

AN ABSTRACT OF THE THESIS OF

Bernard Gale Sheldon for the degree of Doctor of Philosophy in Chemistry
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Title: I. INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS OF CITRACONIC AND
MESACONIC ESTERS II. STUDIES ON THE SYNTHESIS OF THE NORTHWEST AND
SOUTHEAST SEGMENTS OF BOROMYCIN

Abstract approved: Redacted for privacy
U Dr. James D. White

The thermal cycloaddition of trans,trans-2,4-hexadienyl 3-carboxy-crotonate 95 was found to produce cis-3 α -hydroxymethyl-1 β ,6 α -dimethyl-cyclohex-4-ene-1 α ,2 α -dicarboxylic acid γ -lactone (97), the structure of which was confirmed by reduction of the methyl ester 98, with diisobutyl-aluminum hydride to the acetal 99, exo-1-endo-10-dimethyl-3,5-dioxatricyclo [5.3.1.0^{4,11}] undec-8-ene. An X-ray crystallographic study further confirmed structure 97. Trans,trans-2,4-hexadienyl trans-3-methoxycarbonyl-3-methylacrylate 90 was found to undergo cycloaddition to yield a 4.3:1 mixture of trans-3 α -hydroxymethyl-1 β ,6 α -dimethyl-1 α -methoxycarbonyl-cyclohex-4-ene-2 β -carboxylic acid γ -lactone (117) and cis-3 α -hydroxymethyl-1 α ,6 α -dimethyl-1 β -methoxycarbonylcyclohex-4-ene-2 α -carboxylic acid γ -lactone (113). Epimerization of 117 with sodium hydride produced 98. The citraconic ester 110, trans,trans-2,4-hexadienyl 3-methoxycarbonyl-crotonate, was thermally cyclized to trans-3 α -hydroxymethyl-1 α ,6 α -dimethyl-1 β -methoxycarbonylcyclohex-4-ene-2 α -carboxylic acid γ -lactone (112), which could be epimerized with sodium methoxide to cis-3 α -hydroxymethyl-1 α ,6 α -dimethyl-1 β -methoxycarbonyl-cyclohex-4-ene-2 α -carboxylic acid γ -lactone (113). The citraconic ester 83, trans-2,

4-pentadienyl 3-methoxy-carbonylcrotonate produced trans-3 α -hydroxymethyl-1 α -methyl-1 β -methoxycarbonylcyclohex-4-ene 2 β -carboxylic acid γ -lactone (115), which was epimerized to cis-3 α -hydroxymethyl-1 α -methyl-1 β -methoxycarbonylcyclohex-4-ene 2 α -carboxylic acid γ -lactone (116). The mesaconate 122, trans,trans-2,4-hexadienyl trans-3-methoxycarbonyl-2-methylacrylate, produced 3 α -hydroxymethyl-2 α ,6 α -dimethyl-1 α -methoxycarbonylcyclohex-4-ene-2 β -carboxylic acid γ -lactone (123) and 3 α -hydroxymethyl-2 β ,6 α -dimethyl-1 β -methoxycarbonylcyclohex-4-ene-2 α -carboxylic acid γ -lactone (124) in a ratio of 4.7:1. A reductive sequence based on 112 was examined, leading to 1 β ,3 α -dihydroxymethyl-1 α ,6 α -dimethylcyclohexane-2 α -carboxylic acid 2,3- γ -lactone (131) and 1 β -formyl-3 α -hydroxymethyl-1 α ,6 α -dimethylcyclohexane-2 α -carboxylic acid γ -lactone (132). A rationalization of the stereochemical results of these intramolecular Diels-Alder cycloadditions was presented in terms of concerted, but non-synchronous, bond formation in the transition states for these cycloadditions. Finally, trans,trans-3,4-hexadienyl tetrolate (136) was cyclized to 3 α -hydroxymethyl-1,6 α -dimethylcyclohexa-1,4-dienecarboxylic acid γ -lactone (137). Hydrogenation of 137 over Adams' catalyst afforded 3 α -hydroxymethyl-1,6 α -dimethylcyclohexenecarboxylic acid γ -lactone (139). Attempts to alkylate 137 and 139 with lithium dimethylcuprate failed.

II

The stereocontrolled preparation of segments corresponding to the northwest (C-11 to C-17) and southeast (C-11 to C-17) quadrants of boromycin has been accomplished. Synthesis of the southeast segment was achieved by alkylation of lithio-3-tetrahydropyranyloxypropyne 19 with erythro-1,2-epoxy-3-butanol 25 to yield erythro-1-tetrahydropyranyloxy-

2-heptyn-5,6-diol 26. Reduction of 26 with hydrogen over palladium on barium sulfate poisoned with quinoline produced the cis, erythro-tetrahydropyranyloxy-2-hepten-5,6-diol (27). Deprotection of the primary alcohol, protection of the vicinal secondary alcohols and bromination produced cis, erythro-1-bromo-5,6-O-isopropylidene-2-hepten-5,6-diol. Formation of the northwest segment was accomplished by intramolecular oxymercuration of 27 with mercuric pivalate to yield diastereomeric tetrahydrofurans 31 and 32 which could be separated as 3 α -t-butyltrimethylsilyloxy-5 α,β -(2-hydroxyethyl)-3 β -methyltetrahydrofurans 38 and 39. Preparation of 3 α -benzyloxy-5 α -(2-bromoethyl)-2 β -methyltetrahydrofuran 43 completed synthesis of a segment corresponding to the northwest quadrant of boromycin.

INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS
OF CITRACONIC AND MESACONIC ESTERS

and

STUDIES ON THE SYNTHESIS OF THE NORTHWEST AND
SOUTHEAST SEGMENTS OF BOROMYCIN

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Redacted for privacy

Dean of Graduate School

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Typed by Helena Smith for Bernard G. Sheldon

To Monique, always joyful.

Our birth is but a sleep and a forgetting:

The soul that rises with us, our life's star,

Hath had elsewhere its setting,

And cometh from afar:

Not in entire forgetfulness,

And not in utter nakedness,

But trailing clouds of glory do we come

From God, who is our home:

Heaven lies about us in our infancy!

Wordsworth

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The financial and moral support which came from my parents and from Maria and which was so necessary and so generously given is a happy debt we owe. Finally, to Nikki, who knows better than anyone else that it wasn't easy, thanks for trying so hard. Without you I could not have done it.

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PART I

INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS OF CITRACONIC AND MESACONIC ESTERS

A. INTRODUCTION

The Diels-Alder reaction is a well-known and widely used cycloaddition in which a conjugated diene unit A reacts with an olefin B, the dienophile, to form a cyclohexene derivative C (Figure 1).

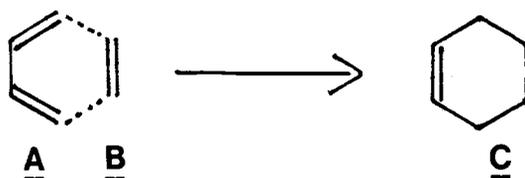


Figure 1.

Woodward and Hoffmann have shown that a concerted pericyclic reaction will be thermally allowed if it has an odd number of bonds reacting in a suprafacial sense (1). For a reacting π system, a suprafacial process is one in which σ bond formation takes place on the same side at both ends of the π system; more precisely σ bonds are generated using p-orbital lobes of the same sign so that "orbital symmetry is conserved." A stereochemical consequence of this principle for the Diels-Alder reaction is that groups R_1 and R_2 occupy a cis relationship in the newly formed cyclohexene (Figure 2). In fact, the Diels-Alder reaction is found to almost invariably produce the cis products predicted

from a concerted 1,4-cycloaddition. It is frequently assumed, therefore, that the reaction is indeed concerted.

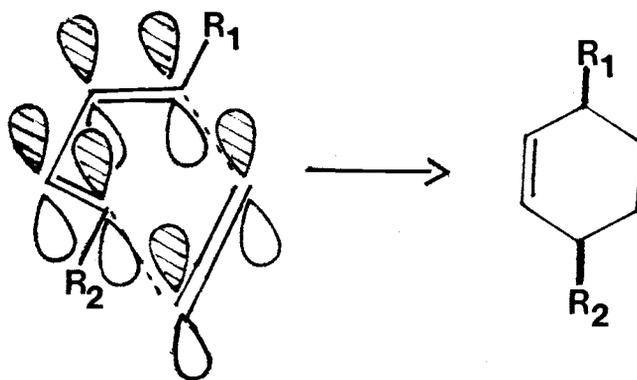
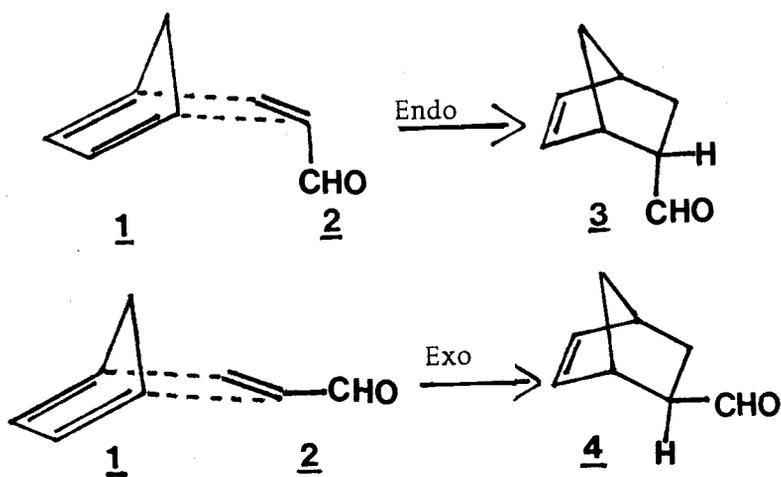


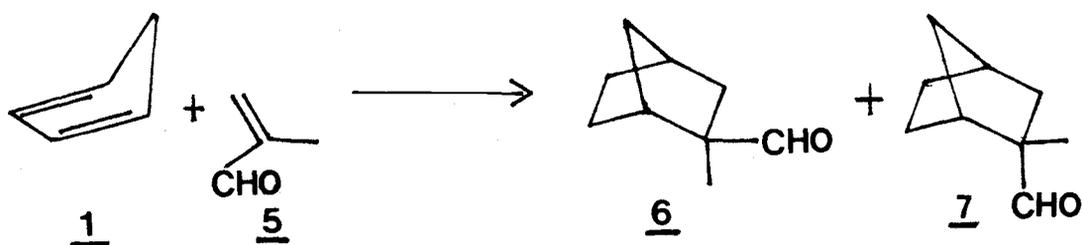
Figure 2.

A second feature of the Diels-Alder reaction is the preference of the reactants to form endo products rather than the thermodynamically favored exo products, a generalization which is summarized in the Alder rule (2). This principle is illustrated by cyclopentadiene 1 in reaction with a dienophile, such as acrolein 2. In this case, preference for the



endo isomer 3 over the exo structure 4 is 3 to 1 (3,4). While the endo product usually predominates in the Diels-Alder reaction, exceptions

are common. For example, with methacrolein 5 and cyclopentadiene the ratio of 6 (exo with respect to the aldehyde) to 7 is 4 to 1 (3,5). The definitive explanation for endo preference has not been presented, but is probably a combination of factors which vary in relative importance from case to case, and which include the Woodward-Hoffman concept of



secondary orbital overlap (6), the improved geometry of primary orbital overlap in the endo transition state (7), dipole interactions (8,9), and steric hindrance between substituents in special cases (10).

The third aspect of the Diels-Alder reaction which must be considered is its regiochemistry. When two unsymmetrical components (A and B) react, the products will be predominantly the "ortho" or "para" substituted cyclohexene (Figure 3). An examination of the dipole interactions in the diene and dienophile will usually provide a reliable means for predicting the orientation of substituents on the products. Thus, the electropositive terminus of the dienophile will bond with the electronegative end of the diene. This somewhat simplistic view has been reinforced by molecular-orbital considerations (11). Superimposed on these various factors influencing the Diels-Alder reaction is its large negative entropy of activation. For example, additions to

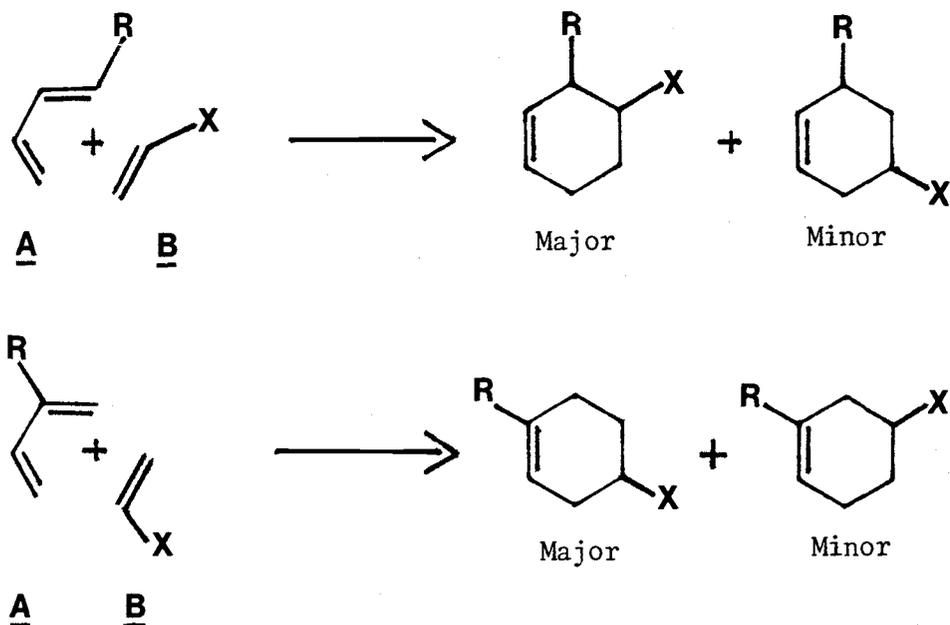


Figure 3.

cyclopentadiene show a ΔS^\ddagger of about $-35 \text{ cal mole}^{-1} \text{ deg}^{-1}$ (12). This implies a high degree of order in the transition state.

The intramolecular Diels-Alder reaction is simply a variation in which the diene and dienophile are part of the same molecule. In its simplest form, the intramolecular reaction can be represented by linking the two reactants together with a single connecting chain. This connection of the two reacting species imbues the intramolecular variant with certain important features not found in the intermolecular Diels-Alder reaction. The first of these is regioselectivity. A short connecting link between the diene and dienophile portions of the molecule will limit reaction to orientation C and prevent cycloaddition through the alternative mode D (Figure 4). This aspect of the intramolecular

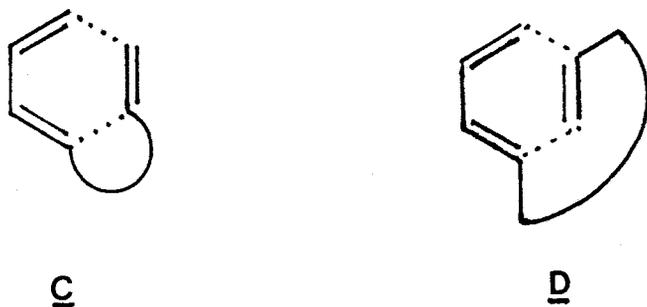
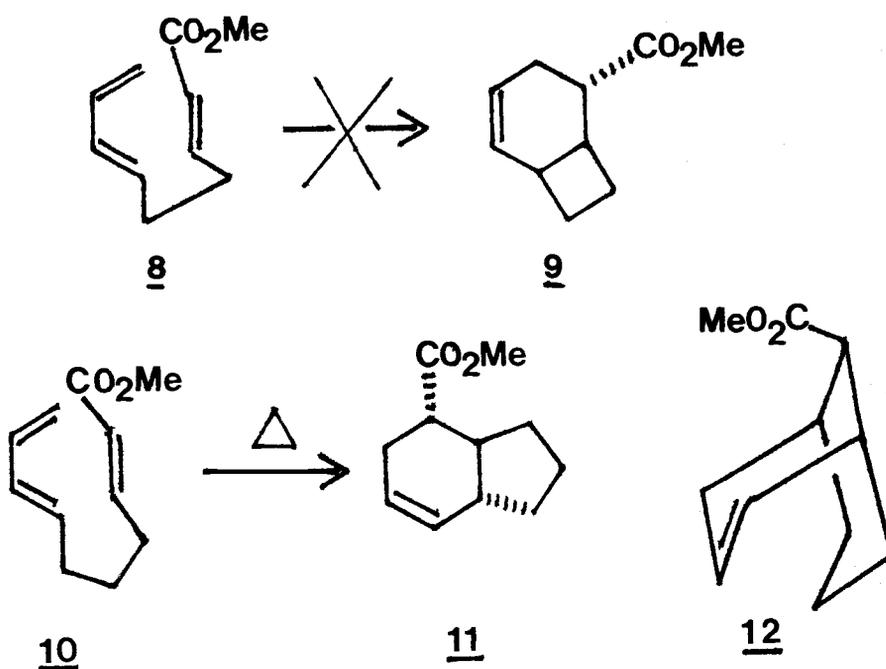
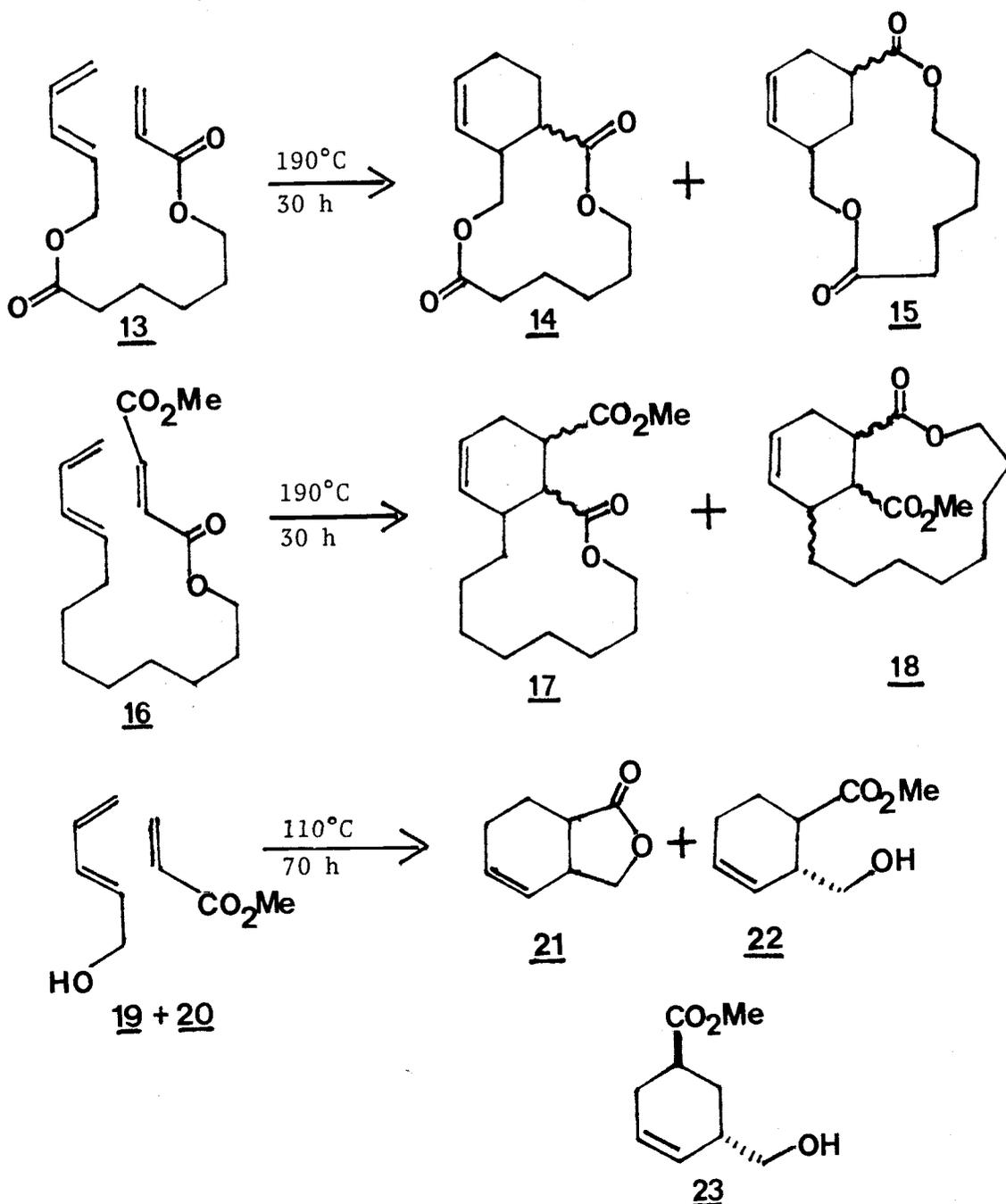


Figure 4.

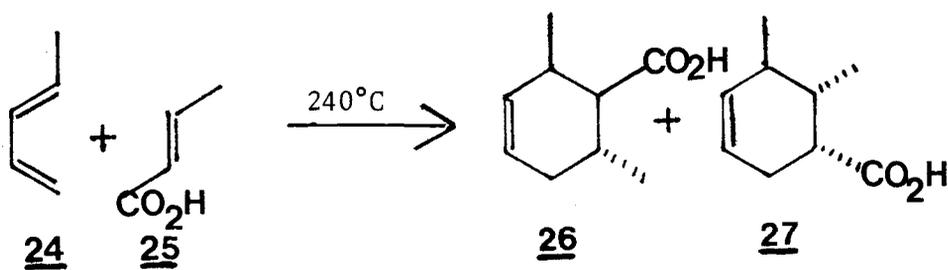
Diels-Alder reaction was studied by House and Cronin (13), who found that although 8 could not be cyclized to 9, 10 gave a single fused bicyclic 11. The latter must arise via a transition state analogous to C. This demonstrates that a two-atom chain is not long enough for the two reacting segments to adopt the proper orientation for cyclization, whereas a three-atom linkage is sufficient. However, the absence of bridged product 12 shows that a three-atom chain is too short to allow cyclization through mode D.



Cycloaddition through mode D, however, is possible when the chain linking the diene segment of the molecule to the dienophile segment is longer than about ten atoms. Corey and Petrzilka (14) examined the intramolecular Diels-Alder cycloaddition of 13 and 16 and found that 13 gave a 13:1 mixture of fused to bridged products, 14 and 15, representing the preference for cyclization via orientation C over D. It should be noted



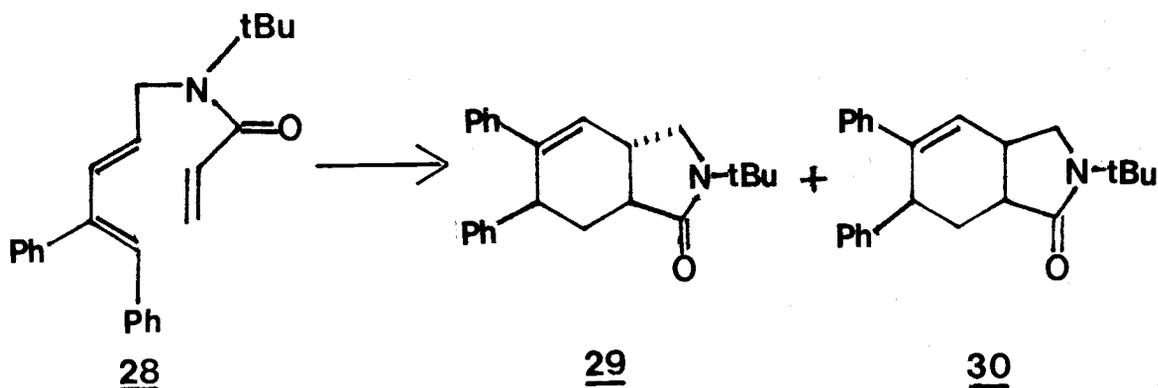
that this reaction has a marked electronic preference for this regioselectivity, as shown by the results of the intermolecular cyclization of 19 with 20 which yields a 5.4:1 mixture of 1,2 (21 and 22) to 1,3 (23) substituted isomers. Diester 16 offers a more valid test of regioselectivity in the intramolecular cyclization, and affords an approximate 2:1 mixture of fused to bridged products (17 and 18). The dienophile segment in the analogous intermolecular reaction would be dimethyl fumarate and would thus exhibit no regiochemistry. The work of House and Cronin (13) also illustrates the ability of the connecting link to control regiochemistry in intramolecular cycloaddition. The intermolecular reaction of piperylene 24 and crotonic acid 25 produces a 9:1 mixture of 26 and 27, the expected "ortho" versus "meta" substituted cyclohexenes. Due to the shortness of the connecting link, only



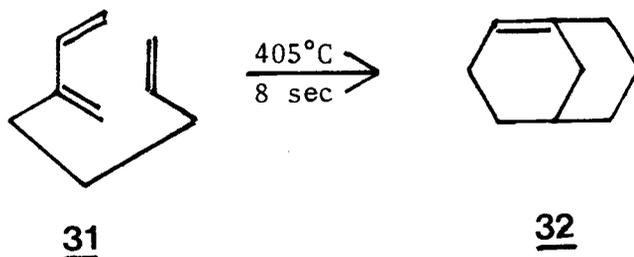
the product analogous to the minor constituent 27 was formed in the intramolecular case, exemplified by the cyclization of 10 to 11.

A significant advantage inherent in any intramolecular process is the enhanced reactivity resulting from the enforced proximity of the reacting entities. A study of the cyclization of amide 28 to lactams 29 and 30 revealed that the entropy of activation (ΔS^\ddagger) was $-14.4 \text{ cal mole}^{-1} \text{ deg}^{-1}$ (15,16). By contrast the ΔS^\ddagger of intramolecular Diels-Alder reactions

is generally between -30 and -40 cal mole⁻¹ deg⁻¹ (12,17). This



translates to a 5-7 kcal/mole lower free energy of activation (ΔG^\ddagger) for the intramolecular reaction (17). Shea's synthesis of the strained anti-Bredt olefin 32 from 31 demonstrates this energetic advantage of the intramolecular Diels-Alder reaction (18).



There are several stereochemical features associated with the intramolecular Diels-Alder reaction that can be predicted as a result of constraints resulting from the geometry of the starting material and from the orbital considerations discussed in connection with the intermolecular reaction. First, due to the suprafacial characteristic of the cycloaddition, the substituents at carbons 4 and 5 (see Figure 5) must retain the relative configuration that they held in the original olefin, whether cis or trans. The stereochemical outcome at the diene terminus can be predicted on the same basis, so that for trans, trans dienes the

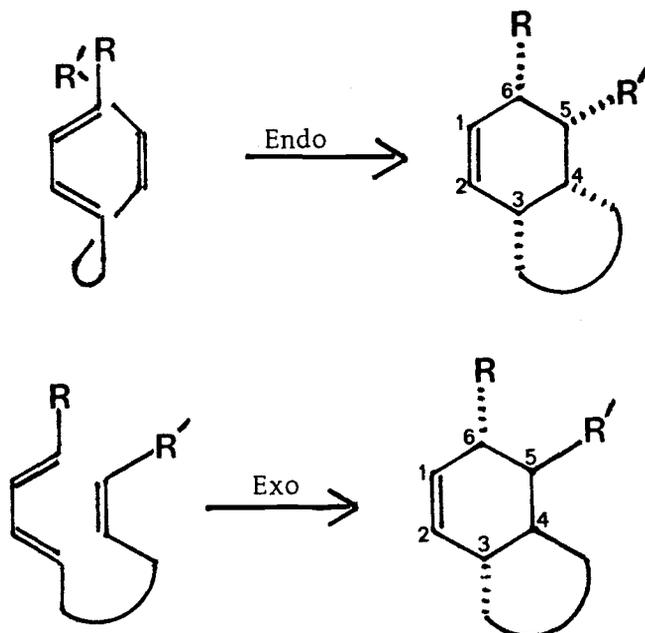


Figure 5.

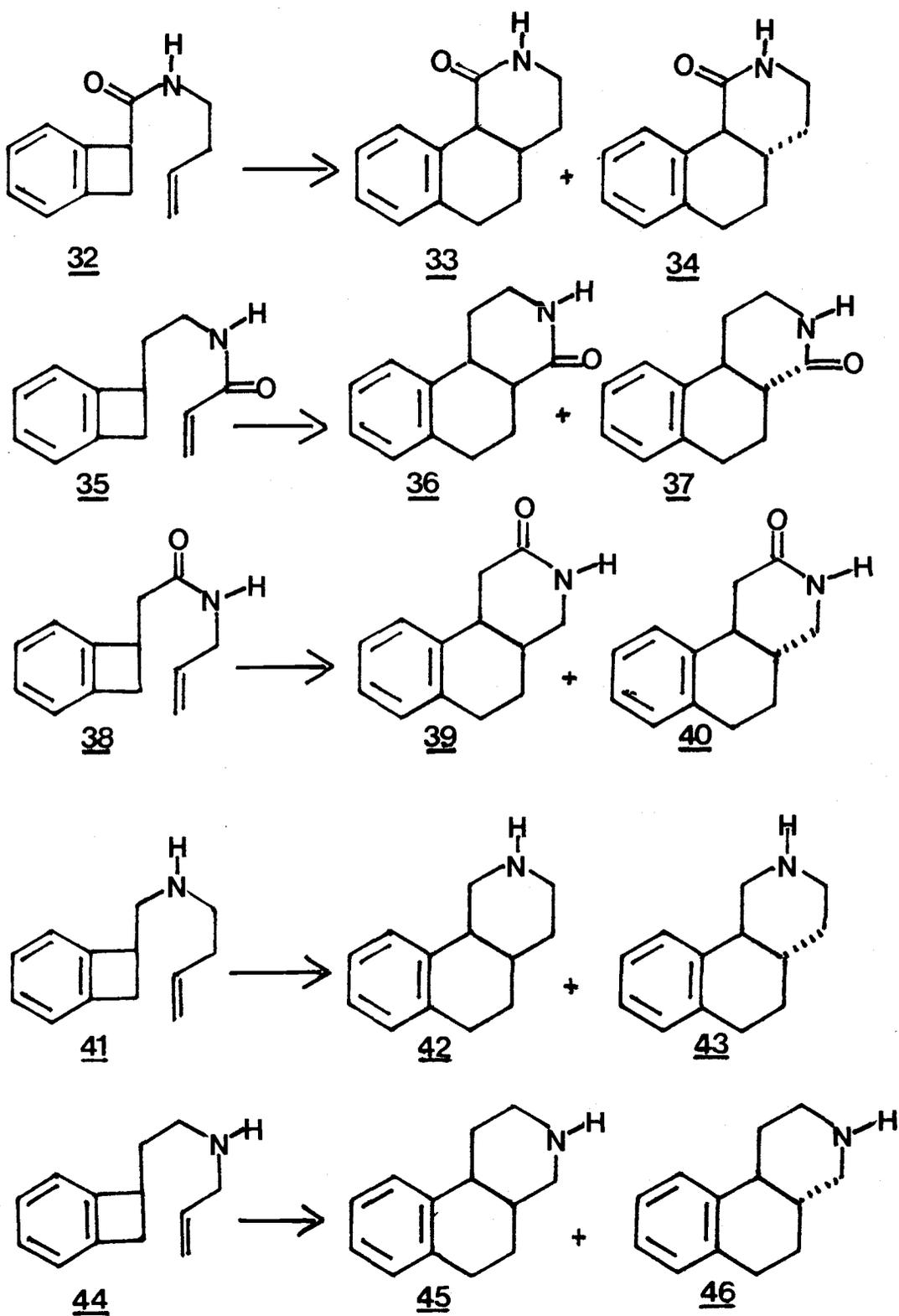
configuration of the substituents at carbons 3 and 6 in the cyclohexene product will be cis. Finally, the selection between exo and endo modes of cyclization (see Figure 5) controls the relative configuration at carbons 3 and 4; this will be trans when the exo mode is followed, cis when the endo mode prevails.

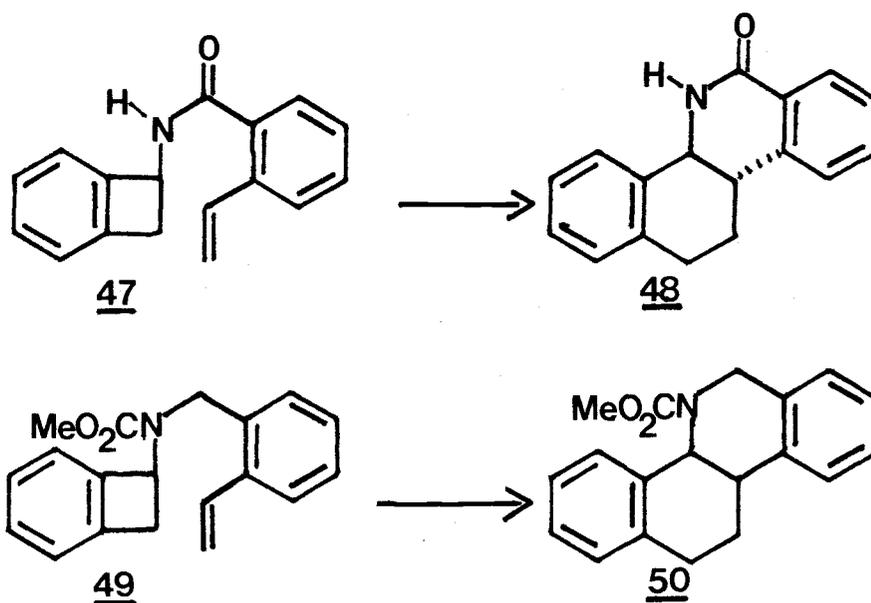
For an intramolecular cycloaddition of a trans, trans diene and cis substituted olefin which proceeds via the endo mode (Figure 5), the linking chain and terminal substituent lie underneath the diene during cyclization as shown and the product will therefore be an all-cis substituted cyclohexene. In particular, the ring fusion will be cis. In the exo mode of cyclization, the product will be a cyclohexene which is trans fused to the second ring. For dienophiles which are trans substituted there is an ambiguity over which group--the connecting link or

the substituent on the terminus of the olefin--defines the exo/endo orientation. For the purposes of this discussion, the orientation of the connecting link with respect to the diene will be used to define the mode of cyclization. By the use of this convention, all cis fused products of the intramolecular Diels-Alder reaction are formed via the endo mode of cyclization and all trans fused products are the result of exo cyclization.

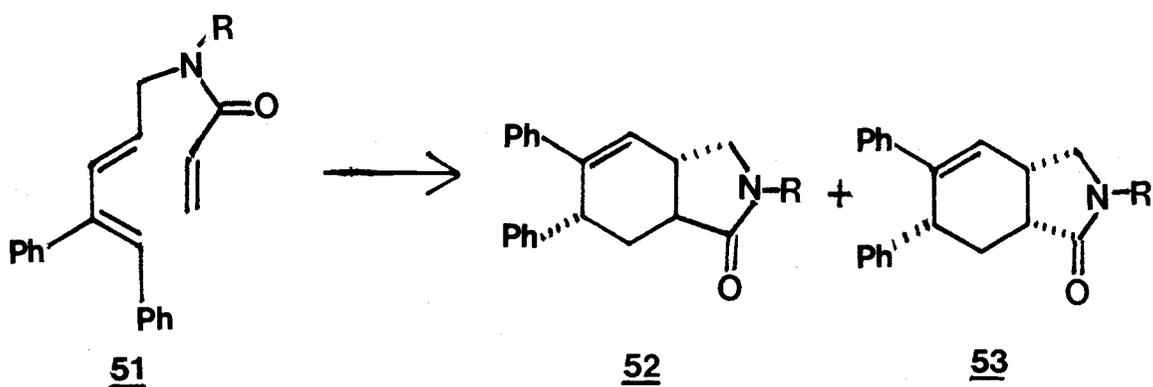
The nature of the connecting chain is highly influential on the ratio of endo to exo cyclization in the intramolecular Diels-Alder reaction. Oppolzer has studied the cyclization of amides 32, 35, 38 and amines 41 and 44 (19,20,21). Heating the amides to 180°C for 16 hours caused in situ formation of the o-quinodimethanes which then cyclized to form the cis fused tricyclic lactams 33, 36 and 39 in ratios varying from about 2:1 to about 5:1 over the trans lactams 34, 37, and 40. In contrast, the amines 41 and 44 showed a preference for exo cyclization, yielding a 3:1 ratio of trans product 43 over cis fused amine 42 from 41 and a 7:1 ratio of 46 to 45 from 44. An interesting extension of this work has been presented, also by Oppolzer (22). In exploratory work directed toward the synthesis of d,1-chelidonine, he found that the amide 47 cyclized to give the trans lactam 48 under identical conditions to those used in the preceding work which afforded predominantly cis lactams. Furthermore, the urethane 49 produced the cis amine derivative 50 rather than the expected trans fused product.

Gschwend has studied the intramolecular Diels-Alder addition of very similar systems (16) and found that the amides 51 produced an approximate 1:1 mixture of 52 and 53, the cis and trans fused γ -lactams derived from endo and exo additions respectively. These cycloadditions

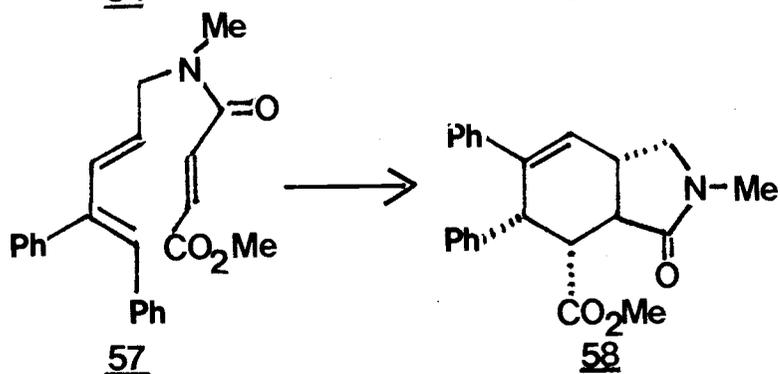
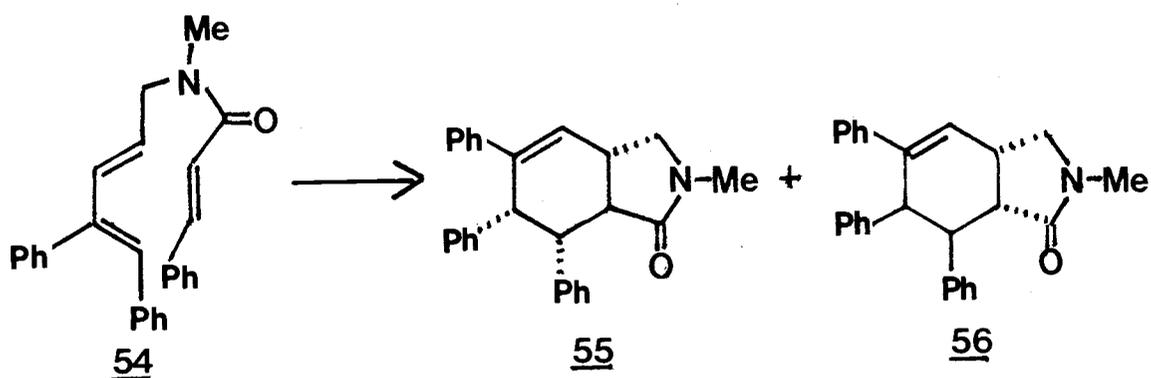




took place between room temperature and 110°C, with the larger N-alkyl groups causing increased reaction rates at low temperature, probably by forcing the two reacting segments into contiguity. The substitution of a phenyl group at the terminus of the dienophile olefin, as in 54, resulted in further preference for exo cyclization, the ratio of trans to cis cycloadducts, 55 to 56, being 8:1. The reaction rates were increased by the introduction of a distal substituent on the dienophile, the cycloaddition of 54 being performed at 90°C for 8 to 12 hours, while 57 cyclized at 0°C. The increasing proportion of fusion products 55 and 58 appears to reflect a preference of the terminal substituent for endo geometry, in accord with the Alder rule. In a trans dienophilic olefin, this effect reinforces the tendency of the carbonyl group in the chain to adopt an exo orientation. This cooperative effect becomes sufficiently pronounced that the alternate cis adduct from 57 is not observed. In contrast with these results, where the linking units

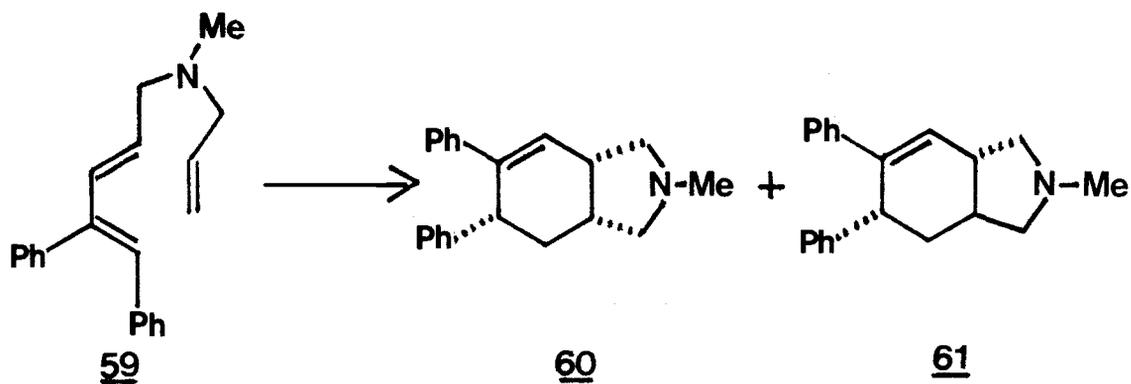


R = Me, Et, i-Pr, t-Bu

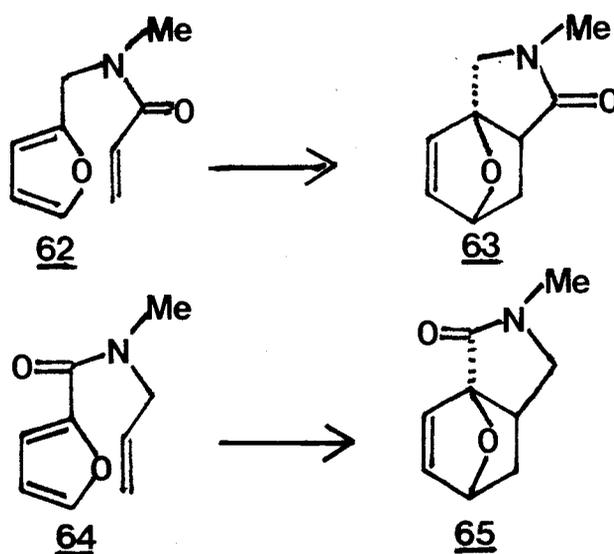


between diene and dienophile contain a carbonyl, the allylamine derivative 59 showed high preference for endo cyclization when heated at 140°C for 12 hours, yielding a 5:1 ratio of cis over trans fused isomers, 60 and 61.

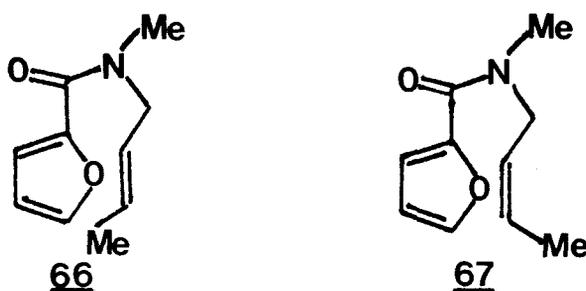
Parker (23) has examined similar cycloadditions using furan as the diene component. For example, amides of the type 62 were converted



to 63 upon heating to 80° for 6 days. The amide 64 cyclized to produce

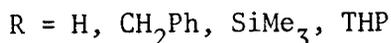
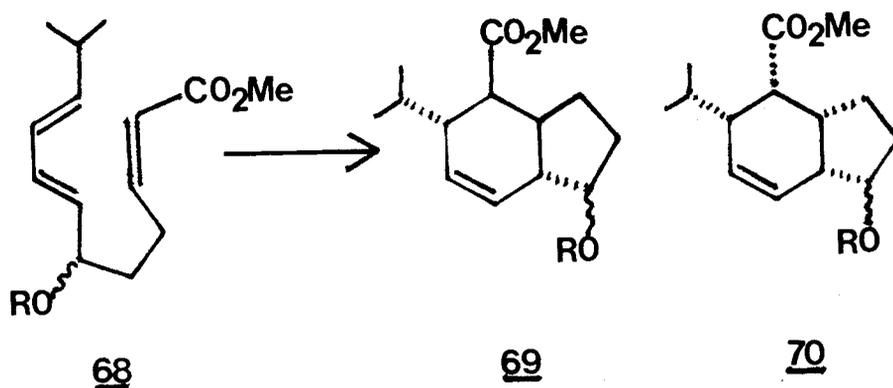


γ -lactam 65 in excellent yield, but substitution at the β -carbon of the dienophile prevented cyclization, since compounds 66 and 67 failed to

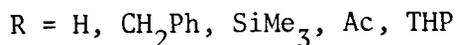
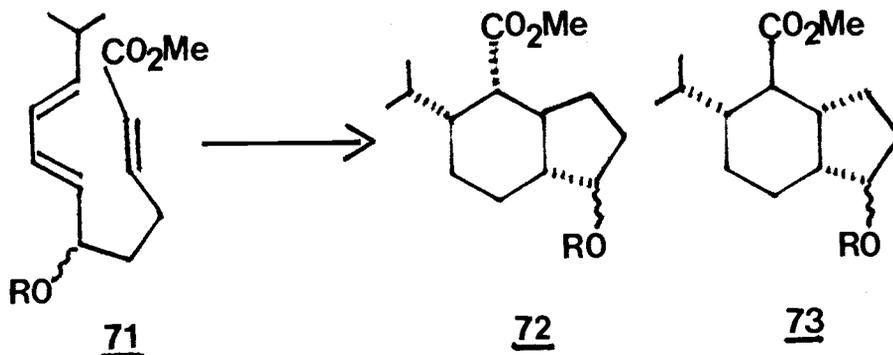


produce cycloadducts when heated under the same conditions.

Roush studied the cyclization of trienes related to 10 in the course of his synthesis of dendrobine (29, 25). For example, 68 closed to a mixture of trans and cis tetrahydroindanes 69 and 70, with ratios of ring fusion isomers ranging from about 2:1 to 3.3:1. The trans



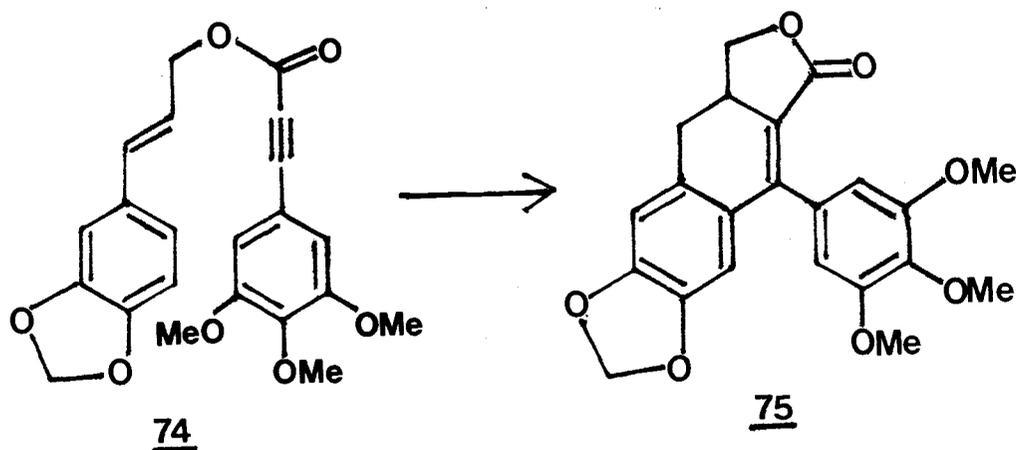
dienophile in 71 caused little change in the ratio of exo versus endo cycloaddition, the ratios of trans to cis products (72 to 73) ranging from about 2.2:1 to 5:1. This observation is somewhat surprising since,



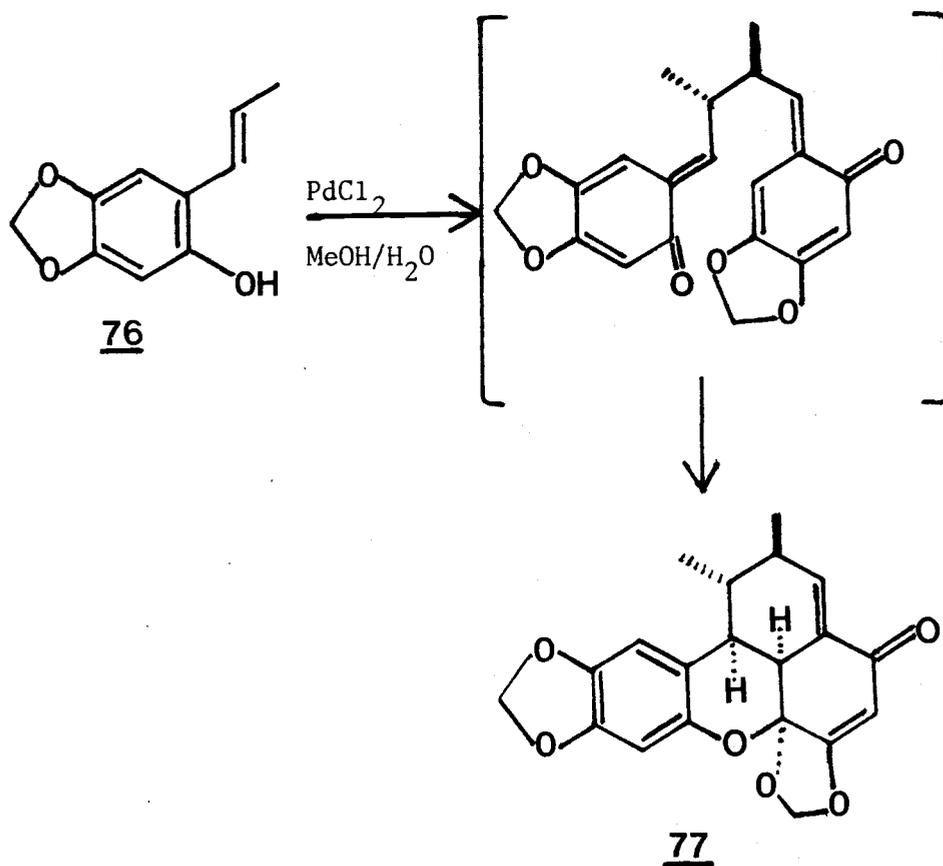
in light of Gschwend's results (16), one would have expected a much higher preference for the formation of 72 through the reinforcing effect of the endo ester interaction. The conformational requirements of the

connecting chain must override any effect due to the ester.

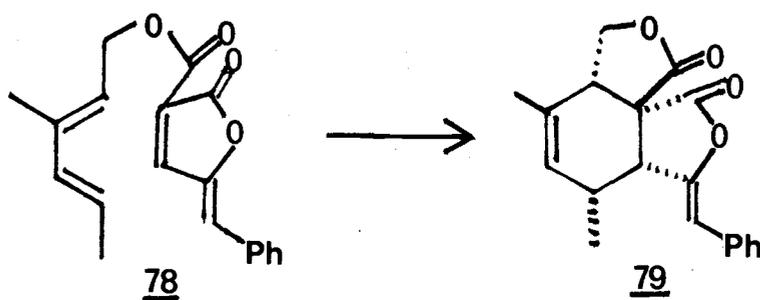
The ability of the intramolecular Diels-Alder cycloaddition to predictably and stereoselectively convert an acyclic precursor into an often highly functionalized bicyclic product has made it of great interest to synthetic organic chemists. Applications of this reaction to natural products chemistry have burgeoned since the first rational use of the reaction by Brieger (26) and by Klemm (27) in 1963. Klemm's synthesis of γ -apopropodophyllin 75 is an especially conspicuous landmark in the use of the intramolecular Diels-Alder reaction (28), and constitutes an excellent example of the formation of a complex, fused ring system from a relatively simple precursor.



The biogenetically patterned synthesis of (\pm)-carpanone 77 by Chapman (29) further illustrates the remarkable ability of the intramolecular Diels-Alder reaction to introduce relative stereochemistry in a controlled fashion. The phenolic coupling of two molecules of 76 yields a bis-o-quinodimethide, which undergoes spontaneous cycloaddition to yield 46% of 77. Yet another demonstration of the tremendous power of the intramolecular Diels-Alder reaction is the cyclization of the



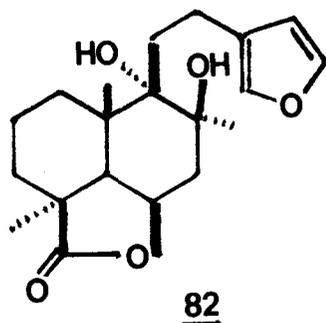
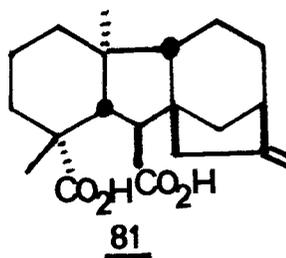
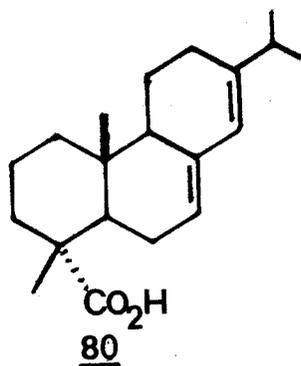
relatively simple, achiral butenolide ester 78 to the highly complex bis lactone 79 which displays the correct relative configuration at all four of the chiral carbons in the newly formed cyclohexene (30) for use as an intermediate in Weinreb's proposed synthesis of proxiphomine.



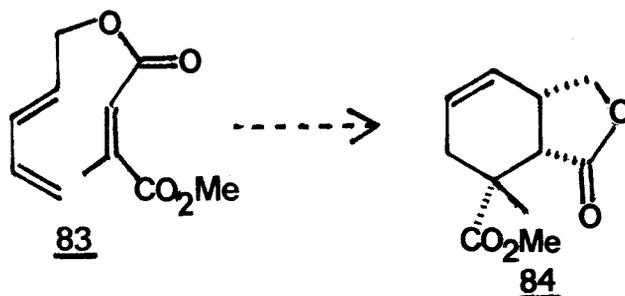
Recent examples of the continuing expansion in the application of the intramolecular Diels-Alder addition to natural products synthesis can be found in Roush's synthesis of (\pm)-dendrobine (24), in the synthesis of (\pm)- α -lycorane By Stork's group (31), in the steroid syntheses by Kametani (32), and by Vollhardt (33), and in the synthesis by Breitholle of (\pm)-cedrene (34).

B. DISCUSSION AND RESULTS

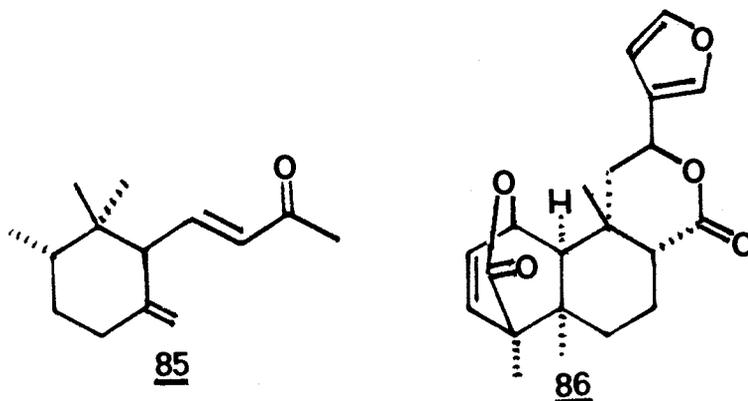
Many terpenoids contain highly functionalized cyclohexane rings as the nucleus of their structures. For example, abietic acid (80) (35), gibberellin A₂₄ (81) (36), and leonitin (82) (37) each displays a cyclohexane ring with a 1,1,2,3,3 substitution pattern. In principle, segments



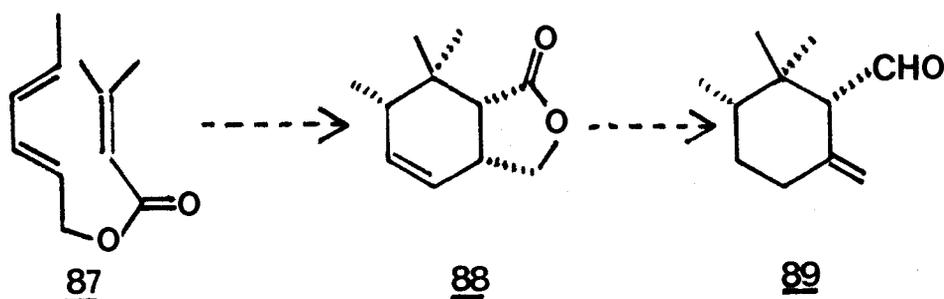
of these structures should be accessible through the intramolecular cycloaddition of an acyclic system such as 83. If this Diels-Alder reaction takes place in a regio- and stereoselective fashion as expected, the bicyclic adduct 84 (resulting from the endo mode of addition) would contain a cyclohexane with four substituents and three contiguous asymmetric centers in the relative configuration shown.



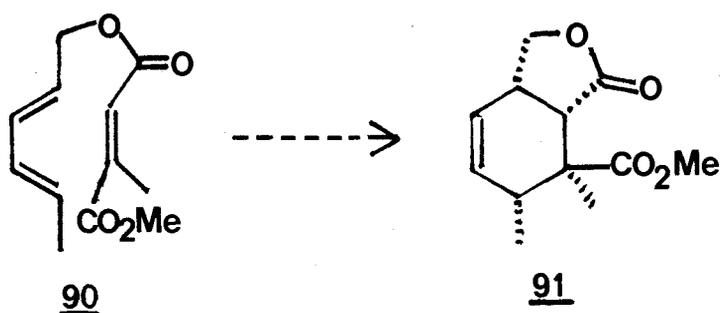
The irregular terpenoids, for example γ -irone (85) (38), and the clerodane family, of which columbin (86) (39) is a member, might also be amenable to synthesis using the intramolecular Diels-Alder cycloaddition to produce a functionalized cyclohexane intermediate for further elaboration. Thus, cyclization of 87 should give 88, which displays the



substitution pattern and relative stereochemistry at C-1 and C-6 needed for a synthesis of the irones. Subsequent adjustment of functionality can be envisaged leading to 89, which would afford an ideal synthon for γ -irone. Likewise, the production of 91 from 90 can be visualized as a useful starting point for the clerodanes since, again, the intramolecular

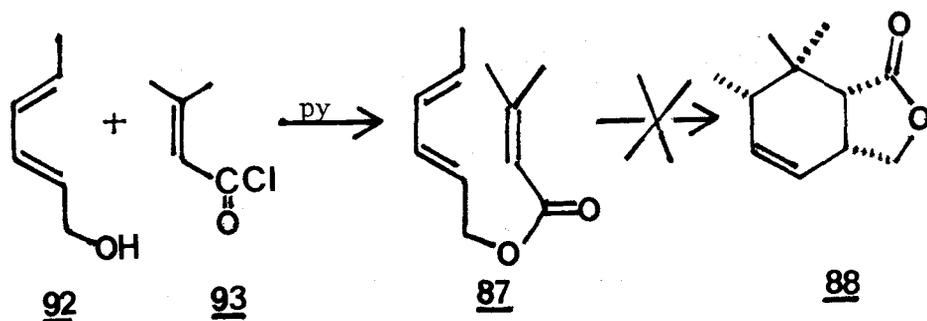


cycloaddition provides firm stereochemical control and opportune placement of functionality for elaboration of the additional ring system.



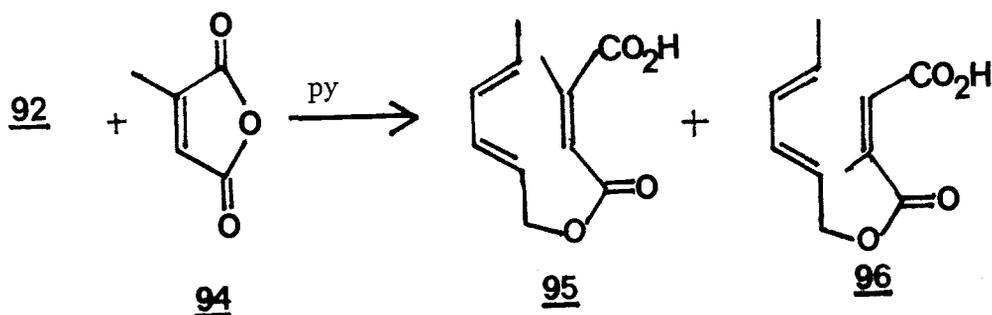
Therefore, we set out to study the intramolecular Diels-Alder reactions of several acyclic esters related to 83, 87, and 90 in the expectation that our findings should be applicable to the synthesis of systems similar to the natural products exemplified above.

The first system investigated was the β,β -dimethylacrylic ester 87, prepared by esterification of commercially available sorbyl alcohol 92 with the acid chloride of β,β -dimethylacrylic acid 93. Regrettably, all attempts to effect an intramolecular Diels-Alder cycloaddition of 87 failed. Reaction conditions examined included heating 87 to 300°C and treatment of the triene with up to one equivalent of a Lewis acid (stannic chloride or boron trifluoride). Relatively mild conditions



returned starting material whereas more severe ones generated intractable mixtures. Steric compression in the transition state arising from the geminal dimethyl groups on the terminus of the dienophile of the molecule in proximity to the terminal methyl on the diene is probably the major reason for the failure of this cyclization. In addition, the two methyl groups in the acrylate moiety reduce its dienophilic character by their inductive effect.

The incorporation of a more reactive dienophile into a system such as 87 was expected to enhance the prospect of cycloaddition. Thus, acylation of sorbyl alcohol with citraconic anhydride 94 gave a 1:1

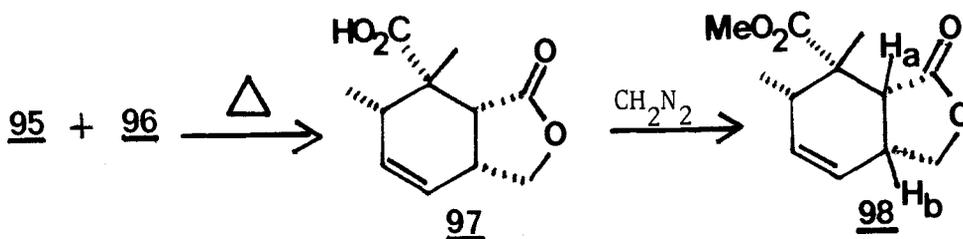


mixture of the regioisomers 95 and 96 which were inseparable by chromatography. Esterification of the mixture with diazomethane gave a mixture of esters which showed two three-proton singlets of equal size in the

δ 3.6 to 3.8 region of its nuclear magnetic resonance (NMR) spectrum.

Heating the mixture of isomeric acids in refluxing xylene for a day, followed by concentration and crystallization from chloroform yielded a single cycloadduct 97 in 25% yield based on sorbyl alcohol. The infrared spectrum (IR) indicated the presence of a γ -lactone (1765 cm^{-1}) and the NMR spectrum was compatible with the structure 97, showing two olefinic protons (δ 5.8 and 5.6), an oxygenated methylene group (δ 4.4-4.2) and two saturated methyl groups (a three-proton singlet at δ 1.5 and a three-proton doublet with a coupling constant of 6 Hz at δ 1.2). Thin-layer chromatographic (TLC) analysis, as well as the NMR spectrum, of the mother liquors showed a complex mixture resulting from polymerization of residual 95 and 96.

Confirmation of the cis fused γ -lactone was obtained by esterification of 97 with diazomethane in ether to produce 98. The NMR spectrum showed a 9 Hz coupling constant of H_a (δ 3.05, doublet) to H_b which is consistent with a cis fusion (40, 41). Reduction of 98 with excess diisobutylaluminum hydride at -70°C yielded a product which proved to be



the acetal 99. The NMR spectrum showed an acetal proton (δ 5.8, s) and two pairs of oxygenated methylene protons (δ 4.2 to 3.5), and the IR spectrum demonstrated the absence of an ester. This substance would be obtained only if the three oxygenated substituents in the precursor

ester were all cis (42). Final confirmation of the structure and relative stereochemistry of the acid 97 was obtained by an X-ray crystallographic study performed by Dr. Jon Clardy at Iowa State University. A three dimensional representation of 97 deduced from the X-ray data is shown in Figure 6.

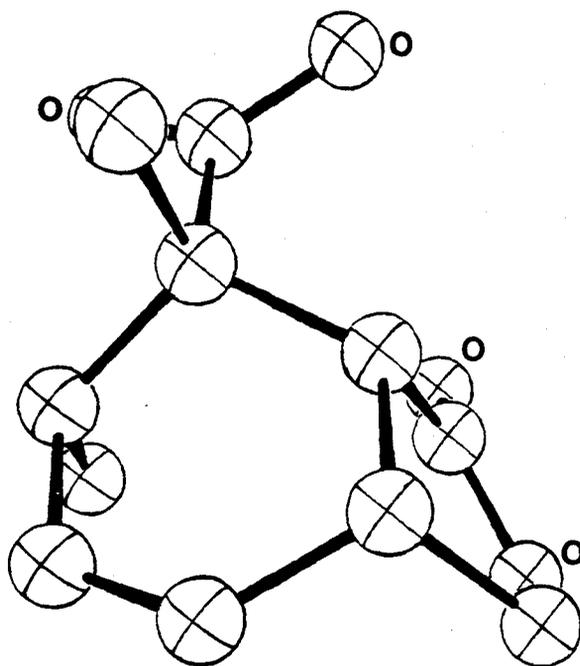
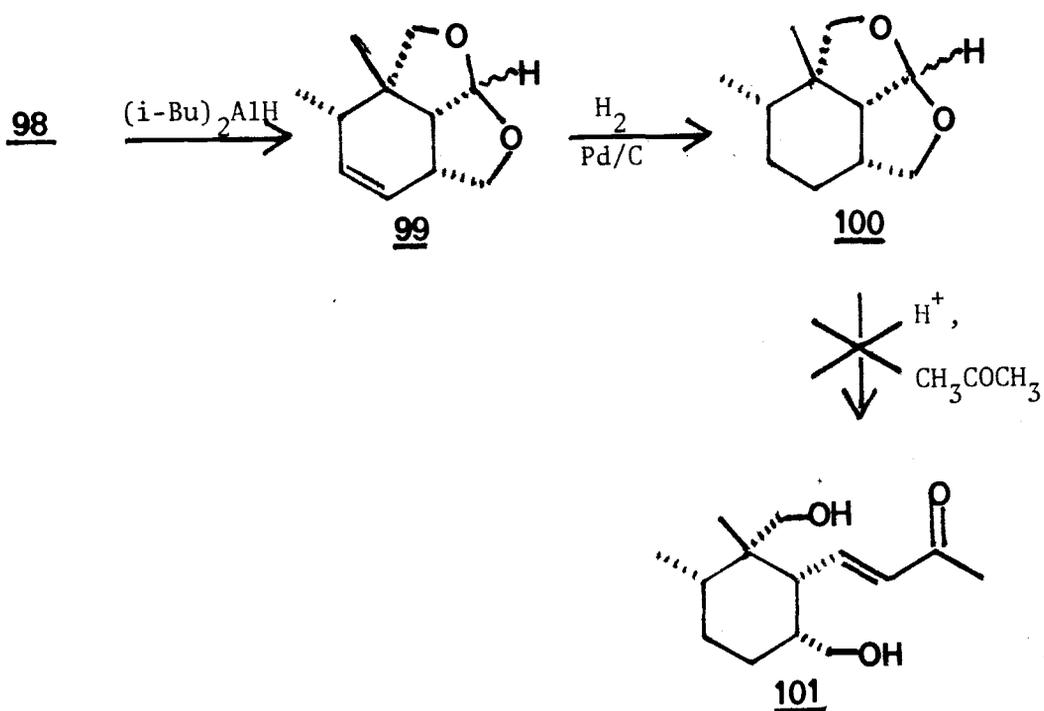


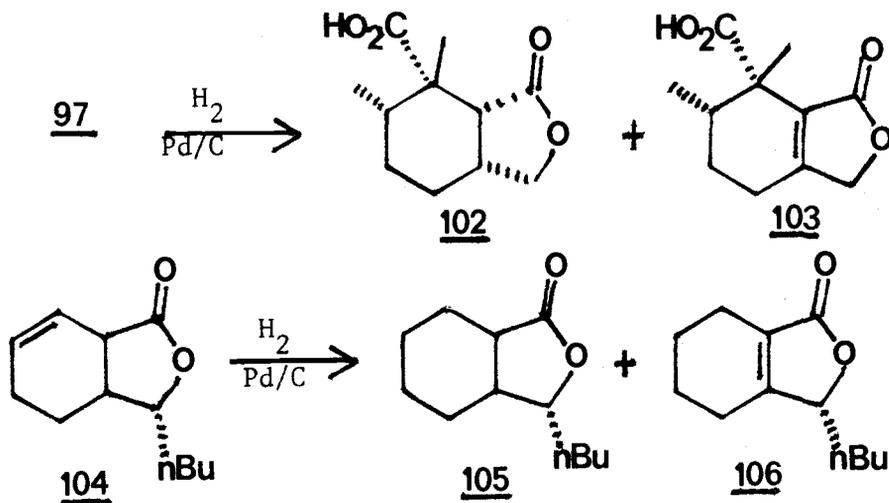
Figure 6.

Hydrogenation of the olefin 99 afforded the dihydro derivative 100. Attempts were made to open the acetal function of the latter by acidic hydrolysis in acetone, but all failed to produce the desired acid-catalyzed aldol product 101. Hydrogenation of 97 over a palladium catalyst produced a mixture of the saturated lactone 102 and an olefin isomerization product 103, whereas reduction of 87 with Adams' catalyst produced 102 cleanly. Precedent exists for double bond migration in a

similar system during hydrogenation (43). Thus, when compound 104 was

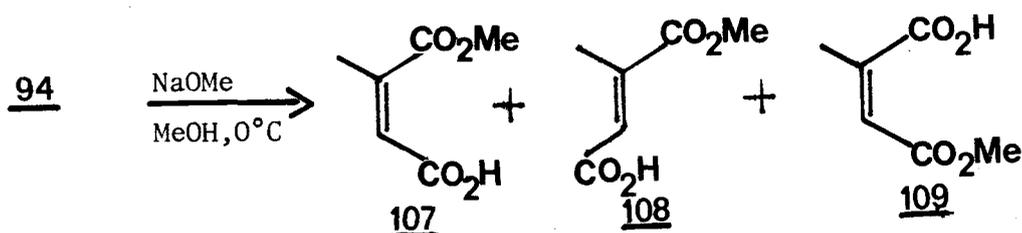


hydrogenated over palladium on charcoal, a 95:5 mixture of 105 and 106 was obtained. Hydrogenation of 104 over Adams' catalyst produced only 105.

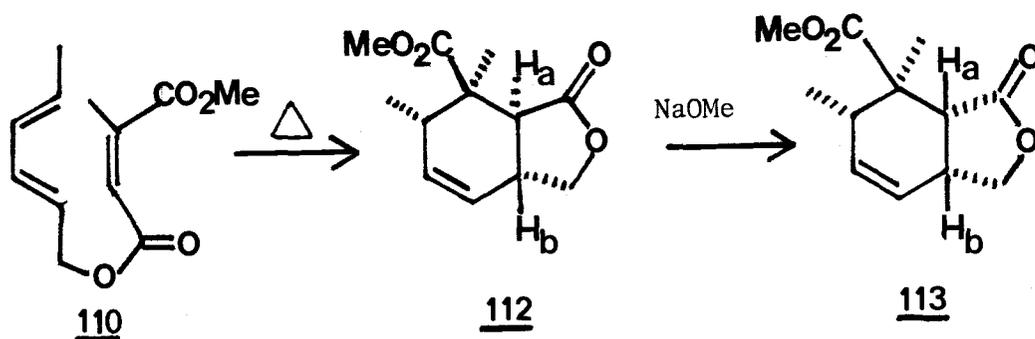


The formation of a 1:1 mixture of regioisomers 95 and 96 in the citraconic anhydride acylation of sorbyl alcohol, coupled to the fact that only 95 apparently underwent cyclization, made this intramolecular

Diels-Alder cycloaddition synthetically unattractive. In this connection, it was interesting to note that a literature report (44) claimed that citraconic anhydride produced mainly one regioisomer, namely 107, when treated with one equivalent of sodium methoxide in cold methanol. Our own results bore this out, although 107 was found to be contaminated with about ten percent each of 108 and 109 by NMR spectroscopy. Treatment of the mixture of half esters 107-109 with oxalyl chloride or thionyl chloride produced a corresponding mixture of acid chlorides which, upon exposure to sorbyl alcohol in pyridine, yielded a mixture of diesters. The citraconate 110 was separated by

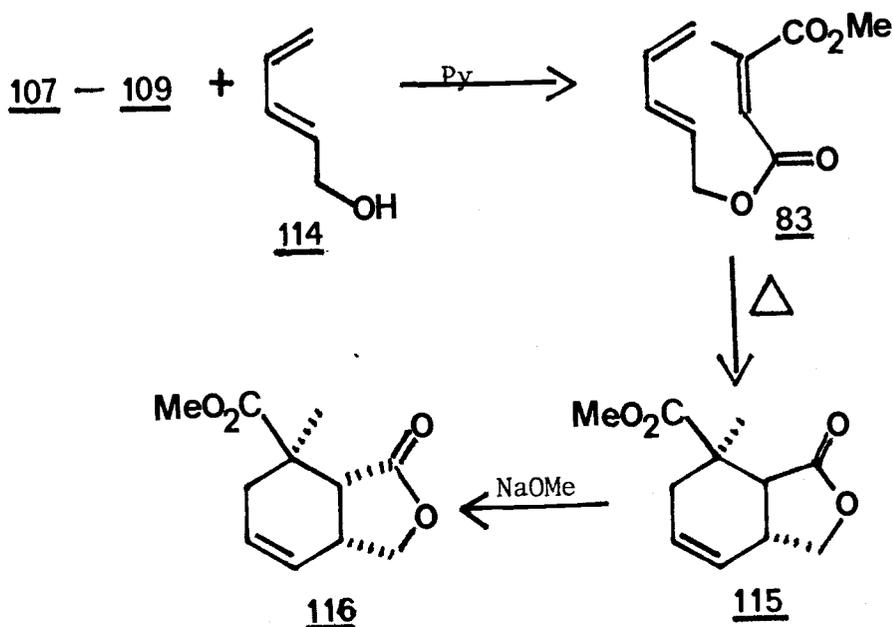


column chromatography and was heated at reflux in xylene for 24 hours under nitrogen in the presence of the radical inhibitor 2,6-di-butyl-p-cresol. The sole product isolated was the trans γ -lactone 112 (1775 cm^{-1}) in 70% yield. The NMR spectrum of 112 showed the proton H_a as a doublet with a 14 Hz coupling constant, clearly consistent with a trans fusion of the γ -lactone. This trans fused lactone is more highly strained than its cis fused counterpart 113, and it was therefore expected that 112 would epimerize when exposed to base. In fact, treatment of compound 112 with 0.1 equivalent of sodium methoxide in methanol afforded a new γ -lactone (1775 cm^{-1}), in which the proton H_a was



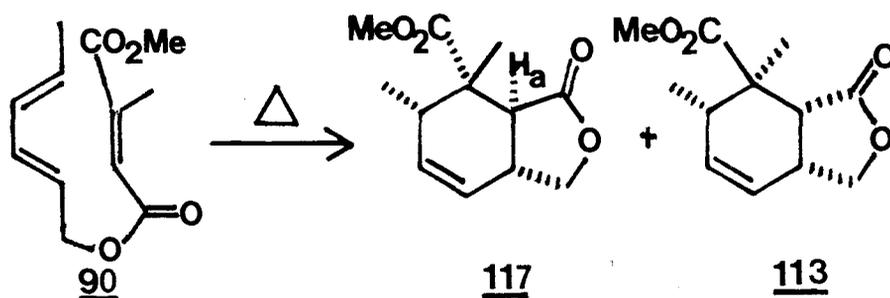
shifted downfield by 1.2 ppm. This is consistent with its location on the same side of the cyclohexane ring as the vicinal ester, and supports the cis fused formulation 113. However, the coupling of H_a was now obscured by coincident signals arising from the allylic protons.

The mixture of acid chlorides from the half acids 107-109 was also treated with 2,4-pentadienol 114, prepared by reduction of ethyl 2,4-pentadienoate with lithium aluminum hydride (43). The major diester 83 was cyclized to 115 in refluxing xylene during 24 hours. Lactone



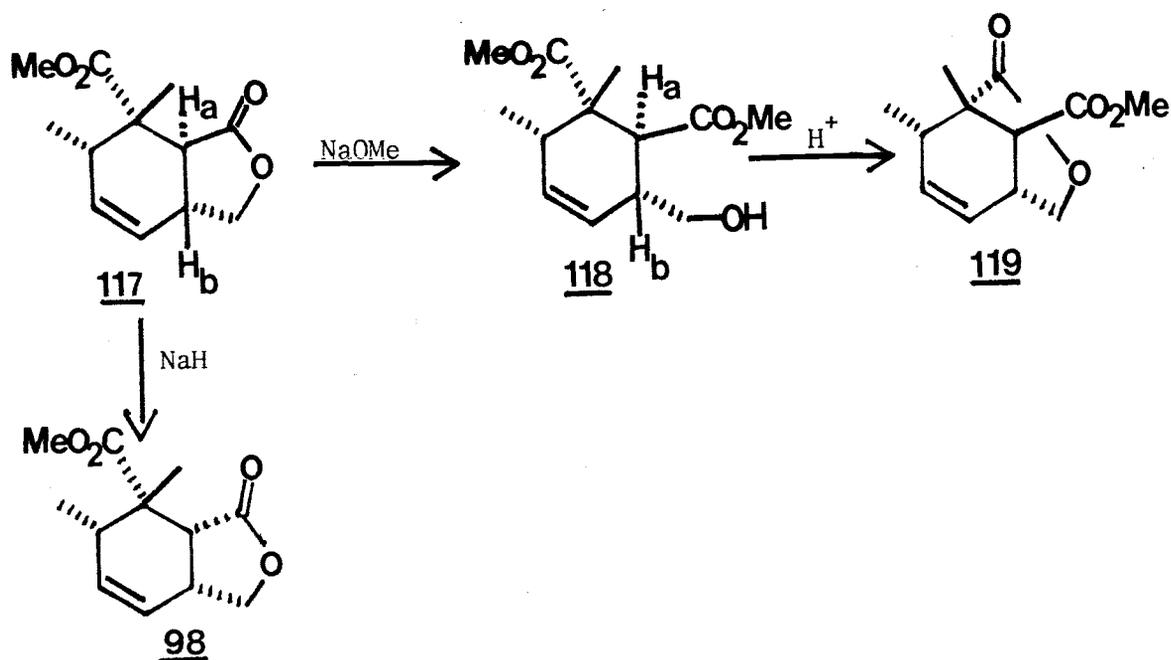
115, obtained in 50% yield, was similar to 112 in its spectroscopic properties. As with 112, the trans fused γ -lactone 115 was susceptible to epimerization, and afforded 116 in good yield when treated with sodium methoxide in methanol.

The mesaconate 90, which was isolated as a byproduct of the acylation of sorbyl alcohol with 107-109, was heated under conditions similar to those used for 110. In this case, Diels-Alder cycloaddition was appreciably slower, and resulted in only 60% conversion after 5 days. A (4.3:1) mixture of 117 and the previously obtained 113 were formed in 84% yield, based on 90 consumed.



Examination of the NMR spectrum of 117 showed the proton H_a at δ 2.8 with its coupling to proton H_b obscured by a coincident resonance. The IR spectrum of 117, with a carbonyl band at 1775 cm^{-1} , established the presence of the γ -lactone. The trans lactone fusion was again expected to be susceptible to basic epimerization to the more stable cis isomer. However, treatment of 117 with sodium methoxide in methanol produced not 98 but a diester 118. The 13 Hz coupling

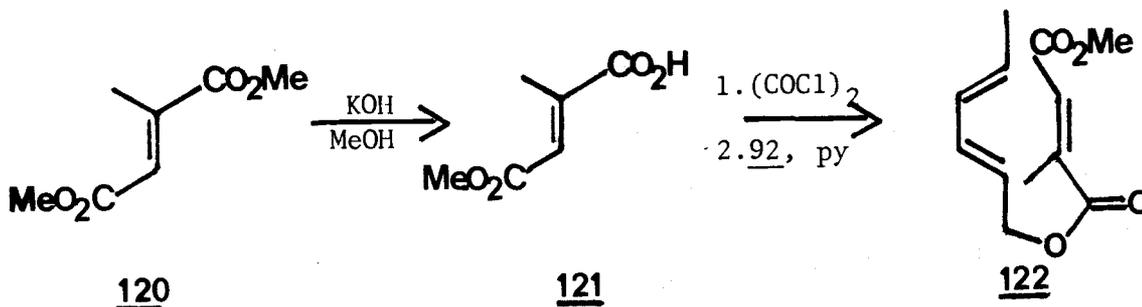
constant of the doublet for H_a indicated that the epimerizable center



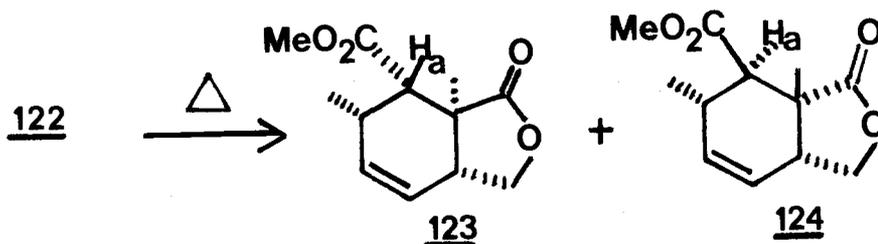
had retained its configuration. The lactone carbonyl in **117** is apparently less hindered than that in **112**, and the lactone ring opens when treated with alkoxide before epimerization can occur. Treatment of **118** with a catalytic amount of p-toluenesulfonic acid in refluxing benzene, using a Dean-Stark apparatus, afforded a new lactone which, according to its IR spectrum (1740 cm^{-1}) was a δ -lactone (30). Structure **119** is assigned to this substance. In contrast with these results, **117** could be cleanly epimerized to the previously isolated ester **98** by treatment with sodium hydride in tetrahydrofuran.

Alkyl substituents at the ring fusion, which are not readily accessible by other routes, should be available via the intramolecular Diels-Alder cycloaddition of compounds with substitution on the proximal end of the dienophile segment. Triene ester **122** was prepared to test this.

Methyl mesaconate 121 was produced by saponification of dimethyl mesaconate 120 (45). Conversion of 121 to its acid chloride, followed

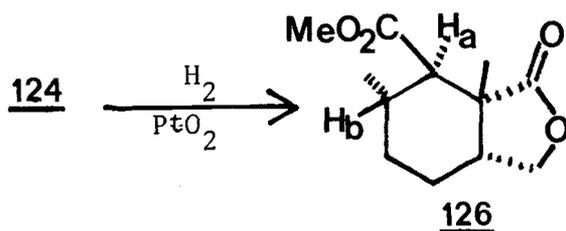
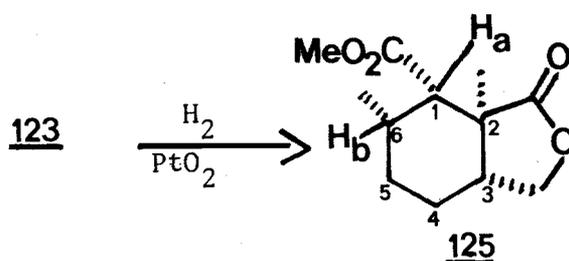


by treatment with sorbyl alcohol in pyridine, gave a good yield of the diester 122. The latter underwent intramolecular Diels-Alder reaction very slowly (eleven days in refluxing xylene) to produce an 85% yield based on 50% conversion of starting material of the lactones 123 and 124. The ratio of 123 to 124 was 4.7:1. The H_a proton in 124 appeared as a doublet with a coupling constant of 12 Hz, suggesting a trans



configuration of the substituents at C-1 and C-6. The analogous coupling in compound 123 was obscured by a coincident allylic proton resonance. In order to put comparison of the coupling constants in the two compounds, and therefore their configuration, on a firmer basis, 123 and 124 were converted to their dihydro derivatives 125 and 126 by hydrogenation with Adams' catalyst in ethyl acetate. The coupling of H_a was now clearly visible in 125 and was 5 Hz, which corresponds well with an axial-

equatorial conformation of the protons H_a and H_b . In compound 126 the coupling of H_a with H_b is 12 Hz, indicative of a trans diaxial relationship. Since the relative configurations at C-1, C-2 and C-3, C-6 are determined by the geometry of the starting material, these results established that 123 is the trans-fused lactone and 124 is the cis-fused lactone.



The striking feature of this work is that, with the exception of the cyclization of 95, the intramolecular Diels-Alder cycloadditions proceed principally through the exo transition state and thus yield trans fused γ -lactones. Those intramolecular Diels-Alder reactions previously studied which lead to fused five- and six-membered rings, that is, those precursors with three atoms connecting the diene with the dienophilic segment, also produce the trans-fused bicyclic skeleton in preference to the cis, in apparent defiance of the Alder "endo" rule. It has been pointed out by Sauer that the endo rule is, at best, a

generalization of the stereochemical facts attendant on the intermolecular Diels-Alder cycloaddition, and that it is not always possible to use the rule to make accurate predictions of product distributions in new systems (46). The reason for this is that the effects which cause a general preference for endo cyclization in intermolecular cases are weak, as evidenced by the low selectivity in certain systems and, especially, by examples where the selectivity is inexplicably reversed. Sauer points out that a product ratio of even 99:1 reflects a difference in activation energies of less than 3 kcal/mole (46).

It would seem, then, that the three-atom chain linking diene and dienophile in these systems must cause sufficient perturbation to override whatever preference the reactants may have had for the endo mode. Roush asserts that, for the case of 68 and 71, molecular models show that the exo transition state is more easily attained than the endo transition state, as a "consequence of the conformations adopted by chain linking the diene and dienophile (25)." However, an examination of Dreiding models by this writer suggests there should be no appreciable difference in strain energy between the endo and exo transition states for either Roush's or our systems. The dienophile is symmetrically disposed with respect to the diene segment vis-a-vis exo or endo addition and requires identical deformations of the linking chain to achieve a reasonable transition state conformation in either exo or endo modes.

A more plausible explanation for the body of results presented in this work, as well as previous experience, would seem to rest on the steric preference for a trans (as opposed to cis) 1,2-disubstituted, five-membered ring in a non-synchronous cycloaddition. The concept of a non-synchronous, concerted reaction mechanism has been proposed by

several authors for the Diels-Alder cycloaddition (47, 48, 49). This idea stipulates that although a concerted reaction must have a transition state in which all bonds made or broken are undergoing their respective change in bonding together, all new bonds are not necessarily formed to the same degree at this transition state. In the transition state of the Diels-Alder reaction, then, the two new σ bonds must be in the process of development, but one bond could be at an advanced stage of formation, while the other could be in the very early stages. Indeed, Dewar (50) has used the MINDO/3 method (his third version of a computer program for performing molecular orbital calculations based on Modified Intermediate Neglect of Differential Overlap of atomic orbitals) to calculate that, in the transition state of the Diels-Alder cycloaddition between ethylene and butadiene, one of the incipient σ bonds is 1.53 Å long--very nearly completely formed--while the other σ bond is 2.80 Å long and is thus almost nonexistent from a bonding point of view. It should be pointed out, however, that this highly asymmetric (yet concerted) visualization of the transition state in a 4+2 cycloaddition is strictly a characteristic of MINDO/3 calculations and is not shared by self consistent field (SCF) theorists (51, 52). In fact, SCF calculations which include configuration-interaction predict a much more nearly synchronous process for bond formation in these and related reactions.

Nevertheless, in the particular case of the intramolecular Diels-Alder cycloaddition of the systems described above, an argument could be made that the bond between atoms 4 and 8 (five-membered ring) is more developed in the transition state than is the bond between atoms 1 and 9 (nine-membered ring) (Figure 7) since five-membered rings are well-known to be much less strained than nine-membered rings. The substituents

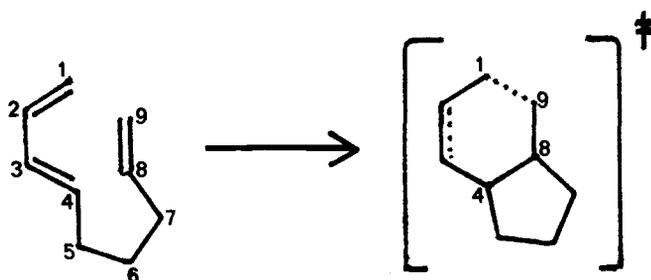


Figure 7.

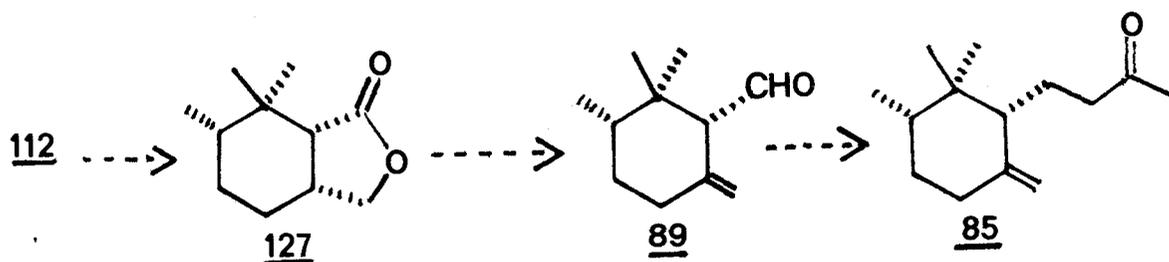
on a 1,2-disubstituted five-membered ring will take up the thermodynamically preferred, trans orientation which will therefore lead to a trans fused bicyclic adduct, nominally the product from the exo transition state. This rationale leaves the intramolecular addition of carboxylic acid 95, which occurs predominantly via the endo mode, as the sole exception among the results cited above. Whether this is associated with an intramolecular hydrogen bond between the carboxyl group and adjacent, cisoid carbonyl of the ester is not known but, conceivably, this could alter the dienophilic properties of the citraconate moiety and enhance the preference for endo addition.

The stereocontrolled synthesis of bicyclic lactones via the intramolecular Diels-Alder methodology described above provides a valuable means for construction of cyclohexane rings containing four contiguous asymmetric centers. In fact, if the cyclohexane double bond is functionalized regio- and stereospecifically, it becomes possible to introduce substituents at all six of the cyclohexane carbons in a stereocontrolled fashion by this method.

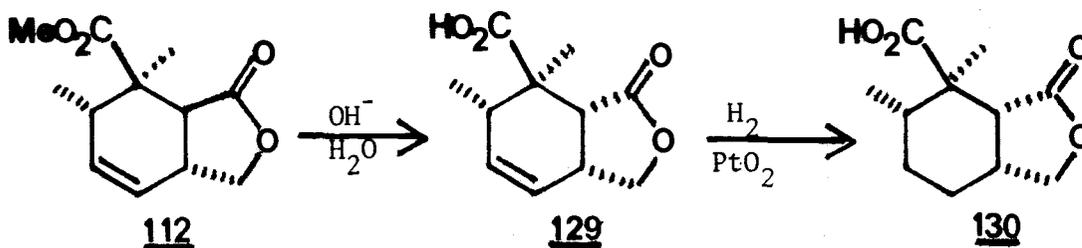
In practical terms, the synthesis targets for which this strategy

is applicable will often have substituents at different oxidation levels from that introduced through the intramolecular Diels-Alder reaction, and means must be found for adjusting these levels through appropriate oxidation or reduction sequences. As pointed out earlier, an example of particular interest is γ -irone, a sesquiterpene (85) isolated from orris root (38, 53) containing a 1,2,2,3,4 substitution pattern on a cyclohexane, for which no fully stereocontrolled synthesis presently exists (54, 55).

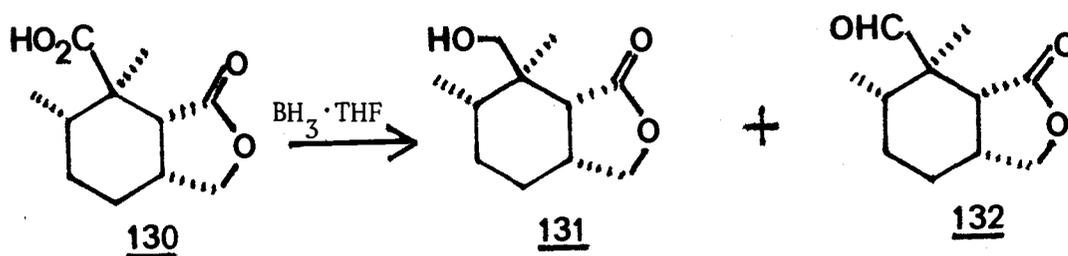
An approach to γ -irone can be envisaged based on 112 along lines shown below. This route, however, requires that the ester function of 112



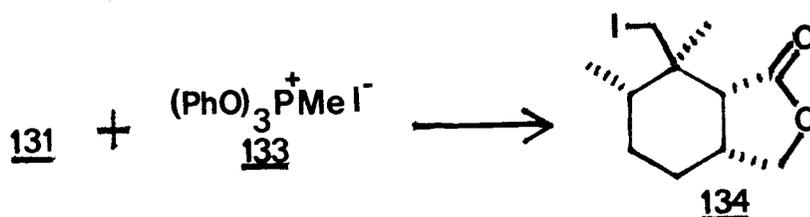
be reduced to a methyl group or, alternatively, that the second methyl substituent of the geminal pair be introduced in a subsequent step. In an attempt to effect conversion of the ester group in 112 to the methyl substituent of γ -irone, a reductive sequence was examined. Lactone 112, from the intramolecular Diels-Alder reaction of 110, was treated with hot aqueous base to yield 129, which was hydrogenated to the cyclohexane derivative 130 over Adams' catalyst. Reduction of the carboxylic acid moiety of 130 was accomplished by treating this substance with borane-tetrahydrofuran complex in tetrahydrofuran at room temperature. Chromatographic purification yielded 60% of 131 and 6% of 132. The alcohol 131 was treated with triphenylphosphite methiodide 133 (56) to produce



the iodide 134. Unfortunately, all attempts to reduce the iodide 134

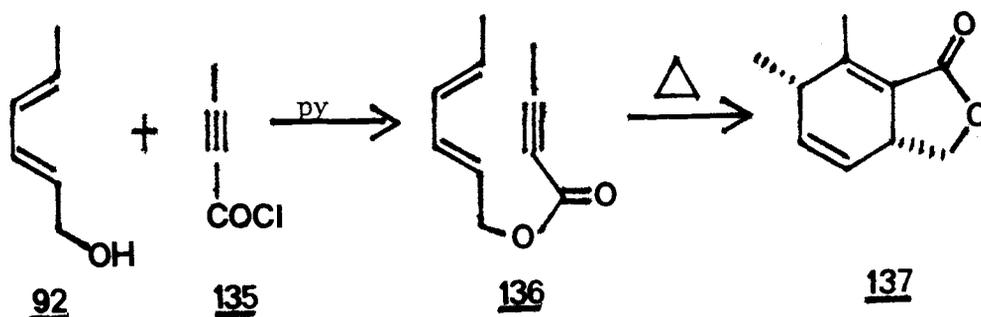


to the corresponding methyl group with tri-*n*-butyltin hydride (57) or sodium cyanoborohydride (58) met with failure. Conceivably, the high degree of steric shielding around the iodide, due particularly to its neopentyl environment, prohibits a normal reduction.

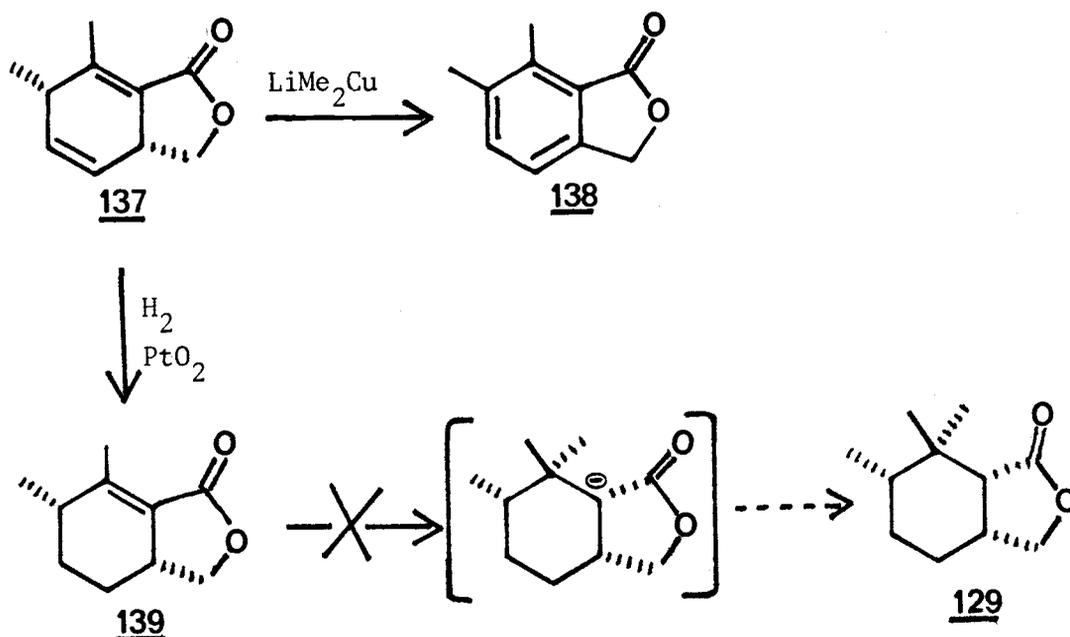


The difficulty in reducing the iodide 134 emphasized the need for an alternate approach to the problem of introducing the geminal methyl substitution of irone. The apparent thermodynamic preference for a cis fused γ -lactone suggested that the desired 2,6-*cis* configuration could be achieved after the initial Diels-Alder reaction and could, perhaps be

generated simultaneously with introduction of the third methyl group. To this end, the sorbyl ester 136 of tetrolic acid, was prepared via the acid chloride 135. The ester 136 cyclized cleanly and in good yield in refluxing xylene (24 hours) to produce Diels-Alder adduct 137. It



was hoped that 137 could be converted directly to the skeleton of irone



by a conjugate addition using lithium dimethylcuprate. However, the only new compound formed upon treatment of 137 with lithium dimethylcuprate was the aromatic lactone 138. In an effort to forestall aromatization, 137 was hydrogenated over Adams' catalyst, resulting in

reduction of the isolated double bond. The α,β -unsaturated lactone 139 was treated with lithium dimethylcuprate as before in the expectation that the enolate formed upon 1,4-addition would afford exclusively the cis lactone 127 when quenched. Regrettably, 139 was inert to lithium dimethylcuprate, a result which is not inconsistent with findings reported by House (59, 60).

In summary, a study of several intramolecular Diels-Alder cycloadditions of citraconic and mesaconic esters has been completed. Products and product distributions have been examined, and a general explanation for the preponderant formation of trans-fused, bicyclic γ -lactones from the intramolecular Diels-Alder cycloaddition has been proposed for these systems. Some of the cycloadditions scrutinized may prove to be of synthetic utility in the preparation of highly functionalized cyclohexane derivatives.

C. EXPERIMENTAL

General

Infrared spectra (IR) were recorded on a Perkin-Elmer 727B infrared spectrophotometer. Nuclear magnetic resonance spectra (NMR) were recorded in Varian EM-360A or HA-100 spectrometers and are reported in parts per million (δ) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) are given in Hertz; the abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra (MS) were obtained on a Varian MAT CH-7 (low resolution) and exact masses were obtained using a CEC-103B spectrometer, at an ionization potential of 70 eV. Combustion analysis was performed by Micro-Tech Laboratories, Skokie, Illinois. Analytical thin-layer chromatography (TLC) was done on Merck TLC sheets precoated with silica gel 60 f-254, 0.2 mm thick. Preparative-layer chromatography was done on Analtech precoated silica gel GF-259 plates, 1 mm thick. Merck silica gel 60 (0.06-0.20 mm) Activity 2-3 was used for column chromatography. All boiling points (bp) and melting points (mp) are uncorrected. Dry tetrahydrofuran (THF) was obtained by distillation, under nitrogen, from sodium/benzophenone ketyl. Hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were dried by distillation from calcium hydride at reduced pressure. Other solvents were purified using standard procedures.

trans, trans-2,4-Hexadienyl 3,3-Dimethylacrylate (87)

A solution of β,β -dimethylacrylic acid (10.0 g, 0.10 mole) in 20 ml of benzene was treated with 20 ml (0.23 mole) of oxalyl chloride. When effervescence had ceased (1h), the excess oxalyl chloride was removed by evaporation in vacuo. The residual acid chloride was added to a solution of sorbyl alcohol (10.0 g, 0.10 mole) and 10 ml (0.127 mole) of pyridine in 100 ml of benzene at 0°C. After stirring overnight at room temperature, the reaction mixture was diluted with ether and washed with water. The organic layer was then washed sequentially with saturated aqueous copper sulfate, water, and saturated aqueous sodium chloride. The ethereal extract was dried (magnesium sulfate), filtered, and the solvent evaporated in vacuo. The residue was distilled to yield 16.0 g (89%) of 87: bp 120-122°C/11 mm; IR (film) 3040, 2950, 2920, 1720, 1660 cm^{-1} ; NMR (CDCl_3) δ 6.6-5.4 (5 H, m), 4.6 (2 H, d, $J = 7$ Hz), 2.2 (3 H, s), 1.9 (3 H, s), 1.7 (3 H, d, $J = 6$ Hz); MS m/e 180.116 (M^+ , calc for $\text{C}_{11}\text{H}_{16}\text{O}_2$ 180.115).

trans,trans-2,4-Hexadienyl 3-Carboxycrotonate (95)

and

trans,trans-2,4-Hexadienyl cis-3-Carboxy-2-methylacrylate (96)

To a solution under nitrogen of sorbyl alcohol (9.8 g, 0.10 mole), pyridine (8.0 ml, 0.1 mole), and 2,6-di-*t*-butyl-*p*-cresol (50 mg) in 20 ml of dry benzene was added 9 ml (11.2 g, 0.10 mole) of citraconic anhydride. The solution darkened and warmed appreciably; the temperature was then raised to 50°C for 8 h. After cooling, the solvent was removed by evaporation in vacuo to yield 12.1 g (60%) of a mixture of 95 and 96,

a pale brown oil: IR (film) 3000, 1725, 1705, 1450 cm^{-1} ; NMR (CDCl_3) δ 10.00 (1 H, s), 6.5-5.5 (5 H, m), 4.75 (2 H, m), 2.08 (3 H, s), 1.8 (3 H, d, $J = 6$ Hz).

3 α -Hydroxymethyl-1 β ,6 α -dimethylcyclohex-4-ene-
1 α ,2 α -dicarboxylic Acid γ -Lactone (97)

The mixture of 95 and 96 was dissolved in 500 ml of xylene (distilled from sodium) and refluxed under a nitrogen atmosphere for 15 h. The solvent was removed by distillation in vacuo to yield 11.7 g of thick brown oil which partially crystallized on standing. Trituration with chloroform-cyclohexane and filtration yielded 2.0 g (10% overall) of 97 as colorless crystals: mp 168-170°C (ethyl acetate-hexane): IR (Nujol) 3000, 1760, 1350, 1200, 1050, 975 cm^{-1} ; NMR (CDCl_3) δ 7.7 (1 H, br s), 5.8 (1 H, dd, $J = 2,9$ Hz), 5.6 (1 H, br d, $J = 10$ Hz), 4.4 (1 H, dd, $J = 8,9$ Hz), 4.2 (1 H, dd, $J = 3,8$ Hz), 3.2 (1 H, m), 3.05 (1 H, d, $J = 9$ Hz), 2.4 (1 H, m), 1.5 (3 H, s), 1.2 (3 H, d, $J = 7$ Hz); MS m/e 210.089 (M^+ , calc for $\text{C}_{11}\text{H}_{14}\text{O}_9$ 210.089).

3 α -Hydroxymethyl-1 β ,6 α -dimethyl-1 α -methoxycarbonyl-
cyclohex-4-ene-2 α -carboxylic Acid γ -Lactone (98)

A sample of 97 (0.210 g, 1.0 mmole) was treated with excess, freshly prepared, ethereal diazomethane. Evaporation in vacuo yielded 0.220 g (98%) of 98 as a pale brown oil: IR (film) 2990, 1770, 1700, 1460, 1380, 1280, 1230, 1140, 1080, 990, 800 cm^{-1} ; NMR (CDCl_3) δ 5.8 (1 H, dq, $J = 2,9$ Hz), 5.5 (1 H, dt, $J = 2,9$ Hz), 4.45 (1 H, dd, $J = 8,9$ Hz), 4.15 (1 H, dd, $J = 4,9$ Hz), 3.75 (3 H, s), 3.18 (1 H, m), 3.05 (1 H, d,

$J = 9$ Hz), 2.4 (1 H, m), 1.50 (3 H, s), 1.20 (3 H, d, $J = 7$ Hz); MS m/e 224.106 (M^+ , calc for $C_{12}H_{16}O_4$ 224.106).

exo-1-endo-10-Dimethyl-3,5-dioxatricyclo[5.3.1.0^{4,11}]undec-8-ene (99)

The ester 98 (530 mg, 2.38 mmole) was dissolved in 25 ml of dry toluene in a dried 50 ml round-bottom flask purged with argon. The solution was cooled to -70°C and 4.8 ml (2 eq) of 1.6 M diisobutylaluminum hydride in hexane was added. After 1.5 h analytical thin-layer chromatography showed only a small percentage of starting material remained. Another equivalent of diisobutylaluminum hydride was added. After a total reaction time of 4 h, 40 ml of 10% aqueous sulfuric acid was added to the cold solution. After warming to room temperature, the layers were separated and the aqueous layer was extracted with three 20 ml portions of diethyl ether. The combined organic layers were washed twice with 20 ml portions of water, once with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to yield 350 mg of a pale yellow oil. Preparative TLC (25% acetone-cyclohexane) yielded 300 mg (60%) of 99 as colorless oil: IR (film) 2980, 2890, 1100, 1020, 960 cm^{-1} ; NMR (CDCl_3) δ 5.82 (1 H, d, $J = 5$ Hz), 5.70 (1 H, ddd, $J = 3, 3, 10$ Hz), 5.50 (1 H, ddd, $J = 2, 2, 10$ Hz), 4.15 (1 H, dd, $J = 8, 8$ Hz), 3.60 (2 H, abq, $J = 6, 12$ Hz), 3.42 (1 H, dd, $J = 8, 10$ Hz), 2.90-2.58 (1 H, m), 2.40 (1 H, dd, $J = 5, 10$ Hz), 2.9-2.2 (1 H, m), 1.18 (3 H, s), 0.98 (3 H, d, $J = 8$ Hz); MS m/e 180.115 (M^+ , calc for $C_{11}H_{16}O_2$ 180.115).

exo-1-endo-10-Dimethyl-3,5-dioxatricyclo[5.3.1.0^{4,11}]undecane (100)

Compound 99 (300 mg, 1.5 mmol) was dissolved in 25 ml of ethanol and hydrogenated over 33 mg of 10% palladium on charcoal. The reduction

was stopped when 1.25 eq of hydrogen was taken up. The catalyst was filtered off and the solvent was removed in vacuo. Preparative TLC (25% acetone-hexane) afforded 180 mg (60%) of 100: IR (film) 2975, 2945, 2880 cm^{-1} ; NMR (CCl_4) δ 5.65 (1 H, d, $J = 3$ Hz), 3.7 (3 H, dd, $J = 2, 4$ Hz), 3.45 (1 H, dd, $J = 2, 6$ Hz), 3.35 (1 H, d, $J = 4$ Hz), 2.2 (m, 2 H), 1.7 (2 H, m), 1.4 (2 H, m), 1.1 (3 H, t), 0.90 (3 H, d, $J = 3$ Hz); MS m/e 182.131 (M^+ , calc for $\text{C}_{11}\text{H}_{18}\text{O}_2$ 182.131).

3 α -Hydroxymethyl-1 β ,6 α -dimethylcyclohexane-
1 α ,2 α -dicarboxylic Acid γ -Lactone (102)

A suspension of platinum oxide (200 mg, 0.90 mmol) in ethyl acetate was stirred under hydrogen until uptake of gas ceased. A solution of the olefin 97 (2.0 g, 9.5 mmol) in 5 ml of ethyl acetate was added. Hydrogen uptake ceased after 30 min at 230 ml (10.0 mmol). Filtration through a Celite pad and evaporation in vacuo afforded 2.02 g (100%) of 102: mp 165-166°C (acetone-petroleum ether); IR (Nujol) 2900, 1760, 1700 cm^{-1} ; NMR (CDCl_3) δ 9.35 (1 H, br s), 4.27 (1 H, dd, $J = 5.5, 9$ Hz), 4.08 (1 H, dd, $J = 3.5, 9$ Hz), 2.83 (1 H, d, $J = 8$ Hz), 2.7 (1 H, m), 1.9 (1 H, m), 1.65 (4 H, m), 1.50 (3 H, s), 1.07 (3 H, d, $J = 6$ Hz); MS m/e 212.104 (M^+ , calc for $\text{C}_{11}\text{H}_{16}\text{O}_4$ 212.105).

trans,trans-2,4-Hexadienyl trans-3-Methoxy-
carbonyl-3-methylacrylate (90)

and

trans,trans-2,4-Hexadienyl 3-Methoxycarbonylcrotonate (110)

A suspension of 1.50 g (10.4 mmol) of acids 107-109 (44) in 10 ml of dry benzene was treated with 6 ml of oxalyl chloride. When the

effervescence had decreased, the solution was warmed to 50°C for 1 h. The excess oxalyl chloride and benzene were removed by evaporation in vacuo. Benzene was added and the solvent was again evaporated in vacuo to yield a mixture of acid chlorides which was added to a solution of 0.93 g (9.5 mmol) of trans,trans-2,4-hexadienol and 0.79 g (10 mmol) of pyridine in 10 ml of dry benzene at 0°C under a nitrogen atmosphere. After standing at room temperature overnight, the reaction mixture was diluted with ether and washed sequentially with saturated aqueous cupric sulfate, dilute sulfuric acid, water, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying (anhydrous magnesium sulfate) and evaporation in vacuo, there remained 1.8 g of a brown oil. Column chromatography (10% ethyl acetate-hexane) of this oil afforded 1.62 g (70%) of 110; IR (film) 2990, 1745, 1665, 1450 cm^{-1} ; NMR (CDCl_3) δ 6.5-5.5 (5 H, m), 5.8 (1 H, d, $J = 2$ Hz), 4.60 (2 H, m), 3.73 (3 H, s), 2.02 (3 H, d, $J = 2$ Hz), 1.78 (3 H, d, $J = 7$ Hz); MS m/e 224.102 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_2$ 224.105); Anal: found C, 63.98%; H, 7.03% (calc for $\text{C}_{12}\text{H}_{16}\text{O}_2$; C, 64.26%; H, 7.20%).

In addition, there was obtained from chromatography 180 mg (10%) of 90: IR (film) 3000, 2950, 1745, 1450, 1170 cm^{-1} ; NMR (CDCl_3) δ 6.80 (1 H, m), 6.5-5.5 (4 H, m), 4.70 (2 H, d, $J = 6$ Hz), 3.80 (3 H, s), 1.29 (3 H, d, $J = 2$ Hz), 1.78 (3 H, d, $J = 6$ Hz); MS m/e 224.102 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_2$ 224.105).

1 β -Carboxymethyl-3 α -hydroxymethyl-1 α ,6 β -dimethylcyclohex-

4-ene-2 β -carboxylic Acid γ -Lactone (112)

The triene ester 110 (1.8 g, 9.0 mmol) and 50 mg of 2,6-di-*t*-butyl-*p*-cresol were dissolved in 150 ml of xylene and refluxed for 24 h

under a nitrogen atmosphere. The solvent was removed by distillation in vacuo to leave a thick brown oil which was purified by column chromatography on 100 g of silica gel, eluting with 300 ml of chloroform followed by 300 ml of 2% methanol in chloroform. Combination of the pure fractions and evaporation in vacuo yielded 0.75 g (40%) of 112; mp 94-96°C (chloroform-cyclohexane); IR (film) 1980, 1775, 1460, 980 cm^{-1} ; NMR (CDCl_3) δ 5.72 (2 H, s), 4.45 (1 H, dd, $J = 7,8$ Hz), 3.8 (1 H, dd, $J = 8,11$ Hz), 3.72 (3 H, s), 3.05 (2 H, m), 2.15 (1 H, d, $J = 13$ Hz), 1.54 (3 H, s), 1.05 (3 H, d, $J = 7$ Hz); MS m/e 224.104 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_4$ 224.105).

3 α -Hydroxymethyl-1 α ,6 α -dimethyl-1 β -methoxycarbonyl-
cyclohex-4-ene-2 α -carboxylic Acid γ -Lactone (113)

A solution of 112 (370 mg, 1.65 mmol) in 5 ml of methanol was treated with 0.6 ml of 5M (3.3 mmol) sodium methoxide in methanol. After stirring at room temperature overnight, the reaction mixture was diluted with 10% aqueous sulfuric acid and extracted with ether. The ether extracts were washed with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, and dried (magnesium sulfate). After filtration, evaporation of solvent in vacuo afforded 247 mg (68%) of 113: mp 89-91°C (methylene chloride-cyclohexane); IR (film) 1775, 1735, 1240 cm^{-1} ; NMR (CDCl_3) δ 5.8 (2 H, m), 4.45 (1 H, m), 3.9 (1 H, m), 3.76 (3 H, s), 3.3 (2 H, m), 2.9-2.6 (1 H, m), 1.27 (3 H, s), 0.97 (3 H, d, $J = 7$ Hz); MS m/e 224.102 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_4$ 224.105).

trans-2,4-Pentadienol (114)

To a suspension of lithium aluminum hydride (1.70 g, 46 mmol) in

50 ml of dry ether cooled to 0°C was added 6.30 g (56 mmol) of methyl trans-2,4-pentadienoate (43) dropwise while maintaining cooling. After stirring for 1.5 h at 0°C, the reduction mixture was quenched with 5 ml of ethyl acetate. The mixture was then carefully treated with 20 ml of 10% aqueous sulfuric acid, the organic layer was separated, and the aqueous layer re-extracted with ether. The organic extracts were combined, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and filtered. To the filtrate was added 100 mg of 2,6-di-*t*-butyl-*p*-cresol and the filtrate was then evaporated in vacuo. The residue was distilled to yield 4.10 g (87%) of 114: bp 60-65°C/18 mm; IR (film) 3420, 2950, 1601 cm^{-1} ; NMR (CDCl_3) δ 6.6-5.5 (3 H, m), 5.3-4.9 (2 H, m), 4.4 (1 H, s, exchanged with D_2O), 4.02 (2 H, d, $J = 6 \text{ Hz}$).

trans-2,4-Pentadienyl 3-Methoxycarbonylcrotonate (83)

A solution of 1.50 g (10.4 mmol) of 107-109 in 10 ml of dry benzene was treated with 13 ml (32 mmol) of oxalyl chloride. After effervescence decreased, the reaction was warmed to 50°C for 1 h. Excess oxalyl chloride and solvent were removed by evaporation in vacuo. Benzene was added and again removed by evaporation in vacuo to provide a clear yellow oil. This was added to a solution of 0.80 g (9.5 mmol) of trans-2,4-pentadienol 114 and 0.79 g (10 mmol) of pyridine in 10 ml of dry benzene cooled to 0°C under nitrogen. After warming to room temperature and standing overnight, the mixture was diluted with ether and washed with portions of saturated aqueous copper sulfate, dilute sulfuric acid, water, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying (magnesium sulfate) and filtering,

evaporation yielded 1.90 g (90%) of 83: IR (film) 2990, 1745, 1665, 1601, 1020, 960 cm^{-1} ; NMR (CDCl_3) δ 6.9-6.2 (2 H, m), 5.9 (1 H, m), 5.4-5.1 (2 H, m), 4.65 (2 H, d, $J = 6$ Hz), 3.8 (3 H, s), 2.1 (3 H, d, $J = 1$ Hz); MS m/e 210 (M^+); Anal: found; C, 63.01%; H, 6.60% (calc for $\text{C}_{11}\text{H}_{14}\text{O}_4$; C, 62.83%; H, 6.72%).

3 α -Hydroxymethyl-1 α -methyl-1 β -methoxycarbonyl-
cyclohex-4-ene-2 β -carboxylic Acid γ -Lactone (115)

A mixture of 83 (3.95 g, 20 mmol) and 100 mg of 2,6-di-*t*-butyl-*p*-cresol was refluxed in 250 ml of xylene for 32 h under a nitrogen atmosphere. The solvent was evaporated in vacuo to yield 3.98 g of semi-crystalline material which was nearly pure by TLC. Chromatography on silica gel (5% ethyl acetate-hexane) afforded 0.40 g (10%) of 83 and 2.00 g (55%) of 115: mp 96-98°C (chloroform-cyclohexane); IR (film) 2980, 2920, 1775, 1735 cm^{-1} ; NMR (CDCl_3) δ 5.78 (2 H, s), 4.48 (1 H, dd, $J = 7, 8$ Hz), 3.80 (1 H, dd, $J = 7, 13$ Hz), 3.73 (3 H, s), 3.1 (1 H, m), 2.95 (1 H, dt, $J = 2, 19$ Hz), 3.19 (1 H, d, $J = 14$ Hz), 2.1 (1 H, ddd, $J = 2, 4, 19$ Hz), 1.53 (3 H, s); MS m/e 210.088 (M^+ , calc for $\text{C}_{11}\text{H}_{14}\text{O}_4$ 210.089).

3 α -Hydroxymethyl-1 α -methyl-1 β -methoxycarbonyl-
cyclohex-4-ene-2 α -carboxylic Acid γ -Lactone (116)

A solution of 115 (210 mg, 1.0 mmol) in 5 ml of methanol was treated with 5 mmol of sodium methoxide. After stirring for 40 h, the reaction mixture was acidified with 10% aqueous sulfuric acid and extracted with ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate. The organic extracts were

subsequently washed with saturated aqueous sodium chloride, dried (magnesium sulfate), and filtered. The solvent was evaporated in vacuo to yield 120 mg (59%) of 116: IR (film) 2950, 2900, 1775, 1735 cm^{-1} ; NMR (CDCl_3) δ 6.0-5.8 (1 H, ddt, $J = 2,5,10$ Hz), 5.56 (1 H, br d, $J = 10$ Hz), 4.36 (1 H, dd, $J = 5,9$ Hz), 4.05 (1 H, d, $J = 9$ Hz), 3.72 (3 H, s), 3.2 (2 H, m), 2.8-2.5 (1 H, m), 2.1 (1 H, dq, $J = 2,18$ Hz), 1.6 (3 H, s); MS m/e 210.088 (M^+ , calc for $\text{C}_{11}\text{H}_{14}\text{O}_4$ 210.089).

3 α -Hydroxymethyl-1 β ,6 α -dimethyl-1 α -methoxycarbonylcyclohex-4-ene-2 β -carboxylic Acid γ -Lactone (117)

A solution of the mesaconate 90 (1.45 g, 6.5 mmol) and 100 mg of 2,6-di-*t*-butyl-*p*-cresol in 250 ml of xylene was refluxed under nitrogen for 5 days. Evaporation of solvent in vacuo afforded a brown solid. Recrystallization (ethyl ether-hexane) allowed isolation of 401 mg (28%) of 117: mp 126-128°C (ethyl acetate-hexane): IR (Nujol) 1775, 1735, 1460, 1260 cm^{-1} ; NMR (CDCl_3) δ 5.72 (2 H, br, s), 4.48 (1 H, m), 3.95 (1 H, m), 3.76 (3 H, s), 2.8 (2 H, m), 2.3 (1 H, m) 1.28 (3 H, s), 0.95 (3 H, d, $J = 6$ Hz); MS m/e 224.108 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_4$ 224.105).

Column chromatography of the mother liquor (30% ethyl acetate in hexane) afforded 576 mg (40%) of starting material and 328 mg (23%) of a thick oil which was homogeneous by TLC but which proved by NMR analysis to be a 60:40 mixture of 117 and the previously isolated 113.

3 α -Hydroxymethyl-1 β ,6 α -dimethyl-1 β -methoxycarbonylcyclohex-4-ene-2 α -carboxylic Acid γ -Lactone (98) from the Epimerization of (117)

A solution of lactone 117 (30 mg, 0.14 mmol) in 1 ml of tetrahydrofuran was treated with sodium hydride (4 mg of a 50% suspension in

mineral oil, 0.08 mmol) and was stirred for 17 h. The reaction mixture was diluted with 0.1 N hydrochloric acid and extracted with ether. The ethereal extracts were combined, washed with water, saturated aqueous sodium chloride, dried (magnesium sulfate), and filtered. Evaporation of solvent in vacuo afforded 32 mg (100%) of 98, identical in all respects with the material prepared previously.

3 α -Hydroxymethyl-1 β ,6 α -dimethyl-1 α ,2 β -
dimethoxycarbonylcyclohex-4-ene (118)

A solution of ester 117 (40 mg, 0.18 mmol) in 2 ml of methanol containing 0.05 mmol of sodium methoxide was stirred for 24 h at room temperature. The reaction mixture was acidified with acetic acid and concentrated in vacuo. The residue was triturated with ethyl ether, and the ethereal extracts were combined, filtered, and evaporated. Chromatography (preparative TLC, ethyl acetate-hexane, 1:1) afforded 30 mg (66%) of 118: IR (film) 3450 (br), 2950, 1740, 1735 cm^{-1} ; NMR (CDCl_3) δ 5.8 (1 H, ddd, $J = 3, 5, 10$ Hz), 5.6 (1 H, d, $J = 10$ Hz), 3.76 (3 H, s), 3.70 (3 H, s), 2.95 (1 H, d, $J = 12$ Hz), 2.6-2.1 (3 H, m, 1 H was exchanged with D_2O), 1.52 (3 H, s), 0.92 (3 H, d, $J = 7$ Hz); MS m/e 238.121 ($\text{M}^+ - 18$, calc for $\text{C}_{13}\text{H}_{18}\text{O}_4$ 238.121).

3 α -Hydroxymethyl-1 β ,6 α -dimethyl-2 β -methoxycarbonylcyclo-
hex-4-ene-1 α -carboxylic Acid δ -Lactone (119)

A solution of 118 (30 mg, 0.12 mmol) in 20 ml of benzene containing 2 mg (0.01 mmol) of p-toluenesulfonic acid was refluxed for 7 h using a Dean-Stark trap. After cooling, the reaction mixture was diluted with ethyl ether, washed with aqueous sodium bicarbonate and

saturated aqueous sodium chloride, dried (magnesium sulfate), filtered and evaporated in vacuo. Preparative TLC (ethyl acetate-hexane, 30:70) afforded 14 mg (53%) of 119: IR (Nujol) 1740, 1733 cm^{-1} ; NMR (CDCl_3) δ 5.74 (2 H, s), 4.21 (1 H, dd, $J = 3, 11$ Hz), 4.15 (1 H, dd, $J = 1, 11$ Hz), 3.70 (3 H, s), 2.90 (2 H, br s), 2.76 (1 H, br q, $J = 9$ Hz), 1.50 (3 H, s), 1.04 (3 H, d, $J = 7$ Hz); MS m/e 224.103 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_4$ 224.105).

trans,trans-2,4-Hexadienyl trans-3-Methoxycarbonyl-2-
methylacrylate (122)

The half ester 121 (45) (3.0 g, 20.8 mmol) was dissolved in 20 ml of benzene and treated at 50°C with 5 ml of oxalyl chloride for 3 h. The oxalyl chloride and benzene were removed by evaporation in vacuo. Benzene was added and again removed by evaporation to afford the acid chloride as a clear, brown oil. This was added to a solution of trans,trans-2,4-hexadienol (2.0 g, 20 mmol) and 2 ml (25 mmol) of pyridine in 20 ml of benzene at 0°C . After warming to room temperature and stirring for 3 h, the reaction mixture was diluted with ether and the ethereal layer was washed sequentially with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying (magnesium sulfate), the ethereal extract was filtered and the solvent was evaporated to afford a brown oil. Column chromatography (10% ethyl acetate-hexane) of this oil provided 3.30 g (71%) of 122: IR (film) 1725, 1645 cm^{-1} ; NMR (CDCl_3) δ 6.7 (1 H, m), 6.5-5.5 (4 H, m), 4.70 (2H, d, $J = 6$ Hz), 3.77 (3 H, s), 2.20 (3 H, d, $J = 2$ Hz), 1.77 (3 H, d, $J = 6$ Hz); MS m/e 224.103 (M^+ , calc for $\text{C}_{12}\text{H}_{16}\text{O}_4$ 224.105).

3 α -Hydroxymethyl-2 α ,6 α -dimethyl-1 α -methoxycarbonylcyclo-
hex-4-ene-2 β -carboxylic Acid γ -Lactone (123)

and

3 α -Hydroxymethyl-2 β ,6 α -dimethyl-1 β -methoxycarbonylcyclo-
hex-4-ene-2 α -carboxylic Acid γ -Lactone (124)

A solution of triene 122 (1.0 g, 4.48 mmol) and 2,6-di-*t*-butyl-*p*-cresol (100 mg) was refluxed in xylene under a nitrogen atmosphere for 11 days. The solvent was removed by evaporation *in vacuo* and the brown oily residue was subjected to column chromatography (30% ethyl acetate-hexane). Along with 495 mg (50%) of starting material 122, was isolated 350 mg (35%, 70% based on recovered starting material) of 123: mp 122-125°C (ethyl acetate-hexane); IR (film) 2950, 1780, 1740 cm^{-1} ; NMR (CDCl_3) δ 5.73 (2 H, s), 4.40 (1 H, dd, $J = 7, 8$ Hz), 4.27 (1 H, dd, $J = 8, 12$ Hz), 3.76 (3 H, s), 3.15-2.8 (3 H, m), 1.45 (3 H, s), 1.10 (3 H, d, $J = 7$ Hz); MS m/e 224.104 (M^+ , calc $\text{C}_{12}\text{H}_{16}\text{O}_4$ 224.105). There was also obtained 75 mg (7.5%, 15% based on recovered starting material) of 124: NMR (CDCl_3) δ 5.70 (2 H, m), 4.48 (1 H, dd, $J = 8, 8$ Hz), 3.90 (1 H, dd, $J = 8, 9$ Hz), 3.70 (3 H, s), 2.95-2.5 (2 H, m), 2.40 (1 H, d, $J = 10$ Hz), 1.26 (3 H, s), 1.04 (3 H, d, $J = 6$ Hz); MS m/e 224 (M^+).

3 α -Hydroxymethyl-2 α ,6 α -dimethyl-1 α -methoxycarbonylcyclo-
hexane-2 β -carboxylic Acid γ -Lactone (125)

A solution of 123 (55 mg, 0.24 mmol) in 1 ml of methanol was added to 6 mg of Adams' catalyst which was being stirred under a hydrogen atmosphere in 3 ml of methanol. After cessation of hydrogen uptake, the mixture was filtered and the solvent was evaporated to

afford 58 mg of 125: IR (film) 2950, 1780, 1740 cm^{-1} ; NMR (CDCl_3) δ 4.28 (1 H, dd, $J = 7,9$ Hz), 4.10 (1 H, dd, $J = 9,11$ Hz), 3.73 (3 H, s), 2.69 (1 H, d, $J = 6$ Hz), 2.55-2.3 (1 H, m), 2.2-1.90 (1 H, m), 1.8-1.5 (4 H, m), 1.48 (3 H, s), 1.05 (3 H, d, $J = 7$ Hz); MS m/e 226.119 (M^+ , calc for $\text{C}_{12}\text{H}_{18}\text{O}_4$ 226.121).

3 α -Hydroxymethyl-2 β ,6 α -dimethyl-1 β -methoxycarbonylcyclohexane-2 α -carboxylic Acid γ -Lactone (126)

A solution of 124 (40 mg, 0.18 mmol) was stirred with 5 mg of Adams' catalyst in 3 ml of methanol under a hydrogen atmosphere until hydrogen uptake ceased. Filtration and evaporation in vacuo afforded 40 mg (98%) of 126: IR (film) 2950, 1775, 1735 cm^{-1} ; NMR (CDCl_3) δ 4.30 (1 H, d, $J = 2$ Hz), 4.20 (1 H, d, $J = 4$ Hz), 3.75 (3 H, s), 2.6-2.2 (2 H, m), 2.35 (1 H, d, $J = 11$ Hz), 2.1-1.6 (4 H, m), 1.33 (3 H, s), 0.98 (3 H, d, $J = 6$ Hz); MS m/e 226.121 (M^+ , calc for $\text{C}_{12}\text{H}_{18}\text{O}_4$ 226.121).

3 α -Hydroxymethyl-1 α ,6 α -dimethylcyclohex-4-ene-1 β ,2 α -dicarboxylic Acid γ -Lactone (129)

The ester 112 (2.4 g, 10.7 mmol) was refluxed in 50 ml of 2N aqueous sodium hydroxide for 3 h, then heated to 80°C overnight. After cooling, the reaction mixture was acidified with 10% aqueous sulfuric acid and heated for 0.5 h to 80°C. It was then cooled and extracted with ether, and the ether extracts were combined, dried over magnesium sulfate, filtered, and evaporated to give 2.20 g (97%) of 129 as a colorless solid: mp 144-147°C (ethyl acetate-hexane); IR (Nujol) 1765, 1700 cm^{-1} ; NMR (acetone- d_6) δ 5.7 (2 H, s), 4.5 (1 H, m), 3.9 (1 H, m), 3.4 (2 H, m), 2.8 (1 H, br q, $J = 7$ Hz), 1.25 (3 H, s), 1.0 (3 H, d,

$J = 7 \text{ Hz}$); MS m/e 210.089 (M^+ , calc for $C_{11}H_{14}O_4$ 210.089).

3 α -Hydroxymethyl-1 α ,6 α -dimethylcyclohexane-
1 β ,2 α -dicarboxylic Acid γ -Lactone (130)

Adams' catalyst (200 mg) was suspended in 100 ml of ethyl acetate and stirred under an atmosphere of hydrogen for 30 min at which time it had taken up 50 ml of hydrogen. A solution of 129 (2.0 g, 9.5 mmol) in ethyl acetate was added with a syringe. Stirring was begun and one equivalent of hydrogen (230 ml) was taken up in 30 min. The reaction mixture was filtered through Celite and evaporated to yield 2.02 g (100%) of 130 as a colorless solid: mp 196-198°C (ethyl acetate-hexane); IR (Nujol) 1760, 1695 cm^{-1} ; NMR (CDCl_3) δ 4.25 (1 H, dd, $J = 5.5, 9 \text{ Hz}$), 3.95 (1 H, dd, $J = 3, 9 \text{ Hz}$), 3.1 (1 H, d, $J = 5.5 \text{ Hz}$), 2.8-2.6 (1 H, m), 2.4-2.2 (1 H, m), 1.8-1.4 (4 H, m), 1.55 (3 H, s), 0.97 (3 H, d, $J = 7 \text{ Hz}$); MS m/e 212.104 (M^+ , calc for $C_{11}H_{14}O_6$ 212.105).

1 β ,3 α -Dihydroxymethyl-1 α ,6 α -dimethylcyclohexane-
2 α -carboxylic Acid 2,3- γ -Lactone (131)

and

1 β -Formyl-3 α -hydroxymethyl-1 α ,6 α -dimethylcyclo-
hexane-2 α -carboxylic Acid γ -Lactone (132)

A solution of 130 (0.212 g, 1.0 mmol) in 5 ml of tetrahydrofuran at 0°C was treated with 1.1 ml (1.1 mmol) of 1 M borane-tetrahydrofuran complex. The reaction was stirred at 0°C for 8 h, then diluted with an equal amount of ethyl acetate, washed with sodium bicarbonate solution, brine, and dried over magnesium sulfate. After filtration, evaporation of the filtrate afforded 146 mg of an oil, which was a mixture of 131

and 132 by TLC. Chromatography of the mixture (ethyl acetate-hexane) gave 115 mg (60%) of colorless, oily 131: IR (film) 3400, 2900, 1755 cm^{-1} ; NMR (CDCl_3) δ 4.25 (1 H, m), 4.0 (1 H, m), 3.55 (2 H, dd, $J = 11$, 18 Hz), 3.4 (1 H, m, exchanged with D_2O), 2.8 (2 H, m), 1.8-1.4 (4 H, m), 0.95 (3 H, d, $J = 6$ Hz), 0.90 (3 H, s); MS m/e 180.116 ($\text{M}^+ - 18$, calc for $\text{C}_{11}\text{H}_{16}\text{O}_2$ 180.115).

Also isolated from the crude product by chromatography was 20 mg (6%) of 132: IR (film) 1760, 1772 cm^{-1} ; NMR (CDCl_3) δ 9.3 (1 H, s) 4.3 (1 H, dd, $J = 5, 9$ Hz), 3.95 (1 H, dd, $J = 2, 9$ Hz), 2.90 (1 H, d, $J = 7$ Hz), 2.8-2.5 (1 H, m), 2.2-1.95 (1 H, m), 1.7-1.4 (4 H, m), 1.38 (3 H, s), 1.05 (3 H, d, $J = 7$ Hz); MS m/e 196.110 (M^+ , calc for $\text{C}_{11}\text{H}_{16}\text{O}_3$ 196.110).

1 α ,6 α -Dimethyl-3 α -hydroxymethyl-1 α -iodomethyl-
cyclohexane-2 α -carboxylic Acid γ -Lactone (134)

A solution of alcohol 131 (198 mg, 1.0 mmol) and triphenylphosphite methiodide 133 (56) (675 mg, 1.5 mmol) was stirred in dimethylformamide under a nitrogen atmosphere for 1.5 h. The reaction was quenched with 1 ml of methanol, diluted with ether, and the ethereal layer was washed sequentially with three portions of water, and one each of 2N sodium hydroxide, water, and brine. After drying (magnesium sulfate) the ethereal extract was filtered, and the solvent was evaporated to leave a colorless oil, which was mainly 134 and diphenyl methylphosphonate by TLC. Column chromatography of this mixture (10% ethyl acetate-hexane followed by 33% ethyl acetate-hexane) gave 80 mg (25%) of 134: IR (film) 3400 (phenol contaminant), 2900, 1755 cm^{-1} ; NMR (CDCl_3) δ 7.3, 6.9, 6.5 (phenol), 4.4-4.0 (2 H, m), 3.8 (1 H, d, $J = 10$ Hz), 3.3 (1 H, d, $J = 10$ Hz), 2.3 (1 H, m), 1.8-1.4 (4 H, m), 1.1 (3 H,

s), 0.90 (3 H, d, $J = 6$ Hz); MS m/e 308.020 (M^+ , calc for $C_{11}H_{17}O_2$ 308.027).

trans,trans-2,4-Hexadienyl Tetrolate (136)

A solution of tetrolic acid (1.64 g, 20 mmol) and 4 ml of oxalyl chloride in 20 ml of dry benzene was heated to 50°C for 1 h. Careful concentration in vacuo (20°C bath) afforded a brown oil. The oil was added slowly to a solution of sorbyl alcohol (1.96 g, 20 mmol) and pyridine (2 ml, 25 mmol) in 20 ml of benzene at 0°C. After stirring at room temperature for 24 h the reaction mixture was diluted with ether, and the ethereal layer was washed with saturated aqueous copper sulfate, water, and saturated aqueous sodium chloride. The ethereal extracts were dried (magnesium sulfate), filtered and evaporated to a brown oil. Column chromatography (30% ethyl acetate-hexane) afforded 1.0 g (50%) of sorbyl alcohol and 1.2 g (42%) of 136: IR (film) 2950, 2250, 1710, 1250 cm^{-1} ; NMR ($CDCl_3$) δ 6.4-5.4 (4 H, m), 4.65 (2 H, d, $J = 6$ Hz), 1.96 (3 H, s), 1.76 (3 H, d, $J = 6$ Hz); MS m/e 164 (M^+).

3 α -Hydroxymethyl-1,6 α -dimethylcyclohexa-1,4-dienecarboxylic Acid γ -Lactone (137)

A solution of 1.20 g (7.3 mmol) of 136 and 100 mg of 2,6-di-*t*-butyl-*p*-cresol was refluxed for 24 h under a nitrogen atmosphere. After cooling, the solvent was removed by evaporation in vacuo to yield 1.25 g (96%) of a light brown oil which was virtually pure 137. Chromatography (30% ethyl acetate-hexane) provided an analytical sample of 137: IR (Nujol) 1745 cm^{-1} ; NMR ($CDCl_3$) δ 6.72 (2 H, s), 4.55 (1 H, dd, $J = 7,7$ Hz), 3.75 (1 H, dd, $J = 7,10$ Hz), 3.7-3.3 (1 H, m), 3.15-2.75 (1 H, m), 2.21

(3 H, t, $J = 1.5$ Hz), 1.25 (3 H, d, $J = 7$ Hz); MS m/e 162.069 ($M^+ - H_2$, calc for $C_{10}H_{10}O_2$ 162.068).

3 α -Hydroxymethyl-1,6 α -dimethylcyclohexene-
carboxylic Acid γ -Lactone (139)

A suspension of 50 mg of platinum oxide in 25 ml of ethyl acetate was stirred under a hydrogen atmosphere until hydrogen uptake stopped, and a solution of 137 (710 mg, 4.3 mmol) in 5 ml of ethyl acetate was added by syringe. Stirring was initiated and the reaction took up 4.3 mmol of hydrogen over a period of 35 min. At this point gas uptake slowed and the reaction mixture was removed from the hydrogen atmosphere and filtered. Evaporation in vacuo afforded 685 mg (95%) of 139: IR (film) 2950, 2870, 1755, 1670 cm^{-1} ; NMR ($CDCl_3$) δ 4.46 (1 H, dd, $J = 8, 8$ Hz), 3.77 (1 H, dd, $J = 8, 10$ Hz), 3.1-2.7 (1 H, m), 2.5-2.2 (1 H, m), 2.13 (3 H, d, $J = 2$ Hz), 2.0-1.6 (4 H, m), 1.12 (3 H, d, $J = 7$ Hz); MS m/e 166.100 (M^+ , calc for $C_{10}H_{14}O_2$ 166.099).

D. BIBLIOGRAPHY

- (1) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim, 1970, p. 65.
- (2) K. Alder and G. Stein, Angew. Chem., 50, 510 (1937).
- (3) P. Laszlo and P.v.R. Schleyer, J. Am. Chem. Soc., 85, 2709 (1963).
- (4) J. M. Mellor and C. F. Webb, J. Chem. Soc. Perkin Trans. II, 17 (1974).
- (5) S. Beckmann and R. Bamberger, Annalen, 580, 198 (1953).
- (6) R. Hoffmann and R. B. Woodward, J. Am. Chem. Soc., 87, 4388 (1965).
- (7) W. C. Herndon and L. H. Hall, Tetrahedron Lett., 3095 (1967).
- (8) Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Fueno, J. Am. Chem. Soc., 94, 3633 (1972).
- (9) J. M. Mellor and D. F. Webb, J. Chem. Soc. Perkin Trans. II, 26 (1974).
- (10) K. N. Houk and L. J. Luskus, J. Am. Chem. Soc., 93, 4606 (1971).
- (11) K. N. Houk, J. Am. Chem. Soc., 95, 4092 (1973).
- (12) R. W. Alder, R. Baker, and J. M. Brown, "Mechanism in Organic Chemistry," John Wiley, London, 1971, p. 262.
- (13) H. O. House and T. H. Cronin, J. Org. Chem., 30, 1061 (1965).
- (14) E. J. Corey and M. Petrzilka, Tetrahedron Lett., 2537 (1975).
- (15) H. W. Gschwend and H. D. Meier, Angew. Chem. Int. Ed. Eng., 11, 294 (1972).
- (16) H. W. Gschwend, A. L. Lee, and H. D. Meier, J. Org. Chem., 38, 2169 (1973).
- (17) W. Oppolzer, Angew. Chem. Int. Ed. Eng., 16, 10 (1977).
- (18) K. J. Shea and S. Wise, J. Am. Chem. Soc., 100, 6519 (1978).
- (19) W. Oppolzer, Tetrahedron Lett., 1001, (1974).
- (20) W. Oppolzer, J. Am. Chem. Soc., 93, 3833 (1971).
- (21) W. Oppolzer, J. Am. Chem. Soc., 93, 3834 (1971).

- (22) W. Oppolzer, J. Am. Chem. Soc., 93, 3836 (1971).
- (23) K. A. Parker and M. R. Adamchuck, Tetrahedron Lett., 1689 (1978).
- (24) W. R. Roush, J. Am. Chem. Soc., 100, 3599 (1978).
- (25) W. R. Roush, J. Org. Chem., 44, 4008 (1979).
- (26) G. Brieger, J. Am. Chem. Soc., 85, 3783 (1963).
- (27) L. H. Klemm and K. W. Gopinath, Tetrahedron Lett., 1243 (1963).
- (28) L. H. Klemm, K. W. Gopinath, D. H. Lee, F. W. Kelly, E. Trod, and T. M. McGuire, Tetrahedron, 22, 1797 (1966).
- (29) O. L. Chapman, M. R. Engel, J. P. Springer, and J. C. Clardy, J. Am. Chem. Soc., 93, 6696 (1971).
- (30) J. Auerbach and S. M. Weinreb, J. Org. Chem., 40, 3311 (1975).
- (31) G. Stork and D. J. Morgans, Jr., J. Am. Chem. Soc., 101, 7110 (1979).
- (32) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, and K. Fukumoto, J. Am. Chem. Soc., 98, 3378 (1976).
- (33) R. L. Funk and K. P. C. Vollhardt, J. Am. Chem. Soc., 99, 5483 (1977).
- (34) E. G. Breitholle and A. G. Fallis, J. Org. Chem., 43, 1964 (1978).
- (35) J. E. Bucher, J. Am. Chem. Soc., 32, 374 (1910).
- (36) D. M. Harrison, J. MacMillan, and R. H. B. Galt, Tetrahedron Lett., 3137 (1968).
- (37) J. D. White, P. S. Manchand, and W. B. Whalley, J. Chem. Soc. Chem. Comm., 1315 (1969).
- (38) V. Rautenstrauch and G. Ohloff, Helv. Chim. Acta, 54, 1776 (1971).
- (39) D. H. R. Barton and D. Elad, J. Chem. Soc., 2085 (1956).
- (40) F. E. Ziegler and J. A. Schwartz, J. Org. Chem., 43, 985 (1978).
- (41) B. B. Snider, D. M. Roush, and T. A. Killinger, J. Am. Chem. Soc., 101, 6023 (1979).
- (42) B. V. Burger, E. duPlessis, C. F. Garbers, and K. G. R. Pachler, J. Chem. Soc. Perkin Trans. I, 584 (1973).
- (43) W. Cocker, T. B. H. McMurry, and D. M. Sainsbury, J. Chem. Soc. (C), 1152 (1966).

- (44) S. Veibel and C. Pedersen, Acta Chem. Scand., 9, 1674 (1955).
- (45) J. E. H. Hancock and R. P. Linstead, J. Chem. Soc., 3490 (1953).
- (46) J. Sauer, Angew. Chem. Int. Ed. Eng., 6, 16 (1967).
- (47) M. T. H. Lin and C. Schmidt, Tetrahedron, 27, 5289 (1971).
- (48) M. J. S. Dewar and R. S. Pyron, J. Am. Chem. Soc., 92, 3098 (1970).
- (49) J. W. McIver, Jr., Acc. Chem. Res., 7, 72 (1974).
- (50) M. J. S. Dewar, S. Olivella, and H. S. Rzepa, J. Am. Chem. Soc., 100, 5650 (1978).
- (51) R. E. Townshend, G. Ramunni, G. A. Segal, W. J. Hehre, and L. Salem, J. Am. Chem. Soc., 98, 2190 (1976).
- (52) K. N. Houk, Acc. Chem. Res., 8, 361 (1975).
- (53) F. Tiemann and P. Krüger, Chem. Ber., 26, 2675 (1893).
- (54) J. Garnero and D. Joulain, Bull. Chem. Soc. Fr. II, 15 (1979).
- (55) S. Torii, K. Uneyama, and S. Matsunami, J. Org. Chem., 45, 16 (1980).
- (56) J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., 35, 2319 (1970).
- (57) E. J. Corey and J. W. Suggs, J. Org. Chem., 40, 2554 (1975).
- (58) R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, J. Chem. Soc. Chem. Comm., 1097 (1971).
- (59) H. O. House and J. Umen, J. Am. Chem. Soc., 94, 5495 (1972).
- (60) H. O. House, L. E. Huber, and J. Umen, J. Am. Chem. Soc., 94, 8471 (1972).

PART II

STUDIES ON THE SYNTHESIS OF THE
NORTHWEST AND SOUTHEAST SEGMENTS
OF BOROMYCIN

A. INTRODUCTION

Boromycin was first reported in 1967 by Prelog's group at the Eidgenössische Technische Hochschule in Switzerland, where it was isolated from an extract of a culture of Streptomyces antibioticus (Waksman et Woodruff), ETH 28829 (1). The complete structure determination had to await the completion of an X-ray crystallographic study in 1971 (2), from which the structure was revealed to be 1. The crystallographic determination was actually performed on the rubidium salt of desvalyl-boromycin, obtained by saponification of the D-valine ester with rubidium hydroxide.

Several interesting features can be seen in the structure of boromycin. The first is the tetrahedral Böeseken complex of the boron with four hydroxyl groups. The second is the close similarity in structure between the so-called northern and southern halves, if a division of the molecule is made through the lactone functions and the boron. The configurations at each chiral center are the same in the two halves with the exception of C-9 and C-9', which are respectively R and S. Third, the northern half displays a tetrahydrofuran unit which can be viewed, in principle at least, as the result of a cyclization of the analogous hydroxy olefin segment found in the southern half. Also of note is the fact that boromycin is an ester of the unusual D optical isomer of valine.

The aplasmomycins are also metabolites of a Streptomyces strain, in this case Streptomyces Griseus SS-20, isolated from shallow sea mud (3). Interestingly, the best growth medium for aplasmomycin production by this strain was one containing a relatively high concentration of sodium chloride (1.5%) and a powdered sea-weed, Kobu-Cha (1%). The structure of aplasmomycin 2 was determined by X-ray crystallography of the silver salt and was reported in 1977 (4).

The structure of aplasmomycin is very similar to that of boromycin. The northern and southern halves are identical in this case, both containing the tetrahydrofuran moiety characteristic of the northern half of boromycin, along with an additional olefinic linkage. Aplasmomycins B and C, respectively 3 and 4, were reported in 1978 (5) and are the mono- and di-acetates of aplasmomycin. Boromycin and the aplasmomycins are unique in being the only well-characterized boron-containing organic natural products (2).

The biological activity of boromycin and aplasmomycin differ only slightly. Boromycin is active against gram-positive bacteria (1) such as Staphylococcus aureus SG 511, Streptococcus mitis, and Bacillus subtilis ATCC 6633 in minimum inhibitory concentrations ranging around 0.5 micrograms per milliliter of culture medium. Aplasmomycin has a similar spectrum of activity (3), but appears to require concentrations 2 to 5 times higher to inhibit bacterial growth. Both are active against Plasmodium berghei in mice by injection or oral administration (15 mg/kg for boromycin, 100 mg/kg for aplasmomycin). The acute toxic dose in the mouse (LD_{50}) for boromycin is 180 mg/kg administered orally, while that for aplasmomycin is 125 mg/kg by intraperitoneal injection. The Merck Co. has patented boromycin and its acid-hydrolysis products as

anticoccidiocis agents in chickens, both therapeutically and prophylactically (6, 7).

The antibiotic activity for aplasmomycin B (3) is essentially the same as aplasmomycin. Aplasmomycin C (4) is virtually inactive as an antibiotic (5). Aplasmomycin and boromycin from which the boron has been removed by mild acidic hydrolysis are also inactive, while desvalyl-boromycin is active.

The ability of these compounds to complex potassium ions parallels their biological activity exactly. This is an agreement with present ideas about their mode of action, which is that they act as ionophoric antibiotics engaging in the active transport of potassium out of cells, and thus disrupt cell energetics. Boromycin has been shown to bind to cell walls and to engage in active transport of potassium ions, an activity inhibited by high extracellular potassium ion concentrations (8, 9).

Floss has published the results of a study of the biosynthesis of aplasmomycin (10). The backbone of this molecule is derived from acetate built onto a three-carbon starter unit which probably originates from glycerol. The additional methyl groups at carbons 18, 19, and 20 come from methionine.

As previously noted, alkaline hydrolysis of boromycin, followed by acidic hydrolysis, yielded desvalyl-desboro-boromycin 5 (1). Oxidation of 5 with osmium tetroxide, followed by treatment with periodate, produced acetaldehyde, the neutral fragment 6 corresponding to a segment of the northern half, and the acid 7 from the southern half (2). No other chemical studies on boromycin have been reported.

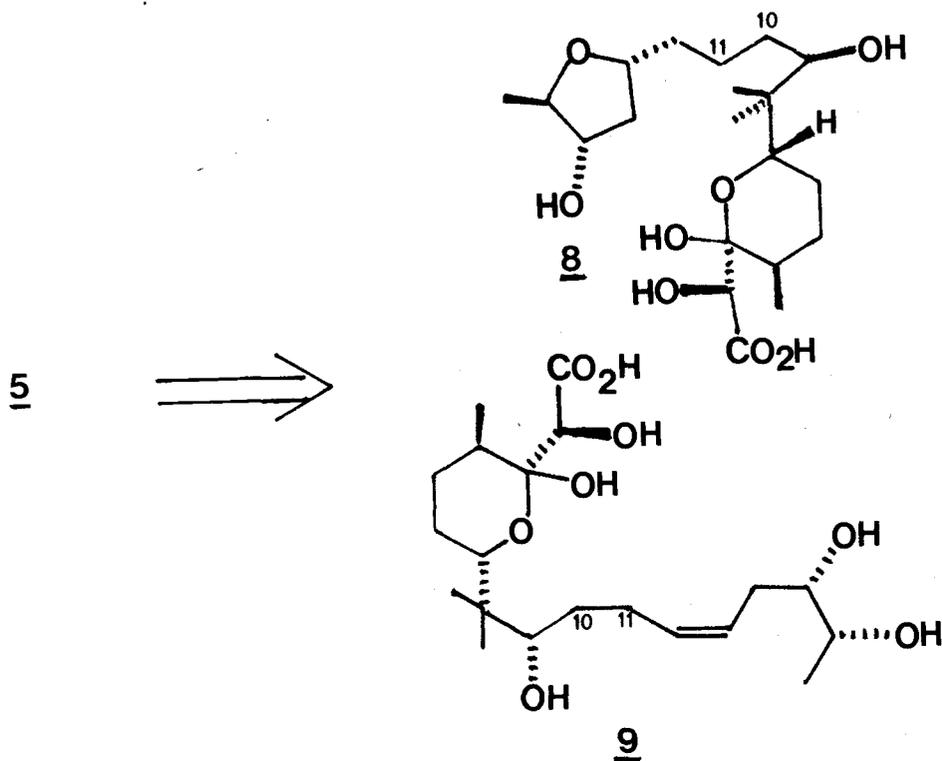
Studies on the synthesis of boromycin, in addition to defining

methodology for the construction of a compound of high complexity, would allow information to be gained which would be applicable in a number of ways. These include the chemical modification of the boromycin-aplasmomycin antibiotics for further study of their mode of action, formulation of structure-activity relationships, and perhaps improvement or alteration of their pharmacologic properties.

B. DISCUSSION AND RESULTS

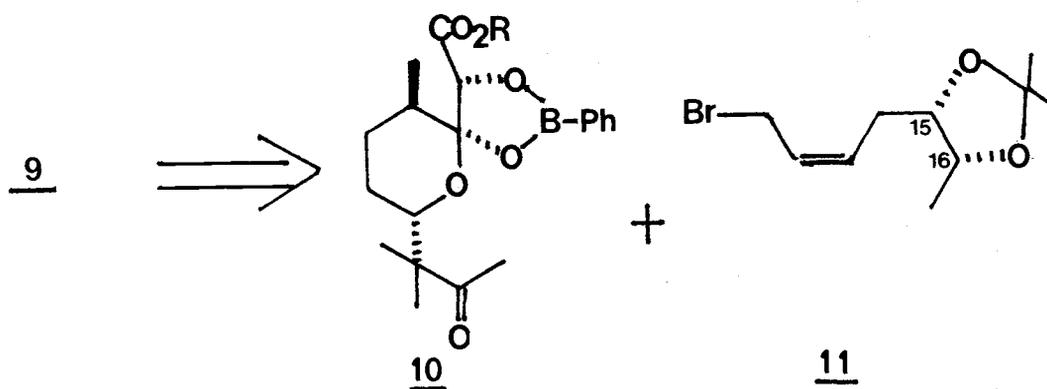
The synthesis of such a highly complex target as boromycin, with its 28-membered macrolide ring, 17 chiral centers, and varied functionality, should embrace at least two major features. The first of these is the introduction of some of the chiral centers in their correct absolute configurations early in the scheme. The second is a plan of construction which is convergent, providing for the preparation of subunits of the molecule which can be combined to furnish the completed target. This convergence permits flexibility in the synthesis design and also affords economy in both the utilization of materials and manpower.

As was pointed out earlier, cleavage of the lactone linkages would produce two very similar halves, 8 and 9, of desvalyldesboro-boromycin 5,



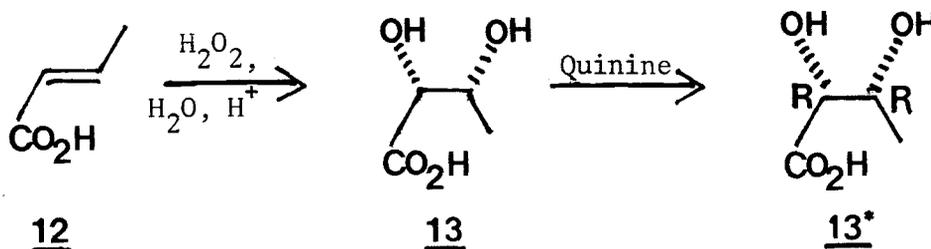
differing only in the configuration of the C-9, C-9' alcohols and the presence of a tetrahydrofuran in the northern half which could be viewed as the product of cyclization of the C-16 alcohol onto the C-13 terminus of the olefin in the southern half.

The next disconnection to be made in this retrosynthetic analysis would be the cleavage of 9 between C-10 and C-11. This, along with oxidation of the C-9 alcohol to a ketone and provision for suitable functionality (halide or tosylate) on carbon 11 would afford the means for connection of the two units via alkylation of the enolate of methyl ketone 10. On this basis, bromide 11 became a primary target for synthesis. In particular, a convergent synthesis for 11 was desired

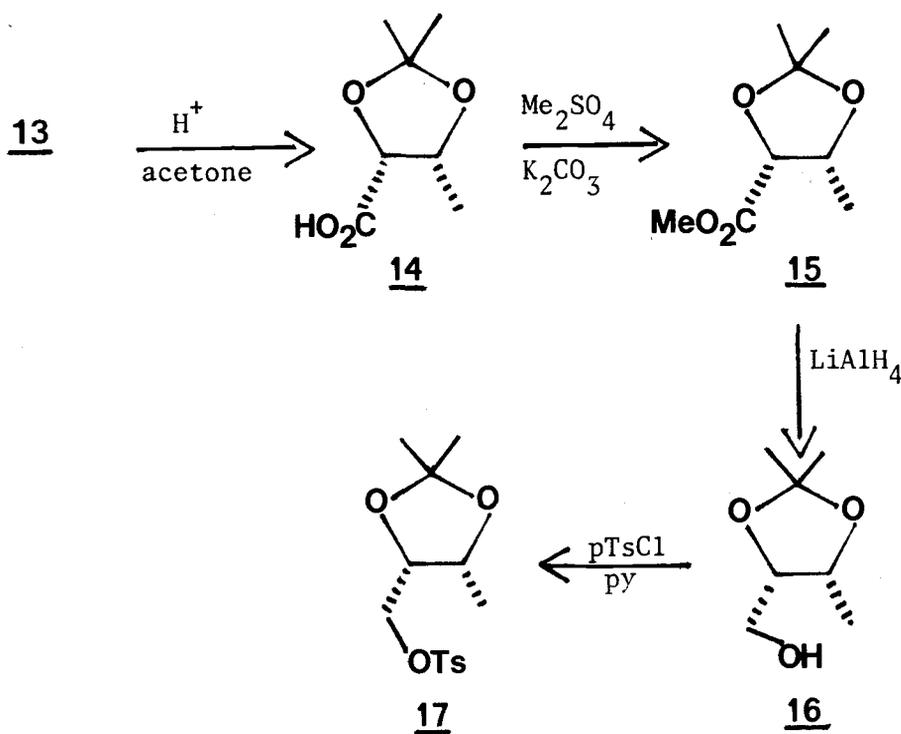


which would allow for inclusion of optical activity at carbons 15 and 16.

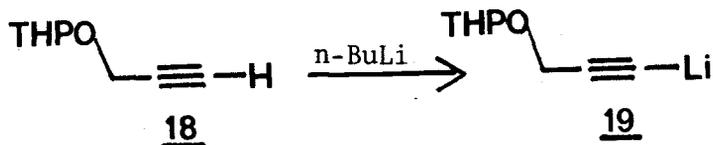
Crotonic acid 12 has been converted to the erythro diol 13 by oxidation with aqueous hydrogen peroxide catalyzed by tungstic acid (11).



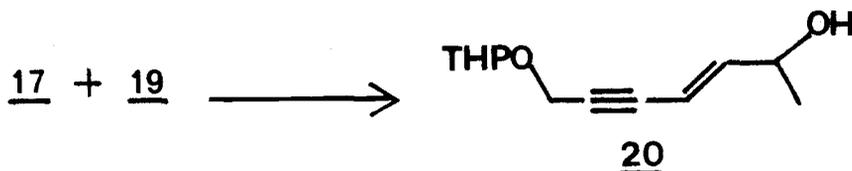
The dihydroxy acid has also been resolved via the quinine salt and the absolute configuration of the resultant levorotatory isomer has been shown to be 2R, 3R by correlation of optical rotatory dispersion curves with tartaric acid (11). The erythro diol 13 was prepared by the method of Bachelor (11) and was protected as its acetonide 14. The carboxyl group of 14 was converted with dimethyl sulfate to its ester 15 which was reduced to the alcohol 16 (12) with lithium aluminum hydride. The tosylate 17 was prepared under standard conditions.



The tetrahydropyranyl ether 18 was obtained by treatment of propargyl alcohol with dihydropyran and p-toluenesulfonic acid (13, 14), and was converted to the lithio acetylide 19 (15) with butyllithium in the hope of effecting alkylation with 17. However several attempts to perform this reaction met with failure. The sole product isolated from these attempts was identified as the enyne 20, obtained in low yield.

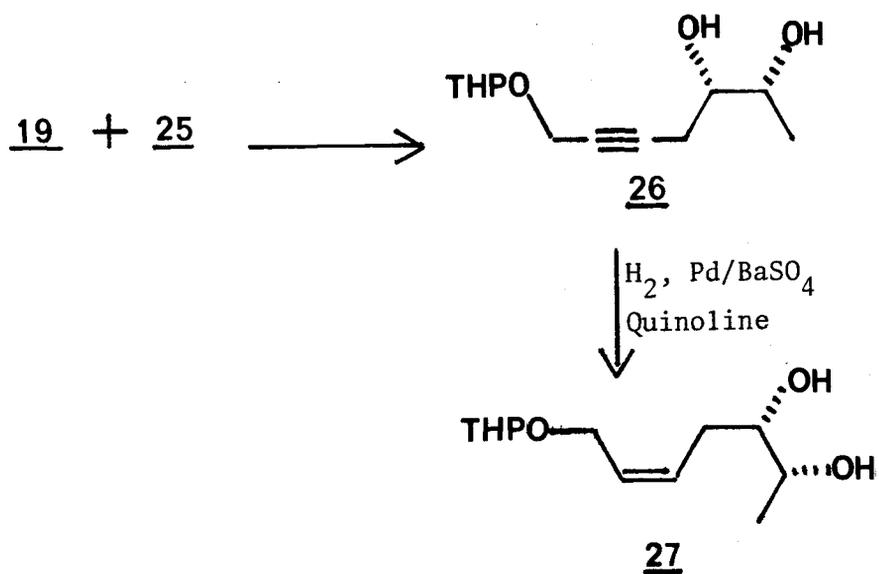
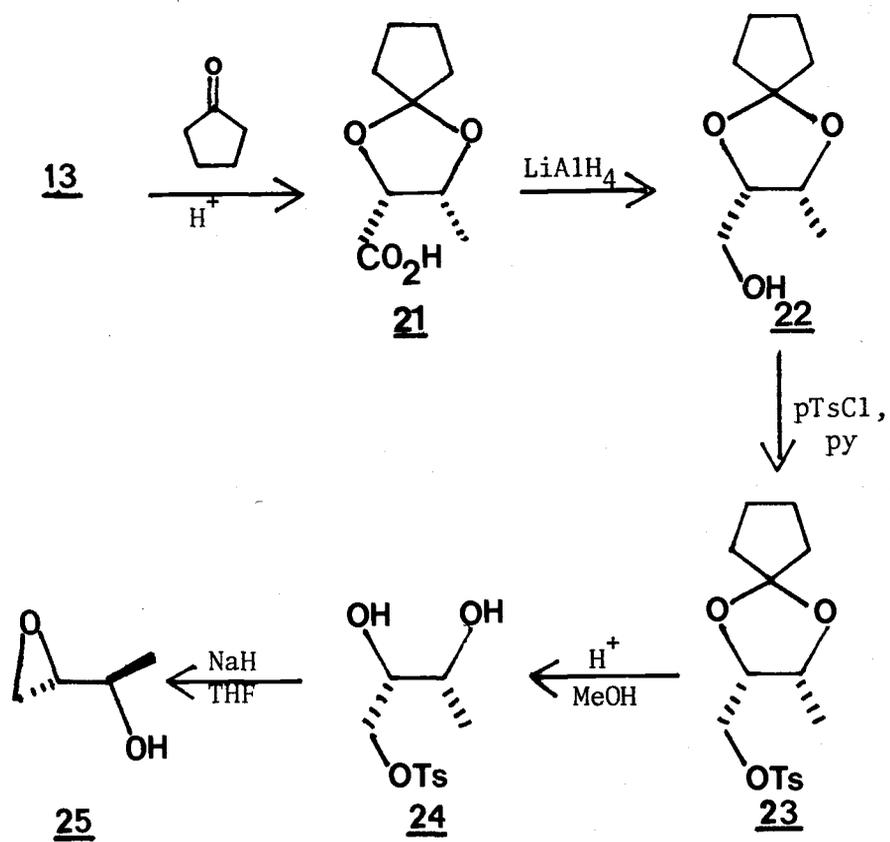


This low yield of alkylation product from 17 is probably due to steric effects. The preferred conformation of 17 appears to be one in which the tosylate is oriented in such a way that a bimolecular displacement would require the nucleophile to travel past one of the acetonide methyl groups in order to achieve backside attack.

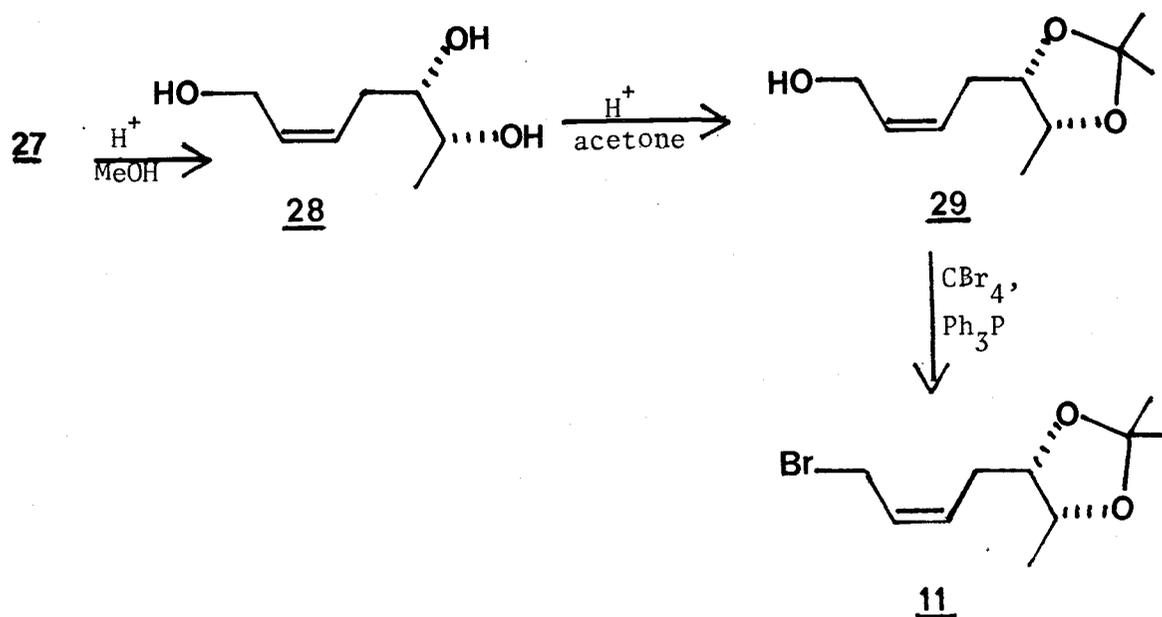


With this steric difficulty in mind, a modified route was developed in which the diol 13 was protected as the more labile cyclopentylidene derivative 21. Reduction to 22 and tosylation as before led to 23. The hydroxyl groups were now released with p-toluenesulfonic acid in methanol without damage to the tosylate to yield 24. Subsequent treatment of 24 with sodium hydride in tetrahydrofuran afforded the epoxide 25 (16).

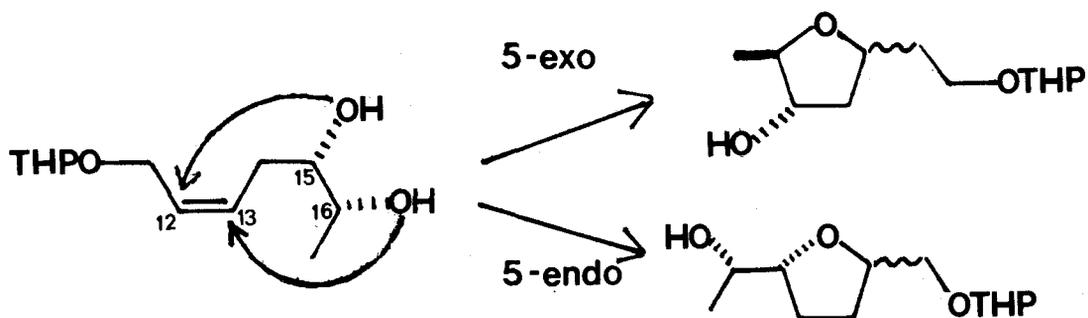
The work of Borch (17) and others (14) suggested that 25 would be a reactive substrate toward alkylation by 19. Although an epoxide is generally less reactive toward alkylation than a tosylate, in this case 25 lacks the steric barrier associated with 17. Indeed, alkylation of 25 with two equivalents of acetylide 19 in tetrahydrofuran and an equimolar amount of hexamethylphosphorus triamide proceeded in good yield to 26. Separation of 26 from excess 18 could be easily accomplished using column chromatography.



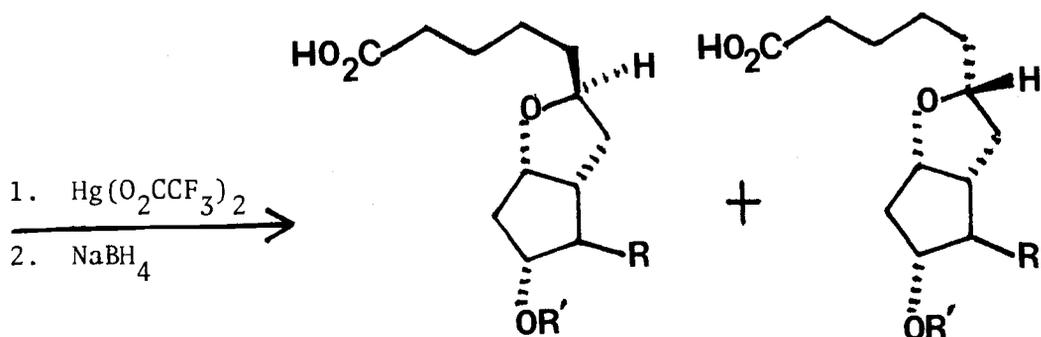
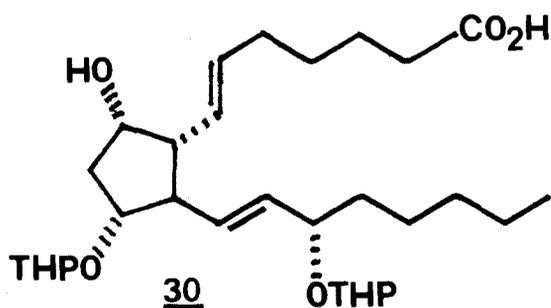
Reduction of the acetylene 26 to the cis olefin 27 was accomplished in quantitative yield by catalytic hydrogenation over 10% palladium on barium sulfate poisoned with quinoline (18). Removal of the protecting tetrahydropyranyl group from 27 with p-toluenesulfonic acid in methanol afforded 28, which was converted to its acetonide 29 by addition of acetone in benzene with azeotropic removal of water. The allylic alcohol function was then cleanly converted to the bromide 11 using triphenylphosphine and carbon tetrabromide.



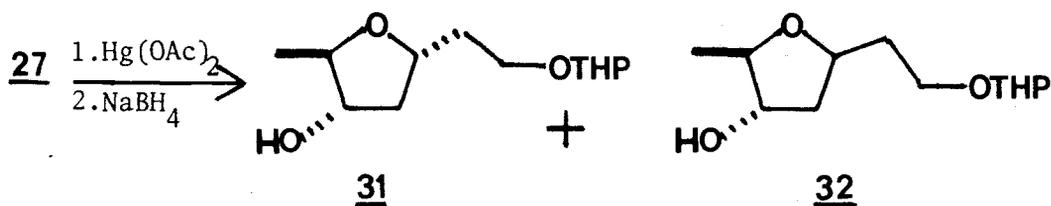
The plan for construction of the tetrahydrofuran moiety of the northern half of boromycin hinged on closure of the C-16 (boromycin numbering) hydroxyl onto C-13 of the olefin in 27 in an intramolecular oxymercuration. The desired closure would be designated a 5-exo-trig cyclization in the Baldwin nomenclature, and his analysis of vectorial approach in similar systems predicts this cyclization mode to be favored over the alternate attack of the C-15 hydroxyl on C-12 in a 5-endo-trig cyclization (19). Experimental precedent is also available which shows



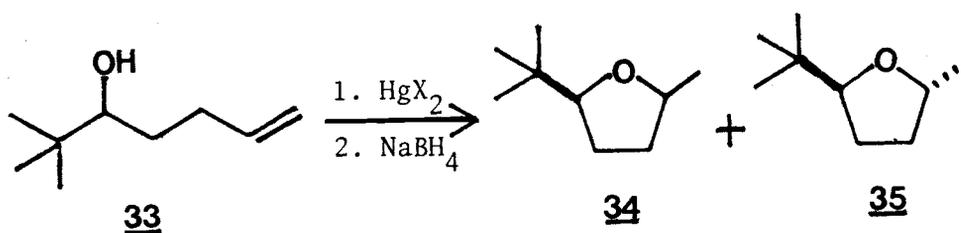
that cyclization in the 5-exo-trig fashion is facile, having been studied extensively in the prostaglandin field, among others (20). For example, Corey (21) treated the $\text{PGF}_{2\alpha}$ derivative 30 with mercuric trifluoroacetate, and isolated the corresponding tetrahydrofuran derivative in good yield.



When 27 was treated with mercuric acetate, the tetrahydrofurans 31 and 32 were obtained after treatment in situ of the cyclization products with sodium borohydride. NMR analysis of the mixture indicated



the presence of two diastereomers in approximately a 1:1 ratio, and these are assigned cis and trans configurations as shown. The stereochemistry of the tetrahydrofuran depends upon which face of the olefin is attacked by the hydroxyl, and this in turn is controlled in the formation of the mercurinium ion intermediate preceding the cyclization. A study of the intramolecular oxymercuration reaction by French workers (22) has demonstrated that the stereochemistry of cyclization varies with the mercuric salt used. For example, the olefinic alcohol **33** gave a nearly 2:1 mixture of cis (**34**) to trans (**35**) isomers on treatment with mercuric chloride, whereas mercuric acetate reversed this stereoselectivity. In view of this evident variability in stereocontrol, it was felt that a bulkier ligand on the mercury, and perhaps a less reactive mercury salt, would promote formation of the desired 2,5-trans substituted isomer **31**.

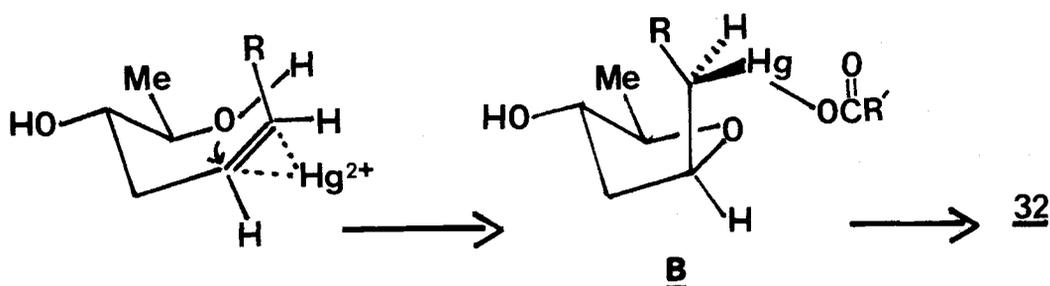
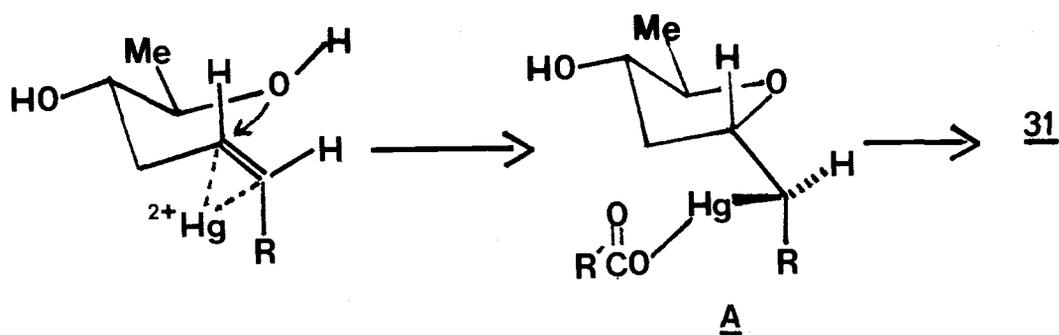


X = Cl ⁻	64	:	36
X = Ac ⁻	24	:	76

Mercuric pivalate was prepared (23) and this substance was explored as a reagent for cyclization of the diol olefin 27 in tetrahydrofuran. The rate of the reaction appeared to be slower than with mercuric acetate, as evidenced by chromatographic analysis. Thus, although disappearance of starting material occurred rapidly (by TLC), when an aliquot of the reaction mixture was treated with sodium borohydride prior to chromatography, starting material was still present in substantial amounts. The implication of this finding is that, while the formation of the mercurinium intermediate is relatively rapid, the cyclization is slow. At room temperature, the reaction with 27 required several hours for completion using an excess of mercuric pivalate. More important, the ratio of trans (31) to cis (32) isomers was found to be about 2:1. The explanation for this change in product distribution probably lies in the different thermodynamic stabilities of the transition states for the trans and cis products.

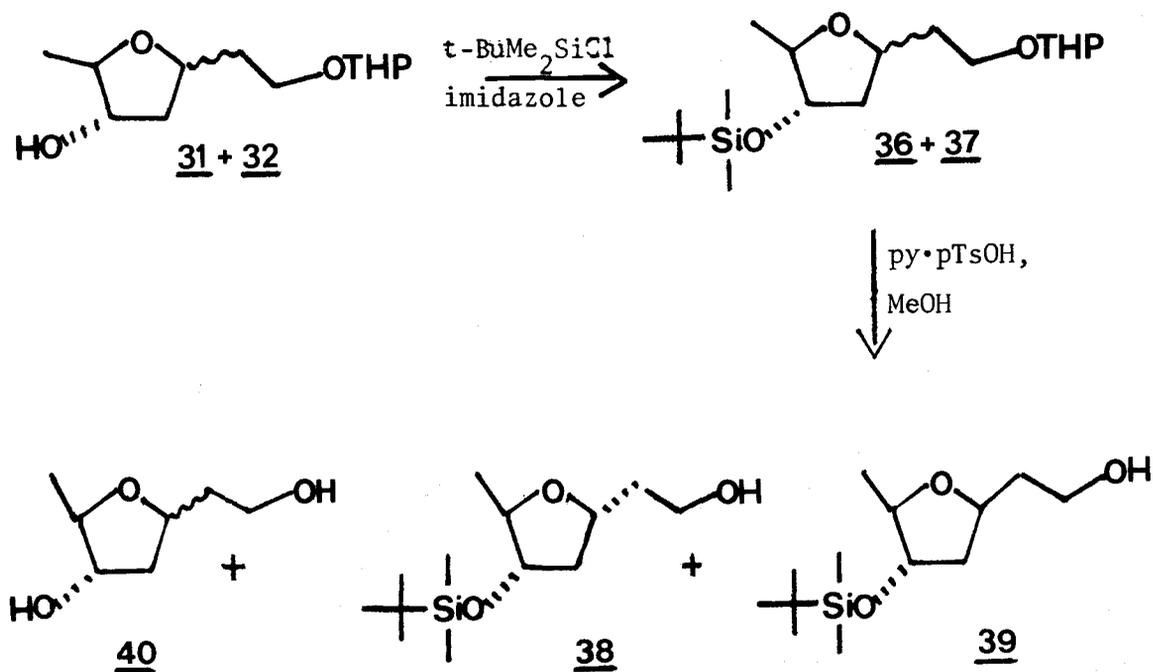
In the case of the desired trans product, the transition state leading to A has the alkylmercury side-chain in a developing pseudo-equatorial conformation whereas the cis product requires a transition state leading to B in which the alkylmercury group occupies a developing pseudo-axial conformation. The latter is thermodynamically less favored and, on this basis, it is not unexpected that increasing steric bulk around the mercury atom will promote formation of the more stable trans 2,5-disubstituted furan 31.

Unfortunately, the two diastereomers 31 and 32 proved to be inseparable by chromatography, so that, for the purpose of continuing the synthesis, it was necessary to carry the mixture forward in the hope that separation could be effected at a later stage. The t-butyldimethyl-



silyl ethers of 31 and 32 were formed in high yield using Corey's procedure (*t*-butyldimethylsilyl chloride and imidazole in dimethylformamide) (24). However, the selective removal of the protecting group from the primary alcohols 36 and 37 was found to be troublesome. Thus, hydrolysis of 36 and 37 using acidic conditions (aqueous acetic acid, aqueous oxalic acid, *p*-toluenesulfonic acid in methanol) showed that the loss of silyl ether proceeded at about the same rate as removal of the tetrahydropyranyl ether. The most suitable reagent for deprotection of the primary alcohol was found to be pyridinium *p*-toluenesulfonate in methanol (25) but, even with this mildly acidic catalyst, the ratio of 38 and 39 to diol 40 was about 70:30 (26). Most interesting, however, was the observation that the primary alcohols 38 and 39 were now chromatographically distinct. Separation of *trans* 38 and *cis* 39 isomers was effected by careful chromatography on silica gel, eluting with a mixture of 30% ethyl acetate in hexane. While the NMR spectra of the

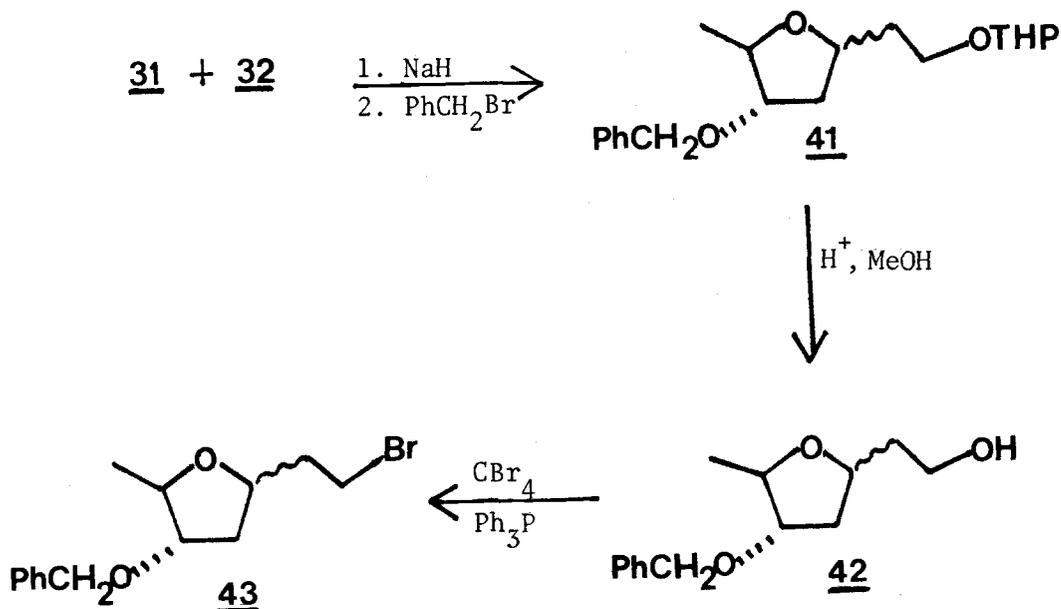
separated isomers were virtually identical, a shift reagent study of a sample containing both 38 and 39 confirmed the stereochemical assignments shown. It was expected that, with complexation of the shift reagent tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium to the primary alcohol, a slightly greater downfield shift of the methyl group at the 2-position of the tetrahydrofuran would occur in the cis isomer 39 than in the trans compound 38 due to the greater



proximity of shift reagent to methyl in 39. This proved to be the case, as the smaller of the two methyl doublets in the NMR spectrum of the mixture was shifted further downfield than the major one. The major isomer is therefore the trans 2,5-isomer 38.

For the purpose of developing the alkylation chemistry necessary for construction of the northern half of boromycin, the mixture of diastereomers 31 and 32 was used. Thus, 31 and 32 were first converted to the benzyl ether 41 with benzyl bromide and sodium hydride. The tetrahydropyranyl protecting group was then removed by treatment with

p-toluenesulfonic acid in methanol to expose the primary alcohol 42. Transformation of 42 to the bromide 43 was carried out using carbon tetrabromide and triphenylphosphine.



In conclusion, the initial aim of this project, the stereo-controlled preparation of segments corresponding to northwestern and southeastern quadrants of boromycin, has been accomplished. These segments stand ready for connection to a fragment, already constructed, corresponding to the southwestern and northeastern quadrants of the macrolide, so that completion of the two halves of boromycin is now conceptually within reach.

C. EXPERIMENTAL

Methyl erythro-2,3-Dihydroxy-2,3-isopropylidenebutyrate (15)

A solution of 10.0 g (84.5 mmol) of erythro-2,3-dihydroxybutyric acid (11) and 200 mg of p-toluenesulfonic acid in 100 ml of acetone was refluxed for 4 h through a Soxhlet extractor containing 100 g of 4Å molecular sieves. The solution was cooled and filtered, and then 6.6 g (46 mmol) of anhydrous potassium carbonate and 4.5 ml (5.8 g, 46 mmol) of dimethyl sulfate were added. This mixture was refluxed for 1 h with vigorous stirring. The mixture was cooled, filtered, concentrated in vacuo, and diluted with ethyl ether. The ethereal solution was washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, and was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent gave a yellow oil which was distilled to afford 5.1 g (34%) of 15 as a colorless oil: bp 85-95°C/12 mm; IR (film) 1800, 1760, 1740 cm^{-1} ; NMR (CDCl_3) δ 4.6 (2 H, m), 3.8 (3 H, s), 1.6 (3 H, s), 1.4 (3 H, s), 1.2 (3 H, d, $J = 5$ Hz); MS m/e 174 (M^+).

erythro-2,3-0-Isopropylidene-1,2,3-butanetriol (16)

A suspension of 0.8 g (21 mmol) of lithium aluminum hydride in 50 ml of anhydrous ethyl ether in a three-necked, round-bottom flask equipped with condenser, addition funnel, nitrogen inlet, and magnetic stir-bar was cooled under nitrogen in an ice-water bath. The butyrate 15 (5.00 g, 28.7 mmol) in 10 ml of ether was added dropwise with vigorous stirring over a period of 10 min. After 30 min the reaction mixture was warmed to reflux for a further 30 min. The mixture was then cooled and quenched by careful sequential addition of 2 ml of ethyl acetate, 0.8 ml of

water, 0.8 ml of 15% aqueous sodium hydroxide, and 2.4 ml of water. The resultant, white precipitate was removed by filtration and washed four times with 20 ml portions of ether. The combined ether washes and filtrate were dried (anhydrous magnesium sulfate), filtered, and evaporated to give 4.1 g (98%) of 16 as a clear oil: bp 85-95°C/20 mm (lit. (12) 74-78°C/10 mm); IR (film) 3430 cm^{-1} ; NMR (CDCl_3) δ 4.2 (2 H, m), 3.6 (2 H, d, $J = 5$ Hz), 3.3 (1 H, bs), 1.4 (3 H, s), 1.3 (3 H, s) 1.2 (3 H, d, $J = 5$ Hz); MS m/e 146 (M^+).

erythro-2,3-O-Isopropylidene-1-p-toluene-
sulfonyloxy-2,3-butanediol (17)

A solution of 4.00 g (27.4 mmol) of 16 in 50 ml of anhydrous pyridine under a nitrogen atmosphere was cooled in an ice-water bath and p-toluenesulfonyl chloride (6.1 g, 31 mmol) was added in portions. The mixture was allowed to warm to room temperature and then stand overnight. The mixture was diluted with ether, washed sequentially with saturated aqueous copper sulfate, water, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over magnesium sulfate, the ether extract was filtered and evaporated to give 6.4 g (79%) of 17 as a viscous oil which solidified on standing. Purification by column chromatography (10% acetone-cyclohexane) afforded analytically pure 17: mp 54-55°C; IR (Nujol) 1350, 1170, 1090, 970 cm^{-1} ; NMR (CDCl_3) δ 7.8 (2 H, d, $J = 9$ Hz), 7.3 (2 H, d, $J = 9$ Hz), 4.4-3.8 (4 H, m), 2.4 (3 H, s), 1.3 (6 H, s), 1.2 (3 H, d, $J = 6$ Hz); MS m/e 285.078 ($\text{M}^+ - 15$, calc for $\text{C}_{13}\text{H}_{17}\text{O}_5\text{S}$ 285.080).

1-Tetrahydropyranyloxy-4-hepten-2-yne-6-ol (20)

A solution of propargyl alcohol tetrahydropyranyl ether (13) (0.21 g, 1.5 mmol) in 5 ml of tetrahydrofuran under a nitrogen atmosphere was cooled in a Dry Ice/acetone bath and was treated with 1 ml of n-butyllithium (1.6 M, 1.6 mmol). After 15 min the acetylide solution was added to a solution of 0.3 g (1 mmol) of 17 in a mixture of 3 ml of HMPA and 4 ml of THF heated to 90°C. After 3 h, the reaction mixture was cooled, diluted with ether, and washed with water and brine. The ethereal solution was dried (magnesium sulfate), filtered, and the solvent was evaporated to give 280 mg of a yellow oil. This oil was fractionated by preparative TLC (25% acetone-cyclohexane) and yielded 57 mg (27%) of propargyl alcohol tetrahydropyranyl ether, 25 mg (8%) of 17 and 30 mg (6%) of 20: IR (film) 3400, 2950, 2870 cm^{-1} ; NMR (CDCl_3) δ 5.95 (1 H, m), 4.8 (1 H, m), 4.4 (2 H, br s), 4.3 (1 H, s), 4.0-3.7 (1 H, m), 3.7-3.4 (1 H, m), 2.2 (1 H, s), 1.7 (8 H, m), 1.5 (3 H, s) 1.3 (3 H, d, $J = 6 \text{ Hz}$); MS m/e 210 (M^+).

erythro-2,3-O-Cyclopentylidene-2,3-dihydroxybutyric Acid (21)

Erythro-2,3-dihydroxybutyric acid (12.0 g, 0.10 mole) was refluxed in 150 ml of benzene containing 10 mg of p-toluenesulfonic acid and 10.0 g (0.12 mole) of cyclopentanone. After 4 h the reaction mixture was cooled, decanted from a small amount of brown residue, and concentrated in vacuo to constant weight, yielding 17.0 g (91%) of 21. An analytical sample was prepared by recrystallization of a small portion (ethyl acetate-hexane) to yield colorless needles of 21: mp 79-81.5°C; IR (film) 3430 (br), 2980, 1800, 1740 cm^{-1} ; NMR (CDCl_3) δ 4.6-4.1 (2 H, m),

1.7 (8 H, br s), 1.2 (3 H, d, $J = 6$ Hz); MS m/e 186 (M^+).

erythro-2,3-O-Cyclopentylidene-1,2,3-butanetriol (22)

To a suspension of lithium aluminum hydride (3.80 g, 0.10 mole) in 200 ml of freshly distilled tetrahydrofuran under nitrogen was added 17.0 g (0.91 mole) of 21 in 100 ml tetrahydrofuran at such a rate as to maintain a gentle reflux (30 min). The mixture was refluxed for 1 h, cooled, and quenched with 5 ml of ethyl acetate. Workup was accomplished by adding sequentially 4 ml of water, 4 ml of 15% sodium hydroxide, and 12 ml of water. Filtration and evaporation of the filtrate produced 12.3 g (82%) of 22 as a colorless oil: IR (film) 3400, 2960, 1340 cm^{-1} ; NMR (CDCl_3) δ 3.5 (2 H, d, $J = 6$ Hz), 3.25 (1 H, br s, exchanges with D_2O), 1.6 (8 H, br s), 1.15 (3 H, d, $J = 6$ Hz); MS m/e 172.108 (M^+ , calc for $\text{C}_9\text{H}_{16}\text{O}_3$ 172.110).

erythro-2,3-O-Cyclopentylidene-1-p-toluene-
sulfonyloxy-2,3-butanediol (23)

A solution of 22 (12.3 g, 0.072 mole) in 150 ml of dry pyridine was cooled in an ice-bath. p-Toluenesulfonyl chloride (freshly recrystallized from chloroform-petroleum ether; 25.0 g, 0.14 mole) was added in several portions with stirring. The reaction mixture was placed in the freezer and, after 24 h, was worked up by pouring onto 400 g of ice and extracting the resultant aqueous solution with three 150 ml portions of ether. The combined organic extracts were washed with aqueous copper sulfate, water, and brine, and then evaporated in vacuo to yield 22.0 g (95%) of 23: IR (Nujol) 1360, 1180, 660 cm^{-1} ; NMR

(CDCl₃) δ 7.8 (2 H, d, J = 7 Hz), 7.3 (2 H, d, J = 7 Hz), 4.0 (4 H, m), 2.4 (3 H, s), -.7 (8 H, s), 1.2 (3 H, d, J = 7 Hz); MS m/e 326.118 (M⁺, calc for C₁₆H₂₂SO₅ 326.119).

erythro-1-p-Toluenesulfonyloxy-2,3-butanediol (24)

A solution of 23 (13.3 g, 41 mmol) and p-toluenesulfonic acid (200 mg, 1.0 mmol) was stirred in 150 ml of methanol. After 8 h at room temperature, potassium carbonate (100 mg) was added and the solvent was removed in vacuo to yield 7.70 g (73%) of 25: mp 61-63°C (methylene chloride-carbon tetrachloride); IR (Nujol) 3550, 1600, 1350 cm⁻¹; NMR (CDCl₃) δ 7.8 (2 H, d, J = 8 Hz), 7.4 (2 H, d, J = 8 Hz), 4.20 (1 H, s), 4.15 (1 H, d, J = 2 Hz), 4.0-3.7 (2 H, m), 2.8 (2 H, s, exchanges with D₂O), 2.45 (3 H, s), 1.16 (3 H, d, J = 6 Hz); MS m/e 215 (M⁺-45).

erythro-1,2-Epoxy-3-butanol (25)

A solution of 13.0 g (50.0 mmol) of 24 and 2 drops of dimethylsulfoxide in freshly distilled tetrahydrofuran under nitrogen was treated with 2.28 g (47.5 mmol) of 50% sodium hydride in oil. After stirring at room temperature for 8 h, the reaction mixture was filtered and the solvent was evaporated. The resulting brown oil was distilled (25-35°C/1 mm) to yield 3.00 g (72%) of 25: IR (film) 3440, 1740, 1240 cm⁻¹; NMR (CDCl₃) δ 4.1-3.6 (2 H, m), 3.5 (1 H, br s, exchange with D₂O), 3.0 (1 H, q, J = 3 Hz), 2.7 (1 H, d, J = 3 Hz), 1.2 (3 H, d, J = 6 Hz); MS m/e 88.051 (M⁺, calc for C₄H₈O₂ 88.052).

erythro-1-Tetrahydropyranyloxy-2-heptyn-5,6-diol (26)

Propargyl alcohol tetrahydropyranyl ether (7.40 g, 52 mmol) in

30 ml of freshly distilled tetrahydrofuran was cooled under nitrogen in a Dry Ice/acetone bath. *n*-Butyllithium (1.6 M in hexane, 32 ml, 52 mmol) was added with stirring. After 15 min this solution was added to a stirred solution of 25 (2.03 g, 26 mmol) in 30 ml of tetrahydrofuran at -70°C. After 3 days at room temperature, the reaction mixture was diluted with ether and washed with brine. Drying (magnesium sulfate) of the ether extract, followed by filtration and evaporation in vacuo afforded 9.5 g of a pale brown oil. Column chromatography of this material (300 g silica gel, gradient elution from 1:1 ethyl acetate-hexane to ethyl acetate) afforded 4.40 g (74%) of 27: IR (film) 3400, 2590, 2870 cm^{-1} ; NMR (CDCl_3) δ 4.8 (1 H, br s), 4.3 (2 H, d, $J = 2$ Hz), 4.0-3.6 (2 H, m), 3.6 (2 H, br s, exchanges with D_2O), 2.45 (2 H, dt, $J = 2, 6$ Hz), 1.8-1.4 (6 H, m), 1.2 (3 H, d, $J = 6$ Hz); MS m/e 183.099 ($\text{M}^+ - 45$, calc for $\text{C}_{10}\text{H}_{15}\text{O}_4$ 183.098).

cis,erythro-1-Tetrahydropyranyloxy-2-hepten-5,6-diol (27)

A suspension of 60 mg of 10% palladium on barium sulfate was stirred in 60 ml of methanol under a hydrogen atmosphere for 20 min. A solution of 26 (1.50 g, 6.6 mmol) in 15 ml of methanol containing 15 mg of quinoline was added. The mixture took up one equivalent of hydrogen (130 ml) in 30 min, after which the catalyst was removed by filtration through Celite and the methanol was evaporated. The residue was taken up into ether, the solution was filtered and the solvent was evaporated to yield 1.50 g (98%) of 27: IR (film) 3400, 2950 cm^{-1} ; NMR (CDCl_3) δ 5.75 (2 H, m), 4.7 (1 H, br s), 4.4-4.1 (2 H, m), 3.9-3.6 (2 H, m), 3.5 (2 H, br s, exchanges with D_2O), 2.3 (2 H, m), 1.8-1.4 (6 H, m), 1.1 (3 H, d, $J = 6$ Hz); MS m/e 231 ($\text{M}^+ + 1$).

cis,erythro-5,6-O-Isopropylidene-2-hepten-1,5,6-triol (29)

A solution of 27 (460 mg, 2 mmol) in 5 ml of methanol containing 40 mg (0.2 mmol) of p-toluenesulfonic acid was stirred for 1 h at room temperature. The methanol and methoxytetrahydropyran were removed by evaporation in vacuo. The residue was taken up into benzene (10 ml) and acetone (10 ml) and the solution was heated to reflux. A total of 15 ml of distillate was collected (1 h). Solid sodium bicarbonate was added to the mixture and, after filtration, the reaction mixture was concentrated in vacuo. Purification of the residue by chromatography (silica gel, gradient elution from 30% ethyl acetate-hexane to 75% ethyl acetate-hexane) afforded 270 mg (78%) of pure 29: IR (film) 3430, 1380, 1220, 1080 cm^{-1} ; NMR (CDCl_3) δ 5.7 (2 H, m), 4.2 (5 H, m), 3.2 (1 H, br s, exchanges with D_2O), 2.3 (2 H, d of d, $J = 6, 14$ Hz), 1.45 (3 H, s), 1.30 (3 H, s), 1.17 (3 H, d, $J = 6$ Hz); MS m/e 186.124 (M^+ , calc for $\text{C}_{10}\text{H}_{18}\text{O}_3$ 186.126).

cis,erythro-1-Bromo-5,6-O-isopropylidene-2-hepten-5,6-diol (11)

The alcohol 29 (180 mg, 1.0 mmol) and 420 mg (1.25 mmol) of carbon tetrabromide (sublimed) were dissolved in 5 ml of dry methylene chloride. After cooling to 0°C , the solution was treated with 394 mg (1.5 mmol) of triphenylphosphine in portions. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The mixture was quenched with 100 μl of saturated aqueous sodium bicarbonate and diluted with ether. The ethereal solution was washed with water and then with brine. After drying (magnesium sulfate), filtration of the ethereal extract and evaporation in vacuo afforded a pale yellow gum that was triturated with

ether. The ethereal solution was washed with water and then with brine. After drying (magnesium sulfate), filtration of the ethereal extract and evaporation in vacuo afforded a pale yellow gum that was triturated with ether. The ethereal extracts were combined and evaporated in vacuo to provide a yellow oil, which was further purified by chromatography (silica gel, 20% ethyl acetate-hexane) to yield 98 mg (40%) of 11: IR (film) 2970, 1650, 1205, 1160 cm^{-1} ; NMR (CDCl_3) δ 5.9-5.6 (2 H, m) 4.4-3.7 (4 H, m), 2.4-2.2 (2 H, m), 1.5 (3 H, s), 1.35 (3 H, s), 1.22 (3 H, d, $J = 6$ Hz).

2 α -Hydroxy-1 β -methyl-5 α , β -(2-tetrahydropyranyloxyethyl)-
tetrahydrofuran (31) and (32)

A. Mercuric Acetate Induced Cyclization of (27)

To a solution of 27 (384 mg, 166 mmol) dissolved in 10 ml of 50% aqueous tetrahydrofuran was added mercuric acetate (580 mg, 1.8 mmol) and the reaction mixture was stirred for 4 h. Excess 1 M sodium borohydride in 10% aqueous sodium hydroxide was carefully added, and the reaction mixture was then diluted with ether and decanted from the precipitated elemental mercury. The combined organic extracts were washed with aqueous sodium bicarbonate, water, and brine, and dried over magnesium sulfate. Filtration and evaporation of the solvent afforded 348 mg (93%) of 31 and 32 which showed a single spot by TLC analysis: IR (film) 3450 cm^{-1} ; NMR (CDCl_3) δ 4.6 (1 H, br s), 4.4-4.1 (2 H, m), 4.1-3.7 (3 H, m), 3.65-3.4 (2 H, m), 2.8 (br s, 1 H), 2.1-1.8 (4 H, m), 1.8-1.4 (6 H, m), 1.20 (3 H, d, $J = 6$ Hz, α -isomer), 1.15 (3 H, d, $J = 6$ Hz β -isomer); MS m/e 230.151 (M^+ , calc for $\text{C}_{12}\text{H}_{22}\text{O}_4$ 230.152).

B. Mercuric Pivalate Induced Cyclization of (27)

A solution of 1.0 g (4.3 mmol) of 27 in 25 ml of tetrahydrofuran cooled to 0°C was treated with 2.8 g (7.0 mmol) of mercuric pivalate. After stirring for 24 h, the reaction was quenched with excess 1 M sodium borohydride in 10% aqueous sodium hydroxide. The supernatant was decanted from precipitated mercury, subjected to the same workup conditions as the preceding cyclization, dried, and evaporated to afford 0.96 g (96%) of 31 and 32. The NMR showed two methyl doublets at δ 1.15 and δ 1.20, with relative intensity about 1:2 respectively.

3 α -t-Butyldimethylsilyloxy-3 β -methyl-5 α,β -(2-tetrahydro-pyranyloxyethyl)-tetrahydrofuran (36) and (37)

A solution of imidazole (450 mg, 6.7 mmol) and t-butyldimethylsilyl chloride (500 mg, 3.2 mmol) was prepared in 10 ml of dimethylformamide. After stirring the mixture for 10 minutes, a solution of 31 and 32 (660 mg, 2.9 mmol) in 2 ml of dimethylformamide was added to it. The reaction mixture was stirred at room temperature for 18 h, after which it was diluted with ether, washed with saturated aqueous copper sulfate, water, and saturated aqueous sodium chloride. The combined organic extracts were dried (magnesium sulfate), filtered, and evaporated to yield 0.92 g (94%) of 36 and 37: IR (film) 2950, 1260, 1120 cm^{-1} ; NMR (CDCl_3) δ 4.6 (1 H, br s), 4.3-4.0 (1 H, m), 4.0-3.6 (4 H, m), 3.6-3.4 (2 H, m), 2.0-1.4 (10 H, m), 1.18 (3 H, d, $J = 6$ Hz, α -isomer), 1.15 (3 H, d, $J = 6$ Hz, β -isomer), 0.88 (9 H, s); MS m/e 287.169 ($M^+ - 57$, calc for $\text{C}_{14}\text{H}_{27}\text{O}_4\text{Si}$ 287.167).

3 α -t-Butyldimethylsilyloxy-5 α , β -(2-hydroxyethyl)-3 β -
methyltetrahydrofuran (38) and (39)

A solution of 36 and 37 (515 mg, 1.5 mmol) and dried pyridinium p-toluenesulfonate (from pyridine and p-toluenesulfonic acid in ether, 190 mg, 0.75 mmol) was heated to 60°C in 20 ml of methanol. Analysis by TLC after 3 h indicated that the reaction was essentially complete. The cooled reaction mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate. Evaporation of the organic extracts in vacuo afforded 312 mg of a viscous oil. From this, 250 mg was taken and chromatographed (medium pressure LC, 1 cm x 50 cm column, 30% ethyl acetate-hexane) to yield 55 mg of the less polar isomer 38, 56 mg of mixed isomers 38 and 39, and 40 mg of the more polar isomer 39. Compound 38: IR (film) 3400, 2950, 1260, 1110, 1045 cm^{-1} ; NMR (CDCl_3) δ 4.3-4.0 (1 H, m), 3.9-3.6 (4 H, m), 3.44 (1 H, br s), 2.8-2.6 (4 H, m), 1.13 (3 H, d, J = 6 Hz), 0.84 (9 H, s); MS m/e 203.111 (M^+ -57, calc for $\text{C}_9\text{H}_{19}\text{O}_3\text{Si}$ 203.110). Compound 39: NMR (CDCl_3) δ 4.4-4.0 (1 H, m), 3.9-3.6 (4 H, m), 3.3 (1 H, br s), 2.4-2.1 (1 H, m), 2.0-1.4 (3 H, m), 1.10 (3 H, d, J = 6 Hz), 0.83 (9 H, s).

3 α -Benzyloxy-2 β -methyl-5 α , β -(2-tetrahydro-
pyranyloxyethyl)-tetrahydrofuran (41)

A solution of 31 and 32 (230 mg, 1.0 mmol) in 4 ml of dry dimethylformamide was treated with sodium hydride (50% suspension in oil, 55 mg, 1.1 mmol). After 5 min, benzyl bromide (132 μl , 1.1 mmol) was added and the reaction mixture was then stirred at room temperature overnight. The mixture was diluted with ether, washed with water and saturated aqueous

sodium chloride, and dried (magnesium sulfate). Filtration of the mixture and evaporation of solvent in vacuo provided crude 41 which was purified by chromatography (30% ethyl acetate-hexane) to yield 240 mg (75%) of 41: IR (film) 2950, 2890, 1120, 1035 cm^{-1} ; NMR (CDCl_3) δ 7.3 (5 H, s), 4.55 (1 H, br s), 4.48 (2 H, s), 4.3-3.3 (7 H, m), 2.2-1.3 (10 H, m), 1.18 (α -isomer, 3 H, d, $J = 6$ Hz), 1.13 (β -isomer, 3 H, d, $J = 6$ Hz); MS m/e 235.134 ($\text{M}^+ - 85$, calc for $\text{C}_{14}\text{H}_{19}\text{O}_3$ 235.133).

3 α -Benzyloxy-5 α,β -(2-bromoethyl)-2 β -methyltetrahydrofuran (43)

A solution of 41 (500 mg, 1.55 mmol) and 20 mg (0.1 mmol) of *p*-toluenesulfonic acid in 4 ml of methanol was stirred for 4 h at room temperature. The mixture was neutralized with 100 mg of solid sodium bicarbonate and was concentrated in vacuo. The residue was taken up into ether, and the ethereal solution was filtered and evaporated to provide 320 mg (89%) of crude 42. This material (300 mg, 1.28 mmol) was dissolved in 3 ml of methylene chloride containing 540 mg (1.63 mmol) of sublimed carbon tetrabromide. The stirred solution was cooled to 0°C and triphenylphosphine (510 mg, 1.95 mmol) was added in portions. The reaction mixture was stirred for 30 min in ice and then was allowed to warm to room temperature and was stirred for 1 h. The mixture was treated with aqueous sodium bicarbonate and extracted with ether, and the combined ethereal extracts were washed with water and then with saturated aqueous sodium chloride. After drying (magnesium sulfate) and filtering the ethereal extract was concentrated in vacuo. The residue was triturated with ether which was subsequently filtered and evaporated. This procedure was repeated twice more to yield 416 mg (108%, triphenylphosphine oxide contaminant) of 43: IR (film) 2980, 2940, 2870, 1440,

1110 cm^{-1} ; NMR (CDCl_3) δ 7.2 (5 H, m), 4.5 (2 H, s), 4.3-3.9 (2 H, m), 3.8-3.6 (1 H, m), 3.46 (2 H, t, $J = 8$ Hz), 2.4-1.95 (3 H, m), 1.8-1.5 (1 H, m), 1.20 (3 H, d, $J = 6$ Hz, 5α -isomer), 1.16 (3 H, d, $J = 6$ Hz, 5β -isomer); MS m/e 298.055 (M^+ , calc for $\text{C}_{14}\text{H}_{19}\text{O}_2^{79}\text{Br}$ 298.057).

D. BIBLIOGRAPHY

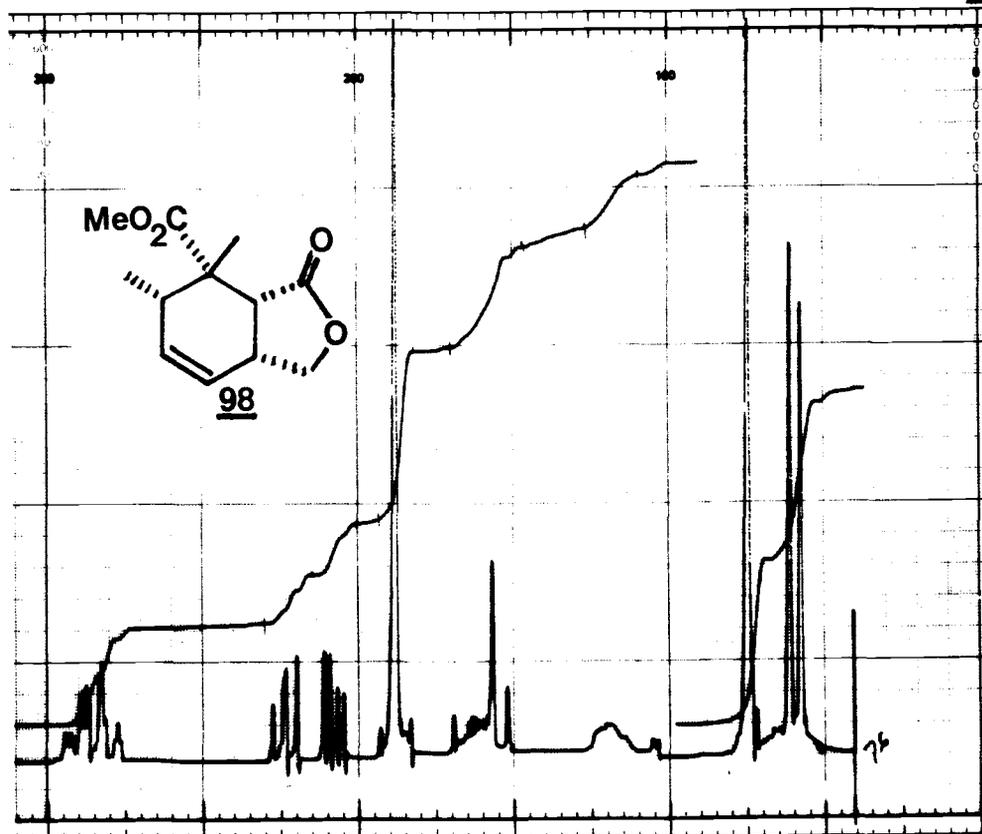
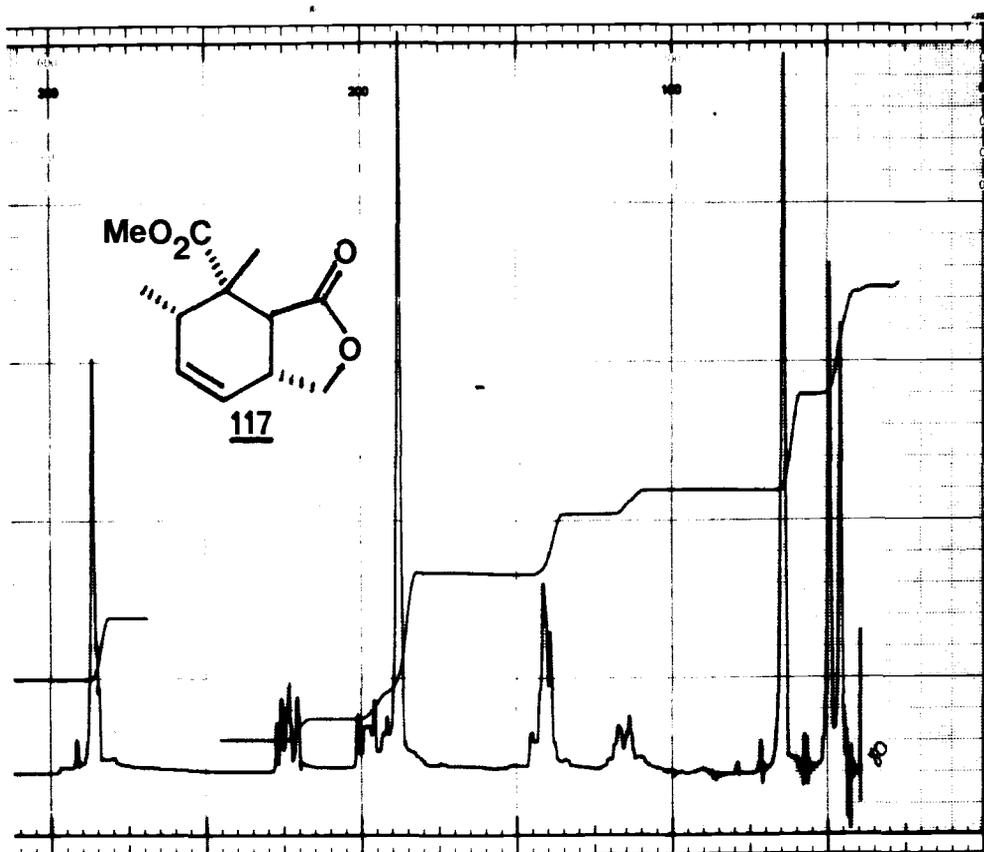
- (1) R. Hütter, W. Keller-Schierlein, F. Knüsel, V. Prelog, G. C. Rodgers, Jr., P. Suter, G. Vogel, W. Voser, and H. Zähler, Helv. Chim. Acta, 50, 1533 (1967).
- (2) J. D. Dunitz, D. M. Hawley, D. Miklos, D. N. J. White, Y. Berlin, R. Marusic, and V. Prelog, Helv. Chim. Acta, 54, 1709 (1971).
- (3) Y. Okami, T. Okazaki, T. Kitahara, and H. Umezawa, J. Antibiotics, 29, 1019 (1976).
- (4) H. Nakamura, Y. Iitaka, T. Kitahara, T. Okazaki, and Y. Okami, J. Antibiotics, 30, 714 (1977).
- (5) K. Sato, T. Okazaki, K. Maeda, and Y. Okami, J. Antibiotics, 31, 632 (1978).
- (6) B. M. Miller and R. W. Burg, U.S. Patent 3,864,479 (1974); Chem. Abstr., 83, 939 (1975).
- (7) I. Putter and L. J. Cole, U.S. Patent 4,102,007 (1976); Chem. Abstr., 90, 12317 (1979).
- (8) W. Pache and H. Zähler, Arch. Microbiol., 67, 156 (1969).
- (9) R. B. L. Gwattein, G. H. Rasmusson, and D. T. Williams, J. Reprod. Fertil., 47, 299 (1976).
- (10) T. S. S. Chen, C-j. Chang, and H. G. Floss, J. Am. Chem. Soc., 101, 5826 (1979).
- (11) F. W. Bachelor and G. A. Miana, Can. J. Chem. 47, 4089 (1969).
- (12) P. Calinaud and J. Gelas, Bull. Soc. Chem. Fr., 1228 (1975).
- (13) H. B. Henbest, E. R. H. Jones, and I. M. S. Walls, J. Chem. Soc., 3646 (1950).
- (14) K. Lougren and J. L. G. Nilsson, Acta Pharm. Suec., 12, 379 (1975).
- (15) M. Schwartz and R. M. Waters, Synthesis, 567 (1972).
- (16) J.-L. Pierre, P. Chantemps, and P. Arnaud, Bull. Chim. Soc. Fr., 1317 (1976).
- (17) R. A. Borch, A. J. Evans, and J. J. Wade, J. Am. Chem. Soc., 97, 6286 (1975).
- (18) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, 1965, p. 69.

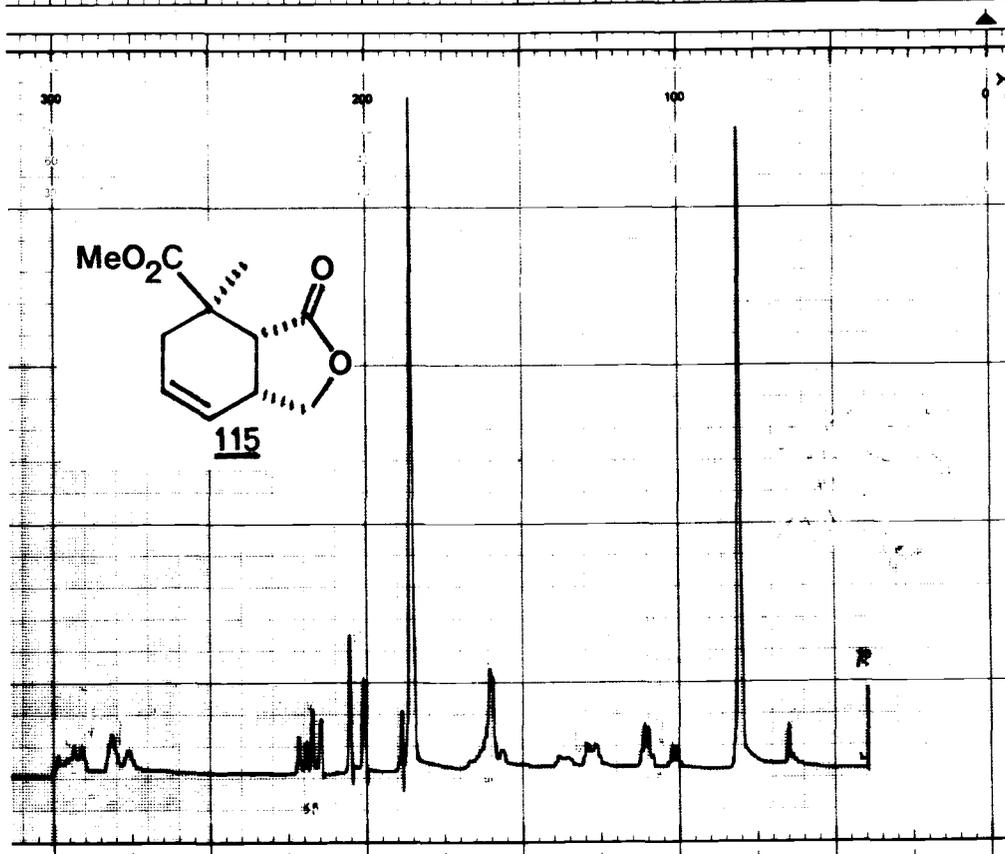
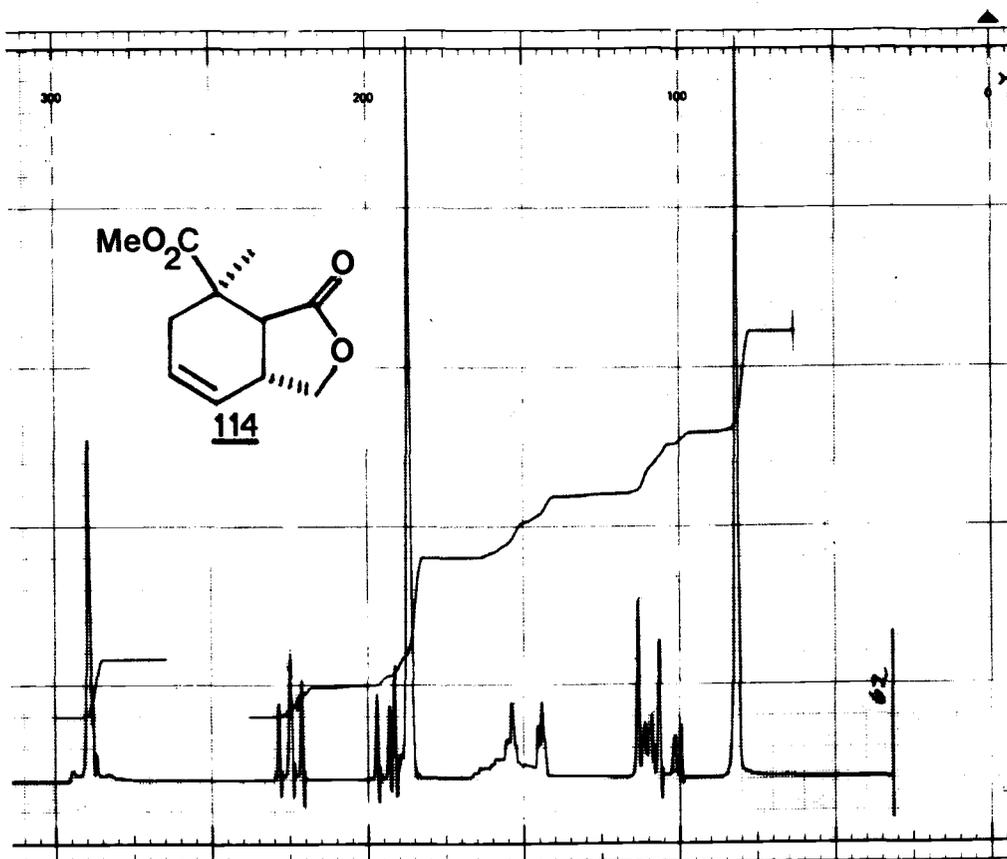
- (19) J. E. Baldwin, J. Chem. Soc., Chem. Comm., 734, 738 (1976).
- (20) J. E. Baldwin, J. Chem. Soc., Chem. Comm., 736 (1976).
- (21) E. J. Corey, G. E. Keck, and I. Szekely, J. Am. Chem. Soc., 99, 2006 (1977).
- (22) V. Speziale, J. Roussel, and A. Luttes, J. Heterocyclic Chem., 11, 771 (1974).
- (23) N. J. Bunce, J. Org. Chem., 37, 664 (1972).
- (24) E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).
- (25) M. Miyashita, A. Yoskikoshi, and P. A. Grieco, J. Org. Chem., 42, 3772 (1977).
- (26) B. M. Trost, P. R. Bernstein, and P. C. Funfschilling, J. Am. Chem. Soc., 101, 4378 (1979).

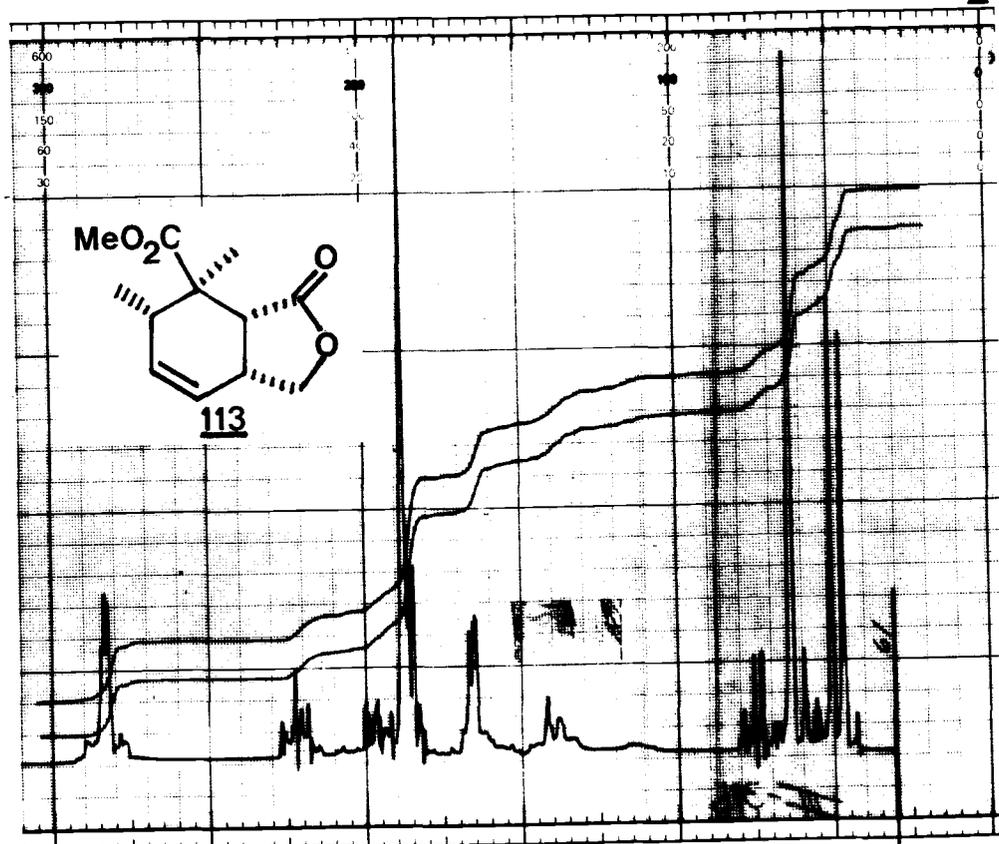
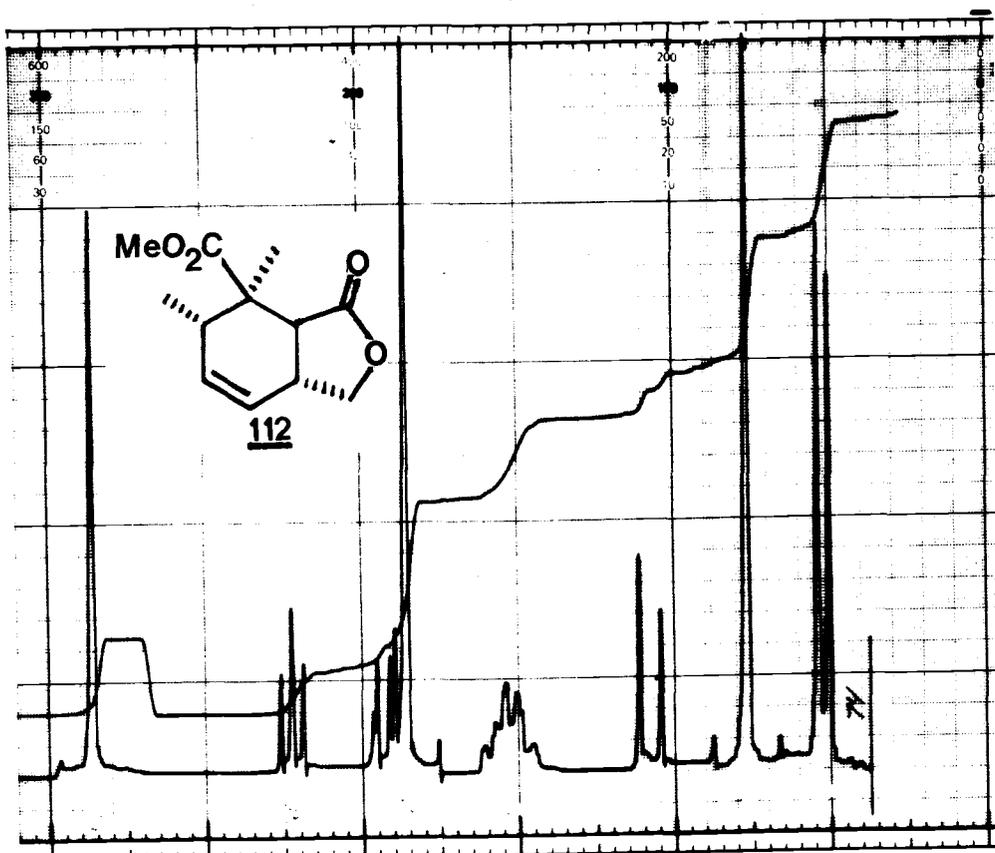
APPENDICES

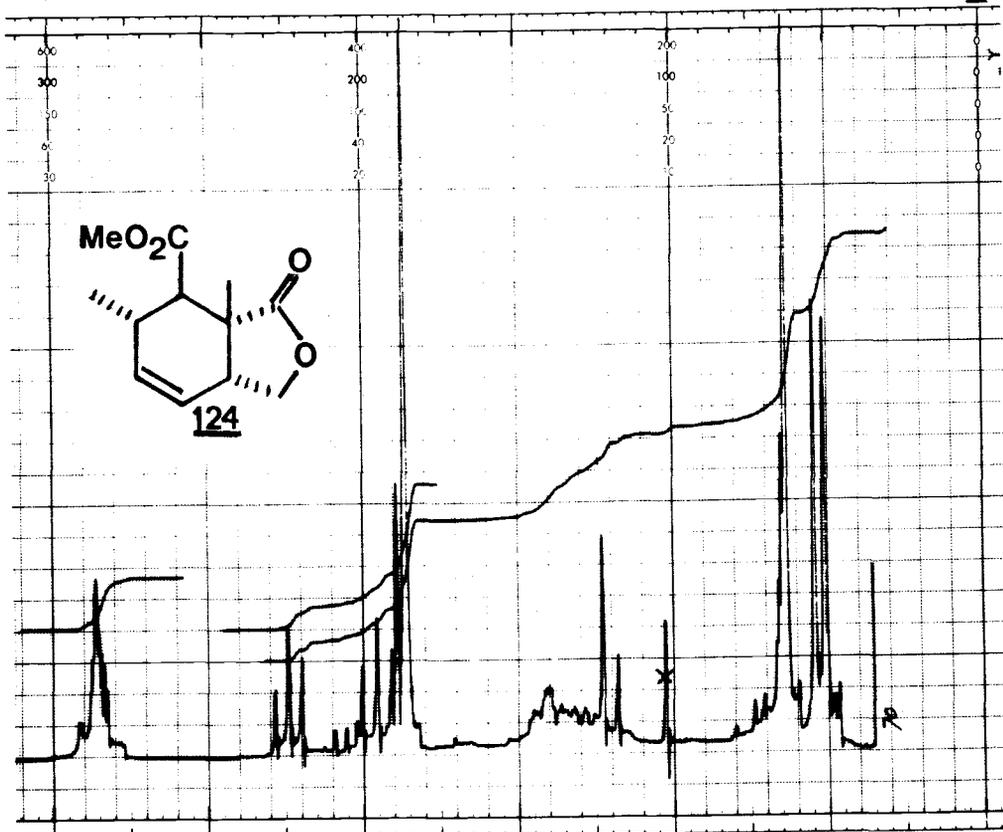
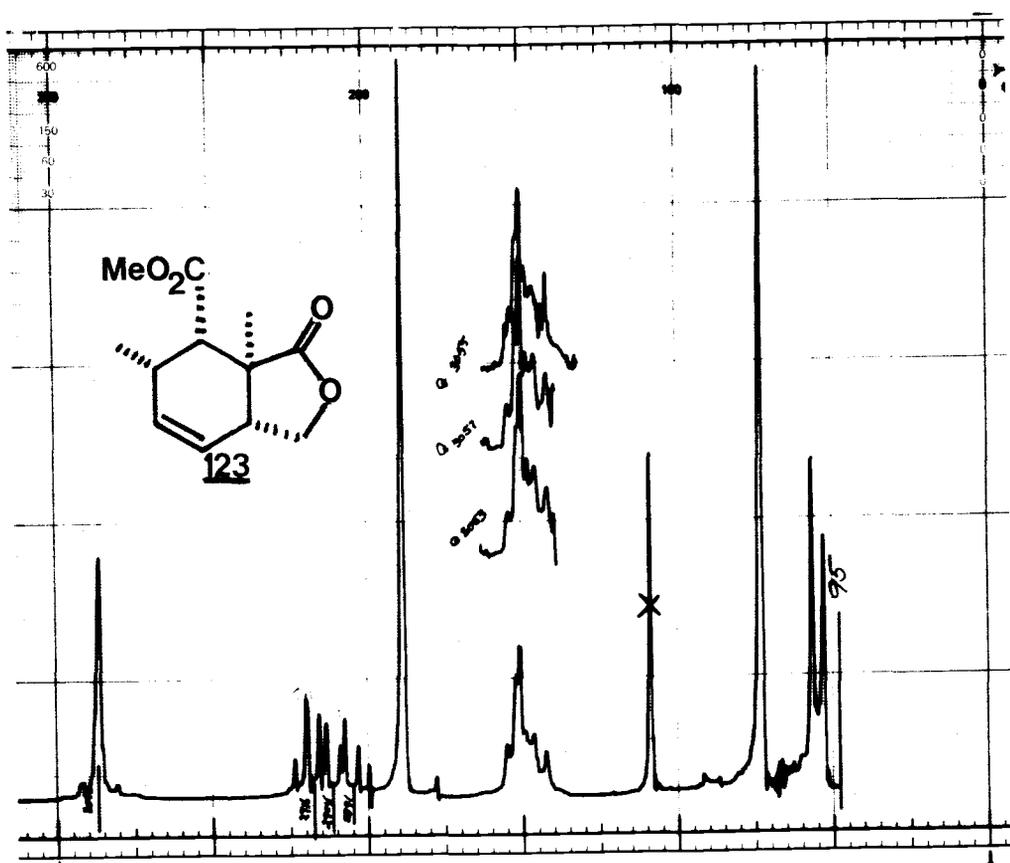
APPENDIX A.

PROTON MAGNETIC RESONANCE SPECTRA OF
SELECTED CYCLOADDITION PRODUCTS





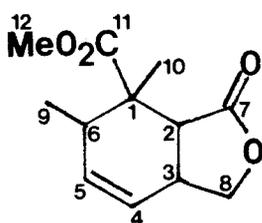




APPENDIX B.

TABULATION OF CARBON-13 MAGNETIC
RESONANCE SPECTRAL DATA

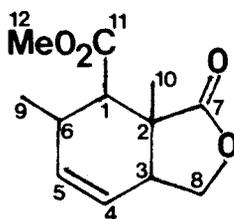
Assignments of carbon-13 magnetic resonance spectra are based on the numberings shown below.



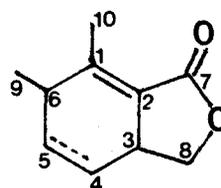
98, 112, 113,

115, 116, 117,

118, 119



123, 124



137, 139

Compound Number	Carbon-13 Shift ^a for Carbon Number												
	1	2	3 ^b	4 ^c	5 ^c	6 ^b	7 ^d	8	9 ^e	10 ^e	11 ^d	12	13
<u>98</u>	45.5	44.4	37.6	123.6	133.8	35.0	176.7	70.9	17.3	25.4	174.7	51.6	
<u>112</u>	46.0	44.8	38.0	122.1	136.2	38.7	174.1	69.5	16.8	19.7	175.8	52.1	
<u>113</u>	46.3	44.2	35.0	122.9	133.7	35.8	176.2	70.8	14.7	15.7	177.0	52.4	
<u>115</u>	43.0	48.9	38.0	123.6	129.1	38.7	173.9	69.9		24.0	175.0	52.3	
<u>116</u>	43.0	43.9	37.1	125.9	129.6	30.8	176.1	71.0		22.4	176.3	52.4	
<u>117</u>	43.9	44.0	37.4	121.0	134.6	41.2	173.5	69.7	17.9	18.2	173.7	51.3	
<u>118</u>	48.7	41.6	40.2	125.7	132.3	40.4	not OBS	64.6	17.7	18.9	not OBS	51.6 ^f	51.8 ^f
<u>119</u>	45.2	47.4	33.4	122.7	135.6	36.8	not OBS	72.2	15.6	21.6	not OBS	51.9	
<u>123</u>	32.8	42.1	45.9	120.2	135.7	47.8	171.5	68.0	11.1	18.6	177.7	51.3	
<u>124</u>	29.9	42.6	44.0	121.4	134.0	48.0	172.6	70.2	17.4	19.6	not OBS	51.7	
<u>137</u>	120.2	150.3	36.6	122.3	133.7	38.8	169.4	69.5	14.6	18.3			
<u>139</u>	119.9	135.4	39.8	29.4	21.3	35.0	153.0	71.5	16.5	19.8			

^aIn parts per million downfield from tetramethylsilane

^{b-f}Assignments may be reversed for each pair