THE SYNTHESIS OF TRICYCLO[7.3.0.0^{4, 12}]-DODECA-2,5,7,10-TETRAENE

> Thesis for the Degree of Ph. D. MICHIGAN STATE UNIVERSITY ALFRED ARTHUR HAGEDORN III 1974



This is to certify that the

thesis entitled THE SYNTHESIS OF TRICYCLO[7.3.0.0^{4,12}]-DODECA-2,5,7,10-TETRAENE

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ABSTRACT

THE SYNTHESIS OF TRICYCLO[7.3.0.0⁴,¹²]-DODECA-2,5,7,10-TETRAENE

by

Alfred Arthur Hagedorn III

The title compound, l, has been synthesized using the reaction sequence shown. This compound is predicted to undergo a series of structurally degenerate Cope rearrangements which scramble the (CH) units into one set of eight equivalent positions, and another set of four. Although the rigid geometry of l appears ideal for the Cope rearrangement, no changes in the proton nmr spectrum of l were observed up to 141°. It is concluded that the absence of a small ring, with its accompanying strain, is the cause of this result.

In addition to the intermediates shown, a variety of other compounds containing the bicyclo[3.3.0]octane skeleton has been prepared.











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THE SYNTHESIS OF TRICYCLO[7.3.0.0⁴,¹²]-DODECA-2,5,7,10-TETRAENE

By

Alfred Arthur Hagedorn III

A THESIS

Submitted to Michigan State University in partial fulfillment of the requirements for the degree of

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DEDICATION

To my parents; without their aid and guidance this work could never have begun,

and

To my wife Myrna; without her love this work could never have been so happily ended.



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I am deeply indebted to Professor Donald G. Farnum for suggesting this project, and for his many valuable suggestions. His chemical knowledge and warm friendship have made my stay at Michigan State richly rewarding.

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INTRODUCTION

The design and synthesis of new compounds to test chemical theories has long been a favorite pastime of chemists. Willstätter's synthesis of cyclooctatetraene, which had been predicted to be aromatic since it was a fully conjugated cyclic system, is probably the best known example of this kind of research (the experimental fact that Willstätter's compound showed olefinic properties led the chemists of that time to suspect the experiment - a not infrequent situation)¹. After Huckel's enunciation of the "4n + 2" rule, a large number of syntheses were attempted to test this theory². Much more recently, the concept of "orbital symmetry" has led many chemists to design systems to explore concerted reactions. This thesis describes the synthesis of a compound of such "theoretical interest".

The Cope rearrangement, shown in its simplest form below, has been extensively studied³; its intramolecular nature was deduced from



the first-order kinetics and the absence of "crossover" products when a mixture of reactants was heated. The rather large negative entropy of activation (<u>ca</u>. - 12 e.u.)

interpreted as evidence that the reaction proceeds through a cyclic "complex"].

According to Woodward and Hoffmann⁴, the reaction is a [3,3]-sigmatropic rearrangement (alternatively, a $\pi^2_s + \sigma^2_s + \pi^2_s$ reaction⁵), and therefore a concerted process is "allowed" by orbital symmetry considerations. The remainder of this discussion will be in terms of a concerted reaction, but it should be realized that other mechanistic options are available, and that these are sometimes employed. For example, a cleavage-recombination mechanism is operative (probably in competition with the concerted mechanism) in the diphenylhexadiene 2, below⁸. At the other extreme, formation of a 1,4-cyclohexylene



intermediate (biradical) $\frac{1}{4}$ has been suggested for the derivatives $\frac{3}{4}$ (R = H or Ph)⁹ and may be involved (at least, is energetically feasible) for 1,5-hexadiene itself¹⁰. A recent calculation¹¹ suggests that this latter possibility is indeed the case, although this can not be taken as proof.





from bond-breaking preceding bond-making to the opposite, formation of the new σ -bond preceding rupture of the old one. The concerted mechanism lies between these extremes.

The classic study by Doering and Roth^{12,13} demonstrated that this "complex" (more precisely, the transition state in the step determining the stereochemistry of the product) had a "chair-like" four-center arrangement ξ and not the alternative boat-like (six center) geometry β ; the energy difference between the two geometries was estimated to be



"at least 5.7 kcal/mole." A "qualitative quantum mechanical explanation" was advanced to account for this preference. More recently, Woodward and Hoffmann have used a similar argument, treating it as a "secondary effect" of orbital symmetry¹⁴. Thus, although a concerted reaction is "allowed" for a Cope rearrangement proceeding through either transition state ξ or ξ , there is an antibonding interaction between the central atoms of the two allyl units; clearly, this effect would be greater in the boat geometry, and the chair would be preferred. Fukui¹⁵ reached the same conclusion with a slightly different approach, and estimated an energy difference of 5-6 kcal/mole from a Hückel-type calculation.

Although the chair geometry is preferred, a number of compounds constrained to react <u>via</u> the boat geometry do in fact rearrange very easily¹⁶. <u>Cis</u>-divinylcyclopropane χ and <u>cis</u>-divinylcyclobutane & rearranged at -50° and 120° respectively. The corresponding <u>trans</u> isomers, g and 10,



in which the formation of a cyclic "complex" introduces prohibitive strain, required much higher temperatures for reaction; the <u>trans</u>-divinylcyclobutane gave different products as well. In the next homolog, the strain-free divinylcyclopentane L, rearrangement to the monocyclic product was not observed; <u>cis-trans</u> isomerization was the only reaction noticed. Strain may have a thermodynamic effect in this case - the strain of the medium sized ring would cause



the divinylcyclopentane to be favored. Similarly, in the cyclodecadiene-divinylcyclohexane system, the reaction proceeds to give the unstrained cyclohexane derivative. Thus, ring strain may affect both the rate and equilibrium in Cope systems. This importance of strain was clearly recognized by Vogel¹⁶ (who studied most of the examples just given), and Doering and Roth^{13,17}.

The latter authors proposed to counteract the unfavorable entropy of activation by connecting the ends of a divinylcyclopropane with a methylene group, thus holding the vinyls in a geometry suitable for a cyclic process. The resulting molecule, bicyclo[5.1.0]octa-2,5-diene 12 (homotropilidene), is set up for a degenerate Cope rearrangement; the reactant and product have the same structure. That this degenerate rearrangement was indeed occurring was evident



from the temperature dependent nmr spectrum of $12^{13,17}$. It was estimated that rearrangement took place about once per second at -50°, and about 10³ times per second at 180°. This "fluxional" behavior could be further enhanced by tying together the two ends of the homotropilidene, as in ketone 13 (barbaralone)^{13,18}. This has the effect of



eliminating the unreactive conformation 14 of homotropilidene, leaving only the reactive conformer 15. In an inspired



flight of imagination, Doering and Roth proposed^{13,17} joining the "ends" of the homotropilidene by means of another double bond, giving structure 16. This molecule could



undergo a series of Cope rearrangements leading to the equivalencing of all ten protons, and the interconversion of the more than 1.2 million (10!/3) "isomers" (connectivities) of \downarrow 6; thus, every carbon atom becomes bonded to every other. In discussing this hypothetical compound, Doering and Roth declared "...all ten carbon atoms inevitably wander over the surface of a sphere in ever changing relationship to each other. Such a fluxional structure will have had no precedent in organic chemistry." \downarrow 6 is, of course, bullvalene; the synthesis by Schröder in 1963¹⁹, with the demonstration of its fluxional nature, fully confirming Doering and Roth's speculations, is among the most dramatic discoveries in modern organic chemistry.

A number of other fluxional molecules are known, with varying tendencies to rearrange. Several of these are shown in Table 1 with their measured energies of activation²⁰. As can be seen, the activation energies span a considerable range. The values for 1,5-hexadiene and benzene are appended for comparison (benzene may be regarded as a "transition state" for Cope rearrangement of cyclohexatriene, with an energy below that of the starting material²⁰).

The molecules shown in Table 1 all contain a homotropilidene unit, and the question arises whether this structural feature is essential for rapid rearrangement to occur. To this writer's knowledge, the only neutral molecule not containing a homotropilidene which exhibits rapid fluxional behavior is the (CH)₁₀ hydrocarbon 19 ("hypostrophene")²³. Although the Cope rearrangement is too slow to be detected



by collapse of the nmr spectrum (<u>vide infra</u>), its operation was demonstrated by deuterium labelling. High temperature nmr studies were not possible, as 19 rearranges to another (CH)₁₀ hydrocarbon, 20, at temperatures over 80°. The diradical 21 was suggested as an intermediate in this "forbidden" reaction. This rearrangement clearly shows





(a) Taken in part from Ref. 20. (b) Calculated (MINDO/2) ΔE^{+} , Ref. 21. (c) Calculated (MINDO/2) ΔE^{+} , Ref. 22.



that LQ is strained; steric acceleration of the Cope rearrangement is probably operating here, as in the homotropilidene derived cases, although there may be a decelerating effect due to closing a cyclobutane ring.

Recently, this idea of strain being the principal factor in the low activation energies for Cope rearrangement of tropilidene "derivatives" has received theoretical support. Dewar and coworkers used the MINDO/2 approximation to calculate the energy of the ground and transition states for 1,5-hexadiene and several homotropilidene-based molecules^{21,22,24}. This approximate theory gave rather poor agreement with the experimental activation energies for 1,5-hexadiene, the calculated energies being ca. 10 - 11 kcal/mole low; Dewar attributed this to "a known failing of MINDO/2... a tending to over-estimate the stability of cyclic compounds"²¹. The <u>ca</u>. 6 kcal/mole preference for the chair-type transition state was reproduced very well, however, and much better agreement was obtained for the homotropilidene derivatives ("...errors due to the presence of rings should cancel"²¹).

In the original MINDO/2 calculations on the homotropilidene derivatives²¹, Dewar and Schoeller indicated that the rate enhancement in bullvalene $\frac{16}{50}$ compared to a boat form of 1,5-hexadiene is probably due to ring strain being relieved in the former case. A later study²² included "energy partitioning²⁵", whereby the total molecular energy is apportioned among the bonds and atoms of the molecule. Although the results were not completely clear, the same conclusion was drawn - the greater reactivity of molecules containing a homotropilidene unit is "primarily due to ring strain".

Although not really relevant to this discussion, the proposed explanation for the sequence of reactivity bull-16<barbaralane<17 semibullvalene 18 (see Table 1) valene is of some interest, particularly in contrast to the steric argument just given. For these three compounds, the "bond energy" effects are small; the greater amount of strain released is roughly balanced by the weaker bonding in the transition state, which more and more resembles a pair of allyl radicals in the order 16, 17, 18. Instead, the geometric change leading to this separation of the allyl units leads to the six atoms actually involved in the Cope rearrangement becoming effectively more electronegative. The resulting changes in the one-center contributions to the energy are what lead to the order of reactivity lo<ll<lo. By applying perturbation theory and extended Hückel calculations, Hoffmann and Stohrer reached a similar conclusion for substituted semibullvalenes²⁰.

To return to the problem at hand, several points

deserve recapitulation. First, a chair-like transition state is preferred over a boat-like geometry, although, secondly, rearrangement <u>via</u> a boat may be facilitated by a rigid geometry in the starting material. Finally, release of strain is an important factor involved in increasing the rate of Cope rearrangement.

The goal of this project was the synthesis of a molecule designed to explore these last two points, the $(CH)_{12}$ hydrocarbon χ^2_{λ} , tricyclo[7.3.0.0^{4,12}]dodeca-2,5,7,10-tetraene. The architect of this molecule was Roald Hoffmann²⁶; except



for brief mention by Balaban in his compilation of structures of the formula $(CH)_{12}^{27}$ and his survey of possible degenerate Cope rearrangements in the $(CH)_n$ families²⁸, 22 has not appeared in the literature.

The alternate name 1,3a,4,6a-tetrahydro-1,4-(1',3'-butadieno)pentalene gives a clearer idea of the structure -- a bicyclo[3.3.0]octa-2,6-diene (a tetrahydropentalene) bridged on the "underside" by a 1,3-butadiene unit. This is evident from the top view 22a and the "unfolded" view 22b. Molecular models show that the butadiene bridge is twisted out of

1

conjugation (skewed) by about 75°; this aspect of the structure is depicted in 22c. An important conclusion which can be drawn from the model is that introduction of the butadiene adds little significant strain above that already present in the tetrahydropentalene nucleus. Although estimation of the strain energy of the bicyclooctadiene fragment is somewhat ambiguous, 13-20 kcal/mole appears reasonable²⁹. This is less than the 27 kcal/mole or so reported³⁰ for cyclopropane, and thus 22 surely is far less strained than a homotropilidene-derived molecule such as bullvalene. As a result, release of strain should be a less important factor in the reactions of 22 than is the case with the known fluxional molecules 16, 17, and 18.

Inspection of compound 22 shows it to contain two 1,5hexadiene units (equivalent because of the twofold axis), suitably arranged for a Cope rearrangement. The geometry is "boat-like", and the molecular model shows that this geometry is very rigidly fixed. Considering just one of the hexadiene fragments, the interatomic distances (measured from a Dreiding model) are shown in Table 2; the calculated²² distances for the boat-like transition state of 1,5-hexadiene and for the ground and transition state of bullvalene are also included. The interatomic distances are labelled as in 23. Granting the crudity of this method,

Ь

23

Table 2

Interatomic Distances in Cope Systems

Compound	"a"	"Ъ"	"c"	notes
	1.628 Å	2.577 Å	1.628 Å	a
	1.630	2.630	1.630	Ъ
ransition state)				

(tr



1.506	2.428	3.043	с
1.544			d

(16, ground state)



1.626 2.808 1.626 a,	1.626	2.808	1.626	a,b

(lf, transition state)



1.54	2.36	2.68	е
1.01	2.00	2.00	C

(22, ground state)

(a)	Calculated	(MINDO/2)	transition	state	geometry,	Ref.	21.
(ኬ)	Caloulated	(MTNDO/2)	+noncition	o+ + + 0	goomotru	Pof	22

(b) Calculated (MINDO/2) transition state geometry, Ref. 22.
(c) Calculated (MINDO/2) ground state geometry, Ref. 22.
(d) Electron diffraction result, Ref. 31.

(e) Distances measured on a Dreiding model.

the geometry of 22 appears excellent for Cope rearrangement. Thus, the distance "c", which represents the bond to be formed, is substantially less in 22 than in bullvalene 16; "b", which corresponds to an antibonding interaction between the allyl units, is comparable for the two systems.

From these considerations we conclude that the Cope rearrangement of 22 appears reasonable, and may now ask what structural effect such a reaction would have. This is shown below for a single such rearrangement; the degeneracy is



obvious. Clearly, the other Cope system could equally well react, and a cycle of Cope rearrangements becomes possible. The complete cycle is shown in Figure 1, using Doering and Roth's convenient scheme^{13,17} for indicating which bonds are made and broken.

As can be seen in Figure 1, a considerable amount of position scrambling occurs in this cycle of rearrangements, leading to two sets of equivalent positions, (1,3,4,6,7,9, 10,12) and (2,5,8,11). This is represented in 24, the group of eight equivalent positions being marked (•), the other group (of four) being unmarked.





Degenerate Cope Rearrangement of Tricyclo-[7.3.0.0⁴,¹²]dodeca-2,5,7,10-tetraene



24

This pattern may be derived in other, less involved ways. For example, the view shown in 25 reveals that the indicated Cope rearrangement reflects the molecule through a mirror plane passing through atoms 5 and 11 and bisecting bond Thus, position 4 reflects into 6, 3 into 7, etc. 1-9. The other Cope system similarly generates another plane (not shown), passing through positions 2 and 8 and the 4-12 bond, reflecting 7 into 9, 6 into 10, and so on. These reflections lead to four groups of equivalent positions, group A = (4, 6, 10, 12), B = (1, 3, 7, 9), C = (2, 8), and D = (5,11). The two-fold axis of rotation present in the molecule then makes groups A and B equivalent giving the eight equivalent positions marked in 24. Similarly, groups C and D are interchanged by the C_2 axis, giving the other group of four positions.



This argument can be condensed even further, by considering the result of simultaneous rearrangement of both
Cope systems. Structure 26 illustrates the transition state (or intermediate) for the hypothetical - and unlikely reaction; a biradical is used for illustrative purposes



only. By virtue of the considerable symmetry (D_{2d}) which 26 possesses, the eight "bonded" atoms are made equivalent, as are the four "radical centers". The scrambling pattern is the same as that derived earlier, as of course it must be.

Thus, the series of degenerate Cope rearrangements in 22 could be detected by observing the scrambling of positions into the two sets (1,3,4,6,7,9,10,12) and (2,5,8,11). Indeed, this is the usual test for fluxional behavior. If the rate of rearrangement were sufficiently high, this could be detected by observing the temperature dependence of the nmr spectrum of 22; at low temperatures a pattern consistent with structure 22 - eight vinyl and four aliphatic protons - would obtain, but this would be transformed at higher temperatures into a new pattern, with four vinyl protons and eight protons "averaged" between vinyl and aliphatic. If the rearrangement were too slow to be observable at temperatures accessible in the nmr experiment, or if some other reaction were to intervene, the position scrambling could still be detected by introducing a label (ideally

deuterium) specifically at a certain site (or sites) in 22. For instance, deuterium placed at the bridgeheads of the bicyclooctyl nucleus (positions 1 and 12 of the tricyclododecyl system) would ultimately appear uniformly distributed over the eight marked positions in structure 24 (p.16). By one or the other of these techniques, the rate of equivalencing the positions, and thereby, the rate of Cope rearrangement, could be determined.

Tricyclododecatetraene χ_{χ}^{2} has another unusual feature which has not been discussed - namely, it is chiral (point group C_{2})²⁴. The effect of Cope rearrangement on this property of χ_{χ}^{2} is easily determined "by inspection". As shown, each Cope rearrangement converts the starting struc-



ture into its enantiomer; this can also be seen by considering view 25. This provides a second means of observing the degenerate Cope rearrangement, as this reaction would lead to racemization of initially resolved 22 (only partial resolution would be necessary). As two Cope rearrangements are needed for complete scrambling while only one is needed for racemization, the rates of these two "reactions" should be in the ratio of 1:2. In the event that rearrangement is slow on the nmr time scale, racemization studies could provide information on the rate, without having to prepare the labelled compound. The price of this, of course, is that 22 would have to be resolved.

Although position scrambling is the usual test for a degenerate rearrangement, such as stereochemical proof has been used occasionally. For example, Cope rearrangement in hydrocarbon 27 was followed by monitoring the loss of



optical activity in the partly resolved compound³². In a non-Cope system, the photolytically induced racemization of the dihydropyrazine derivative 28 demonstrated that the indicated degenerate photoisomerization was occurring³³.



Another amusing possibility based upon the enantiomerization which accompanies Cope rearrangement in 22 is complete conversion of the racemic mixture to a single enantiomer. It is possible (though unlikely) that this could be achieved by crystallization of 22, by analogy to the results of Pincock with 1,1'-binapthyl³⁴. A somewhat more probable means of such "resolution" requires the intervention of another chiral influence. Thus, treatment of racemic 22 with an optically active complexing agent, such as Cope's platinum complex³⁵, might lead to complete formation of the more stable diastereomer. A similar result can be imagined to result from chromatography on a chiral adsorbent. Such a result would be most unusual, and the possibility deserves mention, even though it seems remote.

The final comments in this section are devoted to an even less likely possible behavior of 22, one which has a startling result. The <u>simultaneous</u> rearrangement of both Cope systems was mentioned previously (p.15) and the result in terms of position scrambling was shown to be identical to that resulting from sequential Copes. When the stereochemical outcome of this "double Cope" is determined, however, a difference appears:



This mechanism predicts scrambling without racemization! This possibility may be added to the cycle of Cope rearrangements, resulting in the pattern shown in Figure 2. The operation of this mechanism could be detected by accurately measuring the rates of racemization and scrambling; if racemization takes place with any rate less than twice the rate of scrambling, the "double Cope" must be involved.

The probability of observing this unusual reaction is of course determined by the activation energies of the "single"



double Cope



Possible Degenerate Rearrangements

of Tricyclododecatetraene 22

and "double" Cope rearrangements. To the extent that there is no interaction between the two Cope systems, the activation energy for the double rearrangement would be roughly twice that for the single. Assuming an activation energy for the simple Cope rearrangement comparable to that in bullvalene, ca. 12 kcal/mole, this puts the double Cope practically out of reach, at least as far as detection is concerned. Although the operation of the double Cope probably will not be observable in 22, it might be found in some derivative; application of perturbation theory and approximate calculations may lead to the design of such derivatives, as was done in designing semibullvalenes predicted to have "negative activation energies^{20,21}." Similarly, the structural features in 22 might be translated into some other molecule which would be more likely to show the simultaneous double rearrangement.

To summarize this section, tricyclododecatetraene 2λ appeared to be an interesting molecule for the following reasons:

(1) 22 is a potentially fluxional molecule, the twelve
(CH) units being scrambled into groups of eight and
four by a series of degenerate Cope rearrangements.
(2) The molecule is held rigidly in a geometry corresponding to a boat-like transition state for the
Cope. However, the strain is considerably less for
22 than for molecules - bullvalene, barbaralane, etc.
- containing a homotropilidene unit. The importance

of release of ring strain in accelerating the Cope rearrangement could thus be estimated.

(3) 22 is chiral, and the Cope rearrangement should lead to enantiomerization. This could be observed by following the racemization of resolved 22, which should occur twice as fast as position scrambling.

(4) Other unusual properties might result from the relationship between the Cope rearrangement and the chirality of 22.

For these reasons, and because it looked like fun, the synthesis of compound 22 was undertaken.

SELECTION OF A SYNTHETIC APPROACH - A PRELUDE

Our interest in the synthesis of the (CH)₁₂ tetraene 22 was due in part to the recognition that it might arise from the combination of cyclopropenyl cation and cyclononatetrenyl anion:



22

However, preliminary results on this reaction have not been promising³⁶, and in a more heavily functionalized case a different sequence occurs³⁷. In view of the difficulties inherent in this reaction, and the multitude of products which would probably arise, a tactical synthesis of 22 was desirable.

In designing such a synthesis, a number of approaches came to mind. Several of these are outlined in this section; the advantages and disadvantages of each are briefly considered, and the scheme finally chosen is presented in some detail.



The first approach considered has as its key step a fragmentation reaction of a tetracyclic precursor, 29a or 29b, as illustrated:



Inspection of molecular models suggests that the orbitals involved are favorably aligned for this reaction to occur. The indicated interconversion of 29a and 29b <u>via</u> a Cope rearrangement is an amusing feature of this scheme. However, the attractive features of this approach are more than balanced by the complexity of the necessary precursor 29. Design of a reasonable synthesis of just the carbon skeleton of 29 is not easy, and the necessary stereochemistry of the substituents further complicates the situation.

Another approach which was considered involved fusing an additional five membered ring onto a bicyclo[5.2.1]decane derivative (X_n represents "necessary functionality"):



In particular, an intramolecular alkylation (32 + 31) or an intramolecular Michael addition (32 + 33) appeared likely.

However, attack might take place at the wrong position, to give a derivative of the known³⁸ compound 34.



In any event, these routes were not pursued experimentally, mainly because reasonably straightforward synthesis of the necessary precursors, such as 30 and 32, were not obvious.

The preceding two ideas are basically traditional in approach, using classical methods of bond formation. Two other synthesis were devised, which utilized more modern reactions. The first required photoaddition of acetylene (or its synthetic equivalent) to the known^{39,40} (CH)₁₀ hydrocarbon 35, "lumibullvalene". Opening (disrotatory and therefore photochemical) of the resulting cyclobutene 36 would then give 22. The problem evident here is that the other double bonds in 35 might react with the acetylene, giving unwanted products. There is no obvious way of preventing



this side reaction. The known⁴¹ photocyclization of 35 to 37 would be another problem, although this might be suppressed by having a sufficiently high concentration of acetylene present. A less compelling objection is purely personal.



This route appears rather dry; the results would be determined largely by what the molecules "want to do", and the amount of interesting chemistry might be small. As 35 is quite readily available from cyclooctatetraene⁴⁰, this route might well deserve further consideration.

Another "modern" synthesis is outlined below:



Thus, sensitized photocyclization of a cyclododeca-1,5-diene derivative 38 would be expected⁴² to give a product of type Four double bonds would then be introduced (giving 40), 32. which might rearrange thermally to 22 as shown. The rearrangement is an "allowed" 1,5-shift, and might be facilitated by release of strain and the reasonably good geometry of The objections to this rather intriguing approach to 4Q. 22 mainly revolve around introducing the necessary unsaturation, that is, the $39 \rightarrow 40$ transformation. There is some evidence that the monocyclic precursor 38 could not have any additional double bonds. Thus, 1,5,9-cyclododecatriene 41, when photolyzed in aromatic hydrocarbons, gives a low yield of the divinylbicyclo[3.3.0]octane 42 (cis-trans isomerism of 41 is the main photoreaction, and only the minor all-<u>cis</u> isomer goes on to 42)⁴³; the proposed mechanism



is shown. This implies that a considerable amount of functionality (X_n) would be needed in 38. Furthermore, all of

this functionality would have to survive the photocyclization, which might exclude halogen substituents. Although this problem probably could be solved, the multitude of possible approaches at such an early stage in the synthesis seemed very undesirable.

The rejection of the four schemes just discussed, and of other, more arcane routes, was assisted by the conception of another, to our minds far superior plan. This required the coupling of the termini of two 2-carbon bridges attached "cis, endo" to the underside of a bicyclooctadiene:



In particular, an acyloin condensation⁴⁴, or the Bloomfield-Rühlmann modification thereof⁴⁵, appeared ideally suited for this transformation. By these procedures, the diester $\frac{43}{2}$ would be converted to the tricyclic α -ketol $\frac{44}{2}$, or the <u>bis(trimethylsiloxy)triene $\frac{45}{2}$; further elaboration to give</u> $\frac{22}{2}$ appeared straightforward.



Of these two possible reactions, the modified acyloin⁴⁵ appeared preferable. This method has the advantage that side reactions (particularly Dieckmann cyclization) are greatly reduced, and even strained systems such as 46 and 47 can be made in this way⁴⁵. In addition, the <u>bis</u>(trimethyl-



silyl)enediol ethers which result from this reaction can be subjected to a variety of further reactions⁴⁵.

The necessary synthetic intermediate then becomes diester 43, or some other compound easily transformable into 43. It is at this stage, then, that the <u>cis-endo</u> disposition of the two-carbon side chains must be established. Once this orientation is established, it is very unlikely that it would be lost, as no easily epimerizable centers are present in 43. The most serious problem that we imagined was antarafacial Cope rearrangement, which would take 43 into the <u>cis-exo</u> isomer 48. However, as the antarafacial Cope rearrangement now appears⁷ to be nonexistent, this



reaction did not seem very likely.

After some consideration, we decided that the method of choice for introducing the two-carbon chains was a Claisen rearrangement⁴⁶⁻⁴⁸ (the oxa-analogue of the Cope), or one of the many modifications of that reaction. The well known⁴⁸ stereospecificity of the Claisen rearrangement insures that a vinyl ether starting "under" the bicyclic skeleton will appear as an acetaldehyde chain, again "under" the [3.3.0] system. For example, thermolysis of the enol ether 5Q, derivable from the <u>cis-endo</u> diol 42, should give dialdehyde ξ_{1} . The conversion of the dialdehyde into the diester 43would probably be easy. As just mentioned, a number of



variations on the Claisen theme are also known. Several which have been useful in synthesis are shown in Figure 3;

Claisen Rearrangement 46-49

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Meerwein - Eschenmoser Reaction 50-52





Figure 3

Claisen-type Rearrangements

an example of each is included. Several points about these deserve mention. The Claisen sequence proper, giving the aldehyde, is quite sensitive to steric effects, particularly in the step of forming the vinyl ether. Also, the yield (for the two steps) varies widely. The Meerwein-Eschenmoser reaction is suitable for hindered systems, but again the yields vary over a considerable range. As our synthetic route called for the diester $\frac{43}{23}$, the orthoester modification⁵³ of the Claisen rearrangement appeared ideal. At the time this project was begun, no examples of the orthoester Claisen in cyclic systems had been reported, and the effects of steric hindrance were completely unknown. We decided to try the orthoester procedure, fully expecting that some problems might develop in putting two substituents under the bicyclooctadiene framework. Whether the reaction could be done on the diol 42 was unknown, but we believed that, if necessary, the side chains could be put on sequentially, with appropriate protecting steps along the line.

Thus, the necessary compound for this approach is <u>cis</u>-<u>endo</u>-bicyclo[3.3.0]octa-3,7-diene-2,6-diol 49. The obvious precursor to this diol is the known^{29,54,55} dienedione 52 - reduction of the carbonyl groups would be expected to give the desired <u>endo</u> orientation of the hydroxyls, provided a reasonably bulky reducing agent was used. Although Dauben and his students had been unable to reduce the carbonyls of 52 without partially reducing the carbon-carbon double bonds⁵⁵,



we anticipated that some reagent could be found which would give usable yield of the diol 49. In particular, diisobutyl aluminum hydride appeared a likely candidate, as this reagent had been found to give clean reduction of α , β -unsaturated ketones to allylic alcohols⁵⁶. The bulkiness of this reagent would also be expected to lead to the necessary <u>cis</u>endo stereochemistry.

A final point which helped us choose this approach to 22 was the availability, from other research in this laboratory, of bicyclooctanedione 53. As a procedure for converting 53 to 52 had been worked out by the Dauben group 29,54,55 , this simplified the planning necessary.

Figure 4 shows the proposed synthesis of tetraene χ_{χ}^{2} . The reasons for choosing this scheme can be condensed into the following. First, the sequence appeared promising, with no really bad steps. At the same time, the chemistry involved would not be trivial, and the use of some new reagents and procedures might lead to improved knowledge of them. Having the starting material in hand was an added bonus. Finally, most of the synthetic intermediates possess the same C₂ symmetry as the final product, and as each step transforms the symmetry-related functional groups in the same way, a certain economy of steps is maintained.













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Proposed Route to Tricyclododecatetraene 22

RESULTS AND DISCUSSION

Synthesis of Bicyclo[3.3.0]octa-3,7-diene-2,6-dione

The synthetic plan just outlined required bicyclo-[3.3.0]octa-3,7-diene-2,6-dione 52 as the starting material. As mentioned previously, Dauben and coworkers had reported



the preparation of this compound in 1952^{54} , from the dione 53, and had subsequently improved the procedure^{29,55}. Our first preparations of the dienedione utilized the most recent (1966) recipe of the Dauben group, that of Simpson⁵⁵. The precursor, dione 53, was prepared by Glen R. Elliott, also using Simpson's procedure. The entire scheme, with yields we obtained, is presented in Figure 5; the details are given in the Experimental section. For comparison, the yields reported by Simpson are given in parenthesis.

Although this sequence afforded 52, albeit in rather low yield (22-23% from 53), the time required (10 days minimum for the 53 \rightarrow 52 conversion) appeared excessive. Considering the number of synthetic steps beyond 52 which we contemplated, we were sure to need large quantities of 52 and a sequence affording higher yields and permitting scaling up appeared desirable. Accordingly, a considerable







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Original Route to Dienedione 52

effort was expended in developing a more efficient large scale synthesis of 52.

Figure 6 presents the results of this effort, which also led to a substantial improvement in the preparation of bicyclooctanedione §3. The synthesis largely parallels that of the Dauben group^{29,54,55}; the main differences are in the preparation of the bromoketal §9, and in the conditions for the double dehydrobromination of §9 to 60. The full details are given in the Experimental section; only the results - and some interpretation - are presented here.

Tetramethyl 1,3,4,6-hexane tetracarboxylate 55 was prepared by the free radical induced coupling of dimethyl glutarate 54, using essentially the procedure developed by Osborne²⁹ and used by Simpson⁵⁵. As reported by Osborne, both diastereomers of 55 are formed in this reaction. It was noted long ago by Ruzicka⁵⁷ that both isomers undergo Dieckmann cyclization to give the same product, <u>bis</u>(ketoester) 56 with the <u>cis</u> ring fusion. Thus, separation of the isomers is not necessary. However, an additional product was formed, amounting to about 15% of the distilled product. This compound has not been identified, but is almost surely the isomeric tetraester 52. The relative rates of abstrac-



tion of the α - and β - hydrogens of propionic acid by methyl









Figure 6

New Synthesis of Dienedione 52

radical are 7.8 and 1.0, respectively (on a per-hydrogen basis)⁵⁸. Dimethyl glutarate has four α - and two " β -like" hydrogens; applying the relative reactivities of the propionic acid hydrogens to dimethyl glutarate, and assuming that the coupling of the resulting radicals is random, about 12% of the "wrong" tetraester $\beta \chi$ should be formed. The agreement with the observed result, 15%, is embarrassing, considering the assumptions made in the "calculation". Osborne²⁹ had concluded that isomers of $\xi \xi$ were formed in only small amounts; our results are in contrast to that conclusion.

In any event, this impurity is removed quite easily by recrystallization from methanol. If this is not done, the product from the Dieckmann cyclization of 55 to 56 is quite impure, and usually liquid. We found that this cyclization may be carried out using sodium methoxide in dimethylsulfoxide (DMSO), provided water is excluded. This gives a somewhat higher yield than the old reagent, potassium t-butoxide in t-butanol. In addition, the hazards of handling potassium are avoided, and large scale preparations (0.5-0.6 mole) can be run without difficulty. The product, ketoester 56, was obtained as a finely divided solid. This material can be used directly in the next step, hydrolysis decarboxylation to 53, without purification. Dione 53 is quite soluble in water, and extraction with ether requires an extended continuous extraction. We observed that the use of chloroform permits nearly complete extraction of

the dione with only a few separatory funnel extractions. The crude dione is suitable for use in the next step; it can be purified by sublimation (97% recovery) if desired.

The use of DMSO as a solvent for Dieckmann cyclizations is not new; in some cases it has been found to give faster reaction and higher yields⁵⁹. However, side reactions have also been reported^{59b}; these have been attributed to oxidation of the reactants by the solvent. In this regard, we have noticed that high reaction temperatures (over 90°) lead to extensive darkening of the product. In these cases, the odor of dimethyl sulfide was easily detected.

The rest of the synthesis of dienedione 52 required introducing the two double bonds. The sequence of ketalization, bromination, elimination, and deketalization as used by Eaton in the structurally similar transformation $63 + 64^{60}$, appeared suitable for the conversion 53 + 52. After some



initial trials, an efficient synthesis of 52 was developed along these lines.

Ketalization of 53 proceeded cleanly and in nearly quantitative yield. The liquid diketal 61 was then brominated with pyridinium tribromide ("pyridinium hydrobromide perbromide") in tetrahydrofuran. Provided the reaction was

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run at low temperatures, good yields of the dibromodiketal 52 were obtained. Alternatively, 52 could be prepared by direct bromination of dione 53 in ethylene glycol⁶¹; however, this gave lower yields and was suitable for small scale preparations only. Our results permit some definite statements as to the stereochemistries of the different isomers of 52, and clarify the results of the Dauben group in this area, which were summarized by Osborne²⁹.

Originally, 52 was prepared by ketalization of the dibromodione $\xi\xi$, prepared by direct halogenation of $\xi\xi$. Three isomers of 59 were reported, designated alpha, beta, and gamma in order of decreasing melting point (and increasing solubility in ethanol). These were found to be in the approximate ratio 1:8:8. In contrast, Osborne found that bromination of the enol acetate 57, followed by ketalization, afforded the γ -isomer exclusively. In our procedure (pyridinium tribromide, tetrahydrofuran, -70°), only the α - and β -isomers were formed, in a ratio of about 10:1. The nmr spectra of these two isomers, summarized in the Experimental section, permit assigning the α -isomer as the cis, exo isomer 59a, and the β -isomer the trans structure Specifically, the near equivalence of the protons of 59b. the ethylene units, and the appearance of the 3- and 7-



Br 0 592

protons as a triplet (J = 6.7 Hz) support the <u>cis,exo</u> configuration of the α -isomer. In contrast, the extreme complexity of the 4.55-3.75 & region in the nmr spectrum of the β -isomer showed this material to have the <u>trans</u> configuration. These results are what one would intuitively expect - attack of bromine on the intermediate enol ether should occur predominantly on the <u>exo</u> side, leading to the preponderance of 59a in the product.

By the process of elimination, the γ -isomer must be the <u>cis,endo</u> isomer 59c. However, it appeared very unusual that this very hindered product would be the major (let alone



the exclusive) product of bromination, followed by ketalization, of dione 53 or enol acetate 57. When the enol acetate sequence was repeated, we obtained material with a melting point slightly higher than that reported previously²⁹. The ir and nmr spectra of this material led us to suspect that it was a mixture of the α - and β -isomers--every peak in a spectrum of the presumed γ -form could be found in the spectrum of one of the known isomers 59a or 59b. Confirmation of this hypothesis was obtained by gas chromatography. When the " γ -isomer" was analyzed under conditions which effected separation of 59a and 59b, the " γ -isomer" was shown to be a roughly 1:1 mixture of these latter pure compounds. Evidently, when the <u>cis,exo</u> and <u>trans</u> isomers are present in roughly equal amounts, crystallization can fail to separate them. To summarize these conclusions, the " α -isomer", mp 160-160.5°, has the bromines <u>cis</u> and <u>exo</u>, as in <u>59a</u>; the " β -isomer", mp 144-145°, has them <u>trans</u> (<u>59b</u>). The alleged " γ -isomer", mp <u>ca</u>. 125°, is a mixture (approximately 1:1) of these two. Thus, the <u>cis,endo</u> form <u>59c</u> is unknown.

To return to the synthesis of dienedione 52, crystallization of 59 was not necessary for the next step; thorough washing with methanol gave suitable material. As dehydrobromination with potassium hydroxide in ethanol gave considerable "mono-eliminated" material, we searched for other bases and/or solvents which would give faster, cleaner reaction. As was the case in the Dieckmann reaction, sodium methoxide in dimethylsulfoxide was the combination of choice. Provided the initial exotherm was checked, high yields (89-92% after recrystallization) of the diene diketal 60 were easily obtained.

The final step in the preparation of bicyclooctadienedione 52, removal of the ketal protecting groups in 60, was carried out using a variation on the ketal exchange procedure of the Dauben group^{29,54,55}. In our hands, the elaborate precautions used by those workers - carefully dried glassware and acetone and an inert atmosphere - were unnecessary. Ketal exchange appeared to be complete within a few minutes after adding 60 to acetone containing a trace of acid. Removal of the solvent (and the byproduct, the

ethylene ketal of acetone) and sublimation gave very high yields of pure dienedione 52. Hydrolysis with aqueous phosphoric acid could also be used, but was much less convenient.

Thus, the sequence outlined in Figure 6 makes bicyclo-[3.3.0]octa-3,7-diene-2,6-dione easily available. All of the reactions have been run on a 0.2 mole scale or larger, making the dienedione suitable for synthetic uses. Furthermore, the entire preparation, from dimethyl glutarate to $\xi \chi$, can be run in slightly over a week, and, provided the usual care is taken, it is free from hazard. Some new studies on the chemistry of dienedione $\xi \chi$ have already been made⁶¹, and we anticipate that more interesting chemistry awaits discovery. In view of the current interest in cyclopentanecontaining molecules⁶², the bicyclooctane derivatives made available by this route deserve consideration as synthetic intermediates.

Reduction of Bicyclo[3.3.0]octa-3,7-diene-2,6-dione.

The first venture into really new chemistry required reduction of bicyclooctadienedione 52 to the <u>cis,endo</u>-bicyclooctadienediol 49. Although this transformation appears straightforward, Dauben and coworkers had been frustrated in their attempts to reduce 52 to 49 (or to other stereoisomers of 49)⁵⁵. These workers, who wanted the diol for attempted conversion to pentalene, had tried a large variety of reducing agents without success; sodium and lithium borohydride (in several solvents), lithium aluminum hydride (normal and inverse addition), aluminum hydride generated from lithium aluminum hydride and aluminum chloride, and several tin hydride reducing agents failed to give the desired dienediol. Indeed, no products were characterized from any of these reactions. The spectral data (ir and nmr) showed that reduction of the carbon-carbon double bonds was the interfering reaction - in most cases, saturated alcohols and ketones were the main products. Here, the well known difficulties in reducing α , β -unsaturated carbonyl compounds (in particular cyclopentenones) are complicated by the extraordinary base sensitivity of dienedione 52. Brief contact with dilute bicarbonate solutions leads to extensive destruction of 52, and Michigan State University tap water has a similar, if slower, effect⁶⁴. Accordingly, we searched for other reducing agents, preferably showing Lewis acidity, for this step.

Aluminum hydride, generated by the procedure of Brown and Yoon⁶⁵, was considered, as this reagent was shown to reduce cyclopentenones to cyclopentenols with only slight overreduction. However, while this work was still in the planning stages, Masamune reported the suitability of diisobutyl aluminum hydride for reducing enones (and enediones) very cleanly, and in high yields, to allylic alcohols⁵⁶. Although the reducing ability of such alkyl aluminum compounds had long been known⁶⁶, this was apparently the first demonstration of their great preference to react "1,2" and

not "1,4" with α,β -enones. As the $52 \rightarrow 42$ conversion had already been shown to be a worse case than most, we decided to apply this reagent to our problem.

Preliminary trials showed the reaction to work as expected, and a productive method was easily worked out. Although Masamune and coworkers had used inverse addition, adding the hydride to the enone, we found this to be unnecessary, and used the simpler (and safer) normal addition. Toluene was used as the solvent instead of benzene, to permit lower reaction temperatures. The yields in this reaction were very high, runs on the 0.05 to 0.125 mole scale giving 80-88% yields of distilled diol (a mixture of stereoisomers, <u>vide infra</u>). This material was a white, paraffin-like solid, quite sensitive to acid; the spectral properties left no doubt that only carbonyl reduction had occurred.

Gas chromatographic analysis of this product showed it to contain three components (in the ratio 77:21:2 for a -40° reaction), presumably the three stereoisomers <u>cis</u>, <u>endo $\frac{19}{2}$, trans 65</u> and <u>cis</u>, exo 66, respectively. The proof



of this is given later. Although one compound predominated, separation on a preparatively useful scale proved difficult. Chromatography gave rather mediocre results, and

crystallization from most of the solvents tried was unsuccessful. As a result, some of the subsequent reactions were run with this mixture of epimers. Finally, it was found that most of the major isomer could be separated by crystallization from acetone, although the diol is extremely soluble in this solvent.

The spectra of the crystallized material (prisms, mp 93-93.7°) were consistent with the anticipated structure $\frac{1}{22}$ (having the hydroxyls <u>cis</u>,endo); the nmr spectrum is reproduced in Figure A3. However, as was the case with the <u>cis</u>,exo-dibromide $\frac{6}{22}$ ⁶⁷, the stereochemistry could not be definitely assigned from the spectra. As the <u>cis</u>,endo-stereochemistry is absolutely essential for the rest of the synthesis, we worried a great deal about this problem, even beginning a single-crystal X-ray diffraction study of a derivative. The following discussion treats the results of several other studies which convinced us that the major isomer was indeed the desired <u>cis</u>,endo-diol $\frac{1}{22}$.

Formation of cyclic derivatives - carbonate, oxalate, acetonide - was unsuccessful. However, the mixture of epimeric diols was converted to a mixture of epimeric diacetates in high yield; the ratio of the two major diacetate isomers was shown by gc to be about 4:1, corresponding very closely to the proportions in the diol mixture. The major diacetate could be purified, with fairly good recovery, by crystallization from hydrocarbon solvents; this material, mp 93.6-94.1°, showed a sharp singlet for the acetate methyls,

consistent with a <u>cis</u>-disposition of the acetate units, as in structure 68. Examination of the nmr spectrum of the



acetate mixture showed, in addition to the singlet for the major isomer, a closely spaced pair of singlets, of equal intensity, for the less abundant isomer 69. Careful integration of these acetate methyl signals gave a composition in excellent agreement with that obtained by gc.

Thus, the diol formed in intermediate amounts (<u>ca</u>. 20% in reductions done at -40°) must be the <u>trans</u>-isomer §5. That the major diol isomer is the <u>cis</u>,<u>endo</u>-diol 49, and not the <u>cis</u>,<u>exo</u>-isomer §6, follows from two other observations. First, treatment of the major isomer with aqueous acetone containing a <u>trace</u> of acid led to its conversion into a mixture (<u>ca</u>. 1:1) of the other isomers (prolonged refluxing under these conditions led to the slow formation of a fourth product, presumably one of the structural isomers 70). This result suggests that the major isomer is the least stable,



as would be expected were it the <u>cis,endo</u>, 42. This conclusion was supported by the results of reduction at several different temperatures, as shown in Table 3. These results

Table 3

Temperature Study of the Diisobutyl Aluminum Hydride Reduction of $52^{(a)}$

Reaction Temperature	Produc	Product Composition, % ^(b)		
	42	免된	। <u></u>	
30-35°	68.0	30.0	2.0	
0-5°	73.0	25.2	1.8	
-40°	77.7	20.3	2.0	
-60°	77.5	20.4	2.1	

(a) Reductions were carried out in toluene, using a 100% excess of the reducing agent (see Experimental). (b) Analysis by gc on Carbowax 20M (see Experimental); the compositions given are the averages for three analysis, uncorrected for detector response, and are believed accurate to ±0.5%.

clearly indicate that the major isomer is the <u>cis</u>,<u>endo</u>, as the formation of this isomer should be the least hindered.

The results in Table 3 prompt some additional comments and speculation. In particular, the amount of the <u>trans</u> isomer & appears rather high, and the temperature dependence of the composition is less than might be expected. For comparison, the relative rates of <u>exo</u> to <u>endo</u> attack for some reactions of bicyclooct-2-ene, 71, bicyclooctane-2-one, 72, and 2-methylenebicyclooctane, 73, determined by Brown and coworkers⁶⁸, are given in Table 4. Although these



substrates are somewhat more hindered to attack on the

Table 4

Addition to Bicyclooctyl Derivatives

Substrate		Exo:Endo Attack Ratio
ZŁ	hydroboration-oxidation	24
	epoxidation	6.7
	oxymercuration-demercuration	8
ん lithium reductio CH ₃ MgX a	lithium aluminum hydride reduction	3
	CH ₃ MgX addition	50
ZZ	oxymercuration-demercuration	8.1

endo-side than is dienedione $\xi \chi$, it is apparent that most of these reactions are much more selective than the reduction of $\xi \chi$. An explanation for the low selectivity which comes to mind (and which also accounts for the relatively slight temperature dependence) involves formal transfer of a hydride <u>from an isobutyl group</u>. Thus, reduction of the first carbonyl in $\xi \chi$ occurs very predominantly from the <u>exo</u> face, giving an intermediate such as $\chi \mu$; this can
then react "normally", and again on the <u>exo</u> face (of the other ring) to give, after hydrolysis, the <u>cis,endo</u>-isomer 42. However, 74 can also undergo an intramolecular hydride transfer, as shown, to ultimately give the <u>trans</u>-diol $\pounds 5$. As triisobutyl aluminum can be used to reduce ketones to



alcohols⁶⁵, such a sequence is reasonable. The activation energy for the intramolecular reduction would probably be low, and hence the influence of temperature would probably be small. The observed temperature dependence of the reduction is probably the result of decreasing the amount of initial attack on the <u>endo</u>-face of $\frac{52}{4}$.

In any event, the diisobutyl aluminum hydride reduction has been shown to give a high yield of allylic diols, demonstrating the applicability of this reagent in a very difficult case, where other reagents fail⁵⁵. Also, it provided the necessary stereoisomer, <u>cis,endo</u>-diol $\frac{40}{20}$, in quite good yield, although isolation of this material was initially troublesome.

Orthoester Claisen Reaction of Bicyclooctadienediol.

The introduction of two acetic ester side chains to the "underside" of the bicyclooctadiene system was the next problem to be faced. As discussed previously, the intended approach was to utilize the orthoester modification of the Claisen rearrangement⁵³; thus, dienediol 49 would be converted into a diester 42, formally <u>via</u> the intermediates orthoacetate 75 and ketene acetal 76. For several reasons - a fairly high boiling point, commercial availability, and the fact that it had been used previously⁵³ - triethyl orthoacetate was chosen as the orthoester component in the reaction mixture. The ethyl ester 77 was thus the desired product of this reaction.

As described in the previous section on the reduction of dienedione 52 to 49, the isolation of the pure <u>cis,endo-</u> diol 49 was a problem of some severity. Accordingly, preliminary studies on the orthoester Claisen step were carried out using the distilled mixture of diol isomers 49, 65 and 56 (approximately 77%, 21% and 2%, respectively).

In these early studies several problems became apparent. Technically, the most troublesome were the complexity of the mixture of products, and the lack of a really good method for analyzing this mixture. Gas chromatography of the product mixtures from the early trials (starting with the mixture of diols) showed over twenty "significant" components; these were eluted too closely to permit collecting the individual components. Similarly, thin layer









ZZ

chromatography showed that clean separations could not be obtained in this way either. Although the shower of products was partly the result of the impurity of the starting material, we were faced with the problem of not knowing which components needed to be maximized.

The most useful analytical technique found was nmr spectroscopy; the appearance of a quartet near δ 4.0 was evidence that an ethyl ester was formed. This method obviously had the defect that the desired product $\chi\chi$ could not be distinguished from other compounds containing an ethyl ester unit. Nevertheless, this technique was better than nothing, and was used until pure $\chi\chi$ finally was isolated; at that time the gc analysis became practical.

It quickly became apparent from the early studies that the very mild conditions used by Johnson, <u>et al</u>.⁵³ in acyclic cases - several hours at 138° with continuous removal of ethanol - were woefully inadequate for the transformation $\frac{1}{2}$? $\frac{2}{2}$. This situation was not unexpected in view of the considerable steric congestion "underneath" the bicyclic framework. However, as more and more vigorous conditions were tried, all without success, we concluded that some factor or factors were operating to our disadvantage.

In particular, the nmr spectra of the distillates from these early experiments suggested that the main compounds formed were the mixed orthoacetate 75 (R = C₂H₅). That 75could survive such treatment as several weeks in refluxing acidified xylene was taken to mean either (1) the intermediate

ketene acetal χ_{δ} was not being formed, or (2) χ_{δ} was failing to undergo the Claisen-type rearrangement to χ_{δ} . As ketene acetals were formed under the mild conditions of Johnson, et al.⁵³, and there appeared to be no reason for elimination of ethanol from χ_{δ} to be unfavorable by comparison, we concluded that the problems involved the rearrangement itself. Thus, a ketene acetal probably was being formed, but the temperature was too low to force rearrangement; under these circumstances, polymerization of the ketene acetal would probably become dominant. Although these conclusions are in fact incorrect, they led to the development of conditions which did produce the desired product, diester χ_{δ} .

Having convinced ourselves that a higher temperature was needed, the reaction was attempted using <u>o</u>-dichlorobenzene (bp 178°) as solvent. Pivalic acid (trimethyl acetic acid) was chosen as the acid catalyst for several reasons: (1) its high boiling point - 163° - should reduce the amount lost by distillation. (2) The bulk of the <u>t</u>butyl group should minimize the incorporation of the pivaloyl unit into the bicyclooctadienyl system (esterification of the diol by the catalyst appeared to be a problem when propionic acid was used). Finally, (3), any such pivalatederived products should be easily identified, the nine-proton singlet of the <u>t</u>-butyl group being readily recognizable.

Using a fourfold excess of triethyl orthoacetate in boiling <u>o</u>-dichlorobenzene, occasional additions of pivalic

acid, and removal of material boiling below 100° , a four day reaction period afforded the usual plethora of products. Of these, the two of longest retention times predominated, each comprising about 35% of the mixture. The nmr spectrum of this mixture showed a vinyl:ester methylene ratio of about 5:3. Assuming the only ethyl esters present to be $\chi\chi$ and epimers, this represents about 60% rearrangement in the product mixture.

Further data on this mixture showed that diester $\chi\chi$ (and epimers) definitely was formed. The mass spectrum of the mixture showed a very intense peak at m/e 278, as expected for $\chi\chi$ (or isomers). The two major components mentioned above (the "longest retention time" products) showed gas chromatographic behavior similar to the structurally related compounds $\chi\chi$ and $\chi\chi$ (see below). Finally, the following chemical transformations definitely prove that, at the least, the desired skeleton $\chi\chi$ had been formed.



The mixture of stereoisomeric α,β -unsaturated diesters 78 was prepared in fair yield (60-70%) by Wittig reaction of bicyclooctanedione 53 and carboethoxymethylenetriphenylphosphorane⁶⁹; the addition of benzoic acid as catalyst⁷⁰ was found to increase the reaction rate significantly.

Z& was separated from the two isomers of ketoester & and an assortment of other products by column chromatography.



The isomer of 78 which was eluted first (and which had the shortest retention time on a QF-1 gc column) proved to be crystalline; further characterization of 78 was carried out on this isomer. Several recrystallizations (two from pentane, three from ethanol-water) gave fine white needles, mp 54.6-55.0°, raised to 55.0-55.2° by sublimation. The combustion analysis and spectral data were in complete accord with structure 78. Certain features of the nmr spectrum suggest that this compound is the isomer 78a. In particular,



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the two-proton multiplet at δ 4.0-3.5 is presumably due to the bridgehead protons. The mixture of the three isomers (in the ratio 35:50:15) showed this peak in diminished amounts (<u>ca</u>. 1.4 proton), while the series of multiplets at higher field (δ 2.7-2.0) increased in intensity (from 8H to 8.6H) and spread to lower field (δ 3.3-2.1). Deshielding of the bridgehead protons in χ_{RA} by the proximate ester groups is the most likely origin of this shift; this argument, which has been used before⁷¹, leads to the assigned stereochemistry.

Catalytic reduction of either χ_{RA} or the mixture of isomers of χ_{R} gave all three isomers of the saturated diester χ_{R}^{2} . No attempt was made to separate these isomers, but the



gross structure was evident from the spectra, as well as from the unambiguous synthesis. <u>Reduction of the product</u> <u>mixture from the orthoester Claisen gave the same saturated</u> <u>diesters</u> (as well as an assortment of minor products of shorter retention time). Thus, the Claisen-type reaction was working, producing from the mixture of epimeric diols several compounds of the desired gross structure gg.

With the knowledge that the reaction was working, and reasonable certainty that the two major "longest retention time" products were 22 and its <u>trans</u> isomer, the best conditions for this reaction were worked out, still starting with the mixture of diols. It was found that several days reaction in neat boiling triethyl orthoacetate, followed by several days more in dichlorobenzene, gave improved yields of diester 22. Fortunately, the development of suitable conditions for this reaction coincided with the discovery

of a method for obtaining the pure <u>cis</u>,<u>endo</u>-diol 42, and the orthoester Claisen could be tried on this material.

After some minor adjustments, a productive method was developed which gave 22 in good purity and fair yield (35-40% isolated). The procedure used is described in the Experimental section, together with full characterization of the cis, endo-diester 22. This material, an oil, had the anticipated spectral properties, although, as was the case with the diol 42, positive assignment of the cis, endo-stereochemistry could not be made on the basis of the nmr spectrum. That it should be the cis, endo-isomer followed from the mechanism; evidence that this assignment was correct came from the catalytic hydrogenation mentioned before. Pure 22 gave a single isomer of 79, with only a small amount of epimers of 79 being formed. This product had the longest retention time on QF-1 of the three isomers of 22; significantly, this isomer was the major isomer formed in the catalytic hydrogenation of 78. As the latter reduction should involve hydrogen transfer to the less hindered exo-face of 28, the cis, endo-product should predominate.

It was mentioned previously that the use of dichlorobenzene as solvent resulted from the belief that the Claisen rearrangement step itself was not proceeding at $140-145^{\circ}$. This conclusion is in fact wrong; the problem with the early trials was that the necessary ketene acetal intermediates (<u>eg 76</u>) were not being formed efficiently. By using neat triethylorthoacetate as solvent, but forcing the removal

of evolved ethanol by slow, continuous distillation of the solvent, substantially improved yields of $\chi\chi$ (and much less polymer) were obtained. Using this procedure, the isolated yield (after chromatography) of $\chi\chi$ was increased to 50-55%; the gc yields were around 60%. Taking into account the byproducts (<u>vide infra</u>), 85-90% of the starting diol could be accounted for. The higher yields were somewhat offset by the necessity of monitoring the distillation rate quite closely, which made the process rather tedious. As was the case with reactions run in <u>o</u>-dichlorobenzene, it was necessary to add the pivalic acid catalyst in portions throughout the reaction period, as various side reactions consumed the catalyst.

That elimination of ethanol from χ_{Σ} to give ketene acetal χ_{Ω} should be so difficult - or, alternatively, that capture of ethanol by χ_{Ω} should be so easy - is quite unusual. In cases where intermediates have been isolated⁷², they have been ketene acetals (analagous to χ_{Ω}) and <u>not</u> the mixed orthoacetates (analagous to χ_{Σ}). In our case, one



would expect that χ_{Σ} would be destabilized (relative to χ_{Σ}) by virtue of the additional steric interactions present in the former; in χ_{Σ} , the lesser bulk of the pendant groups should relieve the crowding underneath the bicyclic skeleton. Reluctance of χ_{Σ} to undergo rearrangement would be easily understandable, as the preferred chair-type transition state is impossible, and the boat-like geometry is still severely hindered. However, a relatively strain-free conformation is available, with the attached groups extended away from the bicyclic nucleus. The reasons for our original isolation of χ_{Σ} and not χ_{Σ} , in spite of the availability of this strain-free conformation, are not clear.

Some Byproducts of the Orthoester Claisen.

As has been stated repeatedly, a variety of products was formed in addition to the desired diester 77. Although the complexity of the mixture decreased when only the pure <u>cis,endo</u>-diol 42 was used, quite a few products were still formed. In this section the structures of several of these are presented.

The most abundant product after diester $\chi\chi$ was the lactone $\chi\chi$. This material is a solid, permitting nearly quantitative separation from the other products by simply adding hexane. The substance was obtained in yields of <u>ca</u>. 20% as fine needles, mp 84.8-85.2°. The structure was deduced from the (spectral) data, which are given in the Experimental section. The stereochemistry was not apparent from the

nmr spectrum; however, inspection of models convinced us that the only possible stereochemistry for the ring fusions is that indicated in structure 82.

The only other product formed to any significant degree had a structure basically similar to &2 - this is the pivalate ester &3. This material, formed in about 12% yield, was isolated in the course of the chromatographic purification of diester ZZ; &3 was eluted before the diester. This material was obtained as a pale yellow oil with an odor "reminiscent of musty places"⁷³. The structure was established by the spectra, particularly the nmr; the nine-proton singlet at &3 1.20 demonstrated the presence of the pivaloyl unit. Again, the stereochemistry was not obvious from the spectra; however, the nmr spectrum of &3 closely resembled that of &2, supporting their stereochemical similarity.

Another product of similar structure was 84, the acetate analogue of 83. This material was isolated in trace amounts (18) during the chromatography of 22; 84 was eluted <u>after</u>



the diester. As was the case with &, the gross structure followed from the spectra, and the stereochemistry is analagous to that of the other products.

Two other products of somewhat different structure have also been isolated (again in trace quantities) from the reaction mixture. In the chromatography of the reaction mixture a purple band was eluted very early; this material possessed a strong, rather pleasant, sweet odor. As gc analysis showed it to contain three components in roughly equal amounts, preparative gc was used to isolate them. The component of shortest retention time was too close to the solvent peak to permit effective isolation, but the second and third main components were cleanly separated from each other and from the numerous very minor impurities.

The component of intermediate retention time was obviously the source of the strong odor. However, the small amount of material obtained prevented accurate integration of the nmr spectrum. An ethyl ester and considerable unsaturation were present, and mechanistic considerations led us to consider structure g_{Σ} (or a double bond isomer) for this compound. However, the mass spectrum showed a parent



peak at m/e 192, which demands that this product be a dihydroderivative of 85 - that is, 86 or an isomer.



It is hard to account for the formation of structure such as §§. Compounds such as §§ might well be expected, arising from Claisen rearrangement in one ring and dehydration in the other. No such obvious pathway to §§ is available. It may arise <u>via</u> reduction of §§, or more likely by cleavage of an intermediate such as §7, followed by hydrogen atom abstraction from solvent.



The component of the purple band with the longest retention time was easily identified as 1,3,5-triethoxybenzene && from the nmr and ir spectra. This was confirmed by the melting point (needles from methanol-water, mp 41.0-41.3°) which agreed with that reported long ago⁷⁴. The origin of this aromatic compound is left as an exercise for the reader.

The structural similarity of compounds &2, &3, and &4 suggests a common mode of formation, and speculation along these lines is amusing. It is possible that all arise from Claisen rearrangement in one ring, followed by some sort of capture of the remaining hydroxyl:



However, an alternate mechanism is possible, as shown below:



This mechanism involves formation of the bridged orthoacetate \Re . Loss of ethanol would give the bridged ketene acetal \Re , which could yield lactone \Re directly upon Claisen rearrangement. Inspection of models suggests that neither \Re nor \Re is excessively strained; furthermore, Claisen rearrangement of 91 appears reasonable, a slightly distorted chair-like transition state being available. Our failure to prepare any cyclic derivatives of diol \Re may be taken as evidence against this second mechanism, but this argument must face the <u>caveat</u> applying to any statement based upon negative evidence. In any event, this second mechanism is an interesting possibility.

No attempts have been made to increase the yields of any of these byproducts, as they represent an unwanted diversion of the rather precious diol 42 from our goal. However, it appears that formation of lactone 82 is favored by the use of relatively small amounts of excess triethyl orthoacetate, and by the use of the dichlorobenzene cosolvent from the start of the reaction. The amount of pivalate &2 could probably be increased by using larger amounts of pivalic acid. In the event that either &2 or &3 were desired, it could probably be made the major product by finding the right conditions.

This concludes the discussion of the key reaction in the synthesis of tetraene 22, the attachment of the two 2carbon chains. Although the discussion has been rather lengthy, the crucial importance of this step and the

interesting results finally obtained justify this much detail.

Completion of the Synthesis

With the diester $\chi\chi$ finally in hand, it remained to join the ends of the two-carbon chains and introduce the necessary unsaturation into the resulting four carbon bridge. As outlined earlier, we chose to use the acyloin condensation⁴⁴, or the chlorotrimethylsilane modification of the acyloin, to achieve the cyclization. The expected products, ketol 44 and <u>bis(trimethylsiloxy)olefin 45</u>, appeared well suited for further transformations to $\chi\chi$.



A single attempt was made to achieve the cyclization to 44 using the "traditional" acyloin procedure - that is, running the reaction at high dilution without the addition of the chlorosilane. This procedure gave, in a low recovery, a mixture of four "major" products and a host of minor components. Due to the complexity of this mixture, and the low yield, this procedure was not investigated further, and we turned our attention to the chlorosilane modification.

For a model, the cyclization of the saturated diester χ_2 was attempted. Starting with a mixture of stereoisomers of χ_2 , containing about 50% of the <u>cis</u>,<u>endo</u>-isomer (<u>vide</u> <u>supra</u>), the reaction gave a fair yield (<u>ca</u>. 60% on the basis



of 50% purity of χ_2) of the trimethylsiloxy product χ_2 . Although a mixture of products was formed, the spectral data of this mixture supported the assigned structure χ_2 . With the knowledge that the cyclization was successful for the saturated case, we tried the unsaturated diester χ_2 and soon worked out a useful procedure for converting χ_2 to χ_2 .

Treatment of ZZ with finely divided sodium and chlorotrimethylsilane in hot (60-110°) toluene gave a complex mixture of volatile products; the desired <u>bis</u>(trimethylsiloxy)olefin 45 was the major (65-85%) component. The yield of 45 was only fair (40-55%), and varied without

any obvious relationship to the experimental parameters. The only consistent pattern observed was that larger scale reactions gave slightly higher yields.

That the main component was indeed 45 was apparent from the spectral properties of the mixture (summarized in the Experimental section). An attempt was made to purify 45 by preparative gc, but it decomposed badly under the gc conditions, giving two new products. As the crude (distilled) 45 was quite sensitive, no attempts at purification using other techniques were tried. Fortunately, as described later, the impure distillate was suitable for the subsequent steps.

While monitoring the reaction by gc, it was noted that the composition of an aliquot changed quite drastically upon exposure to moist air; 45 was rapidly converted to a new product of longer retention time. The distilled product did not show this reaction, suggesting that it was catalyzed by some very volatile component in the crude mixture. This conversion was carried out on a larger scale by overnight exposure of the reaction mixture to the air, followed by distillation and preparative gc. The new compound was assigned the structure 93 on the basis of the spectral data. Thus, the molecular weight, the carbonyl stretch in the ir, and the nine proton Si-CH₃ signal left little doubt as to the gross structure. The stereochemistry is not known, as molecular models show that either epimer of 23 can adopt a conformation which should give the observed



couplings of the methine hydrogen <u>alpha</u> to the ketone. Siloxyketone 23 is a hydrolysis product of the siloxyolefin 45, the reaction being catalyzed by hydrogen chloride formed by hydrolysis of the chlorosilane in the reaction mixture.

Originally, we planned to hydrolyze 45 completely to ketol 44 and proceed to the final product tetraene 22 using



fairly standard reactions. However, although one trimethylsilyl group was lost very easily (giving siloxyketone 23), the removal of <u>both</u> proved to be extremely difficult. The standard procedures for such transformations^{45,75} gave either no reaction, or led to the formation of complex mixtures and polymer. The only reaction which gave a single product in reasonable yield was treatment of 45 with a trace of concentrated hydrochloric acid. <u>Via</u> the intermediacy of 23, this gave a tetracyclic ketol, which we believe to be either 94 or 95.



Structure 94 is supported by the 5.73µ absorption in the ir, which suggests a cyclopentanone; however, such an assignment of ring size may not be valid in such a highly condensed polycyclic system. In any event, this material was definitely tetracyclic, showing that the double bonds in the bicyclic nucleus had gotten into the act in an unfortunate way.

The sensitivity of acyloins, particularly towards base, is well known⁴⁴; oxidation and polymerization are very facile under these conditions. Initially, this fact led us to avoid basic conditions for the "hydrolysis". In fact, treatment of 45 with methanolic base did give a complex mixture. However, LeGoff and Kovar had discovered that methanolic borohydride (which is surely quite basic) could be used to reduce <u>bis</u>(trimethylsilyl)enediol ethers to the corresponding diols, albeit in rather low yield⁷⁶. For example, the conversion 26 + 27 was accomplished in this manner in <u>ca</u>. 30% yield. Preliminary trials of this method on our



material appeared promising, and a satisfactory procedure was worked out.

Slow addition of a benzene solution of 45 to a huge excess (20-60 fold) of sodium borohydride in 80% aqueous ethanol containing a little alkali afforded, after acidification, extraction and distillation, fairly good yields of a gummy product rich (<u>ca</u>. 90%) in the desired diol 28. Yields assuming 100% purity of the starting <u>bis</u>(trimethyl-



silyl)ether were in the range 55-70%. As 42 was known to be impure, the actual yields are considerably higher (70-85%).

Further purification of diol 28 was achieved by chromatography on silica gel with ethyl acetate as the eluent. The material so obtained was a colorless, very thick goo which tenaciously retained solvent. After the last traces of solvent were removed in a stream of dry nitrogen or in high vacuum, the material slowly solidified to a hard white wax, which decomposed without melting. All attempts at recrystallization were unsuccessful; sublimation could be achieved, but led to some decomposition. As the material isolated in this fashion was <u>ca</u>. 98% pure (gc), it was used without further purification. The yield of pure diol was in the neighborhood of 60%.

That this compound had the gross structure $\frac{98}{28}$ was clear from the spectra (molecular weight 192; hydroxyl but no carbonyl in the ir; four vinyl protons and a two proton singlet exchangeable with D_20 in the nmr); the stereochemistry will be discussed shortly. Further proof of the structure was obtained by chemical means. Thus, Malaprade-type oxidation of $\frac{98}{28}$ with periodic acid in dry ether⁷⁷ gave a high yield of the dialdehyde $\frac{99}{29}$; for comparison, this dialdehyde was prepared unambiguously from diester $\frac{72}{24}$ as shown (60% yield, not optimized). The formation of $\frac{99}{28}$ was observed by



gc, ir, and by an even more sensitive technique, smell. Amounts of 99 barely detectable by gc could be easily detected in a small room; as the odor is quite pleasant, this was an enjoyable analytical tool. 99 was very unstable, decomposing upon standing overnight in the air. Sublimation gave wet-looking needles, mp 53-58°, but further purification was deterred by the instability of the compound.

The structure was obvious from the spectral data, which are summarized in the Experimental section.

To return to the structural arguments, the periodic acid cleavage left no doubt that this compound was in fact the desired 6,7-dihydroxytricyclo[7.3.0.0⁴,¹²]dodeca-2,10diene \Re . This conversion establishes that the acyloin cyclization had occurred as intended, thereby confirming the <u>cis</u>,<u>endo</u>-stereochemistry of diester 77.

The final comments here deal with the stereochemistry of the diol. As indicated in structure 22, this compound has the hydroxyls cis. This assignment follows from the nmr spectrum of the diol, and, more convincingly, from the spectra of several derivatives. Thus, the vinyl protons of 28 appear as a three proton multiplet accompanied by a one-hydrogen doublet of doublets. Furthermore, the two methine protons on the hydroxyl-bearing carbons are not equivalent, appearing as distinct multiplets. Of the three possible diastereomeric structures 28, 100 and 101, only the first would be expected to show such nonequivalence. As shown, 100 and 101 both possess a two-fold axis, at least in the "flattened out" conformation shown. Molecular models confirm these conclusions; the preferred conformation of both trans isomers 100 and 101 would be symmetrical and show equivalent methines (α - to the hydroxyls). Also, the C₂ symmetry of the <u>trans</u> isomers would influence the vinyl region of the nmr spectrum, and a pattern markedly simpler than that observed would be expected.



These arguments are greatly strengthened by the nmr data of several derivatives of the diol, namely the dimesylate LO2 and the diacetate LO3. In both of these, the methyls are clearly nonequivalent, appearing as distinct, equally



intense singlets. Again, the methine protons <u>alpha</u>- to the oxygens give rise to two separate multiplets, and the vinyl protons give the same complex pattern - a broad two-proton singlet and two l-proton multiplets - observed for the diol

itself.

Although this evidence is quite convincing, the argument suffers slightly from being based upon data for only one isomer. Fortuitously, we have obtained one of the trans-diacetates 104 or 105. Chromatography of the pot



residue from distillation of the diol afforded a small amount of material which on cursory chromatographic analysis (tlc and vpc on a single column) behaved identically to the purified diol 98. Acetylation of this material, however, gave the "old" diacetate 103 in only <u>ca</u>. 20% yield. The major product (ca. 75%) was a new diacetate, shown to be isomeric with 103 by its mass spectrum. However, the nmr was strikingly different; the vinyl hydrogens appeared as an extreme AB-quartet type pattern, the methines alphato the acetoxyls gave a single multiplet, and the acetate methyls gave a sharp singlet. These data clearly support a symmetrical structure, that is, one of the two transisomers 104 and 105; which isomer we obtained is not known. The nmr spectra of the cis- and trans- diacetates are shown in Figures A7 and A8 to permit visual comparison; these results demonstrate the <u>cis</u>-stereochemistry of 103, and hence of the diol 98.

With the structure of the diol firmly established, we were faced with double dehydration (or its equivalent) of the compound. Several problems of unknown severity were envisioned for this step, the most serious being the possibility of elimination the "wrong" way to give an enol (102, X = OH) or an enol derivative (<u>eg</u>., an enol tosylate, 102, X = OTs). This possibility appeared quite likely in view of the <u>cis</u>-stereochemistry of diol <u>98</u> and hence of a



derivative LLQ - the preferred conformations of LQQ both are set up for a <u>trans</u>-elimination in this "wrong" way. Molecular models show that the desired eliminations (E2) to 22 cannot both proceed <u>via</u> the preferred <u>trans</u> elimination pathway; one of the double bonds must be formed with a proton and the substituent (X) leaving in a <u>cis</u>-manner. This suggested that rather vigorous conditions might be needed for this reaction.

The use of strongly basic conditions for this elimination appeared to offer the solution to both of these problems. With a sufficiently strong base, the fact that elimination must be <u>cis</u> would not be a serious problem. At the same time, if the "wrong" elimination were to take place first, two reasonable pathways appeared open which

would still lead to the desired tetraene 22. Thus, 102 could be equilibrated to the allylic isomer 108, from which elimination to 22 is possible. Alternatively, 102 might undergo elimination to the allene 109, which should isomerize to the desired isomer 22. Molecular models show that allene 109 is not impossibly strained, but that it <u>is</u> less stable than the "1,3-diene" 22.



The first attempt at dehydration of diol 28 utilized distillation from alumina, a brute force method which has, in fact, been successful in some rather unpromising situations. Atmospheric pressure distillation of 28 from alumina treated according to von Rudloff⁷⁸ (Woelm, neutral, Activity I, plus 2% pyridine) gave a complex mixture; only a trace component of this mixture showed gas chromatographic behavior

consistent with a C12 hydrocarbon.

The major component of the mixture was clearly a carbonyl compound, as shown by its behavior on the carbonylspecific gc liquid phase QF-1; on this fluorosilicone the major product had by far the longest retention time of any of the products, while on SE-30 it appeared in the midst of the other peaks. The ir spectrum of the mixture showed strong carbonyl absorption (5.90μ) ; the nmr spectrum of the mixture was practically incomprehensible, but showed no obvious aldehyde or ester peaks. These results led us to suspect that this major product was ketone LLQ, formed by dehydration the "wrong" way to an enol (LQZ, X = OH) and



tautomerization. Further support of this structure came when it was isolated in another reaction, and spectral data obtained on a fairly pure sample; these results will be discussed shortly.

When the reaction was repeated using strongly basic alumina, no compounds behaving like a C₁₂ hydrocarbon were formed; under these conditions the amount of the ketonic product <u>ll0</u> increased slightly.

As it was apparent that direct dehydration was taking an undesired course we examined the possibility of achieving base catalyzed elimination of a sulfonate ester. Attempts to prepare the ditosylate were unsuccessful, as only one of the hydroxyl groups of 98 reacted with <u>p</u>-toluenesulfonyl chloride. As the <u>cis</u>-configuration of the diol results in one very hindered hydroxyl, this result is not surprising. In contrast, reaction with the smaller reagent methanesulfonyl chloride took place at both hydroxyls, affording the dimesylate 102 in 62% yield after recrystallization. This material, mp 99.5-101° (dec), exhibited the expected spectral properties. As was mentioned previously, the methyl groups were nonequivalent, in accord with the <u>cis</u>-stereochemistry. This dimesylate was somewhat unstable, gradually



yellowing even at -35°, we suspect that considerable decomposition accompanied this discoloration, as the next step gave cleaner products when freshly prepared $\chi \chi \chi$ was used (<u>vi</u>de infra).

Base catalyzed elimination of dimesylate LLL was the final step in the synthesis. It should be emphasized that the results given here are preliminary, and that this last step will undoubtedly be improved. As elimination using l, S-diazabicyclo[4.3.0]non-5-ene and sodium methoxide (in dimethylsulfoxide) as the base appeared unpromising, we

concentrated on using potassium t-butoxide in dimethylsulfoxide. Treatment of 102 with this powerfully basic combination afforded a complex mixture, quite similar to that obtained by distillation from alumina. The major difference, and a very welcome one, was the appearance of relatively large quantities (10-20%) of a component with retention behavior similar to 1,5,9-cyclododecatriene and other C_{12} hydrocarbons on gc columns loaded with several liquid phases. The mixture was analyzed by coupled gas chromatography-mass spectrometry, which established that this component had the expected molecular weight, the parent peak appearing at m/e 156 (calculated for 22, 156). That the material was a hydrocarbon was evident from the gc results, and from its behavior when chromatographed on alumina (vide infra). Thus, the compound had to have the formula $C_{12}H_{12}$, corresponding to the desired product 22.

Isolation of this compound was achieved by chromatography on Activity I alumina (neutral or basic); it was eluted very quickly with hexane as eluent. This process gave material of 70-90% purity, the impurities varying from run to run. Isolated yields were in the range 4-9%. The material, a soft white solid, possessed a typical olefinlike odor, somewhat reminiscent of norbornadiene. In light of the spectral data given later, there is no doubt that this compound is in fact the desired tricyclododecatetraene 22.

In the <u>t</u>-butoxide induced elimination of the dimesylate

102, one of the major byproducts was the same ketone (110) formed in the alumina pyrolysis. The molecular weight of this compound was determined in gc-mass spectrometry experiment, and had the expected value 174. The fragmentation pattern of this compound was also in accord with structure 110. Further evidence supporting this structure came from the spectral data obtained on material isolated by chromatography (eluting with hexane-chloroform after tetraene 22 had come off the column with hexane). This material, a pale yellow, waxy solid, was <u>ca</u>. 90% pure by gas chromatography; it decomposed, with sublimation, at elevated temperatures. The appearance of a carbonyl band at 5.90µ suggests a medium sized ring ketone (compare cycloheptanone, 5.89µ); the nmr data given in the Experimental section are also in complete agreement with structure 110.

Many other products are formed in the base induced elimination of $\downarrow 02$, but none have been identified. In this regard, the results of our most recent preparation of mesylate $\downarrow 02$, and the subsequent elimination, deserve special comment. The first exploratory runs, using freshly sublimed potassium <u>t</u>-butoxide and fresh dimesylate afforded 22 in yields of <u>ca</u>. 35% (determined by gc), with only traces of other products being formed. As the conditions were varied in an attempt to improve the yield, the amounts of the byproducts steadily rose, until, six days after preparation of the mesylate, they accounted for <u>ca</u>. 90% of the volatile products formed. The problem was with the mesylate,

as subliming the <u>t</u>-butoxide immediately before use did not reverse this trend. Proof of this came from a melting point determination - two week-old 102, although only slightly yellowed, melted with decomposition at 103.5-106.5°, <u>higher</u> than the melting point of freshly prepared material (99.5-101° (dec)). We have not made any attempt to determine the nature of this curious solid state reaction; in terms of preparing tetraene 22, however, the conclusion is obvious - the dimesylate should be used soon after preparation.

Properties of Tricyclododecatetraene 22.

As mentioned previously, the final product of this synthesis was a soft, white solid; impure samples were liquids. As evidenced by the strong odor, the volatility of this material was quite high. In fact, attempts to determine the melting point in an open capillary were thwarted by rapid sublimation, even at temperatures as low as 50°. This property bespeaks a compact, ball-like structure, as is the case with tetraene 22.

The spectral data obtained on reasonably pure material (<u>ca</u>. 90%) are also in agreement with the assigned structure 22. Thus, the infrared spectrum shows peaks typical of an olefinic hydrocarbon--C-H bands at 3.31, 3.37 and 3.45μ , weak C=C bands at 6.09 and 6.20μ , a variety of weak absorptions between 6.7 and 12 μ , and a series of fairly strong bands at 12.5-14.02 μ presumably arising from various C-H

bending modes. While these data do not prove the structure, they do permit ruling out other, isomeric $C_{12}H_{12}$ structures, such as the allene 109.

As was discussed in some detail in the introduction, the main reason for making tetraene 22 was its potential to undergo a series of degenerate Cope rearrangements. These rearrangements lead to the scrambling of positions 1,3,4,6,7,9,10, and 12 into a set of eight equivalent positions, and of the remaining four (CH) units into a second set of equivalent positions; this is depicted in structure 24, the group of eight scrambled positions being marked.



24

If the rearrangement were sufficiently rapid, the scrambling shown in 24 would be evident in the nmr spectrum. The proton nmr spectrum (60 MHz) of the purest sample of 22 yet obtained (<u>ca</u>. 90%) is reproduced on the next page as Figure 7. Other, less pure preparations gave essentially similar spectra; the impurities varied from run to run, permitting assignment of which bands were due to the tetraene. Of the peaks present in Figure 7, the series of multiplets in the vinyl region (δ 6-5) and the broad singlet at δ 3.21 were invariably present in the spectra of other preparations. The singlet at 4.38, the bands at high field (1.6-0.9), Figure 7

Proton NMR Spectrum (60 MHz) of Tetraene $\chi\chi$


and the extremely broad absorptions at 3.6-2.3 and 2.2-0.9 are due to impurities. Integration of this spectrum, and of others, demonstrates that the intensities of the vinyl absorptions and the δ 3.21 signal are in the ratio 2:1, or, considering the molecular formula $C_{12}H_{12}$, 8:4.

We believe that this spectrum completely supports the assignment of structure 22 to the $C_{12}H_{12}$ hydrocarbon obtained from base catalyzed elimination of dimesylate 122; furthermore, Cope rearrangement of 22 is slow on the nmr time scale. Thus, the peak at 3.21 ppm is due to the four bridgehead hydrogens at positions 1,4,9, and 12. In the seven other tricyclododeca-2,10-diene derivatives synthesized in the course of this work (45, 23, 28, 122, 123, 124 or 125, and 112), these four protons absorb in the range 2.7-3.45 ppm, a range which easily accommodates the δ 3.21 signal. The near equivalence of these four protons is coincidental, but certainly not remarkable.

Interpretation of the vinyl region of this spectrum is less straightforward, due to the overlapping of several multiplets. A better resolved spectrum (100 MHz) of this region is shown in Figure 8; unfortunately, this sample was less pure, somewhat offsetting the increased resulution. One <u>possible</u> first-order analysis of the vinyl region is included in Figure 8. Complete analysis must await better spectra and, more important, spin decoupling data. In any event, several AB-type patterns may be picked out. The rigid structure of the tetraene, with the accompanying Figure 8 Olefinic Region of the Proton NMR Spectrum (100 MHz) of Tetraene 22



Figure 8

anisotropies, makes meaningful discussion of the observed chemical shifts impossible. That the intensity of the vinyl resonances is eight protons, however, requires that the rearrangement be frozen out at ambient temperature -Figure 7 is the spectrum of the static structure 22.

This brings up the final result, the temperature dependence of the nmr spectrum of 22. This has been studied up to 141° in tetrachloroethylene solution. For technical reasons, this study was made at 100 MHz. <u>Over a temperature</u> <u>range of more than 100°</u>, there was essentially no change <u>in the nmr spectrum</u>. The only perceptible change took place in the vinyl region; the doublet at highest field (<u>ca</u>. 5.1 ppm) changed slightly in appearance, the two peaks becoming approximately equal in intensity. With this single exception, the spectrum obtained at 141° was superimposable on that obtained near 35°. Clearly, the rate of Cope rearrangement is still slow, even at fairly high temperatures.

SUMMARY

"Inanimate objects could do what they wanted. Not what they wanted because things do not want; only men. But things do what they do"

Thomas Pynchon, "V."

The synthesis of tricyclo[7.3.0.0^{4,12}]dodeca-2,5,7,10tetraene 2ℓ has been achieved, utilizing a fourteen step sequence starting with glutaric anhydride. The second half of this synthesis, from bicyclooctadienedione 5ℓ on, is shown in Figure 9; the preparation of 5ℓ was given previously (Figure 6). As can be determined from the yields given in Figure 9, the overall efficiency is low. Except for the last step, however, the yields are acceptable. As we now realize that the dimesylate 10ℓ is unstable, even at -35°, the last step can probably be improved substantially; milder conditions in the preparation of 10ℓ may give better results there as well.

The nmr spectrum of 22 shows that the Cope rearrangement, which makes 22 potentially fluxional, is slow on the nmr time scale, even at 141°. As there is no reason to expect that the Cope will be immeasurably slow, three further lines of investigations are open. First, the nmr studies may be extended to higher temperatures. Secondly, a deuterium label could be introduced. As the dienedione 52 can be





२२ (50-60%)

45 (40-55% crude)

OSO₂CH₃

кос(СН₃)₃

(CH₃)₂SO



રૂફ

(50-60%)

CH₃SO₂Cl Pyridine

१९२ (60%)



22 ~~ (5-9%)

Figure 9

Synthesis of Tricyclo[7.3.0.0^{4,12}]dodeca-

2,5,7,11-tetraene

deuterated selectively at the bridgehead positions⁶², this is an attractive option, although the rearrangement may well be too fast to permit isolation of 22 before extensive scrambling has occurred. Finally, as the Cope rearrangements of 22 interconvert the enantiomeric forms of this chiral structure, resolution of 22 and observation of its racemization deserve attention. Resolution of one of the precursors of 22 is surely possible, although, as with the deuterium labelling, this may not yield the desired information. The possibility of resolving the tetraene itself, <u>via</u> formation of an optically active complex or chromatography on an optically active adsorbent, was mentioned in the Introduction, and certainly merits experimental effort.

The conception of tetraene $2\chi^{26}$, and this synthesis, were motivated by curiosity about the structural requirements for rapid Cope rearrangement. From the nmr results which we have obtained, it is clear that 2χ does not meet those requirements, at least in contrast to fluxional molecules such as bullvalene. As discussed in the Introduction, the main feature lacking in 2χ is a small ring, with its accompanying strain. In light of the arguments about the importance of strain effects on Cope rearrangement given earlier, the failure of 2χ to show fluxional behavior is not surprising. More exact statements about the effects operating in 2χ must await activation data, which in turn depend on finding a means of observing the rearrangement.

Thus, regrettably, this project is not finished; the

characterization of the final product is just begun. In addition to measuring the rate of rearrangement, the chemistry of the tetraene, and indeed of the tricyclic ring system itself, deserves further study. The relationship of this compound to other (CH)₁₂ isomers is but one area that may prove fruitful.

Lest the impression be given that this project was unsuccessful, it should be emphasized that our concern was synthetic. In addition to the success of our synthetic plan, several other results, of greater practical value, have come out of this research. Among these may be mentioned (1) the success of diisobutyl aluminum hydride in achieving a previously "impossible" reduction; (2) the demonstration that the orthoester Claisen procedure is applicable to cyclic systems, even when steric effects are very unfavorable; (3) the synthesis of a number of functionalized bicyclo[3.3.0]octane derivatives in synthetically useful quantities; and (4), a reasonably efficient entry into the new tricyclo[7.3.0.0^{4,12}]dodecane ring system.

EXPERIMENTAL

<u>General</u>. All melting points were measured in open capillaries with a Thomas-Hoover apparatus and are uncorrected; boiling points are also uncorrected. Combustion analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Unless noted otherwise, reagents and solvents were reagent grade materials used as received. Solvents for chromatography were treated as follows: pentane and hexane were washed with concentrated sulfuric acid and distilled; ethyl acetate was distilled and passed through a column of neutral alumina (Activity I); chloroform was distilled and passed through basic alumina immediately before use.

Proton nuclear magnetic resonance (nmr) spectra were run on Varian A-60, A-56/60, and T-60 instruments (60 MHz); variable temperature nmr spectra were recorded on a Varian HA-100 spectrometer (100 MHz) by Mr. Eric Roach. Chemical shifts are reported in ppm downfield of internal tetramethylsilane (δ 0.0). For a few trimethylsilylated compounds, benzene (δ 7.27) was used as the internal reference. Chemical shifts and coupling constants are believed accurate to 0.01 ppm and 0.5 Hz, respectively.

Infrared spectra were measured on a Perkin-Elmer model 137 Spectrophotometer; absorption maxima are reported as wavelength (in microns), referenced to the 6.24µ peak of

polystyrene, and are believed accurate to within 0.01µ. Liquid samples were examined as neat films, and solids as Nujol mulls.

Mass spectra (ms) were run on an Hitachi RMU-6 instrument with an ionizing voltage of 70 eV. A Perkin-Elmer model 881 gas chromatograph interfaced with the RMU-6 was used for coupled gas chromatography-mass spectrometry (gcms); the column used for these studies was a lm × 2mm glass column packed with 3% SE-30 on 100-120 mesh Chromosorb W.

All other gas chromatographic separations were achieved using an F & M model 700 chromatograph equipped with a thermal conductivity detector. Helium was used as the carrier gas at flow rates of 70-80 ml/min; an injector temperature of 240° and a detector temperature of 270° were used in all cases. The compositions reported were calculated from the peak areas (determined by triangulation) without corrections for differing detector responses. The columns employed were 6' × 1/4" aluminum columns packed with the following materials:

column A: 4% QF-1 on 60-80 mesh Chromosorb G, acid and base washed and silanized column B: 5% Carbowax 20M on 60-80 mesh Chromosorb G, acid and base washed and silanized column C: 4% OV-17 on 60-80 mesh Chromosorb G, acid and base washed and silanized column D: 1% SE-30 on 60-80 mesh Chromosorb G (untreated).

Dimethyl glutarate 54. This material was prepared at various times by Glen R. Elliott, E. Irene Pupko and Myrna Sult Hagedorn using Elliott's modification⁷⁹ of Simpson's procedure⁵⁵. Glutaric anhydride (Aldrich technical grade, labelled 70% pure; 2.5 kg) was added slowly to 2 liters of methanol (exothermic!), p-toluenesulfonic acid (1-2g) added, and the mixture refluxed for 20-30 hrs. The reaction mixture was cooled, 1 & of water added, and the mixture made slightly basic by the addition of 10% sodium hydroxide solution. This mixture was extracted with ether $(4 \times 1 \ l)$, and the combined ether layers washed with saturated aqueous sodium chloride solution, dried over Drierite, and freed of solvent on the rotary evaporator. Distillation of the residue afforded impure dimethyl glutarate, bp 90-110°/17 mm. This material was redistilled through a lm Vigreux column and the fraction boiling at 99-101°/17mm collected. This product, a water-white oily liquid, was ca. 99.5% pure by gc (column A, 150°); yields were in the range 45-55%. The ir showed ester carbonyl absorption at 5.72 μ ; nmr (δ ,CCl₁): 3.64 (6H, s), 2.33 (4H, distorted t, J = 6 Hz), 2.15-1.63 (2H, distorted quintet with further splittings, J = 6 Hz).

The aqueous solution from the above extraction was acidified with hydrochloric acid. Extraction of this mixture with ether afforded, after removal of the solvent, <u>ca</u>. 500 ml of very crude monomethyl glutarate. This material was added with the glutaric anhydride at the start of

the next preparation.

Tetramethyl hexane-1,3,4,6-tetracarboxylate 55. Free radical induced coupling of dimethyl glutarate. This procedure, a slight modification of those of Osborne²⁹ and Simpson⁵⁵, was run with the aid of Glen R. Elliott, Charles A. Geraci, and E. Irene Pupko. The reaction vessel was a 5 & three-necked flask equipped as shown in Figure 10. The flask was charged with 2500 ml of dimethyl glutarate (DMG), which was heated to boiling, with stirring, while nitrogen was passed through the apparatus. After 15 min boiling the DMG was cooled to 175°, and the nitrogen flow adjusted to 45-50 ml/min. A mixture of di-t-butyl peroxide (Columbia, 400 ml, ca. 2.17 mole) and DMG (160 ml) was then added to the vigorously stirred DMG, maintaining the temperature at 170-175°; the addition rate was 1 ml/min. After addition was completed, heating was continued until gas evolution ceased (this was determined by temporarily stopping the nitrogen flow and inspecting the gas bubbler at the outlet of the system); this typically required an additional hour. When no more gas was evolved, the contents of the flask were rapidly heated to vigorous boiling until DMG (bp 214°) just began to distill over.

The flask and contents were allowed to cool overnight, and the reaction mixture transferred to a 5 ℓ round bottom flask. Unreacted DMG was then removed by vacuum distillation through a 50 cm Vigreux column; everything boiling up to 140°/17 mm was collected in one fraction; the last drop





of this material contained <u>ca</u>. 40% DMG, 40% numerous unidentified compounds, and 20% of the desired product. Nearly all of this fraction distilled at 95-110°/17 mm. The volume of recovered DMG was 2180 ml, so 480 ml (<u>ca</u>. 520 g, 3.23 mole) of DMG had been consumed.

The residue in the pot was cooled to around 80°, and transferred while hot to a 1 & round bottom flask. Distillation was then continued through the 50 cm Vigreux; three fractions were collected: fraction 1, 20 g, bp 80-135°/ 0.02 mm; fraction 2, 290 g, bp 135°/0.02 mm-155°/0.03 mm (most of this material boiled at 140-143°/0.02 mm), and fraction 3, 20 g, bp 155-180°/0.03 mm. The dark pot residue was discarded.

All of these fractions eventually solidified to give mushy white crystals. Fraction 2 contained about 85% of the desired product (two barely separated peaks) and about 15% of an additional compound (gc on column A, 210°). Further purification was achieved by recrystallization from methanol. Fraction 2 was dissolved in an equal volume of methanol (warming necessary) and cooled to 10°, affording 165 g of white crystals (a mixture of needles and tablets). Two more crops, 54 g and 6.5 g, were obtained by cooling the mother liquor to -10° and then to -60° . Fractions 1 and 3 were combined and crystallized in the same manner to give 11 g more $\xi\xi$ (two crops, 10° and -60°). Thus, the total recrystallized product came to 236.5 g (0.745 mole). This corresponds to a yield of approximately 46% based on

the DMG consumed, or 34% based on the di-t-butyl peroxide.

Subsequent runs were made in the same manner, using the recovered DMG; after four or five batches, the DMG was refractionated, as described previously, to remove the impurities which had accumulated. The apparatus and still were not cleaned between runs, so as to minimize losses due to hold-up. A number of preparations afforded recrystallized 55 in yields of 42-55% based on reacted DMG.

The mother liquors from the recrystallization of several preparations were combined and the methanol removed <u>in vacuo</u>. Distillation of the residue afforded fractions similar to those obtained in the distillation of the reaction mixture; that distilling at $135-145^{\circ}/0.02$ mm was recrystallized, as described above, yielding an additional amount of pure tetraester <u>55</u>.

The recrystallized tetraester exhibited mp 48-59°; the broad melting range is undoubtedly due to the presence of a mixture of the <u>meso</u> and <u>d,l</u> diastereomers²⁹. This was confirmed by gc (column A, 210°), which showed two barely separated components in roughly equal amounts. The other data on this mixture are in complete agreement with structure 55: ir (neat melted 55), 5.75μ ; nmr (δ , CCl₄); 3.70 (6H,s), 3.65 (6H, s), 2.68 (2H, broad t, J = 4 Hz), 2.50-2.06 (4H, m), 1.84 (4H, broad m).

<u>Bicyclo</u>[3.3.0]<u>octane</u>-2,6-<u>dione</u> 53. <u>Dieckmann</u> <u>cycliza</u>-<u>tion of tetraester</u> 55, <u>and hydrolysis-decarboxylation of</u> <u>the product, ketoester 56</u>. <u>N.B.!</u> The success of this

procedure depends crucially upon the strict exclusion of water and other sources of hydroxide ion. The use of dry glassware, dry dimethylsulfoxide (DMSO), and fresh sodium methoxide is essential; if these precautions are not taken, the yield drops substantially, even to the point of no product being formed. It should be noted that even freshly opened bottles of commercial reagent grade DMSO usually gave unsatisfactory results. DMSO was purified by stirring with calcium hydride for several days, then vacuum distillation from the same drying agent: bp 77-78°/15 mm.

A l liter three-necked flask was fitted with a mechanical stirrer, addition funnel, thermometer, and provision for an inert atmosphere, and the apparatus dried by flaming while evacuated. Sodium methoxide (Matheson Coleman & Bell, freshly opened, 60 g, 1.1 mole) and dry DMSO (ca. 300 ml) were then added, and a nitrogen atmosphere established by repeated cycles of evacuation and bleeding in nitrogen. Tetraester 55 (159 g, 0.50 mole), dissolved in <u>ca</u>. 150 ml warm DMSO, was then added to the stirred slurry of sodium methoxide. Addition took 15 min, during which the internal temperature rose to 50-60°. An additional portion of sodium methoxide (40 g, 0.74 mole) was added after all the ester had been added. The reaction mixture, which had become deep orange during the ester addition, was then heated at 70-80° for 1.5 hr. The nearly black mixture was then cooled to 20-25° with an ice bath, and ice-cold 6M hydrochloric acid (320 ml) added slowly, with continued stirring. Ice bath



cooling was used to keep the temperature below 30°. As the acid was added, the mixture lightened in color, becoming yellow-brown and finally pink; a finely divided solid precipitated towards the end of the addition. The final slurry was poured into 2500 ml of ice water, and the pH checked to make certain it was acidic. When the temperature of this mixture reached 10° the solid was collected by filtration through a large Buchner funnel, washed several times with cold water, and washed once with cold methanol-water (1:1) and sucked as dry as possible. The crude bis(ketoester) was then dried, first at room temperature and finally in an oven at 85-90°. The oven drying led to considerable sintering and some darkening of the initially yellow or pink, powdery product, but did no harm; the sintering was in fact beneficial in the next step. The crude ketoester \$6 weighed 109.5 g (86.3% crude) and showed mp 91-98° (dec). Further purification was not necessary, but could be achieved by crystallization from methanol (5 ml/g) in 80% recovery. The recrystallized product melted at 93-96°; a second recrystallization, this time from acetone-hexane, gave colorless prisms, mp 92-93° (lit²⁹ 90.4-92.4°).

The entire crude product from the above Dieckmann cyclization was added to 300-400 ml of 6<u>M</u> hydrochloric acid, containing one small drop of Dow-Corning "Antifoam C" defoamer, in a 2 & erlenmeyer flask (the benefits of the defoamer may have been largely psychological). Several Carborundum boiling stones were added, and the mixture



heated on the steam bath with frequent swirling (gas evolution and foaming!); the temperature was kept below 70°, as considerable darkening occurred at higher temperatures, and the foaming became inconveniently vigorous. When gas evolution had ceased (typically, after about one hour of heating), the solution was cooled and filtered with suction through two thicknesses of filter paper. The filtrate was then extracted six times with 200 ml portions of chloroform. The chloroform layers were combined and washed with 5M aqueous sodium hydroxide solution (2 × 25 ml), and concentrated to ca. 500 ml by distillation; this also effected azeotropic drying of the solution. The chloroform solution was filtered through a Drierite cone (to catch the fine particles), whereupon removal of the solvent on the rotary evaporator gave a golden yellow oil which slowly solidified to a pale yellow mass. The yield of crude dione 53 was 57.1 g (96.1% based on the crude ketoester; 82.9% from tetraester 55). yellowish granules mp $43-46^{\circ}$. Again, further purification was not necessary. If desired, purer material could be obtained by sublumation $(35-40^{\circ}/0.01 \text{ mm})$ onto a cold finger kept at 0°. Recovery was about 97%. The sublimed product was in the form of blocky crystals, mp 45.1-46.3° (lit⁵⁵, 46-46.5°) with the expected spectral properties: ir (Nujol): 5.73 μ ; nmr (δ , CCl_µ): 2.90 (2H, broad s), 2.20 (8H, broad s).

2,6-Diacetoxybicyclo[3.3.0]octa-2,6-diene §Z. Enol acetylation of dione § $2^{29,55}$. Purified bicyclooctanedione 53 (13.8 g, 0.1 mole) was dissolved in isopropenyl acetate (Aldrich, redistilled, 100 ml) containing 125 mg of sulfosalicylic acid, and the mixture refluxed under nitrogen for 24 hr. The excess isopropenyl acetate was removed on the rotary evaporator and the black residue vacuum distilled through a 10 cm Vigreux. The fraction boiling at 95-105°/0.3-0.4 mm was collected as a yellow oil which solidified upon scratching. Crystallization from pentane afforded 19.7 g (89%) of white needles, mp 60-62° (lit²⁹ 62.0-62.5). Two other preparations on a somewhat smaller scale gave yields of 78% (recrystallized) and 85% (distilled only).

<u>3,7-Dibromobicyclo</u>[3.3.0]<u>octane-2,6-dione</u> §§. <u>Bro-</u> <u>mination of enol acetate</u> § $\chi^{29,55}$. The <u>bis</u>(enol acetate) § χ (19.6 g, 0.089 mole) was dissolved in carbon tetrachloride (100 ml) and the solution cooled in an ice bath. Bromine (29 g, 0.181 mole) in 30 ml carbon tetrachloride was then added dropwise over about 15 min. The bromine color faded rapidly throughout the reaction, in contrast to Simpson's observation⁵⁵ that it lingers when the reaction nears completion. The precipitated solid was collected by filtration and washed twice with cold carbon tetrachloride

to give 12.5 g (48%) of a yellow-brown powder, mp 120-125° (dec) (lit, 122-125° (dec)⁵⁵; 130.5-131° for recrystallized material²⁹). The ir spectrum showed carbonyl absorption at 5.75 μ (lit⁵⁵ 5.74 μ).

2,2,6,6-Bis(ethylenedioxy)-3,7-dibromobicyclo[3.3.0]octane 52. Ketalization of bromoketone 58⁵⁵. The crude dibromodione 58 (12.0 g, 0.0405 mole if pure) was added to a mixture of ethylene glycol (24 ml), p-toluenesulfonic acid (175 mg) and benzene (300 ml) in a 500 ml flask equipped with a Dean-Stark water separator. The mixture was then heated to boiling with vigorous magnetic stirring to mix the layers. After 2 days, an additional portion (8 ml) of ethylene glycol was added. The reaction was stopped when no more water separated (3 1/4 days). The brown solution was cooled, washed with 100 ml portions of 5% aqueous bicarbonate, water, and saturated sodium chloride solution, and dried over Drierite. The product solidified spontaneously when the benzene solvent was removed on the rotary evaporator. Yield, 14.5 g (93% if pure) of hard, yellow-white granules, mp not determined (but see p. 113, below). The ir spectrum showed some residual carbonyl absorptions in the 5.75 region, suggesting that ketalization had not been complete.



2,2,6,6-Bis(ethylenedioxy)bicyclo[3.3.0]octa-3,7diene 60. Dehydrobromination of bromoketal 59 with ethanolic potassium hydroxide⁵⁵. Crude bromoketal 59 (14.5 g, 0.038 mole), prepared as just described, was added to a freshly prepared solution of potassium hydroxide (25 g) in absolute ethanol (500 ml). This mixture was heated to reflux for four days. The brown mixture was then cooled, filtered with suction, and freed of solvent on the rotary evaporator to give a dark brown mass. This was broken up and refluxed for 1 hr with 400 ml benzene. The resulting red-brown solution was cooled, filtered, and washed, twice with cold water containing a little sodium bicarbonate and twice with saturated sodium chloride solution. Drying (Drierite), filtering and removal of the solvent on the rotary evaporator yielded an orange oil (7.5 g). This was taken up in the minimum volume of boiling cyclohexane and the solution cooled, whereupon pale yellow needles, mp 101-103° were formed (5.12 g, 61%). An additional crop of yellow granules, mp 94-97° (0.51 g, 6%) was obtained by concentrating the mother liquor. The reported mp is 101-103055. The ir spectrum (Nujol) showed C=C absorption at 6.13µ and other strong bands at 7.93, 8.69, 9.28, 9.80, 10.15 and 12.22µ; the carbonyl region was free of absorptions. The nmr spectrum was in complete accord with structure 60: (δ , CCl₁):

5.91 (2H, dt, J = 5.6 Hz, J' = 1.1 Hz), 5.42 (2H, dd, J = 5.6 Hz, J' = 0.9 Hz), 3.89 (6H, s), 3.18 (2H, m).

2,2,6,6-Bis(ethylenedioxy)bicyclo[3.3.0]octane 61. Ketalization of bicyclooctanedione 53. The crude dione (209 g, 1.5 mole) was added to a mixture of ethylene glycol (220 ml, ca. 3.95 mole, 32% excess), p-toluenesulfonic acid hydrate (3.8 g, 0.02 mole) and benzene (1500 ml). This mixture was refluxed with separation of water (Dean-Stark trap) and magnetic stirring for 44 hr. The volume of water collected was 64 ml (118% of the theoretical, assuming that all the reactants were dry and that the water was free of ethylene glycol); nearly all of the water distilled over during the first 12 hrs. The brownish solution was cooled and washed as follows: 1 × 100 ml saturated aqueous sodium bicarbonate, 2 × 200 ml water, and 2 × 200 ml saturated aqueous sodium chloride solution. The combined aqueous washings were extracted four times with 200 ml portions of ether, and the combined ether layers washed once with saturated sodium chloride solution. This ether extract was combined with the original benzene layer, and the solution filtered through a Drierite cone. Removal of the solvent on the rotary evaporator gave a brownish, oily liquid, which was distilled in vacuum; the volatile material was collected in a single fraction, bp 93-95°/0.15 mm, which was homogeneous by gc (column A, 170°; column B, 190°). The yield was 327 g (96.5%) of a colorless, oily liquid. An analytical sample was obtained by repeated fractional freezing of this liquid in an ice-acetone bath. The spectra of this purified material (mp <u>ca</u>. -1°), which were superimposable on those obtained from the distillate, were as follows: ir (neat): 3.41, 3.49, 6.82, 7.47, 8.24, 8.6-9.15, 9.64, and 10.53µ, and other, weaker bands; nmr (δ , CCl₄): 3.87 (8H, s), 2.37 (2H, broad m), 1.62 (8H, broad m).

<u>Anal</u>. Calc for C₁₂H₁₈O₄: C, 63.70; H, 8.02. Found: C, 63.67; H, 8.02.

Other preparations, on 0.2 - 0.6 mole scales, gave yields of 96.1-96.4%. In view of the <u>ca</u>. 97% purity of the crude dione 53, the yield must be close to quantitative. Other boiling points observed were $100^{\circ}/0.2$ mm, $88^{\circ}/0.05$ mm, and $84^{\circ}/0.015$ mm.

2,2,6,6-<u>Bis(ethylenedioxy)-3,7-dibromobicyclo</u>[3.3.0]octane 59. Bromination of ketal 61. Pyridinium tribromide was prepared according to Fieser and Fieser⁸⁰, starting with approximately 1 lb of bromine and scaling the other reactants accordingly. During the recrystallization of the product from acetic acid, the mixture was stirred frequently to keep the crystals small. We and others⁸¹ have found that finely divided tribromide gives better results than coarse material. Yields of the purified tribromide were in the range 72-78%.

The diketal \pounds (45.2 g, 0.2 mole) was dissolved in dry tetrahydrofuran (400 ml, distilled from CaH₂) in a l liter three-necked flask equipped with a mechanical stirrer and



a drving tube; the unused neck was stoppered. This solution was cooled, with stirring, to ca. -70° in a Drv Ice - acetone bath, and pyridinium tribromide (140 g, 0.438 mole) added in one portion. The mixture, which rapidly decolorized, was stirred at ca. -70° for 1 hr, then allowed to warm to room temperature. The pale yellow suspension was then poured slowly into 2500-3000 ml of vigorously stirred cold water, whereupon the product precipitated. After 5 min more stirring, the solid was collected by filtration and washed repeatedly with water, and sucked fairly dry. This vellowish product was then covered with methanol (ca. 200 ml), the lumps broken up, and the stirred mixture gently boiled for a few minutes; it was then cooled to -10° for several hours, and the white product collected, washed once with cold methanol, and air dried. Yield, 69 g (90%) of white crystals (needles and granules), mp 152-156° (sinters 128°, further softens 142-145°, with gradual darkening from 128° on). Other runs on a similar scale (0.2-0.25 mole) gave vields in the range 88-91%.

Although not necessary for the next step, this material could be further purified by recrystallization from a variety of solvents. For example, the product was dissolved in hot acetone (10-12 ml/g); treated with Norite, filtered and cooled. A second crop was obtained by concentrating the mother liquor; addition of water and cooling afforded two more crops of crystals. The overall recovery of the bromoketal was about 85-90%.



The first crop obtained from the acetone recrystallization was recrystallized from cyclohexane giving the " α -isomer" (the <u>cis,exo</u> isomer §9a), white prisms, mp 157-159° (slight darkening); an additional recrystallization from cyclohexane raised the melting point to 160-160.5°. The spectral properties of this material are as follows: ir (Nujol): 7.51, 8.22, 8.58, 9.18, 9.55, 10.54, 12.38, 12.57 and 13.07 μ , among others; nmr (δ , CDCl₃): 4.25 (2H, t, J = 6.7 Hz), 4.10 (8H, broad s, $\Delta v_{1/2}$ = 2Hz), 3.10-2.70 (2H, m), 2.40-1.98 (4H, m).

The first crop of crystals obtained after addition of water to the acetone mother liquor (<u>vide supra</u>) was recrystallized twice from cyclohexane to give the " β -isomer" (<u>trans</u> bromines, 59b), colorless needles mp 144-145°. This compound gave the following spectra: ir (Nujol): 7.72, 8.33, 8.59, 8.79, 9.58, 9.85, 9.97, 10.45-10.53, 10.98, 11.97, 12.96, 13.51, 13.81µ, and others; nmr (δ , CDCl₃): 4.55-3.75 (10H, extremely complex multiplet), 2.83-2.45 (2H, m), 2.40-1.75 (4H, complex). The nmr spectra of this material, and the " α -isomer" just described, are given in the Appendix as Figures Al and A2. The complexity of the spectrum of the " β -form" shows it to be the unsymmetrical, <u>trans</u>-isomer 52b.

The proportions of the isomers formed in this reaction are not accurately known; inspection of the ir spectrum of the crude (methanol washed) material (comparison of the absorbances at 13.07 and 11.97 for 59a and 59b, respectively)



suggested a ratio of about 10:1, the <u>cis,exo</u>-isomer $\underbrace{598}_{2}$ predominating. Although the isomers could be separated by gc (column A, 220°) (the <u>trans</u>-isomer $\underbrace{598}_{2}$ is eluted first), the peaks overlapped enough to prevent accurate measurement of the composition. A <u>very rough</u> estimate would be 5-10% of $\underbrace{598}_{2}$.

Having pure samples of two of the isomers of 59, the sequence of Osborne²⁹ and Simpson⁵⁵, which was reported to give a third isomer, was repeated. The preparation, carried out by Miss Barbara A. Duhl, followed exactly the procedure given earlier (pp 106-107). The crude bromoketal was recrystallized twice from cyclohexane to give needles, mp 128-130° (lit⁵⁵ 123-125°). The ir and nmr spectra of this material, however, were essentially a superposition of the spectra of the other two isomers. In particular, the ir spectrum of the alleged "y-isomer" contained every band found in the spectra of 59g and 59b, and no new bands. With this evidence that the "y-form" was really a mixture, the material was analyzed by gc using conditions (column A, 220°) under which 59a and 59b could be barely, but unequivocally separated. This analysis showed the presence of both 59a and 59b, in a ratio (peak heights) of ca. 1.3:1. Thus, the " γ -form" is not the third isomer, but a mixture of the other two.

2,2,6,6-<u>Bis(ethyelendioxy)-3,7</u>-dibromobicyclo[3.3.0]octane 52. <u>Direct bromination of dione 53 in ethylene</u> <u>glycol</u>⁶¹. Sublimed bicyclooctanedione 53 (1.38 g, 0.01



mole) was dissolved in about 50 ml of warm (\underline{ca} . 40°) ethylene glycol. Bromine (1.5 ml) was then added dropwise at such a rate that the bromine color never completely disappeared; about 30 min was required for this addition, during which the mixture was gently heated to maintain a temperature of 40-50°. The pale yellow reaction mixture was then poured into 200 ml of water, stirred for several minutes, and the product collected, washed with water, and dried. This gave 3.06 g (80%) of white granules, mp 122-134° (dec).

The spectra of this material showed no hydroxyl or carbonyl absorbtions, but did show the characteristic peaks of both the <u>cis,exo</u>- and the <u>trans</u>-isomers $\xi g g$ and $\xi g g$. This was confirmed by gc (column A, 220°) which showed the $\xi g g$: $\xi g g$ ratio to be about 1.6 : 1.

2,2,6,6-<u>Bis(ethyelendioxy)bicyclo[3.3.0]octa-3,7-diene</u> §Q. <u>Dehydrobromination of bromoketal</u> §Q. The methanol washed mixture of isomeric bromoketals (87 g, 0.227 mole) prepared by bromination of §L was added in one portion to a stirred slurry of sodium methoxide (73.5 g, 200% excess) in dimethylsulfoxide (400 ml); a 1 liter, three-necked flask equipped with a mechanical stirrer, thermometer and a gas bubbler (to reduce entry of air into the flask, thus reducing autoxidation of the solvent) was used for the reaction vessel. Occasional cooling (ice bath) was used to keep the reaction temperature below 60°. After the exothermic reaction had ceased (ca. 30 min) the mixture



was heated to 70° for 2 hrs. It was then cooled to room temperature and poured into 2500 ml of stirred water and ice; the flask was rinsed with an additional 100 ml of water. Solid sodium chloride was added to nearly saturate the solution, and the crude solid product was collected by filtration. The filtrate was then extracted eight times with 500 ml portions of ether; each ether layer was roughly dried by washing with 50 ml of saturated sodium chloride. To keep the volume manageable it was best to evaporate each 500 ml portion as it was obtained. The solvent was removed and the residue combined with the solid product originally filtered off. This product was dissolved in cyclohexane (ca. 1200 ml) and refluxed with water separation (Dean-Stark trap). When water ceased to distill over, the hot cyclohexane solution was filtered, concentrated by distillation to a volume of about 500 ml and allowed to cool. The product, 44.8 g (89%) of fine colorless needles, mp 101-102°, was then collected. Concentration of the mother liquor afforded an additional crop (1.5 g, 3%) of slightly yellowish needles, mp 97-100°. The total yield of crystalline 60 was thus 92%; other runs on the same scale gave yields of 89-93%.

The spectral data for this material were identical with those reported previously (pp. 108-109).

Bicyclo[3.3.0]octa-3,7-diene-2,6-dione 52. Deketalization of ketal 60. The dienediketal 60 (44.5 g, 0.2 mole) and sulfosalicyclic acid (0.3 g) were dissolved in acetone
(500 ml) with gentle warming, and the solution allowed to stand at room temperature for 1-12 hrs. The acetone, together with the ethylene ketal of acetone, was then removed on the rotary evaporator; the residue was taken up in acetone, allowed to stand for 30 min, and the volatile material again removed. After a third acetone treatment, the solid residue was sublimed at 70°/0.01 mm onto a carbon tetrachloride-slush cooled condenser, yielding 25.2 g (94%) of white, blocky crystals, mp 76.5-78.5°. Recrystallization of this material, although not necessary, could be achieved using cyclohexane as solvent. This gave colorless or white needles, mp 78-79° (lit⁵⁵ mp 78-79.5) in nearly quantitative recovery (three crops).

The spectra of this material were entirely consistent with the structure ξ_{χ} : ir (Nujol), 5.88 (strong and broad), 6.35µ, and others; nmr (δ , CCl_µ), 7.66 (2H, d of m, J = 5.6 Hz), 6.08 (2H, d of d with additional fine structure, J = 5.6 Hz, J' = 1.4 Hz), 3.67 (2H, m).

<u>Cis,endo-2,6-dihydroxybicyclo</u>[3.3.0]<u>octa-3,7-diene</u> 42. <u>Diisobutyl aluminum hydride reduction of dienedione</u> 52. Caution! As diisobutyl aluminum hydride is pyrophoric and reacts explosively with protic solvents, due care should be exercised in its use. <u>It is strongly recommended that</u> <u>this preparation not be run on a scale larger than that</u> <u>described below</u>, as the destruction of the excess reagent can be treacherous.

A l liter three-necked flask equipped with a sealed

mechanical stirrer, constant addition funnel, low temperature thermometer and gas inlet/outlet was dried by flaming under vacuum and purging with dry nitrogen. A nitrogen atmosphere was established, and the flask charged with diisobutyl aluminum hydride in toluene (250 ml of a 2.0 M solution, 0.5 mole). This solution was cooled with stirring to -45° , and the dienedione 52 (16.7 g, 0.125 mole) in toluene (300 ml) added dropwise over 4 hr, during which time the temperature was kept between -40 and -50° . The reaction mixture, which had become quite yellow and viscous during the addition, was stirred for an hour more at ca. -45°, then allowed to warm to 0° over an additional hour; the mixture lightened to a very pale yellow during this time. Saturated sodium sulfate solution (35 ml) was then added, very slowly at first; cooling with an ice bath was used to keep the internal temperature below 10°. Due to the rather vigorous gas evolution, this addition required about one hour (when about half of the sulfate solution had been added the mixture became very gummy, but with continued stirring it reliquified). Methanol (50 ml) was then added, and the mixture slowly brought to room temperature. When the gas evolution slackened an additional 200 ml of methanol was added, and the contents of the reaction flask transferred to a 2 liter Erlenmeyer. More methanol was added to bring the volume to ca. 1.5 liter, and the flask heated on the



steam bath with swirling (bumping and considerable gas evolution!). When the temperature of the white suspension reached 65° it was boiled for an additional ten minutes, cooled, and filtered with suction. The white solid residue was then extracted twice with boiling methanol, boiling for 15 min each time. The combined filtrates were stripped of solvent on the rotary evaporator to give a very thick brown oil which was taken up in acetone (400 ml), filtered, and again freed of solvent. Kugelrohr distillation (40-70°/0.01 mm) of the brown residue afforded the mixture of epimeric dienediols 49, 65, and 66 as a waxy solid (15.2 g, 88%). Analysis by gc (column B, 210°) showed these three components to be present in amounts of 77.7% 20.3%, and 2% of the product, respectively; this is also the order of increasing retention times on Carbowax 20 M.

Several runs on a 0.05-0.125 mole scale gave yields of 80-88% of distilled material. "Sublimation" in a large sublimation apparatus with magnetic stirring of the "sublimand" could also be used for purification, but was slower and less convenient than kugelrohr distillation.

Separation of the desired <u>cis</u>,<u>endo</u>-isomer 42 was achieved by dissolving the entire crude product from the above reduction in <u>ca</u>. 40 ml of warm acetone and cooling to 0° overnight; a second crop was obtained by further cooling of the mother liquor to -30° for several days. This process afforded 42in excellent purity (>99% by gc on column B, 210°); yield,

9.86 g of white prisms, mp 93.0-93.7° (57% yield based on dienedione $\xi\chi$, 84% recovery of the desired epimer). The spectra were in agreement with the assigned structure; ir (Nujol): 3.08, 6.12 (weak), 9.42µ <u>inter alia</u>; nmr (δ , CDCl₃ + trace of conc. HCl to cause rapid exchange): 5.89 (4H, broadened AB quartet, J = 6 Hz), 4.95-4.62 (2H, m), 3.62-3.22 (2H, m), 2.72 (2H, s, exchangeable with D₂O); this nmr spectrum is reproduced as Figure A3; ms: m/e 138 (very weak), 120 (36%), 104 (11.5%), 91 (100%), 79, 78, 77, 76 (<u>ca</u>. 15% each), 70 (24%), 66 (25%), 65 (42%), 41 (31%), 39 (79%), among others. Good combustion analyses were not obtained on the diol, but the diacetate gave satisfactory analytical results (vide infra).

The mother liquor from the above crystallization was freed of solvent on the rotary evaporator, and the resulting yellowish oil oxidized back to dienedione 52, as subsequently described (p 122).

<u>Temperature Dependence of the Reduction of Dienedione</u> 52 with Diisobutyl Aluminum Hydride. A solution of diisobutyl aluminum hydride (10 ml of 2.0 <u>M</u> solution) was cooled to the appropriate temperature and dienedione 52 (0.670 g) in a <u>ca</u>. 10 ml toluene added dropwise, with stirring, over 1.5 hr. A nitrogen atmosphere was maintained throughout. The mixture was stirred at the appropriate temperature for 1-2 hrs, then warmed (or cooled) to 0°. Saturated sodium sulfate solution (2 ml) was then added dropwise, followed by 50 ml of methanol. The resulting suspension was briefly boiled, filtered and the precipitate washed twice with boiling methanol. The combined filtrates were freed of solvent on the rotary evaporator, taken up in acetone, filtered, and analyzed by gas chromatography (column B, 210°); the results (averages of three separate analyses, uncorrected for different detector responses) are given in Table 3, p 50.

Epimerization of Cis, endo-2, 6-dihydroxybicyclo[3.3.0]octa-3,7-diene. Recrystallized cis, endo diol 42 (64 mg, 0.5 mmole) was dissolved in acetone (ca. 1 ml) containing 1 drop of water and a tiny crystal of p-toluenesulfonic acid. The mixture was then heated to gentle reflux, and was analyzed by gc (column B, 210°). After 8 hrs the starting material had decreased to about 40% of the mixture, while peaks for the trans and cis, exo-diols 65 and 66 respectively had appeared, in amounts of ca. 45% and 15%. After 12 hrs the composition was roughly 15% 49, 45% 65, 35% 66 and about 5% of a new product of slightly longer retention time (ZQ?). Finally, after 24 hr reflux, the starting material was undetectable, §5 and §6 comprised about 40% of the mixture each, and the new, fourth component came to about 20%. The mass balance could not be checked, as no internal standard was present. However, the amount of solvent lost was very small, and as the same amount of the mixture was analyzed each time, the total area of the product peaks established that little material was being destroyed. The mixture was decidedly yellow, but about 80% of the starting material

could still be accounted for.

Cis, endo-2, 6-diacetoxybicyclo[3.3.0]octa-3, 7-diene 68 and the Trans-isomer 69. Acetylation of bicyclooctadienediols 49 and 65. The distilled mixture of epimeric diols (100 ml, 0.725 mmole containing about 77% 49, 21% 65 and 2% $\xi\xi$) was dissolved in dry pyridine (6 ml), cooled to 0°, and acetic anhydride (1 ml, ca. 7-fold excess) added. The mixture was allowed to stand at room temperature for 1 hr, then heated on the steam bath for an additional hour. The yellow brown reaction mixture was then cooled to 0° and poured into 30 ml of cold water with vigorous stirring. The aqueous solution was then extracted five times with 10 ml portions of ether, and the combined ether layers washed with 2M HCl until the odor of pyridine could not be detected. The ether layer was then washed with 5% sodium hydroxide (2 × 10 ml), with water (15 ml), and with saturated sodium chloride, and filtered through Drierite. Removal of the solvent gave 140 mg (87%) of a pale yellow oil which gradually solidified. Gas chromatographic analysis (column A, 170°) showed the presence of two components in a ratio of about 4:1; the minor component was eluted first.

120 mg of this material was recrystallized from pentane to give 72 mg of 68, white needles, mp 92-93.5°. An analytical sample was obtained by 2 more recrystallizations from hexane and sublimation (50-60°/0.01 mm). This material had mp 93.6-94.1° and gave the following spectra: ir (Nujol): 5.75, 6.14, 8.05µ, among others; nmr (δ , CCl_µ), 5.71 (4H,

broad s), superimposed on 5.80-5.50 (2H, m), 3.83-3.45 (2H, broad m), 2.04 (6H, s).

<u>Anal</u>: Calc for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35 Found : C, 64.80; H, 6.46

The mother liquor from the above crystallization was freed of solvent and the nmr spectrum of the residue taken. Most of the spectrum was indecipherable, but the acetate region showed the $\delta 2.04$ singlet of the <u>cis,endo</u>-isomer ξg , and two singlets of equal intensity at $\delta 2.03$ and 2.02. Careful integration of these signals gave a ratio of $\delta 2.04$: ($\delta 2.03 + \delta 2.02$) = 38:34, hence a $\xi g: \xi g$ ratio of 1.12:1. The ratio determined by gc (column A, 170°) was 1.15:1 (average of three analyses).

<u>Chromium Trioxide-Pyridine Oxidation of the Epimeric</u> <u>Bicyclooctadienediols</u>. The chromium trioxide-pyridine complex was generated <u>in situ</u> according to Ratcliffe and Rodehurst⁸². Thus, pyridine (19 g, 0.24 mole, dried by distillation from calcium hydride) was dissolved in dry methylene chloride (<u>ca</u>. 350 ml), and chromium trioxide (12 g, 0.12 mole, ground, dried by overnight heating at 50°/0.01 mm and stored over P_2O_5) added with magnetic stirring. After 15 min stirring the red-orange solution was cooled in an ice bath, and the residual dienediols from crystallization of the <u>cis,endo</u>-isomer (1.38 g, 0.01 mole) in methylene chloride (30 ml) were added rapidly; the magnetic stirrer usually stopped a few seconds after mixing, and swirling ^{Was} used to effect mixing. After a reaction periodof 2 min the black mixture was poured into 200 ml of $2\underline{M}$ HCl. The black polymeric residue in the reaction flask was rinsed with 50 ml of $2\underline{M}$ HCl and 100 ml methylene chloride, and these washes combined with the rest of the mixture. The organic layer was separated and the aqueous layer extracted one with 100 ml of methylene chloride. The combined organic layers were washed once with 100 ml $2\underline{M}$ HCl, twice with water (100 ml portions), saturated sodium chloride solution (100 ml), and filtered through a Drierite cone. Removal of the solvent gave a thick brown residue, which was sublimed (using a <u>kugelrohr</u> apparatus) to give dienedione $\frac{5}{2}$, 0.95 g (71%), mp 77-79°. Other runs on a similar scale gave vields of 62-78%.

The short reaction period was used to minimize the destruction of the very base-sensitive product by any pyridine present. For the same reason, the usual $step^{86}$ of washing the organic extract with strong aqueous base was not used.

<u>Cis,endo-bicyclo</u>[3.3.0]<u>octa-3,7-diene-2,6-diacetic</u> <u>acid, diethyl ester</u> $\chi\chi$, and <u>endo-8-hydroxy bicyclo</u>[3.3.0]-<u>Octa-3,6-diene-endo-2-ylacetic acid lactone</u> $&\chi$. <u>Orthoester</u> <u>Claisen rearrangement</u>⁵³ <u>of dienediol</u> $&\chi$?. Method A: <u>o-</u> dichlorobenzene solvent. Dienediol $&\chi$? (5.300 g, 3.95 mmole) was added to freshly distilled triethyl orthoacetate (<u>ca</u>. 50 ml) in a 100 ml three-necked flask equipped with a magnetic stirrer, heating mantle, thermometer, nitrogen inlet, and a take-off condenser with a gas bubbler attached to the top of the condenser. A nitrogen atmosphere was established, and a gentle nitrogen sweep (5 ml/min) employed to carry the more volatile products into the condenser. The mixture was warmed until the diol had all dissolved, then 60 mg of pivalic acid in 1 ml triethyl orthoacetate was added. The mixture, which began to turn yellow almost immediately, was then heated to a gentle boil; heating was adjusted so that the orthoester condensed before it reached the takeoff condenser. Collection of the volatile distillate (mainly ethanol, together with some ethyl acetate and triethyl orthoacetate) was begun immediately. Gentle boiling was continued for 48 hrs; approximately every 12 hours during this period an additional 25-35 mg of pivalic acid (dissolved in a little triethyl orthoacetate) was added. After the 48 hr reflux, the reaction mixture was cooled, a short path still head attached, and ca. 35 ml of triethyl orthoacetate removed by distillation (aspirator pressure). o-Dichlorobenzene (ca. 40 ml) was then added, along with an additional 100 mg of pivalic acid, and the deeply colored solution heated to boiling, again with removal of lower boiling products, for an additional 72 hours. Four times during this period additional 10-20 mg portions of pivalic acid were added. The nearly black solution was then cooled, most of the solvent removed by distillation (aspirator pressure), and the residue passed through a 12×2.5 cm. column of Activity III acidic alumina. 250 ml of benzene was used to elute the products from most of the polymer. The eluted

material was concentrated, first on the rotary evaporator to remove benzene, then by trap-to-trap removal of the remaining o-dichlorobenzene. The residue was then kugelrohr distilled at ambient to 110°/0.01 mm to give 6.213 g of yellow oil which partly crystallized. Based on gc analysis (column A, 210°), this material was estimated to contain 72% diester 22, 21% lactone 82, and 7% numerous (unidentified) minor products. This corresponds to a ca. 41% yield of 77. The entire product was dissolved in warm hexane (30 ml), then cooled to -10° for several hours for crystallization of the lactone 82. This material, after a second crystallization from hexane, showed the following properties: white needles mp 84.8-85.2°; ir (Nujol): 5.79μ; nmr (δ, CDCl₃): 6.3-5.1 (5H, complex m), 3.73 (1H, broad s), 3.52-2.95 (2H, m), 2.62-2.33 (2H, m); ms: m/e 162 (19%), 134 (10%), 117 (100%), 115 (25%), 91 (70%), 78 (52%), 39 (50%) inter alia. The sample submitted for combustion analysis was recrystallized a third time from hexane and sublimed (50°/0.01 mm).

<u>Anal</u>. Calc for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found : C, 73.91; H, 6.20.

The desired diester $\chi\chi$ was isolated by chromatography of the mother liquor from the initial crystallization of lactone $\xi\chi$. The hexane solution, containing <u>ca</u>. 90% of $\chi\chi$, was placed on a dry packed column (2.5 × 70 cm) of acidic alumina (Fisher, 80-200 mesh, deactivated to Activity III) and eluted with purified hexane; fractions averaging about

10 ml were collected. When gc analysis showed that diester 27 was beginning to appear in the eluent (typically around fraction #80), the eluting solvent was switched to hexane-5% ether (v/v), and collection of fractions was continued until ZZ stopped coming off the column. Those fractions containing >98% 22 were combined and the solvent removed, to give 3.163 g (29%) of diester 77 as a pale yellow oil. The less pure fractions were combined and chromatographed again; this raised the yield of diester to 3.828 g (35%). An analytical sample of $\chi\chi$ was obtained by preparative gc (column C, 220°). This material gave the following data: ir (neat): 3.25, 3.34, 3.42, 5.76, 8.50-8.66, and 9.67μ , among others; nmr (δ , CCl₄): 5.50 (4H, s), 4.08 (4H, q, J = 7.5 Hz, 3.70-3.37 (2H, m), 3.35-2.95 (2H, m), 2.26 (4H, broad d, J = 7.5 Hz), 1.27 (6H, t, J = 7.5 Hz); ms: m/e 278 (11%), 233 (8%), 205 (9%), 190 (20%), 159 (12%), 131 (19%), 117 (76%), 91 (42%), 57 (49%), 43 (21%), 41 (26%), 39 (19%), and 29 (100%), among others. The nmr spectrum is shown in Figure A4.

<u>Anal</u>. Calc for C₁₆H₂₂O₄ : C, 69.04; H, 7.97. Found : C, 69.05; H, 8.01.

Method B; neat triethyl orthoacetate procedure. Dienediol 42 (2.76 g, 20 mmole) was mixed with freshly distilled triethyl orthoacetate (60 ml) in a 100 ml flask equipped with a thermometer, magnetic stirrer, and Claisen-Vigreux distillation column carrying a thermometer, condenser and receiver. A nitrogen atmosphere was established, and the

mixture warmed. When the diol had completely dissolved, 50 mg of pivalic acid in 1 ml of triethyl orthoacetate was added, and the mixture heated to boiling. When the initial surge of ethanol evolution had subsided, the heating was adjusted to give a distillation rate of about 0.3 ml/hr. Additional 20-30 mg portions of pivalic acid in ca. 1 ml triethyl orthoacetate were added approximately every 6 hrs; after each such addition the temperature at the head of the column rose to 70 to 90°, but soon subsided to 40-50°. The reaction was continued for 90 hrs, during which time about 25 ml of distillate had collected; the total amount of pivalic acid added was 0.52 g. The excess orthoacetate was then removed by distillation at aspirator pressure, and the brown residue kugelrohr distilled to give 4.75 g of yellow oil and crystals. This material showed (gc on column A, 210°) 69% diester 22, 15% lactone 82, 11% pivalate 83 (vide infra) and about 5% of numerous other products. This composition suggests that diester 22 is formed in ca. 60% yield.

The lactone 82 was removed as described in method A, and the diester isolated using the same chromatographic procedure. After reworking the less pure fractions, a total of 2.89 g (52%) of ZZ was obtained.

Several of the byproducts from this reaction were isolated during the chromatographic separation. Thus, a purple band was eluted quite rapidly with hexane (well before the diester ZZ). Gas chromatographic analysis of this



material (column A, 180°) showed three main components and a host of trace materials. Preparative gc (column A, 170°) permitted isolation of the second and third (in order of increasing retention time) of the major components. The second compound was a faint lavender color. On the basis of the following spectral data, it is assigned structure &&: ir (neat), 5.75 μ ; nmr (δ , CCl₄): 5.84-5.34 (4H, m), 4.13 (2H, q, J = 7.4 Hz), 3.73-2.90 (3H, m), 2.61-2.06 (4H, m, including a broad 2H d,J = 7 Hz), 1.27 (3H, t, J = 7.4 Hz); ms: m/e 192 (42%), 163 (13%), 147 (24%), 119 (62%), 118 (75%), 117 (70%), 105 (99%), 104 (100%), 91 (79%), 79 (30%), 78 (27%), 77 (38%), 65 (27%), 41 (56%), 39 (46%), 29 (65%).

The major component of the purple band with the longest retention time was isolated as a colorless oil which solidified to give long white needles. The spectra suggested that the structure was 1,3,5-triethoxybenzene §g: nmr (δ , CCl₄): 5.93 (3H, s), 3.95 (6H, q, J = 7 Hz), 1.38 (9H, t, J = 7 Hz); ir (neat): 3.34, 3.41, 3.46, 6.25, 6.81, 7.19, 8.56, 8.95, 9.40, and 12.28 μ . This structural assignment was confirmed by the melting point of recrystallized material: needles from methanol-water, mp 43.0-43.3° (lit⁷⁴, 43°).

Later in the chromatography, a band was eluted which contained <u>ca</u>. 95% one component, pivalate g_{3} ; this material was eluted shortly before the diester χ_{1} appeared. The spectral data left no doubt as to the structure: ir (neat): 5.75μ; nmr (δ, CCl₄): 6.10 (1H, d of d, J = 6 Hz, J' = 3 Hz), 5.85-5.5 (4H, complex), 4.13 (2H, q, J = 7 Hz), 3.85 (1H, m), 3.55-2.75 (2H, series of m), 2.5 (2H, pseudotriplet, J = 6 Hz), 1.27 (3H, t, J = 7.5 Hz), 1.20 (9H, s).

A considerable time after diester $\chi\chi$ had eluted completely, a small amount of acetate $\xi\chi$ was eluted from the column. The structure followed from the spectral data: ir (neat): 5.76µ; nmr (δ , CCl₄): 6.10 (1H, d of d, J = 5 Hz, J' = 2.5 Hz), 5.93-5.45 (4H, complex), 4.11 (2H, q, J = 7 Hz), 3.8-2.9 (3H, series of m), 2.8-2.2 (2H, complex), 1.97 (3H, s), 1.27 (3H, q, J = 7 Hz).

2,6-Bis(carboethoxymethylene)bicyclo[3.3.0]octane 78. Acid catalyzed Wittig reaction of dione 53 and carboethoxymethylenetriphenylphosphorane⁷⁰. The ylid component of the Wittig reaction was prepared using the method of Isler, et al.⁶⁹, and was purified by recrystallization from ethyl acetate-petroleum ether. Sublimed dione 53 (1.380 g, 10 mmole) and the ylid (7.66 g, 22 mmole, 10% excess) were dissolved in 40 ml of benzene-dioxane (3:1 v/v) and benzoic acid catalyst⁷⁰ (300 mg) added. The mixture was then refluxed under nitrogen for 4 days, during which time it became a deep red-brown color. The solvents were removed on the rotary evaporator and the resulting brown paste taken up in 20 ml carbon tetrachloride. This solution was filtered with suction through a 4 × 3 cm bed of silica gel, and the silica gel washed with 100 ml of carbon tetrachloride. Removal of the solvent from the combined CCl_{μ} layers afforded

6.4 g of a mixture of white crystals in a yellow oil. This material was chromatographed on a 2 × 17 cm dry packed column of silicic acid (Mallinckrodt, 100 mesh), using carbon tetrachloride as the eluting solvent. The column runnings were discarded until evaporation of a drop left a visible residue; then six 20 ml fractions were collected.

The first two fractions were pure diester 78 (a mixture of three stereoisomers) as shown by gc analysis (column A, 200°); together, they weighed 1.302 g (47%). Fraction 1, which contained ca. 75% one isomer (that with the shortest retention time), crystallized on standing. Two recrystallizations of this material from pentane at -20° gave white prisms, mp 54.2-55.0°, containing ca. 97% one isomer. An analytical sample was obtained by three more recrystallizations from ethanol-water, giving needles mp 54.6-55.0°; sublimation (40°/0.005 mm) of this material raised the melting point to 55.0-55.2°. The spectral data showed this to be 78a: ir (Nujol): 5.80, 6.01 μ , inter alia; nmr (δ , CDCl₃): 5.77 (2H, pseudoquartet, J = 1.5 Hz), 4.16 (4H, q, J = 7.2 Hz, 4.0-3.5 (2H, broad m), 2.7-2.0 (6H, m, withmaxima at 2.65, 2.6, and 2.45), 1.8-1.4 (2H, broad m), 1.27 (6H, t, J = 7.2 Hz); ms: m/e 278 (57%), 249 (100%), 233 (43%), 203 (35%), 159 (16%), 131 (13%), 91 (14%) and 29 (8%), among others.

Fraction 2, contained the three isomers of Z& in the ratio 35:50:15, in order of increasing retention time. The nmr spectrum of this mixture was basically similar to

that of the pure isomer χ_{RA}^{a} , with the following differences: the bridgehead absorbtion at δ 4.0-3.5 had decreased in intensity to 1.4H, while a corresponding increase (to 8.6H) was apparent in the higher field absorbtions. Also, these higher field bands had spread out, beginning around δ 3.4, reflecting the contribution of the less shielded bridgehead protons in the other isomers. The ir spectrum (neat) was practically identical to that of pure 78a.

Fractions 3-6 contained mostly a mixture of stereoisomers of ketoester & The weight of this material came to 0.484 g (23%): the ir of this material showed peaks at 5.74, 5.83, and 6.02 μ , demonstrating the presence of both cyclopentanone and α , β -unsaturated ester functionality.

The total recovery of identifiable organic material from this reaction thus is <u>ca</u>. 71%. In two later runs the amount of ylid was increased to 40% excess, and more benzoic acid catalyst used. These gave yields (after a more frugal chromatographic separation) of 67% and 71% of diester $\frac{78}{28}$ (isomer mixture); the ketoester $\frac{81}{28}$ was not isolated.

<u>Bicyclo</u>[3.3.0]<u>octane-2,6-diacetic acid, diethyl ester</u> χ_2 . <u>Catalytic reduction of unsaturated esters</u> χ_2 and χ_2 . The mixture of isomeric diesters χ_2 obtained from the Wittig reaction just described (0.835 g, 3 mmole) was dissolved in ethyl acetate (25 ml), and 30 mg of 10% palladium on charcoal added. This mixture was hydrogenated at atmospheric pressure and <u>ca</u>. 0° (ice bath) until hydrogen uptake ceased. The catalyst was removed by centrifugation and washed with

additional ethyl acetate. Removal of the solvent and molecular distillation (80-100°/0.05 mm) afforded 0.795 g of colorless liquid (94%). Gas chromatographic analysis (column A, 210°) showed this material to contain three components, in the ratio 10:40:50. The spectral data indicate that this material is a mixture of stereoisomers of the saturated diester 72: ir (neat): 5.75μ ; nmr (δ , CCl₄): 4.15 (4H, q, J = 7.3 Hz), 2.75-0.95 (22H, series of peaks, including a broad singlet at 2.34 and a triplet (J = 7.3 Hz) at 1.26).

The purified diester $\chi\chi$ from the orthoester Claisen reaction (<u>ca</u>. 5 mg) was dissolved in 1 ml ethyl acetate and a few mg of 10% Pd/C added. Atmospheric pressure hydrogenation of this material was conducted on this mixture at 0° until hydrogen uptake ceased (<u>ca</u>. 20 min). Gc analysis (column A, 210°) of the solution showed that the starting diester was entirely consumed. The main product was the major saturated diester isomer (of longest retention time) in the preceding preparation. A small amount (<u>ca</u>. 3%) of the intermediate retention time isomer was also formed.

<u> $6,7-Bis(trimethylsiloxy)tricyclo[7.3.0.0^{4,12}]dodec-6-</u>$ <u>ene 92</u>. <u>Acyloin-type cyclization of the saturated diester</u>29. A 100 ml three-necked flask equipped with an additionfunnel, thermometer, magnetic stirrer, reflux condenser andnitrogen inlet/outlet was charged with toluene (40 ml, redistilled and passed through a column of Activity I basicalumina). The toluene was heated to vigorous boiling sothat the vapors flooded the entire apparatus; about 5 ml</u>

of toluene was distilled from the top of the reflux condenser to guarantee dryness. The apparatus was cooled to room temperature while a stream of dry nitrogen was passed through the flask, and clean sodium (0.204 g, 8.87 mg-atoms) added to the toluene. The mixture was heated to reflux with vigorous stirring to disperse the sodium, and cooled to room temperature. Chlorotrimethylsilane (0.985 g, 9.06 mmole) in toluene was added to the stirred sodium suspension, followed by the mixture of isomeric saturated diester 79 (0.556 g, 0.98 mmole; ca. 40% of this material was the cis, endo-epimer) in an additional 10 ml toluene. The addition took 1 hr, after which the mixture was heated to reflux for 3.5 days. Twice during this period (after 24 and 70 hrs reflux) additional 0.1 g portions of sodium and 0.50 g portions of chlorotrimethylsilane were added. The reaction was stopped when all of the diester (all of the three isomers) had been consumed. The reaction mixture was filtered through a medium frit under a nitrogen atmosphere, the purple solid washed with 15 ml toluene, and the solvent removed from the combined toluene solutions on the rotary evaporator. Molecular distillation of the yellow, viscous residue afforded 0.178 g of a very pale yellow liquid; most of the material distilled at 115-125°/0.25 mm. Analysis of this material (gc on column A, 170°) showed one major component (ca. 80%) and numerous minor products. The spectral data for this mixture support the structure 22 for the major component: nmr (δ , CCl₄, referenced to benzene, δ 7.26):

2.7-1.0 (16H, very broad), 0.12 (18H, s); ir (neat): 5.99, 7.98 (Si(CH₃)₃⁸³), 8.62, 9.18 (Si- $0-C^{83}$), 11.6-12.0 (Si(CH₃)₃) and 13.14-13.33µ (Si(CH₃)₃). The mass spectrum of the mixture showed a strong peak at m/e 338, the calculated molecular weight of 92.

6,7-Bis(trimethylsiloxy)tricyclo[7.3.0.04,12]dodeca-2,6,10-triene 45. Acyloin cyclization of unsaturated diester Sodium (0.77 g, 0.0335 g-atoms) was placed in 100 ml 77. toluene (redistilled and passed through a 20 × 2.5 cm column of Activity I basic alumina) in a dry 250 ml three-neck flask fitted with an addition funnel, reflux condenser, thermometer and nitrogen inlet/outlet; a magnetic stir-bar and about twenty 5 mm glass beads were used for mixing. A nitrogen atmosphere was established and maintained throughout the following steps. The sodium was melted and dispersed by heating the toluene to reflux while stirring. The mixture was then cooled to ca. 60° and 5.2 ml of chlorotrimethylsilane (4.44 g, 0.0412 mole) (Aldrich, redistilled, bp 56.1-56.4°) added with stirring. While the temperature was maintained around 60°, the diester 22 (2.00 g, 0.0072 mole) in 40 ml of toluene was added dropwise over 2.6 hrs. Upon completion of the addition, an additional 1.0 ml of chlorotrimethylsilane was added and the mixture heated to reflux. The reaction was monitored by periodic gc analysis (column A, 215°). After 4 hrs reflux the diester had been consumed completely, and the reaction mixture was cooled to room temperature and filtered through a medium frit

using N_2 pressure. The purple residue was washed three times with 25 ml portions of toluene, and the yellow filtrate and washings combined and the toluene removed by distillation (N_2 atmosphere). The thick brown residue was then <u>kugelrohr</u> distilled at 80-100°/0.01 mm, yielding 1.16 g of a pale yellow liquid. The brown nonvolatile residue amounted to 0.94 g.

Chromatographic analysis of the distillate (column A, 190°) showed it to contain three components of short retention time, totalling ll% of the mixture, one of intermediate retention time (84%), and another of longer retention time (5%). Evidence is given below to show that this last component is the α -siloxy ketone $\frac{93}{22}$ and that it is derived from the major component.

Thus, the major component should be the expected <u>bis</u>-(trimethylsilyl)ether $\frac{1}{25}$. Attempts to purify this compound by preparative gc were unsuccessful, as reinjection revealed that decomposition to two new compounds had taken place. However, the spectral data obtained on the mixture are all in accord with structure $\frac{1}{25}$: ms: m/e 338 (calculated for $\frac{4}{25}$, 338) and nothing higher, and others; ir (neat): 7.99 (Si(CH₃)₃⁸³), 8.61, 9.10 and 9.46 (both Si-0-C⁸³), 10.62, 11.45, 11.82 (Si(CH₃)₃⁸³), 12.84 and 13.13-13.27 μ (Si(CH₃)₃⁸³); nmr (δ , CCl₄, referenced to benzene 7.27): 5.77 (4H, nearly degenerate AB pattern, J = <u>ca</u>. 7 Hz), 3.40-2.67 (4H, m), 2.22 (4H, slightly broadened d, J = 4 Hz), and -0.01 (18H, S). This spectrum is reproduced in Figure A5.

The yield of 45 was 40.5% on the basis of 84% purity of the distillate. Including the 5% of 93 in the distillate, the yield of cyclized product came to 43.5%. In several other runs, starting with 1.0-2.8 g of diester 77, this total yield was in the range 40-56%.

7-Trimethylsiloxytricyclo[7.3.0.0⁴,¹²]dodeca-2,10diene-6-one 93. The preceding reaction, acyloin cyclization of the unsaturated diester $\chi\chi$, was repeated on the same scale using an identical procedure. When the diester was completely consumed (gc on column A, 210°), the reaction mixture was cooled, filtered as before, and allowed to stand overnight exposed to the atmosphere; a glass wool plug permitted air, but not particulate matter, to enter The solvent was then removed by distillation the flask. at atmospheric pressure; removal of the last traces of solvent (aspirator vacuum) and kugelrohr distillation of the residue (70-110°/0.01 mm) gave 1.01 g of a light yellow oil containing 31% 45, 54% of the desired product (the "longer retention time" material mentioned above), and a total of 15% of four other products of short retention time (analysis on column A, 190°). Thus, the yield of cyclized material (45 and 23) was 42%.

Preparative gc (column A, 175°) of this mixture afforded a pure sample of 23 as a white, waxy solid which sublimed without melting above 100°. As the material decomposed on standing, a combustion analysis was not obtained. The spectral data confirm structure 23 for this compound: ms: m/e 262 (14%), 247 (7%), 234 (9%), 219 (19%), 169 (22%), 129 (33%), 117 (54%), 91 (23%), 73 (100%), and others; ir (neat): 5.82 μ ; nmr (δ , CCl₄, referenced to benzene): 5.98 (1H, d of d, J = 6 Hz, J' = 2Hz), 5.81 (1H, broad d, J = 6 Hz), 5.66 (2H, broad s, $\Delta v_{1/2} = ca$. 2 Hz), 4.45 (1H, t, J = 7 Hz), 3.43-2.68 (4H, m), 2.53 (1H, broad d, J = 4 Hz), 2.25 (1H, m), 2.05-1.71 (2H, m), and -0.02 (9H, s).

Strong Acid Catalyzed Hydrolysis of Bis(trimethylsiloxy) olefin 45. Formation of tetracyclic ketol 94 or 95. Distilled acyloin product 45 (100 mg, 84% pure, ca. 0.25 mmole) was dissolved in benzene (3 ml) and one tiny drop of 12 M hydrochloric acid added. The mixture was vigorously shaken for 2 min, poured into 5 ml water, and made slightly basic by the addition of sodium bicarbonate. The organic phase was separated and the aqueous layer extracted twice with 5 ml portions of chloroform. The combined organic layers were washed with 5 ml saturated sodium chloride solution, dried over MgSO,, and freed of solvent. Kugelrohr distillation of the residue at 60-100°/0.01 mm gave 38 mg of a thick oil containing ca. 80% one compound and at least four minor components. Preparative gc (column A, 190°) afforded a small amount of the major component as a white wax. The spectral data given below demand a tetracyclic structure, and suggest structure 94 or 95: ms: m/e 190 (100%), 172 (49%), 162 (12%), 146 (73%), 104 (92%) among others; ir (neat film): 2.91, 3.27, 3.39, and 5.73µ, among others;



nmr (δ , CCl₄): 5.9-5.3 (2H, m), 3.94 (1H, broad d, J = <u>ca</u>. 4 Hz), 3.75-1.1 (11H, series of complex m, including a singlet whose shift varied from 3.4 to 3.1 with a two-fold increase in concentration).

Tricyclo[7.3.0.04,12]dodeca-2,10-diene-6,7-diol 28. Reduction of bis(trimethylsilyl)ether 45. A solution of distilled bis(trimethylsiloxy)olefin 45 (1.50 g, 80% pure (column A, 190°, 3.6 mmole) in 15 ml benzene was added dropwise over 2 hr to a gently boiling solution of sodium borohydride (1.6 g, 42 mmole, ca. 46-fold excess) and sodium hydroxide (ca. 100 mg) in 60 ml of 80% aqueous ethanol; a nitrogen atmosphere was maintained throughout the addition and a subsequent 2 hr reflux period. The solution, which had become dark orange during the addition of 45, lightened during this 2 hr period to a light yellow. The cooled mixture was then poured into 150 ml of water, and acidified to pH 3 by the cautious addition, with cooling, of 3M hydrochloric acid (foaming!). The milky solution was heated on the steam bath for 10 min, cooled, and extracted three times with 50 ml portions of chloroform. The combined chloroform extracts were washed with water (50 ml) and saturated sodium chloride solution, and dried $(MgSO_{\mu})$. Removal of the solvent and kugelrohr distillation of the yellow residue at 70-120°/0.01 mm afforded 600 mg of a thick colorless oil which partly solidified on standing. Analysis of this material showed it to contain ca. 85% of one component, diol 98, and numerous trace components.



On this basis, the yield of 98 was 74%. The brown, resinous residue from the distillation contained some of the diol, and was saved for later chromatographic separation.

The above distillate was chromatographed on a column of Woelm silica gel (2.5 × 16 cm, slurry-packed in ethyl acetate) and eluted with ethyl acetate, collecting 5 ml fractions. The desired diol appeared in fractions 20-45; most of the material was in fractions 20-30. Removal of the solvent afforded pure 98 as an extremely viscous oil. As this material retained ethyl acetate tenaciously, a few drops of cyclohexane were added, and the solvents removed on the rotary evaporator (bath temperature 40°). This cyclohexane treatment was repeated twice, and the residue, a colorless oil, freed of the last traces of solvents by application of high vacuum. This caused the material to froth up and gradually solidify to a white wax, which decomposed (blackened) without melting at 100-120°. The yield of this material, which showed only a single component on all gc columns tried (column A, 200°, and programming at 1°/min from 180°; column B, 220°; column C, 220°; column D, 190°), was 420 mg (61%). The acetylation results (vide infra) show that, despite the homogeneity by gc, a small amount (ca. 5%) of one of the trans-isomers was present in this material.

The spectral data obtained on this product which lead to the assignment of structure 98, were as follows: ir (neat): 2.94, 3.27, 3.43, 6.19 (weak), 7.01, 9.43, 9.73,

10.69, 10.94, 12.77 μ <u>inter alia;</u> nmr (δ , CCl₄): 6.24 (1H, d of d, J = 6 Hz, J' = 2.6 Hz), 6.00-5.66 (3H, m), 3.93-3.67 (1H, m), 3.66-2.62 (5H, m), 2.48-2.0 (1H, m), 2.34 (2H, s, exchangable with D₂O), 1.83-1.43 (3H, m); ms: m/e 192 (4%), 174 (59%), 156 (27%), 145 (40%), 117 (95%), 115 (50%), 105 (54%), 91 (100%), 79 (82%), 67 (47%), 39 (44%) and others. The nmr spectrum is reproduced in Figure A6.

The glassy pot residue from the <u>kugelrohr</u> distillation was chromatographed in a similar fashion to that described above for the distillate. This afforded 51 mg of colorless oil; analysis of this material showed only one peak, with identical retention data to the material obtained above. Acetylation of the material recovered from the distillation residue showed it to be largely one of the <u>trans</u>-isomers ($\chi Q Q$ or $\chi Q \chi$), containing <u>ca</u>. 30% of the <u>cis</u> isomer χQ (<u>vide</u> <u>infra</u>). Thus, the total yield of diols was 68.5%. Other runs on a similar scale, using a 20 to 60 fold excess of sodium borohydride, gave yields of chromatographed diol of 57-69%.

Periodic Acid Cleavage of Diol 28. Formation of <u>cis</u>, <u>endo-bicyclo</u>[3.3.0]<u>octa-3,7-diene-2,6-diacetaldehyde</u> 29. A periodic acid solution in ether was prepared according to Ireland⁷⁷ by stirring excess periodic acid with anhydrous ether for 1 hr at 25°. This solution, which is stated^{77b} to contain "about 16 mg/ml" (= <u>ca</u>. 0.07 <u>M</u>), was added in 50 or 100 µl portions to a solution of diol 28 (3.8 mg, 0.02 mmole) in anhydrous ether. The mixture was analyzed

by gc (column A, 210°), after each addition of periodic acid; the volumes injected were increased each time in rough proportion to the increase in volume of the reaction mixture, permitting crude quantitative analysis. After 200 µl of periodic acid had been added, the amount of diol 98 had dropped to about half its original concentration, and a corresponding peak for the dialdehyde 99 had appeared. As more periodic acid was added, the formation of the dialdehyde continued to mirror the disappearance of the diol; however, a new peak, of much shorter retention time than either 28 or 22, began to appear. After 400 µl of periodic acid solution had been added, the diol peak had completely disappeared, the dialdehyde peak accounted for about 80% of the original diol concentration, and the new product came to about 10% of the dialdehyde. When the solution was allowed to stand, this new compound continued to be formed at the expense of the dialdehyde; addition of more periodic acid accelerated this transformation.

A drop of the mixture obtained after all the starting material had disappeared was evaporated on a salt plate, and the ir spectrum recorded. This showed the aldehyde peak for 99 (5.78 μ) along with numerous other peaks. From the first addition of periodic acid on, the odor of the dialdehyde was readily noticable over the odor of the ether solvent.

A sample of the dialdehyde was obtained for comparison <u>via</u> the following unambiguous route. To a stirred solution

of diester 77 (0.361 g, 1.30 mmole) in anhydrous ether (8 ml) was added ethereal lithium aluminum hydride (4.0 ml of a 0.80 M solution, ca. 150% excess). The mixture was stirred at room temperature for 15 min; saturated aqueous sodium sulfate solution (0.5 ml) was then added dropwise, followed by methanol (20 ml). The mixture was refluxed for 10 min and filtered. The precipitate was washed twice with boiling methanol, and the methanol layers concentrated on the rotary evaporator. The thick yellow residue was taken up in chloroform, refluxed briefly, filtered through Drierite and freed of solvent (rotary evaporator) to give 0.226 g (90%) of thick yellowish oil. The nmr spectrum showed this material to be the cis, endo-2, 6-bis-(2-hydroxyethyl)bicyclo[3.3.0]octa-3,7-diene (δ, CDCl₃): 5.64 (4H, nearly degenerate AB pattern, J = ca. 6 Hz), 3.79 (4H, t, J = 7 Hz), 3.64-3.25 (2H, m), 3.15-2.63 (2H, m),1.93-1.45 (6H, series of peaks, including a 2H singlet exchanged with D_20).

This diol (63 mg, 0.325 mmole) in 3 ml methylene chloride was added to 6 mmole of chromium trioxide pyridine complex in methylene chloride, prepared according to Ratcliffe and Rodehurst⁸² from 0.95 g pyridine and 0.60 g chromium trioxide in 15 ml methylene chloride. The reaction mixture was stirred at room temperature for 10 min, the orange methylene chloride solution, separated by decantation, and the gummy black residue washed with 25 ml ether. The combined organic layers were washed with 5% aqueous sodium

hydroxide (6 × 5 ml), 5% aqueous hydrochloric acid (3 × 5 ml), 5% aqueous sodium bicarbonate (15 ml) and saturated aqueous sodium chloride solution (15 ml). Removal of the solvent in vacuo gave 41 mg (66%) of faintly yellow dialdehyde 22 as a waxy solid with a very powerful odor. The material showed a single peak upon gc analysis (column A, 210°); sublimation (40°/0.02 mm) gave a mass of white, soft, wet-looking needles, mp 53-58°. Further purification was not attempted due to the instability of this compound; upon standing overnight in air it was converted to a yellowish, sticky gum. Dilute (ca. 1%) solutions in methylene chloride were stable for several months if kept at -10°, however, permitting storage. The spectral data, obtained on the crude material, fully support the structure 22: ir (neat): 3.26, 3.44, 3.52 (shoulder), 3.65 and 5.78µ, among others; nmr (δ , CCl_u): 9.87 (2H, t, J = 1.4 Hz), 5.51 (4H, extreme AB pattern, J = ca. 6 Hz, 3.85-3.00 (4H, m), 2.50 (4H, d of d, J = 7.5 Hz, J' = 1.4 Hz).

<u>Cis-6,7-diacetoxytricyclo</u>[7.3.0.0^{4,12}]<u>dodeca-2,10-diene</u> 103. Tricyclododecadienediol 98 (19.2 mg, 0.10 mmole), obtained by chromatography of the distillate from reduction of 45, was dissolved in dry pyridine (2 ml), and acetic anhydride (0.2 ml, <u>ca</u>. 10-fold excess) added. After 15 min at room temperature, the yellow mixture was heated on the steam bath for 2 hr, during which it turned brown. The cooled reaction mixture was then poured into 10 ml of cold water, extracted with chloroform (3 × 5 ml); the chloroform layers were washed with 5 ml of 10% aqueous sodium hydroxide, washed with dilute hydrochloric acid until the odor of pyridine could not be detected, and dried over Drierite. The solvent was removed on the rotary evaporator to give a pale yellow oil (26 mg), which contained <u>ca</u>. 90% <u>cis</u>diacetate 103, 5% <u>trans</u>-diacetate (104 or 105) and small amounts of several other compounds.

This material was adsorbed on alumina (1 × 8 cm, Woelm Activity I, dry packed) and eluted with hexane; 2 ml fractions were then collected while the eluting solvent was gradually (over 20 ml) changed to chloroform-hexane (1:1), which was used for the rest of the separation. Fractions 13-15 contained the trans-diacetate (vide infra); the cisisomer was eluted in fractions 17-25. These fractions were combined and freed of solvent to give 19 mg (ca. 69%) of 103 as a colorless oil, containing a trace (<u>ca</u>. 2%) of an unknown contaminant (gc on column A, 200°). The spectral data obtained on this sample of 103 were as follows: ir (neat): 3.27, 3.42, 5.72, 6.19 (weak), 7.30, 8.04, 9.73, and 12.71 μ , among others; nmr (δ , CC1_{μ}): 6.20-5.82 (3H, m), 5.67 (1H, broad d, J = 6 Hz), 5.15-4.74 (2H, two broad multiplets), 3.4-2.6 (4H, m), 2.28-1.48 (4H, series of m), 2.02 (3H, s), 1.87 (3H, s). The material was purified by preparative gc (column C, 210°) prior to mass spectral analysis, to remove the small impurity present, ms: m/e 276 (very weak, ca. 0.03%), 261 (very weak, ca. 0.01%), 234 (ca. 0.3%), 206 (1%), 192 (2%), 174 (9%), 156 (26%),

91 (20%) and 43 (100%), <u>inter alia</u>. The compound was unstable forming a tough clear resin on standing, and was not analyzed. The nmr spectrum is shown in Figure A7.

Trans-6,7-diacetoxytricyclo[7.3.0.04,12]dodeca-2,10diene (104 or 105). The diol mixture (51 mg, 0.266 mmole) obtained by chromatography of the distillation residues was dissolved in dry pyridine (4 ml) and treated with acetic anhydride (1 ml). Heating and workup of this reaction followed the procedure just given for the cis-isomer. The crude product, 67 mg, contained ca. 30% cis-diacetate 103, ca. 60% of the trans-isomer, and ca. 10% of four minor products. Chromatography of this material in the manner described above afforded the trans-isomer (28 mg) as a soft solid, mp 86.5-88.5° after washing the cold hexane. Recrystallization from hexane raised the mp to 88-89.8°. The spectral data for this compound show it to be a trans-isomer (104 or 105) of the cis-diacetate 103: ir (Nujol): 5.73, 8.04, 9.71, 12.50 and 13.07 μ , among others; nmr (δ , CCl₄): 5.97 (4H, nearly degenerate AB pattern), 5.62 (2H, broad t, J = ca. 4.5 Hz), 3.44-2.83 (4H, m), 2.05-1.67 (4H, m), 1.90 (6H, s); ms: m/e 276 (very weak), 261 (very weak), 234 (4%), 216 (1%), 192 (5%), 174 (43%), 156 (35%), 91 (35%) and 43 (100%). The nmr spectrum is reproduced in Figure A8.

<u>Cis-6,7-dihydroxytricyclo</u>[7.3.0.0^{4,12}]<u>dodeca-2,10-diene</u> <u>dimethanesulfonate</u> 122. Diol 28 (192 mg, 1.0 mmole) was dissolved in 8 ml dry pyridine and redistilled methanesulfonyl

chloride (0.78 ml, 5-fold excess) added with cooling. The mixture was allowed to stand at room temperature for 2 hr, then poured into 20 ml of ice and water. This mixture was extracted four times with 5 ml portions of chloroform, and the chloroform layers washed with cold 5% aqueous sodium hydroxide (3×5 ml), cold 5% hydrochloric acid (2×10 ml), 5% aqueous sodium bicarbonate (10 ml) and saturated sodium chloride (10 ml). The chloroform layer was then filtered and the solvent removed on the rotary evaporator to give 285 mg of crude dimesylate LO2 as a colorless oil, which partly solidified on standing. Recrystallization from chloroform-hexane (or benzene-hexane) gave hard, white wedge-like plates, mp 99.5-101° (dec). The quantity of crystalline LO2 obtained was 215 mg (62%).

The spectral data on this crystalline material support the structure (and stereochemistry) assigned: ir (Nujol): strong bands at 7.52, 8.53, 11.17, and 12.65µ and many weak bands; nmr (δ , CDCl₃): 6.15 (1H, d of d, J = 6 Hz, J' = 2.2 Hz), 6.01 (2H, broad s, $\Delta v_{1/2} = \underline{ca}$. 2.5 Hz), 5.74 (1H, broad d, J = 6 Hz), 5.14-4.78 (2H, m), 3.46-2.65 (4H, m), 3.08 (3H, s), 3.03 (3H, s), 2.56-1.60 (4H, series of m); ms: m/e 348 (4%), 307 (6%), 279 (5%), 252 (15%), 173 (23%), 167 (33%), 156 (63%), 149 (100%), 141 (38%), 129 (47%), 117 (45%), 115 (40%), 91 (86%), 79 (45%), 77 (34%), 57 (44%), 55 (44%), 43 (44%), 41 (65%), 39 (34%), <u>inter alia</u>. The nmr spectrum is shown in Figure A9.

The recrystallized dimesylate 102 appears to be unstable

even at -35° . After two weeks at that temperature, the melting point had <u>increased</u> to $103.5-106^{\circ}$ (dec).

Distillation of Tricyclododecadienediol 98 from Alumina. Alumina for dehydration was prepared according to von Rudloff⁷⁸ by adding 2% pyridine (by weight) to Woelm neutral alumina, Activity I, and allowing the stoppered mixture to stand for several days. Diol 98 (50 mg) was adsorbed onto 1 g of this alumina by evaporation of an ether solution, and the residue pyrolyzed at 170-220° at atmospheric pressure. A kugelrohr distillation apparatus was used for this distillation. The distillate, a yellow oil with a pronounced olefin-like odor, weighed 31 mg. Analysis of this material (column A, 150°) showed it to contain ca. 75% one component; the ir spectrum showed a strong band at 5.90µ, suggesting ketone 110. This assignment was subsequently confirmed by the isolation and characterization of this same product from the t-butoxide elimination of mesylate 102.

A very minor component (<u>ca</u>. 2%) of this mixture showed a retention time comparable to 1,5,9-cyclododecatriene on several columns (column A, 150°; column D, 130°).

<u>Tricyclo</u>[7.3.0.0^{4,12}]<u>dodeca-2,5,7,10-tetraene</u> 22 and <u>Tricyclo</u>[7.3.0.0^{4,12}]<u>dodeca-2,10-diene-6-one</u> <u>LLQ</u>. <u>Potas-</u> <u>sium <u>t</u>-butoxide elimination of dimesylate <u>LQZ</u>. Potassium <u>t</u>-butoxide was prepared by refluxing a large excess of <u>t</u>butanol (distilled from calcium hydride) with potassium. The excess <u>t</u>-butanol was removed by bulb-to-bulb distillation, and the residue sublimed at 170°/0.01 mm. The</u>
sublimed potassium <u>t</u>-butoxide was stored under nitrogen in sealed glass ampoules until use.

Dimesylate LQ2 (107 mg, 0.308 mmole) was added in one portion to a stirred solution of potassium <u>t</u>-butoxide (0.72 g, <u>ca</u>. 10-fold excess) in dry dimethylsulfoxide (5 ml). The flask was stoppered tightly and kept at room temperature for 1 hr, and 60-70° for a second hr. The cooled mixture was then poured into 10 ml of cold water and extracted with purified pentane (4 × 10 ml). The combined pentane extracts were washed once with water (10 ml) and most of the pentane removed on the rotary evaporator at a bath temperature of 5-10°. The last of the pentane was removed at <u>ca</u>. -10° (ice-acetone bath) with a stream of dry nitrogen.

The residue (52 mg) was a yellow oil with a strong olefinlike odor. Analysis of this material (column A, 150°) showed it to be a complex mixture containing at least six components. The component of shortest retention time (\underline{ca} . 15% of the mixture) showed a retention time comparable to 1,5,9cyclodecatriene on several columns (column A, 150°; column C, 150°; column D, 130°). The major component (\underline{ca} . 30%) which was eluted last on QF-1 (column A) was identical with the major product from the attempted alumina dehydration.

This mixture was analyzed further by gc-ms, programming the column temperature from 72° upwards at 8°/min, and the mass spectra of the first and last components eluted

determined. These showed parent ions at m/e 156 and 174, respectively, in accord with the structures 22 and 110. More complete mass spectra are given below.

Tetraene 22 was isolated by chromatography of the mixture on alumina (0.4 × 4 cm dry packed, basic, Activity I) with pentane as eluent; 0.5 ml fractions were collected. The first fraction was only pentane, but the second and third contained 22, contaminated with traces of other compounds. Removal of the solvent gave 4.5 mg of 22 of <u>ca</u>. 85% purity (ca. 8% yield). This material, a soft white solid which sublimed at fairly low temperatures (50-60°), exhibited the following properties: ir (neat): 3.31, 3.37, 3.45, 6.09 (weak), 6.20 (weak), 6.90 (weak), 7.45, 7.60, 9.17, 10.26, 10.91, 12.02, 12.50, 12.82, 12.99, 13.10, 13.70 and 14.0 μ ; nmr (δ , CS₂): 6.02-5.03 (8H, complex), 3.21 (4H, broad s). This spectrum is shown on Figure 7. The mass spectrum, determined in the gc-ms experiment, showed the following peaks: m/e 156 (10%), 155 (18%), 153 (10%), 141 (16%), 128 (22%), 115 (28%), 91 (100%), 78 (25%), 77 (12%), 65 (8%), 63 (11%).

Ketone $\downarrow \downarrow \downarrow \downarrow$ was obtained by elution of the column with chloroform-pentane (1:1) after the tetraene $\downarrow \downarrow \downarrow$ had been eluted. Fraction 4 so obtained contained a variety of components and was not investigated further. Fraction 5 contained ketone $\downarrow \downarrow \downarrow \downarrow$ in <u>ca</u> 90% purity; fraction 6 was rich in $\downarrow \downarrow \downarrow \downarrow \downarrow (\underline{ca}. 60\%)$ but was discarded. Removal of the solvent from fraction 5 gave 10.3 mg of $\downarrow \downarrow \downarrow \downarrow$ of 90% purity (17% yield)

as a pale yellow waxy solid which decomposed (and sublimed) at temperatures above 100°. This material had an odor containing both olefin-like and camphor-like elements; the unpleasant olefin odor was the stronger. Spectral data obtained on this material support structure lll: ir (neat): 3.20, 3.44, 5.90, 12.66 and 13.87 μ , <u>inter alia</u>; nmr (δ , CCl₄): 6.09-5.75 (4H, m), 3.5-3.23 (2H, m), 3.17-2.78 (2H, m), 2.76-1.73 (6H, complex). The mass spectrum, from the gcms experiment, showed the following ions: m/e 174 (19%), 146 (8%), 145 (21%), 131 (20%), 128 (17%), 117 (91%), 115 (49%), 104 (33%), 91 (100%), 79, 78, 77 (each about 60%), 65 (43%).

Determination of Temperature Dependence of the nmr Spectrum of 22. The nmr spectrum of the sample 22 prepared above was recorded at 100 MHz in tetrachloroethylene solution at several temperatures between 35° and 141°. The solution of 22 was degassed and sealed under vacuum. Ethylene glycol was used for temperature calibration. The nmr spectra so obtained were independent of the sample temperature; with only very minor differences, the 141° spectrum was superimposable on the 35° spectrum.

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APPENDIX



APPENDIX

Included here are the proton nmr spectra of the key intermediates in this synthesis, and of several other compounds where the spectra permit stereochemical assignments. All of these spectra were recorded on a Varian T-60 spectrometer at 60 MHz (500 Hz sweep width) in the solvents indicated.

Proton NMR Spectrum (60 MHz) of

Cis, exo-3, 7-dibromo-2, 2, 6, 6-bis(ethylenedioxy)-

bicyclo[3.3.0]octane 59a



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Proton NMR Spectrum (60 MHz) of

Trans-3,7-dibromo-2,2,6,6-bis(ethylenedioxy)-

bicyclo[3.3.0]octane 59b









Proton NMR Spectrum (60 MHz) of <u>Cis,endo</u>-2,6-dihydroxybicyclo[3.3.0]octa-3,7-diene 49







Proton NMR Spectrum (60 MHz) of <u>Cis,endo</u>-bicyclo[3.3.0]octa-3,7-diene-2,6-diacetic Acid, Diethyl Ester 22







Proton NMR Spectrum (60 MHz) of

6,7-<u>Bis</u>(trimethylsiloxy)tricyclo[7.3.0.0⁴,¹²]-

dodeca-2,6,10-triene 45






Proton NMR Spectrum (60 MHz) of Tricyclo[7.3.0.0⁴,¹²]dodeca-2,10-diene-6,7-<u>cis</u>-diol 98

169







Proton NMR Spectrum (60 MHz) of <u>Cis</u>-6,7-diacetoxytricyclo[7.3.0.0^{4,12}]dodeca-2,10-diene 103

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Proton NMR Spectrum (60 MHz) of <u>Trans</u>-6,7-diacetoxytricyclo[7.3.0.0⁴,¹²]dodeca-2,10-diene







Proton NMR Spectrum (60 MHz) of <u>Cis</u>-6,7-dihydroxytricyclo[7.3.0.0⁴,¹²]dodeca-2,10-diene Dimethanesulfonate 102

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