 \]  
\[ \text{CO}_2\text{CH}_3 \]  
\[ \text{CO}_2\text{CH}_3 \]  
ref. 65a,c

\[ 150^\circ \text{C}, 40 \text{ h} \]
1.3 eq. Et\textsubscript{2}AlCl, 23\(^\circ\)C, 48 h

\[ >98 : 2 \]

135

\[ \text{H}_2\text{COOC} \]  
\[ \text{H}_2\text{COOC} \]  
\[ \text{H}_2\text{COOC} \]  
ref. 79b

\[ 110^\circ \text{C}, 25 \text{ h} \]
0.95 eq. EtAlCl\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2},  
0\(^\circ\)–23\(^\circ\)C, 1.5 h

\[ 50\% \]  
\[ 11\% \]  
\[ <5\% \]

136

\[ \text{H}_2 \text{COOC} \]  
\[ \text{OTBDMS} \]  
\[ \text{H}_2 \text{COOC} \]  
\[ \text{OTBDMS} \]  
\[ \text{H}_2 \text{COOC} \]  
\[ \text{OTBDMS} \]  

\[ 140^\circ \text{C}, 120 \text{ h}, 65\% \]
1 eq. EtAlCl\textsubscript{2}, 25\(^\circ\)C, 72 h, 69%

\[ 65 : 13 : 22 \]  
\[ 98 : 2 : 0 \]  
ref. 79a
alysis. We were, however, unable to effect Lewis-acid promoted cyclizations of any of the trienes discussed primarily due to decomposition of the trienes under the reaction conditions. Most of these trienes possess oxygen substituents allylic to the diene which presumably complex to the Lewis acids as a prelude to subsequent decomposition reactions. These trienes are very susceptible to pentadienyl carbocation formation, a process which is presumed to be involved in the decomposition of these molecules. Similar problems have plagued other workers in their attempts to effect the Lewis acid promoted cyclizations of related trienes in the perhydroindene series\textsuperscript{65a,69}. It is clear that this mode of decomposition is

\[
\begin{array}{c}
\text{products}
\end{array}
\]

not available to the unsubstituted trienes, \textbf{84} and \textbf{85}; however, diene polymerization competed favorably with cyclization in these cases\textsuperscript{80}. This deleterious polymerization could be suppressed by the introduction of an isopropyl group at C(11)\textsuperscript{69} of trienes \textbf{84} and \textbf{85}. Trienes \textbf{119} and \textbf{120} undergo efficient Lewis-acid promoted cyclizations to afford

80. It was clear from the NMR of the reaction mixture that trienes \textbf{84} and \textbf{85} were polymerizing through the terminal double bond of the diene; the signals for C(11)-H and C(10)-H slowly disappeared while the resonances for C(2)-H, C(3)-H, C(8)-H, and C(9)-H remained unchanged.
the "endo" adduct as the major product in each cyclization (recall that the thermal cyclizations of 119 and 120 afforded approximately 1:1 mixtures of the endo and exo adducts).

**119**

$180^\circ \text{C}, 36 \text{ h}, 72\%$

$\text{EtAlCl}_2 (0.95 \text{ eq.}), 23^\circ \text{C},$

$3 \text{ h}, \text{CH}_2\text{Cl}_2, 88\%$

$55 : 45$

**120**

$160^\circ \text{C}, 48 \text{ h}, 70\%$

$\text{EtAlCl}_2 (0.9 \text{ eq.}), 23^\circ, 3 \text{ h},$

$\text{CH}_2\text{Cl}_2, 68\%$

$\sim 50 : 50$

Because we were unable to improve the ratio of trans:cis-fused products from the cyclizations of 74,79 and 81-82 by Lewis acid catalysis, our attention turned to other factors which might influence the stereochemical outcome of these cyclizations. The hybridization of the atoms in the bridge linking the diene and dienophile is well-known to
influence the stereochemical course of intramolecular Diels-Alder reactions\textsuperscript{81}. Pioneering studies by Oppolzer have shown that \( \text{sp}^2 \)-hybridized atoms at the position allylic to the diene prefer to remain coplanar to the diene in the reaction transition state, thereby maintaining orbital overlap along the reaction coordinate. In some cases, such as \textbf{137} and \textbf{138}, the stereochemical outcome of cyclizations of

\[
\begin{align*}
\textbf{137} & \quad \text{x=0} & \quad 155^\circ\text{C}-180^\circ\text{C}, 78\% & \quad \text{x=0} & \quad \text{cis : trans} & \quad 83 : 16 \\
\textbf{138} & \quad \text{x=H}_2 & \quad 180^\circ\text{C}, 62\% & \quad \text{x=H}_2 & \quad \text{ref. 81c} & \quad 27 : 72
\end{align*}
\]

triene bearing \( \text{sp}^2 \)-hybridized atoms at the position allylic to the diene is opposite to the outcome realized with trienes bearing \( \text{sp}^3 \)-hybridized allylic substituents\textsuperscript{81c}.

This effect is not limited to the atoms allylic to the diene, and in general may be observed for any atoms in the bridge linking the diene and dienophile. Illustrative of this point is an example from Wilson's laboratories. Whereas triene \textbf{124} cyclized to afford

\textsuperscript{81} (a) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* 1977, 16, 10; 
(c) Oppolzer, W. *Tetrahedron Lett.* 1974, 1001; 
trans-fused alcohol 125 in greater than 95% yield\textsuperscript{72}, triene 139 cyclized to produce exclusively cis-fused adduct 140 in 72% yield\textsuperscript{73}.

Thus, a complete reversal in stereoselectivity\textsuperscript{82} was effected by changing the hybridization of C(3) and C(4) from sp\textsuperscript{3} to sp\textsuperscript{2}. We therefore decided to study the Diels-Alder reaction of 141 in order to determine whether a carbonyl group at C(7) would alter the stereochemical course of the reaction in favor of the trans-fused 82. Although triene 139 cyclizes to give exclusively the cis-fused adduct 140, Oppolzer observed that the closely related triene \( v \)

\[
\text{TMS} \quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\quad \begin{array}{c}
\text{OSiEt}_3 \\
\text{OSiEt}_3
\end{array}
\quad \begin{array}{c}
\text{TMS} \\
\text{TMS}
\end{array}
\quad \begin{array}{c}
\text{H} \\
\text{H}
\end{array}
\quad \begin{array}{c}
\text{(1) n-Bu}_4\text{NF} \\
\text{(2) MnO}_2
\end{array}
\quad \begin{array}{c}
\text{70\% overall} \\
\text{cis : trans \textsuperscript{1:1}}
\end{array}
\]

\( v \)

\( v \)

product. Examination of Dreiding molecular models of 141 reveals that if the carbonyl group is constrained to remain coplanar to the butadiene, then bonding geometries are easily obtained only in the transition state which leads to the trans-fused product. Accordingly, heating a toluene solution of 91 at 165°C for 20h resulted in a low conversion (~15%) to cycloadducts. Examination of the crude product by 1H NMR (250 MHz) revealed the presence of only one cycloadduct. This compound was easily assigned the structure of trans-fused ketone 142 by double irradiation experiments, J_{4a,8a} = 12 Hz. The more vigorous conditions (165°C-200°C, 100-140h) required to obtain a reasonable rate of cyclization resulted in the formation of conjugated enones 143 and 144 in varying amounts. For example, heating a solution of 91 in a 165°C oil bath for 138 h afforded a mixture of cycloadducts among which 142 was the major product, contaminated with
smaller amounts of enones 143 and 144. Purification of this mixture by preparative TLC afforded ketone 142 in 52% yield. A cyclization temperature of 200°C (102h) was required to push the reaction to full conversion. This gave unfortunately, a mixture of products consisting mainly of the two conjugated enones 143 and 144. Chromatography of this mixture afforded enone 143 in 41% yield along with a 4:1 mixture of enones 144-143 (41%). The spectroscopic properties of enones 143 and 144 were in full agreement with their assigned structures. The 'H NMR spectrum of both isomers showed a one proton multiplet in the olefinic region centered at 86.72 (for 143) and 86.85 (for 144). The downfield shift of these signals relative to the olefinic resonances in ketone 142, 85.87 for C(8)-H and 85.66 for C(7)-H,
supports the assignement of (E)-α,β-unsaturated ketone structures to these compounds\textsuperscript{45}. Further evidence for these structures derives from their IR spectra; both isomers show absorptions at 1692 cm\textsuperscript{-1} and 1619 cm\textsuperscript{-1} which are consistent with the conjugated enone structures\textsuperscript{83}. Assignment of stereochemistry to the major product, enone 143, was based on the independent acid-catalyzed isomerization of 142 to 143.

The stereochemistry of 142 was further verified by reduction of 142 with BH\textsubscript{3}•NH\textsubscript{3} in methanol which afforded a 2:1 mixture of 60-76 in 60\% yield following chromatography\textsuperscript{84}.

\begin{center}
\begin{align*}
\text{CO}_2\text{CH}_3 & \quad \text{BH}_3\text{•NH}_3 \\
\text{H}_3\text{C} & \quad \text{CH}_3\text{OH}, 0^\circ \text{C} \\
\text{142} & \quad 60\% \\
\text{CO}_2\text{CH}_3 & \quad \text{Me} \\
\text{Me} & \quad \text{OH} \\
\text{60} & \quad + \\
\text{Me} & \quad \text{OH} \\
\text{76} & \quad 2:1
\end{align*}
\end{center}

We presume that enone 144 is the conjugated tautomer of exo-Diels-Alder adduct 145, however, we have not isolated (or detected) ketone 145 from any of the reaction mixtures.

We anticipated that the undesired isomerization of 142 to 143 could be controlled by careful selection of the reaction conditions; therefore, we decided to synthesize the actual trienone needed for the construction of the bottom half of chlorothricolide.

We envisioned that the requisite triene 146 could be assembled efficiently by a series of Wittig reactions as shown in Scheme XIII.


Condensation of methyl 3-formyl-propionate$^{85, 147}$ with α-formylmethylenetriphenylphosphorane$^{86}$ in CH$_2$Cl$_2$ at 23°C afforded the expected (E)-α,β-unsaturated aldehyde 148 in 89% yield. The next reaction required that we prepare a Wittig reagent.


of the general type depicted by structure 149. We anticipated that 149 could be prepared by acylation of methylenetriphenylphosphorane with a suitably-activated carbonyl compound 150. Acyl imidazoles

![Chemical structure](image)

have been used as efficient acylating agents for alkylidenetriphenylphosphoranes\(^{87}\), thus our immediate synthetic objective became acyl-imidazole 151. This reagent was prepared in a straightforward manner as outlined in Scheme XIV. Treatment of a solution of methylenetri-

### SCHEME XIV

![Chemical structures](image)

Key: (a) NaOEt, BrCH\(_2\)CH\(_2\)CHOCH\(_2\)CH\(_2\)O\(^{88}\); (b) LiCl\(^{89}\), DMSO, \(\Delta\); (c) NaOH, H\(_2\)O, MeOH; (d) (C\(_3\)H\(_3\)N\(_2\))\(_2\)S=0, THF.
phenylphosphorane in benzene with imidazolide proceeded smoothly to afford the desired phosphorane in 64% yield after recrystallization from ethyl acetate. Condensation of Wittig reagent with unsaturated aldehyde proceeded smoothly at 23°C to provide dienone in 51% yield. The E-stereochemistry of the new double bond was confirmed by its 'H NMR spectrum; C(6)-H appeared as a doublet of doublets centered at 67.02, J=10 and 15 Hz. Acetal was hydrolyzed in a mixture of THF, H₂O, and HOAc (6:4:1, v/v) to afford aldehyde, which without purification was condensed with α-(carbomethoxy)-ethyldenetriphenylphosphorane in CH₂Cl₂ to give trienone in 79% overall yield from acetal.

Trienone 146 was cyclized in dilute toluene solution (200°C, 102h) to afford a 62:38 mixture of two conjugated enones 157 and 158. Unfortunately, the problems associated with the cyclization of model trienone 91 also occurred in the cyclization of 146. The structures of enones 157 and 158 were assigned by comparison of their 1H NMR spectra to the spectra of model enones 143 and 14491. Initial attempts to suppress the deleterious isomerization of the cyclization products from 146 were not successful. Thus we returned to an examination of model trienone 91 which was available in larger quantities.
Despite considerable effort, our attempts to retard the undesired isomerization of 142 to 143 were only marginally successful. Silylation of the glassware prior to the reaction did suppress isomerization, unfortunately it also retarded the rate of cyclization of 91. These extended reaction times offset the gains provided by silylating the glassware and a mixture of conjugated enones was obtained.

It is clear from our results with trienone 91 that the carbonyl group at C(7) does influence the stereochemical course of this cyclization. With respect to our ultimate goal of achieving the total synthesis of chlorothricolide, however, it appeared that sequences involving trienone cyclizations would not be useful because of our inability to suppress the undesired isomerization. Similar problems have been encountered in a related system. Näf et al. found that dienone 159 cyclized to afford only trans-fused ketone 160, however isomerization to cis-fused 161 occurred under the reaction conditions. This isomerization was favored since it relieves the 1,3-diaxial interaction between the angular methyl group and the ester substituent. In contrast to the isomerization of 142, none of the conjugated tautomer of 160 was isolated.

91. The olefinic protons of 157 and 158 occurred at 66.70 and 86.84 respectively. By comparison, these signals for 143 and 144 occurred at 86.72 and 86.85.

SUMMARY

Although the cyclizations of undecatrienes 74 and 79-83 were interesting in their own right, they clearly were not useful with regard to the synthesis of chlorothricolide. In retrospect, it is apparent that different model systems may have afforded the desired trans-fused cycloadducts. In particular, it would be interesting to examine the cyclization of a triene which possesses a substituent (other than hydrogen) at C(9) of the triene (i.e., 162). Based on
the arguments put forth by Wilson with regard to the cyclization of trienes 123 and 124 (see p. 79), one might expect that trans-fused 163 would be the major product of the intramolecular Diels-Alder reaction of 162. However, the cyclization of 162 may be more complicated than that of 123 and 124 due to the functionality at C(7) of triene 162.

The four possible chair-like transition states are illustrated below. Transition states 164a and 164b would lead to cis-fused products and transition states 165a and 165b would afford trans-fused cycloadducts. Examination of these transition states reveals that serious steric interactions develop in transition states 164a,b and 165a. Transition states 164a and 164b are destabilized by a steric interaction between the C(9)-substituent and an axial C(6)-H. On the other hand, transition state 165a is destabilized because of the severe allylic 1,3-strain between the C(9)-substituent and the C(7)-hydroxyl group. Thus, we would predict transition
state 165b to be utilized to the greatest extent. Cyclization through this transition state would afford the desired trans-fused cycloadduct with the correct relative stereochemistry at all five asymmetric centers.

Since the lower half of chlorothricolide does not possess a substituent at C(9), an approach following this strategy would require that the C(9)-substituent could be removed at a point later in the synthesis. Possible candidates for this "steric directing group" would include halogens or a trimethylsilyl group.

Although this strategy appears to have a good chance to succeed, it was not pursued since an alternate strategy was developed using a simple modification of our original scheme. This modification, which resulted in the total synthesis of the bottom half of chlorothricolide, will be described in the third and final chapter of this thesis.
EXPERIMENTAL SECTION

'H NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270 instruments. Chemical shifts are reported in δ units relative to internal Me₄Si. Infrared spectra were measured on a Perkin-Elmer Model 283B Infrared Spectrophotometer and were calibrated with the 1601 cm⁻¹ absorption of polystyrene. Mass spectra were measured at 70 ev on a Varian MAT 44 instrument. High resolution mass spectra were provided by the Facility supported by NIH Grant RRO317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high resolution mass spectrometer equipped with an IBM 1800 computer system to process data recorded on photographic plates. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried (120°C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from Na-benzophenone ketyl; CH₂Cl₂ and Me₂SO were distilled from CaH₂; toluene was distilled from sodium metal. Preparative thin-layer chromatography (TLC) was performed using 20 x 20 cm plates coated with 0.5- and 2-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether. Column chroma-
tography was performed using activity I Woelm silica gel. Flash chromatography was performed as described by Still. All chromatography solvents were distilled prior to use.

Experimental details for the chemistry outlined in Schemes XIII and XIV (pp. 92-95) appear below. Full experimental details for the remainder of the chemistry described in Chapter 2 have been published and will therefore not be repeated in this thesis.
Alkylation of Diethyl malonate

A 500 mL flask was charged with 200 mL of absolute EtOH. The flask was immersed in a cold water bath and 8.32 g of sodium metal (363 mmol) was added in small pieces. On this scale the addition required 50 min. An Ar purge was maintained during the addition to remove the H₂ which was formed. To this solution was added dropwise 50.0 g of diethyl malonate (312 mmol). After approximately two-thirds of the diethyl malonate had been added, the solution turned into a white gel. After the addition was complete, the reaction mixture was warmed to 30°C at which point the gel dissolved. To this solution was added dropwise 62.2 g of 2-(2-bromo-1-ethyl)-1,3-dioxalane (344 mmol) over 20 min. After being stirred an additional 15 min at 23°C the reaction mixture was heated to reflux for 13 h.

The cooled solution was filtered to remove NaBr. The filter cake was washed with two 100 mL portions of CH₂Cl₂. The filtrate was diluted with 100 mL of CH₂Cl₂ and then washed with two 200 mL portions of H₂O. The combined aqueous extracts were washed once with 150 mL of CH₂Cl₂. The combined CH₂Cl₂ layers were dried over Na₂SO₄ and concentrated in vacuo to give 89.8 g of crude product. This compound was purified by fractional distillation to give 56.7 g of 152 (71%)

Data for 152: bp 124°C (0.1 mm) NMR (60 MHz, CCl₄) δ4.8 (t, J= 5Hz, 1H), 4.15 (q, J= 7Hz, 4H), 3.85 (m, 4H), 3.3 (t, J= 6Hz), 1.8 (m, 4H), 1.2 (t, J= 7Hz, 6H); IR (neat) cm⁻¹ 2980, 1750, 1730; mass spectrum m/e 215 (M - OEt).
2-(3-carboxethoxy-1-propyl)-1,3-dioxolane (153)

To a stirred solution of 52.8 g of 152 (203 mmol) in 335 mL of DMSO was added 3.3 mL of H₂O, 16.9 g of LiCl (406 mmol), and approximately 50 mg of Na₂CO₃. This mixture was slowly heated to reflux under a N₂ purge. The reaction mixture was maintained under slow reflux for 4 h and then allowed to cool slowly overnight.

The cooled reaction mixture was poured into a separatory funnel containing 650 mL of 4:1 hexane-ether and 700 mL H₂O. The aqueous layer was washed with two 400 mL portions of 2:1 hexane-ether. The combined organic layers were back-extracted with 300 mL of H₂O and then dried over Na₂SO₄, filtered and concentrated in vacuo to afford 32.7 g of 153. This compound was purified by fractional distillation to afford 29.8 g of pure 153 (78%).

Data for 153: bp 84°C (1.0 mm) NMR (60 MHz, CCl₄) δ4.8 (m, 1H), 4.05 (q, J= 7Hz, 2H), 3.8 (m, 4H), 2.25 (m, 2H), 1.2 (t, J= 7Hz, 3H); IR (neat)cm⁻¹ 2978, 1725, mass spectrum m/e 143 (M - OEt).

2-(3-carboxy-1-propyl)-1,3-dioxolane (154)

A solution of 26.6 g of 153 (141 mmol) in 200 mL of MeOH was cooled to 0°C. To this stirred solution was added slowly 100 mL of 1N NaOH. When the addition was complete the ice bath was removed and the resulting solution was allowed to warm to 23°C. After being stirred overnight, the reaction mixture was poured into a separatory funnel containing 200 mL of saturated aqueous NaHCO₃ and 150 mL CH₂Cl₂. The CH₂Cl₂ layer was washed with 200 mL of saturated aqueous NaHCO₃. The combined aqueous extracts was acidified to pH = 2.5 by the addition of 10N HCl (during the addition of 10N HCl the flask was cooled in
an ice bath). The acidified layer was washed with four 200 mL portions of CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to give 19.2 g of acid 154 (85%).

Data for 154: NMR (60 MHz, CCl₄) δ4.8 (m, 1H), 3.8 (m, 4H), 2.35 (m, 2H), 1.7 (br s, 4H); IR (CCl₄)cm⁻¹ 3400-2500, 1715; mass spectrum m/e 159 (M - 1).

Imidazolide(151)

To 22 mL of a stirred 0.28M solution of N, N'-thionyldiimidazole in THF (6.1 mmol) was added dropwise a solution of 0.97 g of 5-oxopentanoic acid ethylene glycol acetal 154 (5.11 mmol) in 5 mL of THF. On this scale the addition required 35 min. After being stirred at 23°C for 9 h, the reaction mixture was concentrated in vacuo to afford a yellow oil. The crude product was dissolved in 20 mL of cold (5°C) CH₂Cl₂ and quickly washed with 15 mL of cold H₂O (5°C). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo to give 559 mg of imidazolide 151 (51%). The aqueous layer was back-extracted with 20 mL of CH₂Cl₂. The CH₂Cl₂ layer was dried over MgSO₄ and concentrated in vacuo to afford 0.509 g recovered acid 154 (47%).

Data for 151: NMR (60MHz, CDCl₃) δ7.97 (s, 1H), 7.28 (s, 1H), 6.9 (s, 1H), 4.7 (t, J=5Hz, 1H), 3.65 (m, 4H), 2.72 (t, J=7Hz, 2H), 1.6 (m, 4H); mass spectrum m/e 210 (parent ion).

Synthesis of Phosphorane(149)

To a stirred solution of 0.77 g methyltriphenylphosphonium bromide (2.16 mmol) in 50 mL of dry benzene was added
1.52 mL of a 1.5M phenyllithium solution in benzene-ether (2.27 mmol). This solution was stirred at 23°C for 24 h. To this red-orange solution was added dropwise a solution of 182 mg of imidazolide 151 (0.87 mmol) in 15 mL of benzene. On this scale the addition required 3 min.

The reaction mixture was stirred at 23°C for 20 h and then was washed with three 5 mL portions of benzene. The filter cake was washed with three 5mL portion of benzene. The filtrate was concentrated to a volume of 25 mL and then washed with 10 mL of half-saturated aqueous NaCl. The aqueous extract was washed with two 10 mL portions of benzene. The combined benzene extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo to give 443 mg of crude phosphorane 149 which crystallized on standing. This compound was purified by recrystallization from EtOAC. This gave 233 mg of phosphorane 149 (64%).

Data for 149: NMR (60 MHz, CDC₃) δ7.2 (m, 15H), 4.7 (m, 1H), 3.62 (m, 4H), 2.15 (m, 2H), 1.6 (m, 4H); mass spectrum m/e 419 (parent ion).

Methyl (E)-6-Oxo-4-hexenoate (148)

To a stirred solution of 1.89 g of 14785 (16.3 mmol) in 60 mL of dry CH₂Cl₂ was added 8.00 g of α-formylmethylene-triphenylphosphorane86 (26.3 mmol). This solution was stirred at 23°C for 60 h. The reaction mixture was concentrated in vacuo to a volume of approximately 12 mL. This product was purified by flash chromatography (40 mm column) using 1:1 hexane-ether
as eluant. This gave 2.06 g of aldehyde 148 (89%).

Data for 148: NMR (60 MHz, CCl₄) δ 9.4 (d, J=9 Hz, H₆), 6.8 (m, H₄), 6.0 (dd, J=16, 9 Hz, H₅), 3.6 (s, 3H), 2.5 (m, 4H); mass spectrum m/z 141 (M-1).

Methyl (E,E)-8,12-Dioxo-4,6-dodecadienoate ethylene glycol acetal (155)

To a stirred solution of 0.50 g of aldehyde 148 (3.50 mmol) in 10 mL of dry CH₂Cl₂ was added a solution of 2.33 g of phosphorane 149 (5.55 mmol) in 10 mL of CH₂Cl₂. This solution was stirred at 23°C for 48 h, and then was concentrated in vacuo to give a red semi-viscous oil. The crude product was immediately purified by flash chromatography (40 mm column) using 1:1 hexane-ether as eluant. This gave 503 mg of ketone 155 (51%).

Data for 155: NMR (CDCl₃) δ 7.04 (dd, J= 15.3, 9.8 Hz, H₆), 6.10 (m, 3H), 4.79 (t, J=4.5 Hz, H₁₂), 3.83 (m, 4H), 3.61 (s, 3H), 2.54 (t, J= 7Hz, 2H), 2.41 (m, 2H), 1.64 (m, 4H); mass spectrum m/z 282 (parent ion).

Dimethyl (E,E)-2-Methyl-7-oxo-2,8,10-tetradecatrien-1,14-dicarboxylate (146)

To a stirred solution of 309 mg of acetal 155 (1.10 mmol) in 13.5 mL of THF was added 10.9 mL of H₂O and 2.5 mL of glacial HOAc. This solution was heated to reflux for 13 h. The cooled reaction mixture was poured into a separatory funnel containing
75 mL of saturated aqueous NaHCO₃ and 50 mL of ether. The aqueous layer was washed with two additional 50 mL portions of ether. The combined ether extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo to give 270 mg of crude aldehyde 156. This compound was routinely taken on to the next step without purification.

To a stirred solution of 270 mg of crude aldehyde 156 in 12 mL of dry CH₂Cl₂ was added 537 mg of α-(carbomethoxy)-ethylidenetriphenylphosphorane 42 (1.51 mmol). After being stirred at 23°C for 22 h, the solution was concentrated in vacuo to give the crude ester 146. This compound was purified by flash chromatography (40 mm column) using 1:1 hexane-ether as eluant. Rechromatography of mixed fractions gave 267 mg of pure ester 146 (79% from acetal 155) and 31 mg of recovered acetal 155 (10%).

Data for 146: NMR (CDCl₃) δ 7.06 (dd, J = 9.9, 15.4 Hz, H₆), 6.69 (tq, J = 7.4, 1.3 Hz; 1H), 6.11 (m, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.48 (m, 6H), 2.15 (q, J = 7.4 Hz, 2H), 1.77 (d, J = 1.3 Hz, 3H); IR (CCl₄) cm⁻¹ 3020, 1735, 1710, 1668, 1632, 1590.
Cyclization of 146:

**Methyl 6β-[1-(2-Carbomethoxyethyl)]-5α-methyl-1,2,3,4,4αβ-5,6,7-octahydropnaphthalen-1-one-5β-carboxylate (157)** and **Methyl 6β-[1-(2-Carbomethoxyethyl)]-5β-methyl-1,2,3,4,4αβ,5,6,7-octahydropnaphthalen-1-one-5α-carboxylate (158)**

A solution of 28.3 mg of 146 in 2 mL of dry toluene was added to a resealable Carius tube and was purged with dry Ar for 15 min. To this solution was added 0.1 mg of Na₂CO₃ and then the tube was sealed and placed in a 200°C oil bath for 102 h. The cooled tube was opened and then all volatile components were removed in vacuo to give 28.2 mg crude product. A 15 mg portion of the crude product was purified by preparative TLC using 1:1 hexane-ether as eluant. This gave 8.8 mg of 157 (58%) and 4.0 mg of 158 (26%).

**Data for 157:** NMR (CDCl₃) δ 6.70 (m, 1H), 3.66 (s, 3H), 3.61 (s, 3H), 2.90 (m, 1H), 1.09 (s, 3H); IR (CCl₄) cm⁻¹ 3033, 1727, 1685, 1627; mass spectrum m/e 308 (parent ion). High-resolution mass spectrum. Calcd. for C₁₇H₂₄O₅: 308.1624. Found: 308.1650.

**Data for 158:** NMR (CDCl₃) δ 6.84 (quint., J = 2.7 Hz, H₈), 3.72 (s, sH), 3.64 (s, 3H), 2.90 (m, 1H), 0.93 (s, 3H); IR (CCl₄) cm⁻¹ 3020, 1733, 1690, 1628; mass spectrum m/e 308 (parent ion). High resolution mass spectrum. Calcd. for C₁₇H₂₄O₅: 308.1624. Found: 308.1650.
CHAPTER 3
Rethinking the Strategy - A New Approach

The results which we obtained in the cyclizations of triene esters 74, 79-83, and 146 suggested that we would not be able to use a triene intramolecular Diels-Alder reaction in the synthesis of chlorothricolide. We realized, however, that we could modify our strategy by using diene acetylene 166 as a precursor to the bottom half (54) of the target antibiotic. The consequences of this decision were two-fold. First, this modification preserved a method for control of the critical 1,4-relative stereochemistry at C(6) and C(8a) of 54. Secondly, establishment of the ring-junction stereochemistry and introduction of the axial C(5)-methyl group would necessarily be postponed until after the basic nucleus had been constructed.

Thus, we envisioned that hexahydronaphthalene 167 might under-

\[ \text{X} \quad \text{CO}_2\text{R}^2 \]
\[ \begin{align*}
\text{166} & \rightarrow \quad \text{X} \quad \text{CO}_2\text{R}^2 \\
\text{167} & \downarrow \\
\text{168} & \leftarrow \\
\text{29} & \\
\end{align*} \]

93. The work described in Chapter 3 has been submitted for publication. J. Org. Chem. .
go a dissolving metal reduction to afford the desired trans-fused ring system. Subsequent alkylation of this intermediate (from the less-hindered α-face) would provide the bottom half of chlorothricolide. Ideally, the two later transformations would be accomplished in a single step via a reductive-alkylation sequence.

Since the initiation of this work we were optimistic with regard to the stereochemical outcome of the dissolving metal reduction. Pioneering work by Stork, as well as numerous examples from other laboratories, showed that trans-decalins were the major products in the dissolving metal reductions of perhydronaphthalene derivatives. Although our intermediate would possess an additional double bond in a position which might be expected to decrease the preference for a trans-fused product, the presence of similar systems in the literature led us to believe that our proposed reduction would proceed with good stereoselectivity for trans-fused.

94. (a) Stork, G.; Darling, S.D. J. Am. Chem. Soc. 1964, 86, 1761;


As a test of our strategy we decided to investigate the chemistry of acetylene 90, an intermediate which we had already prepared in our earlier studies. This compound cyclized smoothly at 165°C to afford a 7:3 mixture of two epimeric silyl ethers 172 and 173. Although epimers 172 and 173 were inseparable by silica gel chroma-


98. This ratio was determined by GLC.
tography, we anticipated that the alcohols corresponding to 172 and 173 might be separable. Treatment of the mixture of t-butyldimethyl-silyl ethers with dilute HCl in methanol, however, resulted in exclusive deprotection of the equatorial silyl ether 172 in the presence of its axial isomer 173. Separation of these intermediates was now trivial and afforded alcohol 174 and silyl ether 173 in 63% and 19% yields, respectively. The assignment of stereochemistry to C(1) of these products was based on their 'H NMR spectra; C(1)-H of 174 appeared as a doublet of triplets, J = 4 and 10 Hz. The corresponding signal in 173 appears as a broad doublet (J = 3Hz) almost 0.8 ppm downfield from C(1)-H in 174. The downfield shift and multiplicity of this signal are evidence that this proton occupies an equatorial position on the cyclohexyl ring.

The modest level of asymmetric induction realized in the cyclization of 90 is on the order of that obtained in the intramolecular Diels-Alder reaction of trienes possessing diene-allylic alkoxyl functions (such as 74 and 79-80). The rate of cyclization of 90, however, is substantially slower than the rates of diene acetylene cyclizations in the perhydroindene series (175-176 and 177-178). Examination of molecular models of these systems reveal that 175 and 177

\[ \text{175} \xrightarrow{115^\circ, 5h} \text{176} \]
can cyclize via relatively strain-free transition state 179.

Diene acetylene 90, on the other hand, must cyclize through transition state 180 in which the atoms bridging the diene and dienophile adopt a boat-like conformation.

Attempts to effect the dissolving metal reduction of 173 with excess lithium in ammonia were plagued by overreduction to the saturated alcohol derivative 181 (the complexity of the 250 MHz $^1H$ NMR spectrum of the crude product prevented unambiguous assignment of


stereochemistry to the reaction products). This problem was not unique to this substrate: overreduction is a general problem in the dissolving metal reductions of α,β-unsaturated esters\textsuperscript{95,100}.

In contrast, overreduction is generally not a problem in the dissolving metal reductions of α,β-unsaturated acids\textsuperscript{100b}. Under most circumstances the unsaturated acid would be prepared by hydrolysis of the corresponding methyl ester; however, the sensitive nature of cyclohexadiene esters such as \textbf{173} and \textbf{174} precluded this approach. Attempts to prepare acid \textbf{182} from methyl ester \textbf{173} by either alkaline hydrolysis or SN\textsubscript{2}-type cleavage conditions (LiI, DMF, 150°C)\textsuperscript{101} were plagued by substrate aromatization with concomitant loss of the C(1)-hydroxyl group.

![](image)

Thus it was clear at an early stage in the development of this synthetic scheme that an unsaturated acid would be required as the substrate for the dissolving metal reduction. The above results demonstrated, however, that the acid needed to be protected with a group which would be easily removed under mild, non-hydrolytic conditions. These considerations led to the choice of a trichloro-

ethyl ester\textsuperscript{102} as a protecting group in the sequences outlined below.

It seemed to us that the success of this approach to \textsuperscript{29} would not be critically dependent on the hydroxyl protecting group selected for \textsuperscript{166} nor on the choice of functionality present within the C(11) side chain. This assumption proved, however, to be incorrect, a conclusion which necessitated that two approaches to \textsuperscript{168} be pursued. The remainder of this chapter will describe the results of these studies which culminated in an efficient, stereoselective synthesis of the bottom half of chlorothricolide.

**Total Synthesis of the Bottom Half of Chlorothricolide**

We envisioned that the requisite diene acetylene \textsuperscript{166} could be assembled using the same general strategy which was used in the synthesis of model acetylene \textsuperscript{90}. Thus, our immediate synthetic objective was dienal \textsuperscript{183} which we planned to prepare from aldehyde \textsuperscript{184} by using a series of reactions developed by Whiting\textsuperscript{103}. At this point in the synthetic scheme we were not overly concerned about the nature of \( R^1 \) in \textsuperscript{184}; we anticipated little problem in manipulating the functionality present within the C(11) side chain. We therefore se-


lected aldehyde 185 for use in this sequence since the corresponding ethyl ester 153 was available from our previous synthetic efforts. Reduction of 153 with lithium aluminum hydride followed by pyridinium dichromate 104 oxidation of the intermediate alcohol afforded aldehyde 185 in 51% yield. Condensation of 185 with the lithium anion of 1-methoxybut-1-en-3-yne followed by sequential addition of EtOH, LiAlH₄, and 1N HCl afforded diene aldehyde 186 in 85% yield 103. The (E,E)-stereochemistry of the two newly-formed double bonds was

suggested by similarities of the 'H NMR spectrum of 186 to that of sorbaldehyde and related diene aldehydes\(^{105}\). The isomeric purity of dienal 186 was estimated to be at least 85\% by integration of the vinylic protons in the 250 MHz 'H NMR spectrum. No effort, however, was made at this point to remove the undesired double bond isomers.

Condensation of dienal 186 with the Grignard reagent prepared from 1-(5-bromo-1-pentynyl)trimethylsilane\(^{52}\) provided alcohol 187 which without purification was treated directly with KF in aqueous DMF\(^{55}\) to afford desilylated acetylene 188 in 76\% overall yield from 186.

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The hydroxyl group of 188 was converted to its methoxyethoxymethyl ether derivative (MEM) 189 by treatment with MEM-chloride and diisopropyl ethyl amine in methylene chloride. This intermediate was not purified but converted directly to ester 190 by sequential treatment with n-butyllithium and then excess trichloroethylchloroformate. Chromatography on silica gel was effective at this stage in removing the undesired butadiene isomers. Thus, the overall yield of isomerically pure 190 from 188 was 83%.

Cyclization of acetylene 190 in dilute toluene solution proceeded smoothly at 165°C to afford a 7:3 mixture of cycloadducts.

191 and 192 in 95-98% yield. Although the mixture of cycloadducts could be separated by analytical TLC (two adjacent but well-resolved spots), preparative chromatography effected only partial separation of the two products. This mixture, therefore, was used in subsequent transformations without being separated. The ratio of epimers 191 and 192 was determined by integration of the olefinic protons in the 250 MHz 'H NMR spectrum of the crude reaction mixture.

Assignment of stereochemistry to C(1) of 191 was again based on 'H NMR spectroscopy. The resonance observed for C(1)-H of 191 appeared at δ3.28 as a doublet of triplets, J = 5 and 10 Hz. The corresponding signal in minor adduct 192 was, however, not assignable.

The stage was now set for the key dissolving metal reduction, but first we needed to liberate carboxylic acid 193 by the reductive cleavage of trichloroethyl esters 191 and 192. Treatment of an unseparated mixture of cycloadducts 191 and 192 with zinc dust in THF containing 1M aqueous KH₂PO₄ afforded acid 193 as an inseparable mixture of C(1)-epimers in 83% yield. Several

conditions for reductive alkylation of 193 were examined (Li, NH₃, then CH₃I (-/°+23°C); Li, NH₃, THF, then addition of HMPT and FeCl₃ (to quench excess Li), removal of NH₃ by distillation and addition of CH₃I (-78°→23°C); Li, HMPT then CH₃I), but each attempt resulted in simple reduction with no alkylation. In all cases a mixture of products containing esters 194 and 195 was obtained.

![Chemical structure](image)

193

1) Li, NH₃
2) CH₃I
3) CH₂H₂
81%

194 R = β-H
195 R = α-H

The stereochemistry depicted for the major product 194 was assigned by comparison of the 'H NMR spectroscopic data with that of the stereochemically related ester 99b, the structure of which had been assigned previously (see p.61) by a combination of chemical and spectroscopic methods. In particular, the diagnostic signal of C(5)-H for 194 appears as a doublet, J = 3Hz. The

![Chemical structure](image)

99b
95b

stereochemistry of one of the minor products, 195, was assigned by comparison with the NMR data for ester 95b. The 'H NMR resonance for C(5)-H of 195 appears as a doublet of doublets, J = 5 and 10Hz. The ratio of trans-fused products 194 and 195 was determined to be approximately 5:1 by integration of the 'H NMR resonances for C(5)-H of the two isomers.

Since it appeared that the one step reductive alkylation was not going to be straightforward, we decided to execute this conversion in two separate steps. The crude mixture of acids obtained from the Li, NH₃ reduction of 193 was esterified with CH₂N₂ to afford a mixture of esters 194 and 195, estimated to be approximately 5:1 by 250 MHz 'H NMR, in 81% yield. Attempts to alkylate this mixture, however, with CH₃I under a variety of conditions (LDA, THF, -78°-0°C; LDA, THF, HMPT, -78°-23°C; KN(TMS)₂, THF, -78°C; KN(TMS)₂, THF, HMPT, -78°C-0°C; KO-t-Bu, t-BuOH, THF, reflux; KH, THF, reflux) afforded no detectable amounts of alkylated products (<5%). It was apparent from these results that 194 and 195 were recalcitrant with respect to alkylation, but the reasons for this unexpected behavior were not yet clear. Because we were working with a mixture of diastereomers, we could not rule out the possibility that impurities in these mixtures were responsible for our inability to effect this transformation. For these reasons we decided to rework our synthetic scheme to incorporate a t-butyldimethylsilyl group as the protecting group for the C(7)-hydroxyl

group of 166. Our expectation was, of course, that we would be able to separate the epimeric Diels-Alder cycloadducts by selective hydrolysis of the silyl ethers (vide supra).

Consideration of possible strategies for eventual connection of the top and bottom halves of chlorothricolide led us to select butyraldehyde 196\textsuperscript{110} rather than glutaraldehyde 185 for this synthetic sequence. The requisite diene acetylene was prepared by a series of reactions analogous to those used in the synthesis of acetylene 190.

Condensation of 4-benzylxoybutyraldehyde 196\textsuperscript{110} with the lithium anion of 1-methoxybut-1-en-3-yne followed by sequential addition of EtOH, LiAlH\textsubscript{4}, and aqueous 1N HCl afforded\textsuperscript{103} 97% of crude dienal 197. The isomeric purity of crude dienal 197 was estimated to be at least 85% by integration of the vinylic protons in the 250 MHz \textsuperscript{1}H NMR spectrum. Again, no effort was made to remove the undesired isomers at this stage. The crude product was not purified but instead was treated directly with the Grignard reagent prepared from bromide 86\textsuperscript{52} to afford alcohol 198. Desilylation of this intermediate with KF in aqueous DMF\textsuperscript{55} provided acetylene 199 in 65% overall yield (from 196) after purification by flash chromatography\textsuperscript{43}. The hydroxyl

Key: (a) Li-C≡C-CH=CHOCH₃ (1.2 equiv), THF, 0-23°C, 2h; then EtOH (0.7 equiv), 0°C; (b) LiAlH₄ (3.4 equiv), THF, 0-23°C, 2-5h; (c) 1N HCl, CH₃OH, 23°C, 1h; (d) BrMg(CH₂)₃-C≡C-SiMe₃ (1.5 equiv), THF, 0°C; (e) KF, DMF, H₂O, 23°C, 39h; 65% yield from 196; (f) t-BuMe₂SiCl, DMF, imidazole, 23°C, 53h; (g) n-BuLi (1.3 equiv), THF, -78°C; then excess ClCO₂CH₂CCl₃, -78°C → 0°C.

group of 199 was protected as a t-butyldimethylsilyl ether⁴⁶ to give 200 which, without purification, was converted to acetylenic ester 201 by sequential treatment with n-butyllithium and then excess trichloroethylchloroformate. This series of reactions afforded isomerically pure 201 in 79% overall yield from 199.

The cyclization of 201 proceeded under conditions comparable to those used for 190 (0.2M in toluene, 160°C, 60h) and afforded a 63:37 mixture of cycloadducts 202 and 203 in nearly quantitative
yield. As expected, treatment of this mixture with 1NHCl-CH$_3$OH-THF (1:7:5, v/v) resulted in exclusive deprotection of equatorial silyl ether 202 in the presence of its axial isomer 203. The resulting mixture was easily separated by chromatographic methods which afforded 203 and 204 in 36% and 61% yields, respectively$^{111}$. Alcohol 204 was then converted into its methoxymethyl ether derivative 205 in 70% yield$^{112}$.

111. On one occasion the hydrolysis reaction mixture was terminated short of completion, and a 6:1 mixture of 203:202 was recovered. This mixture was resubjected to the prescribed reaction conditions and, again, only the TBDMS ether of 202 was hydrolyzed. The selectivity of this reaction may prove to be generally useful in other contexts.

     (b) LaForge, F.B. J. Am. Chem. Soc. 1933, 55, 3040.
Cycloadduct 205 was deprotected by treatment with Zn dust in refluxing methanol to afford the highly viscous acid 206 in greater than 95% yield. Addition of a THF solution of acid 206 to a solution of excess lithium in anhydrous ammonia followed by addition of solid NH₄Cl at -78°C afforded, almost exclusively, a mixture of trans-fused hydroxy-acids, 207 and 208. The crude reaction product was treated with excess ethereal diazomethane and then with t-butyldimethylsilyl chloride and imidazole in DMF in order to protect the side chain hydroxyl group. Careful chromatography of this mixture afforded trans-perhydroanaphthalenes 209 and 210 in 71% and 15% yields, respectively, along with approximately 5% of products tentatively as-

\[ \text{PhCH}_2\text{O} \quad \text{CO}_2\text{CH}_2\text{CCl}_3 \quad \text{PhCH}_2\text{O} \quad \text{CO}_2\text{H} \]

\[ \xrightarrow{\text{Zn, MeOH, } \Delta \text{ >95%}} \quad \xrightarrow{1) \text{Li, NH}_3, -78^\circ\text{C}} \quad \xrightarrow{2) \text{NH}_4\text{Cl, -78^\circC}} \]

\[ \text{OCH}_2\text{OCH}_3 \]

\[ \text{HO} \quad \text{CO}_2\text{H} \quad \text{TBDMSO} \quad \text{TBDMSO} \quad \text{TBDMSO} \]

\[ \xrightarrow{1) \text{CH}_2\text{N}_2, 0^\circ\text{C}} \quad \xrightarrow{2) \text{TBMSCl, imidazole}} \quad \text{CO}_2\text{CH}_3 \quad + \quad \text{CO}_2\text{CH}_3 \quad \text{CO}_2\text{CH}_3 \]

\[ \text{OCH}_2\text{OCH}_3 \quad \text{OCH}_2\text{OCH}_3 \quad \text{OCH}_2\text{OCH}_3 \]

\[ 207 \ R = \alpha-\text{H} \quad 208 \ R = \beta-\text{H} \quad 209 \ 71\% \text{ from } 205 \quad 210 \ 15\% \text{ from } 205 \quad \text{plus 5\% cis-fused products} \]
signed cis-ring fusions. The assignment of stereochemistry to 209
and 210 was again based upon 'H NMR spectroscopy. The diagnostic re-
sonance for C(5)-H of the major product 209 appeared as a doublet of
doublets, J = 7 and 10 Hz. The corresponding resonance in the minor
product 210 appeared at δ2.51 as a doublet, J = 3 Hz.

It is clear from these results that the stereoselectivity of the
enolate protonation step in the workup of the dissolving metal reduction
of 206 is completely reversed from that obtained in the reduction of
193. Whereas axial ester 194 is the major product of the dissolving
metal reduction of 193, equatorial ester 209 is the major product
from the reduction of 206. These results are probably related to
the presence of the benzyl ether functionality of 206 which is de-
protected under the reaction conditions. It is possible that the
resultant alkoxy group alters the state of aggregation of 211 re-
lative to that of the carboxylate dianion intermediate generated from
193, and thereby influences the stereoselectivity of the protonation
step. Alternatively, the alkoxy group may coordinate one of the
lithium ions associated with the carboxylate dianion, as depicted

![Diagram](image)

in 212. Protonation of the latter structure might be expected to
proceed preferentially from the less hindered α-face. In any event, this change in selectivity, which initially we regarded as a curious result, proved ultimately to be crucial to the success of the synthetic scheme (vide infra).

With pure 209 and 210 in hand, we next examined the alkylation reactions of these epimeric esters. Treatment of silyl ester 209 with lithium diisopropylamide in THF-HMPT at -78°C with warming to -20°C afforded a mixture of two methylated products, 213 and 214, in 56% and 13% yield, respectively. We anticipated that we would be able to assign stereochemistry to the quaternary center by the chemical shift of the C(5)-methyl group. Unfortunately, this signal appeared at δ1.13 and δ1.12 for 213 and 214, respectively. The stereochemistry assigned to major product 213 was suggested by the similarities of the 'H NMR spectra of 213 and 27, a degradation product of chlorothricin. This assignment was confirmed by the eventual synthesis of 27 from 213 (Scheme XVI). Attempts to al-
kylate 210, on the other hand, were unsuccessful. When 210 was subjected to conditions similar to those described above (enolate solution warmed to -5°C instead of -20°C), only traces (<5%) of alkylated products were obtained along with starting material (60%) and a considerable amount of decomposition products.

The behavior of 210 under these conditions parallels the behavior previously noted for the mixtures of 194 and 195. In retrospect, we suspect that the failure to alkylate 210 (and 194) is a consequence of the stereochemistry of C(5)-H in these intermediates. In 209, C(5)-H occupies a relatively unhindered axial orientation whereas C(5)-H in 210 (and 194), although equatorial, is hindered by the pseudo-axial alkyl chain at C(6). It is likely that the latter group inhibits the approach of bulky dialkylamide bases to C(5)-H, thereby retarding the rate of deprotonation. Although deprotonation appeared to occur to some extent at -5°C, the enolate decomposed under these conditions and no alkylation products were obtained.
Our inability to alkylate 210 prompted us to investigate the dissolving metal reduction of 206 in detail in order to attempt to suppress the formation of 210. Although the reaction temperature did not affect the ratio of 209:210 the amount of cis-fused products was minimized by conducting the reaction at -78°C (approximately 10% of cis-fused products were obtained at -33°C, versus approximately 5% at -78°C). The use of sodium instead of lithium or addition of proton sources such as t-BuOH during the reduction were clearly detrimental since the ratio of 209:210 became nearly 1:1 under these conditions, and the amount of cis-fused products increased slightly. A variety of protonation conditions were examined with no dramatic changes in the ratio of products. It did, however, seem beneficial to conduct the protonation at -78°C by the addition of solid NH₄Cl at this temperature. All things considered, the conditions cited originally proved to give the most favorable ratio of 209:210.

An interesting result which derives from this study is that trichloroethyl ester 205 can be used directly in the dissolving metal reduction without prior deprotection. Although the yield of 209 is only 50% compared to 67% when the deprotection and reduction steps are conducted separately, it is noteworthy that two deprotection steps and a double bond reduction can be performed in a single synthetic operation.

We next turned to the problem posed by the modest stereoselectivity (4:1) realized in the alkylation of 209. That alkylation of the enolate of 209 had occurred preferentially by axial approach of methyl iodide was attributed to a steric interaction between the pseudo-axial C(6) side chain of enolate 209a and methyl iodide in the equatorial alkylation transition state. In the absence of such inter-

actions one would expect the equatorial alkylation mode to predomi-
nate. For example, House and Bare observed that alkylation of con-
formationally locked enolate 215 occurred preferentially via the equatorial mode of attack to afford the two epimeric products in a 6:1 ratio\textsuperscript{114}. 

\[
\begin{array}{c}
\text{CH}_3 \\
\text{o-}
\end{array}
\xrightarrow{\text{equatorial attack}}
\begin{array}{c}
\text{COCH}_3 \\
\text{CH}_3
\end{array}
\text{plus epimer}
\approx 6:1

It was anticipated that the selectivity of the alkylation step could be increased by using lactone 216 as a substrate. Assuming that the lactone enolate 217 retains the cyclohexene half-chair conformation adopted by 216, one expects that the transition state for the equatorial alkylation should be substantially destabilized relative to the axial mode. As bonding begins to develop, the acyl carbon must begin to move into an axial position. Substantial strain must develop for the product, if one were to form from this transition state, would contain a seven-membered ring diallylaxially fused to a six-membered ring.

\textsuperscript{114} House, H.O.; Bare, T.M. \textit{J. Org. Chem.} 1968, \textbf{33}, 943.
The feasibility of this plan was quickly verified. Mild alkaline hydrolysis of 209 proceeded smoothly to afford the corresponding hydroxy acid 207 and ester 218 in 68% and 25% yield, respectively\textsuperscript{115}.

Treatment of 207 with 2-chloro-N-methylpyridinium iodide (Mukaiyama's salt)\textsuperscript{116} afforded lactone 216 in 81% yield. Treatment of 216 with

\textsuperscript{115} Initial attempts to lactonize hydroxy ester 218 were unsuccessful. Treatment of ester 218 with a catalytic amount of p-TsOH in refluxing benzene resulted in slow decomposition of the starting material. On the other hand, treatment of a solution of ester 218 in THF with KO-t-Bu at 23°C for 14h (no change by TLC), followed by 4h at reflux resulted in complete conversion of the starting material to a mixture of products, none of which appeared to be the desired lactone 216.

excess LDA in THF (-78°C→25°C) followed by excess methyl iodide afforded the target lactone 219 as the sole product of alkylation in 75% yield. The stereochemistry of 219 was confirmed as described in a subsequent paragraph. The only problem which now remained was the development of a direct preparation of 216 from the mixture of 207 and 208. Note that the route from 207-208 to 216 presented thus far is rather circuitous. The mixture of epimeric acids was esterified and then converted to their silyl ethers. This transformation allowed us to separate this mixture of epimeric esters by chromatography. Removal of the two protecting groups afforded pure acid 207 which was then lactonized to 216. Clearly, a direct preparation of 216 from the mixture of 207 and 208 was needed.
The unseparated 5:1 mixture of hydroxy-acids 207 and 208, obtained from the dissolving metal reduction of 206, was treated with 2-chloro-N-methylpyridinium iodide in CH₂Cl₂ to give a 6:1 mixture of lactones 216 and 220 in 85% yield. Whereas hydroxy acid 207 can lactonize via a relatively strain-free transition state, 208 cannot lactonize from its preferred conformation which is one in which the C(5)-acyl and C(6)-hydroxypropyl groups occupy axial and pseudoaxial orientations, respectively, on a half-chair cyclohexenyl ring (vide supra).

Thus, 208 must adopt a half-boat (or twist boat) conformation prior to lactonization. The barrier to conformational interconversion of cyclohexenes is quite low, however, and so 208 lactonized readily.

A sample of 220 was purified by chromatography of mixtures of 216 and 220. The 'H NMR data for C(5)-H of 220 (t, J = 7.3Hz) is consistent with a twist-boat conformation for the cyclohexenyl ring. The relatively unhindered nature of C(5)-H in this ring system suggest-

ed that 220 might not be subject to the problems which plagued the attempts to alkylate 194 and 210 (vide supra).

Indeed, treatment of 220 with LDA and then CH₃I under the conditions successfully applied to 216 afforded lactone 219 in 31% yield; 28% of 220 was also recovered. Although the alkylation of 220 proceeded in somewhat lower yield than the alkylation of 216, separation of these isomers prior to alkylation became unnecessary.

Scheme XV

1) Zn, MeOH
2) Li, NH₃, -78°
3) NH₄Cl

205 → 207 R = α-H
         208 R = β-H

1) LDA, THF, HMPT
   -78° + -25°
2) CH₃I, -78° + 23°

216 R = α-H
220 R = β-H
219
The successful completion of the synthesis of 219, therefore, involved lactonization of a mixture of 207 and 208 to a mixture of 216 and 220 (85% yield) which, without separation, was transformed into 219 in 79% yield (Scheme XV). The overall yield of 219 from 4-benzyloxybutyraldehyde 196 was 15% for the fourteen-step sequence.

The stereochemistry of 219 was established unambiguously by correlation with a degradation product of natural chlorothricoline (Scheme XVI). Thus, transesterification of 219 with sodium methoxide in methanol afforded hydroxy ester 221 in 86% yield. This compound was also prepared by desilylation of 213 (n-Bu₄NF, THF, 23°C, 96% yield). Collins' oxidation ¹¹⁸ of 221 afforded the expected aldehyde which was treated with carbomethoxytriphenylphosphorane ⁵⁰ to give unsaturated ester 222 in 73% yield (from 221). Selective reduction of the less hindered double bond of 222 using

**Key:** (a) CrO₃, pyridine; (b) (C₆H₅)₃P = CHCOOCH₃, 23°C (73% from 221); (c) [(C₆H₅)₃P]₃RhCl (0.2 equiv.), H₂, C₆H₆, 23°C, 6h.

Wilkinson's catalyst⁷⁹ afforded synthetic 27²⁹ which was identical in all respects with the exception of optical rotation to a naturally derived sample kindly provided by Professor R.E. Ireland.

**Future Studies** trad.⁸⁰

Although our synthesis of 219 is very efficient (15% overall yield for the fourteen step sequence starting from 4-benzylxybutraldehyde), it is ironic that the intramolecular Diels-Alder reaction of 201 is the least stereoselective transformation in the entire sequence.

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120. The structures represented in this section have been labeled with an asterisk to designate these compounds as chiral intermediates.
It is readily apparent that the minor cycloadduct 203 could be converted into the bottom-half of chlorothricolide (racemic) by inversion of the stereochemistry at C(1). This option was not pursued, however, since it could not be utilized in the planned asymmetric synthesis of lactone 219 by a route which will involve the intramolecular Diels-Alder reaction of a chiral substrate 223 related to 201. If the ultimate transfer of chirality in asymmetric synthesis of 219 originates in an asymmetric synthesis of 223 it is clear that 225 is a useless by-product: epimerization of C(1) of chiral 225 or of intermediates derivable therefrom would lead to the enantiomers of the intermediate derived from chiral 224.

![Chemical structure](image)

Thus, additional work in this area must address the modest level of asymmetric induction in the Diels-Alder reaction. It seems possible that this problem can be solved by introduction of a steric-directing group at C(9) of diene acetylene 226.

![Chemical structure](image)
The transition states involved in the cyclization of 226 are summarized in Scheme XVII. Transition states 228 and 229 can give rise to 227. It is probable that 229 is relatively unimportant, however, as a consequence of a flagpole interaction between C(4)-H and the -OTBDMS group and an interaction between C(6)-H and C(9)-H which should substantially destabilize 229 relative to 228. For 230 on the other hand, transition state 231 should be destabilized relative to 232 owing to a flagpole interaction involving C(4)-H and -OTBDMS, and an eclipsing interaction between C(9)-H and -OTBDMS. The selectivity observed in the cyclization of 190 and 201, then is probably the consequence of the greater stability of transition
state 228 relative to 232 which is destabilized by a steric interaction involving C(6)-H and C(9)-H. Thus, in the proposed cyclization of 226, where R is substantially larger than a hydrogen atom, one expects the energy difference between 232 (and/or 231) versus 228 to be increased dramatically. The choices for R are somewhat limited since this steric directing group must be removed after the Diels-Alder reaction. These considerations suggest that R = SPh, SiMe₃, or halogen might be the most useful substituents in this regard.
EXPERIMENTAL SECTION
Cyclization of 90:

Methyl 1α-Hydroxy-6β-methyl-1β,2,3,4,6α,8α-hexahydronaphthalene-5-carboxylate (174) and Methyl-1β-(t-Butyldimethylsilyloxy)-6β-methyl-1α,2,3,4,6α,8α-hexahydronaphthalene-5-carboxylate (173)

A solution of 1.71 g of 90 (5.1 mmol) in 30 mL of dry toluene was added to a resealable Carius tube and was purged with dry Ar for 30 min. The tube was sealed and placed in a 165°C oil bath for 24 h. The cooled tube was opened and then all volatile components were removed in vacuo. Analysis of the crude product by GLC (10 ft 4% SE-30 column, 190°C, flow = 25 mL/min) showed the presence of two cycloadducts in a ratio of 2.3/1.0.

To a stirred solution of 1.48 g of the crude product in 35 mL of MeOH was added 5 mL of 1N HCl. After being stirred at 23°C for 2h, the reaction mixture was poured into a separatory funnel containing 25 mL each of saturated aqueous NaHCO₃ and CH₂Cl₂. The aqueous layer was combined with 10 mL of saturated aqueous NaCl and then extracted with two 25 mL portions of CH₂Cl₂. The combined organic extracts were dried over NaHCO₃, filtered, and concentrated in vacuo to give 1.30 g of crude product. This product was purified by flash chromatography using 2:1 hexane-ether as eluant. Concentration of fractions 5-6 (25 ml) afforded 263 mg of silyl ether 173 (19%). Concentration of fractions 22-45 gave 578 mg of alcohol 174 (63%).
Data for 174: mp 75-75.5°C; NMR (CDCl$_3$) δ 5.90 (dd, J = 10, 2.5Hz, 1H), 5.74 (ddd, J = 10, 4, 1Hz, 1H), 3.76 (s, 3H), 3.32 (dt, J = 5, 10Hz, H$_1$), 3.19 (m, 1H), 2.95 (br d, J = 12Hz, 1H), 2.55 (m, 1H), 1.06 (d, J = 7Hz, 3H); IR (CCl$_4$) cm$^{-1}$ 3615, 3490, 3030, 1718, 1635; mass spectrum m/e 222 (parent ion). Anal. Calcd. for C$_{13}$H$_{18}$O$_3$: C, 70.24; H, 8.16. Found: C, 70.44; H, 8.12.

Data for 173: NMR (60 MHz, CCl$_4$) δ 5.7 (dd, J = 10, 4Hz, 1H), 5.3 (br d, J = 10Hz, 1H), 4.1 (br s, H$_1$), 3.7 (s, 3H), 1.0 (d, J = 7Hz, 3H), 0.8 (s, 9H), 0.1 (s, 6H).

2-(4-hydroxy-1-buty1)-1,3-dioxolane(233)

A slurry of 1.40 g of LiAlH$_4$ (36.8 mmol) in 100 mL of dry ether was cooled to 0°C. To this stirred slurry was added dropwise over 30 min a solution of 6.61 g of ester 153 (3.51 mmol) in 65 mL of ether. When the addition of 153 was complete, the reaction mixture was allowed to warm to 23°C. After being stirred at 23°C for 3 h, the reaction mixture was quenched by addition of 10 mL of EtOAc followed by the sequential addition of 1.4 mL of H$_2$O, 1.4 mL of 15% NaOH, and 4.2 mL of H$_2$O. This caused the formation of a fine white precipitate which was removed by vacuum filtration. The filter cake was washed with three 25 mL portions of ether. The filtrate was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give 5.43 g of alcohol 233. This compound was purified by short-path distillation to afford 4.53 g of pure 233.
Data for 233: bp 96°C (0.8 mm) NMR (60 MHz, CCl₄) δ4.7 (m, 1H), 3.8 (m, 4H), 3.55 (m, 1H), 1.6 (br s, 6H); mass spectrum m/e 145 (M-1).

2-(4-oxo-1-butyl-1,3-dioxolane (185)\textsuperscript{121}

To a stirred solution of 4.08 g of 233 (27.9 mmol) and 0.2 mL of pyridine (2.5 mmol) in 85 mL of CH₂Cl₂ was added 15.4 g of pyridinium dichromate\textsuperscript{104} (41.3 mmol). After being stirred at 23°C for 2 h, the reaction mixture was diluted with 80 mL of ether. The dark solution was passed through a short pad of Florisil. The black residue was washed with six 25 mL portions of ether which were also passed through the pad of Florisil. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 4.7 g of crude product. Purification was effected by short-path distillation to afford 2.12 g of pure 185 (51%). Examination of the pot residue by 'H NMR spectroscopy suggested that alcohol 233 was the major component of this mixture.

Data for 185: bp 83°C (1.4 mm) NMR (60 MHz, CCl₄) δ9.5 (t, J= 2Hz, 1H), 4.65 (m, 1H), 3.7 (m, 4H), 2.3 (br t, J= 6Hz, 2H), 1.5 (m, 4H).

\textsuperscript{121} This compound has been prepared previously by monoacetalation of glutaraldehyde: Kikumoto, Fyaji, Nakamura, Akio (Mitsubishi Chemical Industries Co., Ltd.) Japan Kokai 73 39, 416.
(E,E)-2-(8-Oxo-4,6-octadienyl)-1,3-dioxolane 186

A solution of 1.19 mL of 1-methoxy-1-buten-3-yne (13.1 mmol) in 35 mL of dry THF was cooled to -78°C. To this solution was added dropwise over 20 min 6.3 mL of 2.4 M n-butyllithium in hexane. This mixture was stirred at -78°C for 40 min before being warmed to 0°C (ice bath). At this point the reaction mixture darkened to form a deep brown solution. To this mixture was added a solution of 1.69g of 2-(4-oxobutryl)-1,3-dioxolane 185 (11.7 mmol) in 20 mL of dry THF. The ice bath was removed and the reaction mixture was allowed to warm to 23°C over 2h. The solution was cooled to 0°C and was then treated sequentially with 0.51 mL of absolute EtOH (8.16 mmol) and a slurry of 0.33g of LiAlH₄ (8.63 mmol) in 25 mL of THF. The reaction mixture was then allowed to warm to 23°C. After being stirred at 23°C for 2h, the reaction mixture was cooled in an ice bath and 0.33 mL of H₂O, 0.33 mL of 15% aqueous NaOH, and 1.0 mL of H₂O were added sequentially. This caused the formation of a tan precipitate which was removed by vacuum filtration. The filter cake was washed with six 20 mL portions of THF. To the filtrate was added 50 mL of 0.5 N HCl and the resultant yellow solution was stirred for 30 min. This reaction mixture was then poured into a separatory funnel containing 200 mL of saturated aqueous NaHCO₃ and 150 mL of ether. The aqueous phase was extracted with three mL portions of ether.
The combined organic extracts were dried over Na₂SO₄ and NaHCO₃, filtered, and concentrated in vacuo to give 2.51 g of crude diene aldehyde 186. Purification was effected by bulb-to-bulb distillation (135°C, 0.35 mm) to afford 1.95 g of pure 186 (85%).

Data for 186: NMR (CDCl₃)δ 9.47 (d, J= 8.1 Hz, CHO), 7.03 (dd, J= 10.2, 15.4Hz, H₂) 6.25 (m, 2H, H₃, H₄), 5.98 (dd, J= 8.1, 15.4 Hz, H₂), 4.81 (t, J= 4.4 Hz, H₉), 3.85 (m, 4H, -OCH₂CH₂O-), 2.22 (q, J= 7Hz, allylic CH₂), 1.59 (m, 4H); IR (CCl₄)cm⁻¹ 3022, 2735, 1690, 1680, 1638, 1595; mass spectrum m/e 196 (parent ion).

(E,E)-2-(8-Hydroxy-4,6-tridecadien-12-ynyl)-1,3-dioxolane(188)

To a vigorously stirred mixture of 0.90 g of Mg turnings (39.2 mg-atom) in 40 mL of dry THF was added a small crystal of I₂. The mixture was heated to reflux and when the I₂ color dissipated a solution of 3.15 g of 1-(5-bromo-1-pentynyl)trimethylsilane 52 (14.4 mmol) in 25 mL of dry THF was added drop-wise. On this scale, the addition required 1h. The mixture was refluxed for an additional 15 min after the addition was complete. The Grignard reagent was then cooled to 0°C and a solution of 1.88 g of diene aldehyde 186 (9.59 mmol) in 5 mL of dry THF was added. The resulting solution was stirred for 30 min (0°C-23°C) before being quenched with 1 mL of MeOH. The reaction mixture was poured through a glass wool plug into a
separatory funnel containing 100 mL each of ether and saturated aqueous NH₄Cl. The ether layer was washed once with 100 mL of saturated NH₄Cl. The combined aqueous extracts were then washed with two 100 mL portions of ether. The combined ether extracts were concentrated in vacuo, dissolved in CH₂Cl₂, filtered through a cotton plug, and concentrated in vacuo to give 4.39 g of crude product. This compound was routinely taken on to the next step without purification. A sample from a small scale run was chromatographed to give alcohol 187 in 74% yield.

Data for 187: NMR (CDCl₃) δ6.04 (m, 2H), 5.62 (dt, J = 14.5, 7.3 Hz, H₁₀), 5.51 (dd, J = 6.8, 14.8 Hz, H₇), 4.78 (t, J = 4.6 Hz, H₁₄), 4.07 (br q, J = 6.5 Hz, H₆), 3.84 (m, -OCH₂CH₂O-), 2.19 (t, J = 6.5 Hz, 2H), 2.08 (q, J = 6.7 Hz, 2H), 1.91 (br s, OH), 1.53 (m, 8H), 0.09 (s, 9H); IR (CCl₄) cm⁻¹ 3620, 3480, 3021, 2180, 1658; mass spectrum m/e 335 (M-1)

To a chilled solution (cold water bath) of 12.2 g of KF·2H₂O (129 mmol) in 15 mL of H₂O and 50 mL of DMF was added a solution of 4.00 g of crude Grignard product in 27 mL of DMF. The resulting two-phase mixture was stirred vigorously at 23°C. After being stirred for 48 h, the reaction mixture was poured into a separatory funnel containing 450 mL of distilled H₂O and 150 mL of 3:1 hexane-ether. The aqueous phase was washed with three 150 mL portions of 3:1 hexane-ether. The combined
ether layers were washed with 100 mL of H₂O, dried over Na₂SO₄ and NaHCO₃, and concentrated in vacuo to give 2.54 g of alcohol 188. The crude product was purified by flash chromatography (40 mm column) using 1:1 hexane-ether as eluant. After a 125 mL fore-
fraction, 25 mL aliquots were collected. Fractions 5-14 were con-
centrated in vacuo to afford 1.75 g of pure diene alcohol 188
(76% yield from 186).

Data for 188: NMR (CDCl₃)δ 6.14 (dd, J= 10.2, 14.8 Hz, 1H),
6.00 (dd, J= 10.2, 14.8 Hz, 1H), 5.66 (dt, J= 14.8, 6.7 Hz, H₁C),
5.54 (dd, J= 7.2, 14.8 Hz, H₇), 4.82 (t, J= 4.6 Hz, H₁₄), 4.11
(br q, J= 6.4 Hz, H₆), 3.88 (m, -OCH₂CH₂O-), 2.19 (m, 2H), 2.11
(q, J= 6.7Hz, allylic CH₂), 1.92 (t, J= 1.7Hz, H₁); IR (CCl₄)cm⁻¹
3610, 3475, 3315, 3017, 2120, 1653; mass spectrum m/e 263 (M-1).

2,2,2-Trichloroethyl (E,E)-15-Oxo-7-(1-oxymethoxyethoxymethyl)-
8,10-pentadecadien-2-ynoate Ethylene Glycol Acetal (190)

To a solution of 1.02 g of 188 (3.87 mmol) in 10 mL of dry CH₂Cl₂
was added 1.00 mL of diisopropylethylamine (6.24 mmol) and 0.67 mL of
MEM-chloride (5.87 mmol)¹⁰⁶. This solution was stirred at 23°C for
12 h. The reaction mixture was diluted with 100 mL of ether and then
was washed with two 50 mL portions of 0.3N HCl. The combined aqueous
extracts were washed with 50 mL of ether. The combined ether extracts
were dried over Na₂SO₄ and NaHCO₃, filtered, and concentrated in vacuo
to give 1.40 g of crude ether 189. This compound was routinely taken on to the next step without purification.

A solution of 0.57 g of crude MEM-ether 189 (1.58 mmol) in 10 mL of dry THF was cooled to -78°C. To this solution was added 1.03 mL of a 2.4 M n-butyllithium solution in hexane (2.47 mmol) over 5 min. This solution was stirred at -78°C for 30 min, and then 0.56 mL of 2,2,2-trichloroethylchloroformate (4.07 mmol) was added. After an additional 30 min at -78°C, the solution was allowed to warm to 0°C and then was quenched with 10 mL of saturated aqueous NaHCO₃. This two-phase mixture was stirred for 30 min at 23°C and then was poured into a separatory funnel containing 10 mL each of H₂O and CH₂Cl₂. The combined organic layers were filtered through a small plug of cotton and concentrated in vacuo to afford 1.29 g of crude ester 190. Purification of ester 190 was effected by flash chromatography (40 mm column) using 1:1 hexane-ether as eluant. Rechromatography of mixed fractions gave 0.68 g of pure ester 190 (83% from 188) and 0.46 g of recovered ether 189 (8%).

Data for ester 190: NMR (CDCl₃)δ 6.13 (dd, J = 10.2, 14.8 Hz, 1H), 5.98 (dd, J = 10.5, 14.8Hz, 1H), 5.65 (dt, J = 14.8, 7.3 Hz, H₅), 5.31 (dd, J = 8.1, 14.8Hz), 4.82 (t, J = 4.6Hz, H₇), 4.76 (s, 2H), 4.72 (d, Jₐb = 7Hz, 1H), 4.58 (d, Jₐb = 7Hz, 1H), 4.02 (m, 1H), 3.9-3.4 (m, 8H), 3.36 (s, 3H), 2.38 (t, J = 6.9Hz, 2H), 2.09 (q, J = 7.3Hz, allylic CH₂); IR (CCl₄)cm⁻¹ 3013, 2885, 2235, 1730, 1656 mass spectrum m/e 421, 423 (M- OCH₂OCH₂CH₂OCH₃).
Data for ether 189: NMR (CDCl₃)δ 6.06 (m, 2H), 5.64 (dt, J = 15, 7Hz, H₅), 5.33 (dd, J = 8.1, 14.8Hz, H₈), 4.82 (t, J = 4.6Hz, H₁), 4.73 (d, Jₐₐ = 7.2Hz, 1H), 4.59 (d, Jₐₐ = 7.2Hz, 1H), 4.00 (m, H₉), 3.5-4.0 (m, 8H), 3.36 (s, 3H), 2.38 (t, J = 6.2Hz, -CH₂-C=C-), 2.18 (m, 2H), 2.10 (q, J = 7Hz, allylic CH₂), 1.91 (t, J = 1.6Hz, H₁₄); IR (CCl₄)cm⁻¹ 3315, 3020, 2115, 1655; mass spectrum m/e 351 (M-1).

Cyclization of Ester 190:
2,2,2-Trichloroethyl 6β-[1-(4-Oxobutyryl)]-1α-(1-oxymethoxyethoxy-methyl)-1β,2,3,4,6α-hexahydranaphthalene-5-carboxylate Ethylene Glycol Acetal (191) and 2,2,2-Trichloro 6β-[1-(4-Oxobutyryl)]-1β-(1-oxymethoxy-ethoxymethyl)-1α,2,3,4,6α-hexahydranaphthalene-5-carboxylate Ethylene Glycol Acetal (192).

A solution of 1.57g of ester 190 in 22mL of dry toluene was added to a resealable Carius tube and was purged with Ar for 20 min. The tube was then sealed and heated in a 165°C oil bath for 50 h. The cooled tube was opened and then all volatile components were removed in vacuo to give 1.49 g of a mixture of two epimeric MEM-ethers, 191 and 192.

Data obtained on a mixture of 191 and 192: NMR (CDCl₃)δ 5.88 (dd, J = 10.4, 3.7Hz, 1H of 191), 5.81 (m, 1H of 192), 5.71 (dd, J = 10.4, 3.7Hz, 1H of 191), 5.48 (m, 1H of 192), 4.8-4.5 (m, 5H), 3.9-3.5 (m, 8H), 3.34 (s, 3H), 3.25 (m, 2H), 3.07 (d, J = 12Hz, 1H), 2.64 (quint, J = 4Hz, H₆ of 191); IR (CCl₄)cm⁻¹ 3025, 1723, 1630.
6β-[1-(4-Oxobutyryl)]-1α-(1-oxyethoxyethoxymethyl)-1β, 2,3,4,6α-hexahydronaphthalene-5-carboxylic acid Ethylene Glycol Acetal and 6β-[1-(4-Oxobutyryl)]-1β-(1-oxyethoxyethoxymethyl)-1α, 2,3,4,6α-hexahydronaphthalene-5-carboxylic acid Ethylene Glycol Acetal (193).

To a stirred solution of 0.64 g of a 7:3 mixture of 191 and 192 (1.2 mmol) in 19 mL of THF was added 0.05 g of Zn dust (1.45 mmol) and 2.5 mL of 1M aqueous KH₂PO₄. This mixture was stirred at 23°C for 11 h. The reaction mixture was then poured into a separatory funnel containing 45 mL each of H₂O and CH₂Cl₂. The aqueous layer was acidified to pH 3 by the addition of 1N HCl. The acidified solution was washed with three 40 mL portions of CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo to give 0.51 g of crude acid 193. This compound was purified by flash chromatography (40 mm column) using 2:1 ether-hexane containing 0.2% HOAc as eluant. This gave 0.37 g of highly viscous 193 (77%).

Data for 193: NMR (CDCl₃)δ 5.58 (dd, J = 2.6, 10.3 Hz, 1H), 5.81 (dd, J = 2.6, 10.3Hz, 1H), 5.74 (dd, J = 2.6, 10.3Hz, 1H), 5.48 (dd, J = 2.6, 10.3Hz, 1H), 4.73 (m, 2H), 4.0-3.6 (m, 6H), 3.53 (t, J = 4.5Hz, 2H), 3.36 (s, 3H), 3.26 (m, 1H), 2.79 (m, 1H), 2.65 (quint., J = 4.7Hz, 1H); IR (CCl₄)cm⁻¹ 3300-2400, 3030, 1685, 1630; mass spectrum m/e 395 (M-1).
Methyl 6β-[1-(4-oxobutyryl)]-1-(1-oxyethoxyethoxymethyl)-1,2,3,4, 4αβ,5β,6α,8α-octahydropaphthalene-5α-carboxylate Ethylene Glycol Acetal (194) and Methyl 6β-[1-(4-oxobutyryl)]-1-(1-oxyethoxyethoxymethyl)-1,2,3,4,4αβ,5α,6α,8α-octahydropaphthalene-5β-carboxylate Ethylene Glycol Acetal (195).

Several small pieces of sodium metal were added to a 100 mL flame-dried flask fitted with a dry-ice condenser. Approximately 60 mL of NH₃ was condensed into this flask. Then approximately 35 mL of ammonia was distilled from the resulting Na/NH₃ solution into a reaction vessel which contained 100 mg of lithium wire (14.3 mmol). The resulting deep blue solution was maintained at slow reflux (-33°C) and a solution of 0.67 g of acid 193 (1.70 mmol) in 7 mL of dry THF was added dropwise. On this scale the addition required 9 min. After the addition was complete, the reaction mixture was allowed to stir for 30 min at -33°C. To this vigorously stirred solution was added gradually 3 g of NH₄Cl (56.2 mmol) (Note: addition of the NH₄Cl in one amount caused violent boiling of the ammonia solution). The blue color dissipated in approximately 90 sec and the colorless mixture was allowed to warm to room temperature with removal of NH₃ by distillation. Saturated aqueous NH₄Cl (25 mL) was then added, followed by 50 mL of ether. The aqueous layer was acidified to pH 2 by the addition of 1N HCl and was extracted with four additional 30 mL portions of ether. The combined ether extracts were dried over Na₂SO₄,
filtered, and concentrated in vacuo to afford a mixture of saturated acids. This product was treated with excess ethereal diazomethane and then was concentrated in vacuo to afford a mixture consisting mainly of methyl esters 194 and 195. The mixture was purified by flash chromatography (40 mm column) using 1:1 hexane-ether as eluant. This gave 0.53 g of an approximate 5:1 mixture of 194 and 195 (77%).

Data for 194: NMR (CDCl₃)δ 5.89 (d, J= 10Hz, H₈), 5.62 (m, H₇), 4.83 (d, JAB = 7Hz, 1H), 4.69 (d, JAB = 7Hz, 1H), 4.0-3.6 (m, 6H), 3.59 (s, 3H), 3.52 (t, J= 5Hz, 2H), 3.34 (s, 3H), 3.11 (dt, J= 4, 11Hz, H₁), 2.45 (d, J= 3Hz, H₅), 2.25 (m, H₆), 2.08 (m, H₄a), 2.00 (m, H₈a); IR (CCl₄)cm⁻¹ 3021, 1734; mass spectrum m/e 412 (parent ion).

Partial NMR data for 195 (obtained on a 5:1 mixture of 194-195): δ 3.58 (dd, J= 6, 12Hz, H₅).
(E,E)-8-Benzylidene-2,4-octadienal (197)

A solution of 7.25 g of 1-methoxy-1-buten-3-yne (88.3 mmol) in 100 mL of dry THF was cooled to -78°C. To this solution was added dropwise over 20 min 42.0 mL of 2.4 M n-butyllithium in hexane. A white precipitate formed after ~75% of the butyllithium had been added, so an additional 20 mL of THF was added. This mixture was stirred at -78°C for 40 min before being warmed to 0°C (ice bath). At this point, the precipitate dissolved to form a dark brown solution. To this solution was added a mixture of 12.3 g of 4-benzylidene-butyraldehyde\textsuperscript{110} 196 (73.5 mmol) in 25 mL of THF. The ice bath was removed and the reaction mixture was allowed to warm to 23°C over 2 h. The solution was cooled to 0°C and was then treated sequentially with 3.11 mL of absolute ethanol (49.8 mmol) and a slurry of 2.33 g of LiAlH\textsubscript{4} (62.2 mmol) in 35 mL of THF. The reaction mixture was then allowed to warm to 23°C. After being stirred for 2 h at 23°C, the reaction mixture was cooled in an ice bath and 2.3 mL of H\textsubscript{2}O, 2.3 mL of 15% aqueous NaOH, and 6.9 mL of H\textsubscript{2}O were added sequentially. This caused the formation of a tan precipitate which was removed by vacuum filtration. To the filtrate was added 40 mL of 1N HCl, 60 mL of H\textsubscript{2}O, 20 mL of MeOH, and 100 mL of THF. This two-phase mixture was vigorously stirred for 45 min. This reaction mixture was then poured into a separatory funnel containing 400 mL of saturated aqueous NaHCO\textsubscript{3}. The aqueous phase was extracted with two 200 mL portions of ether. The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and NaHCO\textsubscript{3}, filtered, and concentrated in vacuo to give 16.4 g of crude diene aldehyde. This compound was routinely taken on to the next step without purification. A sample from a small scale run was chromatographed to give diene aldehyde\textsuperscript{197} in 74% yield: (NMR (CDCl\textsubscript{3}) δ 9.53 (d, J = 8 Hz, 1H), 7.33 (m, 5H), 7.06 (m, 1H), 6.29 (m, 2H), 6.06 (dd, J = 15.4, 8 Hz, =CH=CHO), 4.50 (s, 2H), 3.49 (t, J = 6.2 Hz, 2H), 2.32 (m, 2H,
allylic CH₂), 1.78 (quint, J = 6.3 Hz, 2H); IR (neat) cm⁻¹ 3025, 2735, 1675, 1630, 1595; mass spectrum m/e 230 (parent ion). High resolution mass spectrum. Calcd. for C₁₅H₁₈O₂: 230.1307. Found: 230.1289. Diene aldehyde 197 was further characterized as the semicarbazone, which was recrystallized three times from 50% aqueous EtOH, mp 147.5-149°C.  Analytical data for C₁₆H₂₁N₃O₂: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.03; H, 7.11; N, 14.57.

(E,E)-1-Benzylxyloxy-8-hydroxy-4,6-tridecadien-12-yne (199)

To a vigorously stirred mixture of 3.14 g of Mg turnings (129 mg-atom) in 170 mL of dry THF was added a small crystal of I₂. The mixture was heated to reflux and when the I₂ color dissipated a solution of 12.1 g of 1-(5-bromo-1-pentynyl)trimethylsilane 52 (55.4 mmol) in 140 mL of dry THF was added dropwise. On this scale, the addition required 2 h. The mixture was refluxed for an additional 25 min after the addition was complete. The Grignard reagent was then cooled to 0°C and a solution of 8.45 g of crude diene aldehyde 197 (36.7 mmol) in 20 mL of dry THF was added. The resulting solution was stirred for 30 min (0°C - 23°C) before being quenched with 1 mL of MeOH. The reaction mixture was poured through a glass wool plug into a separatory funnel containing 200 mL each of ether and saturated aqueous NH₄Cl. The ether layer was washed once with 200 mL of saturated aqueous NH₄Cl. The combined aqueous extracts were then washed with two 150 mL portions of ether. The combined ether extracts were concentrated in vacuo, dissolved in CH₂Cl₂, dried over MgSO₄, filtered and concentrated in vacuo to give 14.1 g of a semi-viscous oil. Another experiment, performed on a similar scale yielded 13.7 g of crude product from 7.43 g of starting aldehyde 197. These two samples were combined and taken on to the next step without further purification.
To a chilled solution (cold water bath) of 30.1 g of KF·2H₂O (320 mmol) in 100 mL of distilled H₂O and 200 mL of DMF was added a solution of 27.8 g of crude Grignard product in 200 mL of DMF. Two phases separated, so an additional 200 mL of DMF was added. The resulting mixture was stirred vigorously at 23°C. After being stirred for 39 h, the reaction mixture was poured into a separatory funnel containing 2.5 L of distilled H₂O and 1 L of 1:1 hexane-ether. The aqueous phase was washed with three 1 L portions of 1:1 hexane-ether. The combined ether layers were concentrated in vacuo, dissolved in CH₂Cl₂, filtered through a cotton plug, and concentrated in vacuo to give 23.2 g of crude alcohol. The crude product was purified by chromatography on 645 g of silica gel using 3:1 hexane-ether as eluant for fractions 1-41, and then 5:3 hexane-ether for the remaining fractions. Fractions 44-59 were combined and concentrated in vacuo to give 13.8 g of alcohol (65% overall yield from NMR (CDCl₃) δ 7.31 (m, 5H), 6.08 (m, 2H, H₆ + H₅), 5.67 (dt, J = 14.3, 7 Hz, H₄), 5.55 (dd, J = 15.1, 7 Hz, H₇), 4.48 (s, 2H), 4.13 (broad q, J = 6.3 Hz, -CH(OH)-), 3.46 (t, J = 6.3 Hz, -CH₂-OBzI), 2.18 (m, 4H), 1.94 (t, J = 1.6 Hz, H₁₃); IR (neat) cm⁻¹ 3400, 3280, 3015, 2107, 1675, 1658, 1635; mass spectrum m/e 207 (M - C₇H₇). High resolution mass spectrum. Calcd. for C₁₃H₁₉O₂: 207.1385. Found: 207.1368.  Anal: Calcd. for C₂₀H₂₆O₂: C, 80.50; H, 8.78. Found: C, 80.42; H, 8.71.

(E,E)-1-Benzylloxy-8-(t-butyldimethylsilyloxy)-4,6-tridecadien-12-yne (200)

To a solution of 13.2 g of (44.2 mmol) in 60 mL of dry DMF was added 10.8 g of t-butyldimethylsilylchloride (66.3 mmol) and 9.49 g of imidazole (140 mmol). This solution was stirred for 53 h at 23°C. The reaction mixture was poured into a separatory funnel containing 400 mL of H₂O and 400 mL of 4:1 hexane-ether. The aqueous layer was washed once with 400 mL of 4:1
hexane-ether and then with five 300 mL portions of 3:1 hexane-ether. The combined organic extracts were dried over Na$_2$SO$_4$ and Na$_2$CO$_3$, filtered and concentrated in vacuo to afford 18.4 g of crude 200. This crude product was routinely taken directly to the next step without purification. A small sample (68 mg) was chromatographed on a 0.5 mm silica gel plate using 6:1 hexane-ether as eluant to afford 66.4 mg (98%) of 200 NMR (CDCl$_3$) & 7.32 (m, 5H), 6.03 (m, 2H), 5.60 (dt, J = 14.3, 7 Hz, H$_4$), 5.49 (dd, J = 14.3, 6.6 Hz, H$_7$), 4.48 (s, 2H), 4.12 (m, 1H, -CH(OH)-), 3.46 (t, J = 6.4 Hz, 2H), 2.15 (m, 4H), 1.92 (t, J = 1.6 Hz, H$_{13}$), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); IR (neat) cm$^{-1}$ 3310, 3022, 2115, 1657; mass spectrum m/e 412 (parent ion). High resolution mass spectrum. Calcd. for C$_{26}$H$_{40}$O$_2$Si: 412.2798. Found: 412.2795.

2,2,2-Trichloroethyl·(E,E)-14-benzyloxy-7-(t-butyldimethylsilyloxy)-8,10-tetradecadien-2-ynoate (201)

A solution of 18.2 g of crude silyl ether 200 (43.8 mmol) in 250 mL of dry THF was cooled to -78°C. To this solution was added 23.5 mL of a 2.4 M n-butyllithium solution in hexane (57.0 mmol) over 30 min. This solution was stirred at -78°C for 30 min, and then 12.1 mL of 2,2,2-trichloroethylchloroformate (87.6 mmol) was added. After an additional 55 min at -78°C, the solution was allowed to warm to 0°C and then was quenched with 150 mL of saturated aqueous NaHCO$_3$. This two-phase mixture was stirred for 2 h at 23°C and poured into a separatory funnel containing 200 mL of CH$_2$Cl$_2$ and 100 mL of H$_2$O. The aqueous layer was washed twice with 150 mL of CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to afford 30.0 g of crude ester 201. Purification of ester 201 was effected by chromatography on 600 g of silica gel using 10:1 hexane-ether as eluant. Rechromatography of mixed fractions gave 20.0 g of pure ester 201 (79% from
\textsuperscript{199} NMR (CDCl\textsubscript{3}) \& 7.32 (m, 5H), 6.03 (m, 2H, H\textsubscript{9} + H\textsubscript{10}), 5.63 (dt, J = 14.3, 7.2 Hz, H\textsubscript{11}), 5.47 (dd, J = 14.7, 6.6 Hz, H\textsubscript{8}), 4.78 (s, 2H), 4.48 (s, 2H), 4.14 (m, 1H, -CH(OH)-), 3.46 (t, J = 6.4 Hz, 2H), 2.37 (t, J = 6.3 Hz, 2H), 2.16 (q, J = 7.3 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); IR (neat) cm\textsuperscript{-1} 3025, 2240, 1728, 1658; mass spectrum m/e 571 (M - CH\textsubscript{3}). High resolution mass spectrum. Calcd. for C\textsubscript{29}H\textsubscript{41}Cl\textsubscript{3}O\textsubscript{4}Si: 586.1840. Found: 586.1839. Anal. Calcd. for C\textsubscript{29}H\textsubscript{41}Cl\textsubscript{3}O\textsubscript{4}Si: C, 59.23; H, 7.03. Found: C, 59.28; H, 7.01.

Cyclization of 201:

2,2,2-Trichloroethyl-6\textsubscript{8}-[1-(3-benzyloxypropyl)]-1\textalpha-\textbeta-hydroxy-1\textalpha,2,3,4,6\textalpha-\textbeta-hexahydonaphthalene-5-carboxylate\textsubscript{(204)} and 2,2,2-Trichloroethyl-6\textsubscript{8}-[1-(3-benzyloxypropyl)]-1\textalpha-(t-butyldimethylsilyloxy)-1\textalpha,2,3,4,6\textalpha-hexahydonaphthalene-5-carboxylate\textsubscript{(203)}

A solution of 10.0 g of ester 201 in 55 mL of dry toluene was added to a resealable Carius tube and was purged with dry Ar for 40 min. The tube was then sealed and heated in a 160°C oil bath for 61 h. The cooled tube was opened and then all volatile components were removed in vacuo to give 9.83 g of a mixture of two epimeric silyl ethers, 202 and 203. This mixture was dissolved in 66 mL of THF and 90 mL of MeOH. The resulting solution was purged with Ar, cooled to 10°C, and then 13 mL of 1N aqueous HCl was slowly added. The reaction vessel was allowed to warm to 23°C and was stirred vigorously for 10 h. In another run, 9.40 g of the crude mixture of 202 and 203 (15.8 mmol; obtained from a cyclization of 9.26 g of 201) was treated in the same manner. These two reaction mixtures were combined and poured into a separatory funnel containing 400 mL of saturated aqueous NaHCO\textsubscript{3} and 200 mL of CH\textsubscript{2}Cl\textsubscript{2}. The aqueous layer was extracted with three 200 mL portions of CH\textsubscript{2}Cl\textsubscript{2}. The combined CH\textsubscript{2}Cl\textsubscript{2} extracts were dried over Na\textsubscript{2}CO\textsubscript{3} and concentrated in vacuo.
to give 19.4 g of a mixture of alcohol 204 and silyl ether 203. This mixture was easily separated in a single chromatographic run with a Waters Prep 500 LC using 4:1 hexane-ether as eluant. This afforded 9.81 g (61%) of 204 and 7.12 g of recovered 203 (36%). A small sample of 203 (289 mg) was purified by preparative TLC on a 1.5 mm silica gel plate using 5% ether-hexane as eluant, affording 214 mg of pure 203.

Data for 204: NMR (CDCl₃) δ 7.30 (m, 5H), 5.97 (ddd, J = 9.3, 3.7, 1.1 Hz, H₈), 5.75 (ddd, J = 9.3, 3.7, 1.1 Hz, H₇), 4.81 (d, JAB = 12 Hz, 1H), 4.67 (d, JAB = 12 Hz, 1H), 4.44 (s, 2H), 3.40 (m, 4H, H₈a, -CH₂OBzl, and -CH(OH)-), 3.08 (br d, J = 12.9 Hz, 1H), 2.58 (m, H₅); IR (CCl₄) cm⁻¹ 3618, 3030, 1730, 1630; mass spectrum m/e 454,456 (M - H₂O). Anal. Calcd. for C₂₃H₂₇Cl₃O₄: C, 58.30; H, 5.74; Cl, 22.45. Found: C, 58.25; H, 5.61; Cl, 21.97.

Data for 203: NMR (CDCl₃) δ 7.29 (m, 5H), 5.81 (ddd, J = 10.0, 3.7, 1.5 Hz, 1H), 5.42 (ddd, J = 10.0, 3.0, 1.5 Hz, 1H), 4.82 (d, JAB = 12 Hz, 1H), 4.69 (d, JAB = 12 Hz, 1H), 4.44 (s, 2H, -CH₂-Ph), 4.08 (br s, H₁), 3.39 (t, J = 6.4 Hz, -OCH₂-), 3.18 (m, 2H), 2.75 (m, 1H), 0.81 (s, 9H, tBu), 0.00 (s, 3H), -0.02 (s, 3H); IR (CCl₄) cm⁻¹ 3022, 1730, 1635; mass spectrum m/e 529,531 (M - tBu). High resolution mass spectrum. Calcd. for C₂₅H₃₂Cl₃O₄Si (M - tBu): 529.1136. Found: 529.1153. Anal. Calcd. for C₂₉H₄₁Cl₃O₄Si: C, 59.23; H, 7.03. Found: C, 59.25; H, 7.09.

2,2,2-Trichloroethyl 6₈-[1-(3-benzyloxypropyl)]-1α-(t-oxymethoxymethyl)-1₈;2,3;4,6₆-hexahydronaphthalene-5-carboxylate (205)

To a stirred solution of 9.45 g of alcohol 204 (20.0 mmol), 11 mL of dry diisopropylethylamine (61.8 mmol), and 100 mL of dry CH₂Cl₂ was added 4.45 mL of chloromethyl methyl ether (58.6 mmol). This mixture was then stirred at 23°C for 15 h. The reaction mixture was then poured into a separatory funnel
containing 100 mL of ether and 100 mL of 0.3N aqueous HCl. The organic layer was washed once with 100 mL of 0.3N HCl. The combined aqueous extracts were washed with two 100 mL portions of ether. The combined organic extracts were dried over Na₂SO₄ and NaHCO₃, filtered, and concentrated in vacuo to give 8.57 g of crude 205 (83%). This material was purified by chromatography on a Waters Prep 500™. In this manner, 6.25 g of pure 205 (60%) along with 1.17 g of mixed fractions containing 205 were obtained. Rechromatography of this mixture afforded an additional 1.03 g (10%) of 205.

Data for 205: NMR (CDCl₃) δ 7.30 (m, 5H), 5.94 (ddd, J = 10.3, 3.3, 1.1 Hz, H₈), 5.71 (ddd, J = 10.3, 3.7, 1.1 Hz, H₇), 4.81 (d, J₉AB = 12 Hz, 1H), 4.71 (d, J₉AB = 7 Hz, 1H), 4.69 (d, J₉AB = 12 Hz, 1H, -CH₂CCl₃), 4.61 (d, J₉AB = 7 Hz, 1H, -OCH₂O-), 4.44 (s, -CH₂-Ph), 3.38 (m, 5H, CH₂OBzl and OCH₃), 3.25 (dt, J = 4.7, 10.3 Hz, H₁), 3.08 (br d, 1H), 2.68 (m, H₆), 2.19 (m, 1H), 1.89 (m, 1H); IR (neat) cm⁻¹ 3033, 1730, 1638; mass spectrum m/e 484, 486 (M – MeOH). High resolution mass spectrum. Calcd. for C₂₄H₂₇Cl₃O₄ (M – MeOH): 484.0975. Found: 484.0984. Anal. Calcd. for C₂₅H₃₁Cl₃O₅: C, 57.95; H, 6.03; Cl, 20.54. Found: C, 58.25; H, 6.05; Cl, 21.22.

6β-[1-(3-Benzylxoypropyl)]-1α-(1-oxymethoxymethyl)-18,2,3,4,6α-hexahydro-naphthalene-5-carboxylic acid (206)

A solution of 2.81 g of ester 205 (5.42 mmol) in 80 mL of reagent grade MeOH was purged with a stream of dry N₂ for 25 min. To this stirred solution was added 3.79 g of Zn dust (58.0 mmol). The mixture was then heated to reflux for 2 h. The reaction mixture was cooled and then filtered to remove the spent reagent. The filter cake was washed with several 4 mL portions of MeOH. The filtrate was concentrated in vacuo to afford 3.09 g of crude acid 206. This was purified by flash chromatography (40 mm column) using 1:1
ether-hexane containing 0.5% HOAc as eluant. This gave 2.01 g of highly viscous 206 (96%) and 0.12 g (4%) of a compound which was tentatively assigned the structure of the dichloroethyl ester analogue of 206.

Data for 206: NMR (CDCl₃) δ 7.30 (m, 5H), 5.93 (dd, J = 10.3, 2.6 Hz, H₈), 5.73 (dd, J = 10.3, 2.7 Hz, H₇), 4.72 (d, J₉₋₂ = 6.5 Hz, 1H), 4.62 (d, J₉₋₂ = 6.5 Hz, 1H), 4.46 (s, -CH₂-Ph), 3.43 (t, J = 5 Hz, -CH₂OBzl), 3.34 (s, OCH₃), 3.25 (m, 2H), 2.67 (m, H₆), 2.17 (m, 1H), 1.89 (m, 1H); IR (CCl₄) cm⁻¹ 3032, 3400-2500, 1695, 1638; mass spectrum m/e 386 (parent ion). High resolution mass spectrum. Calcd. for C₂₃H₃₀O₅: 386.2093. Found: 386.2106. Anal. Calcd. for C₂₃H₃₀O₅: C, 71.48; H, 7.82. Found: C, 71.32; H, 7.59.

6β-[(i-(3-Hydroxypropyl)]-1α-(1-oxymethoxymethyl)-1β,2,3,4,4aaβ,5α/6α,8aa-oxatricyclonaphthalene-5 β-carboxylic acid (207) and 6β-[(i-(3-Hydroxypropyl)]-1α-(1-oxymethoxymethyl)-1β,2,3,4,4aaβ,5α/6α,8aa-oxatricyclonaphthalene-5α-carboxylic acid (208)

Several small pieces of sodium metal and several mg of FeCl₃ were added to a 1 L flame-dried flask fitted with a dry-ice condenser. Approximately 500 mL of NH₃ was condensed into this flask. Then approximately 400 mL of ammonia was distilled from the resulting NaNH₂ solution into a reaction vessel which contained 0.21 g of Li wire (30 mmol). The resulting deep blue solution was then cooled to -75°C, and a solution of 2.01 g of acid 206 (5.21 mmol) in 50 mL of dry THF was added dropwise. On this scale the addition required 30 min. Residual acid 206 was rinsed into the reaction mixture with an additional 25 mL of dry THF, which was added dropwise over a period of 10 min. After the addition was complete, the reaction mixture was allowed to stir for 30 min at -75°C. Then 125 mL of dry THF was added over a period of 10 min. To this vigorously stirred solution was added 4.7 g of NH₄Cl (88 mmol) in one portion.
The blue color dissipated in ~90 sec and the colorless mixture was allowed to warm to room temperature with removal of NH₃ by distillation. Saturated aqueous NH₄Cl (50 mL) was then added, followed by 100 mL of ether. The aqueous layer was acidified to pH 3 by the addition of 170 mL of 1N HCl and 20 mL of 2N HCl and was extracted with three additional 150 mL portions of ether. The combined ether extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 1.57 g (100%) of a semi-crystalline mixture of acids 207:208 (~5:1). This mixture was routinely used in subsequent transformations without purification. A pure sample of the major product, acid 207, was obtained by recrystallization of the above mixture from hexane-EtOAc: mp 148-149.5°C; NMR (CDCl₃) δ 5.96 (d, J = 10.3 Hz, 1H), 5.76 (ddd, J = 2.6, 4.4, 10.3 Hz), 4.79 (d, Jₐᵦ = 7 Hz, 1H), 4.64 (d, Jₐᵦ = 7 Hz, 1H), 3.62 (m, 2H), 3.41 (s, 3H), 3.20 (dt, J = 4.4, 10.3 Hz, H₁), 2.67 (dd, J = 6.0, 11.5 Hz, H₅), 2.48 (m, 1H), 2.18 (m, 1H), 2.02 (m, 1H); IR (CHCl₃) cm⁻¹ 3500-2500 broad, 3040, 1708; mass spectrum m/e 280 (M - H₂O). High resolution mass spectrum. Calc'd. for C₁₆H₂₆O₅: 298.1780. Found: 298.1785. Anal. Calc'd. for C₁₆H₂₆O₅: C, 64.41; H, 8.78. Found: C, 64.80; H, 8.89.

Acid 208 was not purified, but its presence was evident by inspection of the ¹H NMR spectrum of the mixture. Partial ¹H NMR data for 208 (obtained on the 5:1 mixture of 207:208): 5.98 (d, J = 10 Hz, 1H), 5.70 (m, 1H), 2.55 (d, J = 3 Hz, 1H).
Methyl 6β-[1-(3-t-butyldimethylsilyloxypropyl)]-1α-(1-oxymethoxymethyl)-1β,2,3,4,4αβ,5α,6α,8αα-octahydrornaphthalene-5β-carboxylate (209) and Methyl 6β-[1-(3-t-butyldimethylsilyloxypropyl)]-1α-(1-oxymethoxymethyl)-1β,2,3,4,4αβ,5β,6α,8αα-octahydrornaphthalene-5α-carboxylate (210)

A solution of the crude mixture of hydroxy acids 207 and 208 (from the Li, NH₃ reduction of 60 mg of acid 206 0.16 mmol) in 3 mL of anhydrous ether was cooled to 0°C. An ethereal solution of diazomethane was added dropwise until a yellow color persisted. After being stirred for an additional 5 min, the solution was purged with a stream of Ar to remove excess diazomethane. The solution was concentrated in vacuo to give a mixture of crude hydroxy esters. These compounds, without separation, were converted into the corresponding t-butyldimethylsilyl ethers by treatment with 184 mg of t-butyldimethylsilylchloride (1.1 mmol) and 108 mg of imidazole (1.6 mmol) in 2 mL of dry DMF (23°C, 48 h). The reaction mixture was then diluted with 10 mL of H₂O and extracted four times with 10 mL portions of 6:1 hexane-ether. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to give 148 mg of crude silyl ethers 209 and 210. These compounds were separated by preparative TLC on a 0.5 mm silica gel plate using 6:1 hexane-ether as eluant to afford 47 mg (71%) of pure silyl ester 209 and 11 mg (17%) of an 8:1 mixture of silyl ester 210 and a cis-fused product.

Data for 209: NMR (CDCl₃) δ 5.91 (d, J = 10.3 Hz, H₉), 5.74 (ddd, J = 2.6, 4.4, 10.3 Hz, H₇), 4.75 (d, J_AB = 6.7 Hz, A of AB), 4.61 (d, J_AB = 6.7 Hz, B of AB), 3.64 (s, 3H), 3.53 (m, 2H), 3.37 (s, 3H), 3.17 (dd, J = 4.4, 10.3 Hz, H₁), 2.61 (dd, J = 7, 11.4 Hz, H₅), 2.37 (m, H₆, J₅₆ = 7 Hz, J₆₇ = 4.4 Hz), 2.13 (m, H₂β, J₁₂β = 4.4 Hz), 1.89 (br d, 1H), 0.86 (s, 9H), 0.01 (s, 6H); IR (neat) cm⁻¹ 3025, 1736, 1652; mass spectrum m/e (no parent observed), 369 (M - t-Bu). High resolution mass spectrum. Calcd. for C₂₃H₄₂O₅Si: 426.2802.
Found: 426.2797.

Data for 210: NMR (CDCl₃) δ 5.96 (d, J = 10.3 Hz, H₈), 5.67 (ddd, J = 2.5, 3.4, 10.3 Hz, H₇), 4.78 (d, Jₐₗₜ = 7 Hz, A of AB), 4.64 (d, Jₐₗₜ = 7 Hz, B of AB), 3.65 (s, 3H), 3.62 (dt, J = 1.5, 6.6 Hz, 2H), 3.40 (s, 3H), 3.12 (dt, J = 4.5, 9.9 Hz, H₆), 2.51 (d, J = 3.3 Hz, H₅), 2.31 (m, H₆), 2.12 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); IR (neat) cm⁻¹ 3025, 1730, 1651; mass spectrum m/e 396 (M - t-Bu).

Methyl 6β- [(1-({3-t-butyldimethylsilyloxypropyl})-1α-(1-oxymethoxymethyl)-5α-methyl-1β,2,3,4,4α₅,5,6α,8α-octahydronaphthalene-5β-carboxylate (213) and Methyl 6β- [(1-({3-t-butyldimethylsilyloxypropyl})-1α-(1-oxymethoxymethyl)-5α-methyl-1β,2,3,4α₅,5,6α,8α-octahydronaphthalene-5α-carboxylate (214)

A solution of 0.07 mL of dry diisopropylamine (0.5 mmol) in 2 mL of THF was cooled to −78°C under argon. To this solution was added 0.19 mL of 2.43 M n-BuLi (0.46 mmol). The resulting solution was stirred for 30 min at −78°C, after which a solution of 60 mg of silyl ether 209 (0.14 mmol) in 2 mL of THF was added in a dropwise manner over a period of one minute. The resulting yellow solution was stirred at −78°C for 20 min, warmed to −20°C for 30 min, and then recooled to −78°C. A solution of 0.1 mL of methyl iodide (1.6 mmol) in 0.8 mL of dry HMPT was added. The resulting solution was stirred at −78°C for 90 min and then the mixture was allowed to warm to 15°C over a period of 3 h. The mixture was stored overnight (11 h) at 0°C and then was quenched by the addition of 0.3 mL of MeOH. The reaction mixture was partitioned between 10 mL of 0.1N HCl and 10 mL of ether. The aqueous layer was extracted with two 10 mL portions of ether. The combined ether extracts were washed with 10 mL of saturated Na₂S₂O₃, dried over Na₂SO₄, and concentrated in vacuo to afford 183 mg of crude product. Purification of this material was effected by
preparative TLC using 10:1 hexane-ether as eluant. This afforded 35 mg of silyl ether 213 (56%), 8 mg of silyl ether 214 (13%) and 10 mg of an unidentified mixture of by-products (15%).

Data for 213: NMR (CDCl₃) δ 5.87 (s, J = 10.3 Hz, H₈), 5.69 (ddd, J = 2.2, 4.7, 10.3 Hz, H₇), 4.75 (d, J_AB = 7 Hz, A of AB), 4.63 (d, J_AB = 7 Hz, B of AB), 3.63 (s, 3H), 3.53 (m, 2H), 3.37 (s, 3H), 3.22 (dt, J = 4.4, 10 Hz, H₁), 2.15 (m, 1H), 1.14 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); IR (neat) cm⁻¹ 3033, 1727, 1656; mass spectrum m/e 440 (parent ion). This compound was further characterized as the hydroxy-acid 234 (see procedure for preparation of 219). Thus, treatment of 11.2 mg of 213 with 1N NaOH in THF (90°C, 20 h) afforded 5.6 mg of 234 (68%) and 2 mg of hydroxyester 221 (25%).

Data for 214: NMR (CDCl₃) δ 5.82 (m, 2H), 4.74 (d, J_AB = 6.8 Hz, A of AB), 4.00 (d, J_AB = 6.8 Hz, B of AB), 3.60 (m, 5H), 3.36 (s, 3H), 3.08 (dt, J = 4.4, 10.3 Hz, H₁), 2.52 (m, 1H), 1.14 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); IR (CCl₄) cm⁻¹ 3030, 2948, 1729; mass spectrum m/e 383 (parent - t-Bu). High resolution mass spectrum. Calcd. for C₂₄H₄₄O₅Si: 440.2958. Found: 440.2956.

6₈[1-(3-Hydroxypropyl)]-1α-(1-oxymethoxymethyl)-18;2,3;4;4αβ;5α;6α,8αα=octahyronaphthalene-5β-carboxylic acid=ε-lactone (216) and 6₈=[1-(3-Hydroxypropyl)]-1α-(1-oxymethoxymethyl)-18;2,3;4;4αβ;5β;6α,8αα=octahyronaphthalene-5α-carboxylic acid=ε-lactone (220)

To a refluxing solution of 3.27 g of 2-chloro-1-methylpyridinium iodide¹¹₆ (12.8 mmol) in 800 mL of dry CH₂Cl₂ under Ar was added dropwise a solution of 1.43 g of a mixture of crude acids 207 and 208 (4.73 mmol), 6.3 mL of dry Et₃N (45.2 mmol), and 500 mL of dry CH₂Cl₂. On this scale the addition required 6 h. After the addition was complete the solution was refluxed for an additional 45 min. The reaction mixture was cooled and concentrated in vacuo
to give a dark residue which was partitioned between 60 mL of ether and 60 mL of H₂O. The aqueous layer was washed with three 60 mL portions of ether. The combined ether layers were dried over Na₂SO₄ and concentrated in vacuo to give 1.56 g of crude product, purification of which was effected by flash chromatography (50 mm column) by using 3:2 hexane-ether as eluant. This afforded 1.12 g (84%) of a 6:1 mixture of 216:220, 0.32 g (3%) of 216, and 0.024 g (2%) of a 1:6 mixture of 216:220. The latter mixture was recrystallized from hexane-EtOAc to afford a pure sample of 220.

Data for 216: NMR (CDCl₃) δ 5.90 (d, J = 9.9 Hz, 1H), 5.62 (ddd, J = 9.9, 4.0, 2.6 Hz, 1H), 4.76 (d, Jₐ₋₈ = 6.8 Hz, A of AB), 4.61 (d, Jₐ₋₈ = 6.8 Hz, B of AB), 4.20 (m, 2H, lactone -CH₂O-), 3.37 (s, 3H), 3.32 (dt, J = 5.5, 9.9 Hz, H₁), 3.08 (dd, J = 10.3, 6.7 Hz, H₅), 2.42 (m, 1H), 2.15 (m, 1H); IR (CCl₄) cm⁻¹ 3030, 2931, 1726, 1640. High resolution mass spectrum. Calcd. for C₁₆H₂₄O₄: 280.1675. Found: 280.1671.

Data for 220: mp 96-98°C; NMR (CDCl₃) δ 6.10 (ddd, J = 2, 3.4, 9.5 Hz, 1H), 5.54 (dt, J = 9.5, 2.5 Hz, 1H), 4.82 (d, J₀₋₈ = 6.7 Hz, A of AB), 4.54 (d, J₀₋₈ = 6.7 Hz, B of AB), 4.33 (m, 2H), 3.41 (s, 3H), 3.16 (dt, J = 4.4, 10.4 Hz, H₁), 2.87 (t, J = 7.4 Hz, H₅); IR (CCl₄) cm⁻¹ 3028, 2927, 1749; mass spectrum m/e 218 (M - HOCH₂OCH₃).

6β-[1α-(3-Hydroxypropyl)]-5α-methyland-1α-(1-oxyethoxymethyl)-
1β,2,3,4,4α,5,6α,8α-octahydropaphthalene-5β-carboxylic acid-ε-lactone (219)

To a solution of 2.7 mL of dry diisopropylamine (19.3 mmol) in 85 mL of dry THF at -78°C was added dropwise 7.2 mL of 2.43 M n-BuLi in hexane (17.5 mmol). This solution was stirred for 40 min at -78°C and then a solution of 1.08 g of a 6:1 mixture of 216:220 (3.86 mmol) in 15 mL of dry THF and 20 mL of dry HMPT was added dropwise. On this scale the addition required 20 min.
This solution was stirred for 15 min at -78°C, warmed to -27°C over 15 min, and then recooled to -78°C. Iodomethane (3 mL) was then added. The resulting solution was stirred at -78°C for 4 h and was then allowed to warm gradually to room temperature overnight (13 h). The reaction was quenched by addition of 0.5 mL of MeOH, and then the solution was poured into a separatory funnel containing 100 mL of 0.2N HCl, 20 mL of H₂O and 120 mL of ether. The aqueous layer was extracted with two additional 120 mL portions of ether. The combined ether layers were washed once with 100 mL of half-saturated Na₂S₂O₃, which was back-extracted with 75 mL ether. The combined ether layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give 2.91 g of crude product, which was purified by flash chromatography (50 mm column, 4:1 hexane-ether) to afford 0.901 g of lactone 219 (79%).

Data for 219: NMR (CDCl₃) δ 5.87 (d, J = 10.3 Hz, 1H), 5.55 (ddd, J = 2.2, 4.1, 10.3 Hz, 1H), 4.75 (dd, J_AB = 7 Hz, 1H), 4.61 (d, J_AB = 7.0 Hz, 1H), 4.37 (dd, J = 5.9, 10.3 Hz, 1H), 3.76 (m, 1H), 3.37 (s, 3H), 3.19 (dt, J = 4.4, 10.1 Hz, H₁), 2.12 (m, 1H), 1.10 (s, 3H); IR (neat) cm⁻¹ 3022, 1733, 1648. High resolution mass spectrum. Calcd. for C₁₇H₂₆O₄: 294.1831. Found: 294.1851. Saponification of lactone 219 afforded the crystalline hydroxy acid 234 which was fully characterized.

Data for 234: mp 102-103°C; NMR (CDCl₃) δ 5.92 (d, J = 10.4 Hz, 1H), 5.72 (ddd, J = 2.2, 4.8, 10.4 Hz, 1H), 4.79 (d, J_AB = 6.8 Hz, 1H), 4.66 (d, J_AB = 6.8 Hz, 1H), 3.62 (m, 2H), 3.48 (s, 3H), 3.25 (dt, J = 4.4, 10 Hz, H₁), 2.18 (m, 1H), 2.00 (m, 1H), 1.20 (s, 3H); IR (CCl₄) cm⁻¹ 3600-2400, 3038, 1695. High resolution mass spectrum. Calcd. for C₁₇H₂₈O₅: 312.1937. Found: 312.1940. Anal. Calcd. for C₁₇H₂₈O₅: C, 65.36; H, 9.03. Found: C, 65.62; H, 8.84.
Alkylation of Lactone 220

A solution of 0.05 mL of dry diisopropylamine (0.36 mmol) in 1.5 mL of dry THF under Ar was cooled to -78°C, and 0.13 mL of 2.43 M n-BuLi (0.31 mmol) was added. The resulting solution was stirred for 40 min at -78°C. A solution of 20 mg of lactone 220 (0.07 mmol) in 0.38 mL of dry HMPT and 1.0 mL of THF was added dropwise. This solution was stirred for 2 h at -78°C, warmed to -25°C for 30 min, and recooled to -78°C. Iodomethane (0.06 mL, 1.0 mmol) was then added and the resulting solution was allowed to warm slowly to 23°C overnight. The reaction was quenched with 0.2 mL of MeOH and partitioned between 10 mL of 0.15N HCl and 10 mL of ether. The aqueous layer was washed twice with 10 mL portions of ether. The combined ether extracts were washed once with 10 mL of half saturated Na₂S₂O₃, dried over Na₂SO₄ and concentrated in vacuo to give 31 mg of crude product. The mixture of products was separated by preparative TLC using 4:1 hexane-ether as eluant, giving 6.5 mg of lactone 219 (31%) and 5.5 mg of recovered 220 (28%).

Methyl 6a-[1-(3-Hydroxypropyl)]-5α-methyl-1α-(1-oxymethoxymethyl)-1α,2,3,4,4α,5,6α,8α-octahydropyrene-5α-carboxylate (221)

A solution of 171 mg of lactone 219 (0.58 mmol) in 5 mL of dry MeOH was added to a resealable Carius tube and purged with a stream of dry Ar for 10 min. To this solution was added 13 mg of NaOMe (0.24 mmol), and the resultant mixture was purged with Ar for an additional 5 min. The tube was then sealed and placed in a 100°C oil bath for 23 h (temperature of the oil bath slowly increased to 105-110°C). The reaction mixture was cooled, neutralized with 0.025 mL of HOAc, and then concentrated in vacuo to give crude ester 221. The crude product was purified by preparative TLC (0.5 mm silica gel) using 1:1 hexane-ether containing 1% HOAc as eluant, giving 161 mg of ester 221 (86%).
NMR (CDCl$_3$) $\delta$ 5.89 (d, J = 10.3 Hz, 1H), 5.68 (ddd, J = 2.2, 4.8, 10.3 Hz, 1H), 4.75 (d, J$_{AB}$ = 6.6 Hz, 1H), 4.63 (d, J$_{AB}$ = 6.6 Hz, 1H), 3.65 (s, 3H), 3.58 (t, J = 6.6 Hz, 2H), 3.38 (s, 3H), 3.22 (dt, J = 4.4, 10 Hz, H$_1$), 2.15 (m, 1H), 1.94 (m, 1H), 1.15 (s, 3H); IR (neat) cm$^{-1}$ 3425, 3022, 1726, 1655.

High resolution mass spectrum. Calcd. for C$_{18}$H$_{30}$O$_5$: 326.2093. Found: 326.2104.

Methyl 5a-methyl-6b-[1-[(3-oxypropyl)]-1a-a-(1-oxymethoxyethyl)-1b,2,3,4,4a,b,5a,6a,8aa-octahydronaphthalene-5b-carboxylate (235)

A solution of 0.97 mL of dry pyridine (12.0 mmol) in 20 mL of dry CH$_2$Cl$_2$ was cooled to 0°C. To this solution was added 599 mg of CrO$_3$ (5.99 mmol) followed by a solution of 155 mg of alcohol$^{221}$ (0.48 mmol) in 5 mL of dry CH$_2$Cl$_2$. After being stirred for 90 min at 0°C, the solution was diluted with 25 mL of dry ether and was filtered through a short pad of Florisil. The black gummy residue in the reaction flask was washed with several 5 mL portions of dry ether which were also passed through the Florisil pad. The combined filtrates were concentrated in vacuo to give crude aldehyde$^{235}$, which was purified by preparative TLC (0.5 mm silica gel plate) using 1:1 hexane-ether as eluant. This gave 120 mg of aldehyde$^{235}$ (78%): NMR (CDCl$_3$) $\delta$ 9.64 (t, J = 1.6 Hz, 1H), 5.87 (d, J = 10.3 Hz, 1H), 5.54 (ddd, J = 2.6, 5.2, 10.3 Hz, 1H), 4.68 (d, J$_{AB}$ = 6.8 Hz, 1H), 4.55 (d, J$_{AB}$ = 6.8 Hz, 1H), 3.60 (s, 3H), 3.30 (s, 3H), 3.15 (dt, J = 4.5, 10 Hz, H$_1$), 2.37 (m, 2H), 2.07 (m, 1H), 1.91 (m, 1H), 1.08 (s, 3H); IR (CCl$_4$) cm$^{-1}$ 3035, 2720, 1727, 1655. High resolution mass spectrum. Calcd. for C$_{18}$H$_{28}$O$_5$: 324.1937. Found: 324.1966.
Methyl 6β-[1-(4-Methoxycarbonyl-3-butenyl)]-1α-(1-oxymethoxymethyl)-5α-methyl-18;2,3,4,4αβ,5,6α,8αα-octahydropnaphthalene-5β-carboxylate (222)

To a stirred solution of 98.5 mg of aldehyde 235 (0.30 mmol) in 5 mL of dry CH₂Cl₂ was added 167 mg of carbomethoxymethylenetriphenylphosphorane 50 (0.5 mmol). The resultant solution was stirred for 20.5 h at 23°C and then was heated to reflux for 45 min. The reaction mixture was cooled and concentrated in vacuo to give the crude product, which was purified by preparative TLC (0.5 mm silica gel plate) using 2:1 hexane-ether as eluant. This gave 108 mg of unsaturated ester 222 (93%): NMR (CDCl₃) δ 6.84 (dt, J = 15.4, 6.8 Hz, 1H), 5.88 (d, J = 10.3 Hz, 1H), 5.75 (dt, J = 15.4, 1.5 Hz, 1H), 5.60 (ddd, J = 2.6, 5.2, 10.3 Hz, 1H), 4.70 (d, J₉α = 6.6 Hz, 1H), 4.58 (d, J₉β = 6.6 Hz, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.33 (s, 3H), 3.18 (dt, J = 4.2, 10.1 Hz, H₁), 1.09 (s, 3H); IR (neat) cm⁻¹ 3031, 1736, 1721, 1656. High resolution mass spectrum. Calcd. for C₂₁H₃₂O₆: 380.2199. Found: 380.2194.

Methyl 6β-[1-(4-Methoxycarbonylbutyl)]-1α-(1-oxymethoxymethyl)-5α-methyl-18;2,3,4,4αβ,5,6α,8αα-octahydropnaphthalene-5β-carboxylate (27)

A solution of 25 mg of tris(triphenylphosphine)chlororhodium 119 (0.027 mmol) in 5 mL of dry benzene was prepared in an Ar-flushed flask. The reaction vessel was then filled with H₂ via several vacuum/purge cycles. This solution was vigorously stirred and then a solution of 52 mg of unsaturated ester 222 in 1 mL of benzene was added. This solution was stirred for 6 h at 23°C by which time a black precipitate had formed on the flask walls. The reaction was then immediately worked-up by filtration and concentration in vacuo. The crude product was purified by preparative TLC (0.5 mm silica gel plate, 3:1 hexane-ether), giving 34 mg (65%) of a 4:1 mixture of starting ester 222 and product 27 and 8.1 mg of pure 27 (15%): NMR (CDCl₃) δ 5.87 (d,
J = 10.3 Hz, 1H), 5.67 (ddd, J = 2.2, 4.8, 10.3 Hz, 1H), 4.75 (d, J_{AB} = 6.6 Hz, 1H), 4.63 (d, J_{AB} = 6.6 Hz, 1H), 3.64 (s, 3H), 3.38 (s, 3H), 3.21 (dt, J = 4, 10 Hz, H_1), 2.26 (t, J = 7.7 Hz, 2H), 2.15 (m, 1H), 1.91 (m, 1H), 1.13 (s, 3H); IR (neat) cm^{-1} 3030, 1730, 1654; mass spectrum m/e 351 (M - MeO). High resolution mass spectrum. Calcd. for C_{21}H_{34}O_{6}: 382.2355. Found: 382.2354.