A new regiocontrolled and stereospecific total synthesis of (+-) modhephene
by David William Wilkening

A thesis submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy in Chemistry
Montana State University

Abstract:
A new approach to cyclopentanoid propellanes of theoretical and synthetic interest is presented, A methodology involving the vicinal dianions of 1,2-diesters is explored as a rapid entry into highly functionalized bicyclic diesters. An investigation of various electrophiles is conducted to examine the strengths and limitations of the dianion methodology. It is found that 1,3-primary dihalides, 3-haloesters, and 3-haloketones all react to give cyclopentanoid compounds with the dianions of cyclopentane and cyclohexane dicarboxylates. Under the conditions employed, the dienolate of dimethylsuccinate does not react to give the expected product with 3-bromopropionate. To demonstrate the utility of dienolates of vicinal diesters in organic synthesis, a regiocontrolled and stereoselective synthesis of racemic modhephene is accomplished.

A NEW REGIOCONTROLLED AND STEREOSPECIFIC TOTAL SYNTHESIS OF (±) MODHEPHENE

by

David William Wilkening

A thesis submitted in partial fulfillment

of the requirements for the degree

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana

May 1984

APPROVAL

of a thesis submitted by

David William Wilkening

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

5/24/84
Date

Bradford P. Mundy
Chairperson, Graduate Committee

Approved for the Major Department

5/24/84
Date

Edwin H Abbott
Head, Major Department

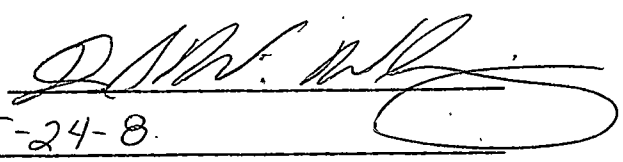
Approved for the College of Graduate Studies

6/4/84
Date

Henry L Parsons
Graduate Dean

STATEMENT OF PERMISSION TO USE

In presenting this thesis in partial fulfillment of the requirements for a doctoral degree at Montana State University, I agree that the Library shall make it available to borrowers under rules of the Library. I further agree that copying this thesis is allowable only for scholarly puposes, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for extensive copying or reproduction of this thesis should be referred to University Microfilms International, 300 North Zeeb Road, Ann Arbor, Michigan 48106, to whom I have granted "the exclusive right to reproduce and distribute copies of the dissertation in and from microfilm and the right to reproduce and distribute by abstract in any format."

Signature 

Date 5-24-8

To my father,

for the countless hours he spent teaching
me to throw a baseball.

"A wise son maketh a glad father." Proverbs 10.1

VITA

David William Wilkening, the first son of Walter D. and Ruth V. Wilkening, was born in Milwaukee, Wisconsin on the 14th day of January, 1958. He spent most of his childhood in Libertyville Illinois, and in June 1976 graduated from Libertyville High School. He then attended Rockford College in Rockford Illinois, where he met and married his wife Angela Sue. In June 1980 he graduated with honors from Rockford College and in September of 1980, he began his graduate studies at Montana State University. From Montana State University he then went to the University of South Carolina as a postdoctoral research associate under Professor Paul Petersen.

ACKNOWLEDGEMENT

In gratitude to those people who helped make this work possible I would like to name the following . . .

Bradford P. Mundy, for trusting in me and for his belief that good guys do finish first.

My mother, for teaching me the virtue of hard work.

My father, for teaching me perseverance.

My wife, for understanding why, and much more.

TABLE OF CONTENTS

LIST OF FIGURES

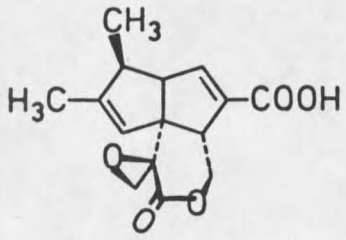
LIST OF COMPOUNDS

ABSTRACT

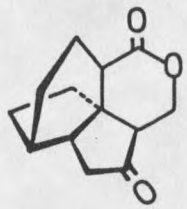
A new approach to cyclopentanoid propellanes of theoretical and synthetic interest is presented. A methodology involving the vicinal dianions of 1,2-diesters is explored as a rapid entry into highly functionalized bicyclic diesters. An investigation of various electrophiles is conducted to examine the strengths and limitations of the dianion methodology. It is found that 1,3-primary dihalides, 3-haloesters, and 3-haloketones all react to give cyclopentanoid compounds with the dianions of cyclopentane and cyclohexane dicarboxylates. Under the conditions employed, the dienolate of dimethylsuccinate does not react to give the expected product with 3-bromopropionate. To demonstrate the utility of dienolates of vicinal diesters in organic synthesis, a regiocontrolled and stereoselective synthesis of racemic modhephene is accomplished.

INTRODUCTION

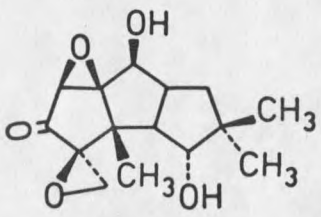
The recent past has witnessed a flourish of interest in cyclopentanoid chemistry[1]. Much of this interest is attributable to the isolation of biologically important cyclopentanoid and polycondensed cyclopentanoid natural products. Examples of this class of compounds are illustrated in Figure 1.



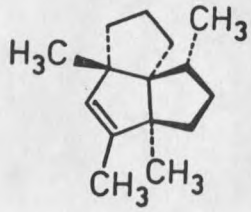
1
Pentalenolactone[2]



2
Quadrone[3]



3
Coriolin[4]



4
Isocomene[5]

Figure 1. Representative Cyclopentanoid Natural Products

As is apparent from these examples, the cyclopentanoids represent a complex challenge to the synthetic chemist, as most of these novel

compounds are highly substituted in addition to possessing the five membered ring skeleton. Furthermore, contrary to the situation in six-membered rings where stereochemistry can be manipulated by exploiting axial/equatorial biases; in order to perform stereoselective transformations in cyclopentanoids, the synthetic chemist must rely upon remote functionality or unique molecular conformation. In spite of these obstacles, and indeed perhaps on account of them, synthetic approaches to the cyclopentanoids have become a very competitive and exciting field of research for synthetic organic chemistry[6].

Our interest in cyclopentane annelation methodology resulted as an offshoot of a structure reactivity project that our group has maintained an active interest in for the past fifteen years. The crux of this problem can be stated as outlined below.

In a study done by Otzenberger in 1971[7], oxymercuration of the tetrahydrophthalan (5) was found to give predominantly syn-alcohol (6) (Figure 2).

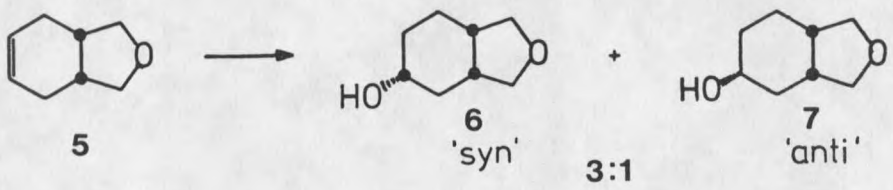
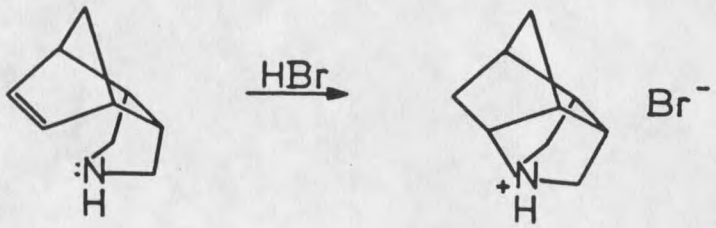


Figure 2. Oxymercuration of cis-8-oxabicyclo-[4.3.0]-oct-3-ene

It had been previously demonstrated for norbornyl systems[8] that heteroatom participation in the transition state leading to the products was responsible for the observed stereoselectivity of chemistry occurring at the double bond (Figure 3). Isolation of the nitrogen alkylated product (9) was interpreted as firm evidence for remote heteroatom participation in these systems.



8 9

Figure 3. Heteroatom Participation in Aza-Norbornyl Systems

Additional support for heteroatom participation in norbornyl systems was presented by the observed rearrangement of the endo-tetrahydropyran analog (10) to its exo-isomer (11) under solvolytic conditions[9] (Figure 4). Since the comparable carbocyclic norbornyl compound did not isomerize under identical conditions, it was proposed that heteroatom participation resulted in charge stabilization, thereby permitting rearrangement.

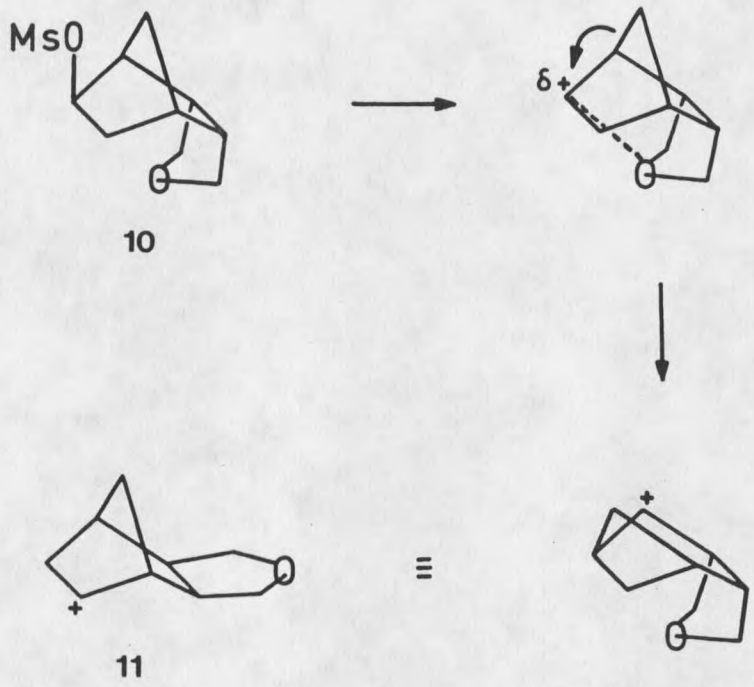


Figure 4. Solvolytic Rearrangement of Oxa-Norbornyl System

The question which faced Otzenberger was, therefore, could the same type of heteroatom effect be operating in the tetrahydrophthalan case? In light of the experimental results, and by analogy to the norbornyl system, Otzenberger suggested that the heteroatom effect was probably the main causative factor in determining the outcome of the oxymercuration of (5). Figure 5 shows the transformation of the tetrahydrophthalan (5) to the syn-alcohol (6) via intermediate (5a), for which Otzenberger proposed that the developing charge of the mercurinium ion was stabilized by the neighboring oxygen atom. Subsequent trans hydroxylation would yield (6).

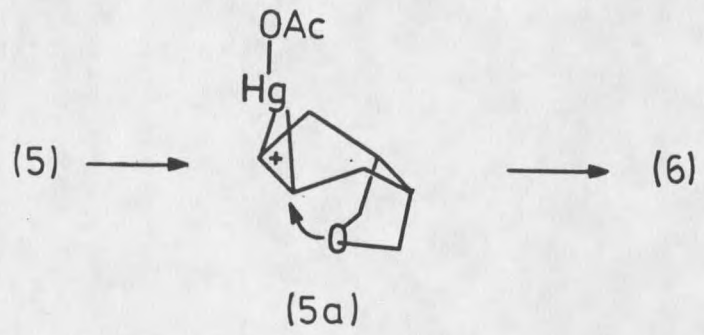


Figure 5. Charge Stabilization by Oxygen Atom in cis-Tetrahydrophthalans

One unexplored possibility pertaining to this question was the potential for simple steric effects to dominate the course of the reaction. As illustrated below, the pi-system of the cyclohexene ring is facially dissimilar (Figure 6); one face of the double bond is syn to the oxapropano group while the opposite face of the double bond experiences only two hydrogen atoms.

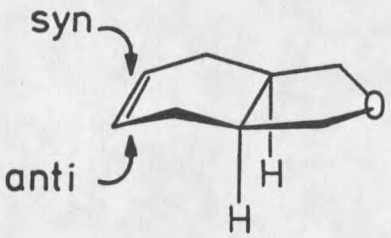
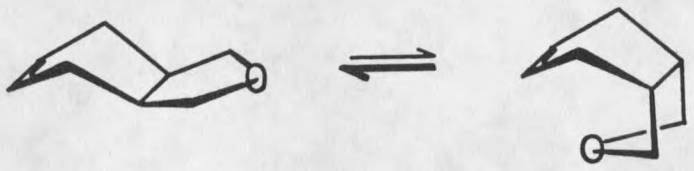


Figure 6. Steric Bias in cis-Tetrahydrophthalans

Thus, the question to be asked was: could observed product ratios be attributed to merely steric factors? Nuclear magnetic resonance experiments had suggested[10] that the conformation of the tetrahydrophthalan molecule was predominantly the more stable 'unfolded' isomer depicted in figure 7.



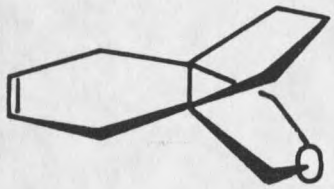
"unfolded" "folded"

Figure 7. Conformational Equilibrium in cis-Tetrahydrophthalans

This was used to support the assertion by Otzenberger that the heteroatom effect was in fact being expressed, since in the unfolded isomer the degree of steric bias is at a minimum for that system. In spite of these facts, the question of steric control remained insoluble for the system at hand.

Clearly, in order to unambiguously address this question, a more propitious candidate for oxymercuration was needed. Ideally, the proposed molecule should eliminate the steric discrepancies inherent in the tetrahydrophthalan system, while concomitantly retaining the relationship of the oxygen atom to the alkene function. The best such

molecule presented itself as the propellane (12) illustrated below (Figure 8).



12

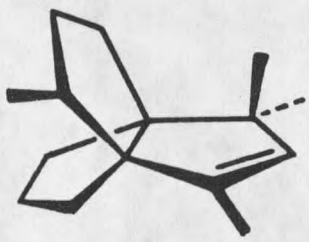
Figure 8. 8-Oxatricyclo-[4.3.3.0]-undec-3-ene

As can be seen from the drawing, the propellane presents nearly identical steric bulk to each face of the double bond; thereby permitting facial distinction only on the basis of heteroatom character. A possible objection to this statement could be proposed on the basis of a conformational preference for the double bond to fold toward or away from the heteroatom (Figure 9); however since the energy required to permit conformational isomerization is on the order of 6.9 kcals/mole[11], no conformational bias seemed likely.

Thus, a synthesis of the propellane (12) was compulsory, and since the major obstacle to achieving this goal was formation of the propano bridge from C-1 to C-6 of the tetrahydrophthalan molecule, we were provided with an impetus to explore methodology for construction of cyclopentanoid rings.

Figure 9. Conformational Equilibrium of Oxa-Propellane

A greater and more important goal which motivated the synthesis of the propellane (12) and the development of cyclopentannelation methods was our intrigue with the unique naturally occurring [3.3.3.0]-propellane modhephene[12] (13) (Figure 10).



13

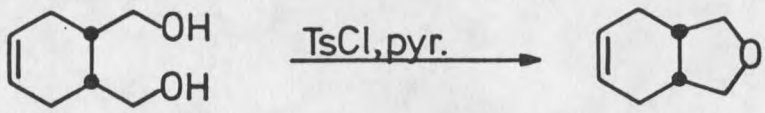
Figure 10. Modhephene

The simplicity of the heteroatom containing propellane (12) suggested to us that it would provide an ideal model system for a new synthesis of modhephene, which, since its isolation from rayless goldenrod in 1978 by Zalkow[13], has attracted considerable attention in the synthetic community[14].

The following text therefore discusses the development of a new cyclopentanoid annelation methodology within the constraints prescribed for the synthesis of the heteroatom propellane (12), and proceeds in a discourse of the further developments and refinements to the methods which were necessitated in order to accomplish the formal and total synthesis of modhephene.

RESULTS AND DISCUSSION

To begin the synthesis of 8-oxatricyclo-[4.3.3.0]-undec-3-ene (12), a suitable retrosynthetic pathway was needed. Previous work suggested that the tetrahydrofuran ring of the propellane was most judiciously constructed by dehydration of a 1,4-diol, as had been demonstrated for the tetrahydrophthalans by Otzenberger[15], as well as others[16] (Figure 11).



14 5

Figure 11. Synthesis of Tetrahydrofurans

Since 1,4-dihydroxy functionality is easily obtained from succinate derivatives, the key intermediate for an expeditious synthesis of the desired propellane was ostensibly the diester (15); which presented two practical options for synthesis (Figure 12). The first of these required an addition of butadiene to a 1,2-dicarboxy-cyclopentene such as the dimethyl ester (16). Literature preparations of (16) gave either unsatisfactory yields[17], or were not reproducible in our hands[18]. There was ample reason for concern regarding the

Diels-Alder reaction of (15) with butadiene as well; as tetra-substituted alkenes are often sterically and/or electronically inhibited as dienophiles[19].

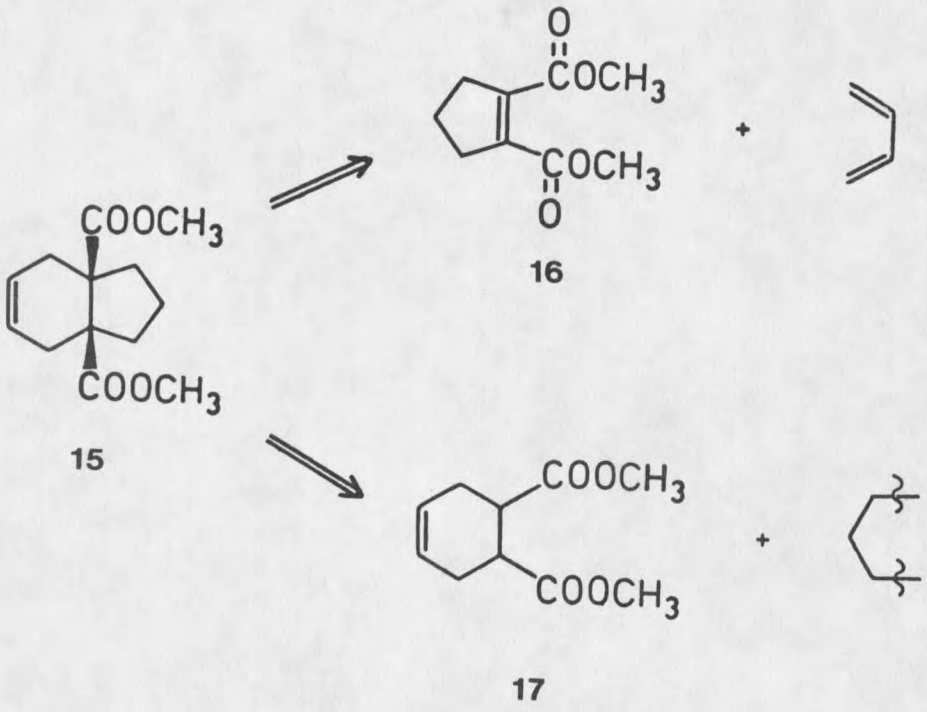


Figure 12. Synthetic Routes to cis-1,6-Dicarbomethoxybicyclo-[4.3.0]-non-3-ene

The alternative approach proceeded from the readily available 3,4-dicarbomethoxycyclohexene (17); but demanded attachment of the propano group by uncertain methods in order to form the cyclopentane ring[20]. Since one goal of this project was to develop this type of transformation as a new synthetic method for constructing five membered rings, we chose to pursue this approach toward the propellane precursor (15).

There have been numerous reviews published dealing with new synthetic entries into the cyclopentanoids[21]; however, no avenue into the class of annelated vicinal dicarboxylates had been reported which would permit facile construction of the type of bicyclodicarboxylate represented by (15). Consideration of the requisite cyclopentane annelation reaction prompted us to explore the possibility of exploiting the ester functionalities as a means of affecting the cyclization. Thus, it was postulated that a vicinal ester dianion generated from (17) might be a legitimate intermediate if a disubstituted propane could be found to act as an electrophile in this reaction (Figure 13).

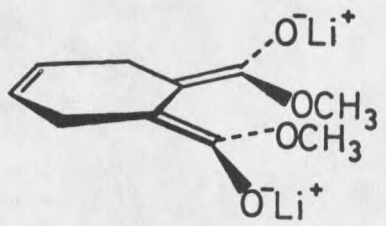
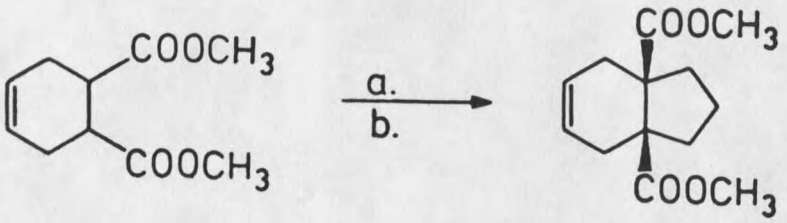


Figure 13. Dianion of 3,4-Dicarbomethoxycyclohexene

Additional credence to this approach was gleaned from the anticipated stability of the dianion generated from the vicinal diester, as conjugation of the enolates would serve to stabilize the developing charge. One final boon this reaction offered was the expected

formation of only cis-vicinal diester. The dienolate being presumably planar to permit conjugation, implied that once the first alkylation had occurred the second displacement would proceed from the same face, since formation of the trans ring juncture would require the propano group to twist between the two ester residues. This hypothesis was examined by performing the experiment outlined in Figure 14.

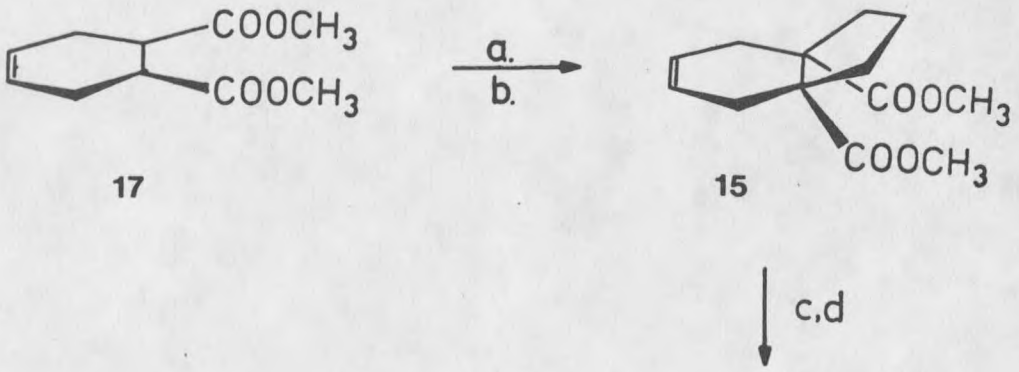
Quite happily, when 1.5 equivalents of 1,3-dibromopropane were added to the cooled, bright red THF solution of the dienolate of 3,4-dicarbomethoxycyclohexene, the bicyclic diester was obtained in high yield.



(a) 2.5 LDA, THF, -78°C. (b) 1,3-dibromopropane

Figure 14. Dianion Mediated Synthesis of cis-1,6-Dicarbomethoxybicyclo-[4.3.0]-non-3-ene

As expected, subsequent cyclization to the tetrahydrofuranyl ether, revealed that only cis-diester had been formed. Having thus established the practicality of the dianion mediated cyclization reaction, the remainder of the synthesis of the propellane was accomplished in a straight-forward manner as described in Figure 15.

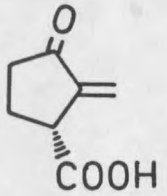


(a) 2.5 LDA, THF, -78°C
(b) 1,3-dibromopropane
(c) LAH, ether
(d) p-toluenesulfonyl chloride

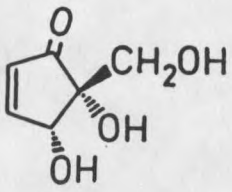
12

Figure 15. Synthesis of 8-Oxatricyclo-[4.3.3.0]-undec-3-ene

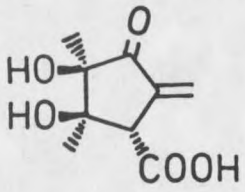
Another versatile aspect of the vicinal ester dianion was revealed during the course of experimentation aimed at the synthesis of 1,2-dicarbomethoxycyclopentene. As stated above, previously reported methods for the preparation of (15) were uniformly unsatisfactory. Due to recent interest in simple cyclopentanoids such as the antibiotic sarkomycin[22], and the related compounds shown below, (Figure 16) we felt that the dianion methodology could be fruitfully employed in this area.



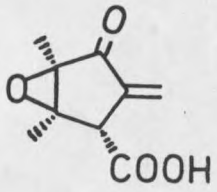
18 Sarkomycin[22]



19 Pentenomycin[23]



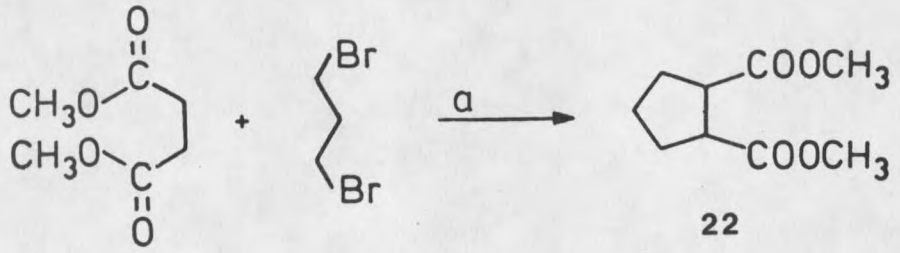
20 Xanthocidin[24]



21 Methylenomycin[25]

Figure 16. Simple Cyclopentanoid Natural Products

Accordingly, when the dianion of dimethylsuccinate was treated with 1,3-dibromopropane, 1,2-dicarbomethoxy (22) was obtained in 51% yield following distillation (Figure 17).

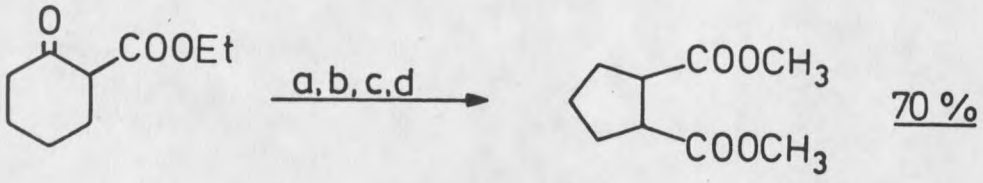


22

(a) 2.5 LDA, THF, -78°C

Figure 17. Synthesis of 1,2-Dimethylcyclopentane Dicarboxylate

In the course of our study, another new synthesis of the cyclopentane diesters was developed involving the Favorski rearrangement[26] of 2-bromo-2-carboxymethylcyclohexanone. Figure 18 outlines this preparation of (22).



22

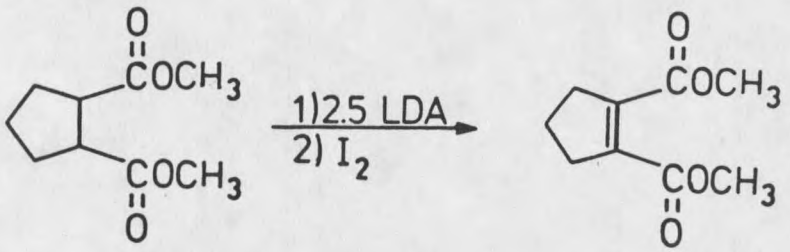
(a) Bromine, CH_2Cl_2. (b) 15% ethanolic KOH, 0°C, 1 hr.
(c) reflux, 18 hr. (d) absolute methanol, H^+, reflux.

Figure 18. Synthesis of 1,2-Dimethylcyclopentane Dicarboxylate by Favorski Rearrangement

In an initial attempt to prepare (22) directly, sodium methoxide was used as the base in the Favorski rearrangement. This resulted in an intractable tar; however, when sodium hydroxide was used in place of the alkoxide, the diacid of 1,2-dimethylcyclopentane dicarboxylate (23) was isolated in good yield. The material prepared by the dianion method was identical in all respects to the Favorski derived product.

In order to introduce the 1,2-double bond in (22), a number of suitable oxidizing agents were tried - all to no avail. However, when

the dienolate of (22) was prepared and reacted with 1.1 equivalents of iodine, the desired cyclopentene (16) was formed in 85% yield (Figure 19).



22 16

Figure 19. Synthesis of 1,2-Dicarboxymethylcyclopentene

The proposed mechanism of this transformation is shown in figure 20. In subsequent experiments it was discovered that cuprous iodide also affected this transformation in high yield, presumably by the same pathway.

Attempted Diels-Alder reaction of the cyclopentene diester (16) with butadiene or 2,3-dimethylbutadiene in the presence of various catalysts[27], and in a number of solvents proved, as anticipated, fruitless.

The experiments just described served to establish that the dienolates of acyclic as well as cyclic systems could be successfully utilized in this reaction, and also defined a new use of the dienolate

as an intermediate in the simple, one pot oxidation of vicinal diester alkanes to alkenes.

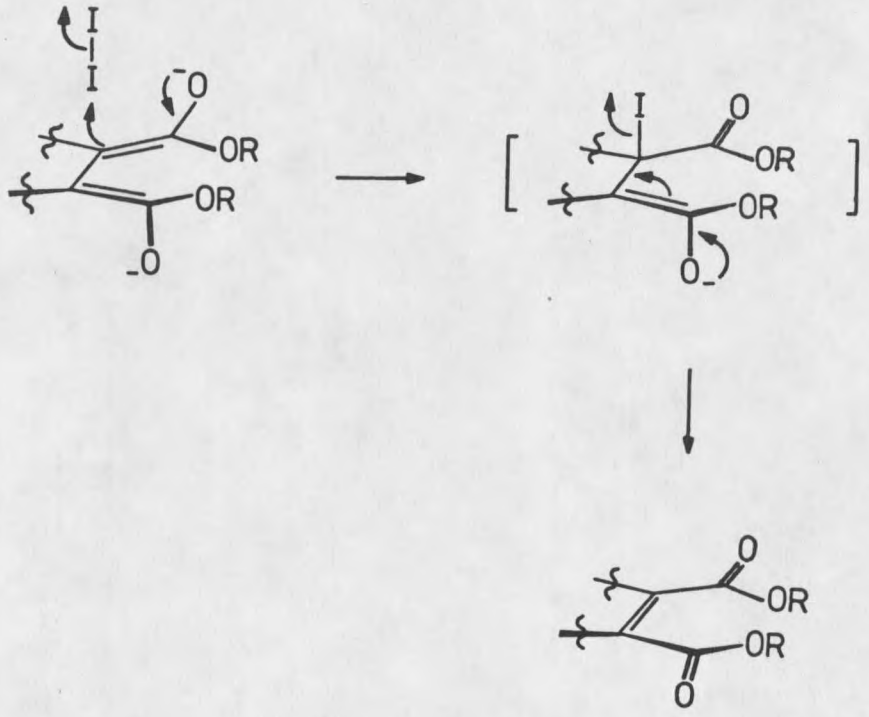


Figure 20. Mechanism of the Dienolate Mediated Oxidation of 1,2-dimethylcyclopentane dicarboxylate

With the synthesis of the propellane (12) accomplished, it now became feasible to repeat the oxymercuration experiments of Otzenberger to examine the steric control hypothesis proposed earlier. Accordingly, the propellane was added to a THF/water slurry of mercuric acetate under conditions identical to those reported by Otzenberger - and much to our chagrin, whereas the tetrahydrophthalans

had reacted quantitatively within 15 minutes at room temperature, the propellane proved to be quite unreactive! Obviously, the steric environment of the double bond had been altered drastically, for even on prolonged exposure to the reaction conditions, no product was observed. It had been reported[28] that oxymercuration reactions could be catalyzed by trace amounts of nitric acid in methanol. When the propellane was subjected to these conditions two methoxy ether propellanes resulted, which by GLC (13% DEGS, 10'x1/4"), were present in a 1:1 ratio (Figure 21).

Epoxidation studies also demonstrated the reduced reactivity of the double bond, however upon extended exposure to metachloroperbenzoic acid at 20°C, two epoxides were obtained, once again in a 1:1 ratio (Figure 21). Spectra which were crucial to the interpretation of these results are contained in Appendix A.

In light of these findings, it was concluded that for the tetrahydrophthalans such as (5), simple steric factors were responsible for the observed product composition, not heteroatom participation as had been initially proposed.

The results of this study also imply that great care must be exercised in drawing analogies between the chemistry characteristic for norbornyl systems and that associated with more common molecules, such as the cyclohexenes employed in our experiments.

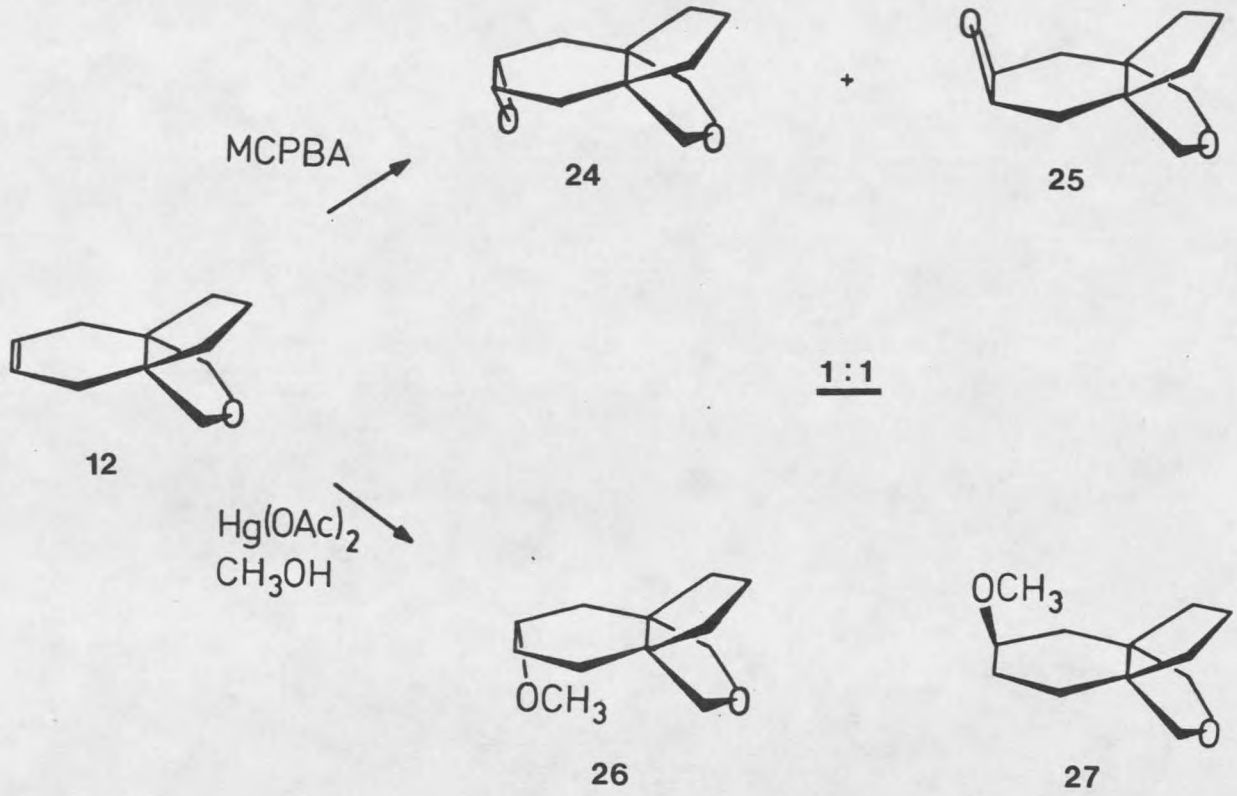


Figure 21. Oxymercuration and Epoxidation Reactions of 8-Oxatricyclo-[4.3.3.0]-undec-3-ene

With the successful completion of the synthesis and deployment of the propellane (12), the preparation of modhephene (13) utilizing the dianion strategy presented itself as the next fertile application of the method. To achieve this goal, the synthetic scheme shown on the following page was devised (Figure 22).

The extraordinary utility of this method for forming the bicyclic intermediate (30) was readily apparent from this analysis. If the ester functionality was a suitable electrophile for this reaction, consecutive dianion mediated annelations could be used to produce (29) in two steps from dimethylsuccinate. Moreover, the back to back annelations could conceivably be achieved by adding 1,3-dibromopropane to the dianion of dimethylsuccinate, as shown in figure 22, or alternatively, by successful addition of 3-bromoethylpropionate to the dienolate of dimethylsuccinate followed by addition of 1,3-dibromopropane. This would result in the desired cis-diester arrangement as well; therefore, this approach was flexible, stereoselective, and direct.

Wittig olefination of the ketone group would provide the alkene (30) which could be stereospecifically catalytically hydrogenated to (31). Construction of the final ring was then anticipated via crotonization of the dimethyl ketone (32), to the propellane (33). Separation of isomers and alkylation would then provide the ultimate target.

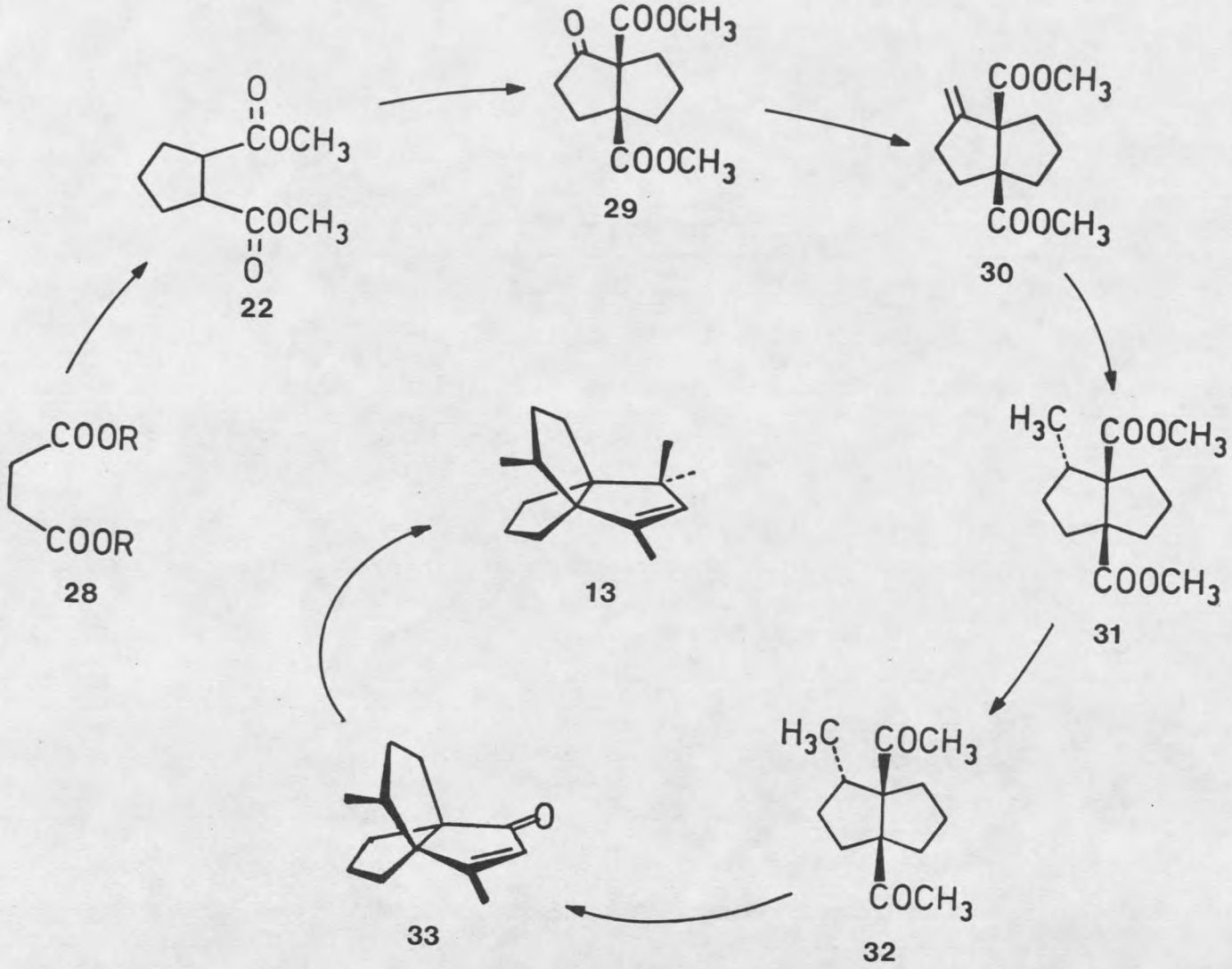


Figure 22. Proposed Synthesis of Modhephene

As a test for the serviceability of esters in the dianion method, 3-bromoethylpropionate was added to the dienolate generated in the usual way from 3,4-dimethylcyclohexene dicarboxylate. Following workup, a respectable yield (60%) of 7-oxo-(cis)-1,6-dicarboxymethyl-bicyclo-[4.3.0]-dec-3-ene (34) was obtained (Figure 23).

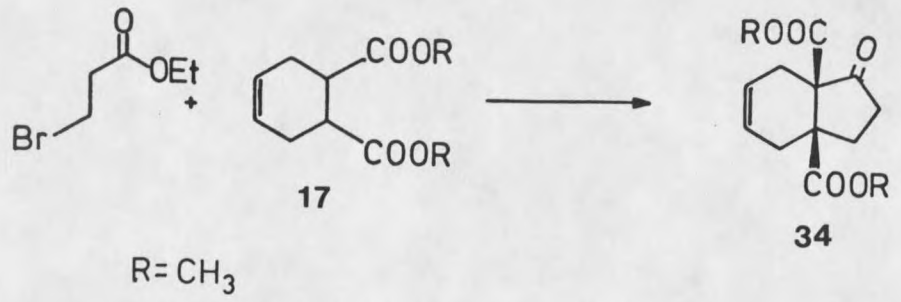
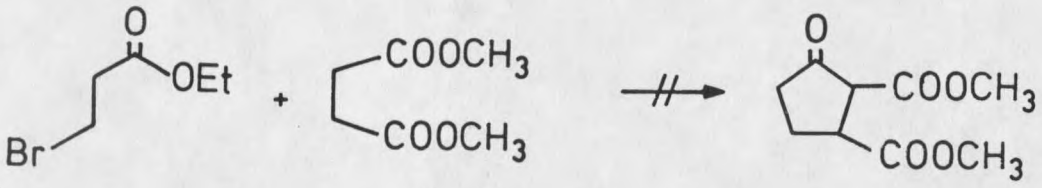


Figure 23. Synthesis of 7-Oxo-(cis)-1,6-dicarboxymethyl-bicyclo-[4.3.0]-non-3-ene

An interesting discovery was noted that although the dienolate of dimethylsuccinate reacted with 1,3-dibromopropane to give (22); when it was exposed to 3-bromoethylpropionate a complex mixture resulted which contained no 2,3-dicarbomethoxycyclopentanone (35) (Figure 24). Apparently the dimethylsuccinate dienolate existed in a transoid geometry and was less reactive than the cisoid dienolate of the cyclic diester systems. In an attempt to examine this hypothesis, N-methyl succinimide was prepared and employed as the dianion in the reaction

with 3-bromoethylpropionate. Once again, the resulting complex mixture contained none of the desired cyclopentanone. Thus, it was concluded that the configuration of the dianion was not the major factor contributing to the failure of the reaction. In an article published subsequent to our investigation of this reaction, Yamamoto[29] reported the successful condensation of the dianion of diisopropylsuccinate with 2-(bromomethyl)ethylacrylate to provide 5-methylene-2,3-diisopropylcyclopentanone dicarboxylate. Yamamoto also reported difficulty in employing 3-bromoethylpropionate in condensations with the dianion of diisopropylsuccinate[30].



35

Figure 24. Attempted Synthesis of 2,3-dicarbomethoxycyclopentanone

By repeating this procedure for the dianion of 1,2-dicarboxymethylcyclopentane, the ketodiester (29) was synthesized in 61% yield following purification. Unfortunately, all attempts to convert the ketone group of (29) to a methylene by Wittig olefination met with failure.

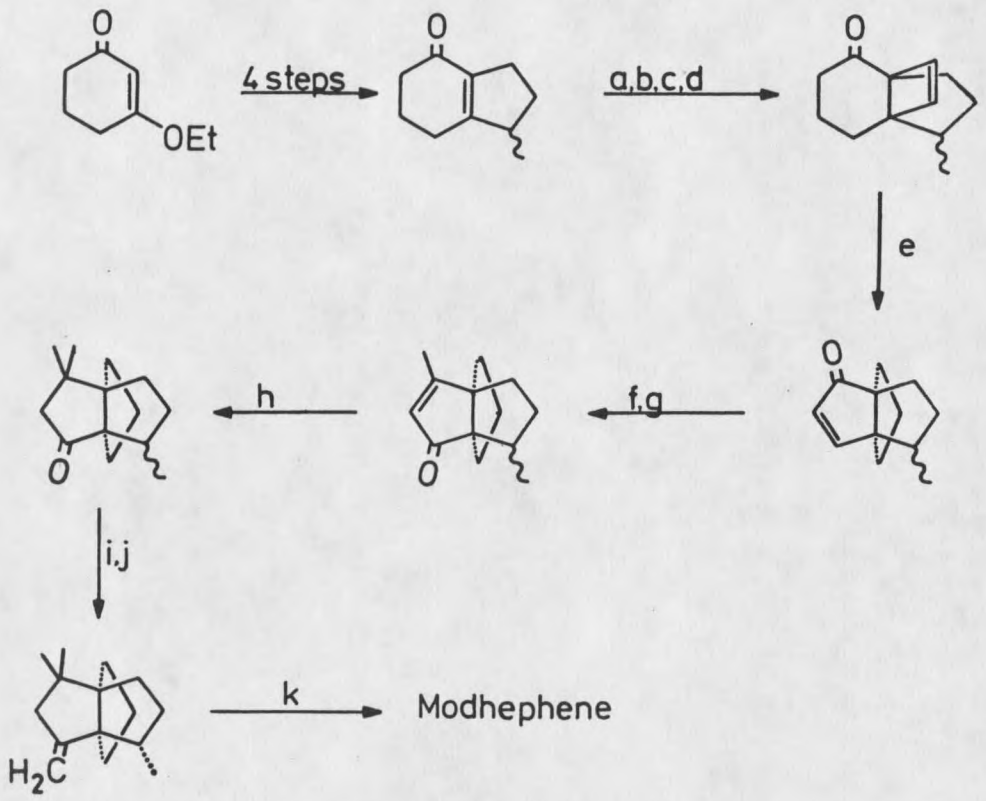
Even under forcing conditions that had been employed successfully by other workers[31] in sterically hindered ketones, (29) proved unreactive. In a related propellane ketone, Smith[32] overcame a similar obstacle by employing methyltriphenylphosphoniumbromide in a preheated toluene solution of potassium t-amylate to provide the olefin (36) in 49% yield (Figure 25).

36

Figure 25. Smith's Wittig Reaction

As can be seen in the diagram below, this Wittig reaction was the ultimate step in Smith's total synthesis of modhephene; he was therefore committed to its success (Figure 26).

We were not bound by the same constraints, so rather than repeating the procedure of Smith, an attempt was made to circumvent the problem entirely.

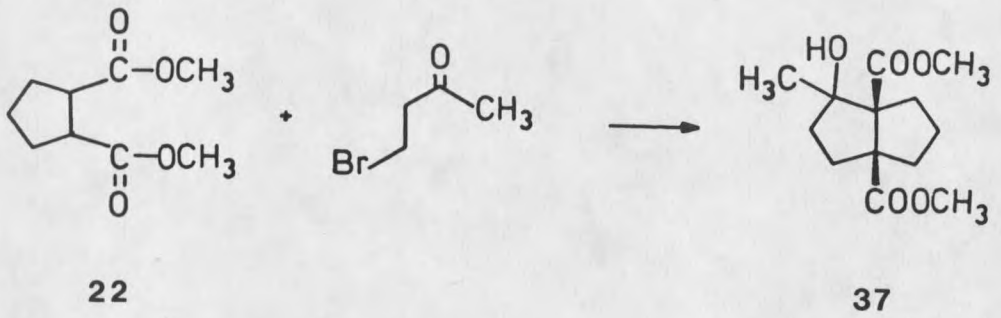


(a) 1,2-dichloroethylene, hv, Corex, 5 hr., 67%. (b) ethylene glycol, acid catalyst, azeotropic removal of water. (c) sodium, ammonia, -30 C, 78%. (d) 2% aqueous sulfuric acid, 91%. (e) p-toluene sulfonic acid, benzene, heat, 4 hr. 93%. (f) methyllithium. (g) Jones oxidation, combined yield: 88%. (h) dimethyl homocuprate, ether, boron trifluoride etherate, -78 C, 70%. (i) methyl Wittig, 49%. (j) chromatography. (k) p-toluene sulfonic acid, dichloromethane, 87%.

Figure 26. Smith's Synthesis of Modhephene

A major asset of the dianion technique is the flexibility afforded by prudent choice of the electrophile. Hence, if introducing

the methyl group onto the bicyclic precursor for modhephene was an inconvenience, perhaps a bromomethylketone could accomplish the annelation and introduce the methyl group in one step. In order to test this hypothesis, 4-bromo-2-butanone was prepared by addition of gaseous HBr to methylvinylketone. When the dianion of the cyclopentane dicarboxylate was combined with this bromoketone, a fair yield of the desired bicyclic alcohol (37) was isolated (Figure 27).

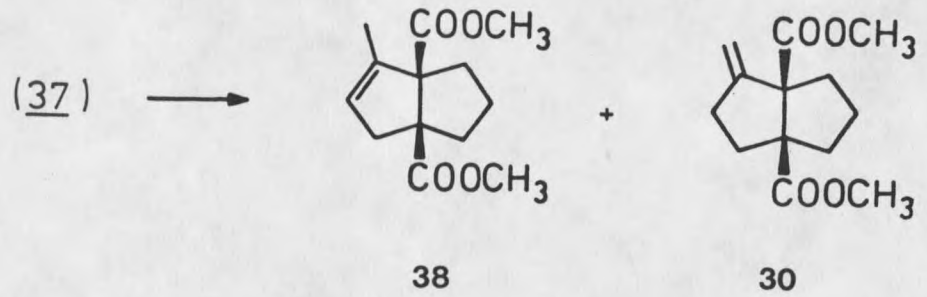


22 37

Figure 27. Synthesis of 2-Hydroxy-2-methyl-(cis)-1,5-dicarboxymethylbicyclo-[3.3.0]-octane

Although the yield of the reaction was somewhat less than spectacular (~30% following purification), the reaction accomplished the task in one step, and was easily reproducible on a larger scale. Since the starting materials were readily available, the low yield was

not a hindrance to our efforts. Dehydration of the epimeric alcohols using phosphorous oxychloride in pyridine[33] gave a 60% yield of the isomeric alkenes (38) and (30) (Figure 28). The formation of this isomeric pair of products was of little concern since both were readily reduced to the requisite alkane (31).



38 30

Figure 28. Dehydration of 2-Hydroxy-2-methyl-(cis)-1,5-dicarboxymethylbicyclo-[3.3.0]-octane

The keystone of the proposed synthesis of modhephene rested upon the next step in the sequence, that being the hydrogenation of the bicyclic alkenes (30) and (38). In the previous syntheses of modhephene, esoteric methods had been used to obtain the desired orientation of the C-8 methyl group, (see appendix B). Based upon our understanding of the nature of the catalytic hydrogenation reaction[34],

we felt confident that reduction would proceed from the ester face of (31) in the manner shown below (Figure 29).

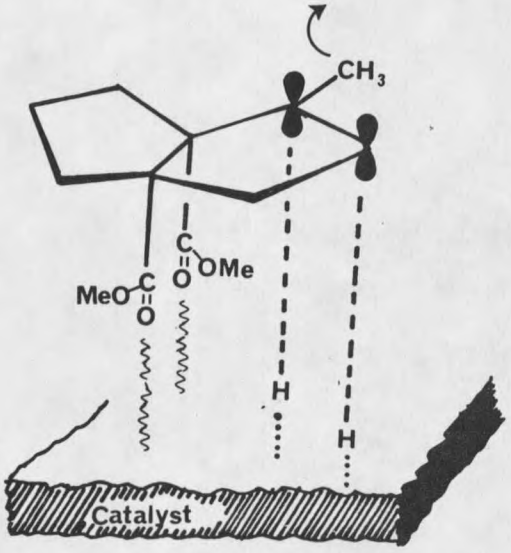
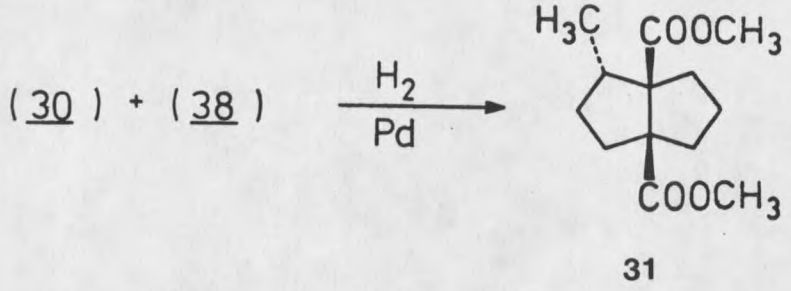


Figure 29. Proposed Mechanism of Hydrogenation of 2-methylene-(cis)-1,5-dicarboxymethylbicyclo-[3.3.0]-octane

Due to the affinity of the catalyst surface for the lone pair of electrons present on the oxygen atoms, the hydrogen delivery would occur so as to place the methyl group in the correct orientation between the two carbocyclic rings. A supporting argument could be proposed in terms of steric reasoning, as the carbomethoxy face might be more open and thereby permit more facile attack by the reducing system.

In practice, when the alkenes were hydrogenated at 60 psi over palladium on alumina, the resulting product showed only one set of

signals by ^{13}C nmr with no trace of olefinic carbons. Other spectral data as well as inspection of the product by TLC and capillary GLC were consistent with the supposition of isomeric purity. The hydrogenation reaction had therefore occurred stereospecifically (Figure 30); however, since this material was a new compound, there was no way to make an unequivocable assignment of the configuration of the methyl group at this stage of the synthesis.



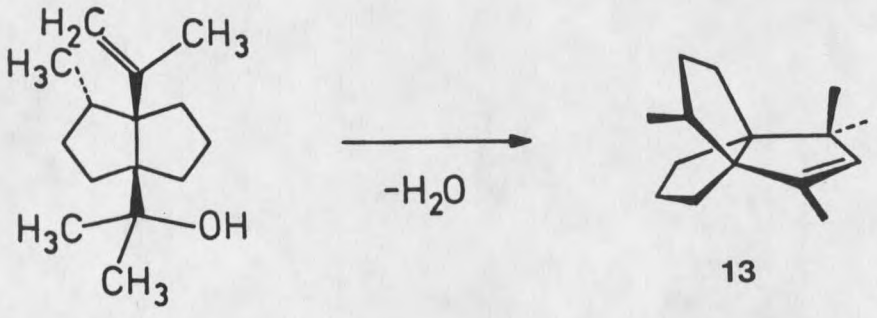
31

Figure 30. Stereospecific Hydrogenation to 2-methyl-(cis)-1,5-dicarboxymethylbicyclo-[3.3.0]-octane

Based upon the reasoning outlined above, it was assumed that the proper stereochemistry had been achieved and the material was carried on to the next step without further concern. Final confirmation of the structure of (31) awaited conversion to a known product.

The completion of the synthesis rested upon forming the final carbocyclic ring from the diester residues. To this end simple methods were sought to convert the ester groups to methyl ketones[35]; however following a few initial disappointments in this regard, the dimethyl ketone (32) was abandoned in favor of a more amenable intermediate.

To conclude the synthesis of modhephene from (31) required fabrication of the five membered ring as well as the regioselective introduction of three methyl groups. Consequently an expedient method of accomplishing this became a priority. An acid catalyzed cyclization of (39), analogous to a polyene cyclization[36], appeared to be the simplest such reaction (Figure 31).



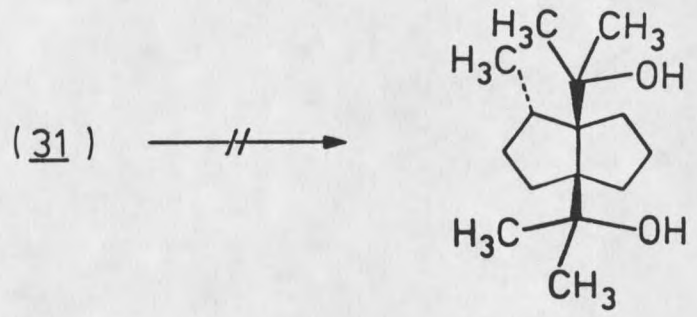
39 13

Figure 31. Proposed Synthesis of Modhephene via Acid Catalyzed Cyclization of 2-Methyl-(cis)-[1-dimethylmethylol-5-(1-methylethenyl)]bicyclo-[3.3.0]-octane

The conformation of (39) appeared to be ideally suited to this approach, as the cyclization would expectedly be facilitated by the close locality of the olefin and alcohol groups in the transition state. However, procurement of (39) presented a serious stumbling stone to the implementation of this idea.

The most direct synthesis of (39) from the diester (31) was envisioned as the straightforward addition of four equivalents of methyl lithium followed by dehydration of one of the alcohols to an alkene. This approach was fraught with problems. Firstly, if the dehydration of the diol (40) could be realized, it would undoubtedly provide a complex mixture of isomeric hydroxy-alkenes along with some diene. Secondly, since the proposed diol could cyclize to a tetrahydrofuran propellane, the ultimate yield of hydroxy-olefin would be dismal at best. To overcome these difficulties, it was hoped that the alkoxide generated by addition of methyl nucleophile could be trapped as the diacetate, or some other suitable intermediate, which could then be pyrolyzed to the olefin.

In practice, the concern over the side reactions of the diol (40) became a moot point. In an experiment employing the diester (31), it was discovered that due to the constraints of the system, (31) could not be alkylated by ordinary methyl nucleophiles to give the diol (40) (Figure 32).



40

Figure 32. Attempted Synthesis of 2-Methyl-1,5-Dimethylmethylol-bicyclo-[3.3.0]-octane

Product analysis of the reaction of four equivalents of methyl lithium with the diester (31) showed primarily the vinyl ether (45), along with a trace amount of the tricyclic lactone (43). Three equivalents of methyl lithium produced 90% vinyl ether in addition to about 5% of the lactone. When two equivalents of the nucleophile were added to the diester, an excellent yield of the lactone resulted. One equivalent of the alkylating agent gave predominantly unreacted diester (31) along with varying amounts of the lactone (43)

Based upon the results of these experiments, the reaction sequence shown in figure 33 was proposed. The proximity of the ester group to the tertiary alkoxide in (42) precluded the formation of any alcohol.

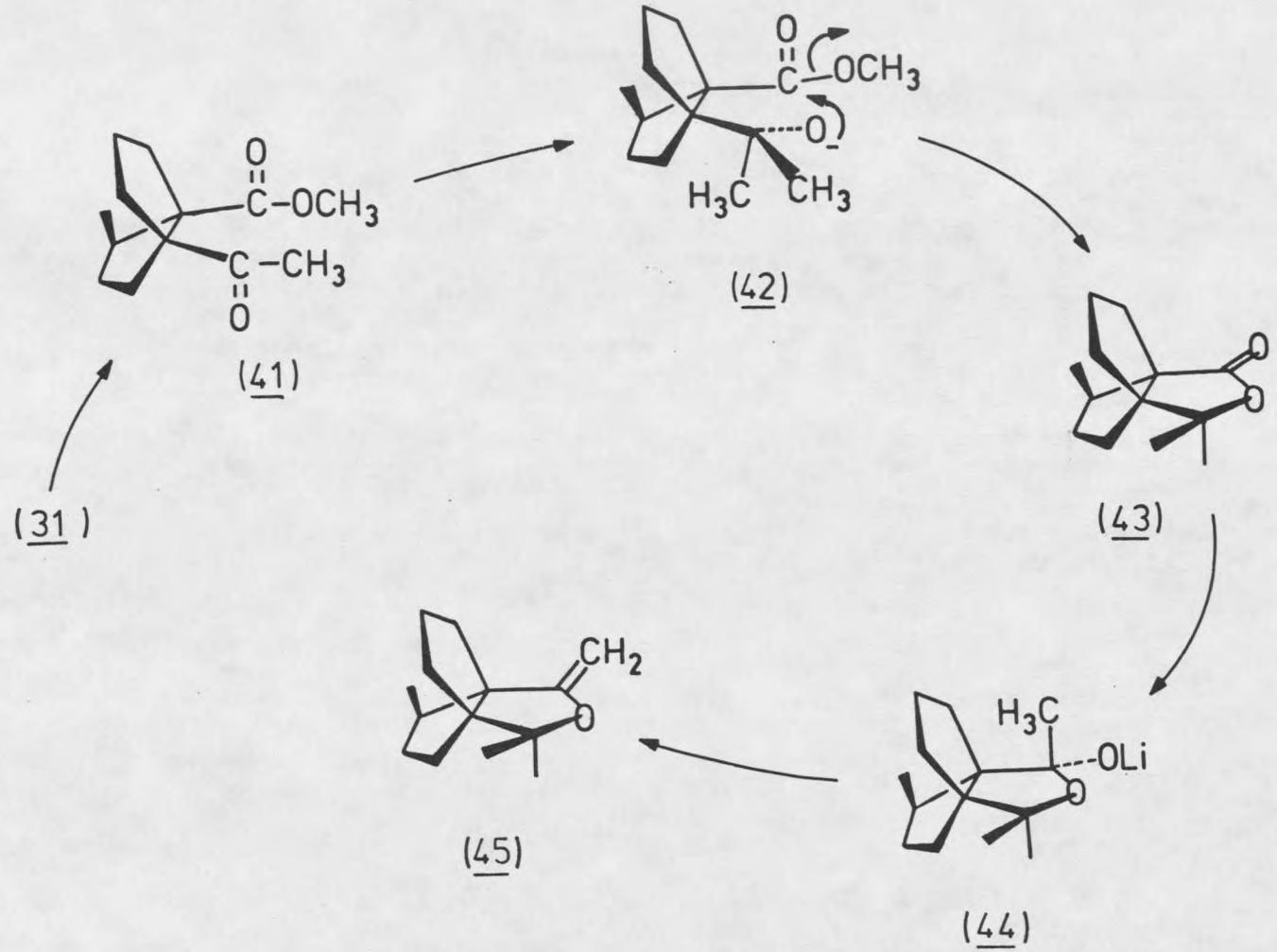
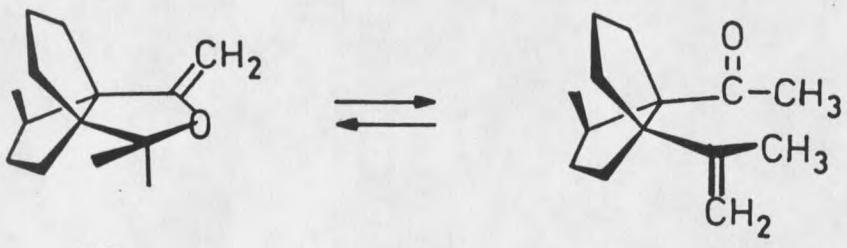


Figure 33. Mechanism of Sequential Addition of Methyllithium to 2-Methyl-(cis)-1,5-dicarboxymethylbicyclo-[3.3.0]-octane

As outlined in this diagram, following initial formation of the methyl ketone (41), subsequent attack by the methyl nucleophile occurred predominantly at the ketone carbonyl to give the alkoxy-ester (42), which cyclized to the lactone (43).

In the presence of excess nucleophile, the lactone presumably underwent further reaction to the hemiketal (44), which due to steric congestion with the beta-methyl group on ring 'B', dehydrated during workup to the vinyl ether (45). The hemiketal itself was not observed under any of the conditions studied.

With the direct preparation of (39) at an obvious impasse, the synthetic utility of the vinyl ether (45) was examined. The keto-olefin (46) depicted in figure 34 was the proposed product of an acid catalyzed ring opening of the vinyl ether moiety.



45 46

Figure 34. Proposed Isomerization of 2-Methylene-3-oxa-4,4,8-trimethyltricyclo-[3.3.3.0]-decane

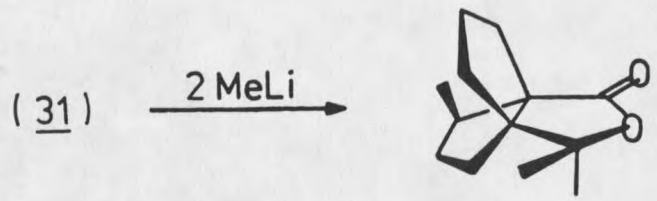
This intermediate was sought on account of the ease with which the vinyl ether could be obtained from the diester, and the manifest resemblance of (46) to the hydroxy-olefin (39) requisite for the proposed cyclization to modhephene. However, all efforts to affect this isomerization were frustrated; gas phase as well as solution chemistry were equally ineffectual and in every case only unreacted vinyl ether was recovered.

The results of this attempted isomerization, in concert with the thwarted synthesis of the diol, portended an inauspicious end to the pursuit of the synthesis of modhephene via the intermediacy of the hydroxy-olefin (39); therefore another avenue of synthesis was examined.

The inherent simplicity of utilizing a nucleophilic addition of methyl lithium to add the required carbons to the diester (31) prompted a consideration of the virtues of the lactone (43) as an intermediate for the synthesis of the target. This impulse was greatly reinforced when exhaustive characterization of a sample of the lactone revealed that it was greater than 95% isomerically pure! This regioselective formation of the lactone (Figure 35) inspired a closer scrutiny of the reaction leading to its formation.

On scale-up of this reaction, when 2.0 equivalents of methyl lithium were slowly injected into a stirred THF solution of the diester (31) at 0°C, a flocculent white solid formed. After a few minutes, the reaction was quenched by adding a few drops of 5% HCl,

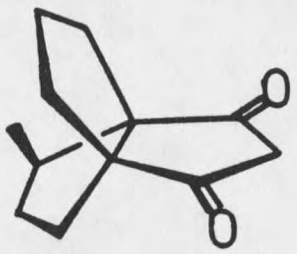
and following extraction, a 60% yield of the lactone was obtained.



43

Figure 35. Synthesis of 2-oxo-3-oxa-4,4,8-trimethyl-tricyclo-[3.3.3.0]-decane

Mass balance considerations indicated that the aqueous phase had retained some product, so it was strongly acidified with concentrated HCl and extracted with ether. This yielded the remaining mass as an off-white colored powder, which was subsequently characterized as the beta-diketone (47) (Figure 36).



47

Figure 36. 6-methyl-2,4-dioxotricyclo-[3.3.3.0]-undecane

In a related experiment, the reaction described above was duplicated in detail with one exception: the methyl lithium was injected into a solution of the diester (31) and 10 equivalents of lithium methoxide generated from methyl lithium and methanol. This experiment provided about 50% of the lactone and 45% of the 1,3-diketone, and was interpreted as implicating the lithium methoxide formed by displacement by the methyl nucleophile at the methyl ester as a base which could then catalyze the condensation to (47) shown in figure 37. The methyl lithium could also act as a base in this context.

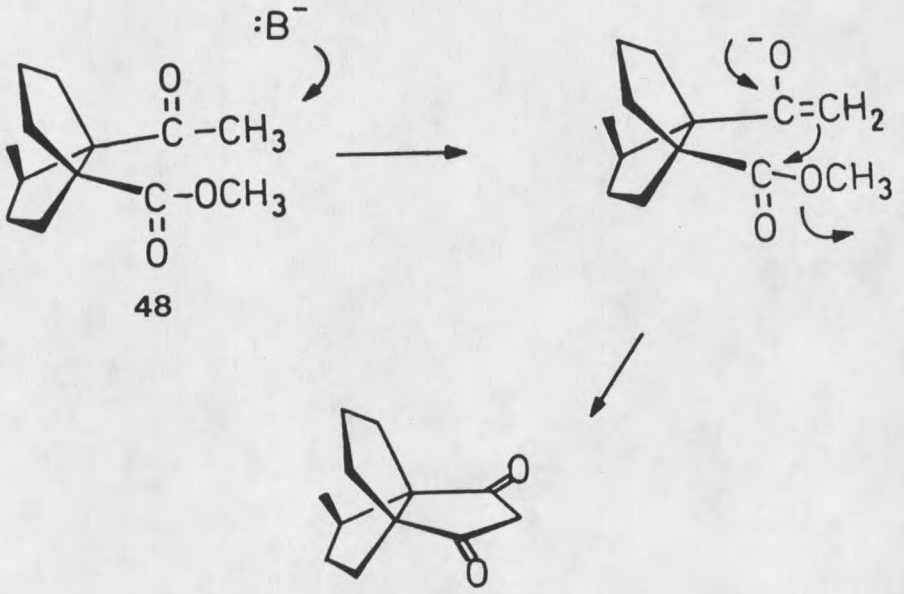


Figure 37. Mechanism of Formation of 6-methyl-2,4-dioxotricyclo-[3.3.3.0]-undecane