The Synthetic Versatility of Titanocene Methylidene Sources and Their Utility in the Total Synthesis of Capnellene

Thesis by

John Robert Stille

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1986

(Submitted November 26, 1985)

©1986

John Robert Stille

All Rights Reserved

To my best friend, Aleta

ACKNOWLEDGMENTS

It affords me great pleasure to take this opportunity to express deep appreciation to those individuals who, unselfishly, made available their time, patience, and understanding during my studies at Caltech. I am beholden to Bob Grubbs for providing this graduate student's dream come true - working in an environment which fosters creativity and individualism. For the innumerable NMR experiments that were successful because of his extra effort, I thank Doug Meinhart; he took the time to treat them as his own. Bernie Santarsiero proved to be an invaluable help. He, along with members of the Ireland group, showed me ways in which my chemical knowledge could develop past the immediate organometallic. My thanks to Scott Virgil for providing his technical abilities on those days when time was of the essence. "Above and beyond the call of duty" is how I describe Laurie Fletcher's professional typing contributions to this thesis. More than her services, she always had a smile and kind word for me. Thank you. To my laboratory partners, Bill, Doug, and Eric, ours was an unusually special lab. I know there'll never be another. "Thanks" doesn't quite cover it.

And to my family, I acknowledge their support in all ways. My parents gave me the blocks upon which to build and encouraged my growth both as a chemist and, moreover, as a person. Their love and confidence have been integral parts of my education. To the most recent addition of my family - my wife, Aleta - I find the words stick and emotions run strong. My productivity and creativity have only increased since our union; her energy, support, and understanding make this thesis as much hers as it is mine. She has given not only her love, but has

been an active participant in bringing this thesis to completion. What does one say to the woman who has been there at all times, who has the ability always to keep life in perspective, who gives because it makes her happy, and who has brought the meaning of marriage and friendship to new heights?

ABSTRACT

The development and application of a synthetically useful metallacycle are described. Using this metallacycle reagent to generate the reactive titanocene methylidene, the methylenation of dialkyl carbonates occurs, producing ketene ketals. The transformation of carbonates to ketene ketals varies dramatically with the O-alkyl substituents on the carbonate. Due to the sensitivity of titanocene methylidene toward steric interference, conversion is substantially higher for dimethyl carbonate than for diphenyl carbonate. Restricting the carbonates to the *s-trans*, *s-trans* conformation, such as in cyclic carbonates, the steric effects are completely overcome.

The reaction of titanocene methylidene sources with acid chloride substrates produces the titanocene chloride enolate of the corresponding methyl ketone. Enolate formation occurs specifically at the methyl group, resulting in only the kinetic enolate, even in a case where the thermodynamic enolate would be stabilized by conjugation to aromatic functionality. Enolate formation with an α-chiral acid chloride followed by hydrolysis showed that less than 0.5% racemization had occurred. The titanocene methylidene selectively attacks the acid chloride functional group even when an ester carbonyl is present. Condensation of the enolate with aldehydes occurs regiospecifically to produce β-hydroxy ketones. Titanocene methylidene also methylenates silyl esters to produce the corresponding kinetic silyl enol ether.

Using a reported method for the generation of bridged titanocene alkylidene complexes, the first trisubstituted titanacyclobutane has been isolated and characterized. A general method by which titanocene alkylidene complexes may be prepared has also beeen investigated. The transmetallation of 1,1-dimetallo complexes of aluminum and zinc to titanocene chloride, forming the heterobimetallic

bridged alkylidenes, was also studied. Although the aluminum complexes do not afford bridged complexes, the 1,1-dizincalkyls appear to undergo transmetallation to give a species which will methylenate ketone functionality.

Cyclopentadiene compounds, tethered to α,β-unsaturated ester functionality, have been prepared by the direct alkylation of the corresponding iodide with cyclopentadienylmagnesium chloride. The cyclopentadienyl Grignard reagent does not display the undesired reactions found to occur with the use of the more basic compounds of lithium and sodium; the organometallic reagent does not catalyze the isomerization of the cyclopentadiene isomers. Alkylation of the iodide is preferred over Michael Addition to the unsaturated ester functional group, but using the corresponding tosylate, conjugate addition is the more prominent reaction. Several functionalized cyclopentadienes are prepared which differed in tether length. These substrates readily undergo intramolecular [4+2] cycloaddition at mild temperatures to produce tricyclic ring systems. The cycloaddition will proceed at even lower temperatures if catalyzed by diethylaluminum chloride. Pathways of cycloaddition favor incorporation of the tether linkage into a five- or six-membered ring.

The reaction of titanocene methylidene with norbornene substrates containing *endo* ester substituents results in metallacycle formation with the strained olefin. The regiochemistry of the cycloaddition to the strained olefin can be completely controlled through the use of a 1-methyl substituent. Thermolysis of these metallacycles proceeds predominantly by ring-opening metathesis of the norbornene substrate to produce a titanocene alkylidene intermediate. This intermediate is subsequently trapped by the intramolecular ester substituent to produce the corresponding bicyclo[3.2.0]heptene enol ether. Similar results are obtained using substituted titanocene alkylidene complexes. The intermedi-

ate trisubstituted metallacycles display an enhanced propensity for ring-opening metathesis to occur.

The synthetic versatility of titanocene methylidene is demonstrated in the total synthesis of $(\pm)\Delta^{(9,12)}$-capnellene from α,α-dimethyl-γ-butyrolactone. Using the intramolecular cycloaddition of the appropriate functionalized cyclopentadiene, the relative stereochemistry of all four asymmetric centers in the natural product is established. Ring-opening metathesis of the resulting strained olefin by titanocene methylidene, followed by intramolecular trapping of the intermediate titanocene alkylidene, produces the required skeleton for capnellene. Only standard modification of existing functionality is required to obtain the reported ketone precursor. Methylenation of this ketone with titanocene methylidene occurs much more efficiently than with the standard Wittig reagent to produce capnellene. This synthesis of capnellene is the first reported to establish the relative stereochemistry of all four asymmetric centers using a single cycloaddition step. The use of titanocene methylidene has led to an efficient synthesis of $(\pm)\Delta^{(9,12)}$-capnellene in 20% overall yield.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES AND SCHEMES

Page

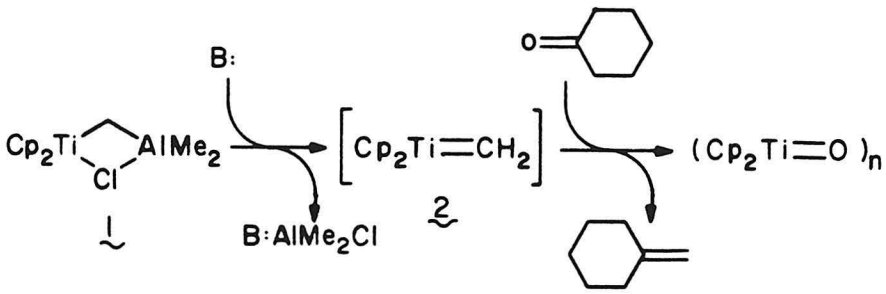
CHAPTER 1

Formation of Ketene Ketals by Reaction of Dialkyl Carbonates with Titanocene Methylidene Sources

Introduction

Formation of the carbon-carbon bond is the backbone to synthetic organic chemistry. Covalently linking smaller molecules allows the construction of larger, more elaborate structures. Of great importance to the fabrication of organic molecules is the homologation of carbonyl functionality in the formation of unsaturated carbon-carbon bonds. The majority of these transformations are accomplished through the use of Wittig reagents, or through one of the many variations of these phosphorous ylides.[1] With the recent advances made in organometallic chemistry, similar transformations were found to occur using alkylidene complexes of the early transition metals. The transition metal ylides of titanium,[2] zirconium,[3] tantalum,[4] and niobium[4] have been shown to react with carbonyl functionality to form olefins.

Investigation into the reactivity of the Tebbe reagent (**1**), the dimethylaluminum chloride complex of titanocene methylidene (**2**), revealed that cyclohexanone was transformed into methylenecyclohexane (eq 1).[2] In addition to

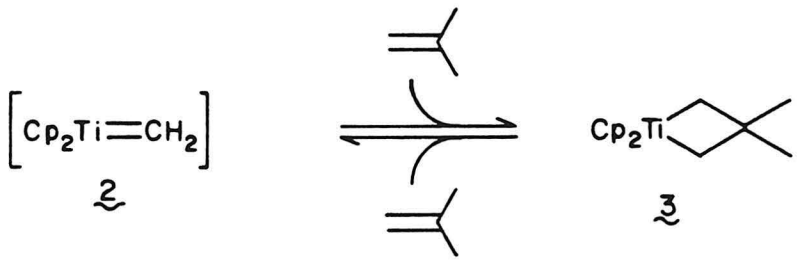


(1)

methylenation of aldehydes and ketones, **1** was also found to convert esters and lactones into vinyl ethers.[2] Because of the importance of this transformation, which cannot be accomplished through the use of phosphorous reagents, **1** has

evolved into a synthetically valuable reagent.[5] The versatility of **1** was further demonstrated by its ability to methylenate amides and imides, producing the corresponding enamines.[6] Due to the efficiency of **1** in the methylenation of esters, the Tebbe reagent has already been used to perform this transformation in the synthesis of natural products.[7] In addition to the unique ability to methylenate esters, **1** does not affect base sensitive functionally as do the phosphorous ylides. Enolizable carbonyl compounds are efficiently converted to the corresponding olefins.[8] Racemization of α-chiral carbonyl stereocenters, which results from use of the basic phosphorous ylides, does not occur upon treatment with **1**.[7a] The use of **1** in a synthetic approach to Lasalocid A was found to be greatly superior to the analogous Wittig reagent.[7a] Recently, the synthetic utility of **1** was further enhanced by the ability to prepare and use this versatile reagent *in situ*.[9]

Titanacyclobutane **3** (eq 2), a complex of **2** with isobutylene, was found to



(2)

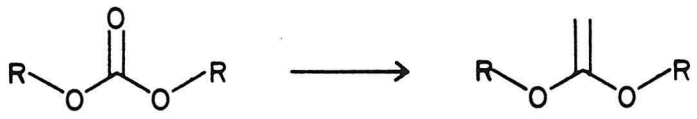
demonstrate similar reaction chemistry.[7a,8,9a] Olefin complexes which are prepared from **1** are certainly not as convenient to use as is **1**; however, the metallacycle has many advantages over the Tebbe reagent as a source of **2**. These advantages stem from the differences between the olefin and the dimethylaluminum chloride adduct, which are produced as by-products of the reaction. Higher yields

demonstrated by the metallacycle reflect the ease with which the product was separated from the olefin in comparison to the aluminum by-products.[8] The greater reactivity of the dimethylaluminum chloride by-product was also found to decompose the sensitive products which resulted from the reaction of **3** with acid chlorides,[10] or anhydrides.[6b] Because the titanacyclobutanes do not require the addition of a Lewis base in order to exhibit behavior of the alkylidene **2**, as does **1**, these metallacycles are also the reagent of choice for investigative NMR reactions. The variety of olefins which can be employed in metallacycle formation, and the varying stability of the resulting titanacyclobutanes, are additional advantages to the use of olefin adducts of **2**.[11] By changing the properties of the olefin, the temperature at which the metallacycle exhibits reactivity characteristic of **2** is also altered. The isobutylene metallacycle (**3**), for example, reacts with ketones at 5°C, whereas the metallacycle resulting from 3,3-dimethylbutene requires temperatures of 60°C.[11]

Both **1** and **3** have proven quite effective in the methylenation of ketones and aldehydes. Demonstrating reactivity beyond that of phosphorous ylides, methylenation has also been achieved in high yield on the more highly oxidized carbon of the carboxylic acid derivatives such as esters and amides. Compared to ketones, however, the reaction with esters was found to proceed more slowly. Competition experiments involving the methylenation of a ketone versus ester carbonyl, using **1**, revealed complete selectivity for the ketone carbonyl.[6a] Metallacycles have displayed similar results.[7a] Selective reaction occurred despite the greater Lewis basicity of the ester carbonyl than that of the ketone, and this trend was expected to continue with the increased oxidation of the carbonyl carbon.

The next highest oxidation state of organic carbonyl functionality is represented by the derivatives of carbonic acid. If methylenation of a dialkyl carbonate

occurs, a 1,1-dialkoxyethene (a ketene ketal) product would result (eq 3). Ketene ketals have been used for a variety of ring-forming processes. The thermal [2 + 2] cycloaddition of a ketene ketal with ethyl propiolate produced a cyclobutene intermediate in the synthesis of (±)-illudol.[12] Cycloaddition with ketones has also



(3)

been reported to occur photochemically[13] or at elevated pressure[14] to produce oxetanes. Reactions with α,β-unsaturated ketones are dependent on the conformation of the conjugated system. When the α,β-unsaturated ketone is confined to the *s-trans* conformation, such as in cyclohexenones, or cyclopentenones, photochemical [2 + 2] cycloaddition with the electron deficient olefin occurs. Cycloaddition to a substituted cyclohexenone produced an intermediate in the total synthesis of paniculides,[15] and similar annulation to cyclopentenones has been developed for application in the synthesis of steroids and tricothecanes.[16] In the *s-cis* conformation, α,β-unsaturated carbonyls undergo [4 + 2] cycloaddition to form substituted pyran derivatives.[17] In addition, allylic ketene ketal compounds are well known for their ability to undergo the Ireland-Claisen rearrangement.[18] Polymerization of 1,1-diethoxyethene with styrene has also been reported.[19]

There are several methods that have been developed for the preparation of 1,1-dialkoxyethene substrates. Dealcoholation of orthoesters of acetic acid has been achieved by pyrolysis[20] and through the use of $Al(OC(CH_3)_3)_3$.[21] Treatment of the orthoester of α-bromoacetic acid with sodium metal produced similar results.[20] Dehydrobromination of the acetal of α-bromo or α-

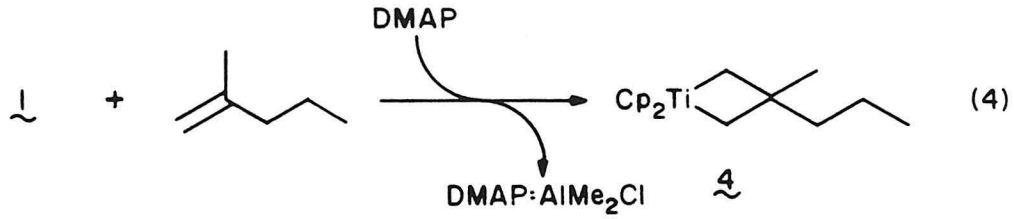
chloroacetaldehyde, however, is the most commonly employed method for preparation of ketene ketals.[20] The direct methylenation of dialkylcarbonates has not been reported, but using an opposite approach, the Horner-Wittig reaction of aldehydes and ketones with dialkoxymethyl diphenylphosphine oxides has produced 1,1-dialkoxyalkenes.[22] The reaction with formaldehyde to form 1,1-dialkoxyethene, however, was not reported. Methylenation of carbonates would provide the most direct synthetic route to 1,1-dialkoxyethene compounds.

To investigate the limitations of **1** and titanacyclobutanes in the reaction with carbonyl functionality, the methylenation of carbonates was examined. For the purpose, the development of a synthetically useful titanacyclobutane is also reported.

Results and Discussion

There has been a wide range of stability demonstrated by metallacycles. For purposes of reaction with carbonyl functionality, however, metallacycles which react in the temperature range of -5°C to 5°C are preferable. Metallacycles which react around 0°C are stable enough to allow facile isolation, yet still allow reaction to occur under mild conditions. With the mild conditions come the desired selectivity of the reagent and the opportunity to observe and isolate sensitive intermediates and products. The titanacyclobutane most used for investigation of substrate reactions with a metallacycle, **3**, is prepared from isobutylene. Because of the symmetrical nature of the regenerated olefin and the occurrence of only two proton resonances, these properties make **3** the reagent of choice for exploratory NMR reactions. For reactions of larger scale, however, the preparation of reagent **3** in large quantities is very inconvenient as it requires the handling of substantial volumes of isobutylene gas. In order for a metallacycle to be appealing as a reagent for organic synthesis, its preparation should not involve any specialized techniques such as measuring volumes of gas. It was apparent that the β,β-disubstituted titanacyclobutanes demonstrated the desired reactivity for synthetic purposes.[11] The olefin selected for this reagent had to be a liquid, yet be volatile enough so that it could be easily removed during metallacycle preparation (-30°C) and during the workup of the methylenated product. Meeting these requirements, 2-methyl-1-pentene was chosen; it is a commercially available liquid with a boiling point (62°C) that allows for easy removal from a reaction mixture.

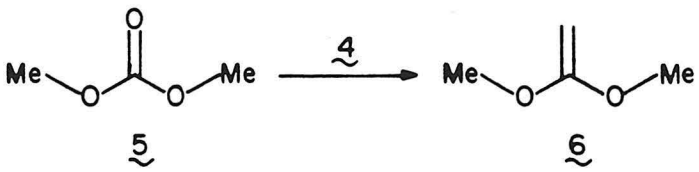
The use of 2-methyl-1-pentene in the preparation of the titanacyclobutane reagent **4** produced quite favorable results (eq 4). After filtration to remove the aluminum-amine adduct, the solvent was removed *in vacuo* at or below -10°C to



(4)

yield a red crystalline solid. This crude solid was isolated in 65% to 75% yield by weight and showed only the metallacycle by ^{1}H NMR. Titration of a solution of **4** with 2.0 equivalents methyl benzoate resulted in the consumption of only 0.78 equivalents (78% metallacycle by weight) of methyl benzoate by ^{1}H NMR. However, comparison of **4** by ^{1}H NMR integration against a known amount of an internal standard, anisole, revealed the powder to be 97% metallacycle by weight. Because of the similarities to the metallacycle of 2-methyl-1-butene, **4** was estimated to be approximately 1.5 kcal/mol less stable than **3**.[11] This difference was reflected by temperature at which these metallacycles were found to react. With carbonyl substrates, **4** was found to react at -5°C while **3** reacted at 5°C. Despite this difference, both reagents produced identical methylenation yields with common substrates, and both were used as sources as **2**. Metallacycle **4** has already been utilized in synthetic transformations.[8]

The effect of **4** as a methylene transfer reagent for carbonates was explored by ^{1}H NMR. Upon warming a mixture of dimethyl carbonate (**5**) and 1.3 equivalents **4** to room temperature, the reaction was complete, as evidenced by the absence of the cyclopentadiene resonance. Methylenation of **5** was accomplished, producing the characteristic 1,1-dimethoxyethene (**6**) olefinic resonance at 3.06 ppm and the methyl peak at 3.19 ppm (eq 5). Comparison of the product to residual starting material (3.31 ppm) by proton integration showed a 62% conversion



5 6 (5)

of **5** to **6** (Table 1). An increase in the relative amount of metallacycle to 1.6 and 1.8 equivalents increased the conversion to only 64% and 65%, respectively. In each of these reactions, metallacycle was absent upon warming the reaction to room temperature, and the only organic compounds observed by ^{1}H NMR were **5, 6** and the olefin 2-methyl-1-pentene. Comparison of **5** and **6** to the

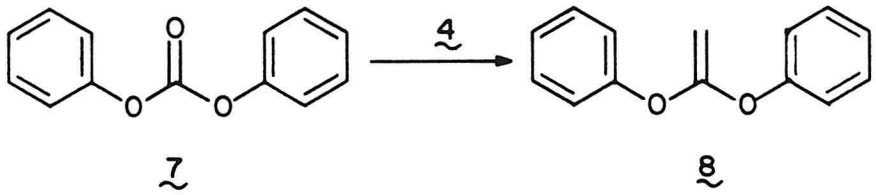
Table I. The Effect of Changing the Equivalents of Reagent **4** on the Conversion of **5**.

4(equivalents)	Conversion (**6**/(**5**+**6**))
1.3	62%
1.6	64%
1.8	65%

2-methyl-1-pentene olefinic resonance by proton integration confirmed that the use of a large excess of **4** was not resulting in the degradation **6**. Using magnetic stirring to perform the reaction of **5** with 1.3 equivalents **4** slightly enhanced

the conversion. Quantification of the products by ^{1}H NMR, using an internal standard, showed that 64% of **5** had been converted to **6**; 30% of **5** was unreacted, and 6% of the substrate was not accounted for. Due probably to the mechanical advantage of magnetic stirring, as opposed to vigorous shaking of the NMR tube, the conversion of this reaction (68%) was slighty higher than that of the reactions in the NMR tubes.

Diphenyl carbonate (**7**) produced even poorer results. By ^{1}H NMR integration versus an internal standard, the conversion of **7** to the ketene ketal **8** using 1.4 equivalents **4** produced only 15% of the ketene ketal (eq 6). The remaining carbonate was not quantified. By placing phenyl group substituents on the carbonate, the conversion to the ketene ketal was greatly reduced. The reduced ability of **4** to methylenate **7** resulted mostly from the increased steric bulk of



7 **8** (6)

the phenyl substituents. Conformational studies, performed by two independent methods, both agree that the favored conformation of **5** is *s-cis, s-cis*.[23] This conformation, which is favored by 2.5 kcal/mol over the *s-cis, s-trans* conformation, is that with the substituents eclipsing the carbonyl oxygen, as shown for structures **5** and **7**. Because of the conformational preference of the carbonates, the carbonyl is very sterically hindered due to the substituents. As seen in Figure 1, for methylenation of the carbonate to occur, the steric interactions between the cyclopentadienyl ligands and the O-alkyl substituents must be overcome.[8]

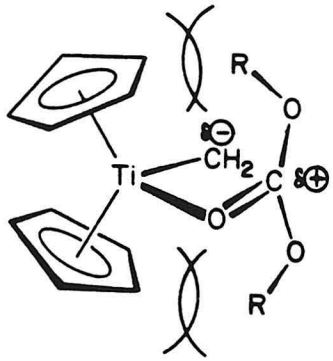
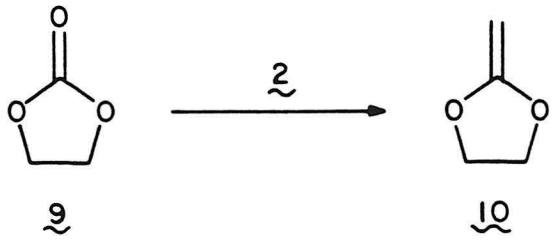


Figure 1. Steric Interactions Between the Cyclopentadienyl Ligands and the O-Alkyl Substituents.

Thus, as the substituent bulk increased from methyl to phenyl, the success of the reaction was significantly reduced.

To overcome this problem, the substituents were restricted to the *s-trans, s-trans* conformation through the use of a cyclic carbonate. Ethylene carbonate **(9)** was completely converted by 1.4 equivalents **4** to the cyclic ketene ketal **10** in 68% yield as determined by NMR integration to an internal standard (eq 7). There was no evidence for any other products by NMR, and all of **9** had



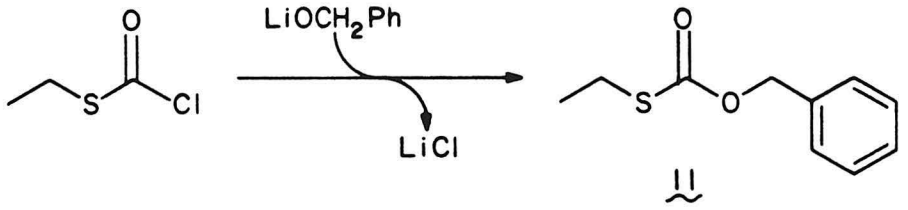
9 **10** (7)

been consumed. A possible fate of the 32% of substrate that was not accounted for was suspected to be due to oligimerization. On a larger scale (1 mmol), **10** was isolated in 56% yield, using 1.2 equivalents **3** as the methylenating agent. Although not pursued, optimization of the reaction conditions, by reducing the equivalents of reagent, was expected to produce an even higher yield.

The steric effects of the O-alkyl substituents greatly impede the reaction of acyclic carbonates with metallacycle sources of **2**. This problem can be controlled through the use of cyclic carbonates, but restrictions such as these limit the utility of a synthetic reagent. For ester functionality, which similarly adopts the *s-cis* conformation,[24] this steric problem was not observed. The methylenation of phenyl benzoate, the ester analog of **7**, proceeded in greater than 95% yield by NMR and allowed isolation of the corresponding enol ether in 94% yield.[5] However, in going from the ester to the carbonate, the electronics of the carbonyl were greatly changed. Replacing a carbon substituent that has an electronegativity value of 2.5, with an oxygen (alkoxy) substituent with an electronegativity of 3.5, the carbonyl oxygen became more basic due to resonance effects. It was suspected that the greater Lewis basicity of the carbonate carbonyl than the ester carbonyl contributed to the rapid deterioration of the methylenation reagent before the steric obstacle of the O-alkyl substituents could be completely overcome. A strong interaction between the very Lewis basic carbonyl and the Lewis acidic titanium metal center (Figure 1) could assist in the unusually rapid decomposition of **4**.

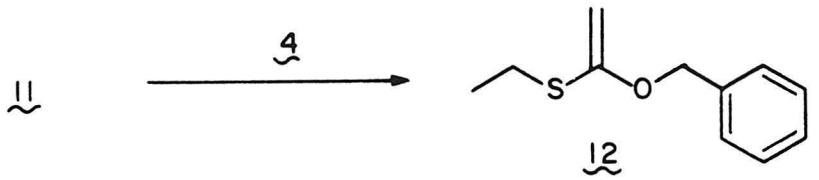
In order to circumvent this problem, a carbonyl substrate of the same oxidation state was prepared that would mimic the electronic characteristics of an ester carbonyl. By replacing an oxygen with sulfur, which has an electronegativity of 2.5, as does carbon, the electronic properties of the highly oxidized

carbonyl would more closely resemble those of an ester carbonyl. The decreased basicity of the carbonyl oxygen might then allow the steric problems inherent in this system to be overcome by the metallacycle reagent. The preparation of **11** was accomplished through the reaction of ethyl chlorothiolformate with lithium benzoate (eq 8). Isolation of **11** was achieved in 83% yield. ^{1}H NMR observation



(8)

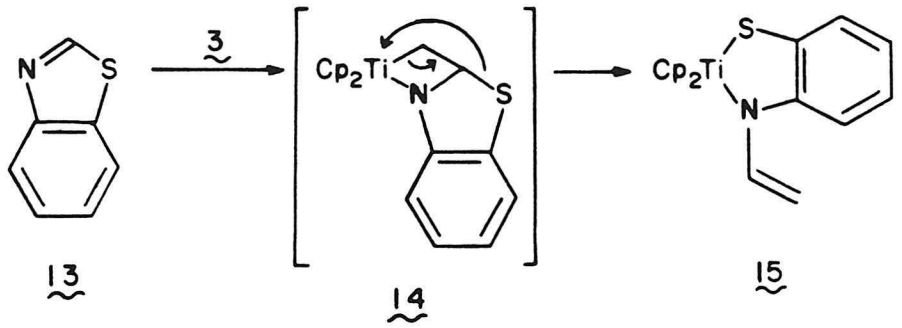
11



(9)

12

of the reaction of **11** with 1.6 equivalents of **4** revealed **11** (44%) and **12** (25%) by integral comparison to the olefinic protons of 2-methyl-1-pentene (eq 9). For substrate **11**, conversion to **12** occurred to an extent of only 36%; however, complications arose. Unidentified products were also produced in addition to the ketene ketal **12**. Although not characterized, the products were suspected to occur as a result of β-elimination of the thiol substituent during the methylenation process. Precedent for this has been established for a similar substrate. Reaction of **13** with **3** proceeded to the proposed intermediate **14**, and then rapidly



13 14 15 (10)

formed **15** by β-elimination of the thiol substituent (eq 10).[25] The structure of **15** was verified by single crystal X-ray analysis. Although the methylenation of **11** was a different process, the similarities suggest β-elimination as an alternative path of reactivity. In any case, the conversion of the carbonate type substrate **11** to the ketene ketal **12** was low due to continued steric difficulties and problems stemming from the leaving group character of the thiol substituent.

For comparison, the methylenation of both **5** and **9** was tried using the Tebbe reagent. The NMR reaction of 1.1 equivalents **1** with **5** produced the desired **6** to a small extent, but many other organic products also formed during the reaction. These by-products interfered with the proton resonances and integration could not be used to calculate a conversion value. A similar reaction with **9** produced only two broad proton resonances due to polymeric product formation. The methylene transfer product, **10**, was not observed.

The use of a metallacycle reagent as a Wittig-type reagent for the conversion of carbonates to ketene ketals was found to be superior to the use of the Tebbe reagent for this process. Because of the delicate nature of the ketene ketal toward the aluminum by-products of **1**, the Tebbe reagent cannot be effectively used to perform this transformation. The transformation of carbonates to ketene ketals using metallacycle reagents varied dramatically with the O-alkyl substituents on the carbonate. Due to the sensitivity of **2** toward steric interference, the

transformation was most efficient for the *s-trans*, *s-trans* cyclic carbonates. As a synthetically useful method, the methylenation of cyclic carbonates using either **3** or **4** showed great promise.

Experimental Section

General Procedures. All manipulations of air and/or moisture sensitive compounds were carried out with use of standard Schlenk or vacuum line techniques. Argon was purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4Å molecular sieves. Solids were transferred in a nitrogen-filled Vacuum Atmospheres Dri-Lab equipped with an MO-40-1 purification train and a DK-3E Dri-Kool. Measurement of weight was conducted after minimizing static interference through the use of a staticmaster ionizing unit (Nuclear Products Company). Flash chromatography was performed according to general procedure of Still,[26] employing Silica Woelm 32-63 (32-63 μm). Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates and visualized by phosphomolybdic acid dip.[27] All reaction temperatures were measured externally.

Materials. 4-Dimethylaminopyridine (DMAP) was obtained from Aldrich Chemical Company, decolorized with activated charcoal, and recrystallized from hot toluene. 2-Methyl-1-pentene was degassed, stirred over sodium-benzophenone ketyl, and vacuum-transferred before use. Preparation of metallacycle **3**[11] and Tebbe reagent[28] were performed according to literature procedure. Anisole was dried over $MgSO_4$ and deoxygenated by bubbling argon through the solution. All other compounds were obtained from the Aldrich Chemical Company and used without further purification. Dichloromethane (CH_2Cl_2) was dried over P_2O_5 and degassed on a vacuum line. Pentane was stirred over H_2SO_4, dried over CaH_2, and vacuum-transferred onto sodium-benzophenone ketyl. Tetrahydrofuran (THF) was dried over CaH_2 and vacuum-transferred onto sodium-benzophenone ketyl. Diethyl ether (ether), toluene, and benzene-d_6 (Cambridge Isotope Laboratories) were degassed and stirred over sodium-

benzophenone ketyl. CD_2Cl_2 was degassed and dried over CaH_2. The dried and degassed solvents were vacuum-transferred into dry vessels equipped with Teflon valve closures and stored under argon. Reagent grade petroleum ether (35-60°C) was used without further purification.

Instrumentation. NMR spectra were recorded on a JEOL GX-400 (399.65 MHz ^1H; 100.40 MHz ^{13}C) or a JEOL FX-90Q (89.60 MHz ^1H; 22.53 MHz ^{13}C). Chemical shifts were reported versus residual solvent signals on the δ scale. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet), coupling constant (Hz) and integration.

Combustion analyses were performed by Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory.

General Procedure for NMR Tube Reactions. An NMR tube was first weighed under static-free conditions in a nitrogen atmosphere. Solids were loaded into the tube, static was removed, and weight was recorded. A latex septum was fitted onto the NMR tube and sealed with Parafilm, and the reaction vessel cooled to -40°C in acetone. Solvent (400 μL) and liquid substrates were added via syringe. The NMR tube was warmed to room temperature by hand warmth and vigorous shaking. Integration standards (anisole or 1,2-dibromoethane) were added via syringe and the products assayed by integration of peak areas. Results of these reactions are described fully in the text of this chapter.

Preparation of 4. To a suspension of DMAP (2.53 g, 20.7 mmol) in 2-methyl-1-pentene (5.89 g, 70.1 mmol) and 15 mL CH_2Cl_2 at -30°C was added to a precooled solution of **1** (5.00 g, 17.5 mmol) in 15 mL CH_2Cl_2. The reaction was allowed to warm to -10°C over the period of 15 min and then cooled again to -30°C. The mixture was then transferred via cannula into 200 mL of vigorously stirred pentane at -30°C. The DMAP·$Al(CH_3)_2Cl$ adduct precipitated

from solution as a yellow-orange mass and was removed from solution by rapid Schlenk filtration maintaining a solution temperature below -10°C. The clear red mother liquor was concentrated to dryness *in vacuo* at or below -30°C to produce 3.35-3.42 g **4** (69-71% yield) as a red powder. This solid was found by ^{1}H NMR integration against an internal standard to contain 97% metallacycle by weight. ^{1}H NMR (90 MHz, CD_2Cl_2, -15°C) δ 5.85 (s, 5H), 5.84 (s, 5H), 2.41 (d, J=9 Hz, 2H), 2.27 (d, J=9 Hz, 2H), 0.91 (s, 3H), 0.75-1.50 (m, 7H). ^{13} C NMR (22 MHz, toluene, -15°C) δ 109.9, 109.7, 80.9, 52.0, 32.7, 18.5, 14.6, 8.4.

2-Methylene-1,3-dioxolane (10). A Schlenk tube, charged with **3** (298 mg, 1.2 mmol) and **9** (88 mg, 1.0 mmol), was cooled to -40°C. After the addition of 4 mL precooled ether, the reaction was allowed to warm to room temperature over the period of 30 min and then was stirred at that temperature for an additional 30 min. Volatiles were vacuum transferred from the reaction mixture. Subsequent removal of isobutylene and ether by distillation under an atmosphere of argon, produced a colorless solution containing minor amounts of precipitate. Vacuum transfer of the volatiles produced 48 mg **10** (56%) as a colorless liquid. Characterization by NMR was in agreement with reported spectral data.[29] ^{1}H NMR (90 MHz, C_6D_6) δ 3.59 (s, 2H), 3.26 (s, 4H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 164.5, 65.4, 54.0.

Preparation of 11. To a solution of benzyl alcohol (2.00 g, 18.5 mmol) in 10 mL THF was added a solution of 7.4 mL *n*-butyllithium (2.5*M* in hexanes, 18.5 mmol) at room temperature. After stirring for 30 min at room temperature, ethyl cholorothiolformate (2.54 g, 20.4 mmol) was slowly added and the reaction mixture stirred for 2 h. The mixture was then filtered through a pad of silica gel and thoroughly washed through with pentane. Isolation through the use of flash chromatography was achieved by eluting with petroleum ether/ether (19:1). The

elutant of R_f=0.43 was concentrated to yield 3.02 g **11** (83%): ^{1}H NMR (400 MHz, C_6D_6) δ 6.99-7.11 (m, 5H), 4.98 (s, 2H), 2.56 (q, J=7.4 Hz, 2H), 1.00 (t, J=7.4 Hz, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 170.7, 135.8, 128.6, 128.5, 128.4, 69.0, 25.9, 15.6. IR (neat) 1711, 1132 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.15; H, 6.11.

References and Notes

(1) (a) Maercker, A. *Org. React. (N.Y.)* **1965**, *14*, 270.(b) House, H.O. "Modern Synthetic Reactions"; Benjamin: Menlo Park, CA 1972; pp. 682-709. (c) Bestman, H.J.; Vostrowsky, O. *Top. Cur. Chem.* **1983**, *109*, 65.

(2) Tebbe, F.N.; Parshall, G.W. ; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(3) (a) Hartner, F.W., Jr.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4979. (b) Hartner, F.W., Jr.; Schwartz, J.; Clift, S.M. *Ibid.* **1983**, *105*, 3270. (c) Clift, S.M.; Schwartz, J. *J. Am Chem. Soc.* **1984**, *106*, 8300.

(4) Schrock, R.R. *J. Am. Chem. Soc.* **1976**, *98*, 5399.

(5) Pine, S.J.; Zahler, R.; Evans, D.A.; Grubbs, R.H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(6) (a) Pine, S.J.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* **1985**, *50*, 1212. (b) Cannizzo, L.; Grubbs, R.H. *J. Org. Chem.* **1985**, *50*, 2316.

(7) (a) Brown-Wensley, K.A.; Buchwald, S.L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhart, D.; Stille, J.R.; Straus, D.; Grubbs, R. H. *Pure Appl Chem.* **1983**, *55*, 1733. (b) Stevenson, J.W.S.; Bryson, T.A. *Chem. Lett.* **1984**, 5. (c) Kinney, W.A.; Coghlan, M.J.; Paquette, L.A. *J. Am. Chem. Soc.* **1984** *106*, 6868. (d) Wilcox, C.S.; Long, G.W.; Suh, H. *Tetrahedron Lett.* **1983**, 395.

(8) Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* **1984**, 5733.

(9) (a) Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* **1985**, *50*, 2386. (b) Chou, T.S.; Huang, S.B.; Hsu, W.H. *J. Chin. Chem. Soc. (Taipei)* **1982**, *30*, 277.

(10) Stille, J.R.; Grubbs, R.H. *J. Am. Chem. Soc.* **1983**, *105*, 1664.

(11) Straus, D.A.; Grubbs, R.H. *Organometallics* **1982**, *1*, 1658.

(12) (a) Semmelhack, M.F.; Tomoda, S.; Hurst, K.M. *J. Am. Chem. Soc.* **1980** *102*, 7567. (b) Semmelhack, M.F.; Tomoda, S.; Nagaoka, H.; Boettger, S.D.; Hurst, K.M. *J. Am. Chem. Soc.* **1982**, *104*, 747.

(13) Koch, H.; Runsink, J.; Scharf, H.D. *Tetrahedron Lett.* **1983**, 3217.

(14) Aben, R.W.M.; Scheeren, H.W. *Tetrahedron Lett.* **1983**, 4613.

(15) Smith, A.B., III; Richmond, R.E. *J. Am. Chem. Soc.* **1983**, *105*, 575.

(16) (a) Jung, M.E.; Hatfield,G.L. *Tetrahedron Lett.* **1983**, 2931. (b) Termont, D.; Keukeleire, D.D.; Vandewalle, M. *J. Chem. Soc. Perking Trans. I* **1977**, 2349.

(17) Dauben, W.G.; Krabbenhoft, H.O. *J. Org. Chem.* **1977**, *42*, 282. (b) Bitter, J.; Leitich, J.; Partale, H.; Polansky, O.E.; Riemer, W.; Ritter-Thomas, U.; Schlamann, B.; Stilkerieg, B. *Chem. Ber.* **1980**, *113*, 1020.

(18) Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(19) Bailey, W.J.; Endo, T.; Shaffer, S.E.; Wu, S.R.; Yamazaki, N.; Yonezawa, K. *J. Macromol. Sci., Chem.* **1984**, *A21*, 979.

(20) McElvain, S.M. *Chem. Rev.* **1949**, *45*, 453.

(21) McElvain, S.M.; Davie, W.R. *J. Am. Chem. Soc.* **1951**, *73*, 1400.

(22) van Schaik, T.A.M.; Henzen, A.V.; van der Gen, A. *Tetrahedron Lett.* **1983**, 1303.

(23) (a) Katon, J.E.; Cohen, M.D. *Can. J. Chem.* **1974**, *52*, 1994. (b) Katon, J.E.; Cohen, M.D. *Ibid.* **1975**, *53*, 1378. (c) Thiebaut, J.-M.; Rivail, J.-L.; Greffe, J.-L. *J. Chem. Soc., Faraday Trans. II* **1976**, *72*, 2024.

(24) Oki, M.; Nakanishi, H.; *Bull. Chem. Soc. Japan* **1971**, *44*, 3144.

(25) Buchwald, S.L.; Clawson, L.E.; Grubbs, R.H., unpublished results.

(26) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(27) Touchstone, J.C.; Dobbins, M.F.; "Practice of Thin Layer Chromatography"; John Wiley & Sons: New York, 1978, p. 207.

(28) Lee, J.B.; Ott, K.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1982**, *104*, 7491.

(29) Taskinen, E.; Pentikainen, M.-L. *Tetrahedron* **1978**, 2365.

CHAPTER 2

The Regioselective Formation and Aldol Condensation of Titanocene Chloride Enolates

Introduction

Enolates are one of the most versatile synthetic tools available to the organic chemist. Using ketone functionality, α-anionic character is easily unmasked by any of the numerous methods available. The enolate can then be used as a nucleophile for alkylation, aldol condensation, or a similar carbon-carbon bond-forming process. One of the most general methods of generating enolates is by deprotonation of the relatively acidic α-hydrogen of a ketone using a strong base of the alkali metals. The resulting enolates can be used as prepared,[1] but are also used in the formation of a variety of other enolate species. Lewis acidic metals, which are ideal for use in enolate chemistry, have found extensive application in organic chemistry.[2]

Of the main group elements used for enolates, the covalent trialkylsilyl enol ethers are the most versatile and have received the most use in synthetic bond formation.[3] There are a vast number of methods by which these enol ethers may be prepared that have been developed due to the significance of this intermediate in organic synthesis. Boron enolates have also received substantial attention involving the aldol condensation reaction and their ability to conduct diastereoselective product formation.[4] More recently, the isolable enolates of tin have been prepared and studied.[5] In addition to these main group enolates, aldol condensation with enolates of the Lewis acidic aluminum were also investigated,[6] although their synthetic use has been limited to the preparation of muscone.[7]

As the enolates of the alkali metals evolved, several of the divalent transition metals also became involved as counterions. The enolates of the Lewis acidic metals magnesium and zinc were easily formed from the corresponding alkali metal enolates.[8] Because these metals were among the best understood in organometallic processes, their enolates could also be generated by other

means, such as through conjugate addition of organometallic reagents to α,β-unsaturated ketones.[9] The reaction of α-bromo carbonyl compounds with zinc, forming the zinc enolate, has received extensive use in the Reformatsky reaction and will slowly react with aldehydes.[10] With the development of organometallic chemistry emerged the untapped potential of the Lewis acidic early transition metals.

Titanium tetrachloride was initially found to activate the cross-aldol condensation of silyl enol ethers with carbonyl-containing molecules. The use of titanium in conjunction with silyl enol ethers has received much attention in the development of synthetic methodology and has found a number of uses in the execution of functional group transformations.[3,11] In many of these processes, enolates of titanium were proposed as intermediates that resulted from the transmetallation of the enol ether from the trimethylsilyl group to the titanium. Enolates of titanium were suggested to participate in not only the cross-aldol condensation reaction,[12] but also in the conjugate addition of trimethyl silyl enol ethers to α,β-unsaturated carbonyl functionality,[13] the coupling of ketene silyl acetal promoted by titanium tetrachloride,[14] and finally, to the reaction of ketene with titanium tetraalkoxide.[15] Only recently was the direct formation of titanium enolates reported. Reaction of titanium halides with enolates of lithium produced titanium enolates, which could be isolated by distillation.[16] This work initiated efforts into the study and characterization of titanium enolates. In the reaction between titanium tetrachloride and silyl enol ethers, the presence of titanium enolates was finally confirmed by NMR.[17] An X-ray structural determination of the titanium-oxygen bound enolate of acetaldehyde soon led to the complete characterization of titanium enolates.[18] Mechanistic studies of the aldol condensation of these enolates have also been reported.[19]

Other examples of transition metal enolates have also been reported. Even before those of titanium, enolates of zirconium were characterized as products resulting from carbonylation of zirconium hydride and alkyl complexes.[20] The reaction of zirconium ketene complexes with ethylene[21] or hydrogen[22] also produced metal enolates. Generation of zirconium enolates by other methods soon found application in synthetic organic chemistry. Conjugate addition of zirconium alkenyl complexes to α,β-unsaturated cyclopentenones resulted in the formation of zirconium enolates which would undergo aldol condensation with formaldehyde and produced a viable route to prostaglandin products.[23] Aldol condensation of zirconium enolates, obtained by reaction of alkali enolates with zirconocene dichloride, has been found to proceed with high *erythro*-selectivity.[24] Enolates of zirconium have also been proposed in the intramolecular conjugate addition of alkali enolates to α,β-unsaturated carbonyl compounds with added zirconium tetraisopropoxide.[25] In the same manner that the carbon-bound[26] zinc enolates were formed, enolates of ruthenium, tungsten, and molybdenum have been prepared by the oxidative addition of α-bromo ketones.[27] These structures were similarly observed to be bound to the α-carbonyl carbon as determined by X-ray crystallographic methods.

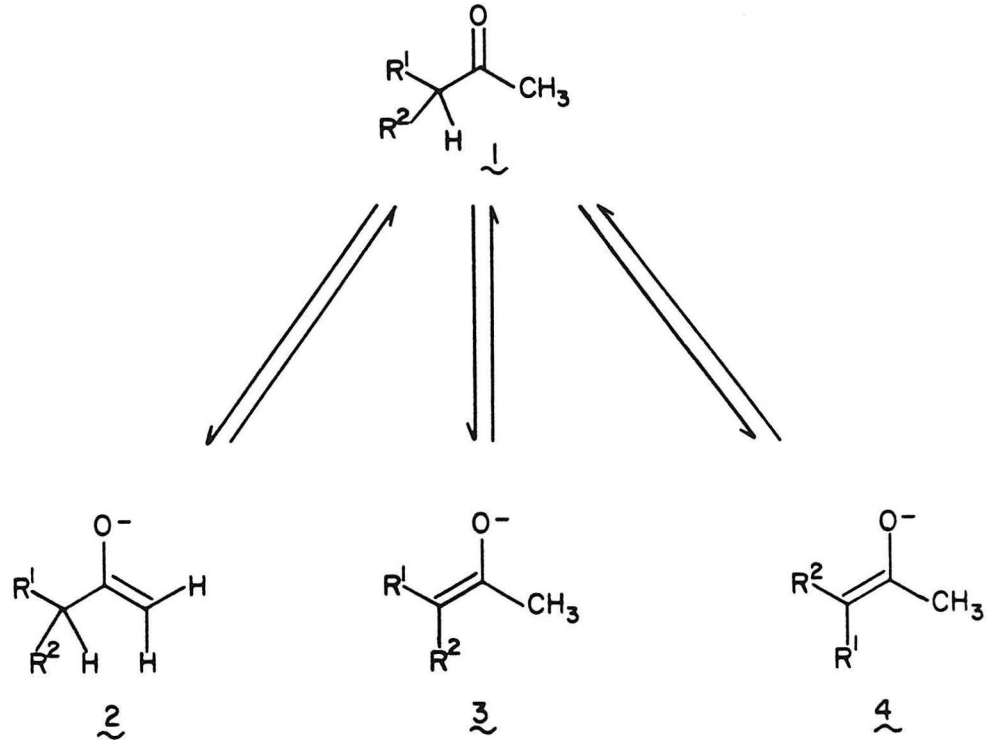
The study of transition metals also uncovered a novel method for the preparation of enolate complexes. From the reaction of tantalum and niobium alkylidene complexes with acid chlorides, enolates of ketones were found to result.[28] This led to our preliminary report on methyl ketone enolate formation from acid chlorides, using a metallacycle source of titanocene methylidene, and the subsequent regiospecific condensation with aldehydes.[29] Subsequently, generation of titanium enolates with an alternate source of titanocene methylidene was reported.[30] Recently, the reaction of zirconium alkylidenes was also found to

transform acid chlorides into enolate complexes.[31] These transition metal enolates, as have many other transition metal complexes in the past, are being incorporated into the arsenal of synthetic methods which can be used to overcome the obstacles encountered in synthetic organic chemistry.

One step beyond enolate generation, the challenge of regioselective enolate formation is encountered. The difficulties that occur are illustrated in Scheme I. Deprotonation of a methyl ketone **(1)**, which has two enolizable α-carbons, produces three isomeric enolates. The kinetic enolate, **2**, is the isomer resulting from the sterically favored deprotonation of the unsubstituted methyl group. The more thermodynamically stable enolates, due to the electron donating properties of the olefinic substituents, are isomers **3** and **4**, which differ in the geometry around the double bond. Enolates **3** and **4** are also different in the rate of their formation and their thermodynamic stability. To complicate the process of deprotonation of methyl ketones, the interconversion of **2, 3**, and **4** can occur in the presence of a catalytic amount of a proton source.

A substantial amount of effort has been directed toward the selective preparation of the thermodynamically less favored enolate **2**.[32] The strategy behind the selective base deprotonation of ketones was to use a bulky base so as to selectively remove a proton from the less sterically hindered methyl group. Using lithium diisopropylamine (LDA) at 0°C, deprotonation of butanone produced only a 71:29 selection for the desired enolate **2a**.[33] Deprotonation by lithium diethylamine/hexamethylphosphoramide (HMPA) at-70°C greatly increased the selectivity (97:3), but aldol condensation yields with this reagent were only moderate.[34] With the more steric *n*-butyl substituent, LDA was more effective (84:16) in the formation of **2b** than **2a** at 0°C,[33] and at -78°C, resulted in exclusive formation of **2b**.[35] For comparison, potasium hydride produced a mixture

Scheme I. Formation of Methyl Ketone Enolates by Deprotonation.



a $R^1 = CH_3$, $R^2 = H$

b $R^1 = n\text{Bu}$, $R^2 = H$

c $R^1 = \text{iPr}$, $R^2 = H$

d $R^1 = PhCH_2$, $R^2 = TMS$

e $R^1 = Ph$, $R^2 = H$

of enolates of which only 46% was **2b**.[36] Deprotonation of the more sterically hindered **1c** by diethylamine at -70°C produced results similar to those obtained for **1a**,[34] whereas the steric anion of triphenylmethane formed the kinetic enolate to an extent of only 75%.[37] In general, the regiospecific deprotonation of methyl ketones has been most successful using hindered amine bases. Variations of these bases have also been developed to further enhance the preference for kinetic enolate formation. Using a dibutylboron triflate complex with diisopropylethylamine, only the boron enolate of the kinetic deprotonation product **2c** was formed.[38] Excellent regioselection has also been achieved using α-silyl ketones to prevent enolization at the substituted α-carbon. Enolization of **1d** resulted in the sole formation of the kinetic enolate.[39]

In spite of the advances in this area, there are still difficulties that arise. Due to the basic reaction conditions, optical activity in α-chiral ketones can be lost through racemization. Limitations of these methods are also encountered when the thermodynamic enolates are stabilized by conjugation. For phenylacetone (**1e**), enolization with LDA has been reported to produce only a mixture of the thermodynamic enolate isomers. The preparation of **2e** has not been reported to contribute to greater than 1% of the isomeric mixture.[33,37]

Solutions to the problems of regiospecific enolate formation have stemmed from two areas of chemistry. The first method involved the use of the regiochemically stable trialkylsilyl enol ethers. In aldol condensation with aldehydes, silyl enol ethers have been activated by titanium tetrachloride, and were found to react with the regiochemical integrity of the silyl enol ether intact.[2,12] Similar retention of regiochemistry was found to result from the fluoride ion-catalyzed aldol condensation.[40] Reaction of alkyllithium reagents with silyl enol ethers,

which produced the corresponding lithium enolates, also reacted with retention of regiochemistry.[41] The second method involved the use of transition metals to form stable enolate complexes by reaction with acid chlorides. In the reaction of acid chlorides with tantalum and niobium alkylidene complexes, regiospecific enolate formation was reported.[28] In a preliminary communication of the reaction of titanocene methylidene complexes with acid chlorides, the regiospecific formation of methyl ketone enolates was also found to result.[29]

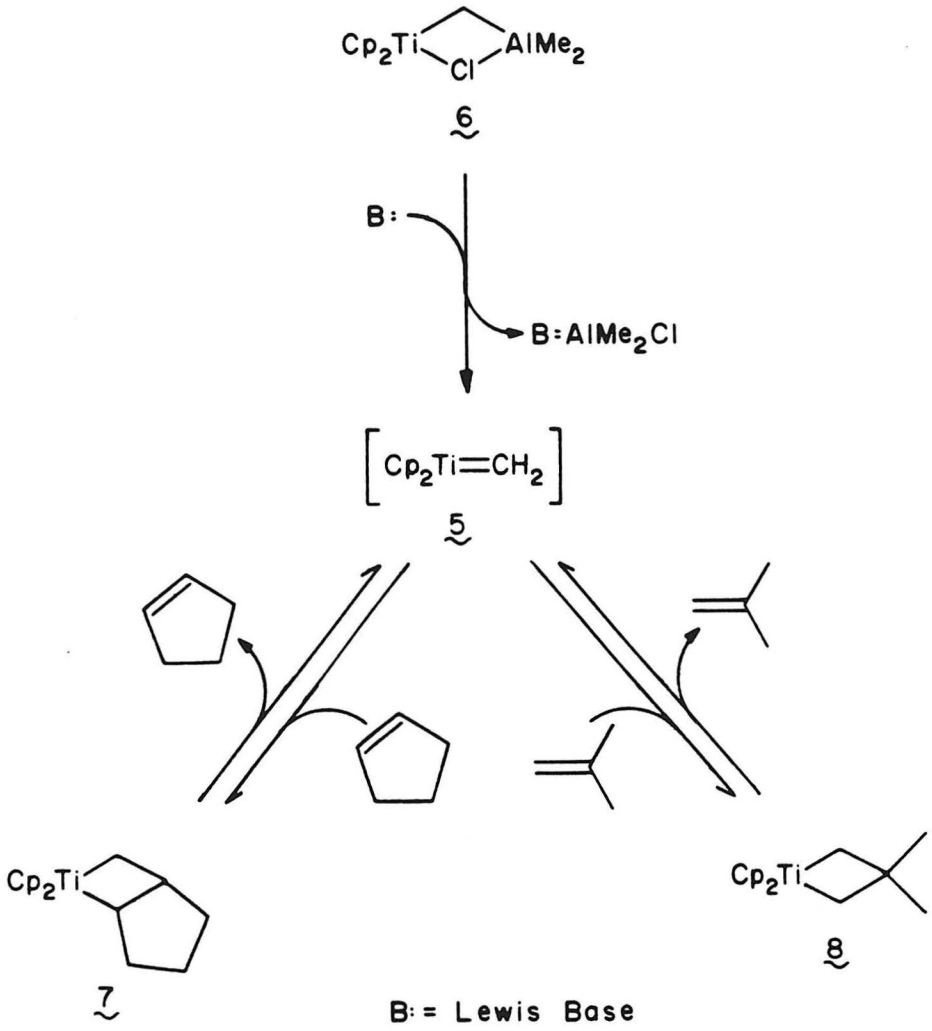
In this work, two applications of titanocene methylidene complexes in the regiospecific formation of the kinetic methyl ketone enolates are reported. First, by reaction with acid chlorides, the kinetic enolates of titanium were formed. These stable enolates were isolated, completely characterized, and their reactivity investigated. During the enolate formation, optical activity of an α-chiral acid chloride was retained. After formation of the complex, isomerization to the thermodynamically more stable isomer was not observed. Acidolysis of these complexes produced the corresponding methyl ketone, while reaction with aldehydes gave regiospecific aldol condensation products. The alkylation of these complexes was also investigated, but limited success was obtained. A second method of regiospecific formation of enolates was achieved by methylenation of silyl esters to give the appropriate kinetic silyl enol ether of a methyl ketone.

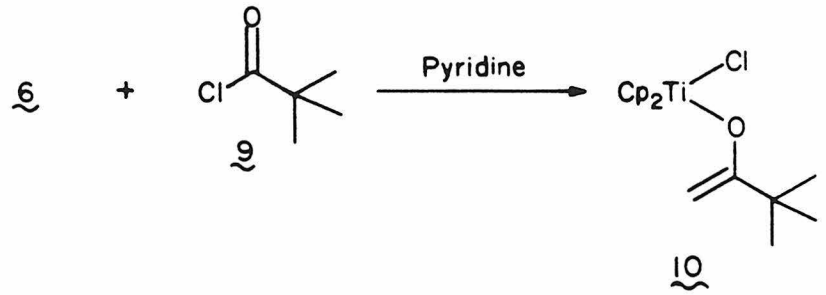
Results and Discussion

Two different methods of generating the titanocene methylidene fragment (**5**) have been reported (Scheme II). All sources of **5** originate from the Tebbe reagent (**6**),[42] which has been demonstrated to be the dimethylaluminum chloride stabilized adduct of **5**. The thermally stable **6** was made labile by the addition of a Lewis base such as 4-dimethylaminopyridine (DMAP). By complexation of DMAP to the Lewis acidic aluminum, the reactive character of **5** was unmasked. This fragment carried the potential to be used in reactions as required, or to be stored as the olefin complex, a titanacyclobutane, from which regeneration of **5** was possible.[43] There were several major advantages to the use of titanacyclobutanes as sources of the fragment **5**. Dissociation of titanacyclobutanes to olefin and **5** was accomplished thermally, and required no additives. The olefin was also much less reactive than the DMAP·$AlMe_2Cl$ adduct generated as a by-product of the Tebbe reagent. Another advantage was the varying stability of metallacycles that could be obtained. Using cyclopentene to generate **7**, a metallacycle was produced, which did not regenerate **5** and olefin until exposed to temperatures of 45°C.[43] On the other hand, the metallacycle of isobutylene, **8**, was thermally unstable at 5°C, regenerating **5** and olefin.

In the reaction of fragment **5** with acid chlorides, each of these three titanocene methylidene sources was examined. A solution of **6** and trimethylacetyl chloride (**9**, pinacolone) in C_6D_6 showed no reaction after 1 h at room temperature by ^1H NMR. After cooling the reaction mixture to 0°C, pyridine was added via syringe, thoroughly mixed at 0°C, and then warmed to ambient temperature. Immediate examination of the reaction mixture revealed the formation of only 18% **10** as found by integral comparison of the olefinic enolate protons at 3.84 ppm and 3.44 ppm to an internal standard (eq 1). After 1 h at ambient tem-

Scheme II. Sources of the Titanocene Methylidene Fragment (**5**).

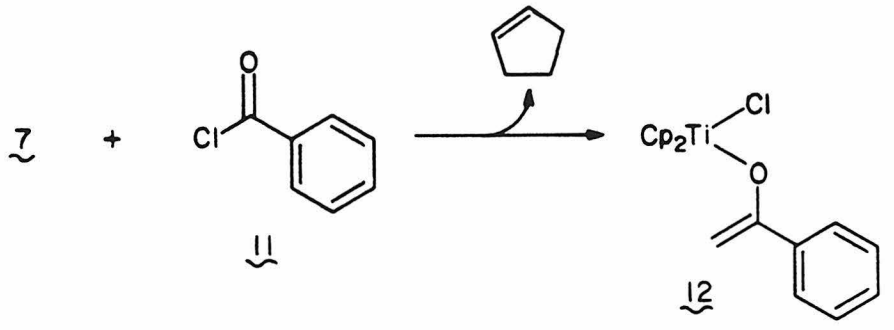




(1)

perature, the resonances due to the enolate protons were absent by ^{1}H NMR; however, vacuum transfer of all volatiles from the reaction mixture under inert conditions produced only the volatile internal standard, anisole. Due to the reactive nature of the pyridine-dimethylalumium chloride adduct, the sensitive titanium enolate rapidly deteriorated.

Regeneration of **5** using metallacycle **7** produced more favorable results. Thermolysis of **7** at 45°C, in the presence of 1.0 equivalent benzoyl chloride (**11**), resulted in the formation of 74% of the corresponding enolate **12**, as evidenced by the presence of enolate protons at 4.32 ppm and 4.77 ppm (eq 2).

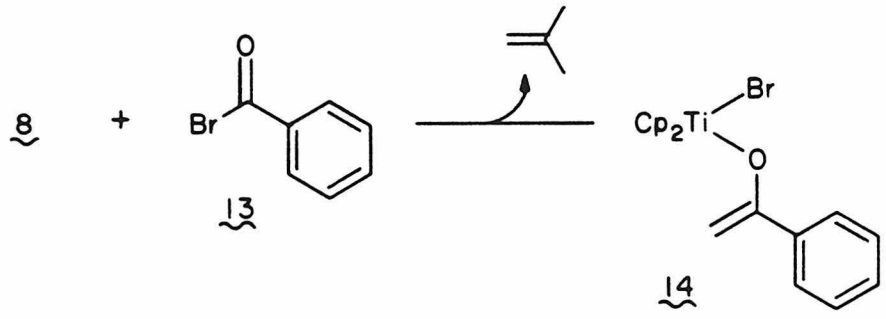


(2)

Continued heating resulted in slow decomposition of the enolate complex. For the purpose of generating fragment **5** under milder conditions, metallacycle **8** was used as the methylidene source. The reaction of **8** with 1.3 equivalents

9, after slowly warming from 0°C to ambient temperature, resulted in a 97% formation of enolate **10** by ^{1}H NMR. Similarly, a quantitative (100%) yield of **12** was obtained upon reaction of **8** with 1.3 equivalents **11**. Using a metallacycle source of **5**, enolate formation was found to be a much cleaner process than using the Tebbe reagent. Addressing this problem, 1.0 equivalent isolated 4-*t*-butylpyridine-dimethylaluminum chloride adduct was added to the enolate complex. Rapid decomposition of the titanium enolate, as evidenced by the disappearance of the olefinic protons, was complete within 20 min. The products of this mixture could not be determined through the use of NMR due to extensive broadening of the proton resonances. Although not a titanocene chloride enolate, the product resulting from the reaction of an acid chloride with **6** has been reported to react as if an enolate.[30]

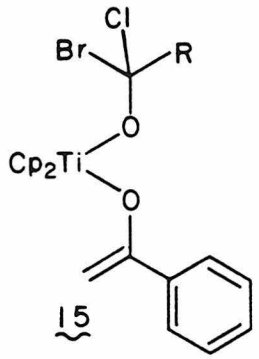
Methyl ketone enolate formation was also found to extend to an acid bromide substrate. The reaction of benzoyl bromide (**13**) with **8** produced the titanocene bromide enolate of acetophenone, which displayed olefinic resonances at 4.78 ppm and 4.34 ppm (**14**, eq 3). Competition between a two-fold excess of **9** and the



(3)

same amount of **13** for the methylidene fragment **5**, resulted in the formation of several enolate products. Of the product mixture, 92% was the result of acetophenone enolate formation. Proton integration of the upfield olefinic protons

of the acetophenone enolate revealed a 2.0:1.0 ratio of **14** to **12**. A set of olefinic resonances was also observed for the pinacolone enolates, which accounted for the remaining 8% of the product mixture. The acetophenone enolate product ratio of 2.0:1.0 displayed no change with time. It appeared from these results that halide scrambling was occurring rapidly to produce an equilibrium mixture of **14** and **12**. Because the only adequate source of chloride for formation of **12** was from excess **9**, the scrambling was proposed to occur by the tetrahedral intermediate **15**. This intermediate, formed by insertion into the titanium-halogen bond, can regenerate the titanocene halide enolates by β-halide elimination.[45,46]



15

The observed ratio of 2:1 was believed to reflect the greater leaving group ability of the bromide in the β-elimination process. Similar competition between **9** and **11** produced a 21:1.0 ratio of **12**:**10**. From these two reactions, the relative rate of reaction for **11** and **13** was calculated by comparison of the formation of acetophenone enolates to the pinacolone enolates for the two reactions. Comparison of the two product ratios suggested that **11** reacted 1.9 times faster than **13**. This value, and its similarity to the ratio of **14** to **12** resulting from halide scrambling, are discussed later, along with the possible relationship to the mechanism of enolate formation.

For purposes of characterization, the titanium enolates were easily formed and isolated. Using typical inert atmosphere techniques, 1.5 equivalents acid chloride were added via syringe to a -20°C solution of **8** in toluene. The solution was allowed to warm to room temperature and was then stirred 5 min. Isolation of the resulting enolate was then accomplished by one of two methods. The enolate complex could be precipitated from solution through addition of pentane and then isolated as a red-orange powder by filtration. Isolation of the complex could also be achieved by removal of the toluene *in vacuo* at 0°C and subsequent washing of the nonvolatiles with pentane. Concentration of the enolate solution at reduced temperature avoided decomposition that occurred upon concentration and isolation at ambient temperature. An alternate method of concentration and isolation involved enolate formation, using benzene as the solvent, followed by lyophilization of the reaction mixture, and washing of the nonvolatile products with pentane. These isolation procedures resulted in yields of 80-90% by weight.

With the exception of **10**, the titanocene enolates were found to decompose slowly with time, even at temperatures below 0°C. As a result, crystallization was accomplished only for **10**. Due to the high solubility of **10**, slowly cooling a toluene solution of the titanium complex from 25°C to -50°C produced only a 25% yield of analytically pure pinacolone enolate. Mixtures of toluene/pentane resulted only in the slow precipitation of **6** from solution. Using diethyl ether, tetrahydrofuran, or methylene chloride as solvent, at temperatures below 0°C, resulted in decomposition of the enolate complex with time.

The isolated enolates were characterized through the use of NMR. The ^{1}H NMR spectrum of **10** is shown in Figure 1. A cyclopentadienyl singlet at 6.35 ppm revealed a symmetrical enolate complex with two inequivalent olefinic protons at 3.46 ppm and 3.86 ppm and the *t*-butyl group at 1.01 ppm. From this

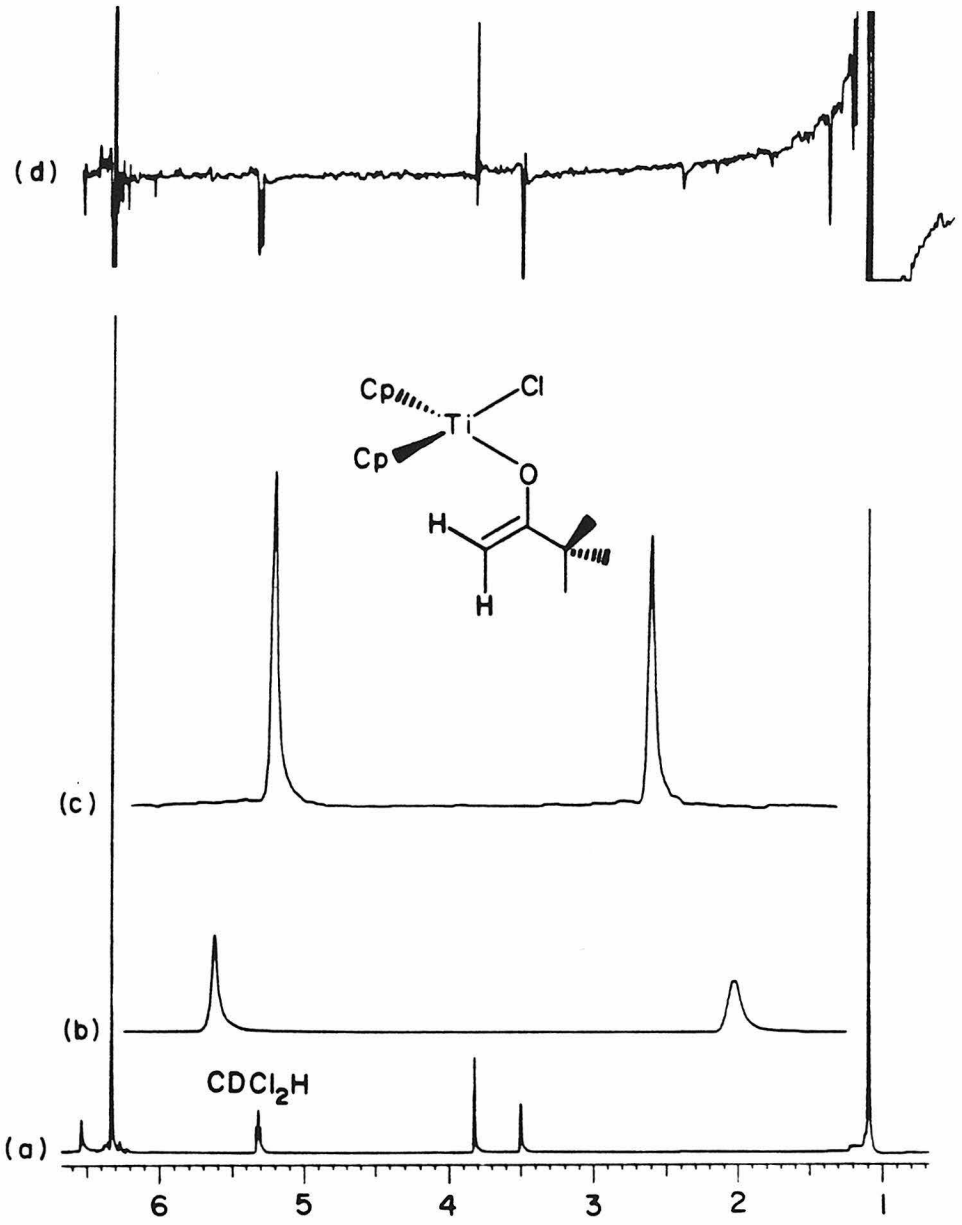
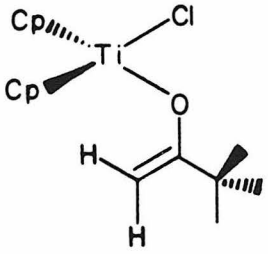
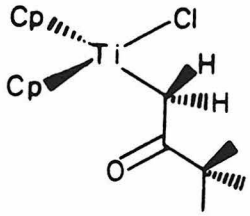


Figure 1. 90 MHz ^{1}H NMR Spectra and Enolate Proton Resonance Assignment of **10** in CD_2Cl_2: (a) ^{1}H NMR Spectrum, (b) Expanded ^{1}H NMR Spectrum of the Enolate Proton Resonances, (c) Expanded Spectrum of the Enolate Proton Resonances with Irradiation of the *t*-Butyl Resonance, (d) Difference NOE Spectrum with Saturation of the *t*-Butyl Resonance.

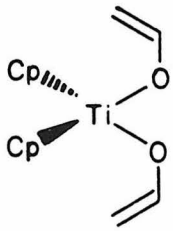
information, **10** was found to be an O-bound enolate rather than the C-bound enolate **16**. Because the enolate protons had such different chemical shifts, while the cyclopentadienyl resonances were equivalent, the C-bound enolate was eliminated as a possible structure. The two olefinic protons, although singlets, showed different peak shape and height. Due to very small, long-range coupling of the *t*-butyl protons to the upfield olefinic proton, this single proton became short and broad (Figure 1). Irradiation of the *t*-butyl group sharpened the upfield olefinic resonance and increased its peak height. Because olefinic coupling to *trans* substituents has been observed to be much greater, the upfield resonance



10



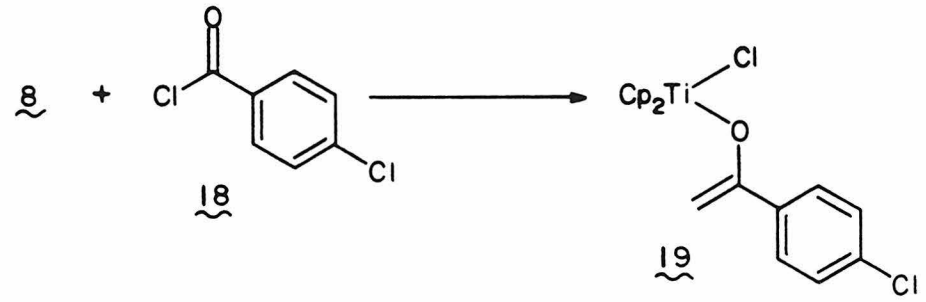
16



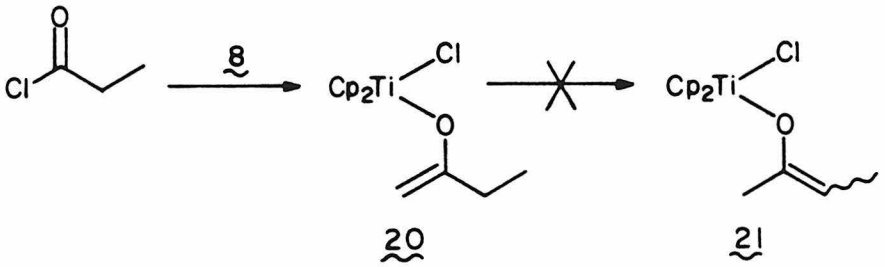
17

was suspected as the proton *cis* to the oxygen substituent. More conclusive evidence was obtained by performing a difference Nuclear Overhauser Experiment (NOE).[47] Saturation of the *t*-butyl group produced enhancement of the downfield proton resonance, which was the proton *cis* to the *t*-butyl substituent, and supported the results of the previous experiment. It was also observed that little enhancement of the cyclopentadienyl resonance had occurred. As a solid, the structure of enolate complex **17** was reported to contain C_2 symmetry, having the conformation with the enolate ligand wrapped around the metal center as illustrated.[18] If adopted by the pinacolone enolate, this conformation would have the orientation illustrated as **10**.

Four titanocene chloride enolates, those of pinacolone, *p*-chloroacetophenone, butanone, and phenylacetone, have been isolated and spectrally characterized. The olefinic proton resonances of **10** at -10°C in CD_2Cl_2, as seen in Figure 1, were found at 3.46 ppm and 3.86 ppm and did not display geminal coupling to one another. As singlets, the cyclopentadienyl ligands and the *t*-butyl group were at 6.35 ppm and 1.01 ppm, respectively. Formation of the *p*-chloroacetophenone enolate (**19**) was accomplished by reaction of **18** with **8** (eq 4). The ^1H NMR spectrum of **19** (Figure 2) revealed that the olefinic protons were shifted down-



(4)



(5)

field relative to the olefinic protons of **10**. A geminal coupling of 0.7 Hz for the enolate protons was also recorded, and the cyclopentadienyl ligands were found at 6.41 ppm. Isolation of the butanone enolate **20** as the only enolate product demonstrated the regiospecificity of this reaction (eq 5). Two olefinic singlets at 3.70 ppm and 3.82 ppm, and an ethyl group with a methylene quartet a 1.97 ppm and a methyl triplet a 0.99 ppm (J=7 Hz), verified the structure as **20**. Isomer-

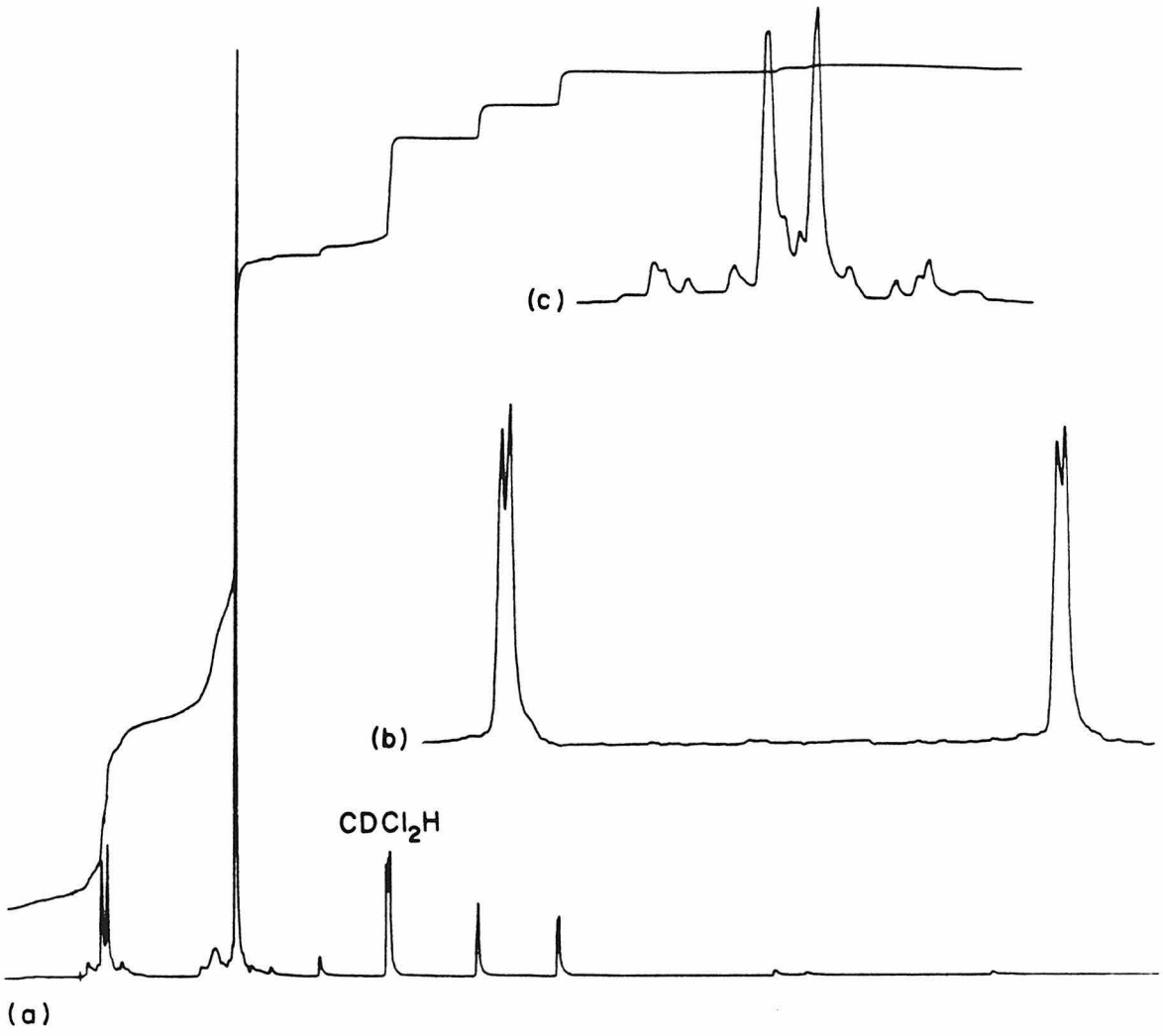
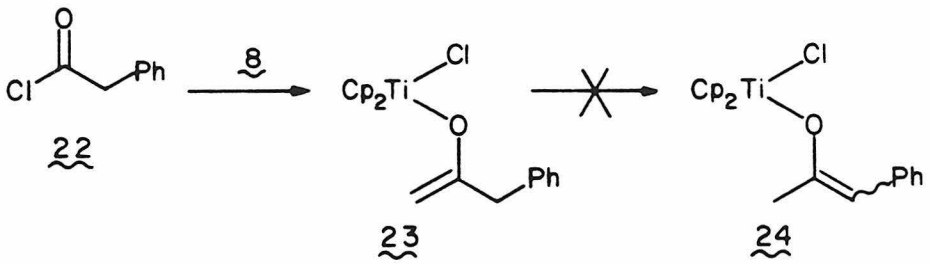


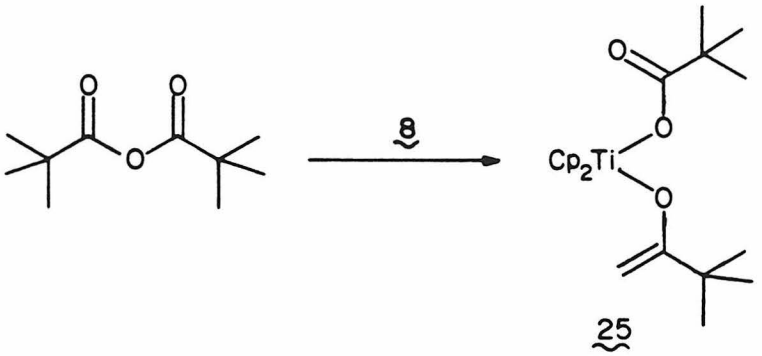
Figure 2. 90 MHz ^{1}H NMR Spectrum of **19** in CD_2Cl_2: (a) ^{1}H NMR Spectrum, (b) Expanded ^{1}H NMR Spectrum of Enolate Proton Resonances, (c) Expanded ^{1}H NMR Spectrum of the Aromatic Proton Resonances.



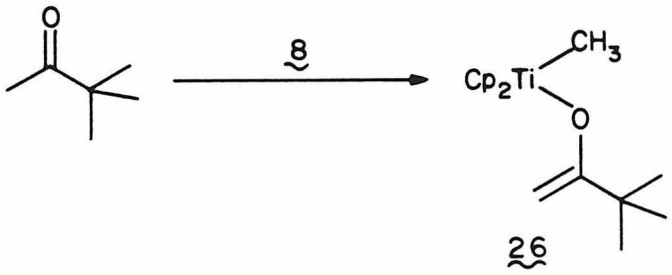
22 23 24 (6)

ization to the thermodynamic enolates (**21**) was not detected. We further tested the regiospecificity of the enolate formation, by allowing phenylacetyl chloride (**22**) to react with **8** (eq 6). Reaction of this acid chloride produced a single enolate complex by ^{1}H NMR. After isolation of this product, this complex was shown to be the same as the product of the reaction mixture by ^{1}H NMR. Geminal methylene proton singlets at 3.85 ppm and 3.96 ppm, along with the methylene singlet at 3.27 ppm, confirmed the product as the kinetic enolate **23**. There was no evidence for isomerization to the thermodynamic enolates (**24**). From the information obtained from these enolate complexes, which are consistent with the chemical shifts reported for other titanium enolates,[11b,18] the reaction of **8** with acid chlorides was shown to result in regiospecific enolate formation.

Two similar routes to formation of titanocene enolates of pinacolone have been developed in this research group. A general method involved the reaction of **8** with acid anhydrides. The reaction of trimethylacetic anhydride with **8** resulted in the formation of enolate **25** (eq 7).[48] This reaction has been found to be general for most acid anhydride substrates. A second method of enolate formation was found to occur upon reaction of sterically hindered ketones with sources of **5**.[49] The reaction of pinacolone with **8** resulted in quantitative formation of enolate **26** (eq 8). Chemical shifts of the olefinic protons in benzene, 3.87 ppm and 3.26 ppm for **25**, and 3.86 ppm and 3.35 ppm for **26**, showed little difference from the



(7)

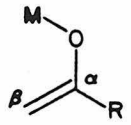


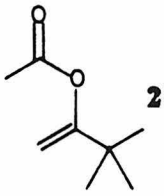
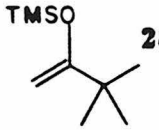
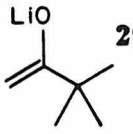
(8)

protons of **10** at 3.89 ppm and 3.42 ppm.

House and coworkers have examined a number of enolates by ^{13}C NMR.[50] They found the chemical shift of the nucleophilic β-carbon of the enolate to reflect the relative electron charge density on that carbon and, thus, its nucleophilicity. Due to the insolubility of the alkali metal enolates, these NMR studies were performed in dimethyoxyethane (DME). A correlation between nucleophilicity and chemical shift was revealed for three enolates of pinacolone (Table I). The enol acetate of pinacolone, **27**, which was the least nucleophilic, was found to have the most downfield chemical shift. Proceeding to the trimethylsilyl enol ether **28** and the lithium enolate **29**, an increase in reactivity paralleled the magnitude of the upfield chemical shift of the β-carbon with respect to **27** ($\Delta\delta$, Table I).

Table I. ^{13}C NMR Data of Enolate Functionality.



Compound	Solvent	C_α(ppm)	C_β(ppm)	$\Delta\delta$(ppm)
10	C_6D_6	182.4	82.4	16.0
	CD_2Cl_2	182.4	82.2	16.2
	DME	182.0	81.3	17.1
25	C_6D_6	182.7	80.8	17.6
	DME	182.5	80.5	17.9
26	C_6D_6	179.2	81.3	17.1
	DME	179.5	80.9	17.5
19	CD_2Cl_2	169.3	87.4	11.0
20	CD_2Cl_2	176.4	84.8	13.6
23	CD_2Cl_2	173.2	87.4	11.0
 **27**	DME	162.2	98.4	0.0
 **28**	DME	166.5	85.5	12.9
 **29**	DME	176.8	73.5	24.9
16	C_6D_6	161.9	87.9	10.5

The titanium pinacolone enolates displayed chemical shifts occurring around 81 ppm for the β-carbon. These three values were located between those of the trimethylsilyl enol ether and the highly reactive lithium enolate. This information suggested that **10** would display a reactivity slightly larger than that of **28**, yet significantly below that of **29**. Although the reactivity of **10** was found to correspond to the predictions made from the chemical shift of the β-carbon, this method was found to be inaccurate for this transition metal system. The reactivity of these enolates was quite dependent on the transition metal center and its ligands. Comparing chemical shifts of **10, 25** and **26** would suggest comparable reactivity toward carbonyl functionality. On the contrary, **10** was found to be much more reactive than **25** in aldol condensation at room temperature, while **26** was completely unreactive toward aldehydes, even at elevated temperatures. Because the titanium metal center and cyclopentadienyl ligands both exhibit substantial shielding and deshielding effects, the use of ^{13}C NMR to predict reactivity of titanium enolates was less accurate than for the non-transition metal enolates. Also included in Table I are the chemical shifts for the enolate functionality of **19, 20, 23,** and **17**.

The infrared stretching frequencies for the carbon-carbon double bond of the enolates were in agreement with those of zirconium enolates.[20] Enolate complex **10** exhibited a frequency of 1620 cm^{-1}. Upon conjugation of the olefin to an aromatic ring, the value was 30 cm^{-1} lower, as expected. The stretching frequency of **19** was found to be 1590 cm^{-1}.

The reactivity of the titanocene chloride enolates was investigated in order to determine the nucleophilicity and the synthetic utility of these complexes. To become synthetically useful, enolate formation with the acid chloride substrate as the limiting reagent had to be efficient. As previously discussed, the quantitative

formation of **12** resulted using an excess of the acid chloride. With the acid chloride as the limiting reagent, optimal enolate formation could be monitored by the amount of methyl ketone obtained upon hydrolysis of the reaction mixture. The methyl ketone product was quantified by gas chromatograph peak integration versus an internal standard. Using **11** as a substrate, the optimal concentration of the substrate and number of equivalents of **8**, required for maximum conversion of the acid chloride to methyl ketone, were determined. From the results of four trials, it became apparent that conversion of substrate to products was most efficient, using 1.2 equivalents of **8** at high reaction concentrations (Table II). Because there was an excess of **8**, a by-product of the reaction, α-methylstyrene (**30**), was also observed. Once the reaction conditions had been optimized for maximum yield of methyl ketone using benzoyl chloride, other substrates were examined.

Due to the differing properties of the acid chlorides, reaction conditions varied slightly for each type of reactant. Typically, 1.2 equivalents **8** were cooled

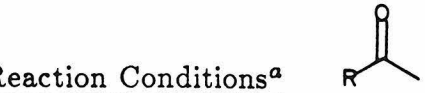
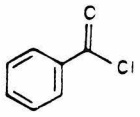
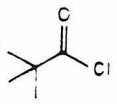
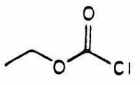
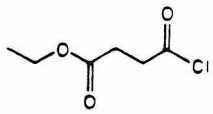
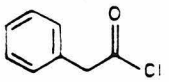
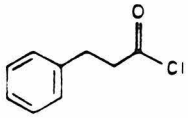
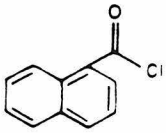
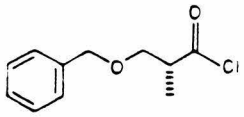
Table II. Dependence of Enolate Formation on the Equivalents of **4** and the Concentration of the Reaction Mixture.

Equivalents	Concentration	Yield (%)		
4	**7**	Acetophenone	α-Methylstyrene	Total
1.50	0.101M	63	6	69
1.24	0.171M	77	8	85
1.07	0.244M	83	4	87
1.20	0.373M	92	8	100

to -20°C and dissolved (0.40*M* solution) in precooled toluene with stirring. The acid chloride was added via syringe and the mixture was warmed to 0°C. At this temperature, titanocene methylidene was generated, allowing the reaction to occur. After a short period of time, as recorded in Table III, the mixture was warmed to a higher temperature so as to ensure reaction completion. Hydrolysis was achieved by cooling the solution to -10°C and introducing 1.5 equivalents HCl gas into the reaction vessel via syringe. All metal precipitated from solution as titanocene dichloride and the supernatant were removed for gas chromatograph analysis or isolation by Kugelrohr distillation.

Transformation of acid chloride substrates to methyl ketones was found to be very efficient for a variety of substrates. Acetophenone was produced to an extent of 92% with the balance of **11** being converted to α-methylstyrene. Although longer reaction times were required for sterically hindered acid chlorides, such as **9**, formation of the methyl ketone was very high, and essentially no olefin by-product resulted. Reaction with ethylchloroformate produced much poorer results; formation of ethyl acetate was achieved in only 48% yield. Even though the olefinic by-product was not detected, substantial amounts of ethanol and several other unidentified products were observed by gas chromatograph analysis. The low yield was attributed to the ability of the ethoxide substituent to act as a β-alkoxide leaving group during enolate formation. Selective reaction of bifunctional substrate **31** was also accomplished using **8**. Formation of the corresponding methyl ketone, ethyl levulinate, was achieved in 89% yield. Olefinic by-products of the ester functionality or the ketone carbonyl were not detected. Conversion of **22** to phenylacetone was 97%, with the balance of the substrate resulting in the olefinic by-product. Isolation of the methyl ketones of **32** and **33**, free of olefin by-product, was easily accomplished in high yield by Kugelrohr dis-

Table III. Methyl Ketone Yields from Hydrolysis of Titanocene Chloride Enolates.

	Acid Chloride	Reaction Conditions[a]					
		0°	3°	15°	20°	Yield(%)[b]	Yield(%)[e]
	**11**	2		5		92[c]	8
	**9**	5			75	96[c]	0.3
		5			15	48[c]	<0.1
	**31**	5	6			89[c]	<0.5
	**22**	5	45			97[c]	3
	**32**	5	45			87[d]	
	**33**	3		5		92[d]	
	**34**	10	45			76[d]	

[a]The numbers reported for each acid chloride are the times, in minutes, that the reaction was allowed to stir first at 0°C and then at a second, higher temperature.

[b]Based on the amount of acid chloride added.

[c]Yield was determined by quantitative VPC analysis.

[d]Yield of isolated product from 1mmol of acid chloride.

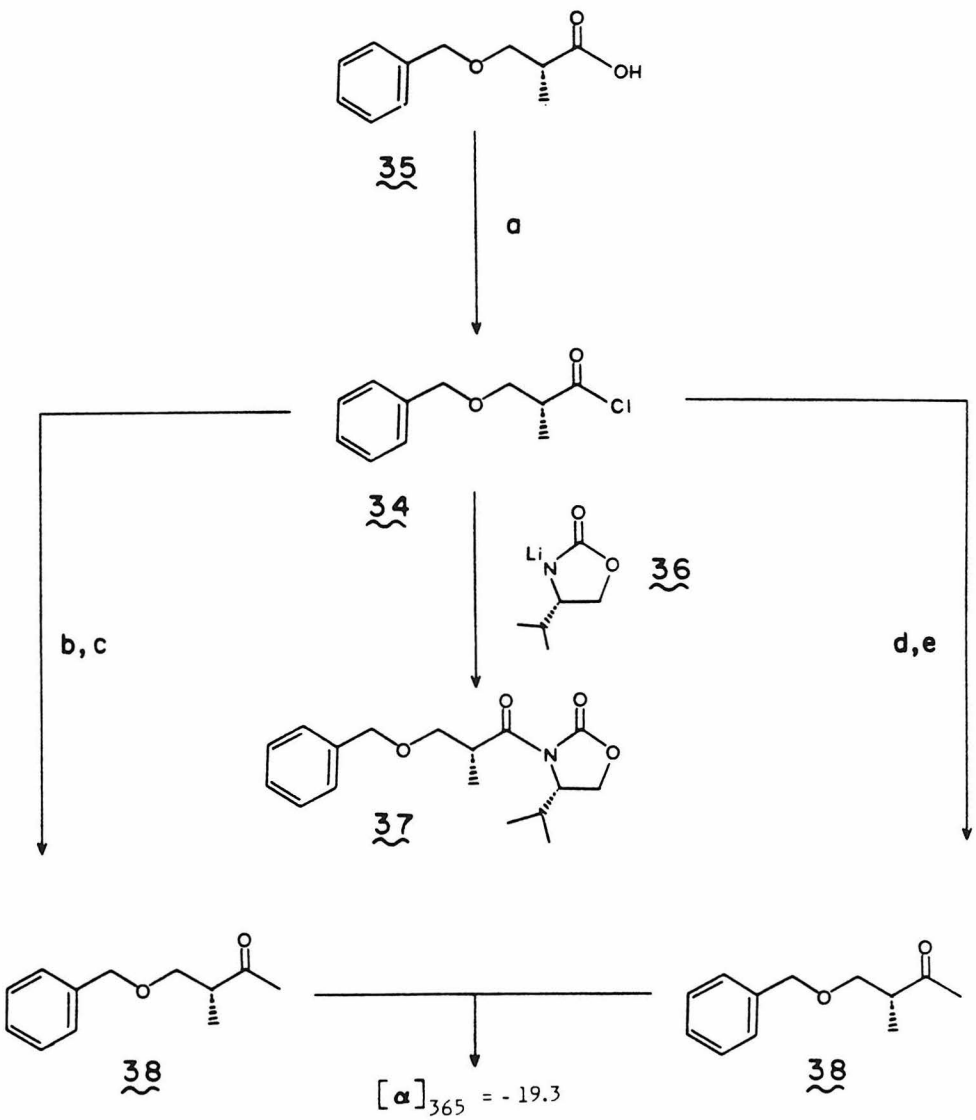
[e]Not quantitated for reactions where isolated yield of methyl ketone was obtained.

tillation at reduced pressure. These yields, obtained by enolate formation with **8**, were substantially greater than those reported for the reaction of acid chlorides with **6**.[30]

The last entry in Table III, **34**, illustrated the enormous potential of **8** as a reagent for enolate formation. Enolate formation by base deprotonation has been found to racemize α-chiral centers by proton abstraction. If this process were to occur, it would greatly reduce the efficiency of the synthetic procedure and complicate the isolation of the desired product by requiring difficult separation processes. Although the reaction of **8** with **22** produced only **23** (eq 6) and showed that no isomerization to enolate **24** had occurred, the reaction of **34** with **8**, followed by hydrolysis of the enolate, was a very sensitive test of enolization at the α-chiral center.

The required acid chloride, **34**, was readily prepared through the conversion of 99.2% optically pure **35** by oxalyl chloride in CH_2Cl_2 (Scheme III).[51] During the transformation to the acid chloride, a small amount of racemization, took place under the reaction conditions. To assay the extent to which racemization had occurred, the acid chloride mixture was treated with the lithium salt of (4S)-4-(2-propyl)-oxazolidin-2-one (**36**). By this procedure, the acid chloride enantiomers were transformed into a mixture of diasteomers. Analysis of the mixture by capillary gas chromatography revealed a 95.2:4.8 mixture of products, of which **37** was the major isomer. Using this method of assaying the acid chloride, it was found that conversion **35** to **34** had occurred with slight racemization producing 95.2% optically pure acid chloride. The remaining portion of **34** was divided into two samples and both fractions were transformed into the methyl ketone **38** by independent methods. A toluene solution of **34** and **8** was allowed to stir at 0°C for 10 min and then at 15°C for 30 min before being quenched

Scheme III.[a] Absence of Racemization of an α-Chiral Acid Chloride Asymmetric Center During Enolate Formation and Hydrolysis.



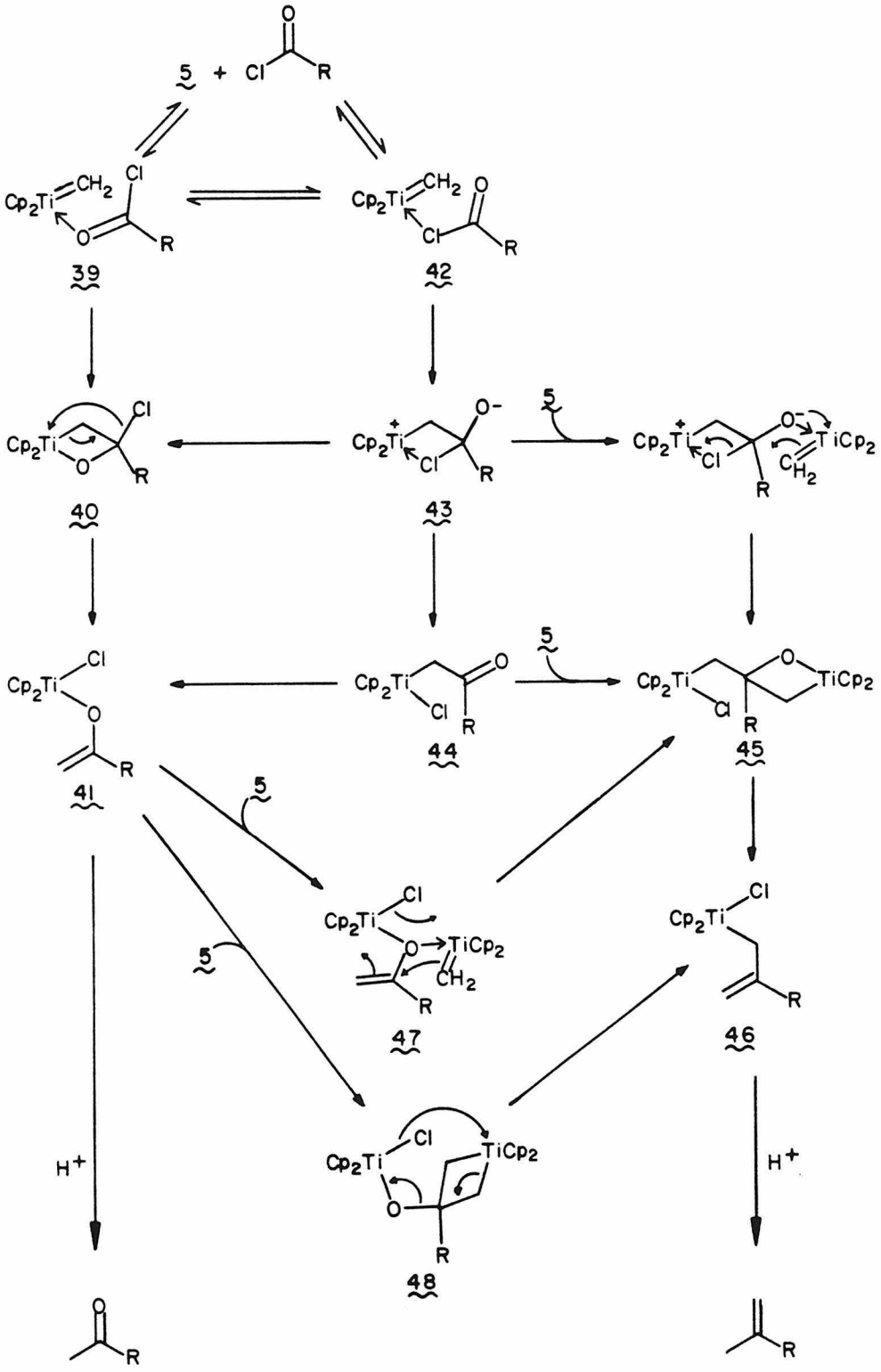
[a](a) $ClCOCOCl$, CH_2Cl_2, 0°C; (b) **4**, Toluene, -20 to 3°C; (c) NH_4Cl, H_20 (76%); (d) Me_2CuLi, Et_2O, -78°*C*; (e) MeOH, -78 to 25°C (72%).

with saturated aqueous ammonium chloride. Isolation by Kugelrohr distillation provided a 76% yield of **38**.[52] The other acid chloride sample was transformed to **38** through the use of $(CH_3)_2CuLi$, a reagent shown not to racemize α-chiral centers.[53] Comparison of the two independently prepared samples of **38**, by optical rotation, showed that less than 0.5% epimerization had occurred in the sample prepared by enolate formation. Correcting for the enantiomeric impurity of the starting acid chloride, the optical rotation of enantiomerically pure **38** was $[\alpha]_{365}$ = -19.3 (31 mg/mL). The retention in asymmetric configuration confirmed the fact that isomerization of the α-chiral center did not occur and that enolate formation was regiospecific.

The formation of olefinic by-products, such as α-methylstyrene in the reaction of **11** with **8**, was unexpected. If methyl ketone was produced under the reaction conditions, then methylenation by the excess metallacycle reagent would account for the olefinic by-product. As previously described, enolate formation using an excess of acid chloride was quantitative and did not generate free methyl ketone. Although no conclusive mechanistic information was obtained, the formation of the olefin product could be rationalized without involving free methyl ketone. Similarly, the possible mechanism of enolate formation from acid chlorides follows.

The initial complexation of the acid chloride could occur in two ways. Interaction of the oxygen of the carbonyl with the Lewis acidic metal center, **39** would result in the oxametallacycle **40** (Scheme IV), as proposed for the reaction with ketones.[49] By an intermolecular or intramolecular β-chloride elimination process, which has been found to occur in similar systems,[45] rearrangement would produce the observed enolate complex **41**. On the other hand, complexation of the acid chloride to the metal center by the halogen (**42**) provides a route to

Scheme IV. Proposed Pathways for Titanocene Chloride Enolate Formation and Generation of Olefin By-product.



complex **43** which would either undergo β-chloro elimination to give the carbon-bound enolate **44** or close to give **40**. If **44** is produced, rearrangement of **44** to **41** is expected to be rapid due to the oxophilic nature of the metal center. Based on past observations of the reactions of **5** with carbonyl functionality, these pathways, or some modification or hybrid of them, appear to be the most likely route of enolate formation.

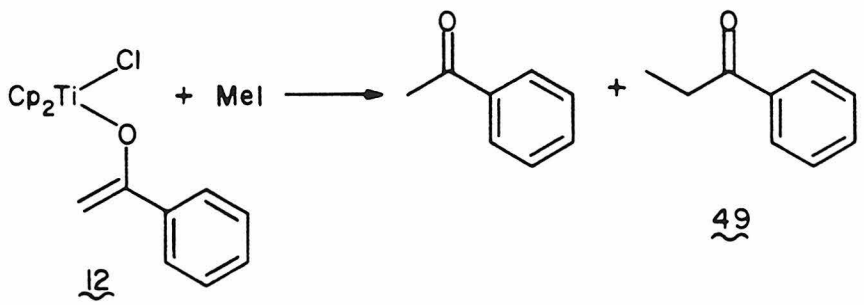
The greater reactivity of benzoyl chloride than of benzoyl bromide could have resulted from one or more of a number of reasons. The greater donor ability of chlorine would result in a stronger complexation in **39** and more rapid formation of **40**, through intramolecular attack of the more electropositive carbonyl carbon. Similarly, the more nucleophilic chlorine would favor formation of **42**, in comparison to the acid bromide, and as the formation of **40** from **39** was enhanced, reaction of complex **42** producing **43** would also be more favorable. Because the formation of **40** or **43** was not a reversible process, the rate at which the acid halide reacted to form these complexes determined the product ratio. The rate at which **40** or **43** underwent β-halide elimination had no effect on the product ratio.

From these routes and their intermediates, the release of the olefinic by-product upon hydrolysis can be rationalized. Intermolecular attack of either intermediate **43** or **44** would produce the oxametallacycle **45**, which results in the formation of the allyl complex **46**. Similarly, formation of **45** could occur by reaction of the coordinated species **47**. An alternate route would involve the direct reaction of the nucleophilic titanium enolate **41** with excess **5**, which would form the metallacycle **48**. Subsequent intramolecular rearrangement would likewise produce **46**. Although investigation of the mechanism of this reaction has not been initiated, the pathways seen in Scheme IV provide a plausible

explanation for the formation of both the methyl ketone product and olefinic by-product.

Probing the nucleophilicity and reactivity of the titanocene chloride enolates, the titanium complexes were treated with alkylating agents. The proposed titanium enolates, formed by reaction of **6** with acid chlorides, have been reported to alkylate with MeI to an extent of 25% in refluxing DME/HMPA (10:1).[30] These studies were performed on the enolate mixture containing the aluminum by-product. For isolated enolates, the reactivity was somewhat different. Heating a solution of **10** and 2.0 equivalents MeI in benzene at 70°C for 18 h showed no change in substrates by ^{1}H NMR. The expected product of alkylation was not detected. The absence of alkylation products was also observed by NMR for the reaction of 1.2 equivalents allyl bromide with **10** in benzene. After 43 h at 70°C, complete scrambling of halides had statistically occurred with no measurable halide preference. Again, no alkylation was observed. The product mixture consisted of the titanocene bromide and chloride enolates, allyl chloride, allyl bromide, and about 30% pinacolone that had been generated by enolate decomposition. Treatment of the enolate with benzyl bromide also resulted in the scrambling of halides and no detectable alkylation.

Because benzene is not known for its ability to promote substitution reactions as compared to the etheral solvents, the use of dimethoxyethane (DME) was examined despite the rapid enolate decomposition that has been observed in these solvent systems. Treatment of a solution of the less hindered enolate **12** with 2.0 equivalents MeI for 12 h at ambient temperature resulted in a heterogeneous mixture. During the course of the reaction, red precipitate had fallen from solution, leaving a lightly colored supernatant that showed no evidence of remaining enolate. The supernatant was analyzed by capillary gas chromatog-

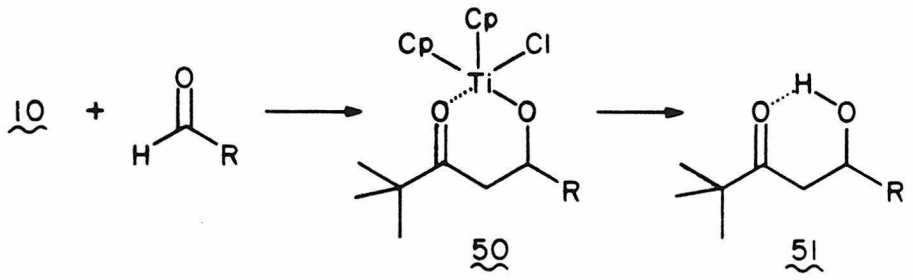


(9)

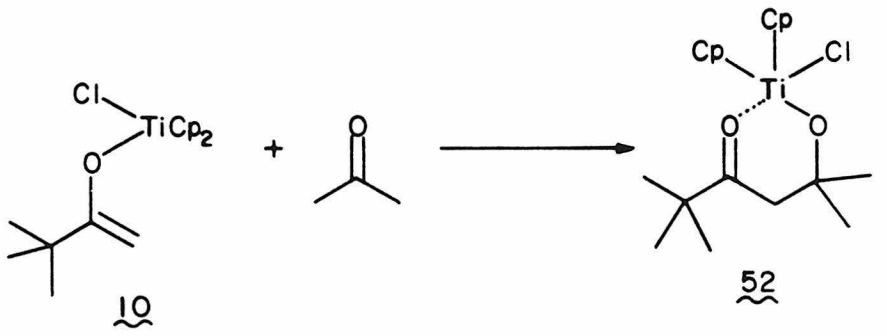
raphy and found to consist of a 96:4 mixture of acetophenone to the alkylation product **49** (eq 9). Because the reports of alkylation of enolates formed from the Tebbe reagent were suspected of involving participation by the aluminum by-product, there existed possibly an aluminum enolate[6] producing the alkylation product. Addition of 1.0 equivalent dimethylaluminum chloride to a solution of **10** in DME produced immediate results. Solids, characteristic of titanocene dichloride, precipitated from the lightly colored solution. After the addition of MeI, the mixture was allowed to react for 12 h at ambient temperature. Analysis by capillary gas chromatography revealed a 89:11 ratio of acetophenone to alkylated product **49**. These results suggested that aluminum helped the alkylation proc-ess, however, as evidenced by the conversion of substrate to alkylated product, this enolate was not as nucleophilic as its reported titanium counterparts.[12–17]

Acylation of the titanocene chloride enolates was less successful than alkylation of these complexes. In benzene, the treatment of **10** with the acid chloride **22** produced complete decomposition of the enolate to pinacolone and titanocene dichloride. The only organic product containing a phenyl group, after hydrolysis, was phenyl acetic acid. Similar results were observed for the treatment of **12** with **11** in DME. The expected product of C-acylation was not detected by ^{1}H NMR, although the O-alkylation product could be formed in this reaction.

The inferior nucleophilicity of the titanocene chloride enolates was also demonstrated by their reactivity in condensation with aldehydes. Enolates formed using titanium tetrachloride[12] or zirconocene dichloride[23–25] react with aldehydes at -78°C to yield aldol condensation products. For the titanocene chloride enolates, temperatures between 0°C and 25°C were required for aldol condensation to proceed at an appreciable rate. With aldehydes, the reaction of **10** was monitored by ^{1}H NMR and found to produce the β-keto alkoxytitanocene



(10)



(11)

intermediate **50** (eq 10). A spectrum of intermediate **50a**, as a result of the reaction of **10** with pivaldehyde, is shown in Figure 3. Hydrolysis of this intermediate yielded the corresponding β-hydroxyketone product **51a**. Condensation was also observed to proceed with ketones, as evidenced by the reaction **10** with acetone (eq 11). In comparison to an internal standard, the reaction with acetone was

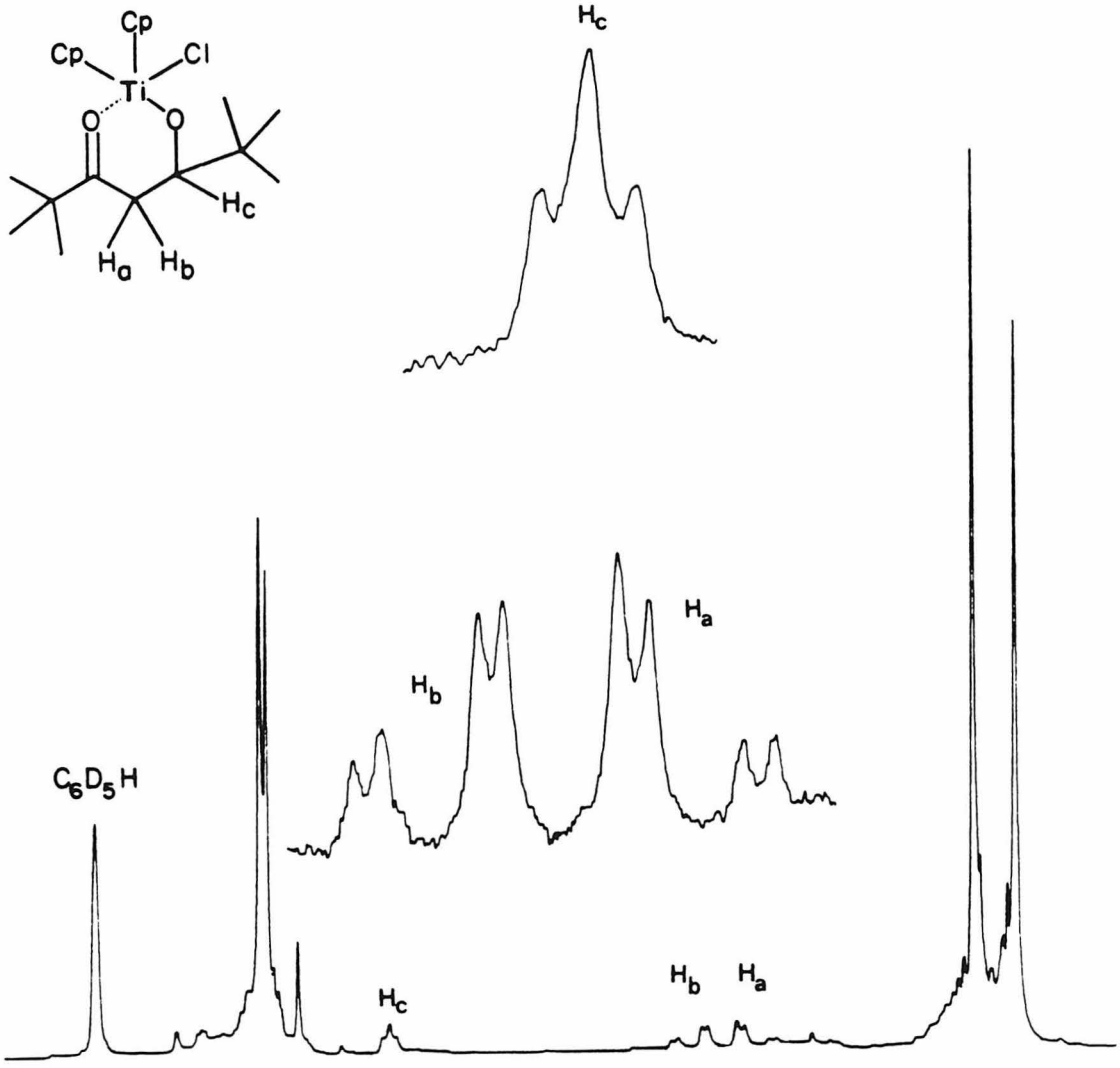


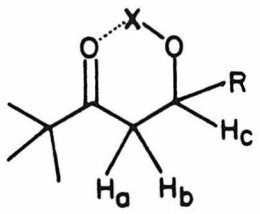
Figure 3. 90 MHz ^{1}H NMR Spectrum of Aldol Condensation Intermediate **50a** in C_6D_6.

found to produce the condensation product **52** in 88% yield by ^{1}H NMR. The oxophilicity of the titanium plays a key role in activating the aldehyde toward condensation and has been proposed to interact with the β-keto functionality of intermediate **50** in order to prevent retro-aldol condensation from occurring.[12]

Both the intermediates and the products of this reaction could be spectrally characterized. Proton NMR data of the aldol condensation intermediates and hydrolysis products are summarized in Table IV. Most obvious is the greater downfield shift of H_c in the titanium intermediate. Protons H_a and H_b also exhibited downfield shifts to a lesser degree. From the ^{13}C NMR data (Table V), there was no significant difference in the ketone carbonyl of **50** and **51** that would suggest an interaction between the carbonyl oxygen and the Lewis acidic metal center. The most accurate measure of any interaction between the ketone and the titanium was available through infrared spectroscopy. Intermediate **50a** exhibited a carbonyl stretching frequency of 1702 cm^{-1}. This value was found to be essentially the same as that for the intramolecularly hydrogen-bound β-hydroxyketone hydrolysis product **51a** (1699 cm^{-1}). A somewhat larger effect was observed for **50b**. The stretching frequency of the carbonyl in the titanium intermediate was found at 1681 cm^{-1}; the hydrolysis product **51b** displayed a carbonyl stretching frequency of 1695 cm^{-1}. All of these values were lower than the 1720 cm^{-1} stretch normally observed for most ketones. Because of the lower carbonyl stretching frequency of the intermediate titanium complex **50**, it was suspected that carbonyl interaction with the titanium metal center was occurring, but only to a small extent.

On a preparative scale, aldol condensation of titanocene chloride enolates produced good yields of β-hydroxyketone products. Typically, the enolates were formed, using the conditions outlined in Table III, and then treated with 1.0

Table IV. ^{1}H NMR Data of Aldol Condensation Intermediates and Hydrolysis Products.



50a: R=tBu, X=$TiClCp_2$

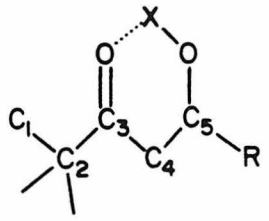
51a: R=tBu, X=D

50b: R=Ph, X=$TiClCp_2$

51b: R=Ph, X=D

Assignment	**50a**	**51a**	**50b**	**51b**
*t*Bu(ppm)	1.10	0.91	0.88	0.89
H_a(ppm)	2.61	2.26	2.59	2.55
H_b(ppm)	3.07	2.50	3.17	2.59
H_c(ppm)	5.13	3.70	6.17	5.13
J_{ab}(Hz)	19.3	17.0	17.1	0.0
J_{ac}(Hz)	4.9	8.6	6.1	4.5
J_{bc}(Hz)	4.2	3.3	6.4	7.7

Table V. ^{13}C NMR Data of Aldol Condensation Intermediates and Hydrolysis Products.



50a: R=tBu, X=$TiClCp_2$

51a: R=tBu, X=D

50b: R=Ph, X=$TiClCp_2$

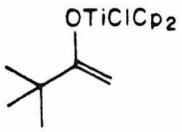
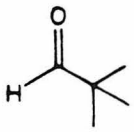
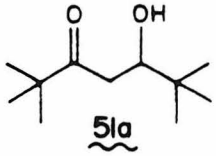
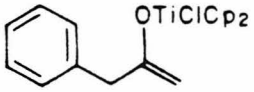
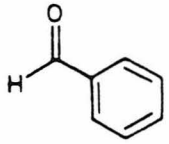
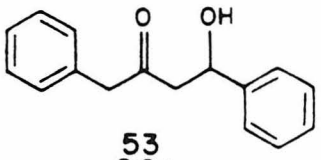
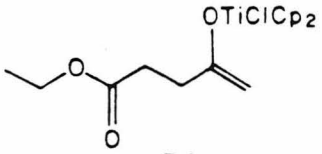
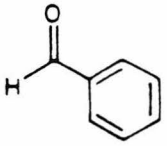
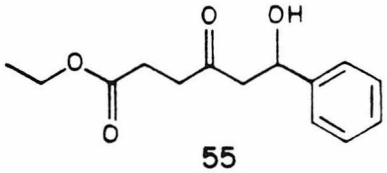
51b: R=Ph, X=D

Carbon	**50a**	**51a**	**50b**	**51b**
1	27.1	26.2	26.0	25.9
2	27.3	37.7	44.2	44.1
3	213.3	218.6	212.3	215.3
4	44.4	37.7	46.7	45.9
5	93.8	74.7	88.7	70.2

equivalent of aldehyde. After allowing to react for 1.75 h at 10°C, the reaction was quenched with saturated aqueous NH_4Cl. Isolation by chromatography on silica gel provided the β-hydroxyketone products. The aldol condensation of three enolates and the resulting products of hydrolysis are shown in Table VI. Condensation of pivaldehyde with **10**, despite the steric bulk of the two *t*-butyl substituents, proceeded smoothly to produce a 67% yield of **51a**. Enolate **23** was found to react regiospecifically with benzaldehyde to allow the isolation of **53** in 69% yield. Regiospecificity was also observed for the bifunctional enolate **54**. The only condensation product isolated from the reaction mixture of **54** and benzaldehyde was **55**. The only other organic products observed in these reaction mixtures were the methyl ketones from the unreacted enolates, and higher yields could be obtained using a twofold excess of aldehyde. Synthetically, the use of titanium enolates in condensation with aldehydes is a very valuable method of regiospecific formation of carbon-carbon bonds without risking racemization of an α-chiral center. The use of the metallacycle reagent to selectively form kinetic methyl ketone enolates from acid chlorides, followed by condensation with aldehydes, provides a powerful new tool for the construction of synthetic targets.

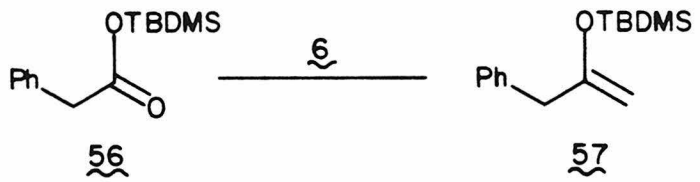
A second method of regiospecific formation of the kinetic enolates of methyl ketones was also accomplished by the reaction of sources of **5** with carbonyl functionality. Because of the retention of the regiochemical integrity of silyl enol ethers when activated for aldol condensation by titanium tetrachloride,[2,12] the synthetic preparation of silyl enol ethers using **6** was investigated. The approach to this problem involved the methylenation of silyl esters to produce the corresponding silyl enol ethers. Because the methylene transfer reagents do not racemize α-chiral carbonyl centers,[50] or isomerize kinetic enolates to the more

Table VI. Aldol Condensation Products and Yields from Titanocene Chloride Enolates.

Enolate	Aldehyde	Product	Yield[a] (%)
		 51a	67
		 53	69
 54		 55	53

[a]Yield of isolated product based on 1 mmol of acid chloride used for *in situ* formation of the enolate.

thermodynamic isomer,[29] the reaction with silyl esters was expected to give similar results. The investigation centered around the difficult preparation of the kinetic silyl enol ether of phenylacetone **57** by methylenation of the silyl ester of phenylacetic acid (**56**, eq 12).

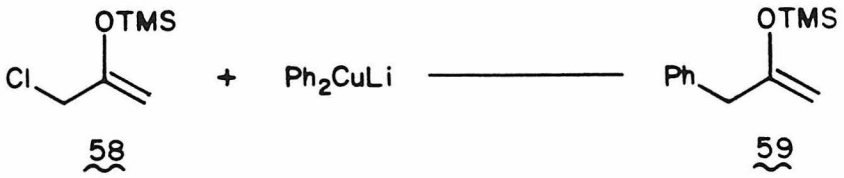


56 **57** (12)

TBDMS = $SiMe_2tBu$

Preparation of **56** from phenylacetic acid was achieved using established esterification methods,[54] and subsequent isolation produced an 82% yield of the ester. Methylenation of **56** with 1.3 equivalents **6** in THF allowed complete conversion of the substrate to **57**. Workup of the reaction mixture by dilution with pentane and filtration through a pad of silica gel produced an 84% yield of **57** as a colorless oil. ^{1}H NMR revealed **57** as the only product, as evidenced by the olefinic resonances at 4.18 ppm and 4.10 ppm, and the methylene resonance at 3.25 ppm. Phenylacetone, the hydrolysis product of **57**, was not formed under the reaction or workup conditions.

The other reported method for preparing the phenylacetone kinetic silyl enol ether involved the coupling of 2-trimethylsiloxyallyl chloride (**58**) with lithium diphenylcuprate to produce **59** (eq 13). This procedure allowed a 78% isolated yield of **59**; however, as a general method, there are two limitations of this means of preparing silyl enol ethers. Because only the alkylation of a primary alkyl halide has been accomplished in this manner, the versatility of this procedure is

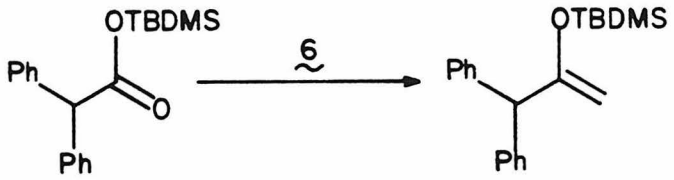


58 59 (13)

TMS = $SiMe_3$

limited. A second limitation arises as the result of the approach of the methodology. From a synthetic point of view, the method is the reverse of that desired for the modification of elaborate synthetic intermediates. In this method, preparation of the kinetic enol ether of these precious intermediates would require the use of valuable synthetic intermediates in excess as the cuprate coupling reagent.

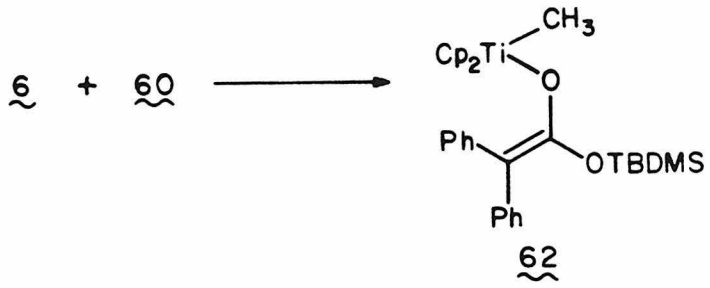
To test the limits of the methylenation of silyl esters with **6**, the transformation of **60** to **61** was explored. Preparation of **60** was accomplished using the procedure employed for the synthesis of **56**, but conversion was very low (eq 14). Probably due to the acidity of the α-proton, **60** was isolated in only 17% yield. The transformation of **60** to **61** was achieved in low conversion. Using



60 61 (14)

0.80 equivalents of **6**, ^1H NMR revealed a 15% conversion to a single product, **61**. The identification of **61** was made by the chemical shifts of the enol ether protons at 4.36 ppm and 4.13 ppm, and the methylene singlet at 4.78

ppm. The low conversion of **60** to **61** was attributed to the extremely sterically hindered α-carbon of the substrate. Because of the large phenyl substituents, the reaction of **60** and **6** might not achieve complete transformation. Low conversion may, in part, be the result of a side reaction to form the corresponding enolate **62** which has been reported for hindered ketones.[49] Hydrolysis of this intermediate enolate would regenerate **60** upon reaction workup (eq 15).



(15)

From the results of the methylenation of **56** and **60**, the use of **6** to transform silyl esters into the kinetic silyl enol ethers showed great promise. With this method, trialkylsilyl esters, formed from carboxylic acid substrates, underwent complete conversion to the corresponding kinetic enol ether as the only product. This process occurred selectively in high yield even when the thermodynamic isomer was further stabilized by aromatic conjugation. Facile non-aqueous workup provided high yields of the desired silyl enol ether for use in subsequent reactions.

Experimental Section

General Procedures. All manipulations of air and/or moisture sensitive compounds were carried out with use of standard Schlenk or vacuum line techniques. Argon was purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4Å molecular sieves. Solids were transferred in a nitrogen-filled Vacuum Atmospheres Dri-Lab equipped with an MO-40-1 purification train and a DK-3E Dri-Kool. Measurement of weight was conducted after minimizing static interference through the use of a staticmaster ionizing unit (Nuclear Products Company). Flash chromatography was performed according to general procedure of Still,[56] employing Silica Woelm 32-63 (32-63 μm). Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates and visualized by iodine vapor. All reaction temperatures were measured externally.

Materials. $Cp_2TiCH_2 \cdot AlMe_2Cl$ was prepared by a reported procedure.[42] 2-Methyl-1-pentene was purchased from Aldrich Chemical Company and was dried before use. Metallacycle **8** was prepared using an established procedure.[43] All acid halides used were purchased from Aldrich with the exception of 1-naphthoyl chloride, and *trans*-crotonyl chloride. 1-Naphthoyl chloride was prepared from 1-naphthoic acid (Aldrich) by stirring in oxalyl chloride (Aldrich) at room temperature for 1 h and subsequent isolation by vacuum distillation. *trans*-Crotonyl chloride was obtained in purified form from K. T. Chapman. Authentic samples of methyl ketones and gas chromatography standards were purchased from Aldrich or MCB chemicals unless otherwise noted. 1′-acetonaphthone was obtained from Kodak. Phenylacetone was synthesized from phenylacetyl chloride according to reported procedure.[53] 3,3-Dimethylbutanone (pinacolone) was purchased from Pfaltz & Bauer. *n*-Octane was obtained from Sigma Chemicals.

(4S)-4-(2-Propyl)-oxazolidine-2-one was obtained from D. J. Mathre. Pivaldehyde was obtained from Aldrich. Benzaldehyde was purchased from MCB chemicals. *n*-BuLi was obtained from Aldrich (1.6*M*) and standardized by titration with diphenylacetic acid (Aldrich).

Toluene, diethyl ether, and tetrahydrofuran (THF) were stirred over CaH_2 and vacuum-transferred onto sodium-benzophenone ketyl. Pentane was stirred over concentrated H_2SO_4, washed with water, dried over $CaCl_2$ and vacuum-transferred onto sodium-benzophenone ketyl in tetraglyme. Dichloromethane was stirred over P_2O_5 and degassed by intermittent evacuation with a high vacuum line. Benzene-d_6 (Merck, Sharpe, & Dohme) and toluene-d_8 (Aldrich) were dried and deoxygenated by stirring over sodium-benzophenone ketyl. Methylene chloride-d_2 (Norell, Inc.) was dried over P_2O_5 and degassed by several freeze-pump-thaw cycles. The dried and degassed solvents were vacuum-transferred into dry vessels equipped with Teflon valve closures and stored under argon.

Instrumentation. NMR spectra were recorded on a Varian EM-390 (90 MHz ^1H), or a JEOL FX-90Q (89.60 MHz ^1H; 22.53 MHz ^{13}C). Chemical shifts are reported versus residual solvent signals on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (Hz), integration, and interpretation. Difference NOE experiments were performed according to published procedures and are described fully in the text of this paper [47] Analytical gas chromatographic analyses were performed on a Varian 1400 flame-ionization instrument equipped with a Spectra-Physics System I computing integrator, or a Hewlett Packard 5880A Series Gas Chromatograph and 5880A series GC Terminal. Analyses were performed using 10′ 10% FFAP on 80/100 Chromosorb PAW and 30m DB1 columns, respectively. Infrared analyses utilized a Beckman 4210

spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Melting points were determined on a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected.

Combustion analyses were performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee), and Schwartzkopf Laboratories (Woodside, New York).

General Procedure for NMR Tube Reactions. An NMR tube was first weighed under static-free conditions in a nitrogen atmosphere. Solids were loaded into the tube, static was removed, and weight was recorded. A latex septum was fitted onto the NMR tube, sealed with Parafilm, and the reaction vessel was cooled to -40°C in acetone. Solvent (400 μL) and liquid substrates were added via syringe. The NMR tube was warmed to room temperature by hand warmth and vigorous shaking. Integration standards were added via syringe and the products assayed by integration of peak areas. Results of these reactions are described fully in the text of this chapter.

General Procedure for Enolate Preparation and Isolation (10, 19, 20, 23). To a solution of **8** (54 mg, 0.22 mmol) in 1 mL toluene at -20°C was added acid chloride (1.5 equivalents, 0.22 mmol) via syringe. The mixture was allowed to warm to room temperature with stirring and was then stirred at room temperature for 5 min. Isolation of the enolate complex was accomplished by one of three methods. The toluene was either removed *in vacuo* and the resulting solid washed with pentane, or the enolate complex was precipitated from solution with pentane, the solution filtered, and the solid washed with pentane. Alternately, the reaction could be run in benzene, lyophilized to yield a powder, and washed with pentane. Removal of residual pentane was achieved *in vacuo* to yield the enolates as light red-orange powders.

10: ^{1}H NMR (90 MHz, CD_2Cl_2, -20°C) δ 6.35 (s, 10H), 3.86 (s, 1H), 3.46

(s, 1H), 1.01 (s, 9H). ^{13}C (22.5 MHz, CD_2Cl_2, -20°C) δ 182.4, 117.2, 82.4, 38.2, 28.5. IR (nujol) 3108, 1620, 1568, 1380, 1300, 1225, 1193, 1040, 1020, 814, 788, 722 cm^{-1}. mp: 128-133° (decomp $\approx$ 175°C).

Anal. Calcd for $C_{16}H_{21}ClOTi$: C, 61.46; H, 6.77. Found: C, 61.34; H, 6.72.

19: ^1H NMR (90 MHz, CD_2Cl_2, -20°C) δ 7.35 (m, 4H), 6.41 (s, 10H), 4.68 (d, J=0.7 Hz, 1H), 4.11 (d, J=0.7 Hz, 1H). ^{13}C NMR (22.5 MHz, CD_2Cl_2, -20°C) δ 169.3, 137.9, 133.9, 128.6, 127.0, 117.9, 87.4. IR (nujol) 3098, 1590, 1485, 1308, 1292, 1115, 1103, 1005, 810 cm^{-1}.

20: ^1H NMR (90 MHz, CD_2Cl_2, -20°C) δ 6.36 (s, 10H), 3.82 (s, 1H), 3.70 (s, 1H), 1.97 (q, J=7.3 Hz, 2H), 0.99 (t, J=7.3 Hz, 3H). ^{13}C NMR (22.5 MHz, CD_2Cl_2, -20°C) δ 176.4, 117.1, 84.8, 29.6, 11.8.

23: ^1H NMR (90 MHz, CD_2Cl_2, -20°C) δ 7.31 (m, 5H), 6.20 (s, 10H), 3.96 (s, 1H), 3.85 (s, 1H), 3.27 (s, 2H). ^{13}C NMR (22.5 MHz, CD_2Cl_2, -20°C) δ 173.2, 139.0, 129.4, 128.3, 126.3, 117.2, 87.4, 43.4.

Preparation of 34.[51] To a solution of **35** (657 mg, 3.38 mmol) in 12 mL CH_2Cl_2 at 0°C was slowly added oxalyl chloride (2.15 g, 16.9 mmol) via syringe. After stirring 5.5 h at 0°C, the evolution of gas, as evidenced by a bubbler, was no longer observed. The mixture was concentrated to a colorless oil *in vacuo* and used without further purification.

Determination of Optical Purity of 34. To a solution of (4S)-4-(2-propyl)-oxazolidine-2-one (39.9 mg, 0.309 mmol) in 8 mL THF at -78°C was added *n*-butyllithium (0.178 mL, 1.64*M*) via syringe. After stirring for 15 min at -78°C, a precooled solution of **34** (54.0 mg, 0.278 mmol) in 1 mL THF was added via cannula. Upon addition of the solution of **34**, the turbid solution of **36** became clear. The solution was allowed to stir for 0.5 h and was then quenched with 2 mL saturated aqueous NH_4Cl. The resulting mixture was warmed to ambient

temperature and was extracted with 20 mL CH_2Cl_2. The combined organics were washed with 10mL saturated aqueous NaCl. The organics were dried ($MgSO_4$) and concentrated to a colorless oil. The oil was dissolved in 2mL CH_2Cl_2 for analysis by capillary gas chromatography. The resulting diastereomeric ratio was found to be 95.2:4.8. Thus, **34** was found to contain 90.4 ee.

General Procedure for Enolate Formation and Hydrolysis with Limiting Acid Chloride. To a solution of **8** (298 mg, 1.20 mmol) in 3 mL of toluene at -20°C was added the acid chloride (1.00 mmol). The solution was allowed to warm to 0°C with stirring, and react for 5-10 min (as recorded in Table III) at 0°C. After this period, the mixture was warmed to a second temperature, as noted in Table III, and allowed to stir for the designated amount of time to ensure completion of the reaction. Following completion, the mixture was cooled to -10°C and hydrolyzed. Hydrolysis was achieved by introducing 1.5 equivalents of HCl gas into the reaction vessel. All titanium precipitated from solution in the form of titanocene dichloride. The supernatant was removed for gas chromatograph analysis or isolation by Kugelrohr distillation.

Gas chromatograph analysis was conducted using *t*-butylbenzene as an internal standard for the reaction mixtures of acetophenone and ethyl acetate. 1-Octadecene was used as the standard for quantitative analysis of ethyl levulinate and phenylacetone. All products were characterized by gas chromatography and ^1H NMR comparison to authentic samples. Isolated products were characterized by ^1H NMR and ^{13}C NMR comparison to authentic samples. Yields are recorded in Table III.

38: ^1H NMR (90 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.45 (s, 2H), 3.61 (dd, J=7.8, 9.0 Hz, 1H), 3.44 (dd, J=5.3 Hz, 9.0 Hz, 1H), 2.62-3.00 (m, 1H), 2.13 (s, 3H), 1.06 (d, J=6.8 Hz, 3H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 210.5, 137.8, 128.2,

127.2, 72.8, 71.7, 46.8, 28.6, 13.0. IR (neat) 2973, 2935, 2860, 1717, 1455, 1361, 1180, 1099, 739, 699 cm^{-1}. $[\alpha]_{365}$ = -19.3 (31 mg/mL).

Anal. Calcd for $C_{12}H_{16}O_2$ = C, 74.97; H, 8.39. Found: C, 74.87; H, 8.24.

Preparation of 38. To a suspension of CuI (891 mg, 4.68 mmol) in 10 mL diethyl ether was added a 7.6 mL solution of MeLi (1.23*M*, 9.36 mmol) at 0°C. The resulting solution was cooled to -78°C and a precooled solution of **34** (332 mg, 1.56 mmol) in 6 mL diethyl ether was added via cannula. After stirring for 15 min at -78°C, the reaction was quenched with methanol (550 mg., 17.2 mmol) and was allowed to warm to room temperature. The reaction mixture was then poured into 20 mL saturated aqueous NH_4Cl and extracted with 3 x 20 mL ether. The organic layers were combined and dried ($MgSO_4$). After concentration of the solution, Kugelrohr distillation produced 215 mg **38** (72%) which was spectroscopically identical to the sample prepared using **8**.

General Procedure for Aldol Condensation with Titanocene Chloride Enolates. To a solution of titanocene chloride enolate, prepared from 1 mmol acid chloride in 3 mL toluene, was added the aldehyde (1.00 mmol) via syringe at 0°C. After stirring for 15 min at 0°C, the reaction was warmed to 10°C and stirred for 1.75 h before hydrolysis with saturated aqueous NH_4Cl. The resulting mixture was extracted thoroughly with ether, dried ($MgSO_4$), and concentrated to an oil. Isolation was achieved using flash chromatography on silica gel and eluting with ether/hexane (7:3) to produce the yields recorded in Table VI.

For the purpose of isolating the aldol condensation intermediate, a solution of **10** in benzene was allowed to react with 2.0 equivalents aldehyde at 10°C for 2 h. The reaction mixture was lyophilized to yield a yellow powder and then washed with pentane.

50a: ^1H NMR (90 MHz, C_6D_6) δ 6.02 (s, 5H), 5.97 (s, 5H), 5.13 (dd, J=4.2,

4.9 Hz, 1H), 3.07 (dd, J=4.2, 19.3 Hz, 1H), 2.61 (dd, J=4.9, 19.3 Hz, 1H), 1.10 (s, 9H), 0.82 (s, 9H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 213.3, 116.5, 116.2, 93.8, 44.4, 39.1, 37.3, 27.1, 26.2. IR (nujol) 3120, 2960, 2870, 1702, 1445, 1365, 1070, 1015 cm^{-1}

50b: ^1H NMR (90 MHz, C_6D_6) δ 7.24 (m, 5H), 6.17 (dd, J=6.1, 6.4 Hz, 1H), 5.99 (s, 5H), 5.95 (s, 5H), 3.17 (dd, J=6.4, 17.1 Hz, 1H), 2.59 (dd, J=6.1, 17.1 Hz, 1H), 0.88 (s 9H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 213.3, 146.1, 128.6, 127.5, 126.4, 116.8, 116.4, 88.7, 46.7, 44.2, 26.0. IR (nujol) 2960, 2920, 1681, 1455, 1355, 1105, 1065, 1030 cm^{-1}

51a: ^1H NMR (90 MHz, C_6D_6) δ 3.70 (dd, J=3.3, 8.6 Hz, 1H), 3.36 (s, 1H, exchanged with D_2O), 2.50 (dd, J=3.3, 17.0 Hz, 1H), 2.26 (dd, J=8.6, 17.0 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H). ^1H NMR (90 MHz, $CDCl_3$) δ 3.66 (dd, J=2.1, 9.7 Hz, 1H), 3.17 (s, 1H, exchanged with D_2O), 2.76 (dd, J=2.1, 17.3 Hz, 1H), 2.40 (dd, J=9.7, 17.3 Hz, 1H), 1.16 (s, 9H), 0.92 (s, 9H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 218.6, 74.7, 44.6, 37.7, 34.1, 26.2, 25.6. IR (CCl_4) 2960, 2870, 1699, 1480, 1365, 1090, 1060, 1000 cm^{-1}. Values were in complete agreement with those reported.[8]

51b: ^1H NMR (90 MHz, C_6D_6) δ 7.16 (m, 5H), 5.36 (br s, 1H, exchanged with D_2O), 5.13 (dd, J=4.5, 7.7 Hz, 1H), 2.59 (d, J=7.7 Hz, 1H), 2.55 (d, J=4.5 Hz, 1H), 0.81 (s, 9H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 215.3, 144.3, 128.5, 127.5, 126.0, 70.2, 45.9, 44.1, 25.9. ^1H NMR (90 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.12 (t, J=6.1 Hz, 1H), 3.65 (br s, 1H, exchanged with D_2O), 2.89 (d, J=6.1 Hz, 2H), 1.13 (s, 9H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 216.9, 143.0, 128.5, 127.6, 125.7, 70.0, 45.4, 44.4, 26.2. IR (CCl_4) 1695 cm^{-1}.

53: ^1H NMR (90 MHz, $CDCl_3$) δ 7.27 (m, 10H), 5.08 (dd, J=5.0, 7.5 Hz, 1H), 3.66 (s, 2H), 3.39 (br s, 1H, exchanged with D_2O), 2.82 (d, J=7.5 Hz, 1H),

2.80 (d, J=5.0 Hz, 1H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 208.4, 142.7, 133.4, 129.4, 128.7, 128.4, 127.6, 127.1, 125.5, 69.9, 50.7, 50.3. IR (CCl_4) 3520, 3064, 3030, 1708, 1496, 1454, 1070, 698 cm^{-1}. mp: 47.0 - 48.0°C.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.87; H, 6.66.

55: ^1H NMR (90 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.17 (dd, J=4.7, 7.7 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 3.38 (br s, 1H, exchanged with D_2O), 2.88 (d, J=7.7 Hz, 1H), 2.85 (d, J=4.7 Hz, 1H), 2.50-2.86 (m, 4H), 1.25 (t, J=7.2 Hz, 3H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 209.1, 172.7, 142.7, 128.5, 127.2, 125.5, 69.9, 60.8, 51.5, 37.9, 27.8, 14.2. IR (CCl_4) 3505, 2980, 2915, 2903, 1738, 1715, 1410, 1377, 1350, 1190, 1098, 1039, 699 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.95; H, 7.06.

Phenylacetic Acid, *t*-Butyldimethylsilyl Ester (56). Phenylacetic acid (2.00 g, 14.7 mmol), *t*-$BuMe_2SiCl$ (2.33 g, 15.4 mmol), and imidazole (2.05 g, 30.1 mmol) were dissolved in 3.0 mL dimethylformamide and stirred at room temperature for 15 h. At this time, the reaction was quenched with 30 mL H_2O and then extracted with 1 x 50 mL pentane. The organic layer was washed with 2 x 40 mL saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). After concentration of the solution, the product was distilled (Kugelrohr, 60°C, 2 mmHg) to give 3.01 g **56** (82%) as a colorless oil: ^1H NMR (90 MHz, $CDCl_3$) δ 7.23 (m, 5H), 3.57 (s, 2H), 0.85 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 171.4, 134.4, 129.1, 128.2, 126.7, 42.9, 25.6, 17.3, -5.1. IR (neat) 2950, 2925, 2860, 1720, 1260, 1165, 840, 820 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_2Si$: C, 67.15; H, 8.86. Found: C, 66.80; H, 8.75.

Preparation of 57. To a solution of **6** (370 mg, 1.30 mmol) in 3 mL THF at 0°C, was added **56** via syringe. After stirring for 5 min at -40°C, the reaction was warmed to room temperature and stirred for 30 min. The solution was diluted

with 100 mL pentane and stirred for 5 min. The solution was filtered through a pad of silica gel and washed through with 100 mL pentane. Concentration of the solution produced 216 mg **57** (86%) as a colorless oil: ^{1}H NMR (90 MHz, C_6D_6) δ 7.14 (m, 5H), 4.18 (d, J=1.0 Hz, 1H), 4.10 (td, J=0.4, 1.0 Hz, 1H), 3.25 (d, J=0.4 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 159.1, 138.8, 129.6, 128.5, 126.6, 91.4, 43.7, 25.8, 18.2, -4.6.

Anal. Calcd for $C_{15}H_{24}OSi$: C, 72.52; H, 9.74. Found: C, 73.28; H, 9.65.

Diphenylacetic Acid, *t*-Butyldimethylsilyl Ester (60). Diphenylacetic acid (3.12 g, 14.7 mmol), *t*-$BuMe_2SiCl$ (2.33 g, 15.4 mmol), and imidazole (2.05 g, 30.1 mmol) were dissolved in 3.0 mL dimethylformamide and stirred at room temperature for 45 min. At that time, the reaction mixture had solidified. An additional 5 mL dimethylformamide was added and the reaction was stirred for an additional 24 h. The reaction was quenched with 50 mL H_2O and then extracted with 60 mL pentane. The pentane was washed with 2 x 40 mL saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Concentration of this solution produced a slushy white solid. This solid was triturated with pentane at -40°C and then concentrated *in vacuo* to give 816 mg **60** (17%) as a white solid: ^{1}H NMR (90 MHz, C_6D_6) δ 6.90-7.40 (m, 10H), 5.00 (s, 1H), 0.79 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 172.5, 139.4, 129.1, 128.7, 127.3, 59.4, 26.0, 18.3, -3.3.

Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 74.09; H, 7.80.

Reaction of 6 with 60. Ester **60** (69 mg, 0.211 mmol) and **6** (48 mg, 0.169 mmol) were dissolved in 1 mL THF at -40°C. After stirring for 5 min at -40°C, the mixture was warmed to room temperature and stirred for 30 min. The solution was then diluted with 50 mL pentane, stirred for 5 min, filtered through a pad of silica gel, and washed through with 50 mL pentane. Concentration of the solution produced a colorless oil.

57: ^{1}H NMR (90 MHz, C_6D_6) δ 6.90-7.40 (m, 10H), 4.78 (br s, 1H), 4.36 (d, J=1.0 Hz, 1H), 4.13 (br s, 1H), 0.79 (s, 9H), 0.22 (s, 6H).

References and Notes

(1) For a review on the structure and reactivity of alkali metal enolates, see: Jackman, L. M.; Lange, B. C. *Tetrahedron*, **1977**, *33*, 2737.

(2) For a review on Lewis acid induced alkylation of carbonyl compounds, see: Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*. 96.

(3) For reviews on silyl enol ethers in organic synthesis, see: (a) Brownbridge, P. *Synthesis* **1983**, 1. (b) Brownbridge, P. *Ibid.* **1983**, 85. (c) Rasmussen, J. K. *Ibid.* **1977**, 91.

(4) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(5) (a) Stille, J. K.; Labadie, S. S. *Tetrahedron* **1984**, 2329. (b) Stille, J. K.; Shenvi, S. *Tetrahedron Lett.* **1982**, 627. (c) Kato, J.; Mukaiyama, T. *Chem. Lett.* **1982**, 1727.

(6) For enolates of aluminum, see Reference 4b, pp 232-233, and references cited therein.

(7) (a) Tsuji, J.; Yajmada, T.; Kaito, M.; Mandai, T. *Bull. Chem. Soc. Japan* **1980**, *53*, 1417. (b) Tsuji, J.; Yamada, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1979**, 2257.

(8) House, H.O.; Crumrine, D. S.; Ternashi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(9) For enolates of magnesium and zinc, see Reference 4b, pp 228-231, and references cited therein.

(10) Spencer, T. A.; Britton, R. W.; Watt, D. S. *J. Am Chem. Soc.* **1967**, *89*, 5727.

(11) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817. (b) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.

(12) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (c) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4039.

(13) El-Abed, D.; Jellal, A.; Santelli, M. *Tetrahedron Lett.* **1984**, 4503.

(14) (a) Hirai, K.; Ojima, I. *Tetrahedron Lett.* **1983**, 785. (b) Inaba, S.-I.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009.

(15) Vuitel, L.; Jacot-Guillarmod, A. *Synthesis* **1972**, 608.

(16) Reetz, M. J.; Peter, R. *Tetrahedron Lett.* **1981**, 4691.

(17) Nakamura, E.; Shimada, J.-I.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, 3341.

(18) Curtis, M. D.; Thanedar, S.; Butler, W. M. *Organometallics* **1984**, *3*, 1855.

(19) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, 3343.

(20) Manriquez, J. M.; McAlister, D. R.; Sanner, R. D.; Bercaw, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 2716.

(21) (a) Moore, E. J.; Staus, D. A.; Armantrout, J.; Santarsiero, B. D.; Grubbs, R. H.; Bercaw, J. E. *J. Am. Chem. Soc.* **1983**, *105*, 2068.
(b) Straus, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 5499.

(22) Manriquez, J. M.; Fagan, P. J.; Marks, T. J.; Day, C. S.; Day, V. W. *J. Am. Chem. Soc.* **1978**, *100*, 7112.

(23) (a) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, 102, 1333. (b) Schwartz, J.; Hayasi, Y. *Tetrahedron Lett.* **1980**, 1497.

(24) (a) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, 3975. (b) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. (c) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, 4607.

(25) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.

(26) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403.

(27) Doney, J. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3724.

(28) Schrock, R. R.; Fellmann, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3359.

(29) Stille, J.R.; Grubbs, R.H.; *J. Am. Chem. Soc.* **1983**, *105*, 1664.

(30) (a) Chou, T.-S.; Huang, S.-B. *Tetrahedron Lett.* **1983**, 2169. (b) Chou, T.-S.; Huang, S.-B. *Bull. Inst. Chem. Acad. Sin.* **1984**, *31*, 41.

(31) Clift, S. M.; Schwartz, J. *J. Organomet. Chem.* **1985**, *285*, C5.

(32) For a review on the regiospecific preparation of enolates, see: d'Angelo, J. *Tetrahedron* **1976**, 2979.

(33) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

(34) Gaudemar-Bardone, F.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *104*, 281.

(35) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

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

(37) House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362.

(38) (a) Mukaiyama, R.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 153. (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1980**, *53*, 174.

(39) (a) Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887. (b) Kuwajima, I.; Sato, T.; Arai, M.; Minami, N. *Tetrahedron Lett.* **1976**, 1817.

(40) (a) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. (b) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *J. Org. Chem.* **1977**, *42*, 4166.

(41) Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

(42) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(43) Straus, D. A.; Grubbs, R. H. *Organometallics* **1982**, *1*, 1658.

(44) Obtained as an isolated white powder from D. A. Straus.

(45) Tam, W.; Rettig, M. F. *J. Organomet. Chem.* **1976**, *108*, C1.

(46) The process of β-fluoride elimination has also been observed. Straus, D. A.; Grubbs, R. H., unpublished results.

(47) (a) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. (b) Sanders, J. K.; Mersh, J. D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 353.

(48) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316.

(49) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, 5733.

(50) House, H. O.; Prabhu, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.

(51) Compound **35**, the procedure for preparation of **34**, and the procedure for analysis of the purity of **34** were obtained from D. J. Mathre at the California Institute of Technology.

(52) To prevent possible racemization due to excessive heating of the product, distillation was not taken to completion.

(53) (a) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106. (b) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1970**. 4647.

(54) Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972.

(55) Sakurai, H., Shirahata, A.; Araki, Y.; Hosomi, A. *Tetrahedron Lett.* **1980**, 2325.

(56) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

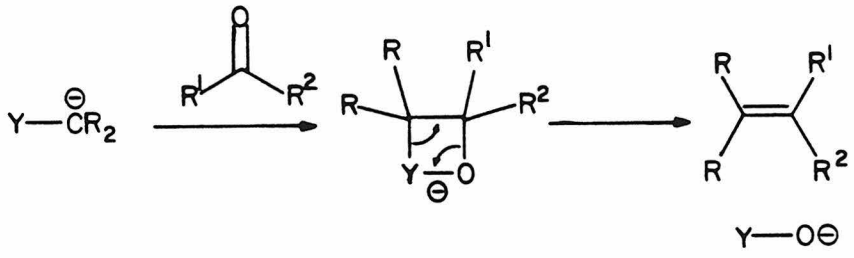
CHAPTER 3

Approaches Toward a General Method of Preparing Titanocene Alkylidene Complexes

Introduction

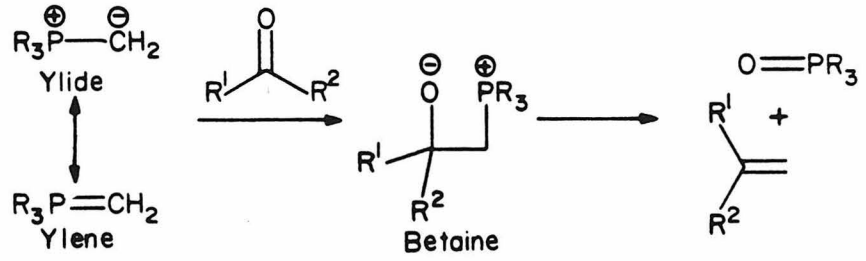
As the methodology of chemical transformations has become more advanced, the synthesis of more elaborate molecules has evolved. Homologation of organic carbonyl functionality has played a key role in the development of synthetic organic chemistry. Because of the value of forming carbon-carbon double bonds from aldehydes and ketones, the Wittig reaction has been an important contribution to organic chemistry.[1] Continued efforts have been directed toward the development of analogous olefination reagents. As a result, a multitude of organophosphorous and sulfur reagents have been utilized for Wittig-type chemistry.

The general strategy to the design of an olefin transfer reagent was to use a functional group (Y, eq 1) that both stabilized negative charge on an α-carbon,



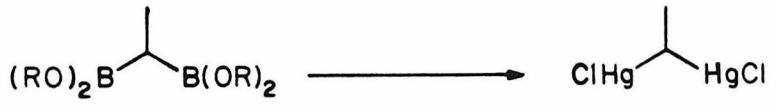
(1)

required for nucleophilic addition to the carbonyl substrate, and possessed sufficient oxophilic character so that the functional group would eliminate with the carbonyl oxygen. The phosphorous reagents were found to fulfill these requirements exceptionally well. Stabilization of negative charge resulted from the resonance contributions of the ylide and ylene structures (eq 2). Nucleophilic addition of the reagent was found to produce a betaine intermediate, which subsequently eliminated phosphine oxide to form the olefin product. Similar approaches have been made using *gem*-dimetallic compounds.



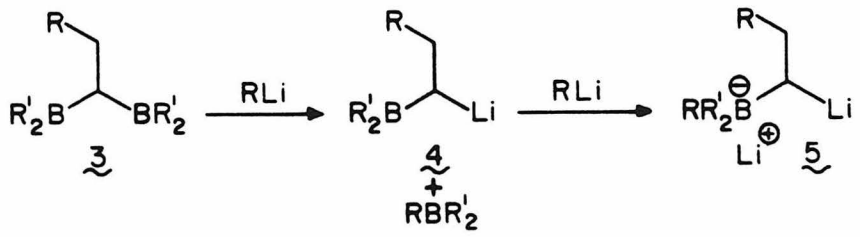
(2)

The discovery that 1,1-dimetalloalkanes would undergo transmetallation initiated much of the exploration into the synthetic utility of these reagents. The transformation of ethane -1,1-diboronic acid (**1**) to ethylidenedimercuric chloride (**2**) was found to proceed upon treatment of **1** with mercuric chloride and aqueous alkali (eq 3).[2] Similar investigations found that the reaction of alkyllithium reagents with the *gem*-organoboron compound **3** produced the heterobimetallic species **4** upon addition of one equivalent alkyllithium (eq 4).[3] The addition of



(3)

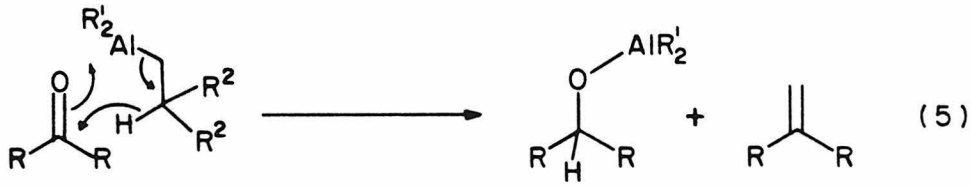
R = nBu



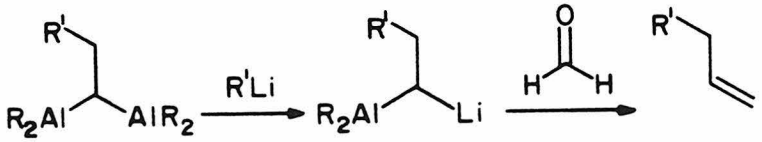
(4)

R = nBu, R' = cyclohexyl

a second equivalent of *n*-BuLi, however, appeared to form complex **5** instead of causing further transmetallation to the 1,1-dilithio species. Treatment of ketones with **5** was found to transform the carbonyl functionality to an olefin in a manner similar to that of the Wittig reagents.[4] Unfortunately, the yield of styrene from benzaldehyde was low (50%) and enolization of ketones was also found to result due to the basic nature of the reagent. By changing the boron substituents to enhance the Wittig-type transformation, **4** was developed into an efficient olefination reagent for enolizable ketones.[5] Analogous work was performed with *bis*-1,1-(diisobutylalanyl)alkanes (**6**), but the reaction with ketones and aldehydes formed the corresponding olefins in only 15-30% yield.[6] Extensive reduction of the carbonyl substrates to the corresponding alcohols was observed as the prominent reaction, a process known to occur with organoaluminum compounds containing β-hydrogens (eq 5). Transmetallation to the heterobimetallic species **7**, however, increased the reactivity of the reagent. The reaction with formaldehyde formed the corresponding terminal olefin in 70% yield (eq 6).[7]



(5)

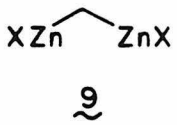


(6)

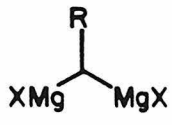
6 7 8

R = iBu, R' = nBu

The foundation established through exploration of organoaluminum and organoboron chemistry has led to the preparation and investigation of a variety of 1,1-dimetalloalkanes. From the 1,1-diiodoalkane compounds, the corresponding zinc reagents were formed. The reaction of diiodomethane with zinc-copper couple produced the zinc complex **9**. This reagent was found to transform ketones to olefins in 90% yield if aided by intramolecular complexation to a hydroxyl



9

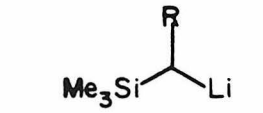


10

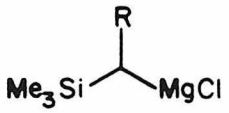
a R = H
b R = Me
c R = Ph

group.[8] In the absence of hydroxyl functionality, the reaction of aldehydes with **9** gave 50% yields at best.[9] Through the use of ultrasound techniques, **9** has been prepared directly from zinc and has produced 70% isolated yields of olefins from aldehydes.[10] Ketones, however, were methylenated to an extent of only 10%. Preparation of the dimetallo complex by the reaction of 1,1-diiodoalkanes with magnesium resulted in the formation of **10**.[11] For both aldehydes and ketones, yields of the corresponding terminal olefins ranged from 65-80% upon reaction with **10a**. Reduction to the alcohol, similar to that observed for the dialumino reagent (eq 5), occurred in preference to olefination when using **10b**. When a reagent which did not have β-hydrogens was used, such as **10c**, only 15% of the carbonyl substrate was converted to olefin. A number of heterobimetallic complexes have also been used for synthetic purposes.

The reaction of α-halosilanes with lithium has generated α-silyl carbanions which olefinate ketones in 50-60% yield.[12] Both **11a** and **11b** work equally well

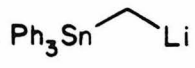


11 a R = H
b R = alkyl



12 a R = H
b R = alkyl

and reduction of the carbonyl was not observed to occur in these systems. Generating the α-silylanions by reaction with magnesium produced the expected α-silyl Grignard reagent **12**.[12,13] The treatment of ketones with **12a** produced the corresponding β-silylcarbinol in yields of 50-60%. Elimination to the olefin was then induced by the addition of a strong base. Again, the use of **12b**, similar to **10b**, resulted mostly in the reduction of the carbonyl. The transformation of both aldehydes and ketones to the corresponding terminal olefins was found to proceed with higher yields (70-90%) using the α-stannyl reagent **13**.[14] Methylenation of aldehydes, but not ketones, was also accomplished using **14**.[15]



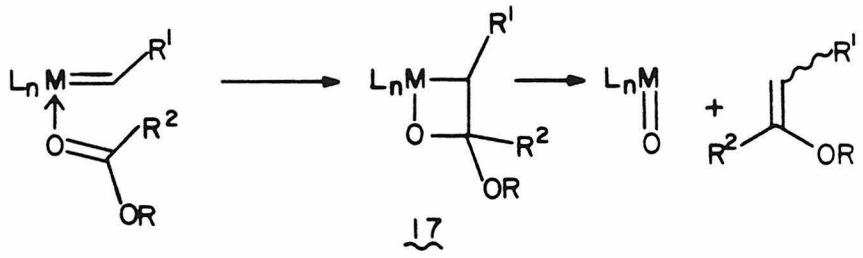
13

14

Although a variety of olefination reagents developed after the incorporation of the Wittig reagent into organic synthesis, few demonstrated any advantages over the easily prepared, reactive phosphorous reagents. The most significant contribution to olefination chemistry occurred with the preparation of transition

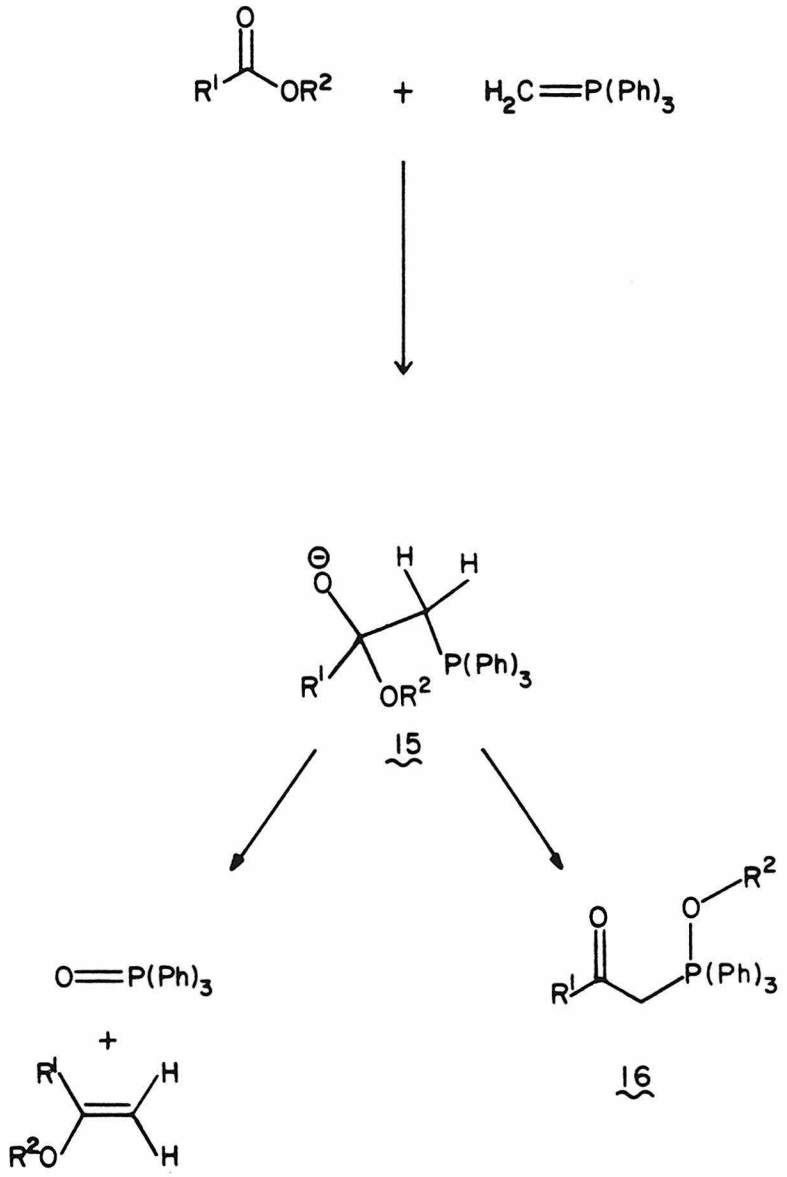
metal alkylidenes. These metallaolefins exhibited reactivity similar to the phosphorous ylides, yet had two distinct advantages. The alkylidene complexes were not strong bases, as were the Wittig reagents, so enolization and decomposition of base sensitive functionality did not occur. Of greater importance was the increased oxophilicity of the metal, which allowed not only olefination of aldehydes and ketones, but also carboxylic acid and carbonic acid derivatives.[16] Such transformations were unprecedented in organic chemistry.

The difference in reactivity centered around the intermediate formed. For ester substrates, the phosphorous reagents formed the intermediate betaine **15** (Scheme I).[17] This species then preferentially eliminated the alkoxide substituent to produce intermediate **16**, resulting in a ketone product. Further reaction of the ketone was found to afford olefinic products. The elimination of phosphine oxide from **15** to produce enol ether compounds led to less than 25% of the product mixture. Metal alkylidenes, on the other hand, underwent facile reaction with esters to produce only the enol ether products. This was attributed to a strong metal-oxygen interaction of a proposed oxametallacycle intermediate **17**, which irreversibly eliminated the metal oxo species (eq 7). As a result of this strong interaction, elimination of the alkoxide does not occur.

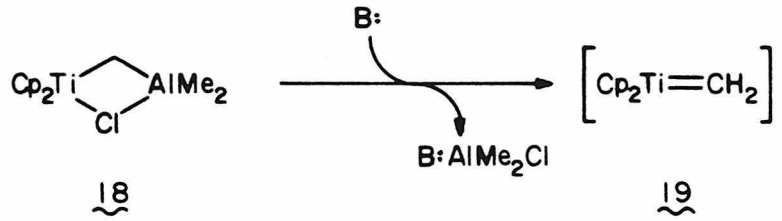


(7)

Scheme I. Product Formation Resulting from the Reaction of Ester Substrates with Phosphorous Ylides.



Olefination of carboxylic acid derivatives was initially found to result from the reaction of esters and amides with alkylidenes of tantalum and niobium.[18] These stable alkylidene complexes were found to be difficult to prepare and were less reactive than those of titanium. Titanocene alkylidenes, which must be generated *in situ*, were found to be much more easily prepared and efficient than other metal alkylidenes.[19] Upon treatment with a Lewis base, Tebbe reagent (**18**) generated the reactive titanocene methylidene fragment (**19**) at a temperature of -40°C (eq 8).[20] Both **18** and the olefin stabilized adducts of **19**, titanacyclobutanes, have already found a variety of synthetic applications.[21] The unique



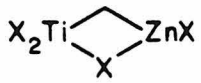
(8)

capabilities of **18** have recently led to the *in situ* preparation of this reagent[22] and extensive investigation of the reaction of **19** with a variety of carbonyl functional groups.[16,21,23] The transition metal methylenation of aldehydes and ketones has been reported for one other proposed metal alkylidene, that of molybdenum; however, yields were substantially lower.[24]

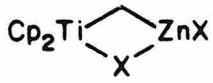
Although the ability to prepare terminal olefins from carbonyl substrates is the most frequently desired transformation, the need for a substituted alkylidene reagent was also apparent. The demand for metal alkylidene reagents has led to considerable effort directed toward their preparation. Much of this attention has been received by the more stable, less reactive zirconium analogs.[25] These complexes have been valuable for the spectroscopic study of zirconocene alkylidenes

and their heterobimetallic precursors, but have been found of little use synthetically. Lower product yields appear to result from elevated reaction temperatures (70°) and an apparent difficulty in isolation of the products.[25a] Difficulties encountered in preparing the zirconium alkylidene precursors have also reduced the desirability of this reagent.[25]

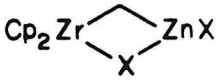
Because of the inability to prepare an α-substituted Tebbe reagent by the same methods used to prepare **18**,[26] alternate routes to a titanium methylene species, bridged to a Lewis acid, were explored. The transmetallation of **9** to titanium,[27] and zirconium[27d] was found to be highly effective for the preparation of **20, 21** and **22**. Although they have not been tested with esters, **20** and **21** reacted with ketones to afford greater than 80% isolated yields of olefin products.



20



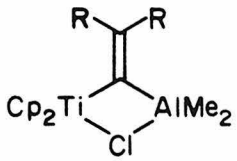
21



22

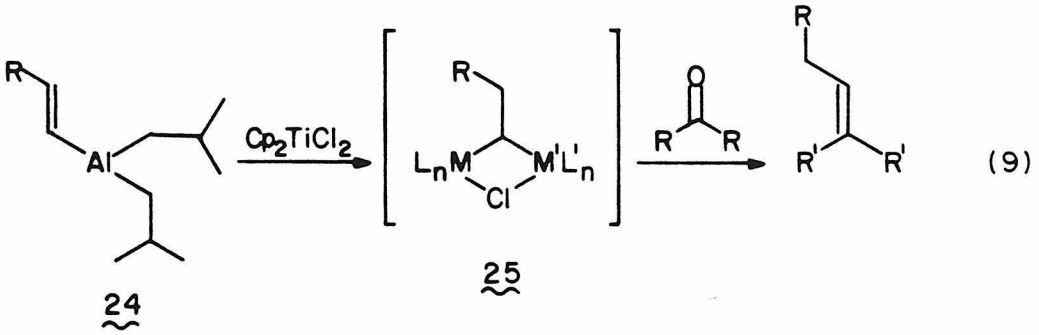
Of considerable interest is the fact that **22** also reacted with benzophenone to produce 1,1-diphenylethylene in 70% yield. In spite of advances in this area, the substituted analogs of these methylene complexes have not been reported.

Substituted analogs of **18** have been reported. Yoshida and Negishi prepared the similar alkenylidene complexes, **23**, and reported their conversion

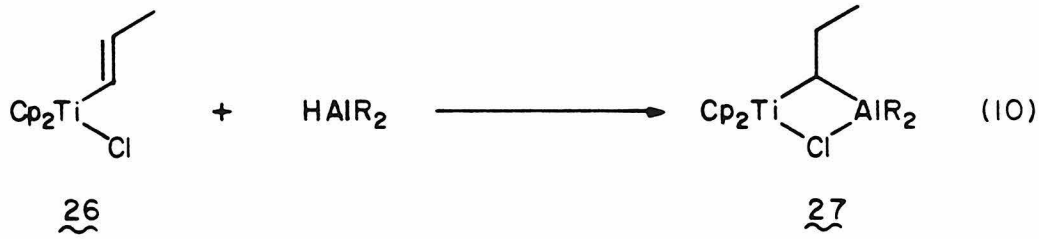


23

of ketones to allenes in high yield.[28] Yoshida subsequently reported that the reaction of 1-alkenyldiisobutylalanes, **24**, with titanocene dichloride (Cp_2TiCl_2) formed complex **25** capable of carbonyl olefination in yields of 60-70% (eq 9).[29] A related reaction was reported to occur upon treatment of the propenyltitanium



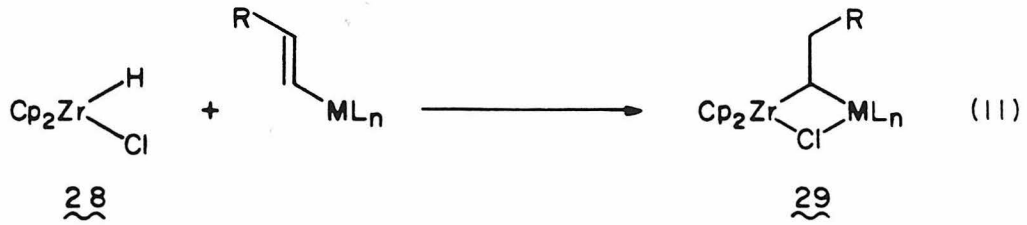
24 **25** (9)



26 **27** (10)

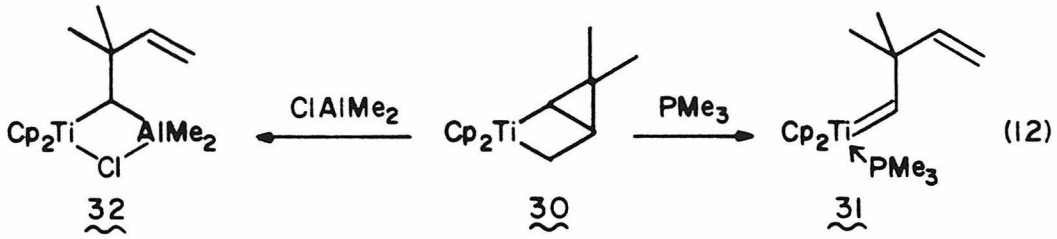
R = iBu

substrate **26**, with diisobutylaluminum hydride (eq 10); however, a lower yield for carbonyl olefination resulted from this reaction and the intermediate complex was not isolated.[25d] The opposite formation of complex **27** has not been accomplished due to the inability to prepare isolable titanocene hydride complexes. The analogous zirconium hydride (**28**), on the other hand, has been prepared.[30] The reaction of **28** with 1-alkenyl aluminum and zinc complexes produced the corresponding bridging alkylidene complexes (**29**, eq 11) which have both been shown to olefinate carbonyl substrates.[24,25] Recently, the first isolated and spectroscopically characterized titanium alkylidene complexes have



28 29 (11)

M = Al, Zn



32 30 31 (12)

been prepared by the ring-opening of the strained metallacycle **30** and trapping the intermediate alkylidene to form the stable adducts **31** and **32** (eq 12).[31]

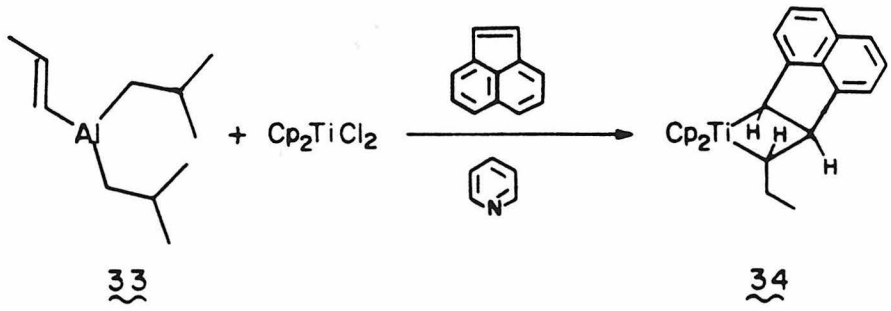
Though there are several methods for preparing substituted analogs of **18**, the search continues for a general method of both cleanly and efficiently generating titanocene alkylidene complexes. This work describes the investigation into the reaction reported by Yoshida[29] and confirms the generation of titanocene alkylidene intermediates. An approach to the preparation of these complexes, by transmetallation of 1,1-dimetallo complexes to titanocene dichloride, is also reported.

Results and Discussion

The most successful approach to the preparation of substituted titanocene alkylidene complexes was reported by Yoshida.[29] This preliminary report announced the olefination of ketones, but further mechanistic and substrate studies have not appeared. In order to further understand the intermediate metal complexes that may be formed during this reaction, this system was studied by ^1H NMR and its product chemistry.

The formation of 1-propenyldiisobutylalane **(33)** was readily accomplished by the reaction of propyne and diisobutylaluminum hydride using established methods.[32] This substrate was isolated in 58% yield by crystallization from pentane. The reaction between **33** and titanocene dichloride in CD_2Cl_2 was monitered by ^1H NMR. Below 0°C, very little change had occurred in the spectrum of the substrates, and only minor amounts of titanocene dichloride had gone into solution. At 0°C, the solution became darker, and after 25 min at room temperature, the aluminum substrate had been completely consumed. The appearance of isobutylene ($\approx$ 0.5 equivalents) was observed along with a broadening of all proton resonances. Although very broad, four distinct cyclopentadienyl resonances were observed between 5.8 ppm and 6.5 ppm and two very broad resonances were found at 9.5 ppm and 10.0 ppm. Based on the value of 9.9 ppm reported for the bridging proton of **27**, the presence of a bridged alkyidene species was suspected.[25d] Repeated attempts to isolate intermediates from this reaction mixture were unsuccessful due to the apparent sensitivity of these complexes.

The presence of a titanocene propylidene complex was verified by trapping the reactive intermediate with an olefin. Addition of acenaphthylene to the reaction mixture of **33** and titanocene dichloride, followed by treatment with pyridine, resulted in metallacycle formation (eq 13). From the product mixture, an



33 34 (13)

α,β,α'- trisubstituted metallacycle was isolated, and the structure was confirmed by NMR as that of **34** (Figure 1). The inequivalent cyclopentadienyl resonances at 5.35 ppm and 4.90 ppm and the α-proton at 5.73 ppm were characteristic of the metallacycle formed from acenaphthylene and **19**. Through the use of difference Nuclear Overhauser Enhancenemt (NOE) experiments, the ethyl substituent was found to be *trans* to the aromatic substituent. Saturation of the downfield cyclopentadienyl resonance (Cp_8) resulted in the enhancement of ring protons H_7 and H_{13}, as well as the substituent methylene protons H_{11} and H_{12}. The enhancement of proton H_{10} and aromatic proton H_6 resulted from saturation of the upfield cyclopentadienyl resonance. Because of the formation of **34** by the reaction of **33** with titanocene dichloride, the generation of an alkylidene species by this mixture was verified.

In order to prepare this species more efficiently, it was possible that the transmetallation of a 1,1-dialuminopropane species to titanocene dichloride would produce the bridged alkylidene **36** (eq 14). Through the addition of 1.0 equivalent diisobutylaluminum hydride (DIBAL) to **33**, and heating in hexane at 90°C for 5 h as reported, a product mixture that did not contain olefinic protons was obtained. Several products were apparent by ^1H NMR, but isolation or purification by crystallization from pentane at -50°C could not be accomplished.

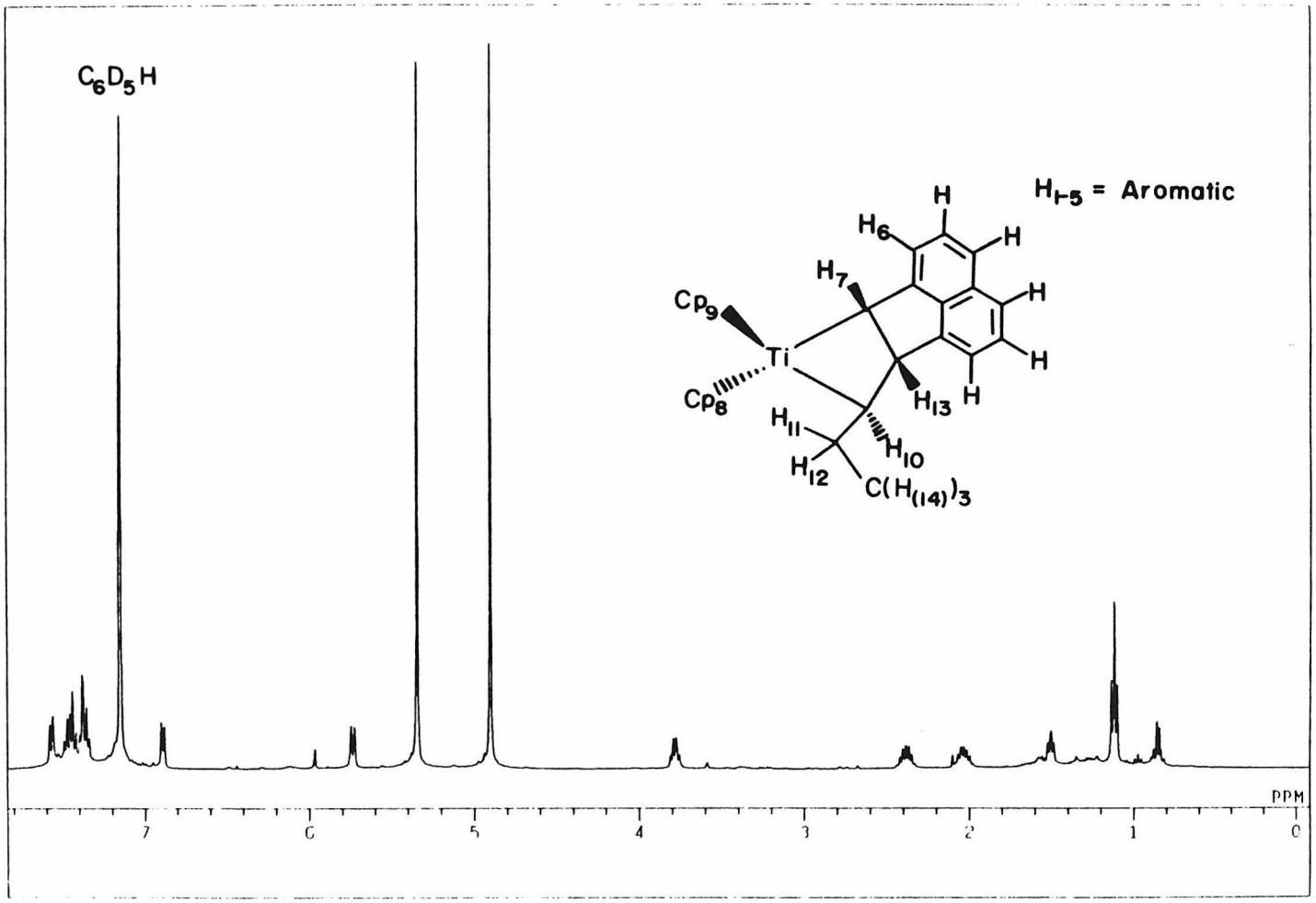
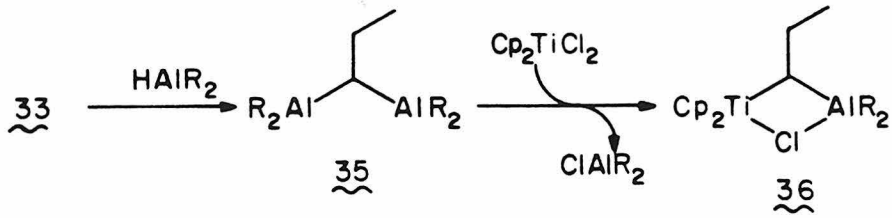


Figure 1. 90 MHz ^{1}H NMR Spectrum and Proton Resonance Assignments of **34** in C_6D_6.

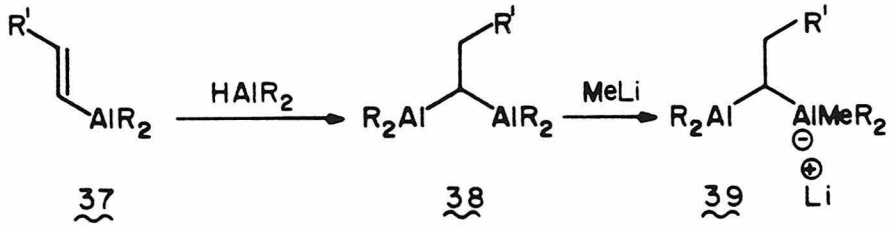


(14)

R = iBu

Because of the inability to isolate **35**, the entire reaction mixture was treated with titanocene dichloride. At -40°C in CH_2Cl_2, the reaction immediately consumed all Cp_2TiCl_2, and turned dark brown-red in color. A head of foam also resulted from the mixture, signifying the evolution of a gaseous by-product. Probing the reaction by ^1H NMR at room temperature gave promising results. A broad cyclopentadienyl resonance at 5.60 ppm, and a resonance at 10.45 ppm in C_6D_6, present in a ratio of 10.4:1.0, suggested the formation of **36**. Substantial amounts of isobutylene had also been produced. Treatment of the reaction mixture with phenyl benzoate, however, did not produce the expected enol ether.

In an attempt to prepare a crystalline analog of **35**, **37** was prepared in a similar fashion from 4-phenyl-1-butyne. The reaction diisobutylaluminum hydride with crystalline **37** was observed by ^1H NMR to be complete within 1 h at 70°C (eq 15). On a preparative scale, **37** could not be purified by crystallization.



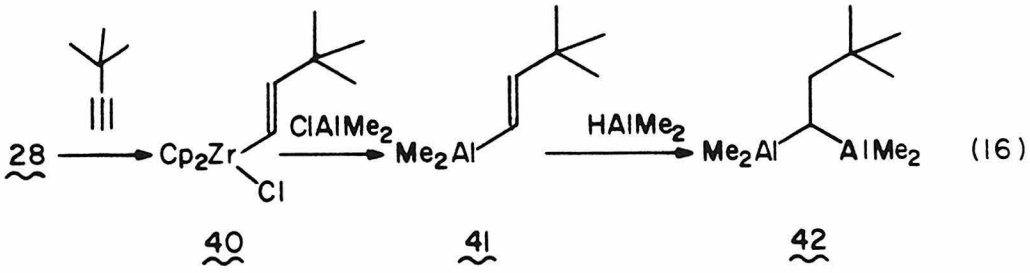
37 38 39

(15)

R = iBu, R' = $PhCH_2CH_2$-

Because **37** was not isolable and the mixture was expected to produce similar results to that of **35**, a different approach was taken. The adduct formed by reaction of **38** with 1.0 equivalent methyllithium, which could be purified through precipitation by pentane, appeared to be **39** by ^{1}H NMR, contrary to the transmetallated product reported to occur as a result of this reaction.[7] Addition of this mixture to titanocene dichloride immediately produced substantial amounts of isobutylene and essentially no bridged alkylidene products were detected by ^{1}H NMR analysis. Because of the presence of the isobutyl ligands on the aluminum, β-hydride reactions, similar to those shown in eq 5, were occurring as evidenced by isobutylene formation. This process was believed to be a major factor in the decomposition of titanium complexes.

To avoid the troubles encountered with the isobutyl ligands, the tetramethyl compound **42** was prepared (eq 16). Using slightly modified procedures of

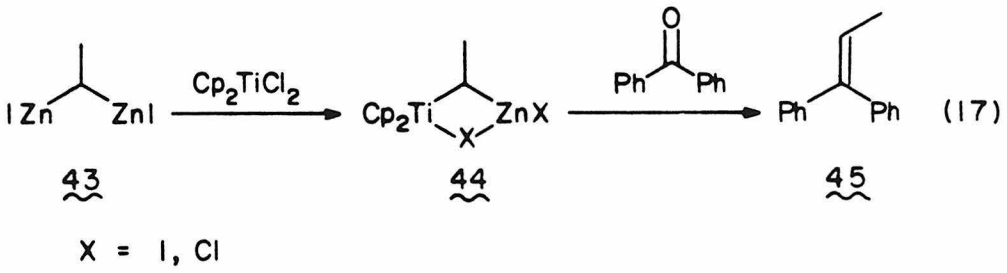


(16)

reported methods, **28** was prepared from [30,34] and transformed to **40** by the addition of 3,3-dimethyl-1-butyne.[34] Transmetallation of the 1-butenyl substituent from zirconium to aluminum was achieved through the addition of dimethylaluminum chloride.[34] Compound **41** was isolated as a crystalline white solid and was characterized by comparison to reported ^{1}H NMR data.[34] The reaction of **41** with dimethylaluminum hydride[35] was observed by ^{1}H NMR to be complete

after 2 h at 70°C and produced **42** as the major product. Although the product mixture solidified with time, crystallization from pentane was unsuccessful even at -78°C. The reaction of **42** with titanocene dichloride was monitered by ^{1}H NMR. Contrary to the treatment of **35** with titanocene dichloride, which reacted at -40°C, relatively little reaction had occurred until the mixture was warmed to room temperature. After 1 h at room temperature, 2.0 equivalents methyl benzoate were added and allowed to react for 24 h. Analysis of the resulting mixture showed that the only organic compound present in the reaction mixture was methyl benzoate. From these results, it became apparent that the 1,1-dialuminoalkane substrates did not form the desired heterobimetallic bridged species. Instead, β-hydride elimination and transmetallation of the nonbridged aluminum alkyls appeared to predominate.

Due to the proficiency of reagent **21**, and the ability of **22** and **29** to transform carbonyl substrates into olefins, the transmetallation of **43** with titanocene dichloride was explored (eq 17). Compound **43** had a definite advantage over the



(17)

1,1-dialumino complex **42**. The preparation of **43** was achieved without the use of reactive hydride reagents and required less care than the extremely pyrophoric aluminum complexes. Compound **43** also had no other alkyl groups that could compete with the bridging alkyl substituent in the transmetallation process.

Following reported procedure, 1,1-diiodoethane was easily prepared from 1,1-dichloroethane.[36] Subsequent treatment of 1,1-diiodoethane with zinc dust produced a THF solution of **43**. As reported for the reaction of titanocene dichloride with **9**,[27d] the THF solution of **43** was added to titanocene dichloride and the mixture stirred for 1 h at ambient temperature. To this deep-red solution was added 0.5 equivalents benzophenone, and the reaction was allowed to stir for 2 h at room temperature. Workup of the reaction gave a product mixture which did not contain benzophenone, as evidenced by capillary gas chromatographic analysis. Although not quantified, the major product was 1,1-diphenylpropene **45**, the olefin expected from the reaction of benzophenone with **44**.

From these initial investigations, the potential of the 1,1-dizinc complexes has been demonstrated. Facile transmetallation of the bridging alkyl substituent from zinc to titanium occurred to produce the heterobimetallic species **44**. Reaction of this complex with benzophenone resulted in the successful Wittig-type transfer of the alkylidene substituent to form the expected olefinic product **45**. This approach to preparing substituted titanocene alkylidene complexes should provide a general synthetic route to these species. The potential applications of this methodology to the olefination of carboxylic acid derivatives greatly enhances the capabilities of the synthetic organic chemist.

Experimental Section

General Procedures. All manipulations of air and/or moisture-sensitive compounds were carried out with use of standard Schlenk or vacuum-line techniques. Argon was purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4Å molecular sieves. Solids were transferred in a nitrogen-filled Vacuum Atmospheres Dri-Lab equipped with an MO-40-1 purification train and a DK-3E Dri-Kool. Measurement of weight was conducted after minimizing static interference through the use of a staticmaster ionizing unit (Nuclear Products Company). All reaction temperatures were measured externally.

Materials. Dimethylaluminum hydride[35] and 1,1-diiodoethane[36] were prepared by reported methods. With the exception of zinc powder (Mallinckrodt), titanocene and zirconocene dichloride (Boulder Scientific Company), and 4-phenyl-1-butyne (Wiley), all chemicals were obtained from Aldrich Chemical Company and used without further purification. Dichloromethane (CH_2Cl_2) was dried over P_2O_5 and degassed on a vacuum line. Pentane was stirred over H_2SO_4, dried over CaH_2, and vacuum-transferred onto sodium-benzophenone ketyl. Tetrahydrofuran (THF) was dried over CaH_2 and vacuum-transferred onto sodium-benzophenone ketyl. Hexane, benzene, diethyl ether (ether), toluene, and benzene-d_6 (Cambridge Isotope Laboratories) were degassed and stirred over sodium-benzophenone ketyl. CD_2Cl_2 was degassed and dried over CaH_2. The dried and degassed solvents were vacuum-transferred into dry vessels equipped with Teflon valve closures and stored under argon.

Instrumentation. NMR spectra were recorded on a JEOL FX-90Q (89.60 MHz ^1H; 22.53 MHz ^{13}C), a Bruker WM-500 (500.13 MHz ^1H), or a Varian EM 390 (90 MHz ^1H). Chemical shifts are reported versus residual solvent signals on the δ scale. Data are reported as follows: chemical shift, multiplicity

(s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad), coupling constant (Hz), and integration. Difference NOE experiments were performed according to published procedures and are described fully in the text of this paper.[37] Analytical gas chromatographic analyses (VPC) were performed on a Shimadzu GE-Mini 2 flame ionization instrument modified for capillary use and equipped with a Hewlett-Packard Model 339A integrator (column: 0.24 mm x 15 m DB1).

General Procedure for NMR Tube Reactions. An NMR tube was first weighed under static-free conditions in a nitrogen atmosphere. Solids were loaded into the tube, static was removed, and weight was recorded. A latex septum was fitted onto the NMR tube, sealed with Parafilm, and the reaction vessel cooled to -40°C in acetone. Solvent (400 μL) and liquid substrates were added via syringe. The reaction was conducted as described in this chapter, and the results of these reactions are described fully in the text of this chapter.

Preparation of 33. Propyne gas (500 mL, 22.3 mmol) was condensed into a 100 mL Fischer-Porter pressure apparatus. To this liquid was added 15 mL diisobutylaluminumhydride (1.0*M*, 15.0 mmol) via syringe at -78°C. The reaction mixture was placed in a -30°C cold bath and allowed to warm to 15°C over a period of 45 min. Placing the reaction vessel in a heating bath, the solution was heated to 50°C and maintained at that temperature for 3 h. During this process, a maximum pressure of 20 psi had developed. The pressure was vented and the mixture concentrated *in vacuo* to yield a light-yellow oil which solidified upon cooling. After dissolving the solid in an equal volume of pentane, the solution was cooled to -50°C to produce crystalline white solid. Recrystallization from pentane yielded 1.60 g **33** (58%) as white crystalline solid: ^{1}H NMR (90 MHz, C_6D_6) δ 7.36 (qd, J=6.1, 20.3 Hz, 1H), 6.47 (qd, J=1.5, 20.3 Hz, 1H), 1.70-2.20

(m, 2H), 1.69 (dd, J=1.5, 6.1 Hz, 3H), 1.10 (d, J=6.4 Hz, 12H), 0.33 (d, J=7.1 Hz, 4H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 181.4, 28.4, 26.9, 26.6, 24.6 (br).

Isolation of 34. Titanocene dichloride (498 mg, 2.0 mmol) and **33** (365 mg, 2.0 mmol) were taken up in 10 mL CH_2Cl_2/toluene (1:1) and stirred for 1 h at room temperature. At this time, acenaphthylene (304 mg, 2.0 mmol) was dissolved in the homogeneous solution and the reaction mixture was then cooled to -40°C. Pyridine (190 mg, 2.4 mmol) was added via syringe and the mixture allowed to warm to 0°C over the period of 20 min. After stirring for 1.5 h at room temperature, the homogeneous solution was concentrated to a total volume of 2 mL, and 15 mL pentane were added. The mother liquor was removed and the insoluble material washed with pentane/toluene (3:1). The soluble fractions were combined and slowly cooled to -50°C. The soluble fraction was concentrated *in vacuo*, dissolved in pentane/toluene (4:1) and slowly cooled to -50°. Again the soluble fraction was removed and concentrated to yield a tar. This fraction was taken up in pentane, filtered, the soluble fraction cooled to -50°C, and the resulting solids isolated and washed with cold pentane. After dissolving the solid material in toluene, the solution was cooled to -50°C. The resulting mother liquor was removed, concentrated, and slowly cooled to -50°C to yield 37 mg **34** as a purple powder: ^{1}H NMR (500 MHz, C_6D_6) δ 7.27-7.60 (m, 5H), 6.89 (d, J=6.5 Hz, 1H), 5.73 (d, J=7.9 Hz, 1H), 5.35 (s, 5H), 4.90 (s, 5H), 3.79 (ddd, J=7.2, 7.3, 7.3 Hz, 1H), 2.39 (dqd, J=7.1, 7.3, 14.0 Hz, 1H), 2.03 (dqd J=7.1, 7.3, 14.0 Hz, 1H), 1.51 (dd, J=7.2, 7.9 Hz, 1H), 1.12 (dd, J=7.1, 7.1 Hz, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 161.0, 153.1, 137.4, 132.6, 123.1, 119.8, 119.5, 116.8, 113.6, 111.0, 109.6, 106.0, 38.9, 24.1, 18.5.

Reaction of 35 with Titanocene Dichloride. To a solution of 182 mg **33** (1.0 mmol) in 1 mL hexane was added 1 mL diisobutylaluminum hydride (1.0*M*, 1.0

mmol) via syringe. The solution was heated at 90°C for 5 h and then concentrated to an oil *in vacuo*. After redissolving the oil in 2 mL toluene, the solution was added to a suspension of titanocene dichloride in 2 mL toluene at -40°C. The reaction mixture turned brown-red and a head of foam developed as most of the titanocene dichloride went into solution. After being stirred for 15 min at -40°C, the reaction mixture was warmed to room temperature for 15 min, and then returned to -40°C. To the reaction mixture were then added 178 mg phenyl benzoate (0.9 mmol) and 95 mg pyridine (1.2 mmol). Over the period of 90 min, the mixture was allowed to warm to room temperature at which time the reaction was quenched with 0.3 mL 15% aqueous NaOH. The resulting mixture was diluted with ether, filtered through a pad of celite, and concentrated to a yellow oil. ^{1}H NMR (90 MHz, C_6D_6) showed the absence of alkylidene transfer products.

Preparation of 37. To a solution of 2.78 g 4-phenyl-1-butyne (21.3 mmol) in 3 mL hexane at -40°C was slowly added diisobutylaluminum hydride (1.0*M*, 21.3 mmol). The reaction mixture was allowed to warm to room temperature over a period of 90 min, and then heated to 50°C. After stirring at 50°C for 2.5 h, the mixture was cooled and concentrated to an oil, which solidified upon standing. The solid was taken up in an equal amount of pentane and slowly cooled to -50°C. Recrystallization of the resulting solid gave 3.20 g **37** (55%) as a white crystalline solid: ^{1}H NMR (90 MHz, C_6D_6) δ 7.42 (td, J=6.3, 20.5 Hz, 1H), 6.80-7.20 (m, 5H), 5.89 (td, J=1.4, 20.5 Hz, 1H), 2.20-2.80 (m, 2H), 1.65-2.20 (m, 2H), 1.08 (d, J=6.3 Hz, 12H), 0.39 (d, J=7.0 Hz, 4H).

Preparation and Reactivity of 38. A solution of 545 mg **37** (2.0 mmol) and 2.0 mL diisobutylaluminum hydride (1.0*M*, 2.0 mmol) was heated to 60°C over the period of 25 min. During the following 25 min, the temperature was allowed

to reach 70°C and the reaction mixture was stirred at that temperature for 1.5 h. After cooling the mixture, all volatiles were removed *in vacuo*, and the nonvolatile products were dissolved in an equal amount of pentane/toluene (1:1). Methyllithium (44 mg, 2.0 mmol) was added to the solution and the reaction mixture was heated for 1.5 h at 50°C. Removal of the volatiles produced a slushy, white solid. After washing with pentane, the solid was dissolved in toluene, precipitated from solution using pentane, and isolated. Removal of residual solvent *in vacuo* gave a viscous oil upon warming to ambient temperature.

Preparation of 28. To a solution of 11.54 g zirconocene dichloride (39.5 mmol) in 250 mL THF was added a solution of 10.05 g $LiAlH(t\text{-}BuO)_3$ (39.5 mmol) in 50 mL THF. After stirring 2 h, the supernatant was removed from the insoluble product. The product was washed with THF (2×), ether (2×) and residual solvent was removed *in vacuo* to yield 7.80 g **28** (77%) as a white powder.

Preparation of 41. To a suspension of **28** in 30 mL benzene was added 1.29 g 3,3-dimethyl-1-butyne (15.7 mmol) via syringe. Protecting the reaction vessel from light, the mixture was allowed to be stirred for 9.5 h. During the progress of the reaction, the mixture had turned green-brown in color and had become homogeneous. The resulting solution was concentrated to a solid material. After repeated washing with pentane, there remained 3.41 g **40** (86%) as a white powder. This white powder (10.0 mmol) was suspended in 30 mL pentane at 0°C, and a solution of 0.927 g dimethylaluminum chloride (10.0 mmol) in 8 mL pentane was added. The reaction mixture was stirred at 0°C for 1.5 h, warmed to ambient temperature, and then stirred for an additional 1.5 h. The supernatant was removed from the heterogeneous reaction mixture, the insoluble material was extracted with pentane, and the soluble organic fractions combined with the supernatant. Concentration of the soluble fractions produced a yellow solid.

Crystallization from pentane produced 0.89 g **41** (63%) as a white, crystalline solid: ^{1}H NMR (90 MHz, C_6D_6) δ 7.51 (d, J=20.8 Hz, 1H), 5.87 (d J=20.8 Hz, 1H), 0.85 (s, 9H), -0.34 (s, 6H).

Preparation and Reactivity of 44. To a suspension of 183 mg zinc dust (2.8 mmol) in 1 mL THF, was added 282 mg 1,1-diiodoethane (1.0 mmol) via syringe. The mixture was heated at 45°C for 1 h and was then allowed to be stirred an additional 1.5 h at ambient temperature. The supernatant was then transferred into a suspension of 249 mg titanocene dichloride (1.0 mmol) in 1 mL THF. After stirring for 1 h at room temperature, benzophenone (91 mg, 0.5 mmol) was added to the reaction mixture. The reaction mixture was allowed to be stirred for 2 h and was then quenched with 10% aqueous NaOH, diluted with ether, and filtered through celite. The ether was dried ($MgSO_4$) and concentrated to an oil. ^{1}H NMR (90 MHz, $CDCl_3$) confirmed the presence of 1,1-diphenylpropene (**45**).

References and Notes

(1) (a) Maercker, A. *Org. React. (N.Y.)* **1965**, *14*, 270. (b) House, H. O. *Modern Synthetic Reactions*. Benjamin: Menlo Park, CA, 1972; pp. 682-709. (c) Bestman, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 65.

(2) Matteson, D. S.; Shdo, J. C. *J. Org. Chem.* **1964**, *29*, 2742.

(3) (a) Cainelli, G.; Bello, G. D.; Zubiani, G. *Tetrahedron Lett.* **1965**, 3429. (b) Zweifel, G.; Arzoumanian, H. *Tetrahedron Lett.* **1966**, 2535.

(4) Cainelli, G.; Bello, G. D.; Zubiani, G. *Tetrahedron Lett.* **1966**, 4315.

(5) Pelter, A.; Singaram, B.; Wilson, J. W. *Tetrahedron Lett.* **1983**, 635.

(6) Cainelli, G.; Bertini, F.; Gresselli, P.; Zubiani, G. *Tetrahedron Lett.* **1967**, 1581.

(7) Zweifel, G.; Steele, R. B. *Tetrahedron Lett.* **1966**, 6021.

(8) (a) Nysted, L. N., U.S. Patent 3,865,848. (b) Turnbull, P.; Syhora, K.; Fried, J. H. *J. Am. Chem. Soc.* **1966**, *88*, 4764. (c) Harrison, I. T.; Rawson, R. J.; Turnbull, P.; Fried, J. H. *J. Org. Chem.* **1971**, *36*, 3515.

(9) (a) Hashimoto, H.; Hida, M.; Miyano, S. *J. Organomet. Chem.* **1967**, *10*, 518. (b) Miyano, S.; Hida, M.; Hashimoto, H. *J. Organomet. Chem.* **1968**, *12*, 263.

(10) Yamashita, J.; Inoue, Y.; Kondo, T.; Hashimoto, H. *Bull. Chem. Soc. Japan* **1984**, *57*, 2335.

(11) Bertini, F.; Grasselli, P.; Zubiani, G.; Cainelli, G. *Tetrahedron* **1970**, *26*, 1281.

(12) (a) Chan, T. H.; Chang, E.; Vinokur, E. *Tetrahedron Lett.* **1970**, 1137. (b) Chan, T. H.; Chang, E. *J. Org. Chem.* **1974**, *39*, 3264. (c) Dumont, W.; Krief, A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 161.

(13) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

(14) Kauffmann, T.; Kriegesmann, R.; Woltermann, A. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 862.

(15) Kauffmann, T.; Konig, R.; Pahde, C.; Tannert, A. *Tetrahedron Lett.* **1981**, 5031.

(16) Chapter 1, this thesis.

(17) Uijttewaal, A. P.; Jonkers, F. L.; van der Gen, A. *J. Org. Chem.* **1979**, *44*, 3157.

(18) Schrock, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 5399.

(19) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(20) Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876.

(21) (a) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhart, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure & Appl. Chem.* **1983**, *55*, 1733. (b) Stevenson, J. W. S.; Bryson, T. A. *Chem. Lett.* **1984**, 5. (c) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868. (d) Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, 395.

(22) (a) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386. (b) Chou, T. S.; Huang, S. B.; Hsu, W. H. *J. Chin. Chem. Soc. (Taipei)* **1982**, *30*, 277.

(23) (a) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (b) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, 5733. (c) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212. (d) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316.

(24) Kauffmann, T.; Feigenbaum, P.; Wieschollek, R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 531.

(25) (a) Clift, S. M.; Schwartz, J. *J. Organomet. Chem.* **1985**, *285*, C5. (b) Clift, S. M.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 8300. (c) Hartner, F. W., Jr.; Schwartz, J.; Clift, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 640. (d) Hartner, F.W., Jr.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4979.

(26) Tebbe, F. N.; Guggenberger, L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 227.

(27) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Japan* **1980**, *53*, 1698. (c)Lombardo, L. *Tetrahedron Lett.* **1982**, 4293. (d) Eisch, J. J.; Piotrowski, A. *Tetrahedron Lett.* **1983**, 2043.

(28) Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 1276.

(29) Yoshida, T. *Chem. Lett.* **1982**, 429.

(30) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405.

(31) Gilliom, L. R.; Grubbs, R. H. *Organometallics* **1986**, *5*, 0000.

(32) (a) Zweifel, G.; Miller, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 6678. (b) Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2754. (c) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520.

(33) Wilke, v. G.; Muller, H. *Ann. Chem.* **1960**, *629*, 222.

(34) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.

(35) Zakharkin, L. I.; Khorlina, I. M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1961**, 1768.

(36) Letsinger, R. L.; Kammeyer, C. W. *J. Am. Chem. Soc.* **1951**, *73*, 4476.

(37) (a) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. (b) Sanders, J. K. M.; Mersh, J. D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**,

15, 353.

CHAPTER 4

The Intramolecular Diels-Alder Reaction of α,β-Unsaturated Ester Dienophiles with Cyclopentadiene and the Dependence upon Tether Length

Introduction

One of the most widely used synthetic methods for ring formation has been the Diels-Alder reaction which results in the formation of two new bonds and, thus, the generation of up to four new asymmetric centers. The predictability and stereoselectivity of this reaction have led to widespread application in the synthesis of natural products. More recently, the intramolecular Diels-Alder has been the focus of considerable attention.[1] Several advantages arise as a result of an intramolecular cycloaddition, with the most prominent being the formation of an additional ring. Increased reactivity due to entropic factors has been observed in these intramolecular systems as well. Due to the linkage between the diene and dienophile, obvious regiochemical constraints are placed upon the system. These constraints have demonstrated a marked increase in stereoselectivity and diastereoselectivity of the cycloaddition process.

Cyclopentadiene has been used extensively for the formation of bicyclo[2.2.1]heptene compounds. The use of cyclopentadiene moieties in the intramolecular cycloaddition with dienophiles produces tricyclic bridged systems similar to the skeletal structures of various natural products.[1c] The occurrence of these naturally occuring bridging sesquiterpenes has led to the development and use of the intramolecular cycloaddition with cyclopentadiene. Subsequent ring expansion of the resulting cycloaddition products has been employed in the total synthesis of several cedrane derivatives, cedrene,[2] cedrol,[2] and cedranediol.[3] The synthesis of sativene has also been achieved through ring expansion of an intramolecular Diels-Alder product.[4] Other examples include the current development of this methodology as an approach to the synthesis of sinularene, longifolene, as well as an alternate route to sativene.[5] Cleavage of the strained olefin, followed by further functional group modification, has led to the recent synthesis

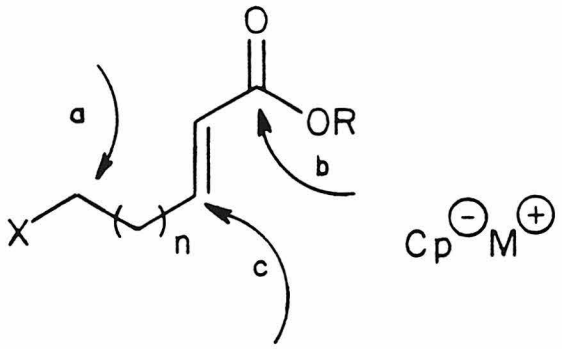
of two naturally occurring triquinanes.[6] Both siliphinene[7] and capnellene[8] have been prepared by this methodology.[9] Recent advances in asymmetric induction of the Diels-Alder reaction[10] have made this cycloaddition a promising method for the synthesis of optically active natural products.

For the purposes of asymmetric induction, it is advantageous to have these reactions proceed under mild conditions. In general, at the elevated temperatures required by past syntheses (around 160-180°C[2,3,5a,8b]), alternate pathways compete with the cycloaddition process. In addition to the occurrence of side reactions, the cyclopentadiene functionality is itself sensitive to decomposition and/or polymerization. To avoid these competing pathways, the intramolecular Diels-Alder ring formation can be enhanced by increasing the reactivity of the olefin through the use of α,β-unsaturated carbonyl dienophiles; milder conditions are expected to result in a greater product selectivity. There are many advantages to the presence of the carbonyl group besides the obvious functionality upon which to elaborate synthetically. The incorporation of carbonyl dienophiles also allows for the use of Lewis acid catalysis which can result in lower reaction temperatures, and, thus, greater product selectivity. The utilization of an acrylate derivative as the dienophile also provides functionality upon which a chiral auxiliary can be effectively positioned for later removal.[10,11] The effect of a chiral auxiliary, coupled with the Lewis acid catalyzed cycloaddition, should result in high diastereoselective product formation. Intramolecular cycloaddition of an asymmetric acrylate derivative with the cyclopentadiene to which it is tethered, would result in a powerful tricyclic synthetic building block. In this single cycloaddition, the asymmetric induction of four new chiral centers occurs. Compounds such as these may be readily isolated diastereomerically pure and allow a facile route to the preparation of optically active natural products.

Intramolecular cycloadditions between cyclopentadiene and α,β-unsaturated carbonyl dienophiles have been reported, but the examples are limited due to the general inaccessibilty of these cyclopentadiene compounds. The routes used to prepare the reported substrates have involved specific diene formation, or required elaborate synthetic construction. In the synthesis of cedranediol, the cyclopentadiene was cleverly masked as a dicyclopentadienyl moiety.[3] Unfortunately, the fabrication of the tether and α,β-unsaturated ester dienophile on the dicyclopentadiene unit was a lengthy synthetic task. A second drawback to this procedure was the elevated temperature (180°C) required to "deprotect" the cyclopentadiene. An alternate method, which involved the *in situ* generation of a specific trisubstituted cyclopentadiene unit, was demonstrated in the synthesis of sativene.[4] Excellent cycloaddition yields were obtained after reaction at 110°C for three days. Recently, approaches toward the synthesis of sinularene and longifolene have utilized a "blocked" cyclopentadiene in the intramolecular cycloaddition with an α,β-unsaturated ester.[5] The reaction proceeded at temperatures around 180°C within 6 h. In the presence of the Lewis acid catalyst $AlCl_3$, the cycloaddition occurred within 3 h at temperatures as low as 23°C! Recent advances in the preparation of functionalized cyclopentadienes have been reported for other systems using organo-zinc and organo-magnesium reagents to open the cyclobutanone ring of a bromobicyclo[3.2.0]heptenone system, producing a monosubstituted cyclopentadiene.[12] Intramolecular cycloaddition of these systems proceeded at room temperature within 20 h. The mild conditions under which these reactions proceed and their enormous synthetic potential encouraged us to investigate a general method for the preparation of compounds containing both the cyclopentadiene moiety and an α,β-unsaturated ester functional group.

Herein we describe studies into the general preparation of these compounds.

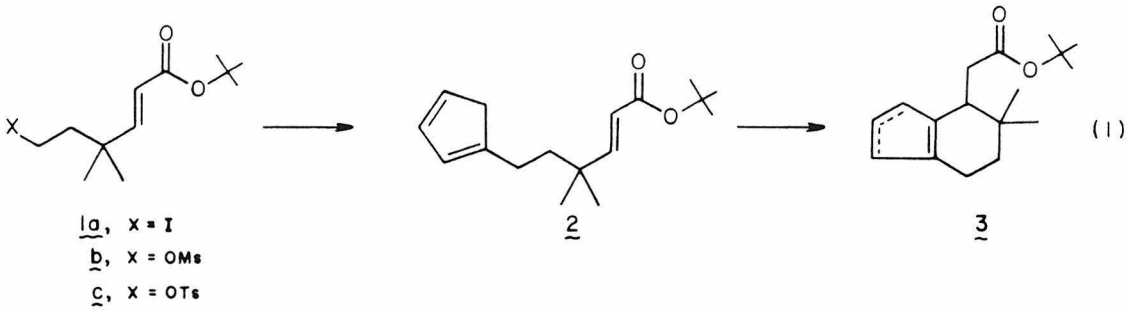
A survey of their cycloaddition reactions through the structural analysis of the tricyclic products was performed using two-dimensional ^1H-^1H correlated NMR and difference Nuclear Overhauser Enhancement experiments. Our approach to the synthesis of these molecules involved the selective reaction of cyclopentadienyl anions with bifunctional substrates (Figure 1). In addition to the desired coupling reaction (path a), both 1,2-addition (path b) and 1,4-addition (path c) to the α,β-unsaturated carbonyl were possible. Several variables were found to effect the selectivity of this reaction. By increasing the tendency for the leaving group to undergo displacement, selective product formation was enhanced. A second variable was altered in order to encourage product formation through the desired reaction pathway. The nature of the metal counterion of the cyclopentadienyl anion was changed to evoke the desired reactivity of the anion. It



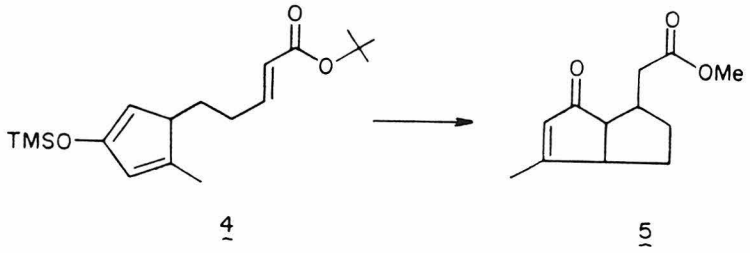
X = leaving group Cp = cyclopentadiene

Figure 1. Modes of Cyclopentadienyl Anion Attack on Substrate.

has been reported that alkylated products of both cyclopentadienyl sodium and lithium are very sensitive to the presence of catalytic amounts of base.[13] With small amounts of base, rapid equilibration of alkylcyclopentadienes occurred by way of the cyclopentadienyl anion, rather than the usual [1,5]-shifts of hydrogen. Difficulties arise if this process takes place with the α,β-unsaturated ester functionalized cyclopentadienes. It was found that the alkylation of **1a** or **1b** with either the cyclopentadienyl anion of sodium or lithium, resulted in the base catalyzed intramolecular conjugate addition of the proposed intermediate **2**, to the two olefinic isomers of **3** (eq 1).[14] A similar substrate, **4**, was also found to be quite sensitive to minor amounts of base.[4a] With base, the transformation of **4** to **5** occurred (eq 2). In order to avoid these problems, the use of a different metal counterion was investigated.

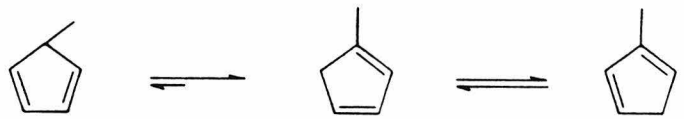


(1)



(2)

The alkylation of cyclopentadienyl magnesium bromide is a well-defined process.[15] Methylation of this anion resulted in the initial formation of 5-methylcyclopentadiene (**6**, eq 3). After 4 h at room temperature, this isomer was almost completely converted to 1-methylcyclopentadiene (**7**) by a [1,5]-sigmatropic shift. Isomerization of the methylcyclopentadienes continued and, after 4 days at 25°C, an equilibrium mixture of the three dienes had been reached.



6 7 8 (3)

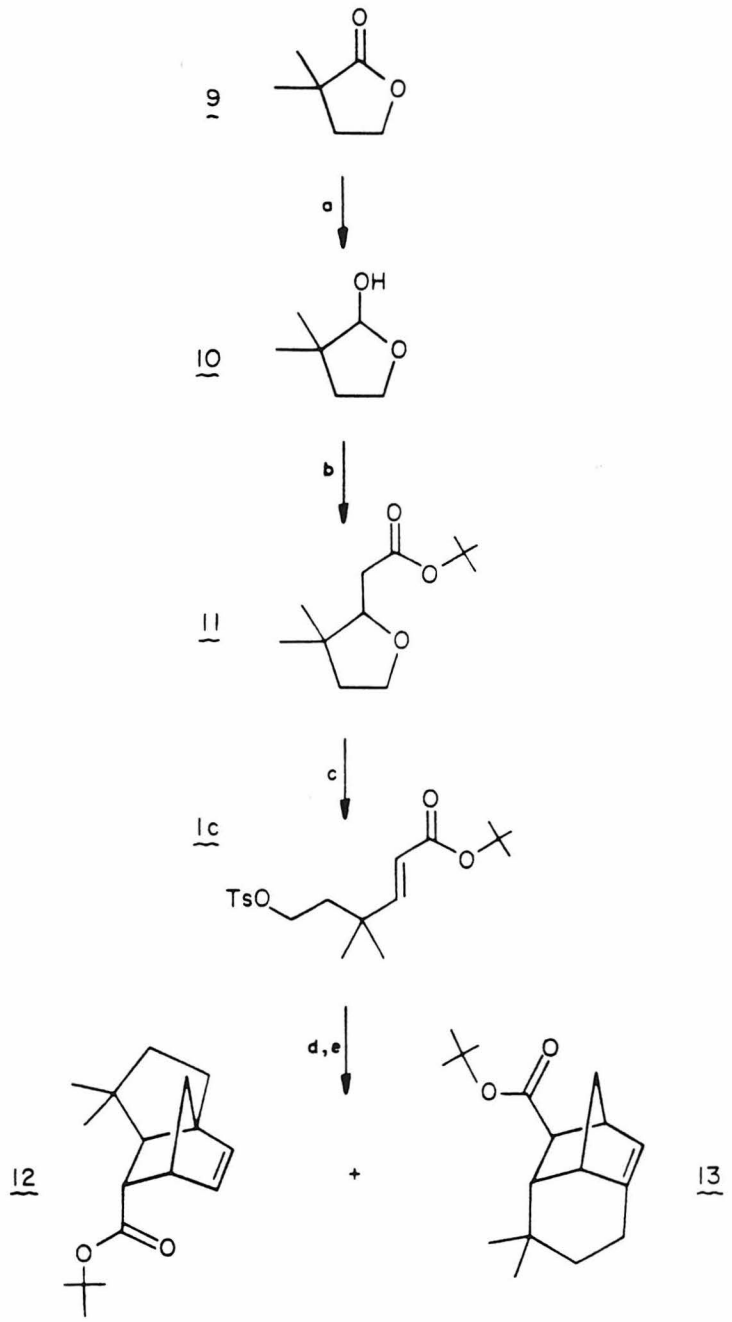
An equilibrium mixture of the dienes was also obtained by distillation (72.5°C, 747mm) of any one of the separate isomers. At equilibrium, the ratio of **7** to **8** was found to be approximately 0.82:1.00 with about 1% **6**. It is important to note that, with cyclopentadienylmagnesium halides, the isomerization proceeds by [1,5]-hydrogen shift and that, under these reaction conditions, a cyclopentadienyl anion is not regenerated as it would cause rapid equilibration of the isomers similar to that observed for the more basic cyclopentadienyl anions. The compatability of Grignard reagents with alkyl cyclopentadienes has also been demonstrated in the preparation of the functionalized dienes previously discussed.[12]

Results And Discussion

Initial investigations were conducted with **1c**, a substrate which was similar to that known to undergo the deprotonation and intramolecular Michael addition to form **3** (eq 1).[14] The selection of tosylate **1c** as the substrate was also influenced by the presence of the geminal dimethyl group which was expected to reduce the possibility of the 1,4-addition to the α,β-unsaturated ester due to the steric hinderance. A third motive for the use of **1c** was the application of the cycloadditon product **12** toward the synthesis of the marine sesquiterpene capnellene.[8a] For the purposes of synthetic application, the existing synthesis of the alcohol precursor to this 4,4-dimethyl substrate was too lengthy.[16]

Instead, **1c** was prepared as shown in Scheme I. Reduction of α,α-dimethyl-γ-butyrolactone (**9**)[17] with diisobutylaluminum hydride produced a solution of the corresponding lactol (**10**).[18,19] Condensation of the lactol with the anion of $(EtO)_2POCH_2CO_2C(CH_3)_3$ was found to proceed rapidly; however, under the basic conditions of the reaction, intramolecular Michael addition of the hyroxyl group to produce the tetrahydrofuran adduct **11** in 89% isolated yield also occurred. Treatment of this product with lithium diisopropylamine, followed by the addition of *p*-toluenesulfonyl chloride, furnished the desired crystalline tosylate **1c** in 83% yield. The coupling reaction of **1c** with cyclopentadienylmagnesium chloride or bromide[20] produced optimal results using 2.0 equivalents of the Grignard reagent. Using an excess of the cyclopentadienyl reagent reduced the reaction time and eliminated sideproducts that result from insufficient amounts of a cyclopentadienyl source. Within 3 h at 0°C, the reaction had consumed all starting tosylate. Analysis of the product mixture by 400 MHz ^{1}H NMR revealed the presence of monosubstituted cyclopentadienes and α,β-unsaturated ester olefinic protons. Despite the use of a two-fold excess of cyclopentadienyl

Scheme I[a] Synthetic Approach to the Preparation of **12**.



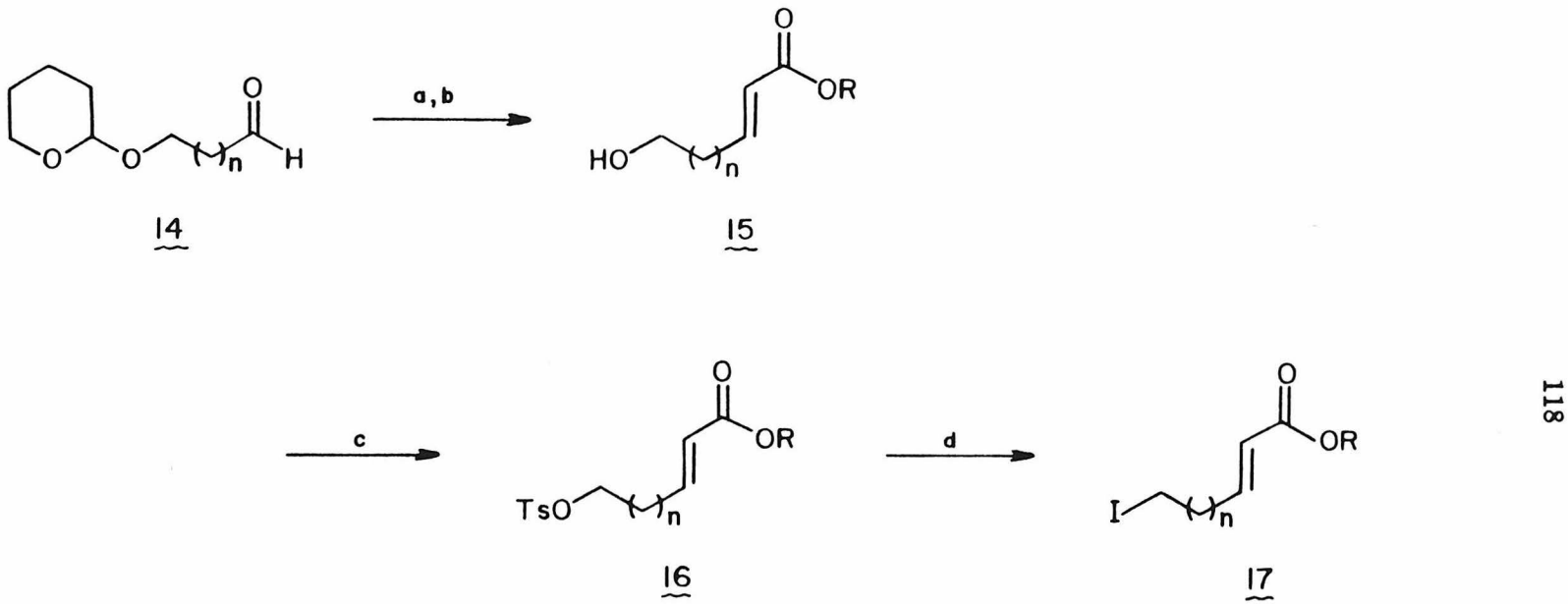
[a](a) DIBAL, -78°C, toluene; (b) $(EtO)_2POCH_2CO_2C(CH_3)_3$, NaH, benzene, 25°C (89%); (c) LDA, *p*-TsCl, THF, -78°C to 25°C (83%); (d) CpMgCl, THF, 25°C; (e) benzene, 75°C (81%).

magnesium reagent, products resulting from the base catalyzed intramolecular conjugate addition reaction were not observed.

It was found that the intramolecular cycloaddition of **2** was dependent upon the temperature of the reaction mixture. When a benzene solution of **2** was heated in a 75°C oil bath for 4 h, a two cycloaddition products, **12** and **13**, were formed in a ratio of 91:9, respectively, as detected by capillary gas chromatography. At 100°C, the ratio of **12** to **13** was 81:19. The major product was identified as **12** by the characteristic doublet at 6.21 ppm and the doublet of doublets at 5.99 ppm as observed by ^{1}H NMR.[21] Although not completely characterized, we suggest that the structure of minor product was that of **13** due to spectral similarities with the tricyclic **27**. Taking advantage of the labile properties of **13**, **12** was easily isolated. After concentration of a diethyl ether solution of the 91:9 product mixture of **12** and **13**, which still contained traces of ether, the mixture was allowed to stand 24 h at ambient temperature during which time **13** completely disappeared and the amount of **12** remained constant. Selective polymerization of the strained, trisubstituted olefin was suspected to account for these results. Distillation of the tricyclic adduct **12** from the nonvolatile products led to the isolation of **12** in 81% yield. From the results of the reaction of cyclopentadienylmagnesium chloride (CpMgCl) with **1c**, the Grignard reagent appeared to be very promising for the general preparation of functionalized cyclopentadienes.

To explore the application of CpMgCl toward the general synthesis of functionalized cyclopentadienes, substrates with unsubstituted chains were prepared that differed in tether length, ester group, and leaving group. All substrates were readily prepared from the known, bifunctional tetrahydropyranoxy aldehydes (**14**).[22] Condensation with the appropriate phosphonate ester, followed by deprotection of the hydroxy group, produced the crude alcohol **15** (Scheme II).

Scheme II[a] Preparation of Tether and Dienophile.



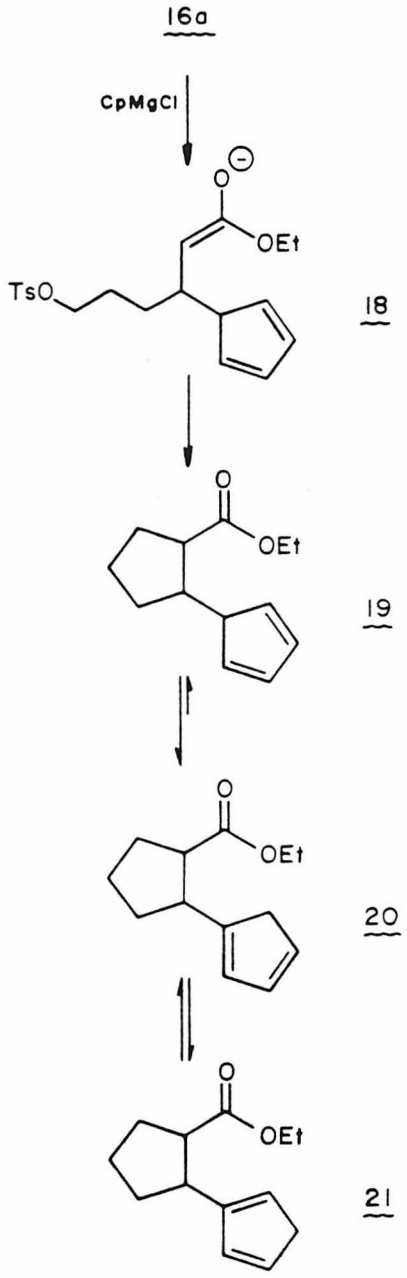
a, R = Et, n = 3; b, R = tBu, n = 3; c, R = tBu, n = 4; d, R = tBu, n = 2

[a](a) NaH, $(EtO)_2POCH_2CO_2R$, benzene, 25°C; (b) EtOH, *p*-TsOH·pyr, 60°C; (c) *p*-TsCl, pyridine, 0°C; (d) NaI, acetone, 45°C.

Reaction with *p*-toluenesulfonyl chloride in pyridine transformed **15** into the tosylate **16** with good overall yield. Conversion to the iodide **17** was achieved in excellent yield using NaI in acetone.

To determine the effects of substituents at the γ position and the ester group, the unsubstituted analog **16a** was examined. After the addition of 1.10 equivalents CpMgCl, tosylate **16a** was completely consumed within 15 min at room temperature. Compared to the intermolecular alkylation of tosylate **1c**, this reaction was quite rapid. Heating a benzene solution of the mixture at reflux for 12 h resulted in only 3% of the desired cycloaddition product. The balance of the mixture consisted of an almost equal mixture of two isomeric monosubstituted cyclopentadienes, determined by both ^{1}H and ^{13}C NMR. Each isomer retained its ester functionality, but the α,β-position was no longer unsaturated and, although the reaction of **16a** was found to proceed at a much more rapid rate than that of **1c**, the tosylate functionality was absent. An explanation for the disappearance of both the tosylate and the unsaturation in the substrate, despite the addition of only one equivalent of CpMgCl, is found in Scheme III. Initial conjugate addition of the cyclopentadienyl anion to **16a** resulted in the generation of enolate intermediate **18**[23] containing a β-chiral center (Scheme III). Rapid diastereoselective intramolecular alkylation by the tosylate would then produce a single 5-alkyl cyclopentadiene **19**, which, upon heating, isomerized to the two more stable substituted cyclopentadienes **20** and **21**. It is important to note that the intramolecular 1,4-addition process observed in eq 1 was not detected. The 1,2-addition to the carbonyl did not occur and, thus, the use of the corresponding *t*-butyl ester **16b**, as expected, gave a similar product distribution upon reaction with CpMgCl. The *t*-butyl esters were used in all subsequent reactions for reasons of spectroscopic convenience.

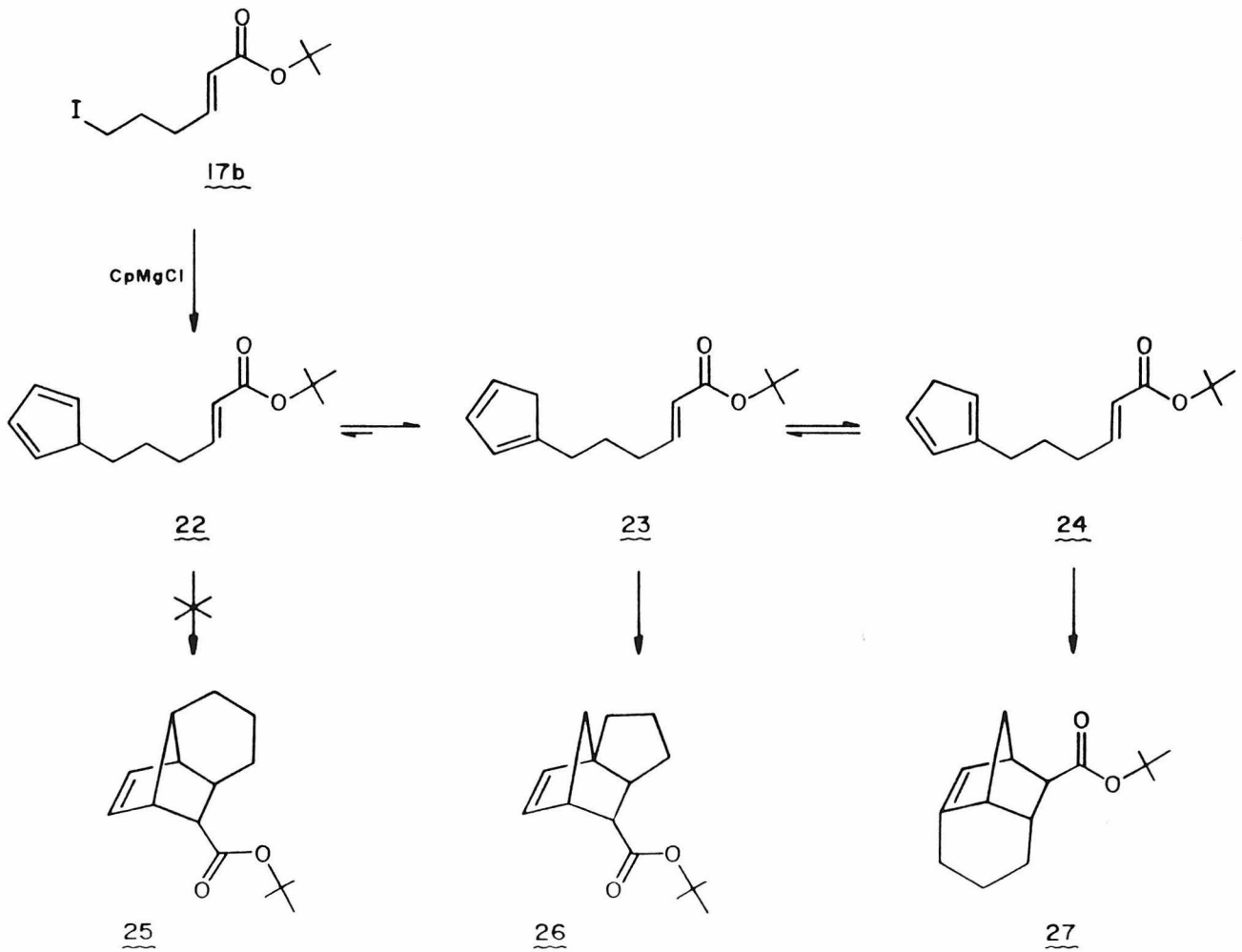
Scheme III. Proposed Pathway for the Reaction of CpMgCl with **16a**.



In order to enhance the desired coupling reaction in preference to the conjugate addition, a better leaving group was employed. Reaction of CpMgCl with the iodide **17b** produced much more favorable results. At 0°C, the coupling of **17b** with CpMgCl was complete within an hour. Following removal of the magnesium salts, a benzene solution of the mixture was maintained at reflux for 2 h until cycloaddition was complete. Analysis of the solution revealed that only 14% of the mixture was due to the unwanted intermolecular Michael addition side products analogous to **20** and **21**. The balance of the mixture was composed of two cycloaddition products that were present in a ratio of 6.4:1.0. The conjugate addition side products were readily separated from the mixture by selective reaction with maleic anhydride and subsequent chromatographic removal. After isolation of each cycloaddition product through the use of flash chromatography, the major isomer **26** (Scheme IV) was easily identified as the unsubstituted analog of **12** through its characteristic ^{1}H NMR olefinic resonances. The doublet at 6.20 ppm and the doublet of doublets at 5.91 ppm confirmed the presence of a bridgehead substituent and, thus, the topology of the tricyclic structure **26**. This product was a result of the intramolecular cycloaddition of the 1-substituted cyclopentadiene **23**.

The presence of minor amounts of a second isomer was unanticipated. Previous examples of intramolecular cycloaddition of olefins to cyclopentadiene, separated by a three-carbon tether, had always produced a single product.[1,3,8b] ^{1}H NMR spectra verified the presence of a bicyclo[2.2.1]hept-2-ene ring skeleton contained within the resulting tricyclic structure. In contrast to **12**, there were two distinctive bridgehead proton signals at 3.00 ppm and 2.59 ppm and only one olefinic proton resonance (5.55 ppm). The carbon spectrum of this product revealed two olefinic carbons, one of which had a proton substituent. ^{1}H NMR

Scheme IV. Rearrangement and Cyclization Pathways Available upon Alkylation of **17b**.



and ^{13}C NMR spectral data suggested a tricyclic skeleton with the structure **27**.[21] This product was formed through the cycloaddition of the 2-substituted cyclopentadiene **24**. The intramolecular cycloaddition of **24** to form a bridgehead olefin was not expected.[2a] To our knowledge this type of skeletal structure, has not been previously reported; however, similar bridgehead olefin compounds have been prepared. The unsubstituted analog, lacking the bridge methylene carbon, bicyclo[3.3.1]non-1-ene(**28**), has been prepared by several independent methods.[24] Another similar compound that contained a bridgehead olefin resulted from the intramolecular Diels-Alder reaction involving a 2-substituted cyclohexadiene in the formation of **29**.[25] Neither of these examples contained the additional conformational strain that is inherent in a bicyclo[2.2.1]hept-2-ene skeleton.

28

29

The structure of **27** was unequivocally determined through the use of ^{1}H-^{1}H correlated two-dimensional NMR[26] and difference Nuclear Overhauser Enhancement (NOE) experiments. The crosspeaks that occurred off the diagonal in ^{1}H-^{1}H correlated two-dimensional NMR, as a result of J-coupling between two protons, were used to trace the carbon framework of the molecule. From the strong coupling of proton H_1 (5.55 ppm) to that of the bridgehead proton at 3.00 ppm, proton H_2 was identified (Figure 2). Proton H_2 displayed strong cou-

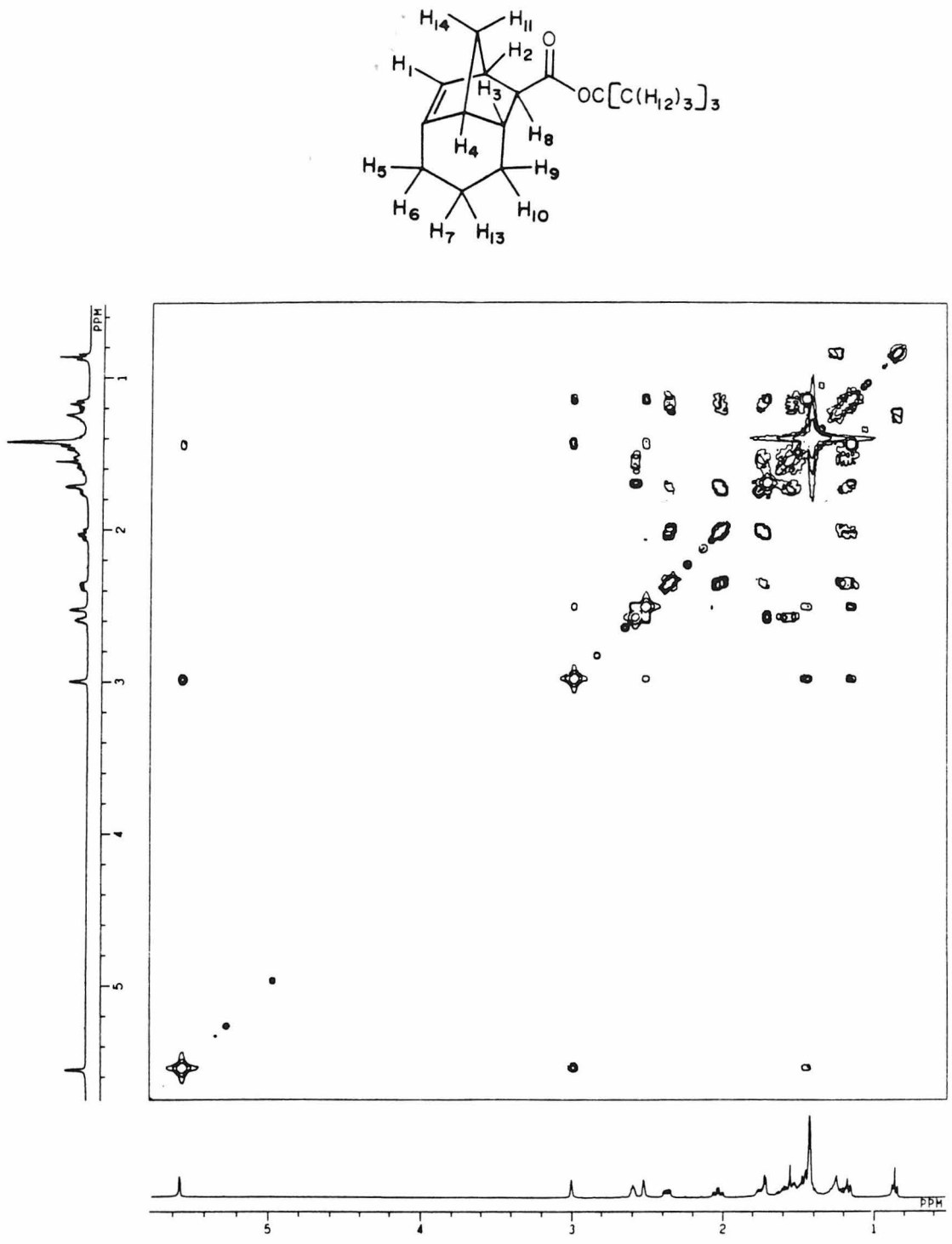


Figure 2. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum and Proton Resonance Assignments of **27** in $CDCl_3$.

pling to both bridge protons H_{11} and H_{14} which, in turn, showed coupling to the other bridgehead proton H_4. Coupling between protons H_2 and H_8 or H_4 and H_3 were not observed. In spite of the absence of coupling, the regiochemistry of the cycloaddition was assumed due to the constraints imposed by the three-carbon tether. Further assignment of proton chemical shifts were made by tracing the coupling of H_8 to H_3, which also displayed J-coupling to H_9 and H_{10}. The overlapping protons H_9 and H_{10} couple to both H_7 and H_{13}, which also coupled to one another. Protons H_7 and H_{13} each coupled to the two allylic proton resonances H_5 and H_6, which also displayed strong J-coupling to one another. Due to the pulse delays chosen for this experiment, weak four-bond coupling between H_1 and H_{11}, and that of proton H_2 and H_4, were observed by the ocurrence of crosspeaks. Through the use of ^1H-^1H correlated two-dimensional NMR, the structure of **27** was verified.

Further information on the regiochemistry that resulted from the cycloaddition was obtained through difference Nuclear Overhauser Enhancement (NOE) studies. Saturation of proton H_1 resulted in the enhancement of proton H_2, H_5, and, to a lesser degree, H_8. Proton H_2, upon saturation, displayed similar enhancement of H_1 and enhancement of H_8. As expected, protons H_1 and H_2 were enhanced upon saturation of H_8. Because H_7 overlapped slightly with H_8, the partial saturation of H_7 occurred, producing enhancement of H_{13}. Although the resonances of H_3 and H_4 were too close to show relative interaction between the two protons, saturation of H_3 did result in the enhancement of both H_8 and H_{11}; the slight enhancement of H_9 and H_{10} were also observed. These experiments verified the regiochemistry of the $4\pi + 2\pi$ cycloaddition. The ester functionality was also demonstrated to be an *exo*-substituent.

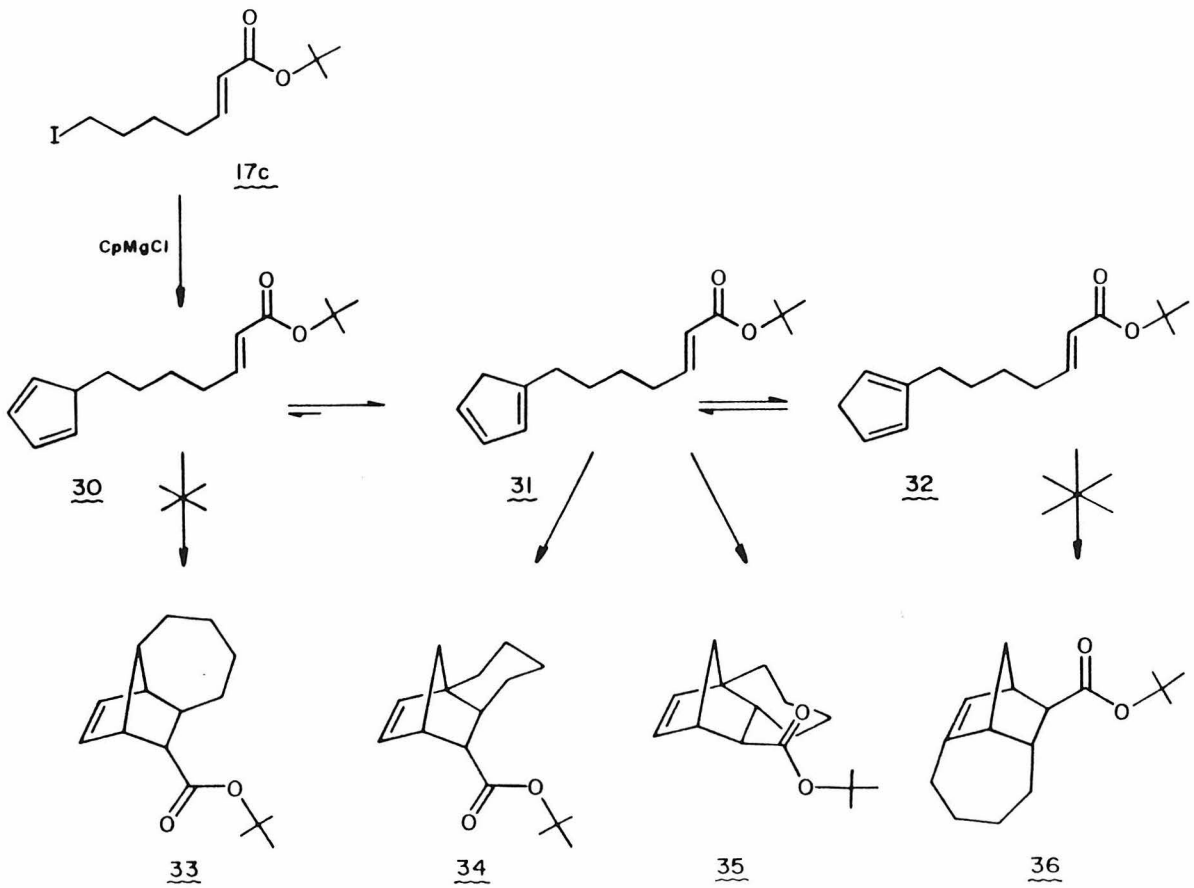
As expected, product selectivity in the cycloaddition reaction was enhanced

at lower temperatures. At room temperature, intramolecular product formation occurred over a 5-day period. Under the milder conditions, the products **26** and **27** were formed in a 98.5:1.5 ratio. At -15°C, the cycloaddition reaction, catalyzed by 1.4 equivalents of Et_2AlCl, produced only **26** as observed by capillary gas chromatography.

With the four-carbon tether, four possible cycloaddition products can arise (Scheme V). The reaction of **17c** with 1.00 equivalents CpMgCl, and subsequent removal of magnesium salts, produced the substituted cyclopentadiene **30**. The mixture was then heated to reflux in benzene for 4 h. After this time, cycloaddition was complete. Analysis of the mixture revealed that intramolecular conjugate addition to the α,β-unsaturated ester had occurred to an extent of only 9%. Two cycloaddition products, in a ratio of 69:31, were present by capillary gas chromatography. Isolation of each of these cycloaddition products was achieved through the use of flash chromatography.

The major isomer was obtained in 40% isolated yield, and the structure of this compound was shown by NMR spectroscopy to be that of **34**. An olefinic resonance at 5.99 ppm appeared as a doublet of doublets; that at 5.85 ppm was a doublet. This coupling pattern indicated that the product was the result of the cycloaddition of the 1-substituted cyclopentadiene **31**. In overall appearance, the proton spectrum was quite similar to that of **26**. Two-dimensional ^1H- ^1H correlated NMR revealed the positions of all the protons not present in the tether (Figure 3). The olefin doublet (proton H_2) displayed coupling to the other olefin resonance (H_1) which showed coupling to the bridgehead proton H_3. Proton H_3 coupled to both H_7 and H_{15} on the methylene bridge, as well as to the α-carbonyl proton H_4. Proton H_8 was assigned as a result of the crosspeak resulting from J-coupling

Scheme V. Rearrangement and Cyclization Pathways Available upon Alkylation of **17c**.



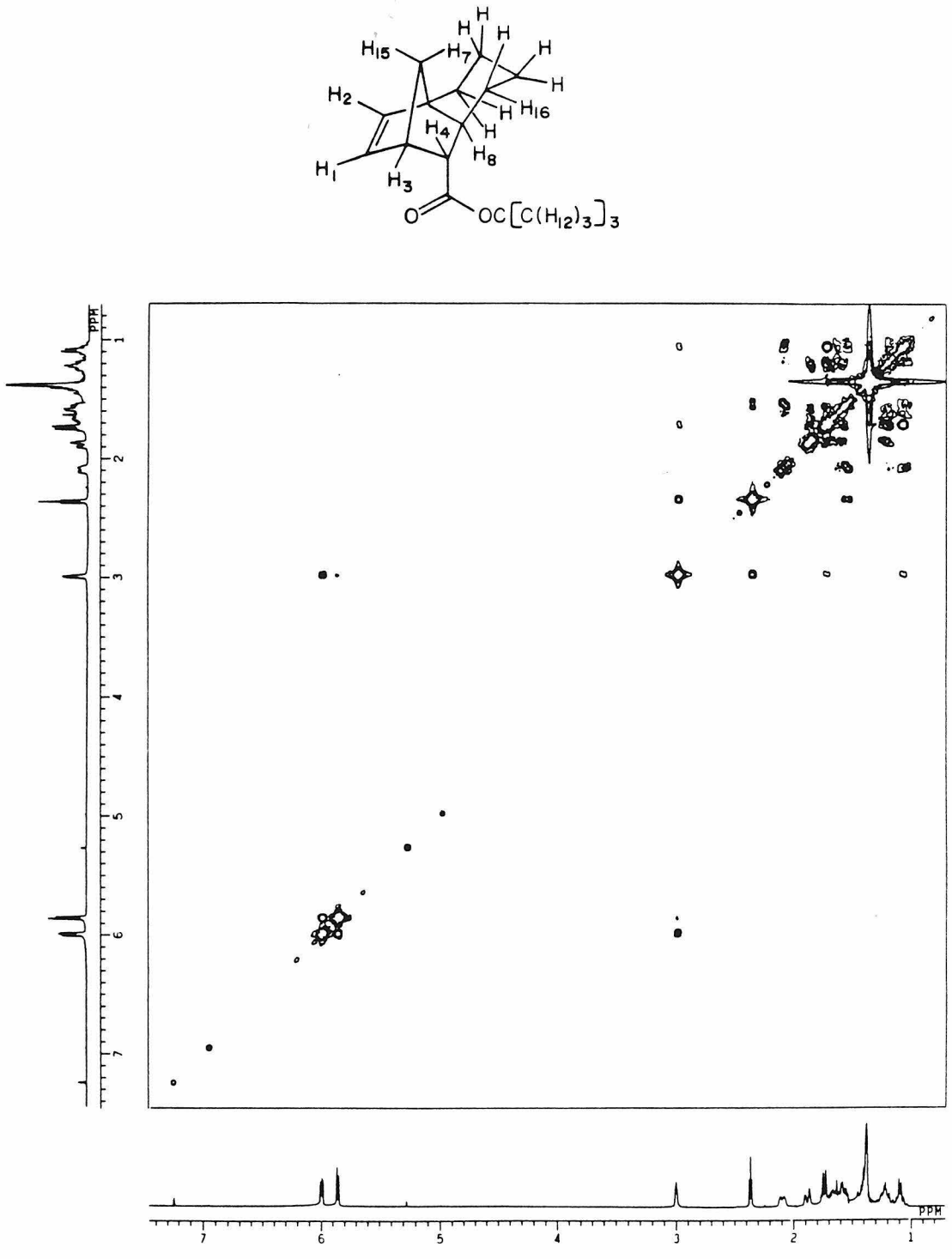


Figure 3. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum and Proton Resonance Assignments of **34** in $CDCl_3$.

to H_4. Due to resonance overlap, assignment of individual tether protons could not be made. The use of two-dimensional ^1H NMR allowed the skeletal connectivity and assignments of individual protons to be made, but could not distinguish between isomers **34** and **35**. Difference NOE studies allowed the structure to be determined. Saturation of the α-carbonyl proton H_4 produced enhancement in protons H_3, H_7, and H_{16}. The enhancement of one of the bridge protons (H_7) verified the structure as the *endo*-substituted isomer **34**. It also appeared as if proton H_{16} was a tether proton that occupied space close to that of proton H_4, and was possibly on the carbon connected to the bridgehead carbon containing H_8.

The minor product was isolated in a 17% yield. The proton NMR spectrum of this compound similarly exhibited the pattern of olefinic protons at 6.23 ppm and 6.01 ppm that resulted from the cycloaddition of **31**. A single bridgehead proton was also observed at 2.79 ppm. These results suggested that the structure of the minor product was that of **35**. The spectrum showed very few other similarities to that of **35** with regard to the patterns and distribution of proton resonances. There were no other proton resonances observed downfield of 2.00 ppm. The inability to distinguish the many overlapping protons that occurred between 1.20 ppm and 1.80 ppm greatly hindered characterization of **35**.

Two-dimensional ^1H-^1H correlated NMR aided in the partial assignment of proton resonances of **35**. (Figure 4). From the two-dimensional spectrum, it was easily seen that the J-coupling between proton H_2 and H_1 was very strong. Proton H_2 also displayed strong coupling to the bridgehead proton H_3 which, in turn, showed crosspeaks resulting from the coupling with the bridge protons H_6 and H_7. The distinctive pattern of the bridge protons could be distinguished among the other protons. As was the case for the *exo*-substituted ester **27**, cou-

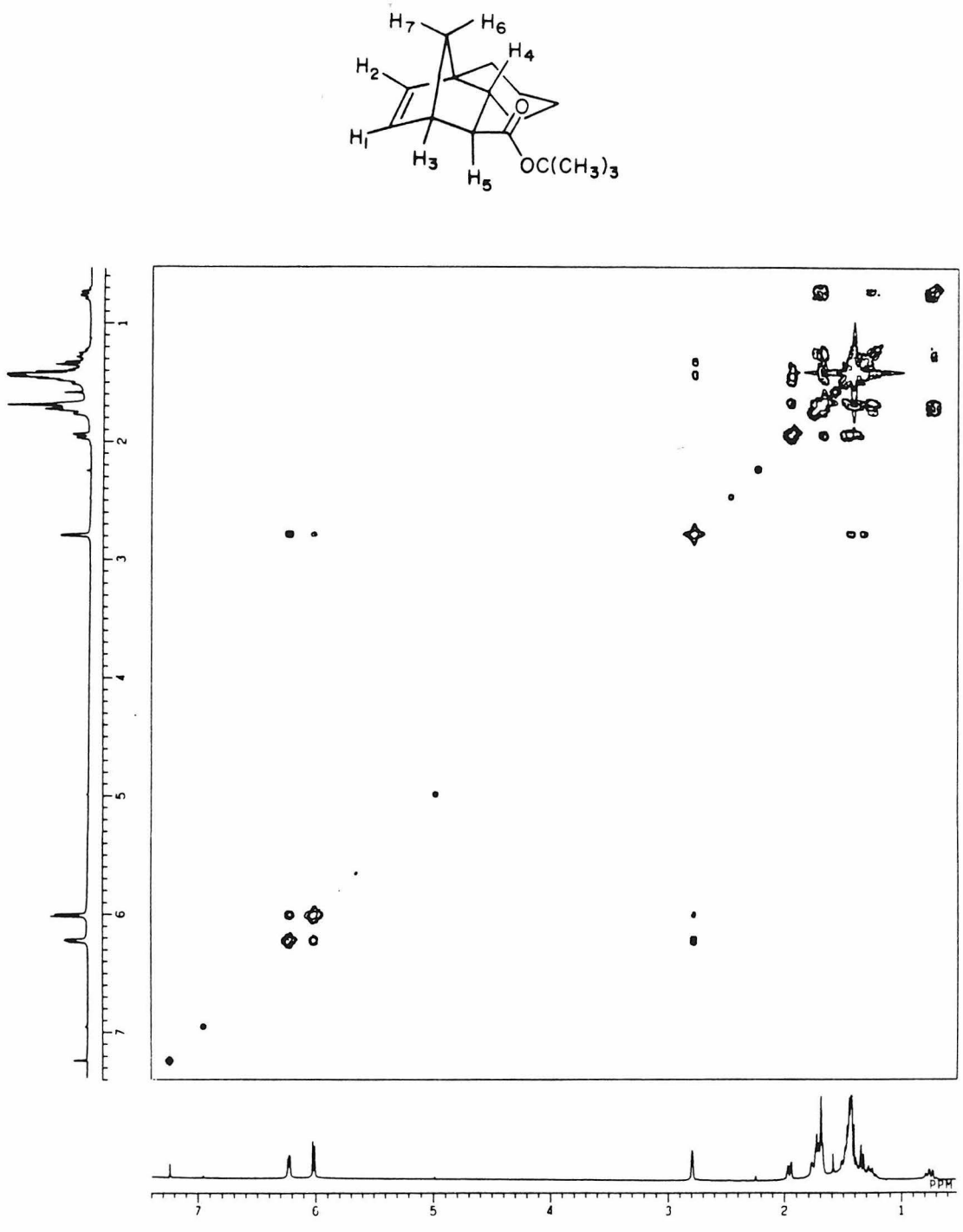


Figure 4. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum and Proton Resonance Assignments of **35** in $CDCl_3$.

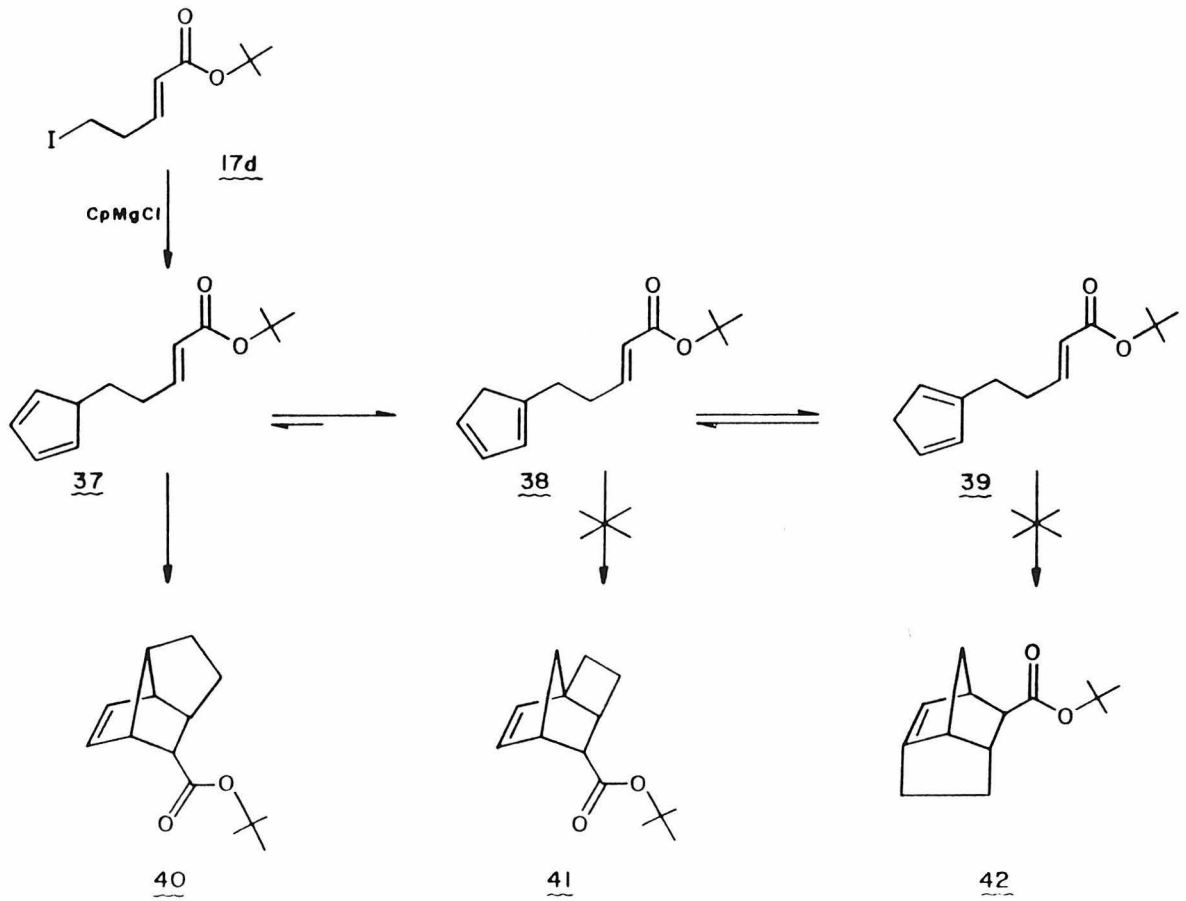
pling between H_3 and H_5 did not surface in the ^1H-^1H correlated spectrum. Through the use of difference NOE experiments, the distinction between *exo* and *endo* substitution was made. Saturation of H_1 showed enhancement of proton H_2 and H_3 as expected, but also enhanced a third proton previously believed to be H_5. Saturation of proton H_4 produced enhancement of the proton known to be H_6 and that suspected of being H_5. The results obtained from these experiments verified the *exo* position of the ester substituent and, thus, the confirmation of **35** as the minor isomer.

In order to enhance product selectivity in the cycloaddition of **31**, a solution of **31** and Et_2AlCl in CH_2Cl_2 was allowed to react at -15°C for 12 h. Analysis of the product distribution by capillary gas chromatography revealed a 73:27 ratio of **34** to **35** as the only cycloaddition products. Very little increase in product selectivity was exhibited under these conditions as compared to the product distribution obtained from the benzene solution at reflux.

Based on previously reported examples, the shorter tether of only two methylene units was expected to give a single product.[1] Following the normal procedure, a solution of 1.00 equivalent of CpMgCl was added to a solution of the iodide **17d** and stirred for 1 h at 0°C. A toluene solution of the product mixture was heated to reflux and maintained at that temperature for 18 h. These conditions produced a single cycloaddition product that contributed to 78% of the reaction mixture, while the remaining 22% was the result of intermolecular Michael addition chemistry. Isolation of the cycloaddition product was achieved in 53% yield.

Through the use of ^1H NMR, the product of the intramolecular Diels-Alder reaction was found to be compound **40**(Scheme VI). The occurrence of two olefinic proton resonances, each with a four-line pattern, and two of the typical broad

Scheme VI. Rearrangement and Cyclization Pathways Available upon Alkylation of **17d**.



singlets that are characteristic of bridgehead protons, strongly suggested the structure of isomer **40**. Again, the use of two-dimensional ^1H NMR experiments confirmed the topology of the tricyclic **40** (Figure 5). The two olefinic resonances, H_1 and proton H_2, coupled to one another and each coupled to a different bridgehead proton. Proton H_1 coupled to H_4; proton H_2 coupled to H_3. In turn, both bridgehead protons H_3 and H_4 displayed coupling to proton H_6 and, as before, weak four-bond coupling between H_3 and H_4 was observed. Coupling between H_4 and H_7 also arose. Proton H_3 displayed J-coupling to H_5, but the coupling between H_5 and H_7 was not detected by ^1H-^1H correlated NMR. This was not surprising as both protons H_6 and H_7 were bridgehead protons, and coupling to these protons is normally small and sometimes not detected. The remaining four protons on the two adjacent methylene groups were present and all coupled to one another. Assignment of their proton resonances could not be determined due to the absence of coupling between H_{12} and both H_6 and H_7, and due to the overlap of peaks H_8 and H_9 and the partial overlap of H_6 and H_7.

As expected from previous work in the area of intramolecular Diels-Alder reactions with the cyclopentadienes, two patterns became evident. Focusing attention on the smallest ring that the tether became incorporated in, these trends were clearly seen. Products tended not to form as a result of a 5-substituted cyclopentadiene intermediate. The products formed also had exclusive preference for five- and six-membered ring formation. From the coupling of **17b** with cyclopentadiene, the tricyclic structures did not arise from **23** even though the tether would have formed a six-membered ring. Instead, the tether became a part of a five-membered ring as in product **26**, and a six-membered ring in **27**. Tricyclic structures which resulted from a four-carbon tether, as in the alkylation of **17c**, produced only **34** and **35**. This demonstrated the preference for the

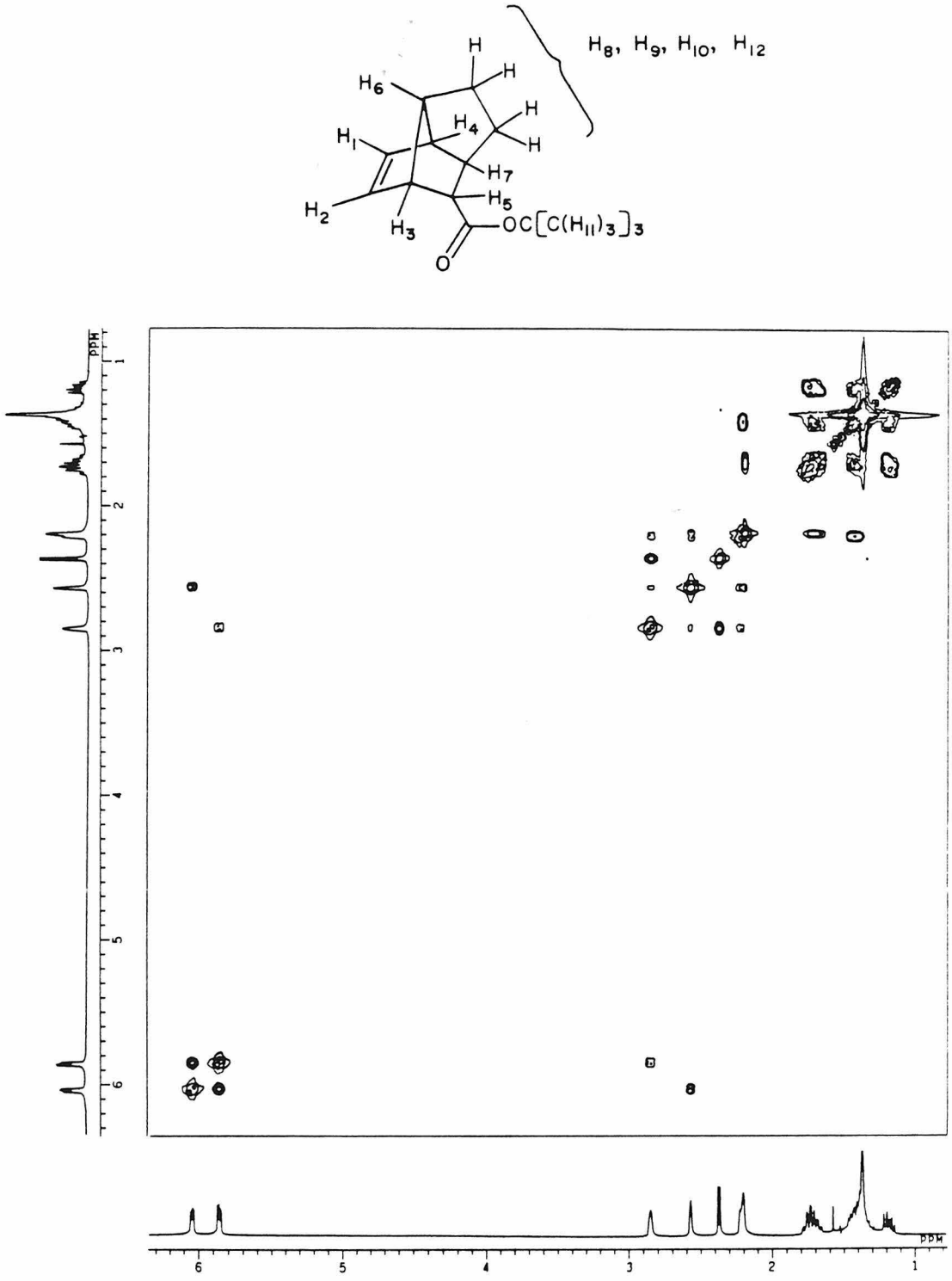


Figure 5. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum and Proton Resonance Assignments of **40** in $CDCl_3$.

six over the seven-membered ring systems of both **33** and **36**. If a stable five- or six-membered ring system could not be formed by any other intramolecular cycloaddition, it could occur from the 5-substituted cyclopentadiene such as **37**. The formation of **42** was unfavorable due to the generation of a structurally disallowed bridgehead olefin. Due to the added strain of a cyclobutane ring, **41** was not observed. However, for the formation of **40** to occur, elevated reaction temperatures and longer reaction times were mandatory.

The use of CpMgCl in the preparation of functionalized cyclopentadienes has already proven valuable as a method to prepare molecules of synthetic and theoretical interest. Incorporation of the use of **12** as a key intermediate in the total synthesis of capnellene provided an efficient route to this naturally occurring sesquiterpene.[8a] In addition, the use of tricyclic systems has exhibited enormous potential for the synthetic application toward the many other polyquinanes that exist.[6] The greater reactivity of the dienophile has also allowed the unexpected formation[2a] and subsequent isolation of the tricyclic bridgehead olefin **27**. The selective formation of functionalized cyclopentadienes through the use of cyclopentadienyl Grignard reagents, followed by intramolecular cycloaddition under mild conditions, provides an attractive route to naturally occurring ring systems.

Experimental Section

General Procedures. All manipulations of air and/or moisture sensitive compounds were carried out with use of standard Schlenk or vacuum line techniques. Argon was purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4Å molecular sieves. Solids were transferred in a nitrogen-filled Vacuum Atmospheres Dri-Lab equipped with an MO-40-1 purification train and a DK-3E Dri-Kool. Flash chromatography was performed according to the general procedure of Still,[27] employing Silica Woelm 32-63 (32-63 μm). Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates and visualized by phosphomolybdic acid dip.[28] All reaction temperatures were measured externally.

Materials. Diisopropylamine (Aldrich) was distilled from CaH_2 before use. Mesitylene (MCB Reagents) was stored over 4Å molecular sieves under argon. Pyridinium *p*-toluenesulfonate,[29] $(EtO)_2POCH_2CO_2C(CH_3)_3$,[30] and **14**[22] were prepared by reported methods. With the exception of NaI (Mallinckrodt), Et_2AlCl (Alfa), hydroquinone (MCB Reagents), and *p*-toluenesulfonyl chloride (MCB Reagents), all other chemicals were obtained from the Aldrich Chemical Company and used without further purification. $CDCl_3$ was stored over 4Å molecular sieves and filtered through Activity I alumina immediately prior to use. Pyridine was stored over 4Å molecular sieves. Dichloromethane was dried over P_2O_5 and degassed on a vacuum line. Pentane was stirred over H_2SO_4, dried over CaH_2, and vacuum-transferred onto sodium-benzophenone ketyl. Benzene and tetrahydrofuran (THF) were dried over CaH_2 and vacuum-transferred onto sodium-benzophenone ketyl. Diethyl ether (ether), toluene, benzene-d_6 (Cambridge Isotope Laboratories), THF-d_8 (Cambridge Isotope Laboratories) were degassed and stirred over sodium-benzophenone ketyl. The dried and degassed

solvents were vacuum-transferred into dry vessels equipped with Teflon valve closures and stored under argon. Reagent grade petroleum ether (35-60°C) was used without further purification.

Instrumentation. NMR spectra were recorded on a JEOL GX-400 (399.65 MHz ^{1}H; 100.40 MHz ^{13}C). Chemical shifts are reported versus residual solvent signals on the δ scale. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad), coupling constant (Hz), integration, and interpretation. Difference NOE experiments were performed according to published procedures and the results are described fully in the text of this paper.[31] Analytical gas chromatographic analysis (VPC) were performed on a Shimadzu GE-Mini 2 flame ionization instrument modified for capillary use and equipped with a Hewlett-Packard Model 339A integrator (column: 0.24 mm x 15 m DB1). The detector and injector temperature were 250°C. Column temperature and retention times (t_r) are as reported. Infrared analyses utilized a Beckman 4210 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Melting points were determined on a Thomas Hoover Unimelt capillary melting point apparatus and were uncorrected.

Combustion analyses were performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee) or by Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory.

Two-Dimensional ^{1}H-^{1}H Correlated NMR Spectra.[26] The data were acquired using a JEOL GX-400 NMR spectrometer operating at 399.65 MHz proton frequency. The pulse sequence was 90°-t_1-45°-Acquisition-Relaxation Delay; the phases of the pulses and receiver were cycled to provide quadrature detection in f_1 and selection of "P-type" peaks. The 90° ^{1}H pulse width on the 5 mm $^{1}H/^{13}C$ probe was 15.0 μs. The f_2 spectral width was 3201.0 Hz and the pulse

delay (PD) was 3.0 s. Two dummy scans were taken before each slice to eliminate nonequilibrium magnetization. Eight transients of 1 K data points were collected for 384 increments of t_1. The total acquistion time was 3.5 h. The data were zero-filled to 512 points in t_1, apodized with a sine-bell window function in both dimensions and Fourier transformed in both dimensions. The absolute value spectrum was calculated and the entire data set symmetrized.

Cyclopentadienylmagnesium Bromide. A solution of 30 mL MeMgBr (2.9*M*, 87.0 mmol in ether) was concentrated *in vacuo* and redissolved in an equal volume of THF. To this solution was added 11.50 g freshly distilled cyclopentadiene (174 mmol) at room temperature. The mixture was then heated to 75°C over the period of 30 min and maintained at that temperature for 4 h. After the solution was allowed to cool to ambient temperature, the mixture was concentrated to a slushy solid and placed under vacuum (0.001 mmHg) for 1 h. The nonvolatiles were dissolved in a minimal amount of ether/THF (1:1), filtered, and the mother liquor was allowed to cool to -25°C. This process produced crystalline material which was subsequently separated from the mother liquor and washed with cold ether (3 x 40 mL) to produce 22.50 g of crystalline solid.

To quantify the amount of CpMgBr per weight of white solid, integration of the cyclopentadienyl singlet (δ 6.03) was compared to that of added mesitylene. To a solution of 40 mg CpMgBr·n(THF) in 0.500 mL THF-d_8 was added mesitylene (8.8 mg, 0.073 mmol). Integral comparison to the mesitylene methyl groups showed the presence of 0.106 mmol CpMgBr. Thus, it was found that there were 377 mg powder per mmol of CpMgBr and that the overall yield of isolated CpMgBr, based on MeMgBr, was 59.6 mmol (69%).

Cyclopentadienylmagnesium Chloride. To 21.7 mL of 3.0*M* MeMgCl (65.0 mmol in THF) under argon atmosphere was added freshly distilled cyclopenta-

diene (8.59 g, 130 mmol). This mixture was stirred for 2 h at room temperature after which 10 mL of THF were added. The reaction mixture was heated to 65°C over the period of 30 min and maintained at that temperature for 2 h. After the solution was allowed to cool to ambient temperature, the mixture was concentrated to a slushy solid and placed under vacuum (0.001 mmHg) for 1 h. The mixture was washed (removal of liquid was performed via cannula) with ether (3 x 10 mL), pentane (2 x 15 mL), and once again with 10 mL ether. Residual solvent was removed *in vacuo* to produce 9.72 g CpMgCl·n(THF) as a white powder.

Analogous to CpMgBr, the amount of CpMgCl per weight of white solid was determined from the integration of the cyclopentadienyl singlet (δ 5.98) compared to that of added mesitylene. To a solution of 79 mg CpMgCl·n(THF) in 0.500 mL THF-d_8 was added mesitylene (16.6 mg, 0.138 mmol). Integral comparison to the mesitylene methyl groups showed the presence of 0.209 mmol CpMgCl. Thus, there were 378 mg powder per mmol of CpMgCl and the overall yield of isolated CpMgCl, based on MeMgCl, was 25.7 mmol (40%).

The reaction was repeated to yield 11.17 g of a white solid (425 mg powder/mmol CpMgCl, 26.3 mmol, 41%).

α,α-Dimethyl-γ-butyrolactone(9). A suspension of 40.83 g oil-free NaH (1.70 mol) in 700 mL dry THF was brought to reflux. To this vigorously stirred suspension was added a mixture of 270.5 g CH_3I (1.91 mol) and 58.6 g γ-butyrolactone (0.68 mol) over the period of 1.5 h. Reflux was then maintained for an additional 1.5 h. After cooling the mixture to 0°C, H_2O was added and the mixture was then acidified with 1*N* HCl. The aqueous mixture was continuously extracted with diethyl ether for 20 h. After removal of the solvent by distillation at atmospheric pressure, the product was distilled (bp 65°C, 8

mmHg) (lit: 10 mmHg, 74°C) to yield a slightly yellow oil. This oil was dissolved in ether, washed with saturated aqueous Na_2SO_3, and the aqueous layer extracted twice with ether. The organics were combined, dried over $MgSO_4$ and evaporated to give 58.86 g **9** (76%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (t, J=7.0 Hz, 2H, CH_2O), 2.06 (t, J=7.0 Hz, 2H, CH_2CH_2O), 1.20 (s, 6H, CH_3). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 181.8, 64.7, 38.7, 37.1, 24.3.

2,2-Dimethyl-4-hydroxybutanal(10). A solution of 10.00 g **9** (87.6 mmol) was dissolved in 200 mL dry, deoxygenated toluene under an argon atmosphere and cooled to -78°C. A solution of 1.00*M* diisobutylaluminum hydride (96.4 mmol in hexanes) was slowly added over the period of 15 min. The reaction mixture was stirred an additional 30 min at -78°C and was then poured into a rapidly stirring mixture of 90 mL acetic acid and 300 g ice. To this mixture was added 650 mL chloroform. After being stirred for 10 min, the aqueous layer was separated, and extracted three times with chloroform. The organic layers were combined, washed twice with saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The solution was then concentrated at reduced pressure (20 mmHg) at or below 0°C until it reached a volume of 225 mL. This solution of **10** was used without further purification.

[(Tetrahydro-3,3-dimethyl-2-furanyl)oxy]acetic Acid, *t*-Butyl Ester (11). A suspension of 2.31 g oil-free NaH (96.4 mmol) in 50 mL dry, deoxygenated benzene was cooled to 0°C. To this suspension, a solution of 24.31 g $(EtO)_2POCH_2CO_2C(CH_3)_3$ in 30 mL benzene was added over the period of 15 min. The reaction mixture was stirred for an additional 15 min at 0°C, warmed to room temperature, and then stirred at ambient temperature for 30 min. The solution of **10** ($\approx$ 87.6 mmol) was added slowly at such a rate so as not to exceed an internal reaction temperature of 35°C. After the the addition was complete,

it was stirred an additional 10 h at room temperature. The reaction mixture was then quenched with water and extracted three times with $CHCl_3$. The organics were washed with water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and then dried over $MgSO_4$. The organics were filtered through a pad of silica gel, washed through with ether, and concentrated *in vacuo*. Distillation from MgO (Kugelrohr, 55°C-65°C, 5 mmHg) yielded 16.73 g **11** (89%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (ddd, J=7.7, 8.4, 8.9 Hz, 1H, OCH_2), 3.77 (ddd, J=4.9, 8.4, 8.9 Hz, 1H, OCH_2), 3.76 (t, J=6.6 Hz, 1H, OCH), 2.24 (d, J=6.6 Hz, 2H, $CH_2CO_2C(CH_3)_3$), 1.74 (ddd, J=8.4, 8.4, 12.1 Hz, 1H, OCH_2CH_2), 1.66 (ddd, J=4.9, 7.7, 12.1 Hz, 1H, OCH_2CH_2), 1.41 (s, 9H, $C(CH_3)_3$), 1.01 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). ^{1}H NMR (400 MHz, C_6D_6) δ 3.97 (dd, J=3.8, 9.4 Hz, 1H, OCH), 3.67 (ddd, J=7.8, 8.2, 8.7 Hz, 1H, OCH_2), 3.59 (ddd, J=4.9, 8.5, 8.7 Hz, 1H, OCH_2), 2.38 (dd, J=9.4, 14.7 Hz, 1H, $CH_2CO_2C(CH_3)_3$), 2.16 (dd, J=3.8, 14.7 Hz, 1H, $CH_2CO_2C(CH_3)_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.35 (ddd, J=8.2, 8.5, 12.2 Hz, 1H, OCH_2CH_2), 1.27 (ddd, J=4.9, 7.8, 12.2 Hz, 1H, OCH_2CH_2), 0.78 (s, 3H, CH_3), 0.66 (s, 3H, CH_3). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 170.7, 82.9, 80.4, 65.5, 41.0, 40.5, 37.1, 28.3, 25.6, 22.0. IR (neat) 2965, 2880, 1734, 1370, 1315, 1150 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.10; H, 10.19.

(*E*)-4,4-Dimethyl-6-[[(4-methylphenyl)sulfonyl]oxy]hex-2-enoic Acid *t*-Butyl Ester (1c). To a solution of 2.48 g diisopropylamine (2.45 mmol) in 70 mL dry, deoxygenated THF under argon at -78°C, was added a solution of 1.60*M* *n*-butyllithium (24.5 mmol in hexanes) via syringe. The mixture was allowed to react 20 min at -78°C and then a solution of 4.78 g **11** (22.3 mmol) in 10 mL THF was slowly added. The reaction mixture was stirred at -78°C for 15 min, then warmed to -40°C. After stirring at -40°C for 20 min, the solution was returned

to -78°C at which time *p*-toluenesulfonyl chloride was added under the heavy flow of argon. The mixture was allowed to warm to room temperature slowly over the period of 8 h and to be stirred an additional 9 h at room temperature. After quenching with 200 mL 1*N* HCl, the mixture was extracted with ether (3 x 200 mL). The organics were combined, washed with 1*N* HCl (1 x 200 mL), saturated aqueous $NaHCO_3$ (2 x 200 mL), saturated aqueous NaCl, and dried over $MgSO_4$. The solution was concentrated to a yellow oil, taken up in petroleum ether/ether (4:1), filtered through a pad of silica gel to decolorize the solution, and washed through with the same solvent mixture. After concentration, the oil was taken up in petroleum ether/ether and slowly cooled to yield 6.83 g **1c** (83%) as a white crystalline solid: mp 71.5-72.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (br d, J=8.2 Hz, 1H, aromatic *H*'s), 7.31 (br d, J=8.2 Hz, 1H, aromatic *H*'s), 6.65 (d, J=15.9 Hz, 1H, C*H*CHCO$_2$R) 1.55 (d, J=15.9 Hz, 1H, CHC*H*CO$_2$R), 3.97 (t, J=7.3 Hz, 2H, CH_2CH_2O), 2.41 (s, 3H, $CH_3C_6H_4$), 1.72 (t, J=7.3 Hz, 2H, CH_2CH_2O), 1.45 (s, 9H, $C(CH_3)_3$), 1.00 (s, 6H, $(CH_3)_2$). ^{13}C (100.4 MHz, $CDCl_3$), δ 165.5, 154.2, 144.4, 132.8, 129.5, 127.6, 120.2, 80.3, 67.7, 40.4, 35.7, 28.3, 26.8, 21.9. IR (CCl_4) 2960, 1715, 1650, 1370, 1180, 1150 cm^{-1}.

Anal. Calcd for $C_{19}H_{28}O_5S$: C, 61.93; H, 7.66. Found: C, 61.97; H, 7.57.

(1S*,5S*,6S*,7R*)-4,4-Dimethyltricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic Acid, *t*-Butyl Ester (12). To a 0°C solution of 4.7 g **1c** (12.8 mmol) in 25 mL dry, deoxygenated THF was slowly added a solution of 25.7 mmol CpMgCl in 75 mL THF. The reaction mixture was stirred 3 h at 0°C and then for 1 h at room temperature. After dilution with 100 mL ether, the mixture was poured into 800 mL petroleum ether. This solution was filtered through a pad of silica gel and washed through with petroleum ether/ether (4:1). The resulting solution was concentrated to an oil and then taken up in 500 mL benzene and 50 mg

hydroquinone. The solution was slowly heated to 75°C over the period of 1 h and then heated at that temperature for 4 h. After cooling to room temperature, the reaction mixture was decolorized by filtration through silica gel and washed through with benzene. VPC analysis at 140°C revealed two cycloaddition products of t_r = 4.32 min (91%) and t_r = 5.88 min (9%). After removal of the volatiles, the resulting oil was taken up in 500 mL ether, concentrated to a colorless oil, which still contained traces of ether, and allowed to stand for 24 h exposed to atmosphere. At this time, the product at t_r = 5.88 min was absent. The oil was distilled (Kugelrohr, 75°C, 0.001 mmHg) to yield 2.73 g **12** (81%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, J=5.6 Hz, 1H), 5.99 (dd, J=2.7, 5.6 Hz, 1H), 3.10 (br s, 1H), 2.79 (dd, J=3.4, 5.6 Hz, 1H), 1.79-1.89 (m, 1H), 1.58-1.74 (m, 3H), 1.51-1.56 (m, 1H), 1.39 (s, 9H), 1.37-1.41 (m, 1H), 1.14 (ddd, J=1.8, 1.8, 8.1 Hz, 1H), 1.04 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 174.1, 142.0, 132.6, 79.6, 64.9, 61.3, 50.9, 47.8, 47.5, 44.4, 36.9, 32.8, 28.4, 27.8, 26.7. IR (neat) 2960, 2870, 1730, 1455, 1365, 1150 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.97; H, 9.94.

(*E*)-6-[[(4-methylphenyl)sulfonyl]oxy]hex-2-enoic Acid, Ethyl Ester (16a). A suspension of oil-free NaH (0.528 g, 22.0 mmol) in 20 mL dry, deoxygenated benzene was cooled to 0°C. To this suspension, 4.4 mL (22.0 mmol) of triethyl phosphonoacetate were slowly added via syringe. The reaction mixture was stirred for an additional 15 min, warmed to room temperature, and then stirred at ambient temperature for 30 min. A solution of **14a** (3.45 g, 20.0 mmol) in 14 mL benzene was slowly added to the mixture at such a rate so as not to exceed an internal reaction temperature of 35°C. After the addition was complete, the reaction was stirred an additional 10 h at room temperature. After quenching the reaction mixture with H_2O, the organics were extracted with Et_2O. The or-

ganics were washed with H_2O, saturated aqueous NaCl, and dried over $MgSO_4$. The mixture was filtered through a pad of silica gel, washed through with Et_2O, and concentrated *in vacuo* to yield a colorless oil. The oil was dissolved in 125 mL EtOH containing 0.525 g pyridinium *p*-toluenesulfonate and then heated to 60°C for 10 h. After the solution was cooled to room temperature, $NaHCO_3$ was added and the mixture was concentrated *in vacuo* at ambient temperature. The mixture was diluted with Et_2O, filtered through a pad of silica gel, and thoroughly washed through with Et_2O. The solution was concentrated *in vacuo* until no EtOH remained. This oil was taken up in 50 mL of dry pyridine and cooled to 0°C. To this pyridine solution was added 5.72 g (30.0 mmol) *p*-toluenesulfonyl chloride. The reaction was stirred at 0°C for 20 h and was then quenched with H_2O. The mixture was extracted three times with Et_2O. The combined organics were washed with 1*N* HCl until the washings were acidic, then washed with H_2O, followed by washing with saturated aqueous $NaHCO_3$, and then a saturated solution of NaCl. The organics were then dried over $MgSO_4$. Once dry, the mixture was concentrated to an oil *in vacuo* and purified by flash chromatography. The tosylate eluted with an R_f of 0.21 with petroleum ether/ether (3:2) and was collected and concentrated *in vacuo* to yield 3.87 g **16a** (62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J=8.0 Hz, 2H, aromatic *H*'s), 7.32 (d, J=8.0 Hz, 2H, aromatic *H*'s), 6.79 (td, J=6.9, 15.6 Hz, 1H, C*H*CHCO$_2$R), 5.70 (td, J=1.6, 15.6 Hz, 1H, CHC*H*CO$_2$R), 4.14 (q, J=7.1 Hz, 2H, OCH_2CH$_3$), 4.01 (t, J=6.4 Hz, 2H, OCH_2CH$_2$), 2.42 (s, 3H, CH_3C$_6$H$_4$), 2.22 (ddt, J=1.6, 6.9, 7.0 Hz, 2H, CH$_2$CH_2CH), 1.78 (m, 2H, CH$_2$CH_2CH$_2$), 1.25 (t, J=7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 165.7, 146.1, 144.5, 132.8, 129.6, 127.6, 122.3, 69.2, 60.3, 28.1, 27.5, 21.9, 14.5. IR (neat) 1731, 1600 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; Found: C, 57.61; H, 6.53.

Reaction of CpMgCl with 16a. To 204 mg (0.653 mmol) **17a** in 4.0 ml dry THF at −40°C was added a solution of 272 mg (0.718 mmol) CpMgCl in 3.0 mL THF. The reaction mixture was allowed to warm to room temperature over the period of 1 h, then was diluted with petroleum ether, and filtered through a pad of silica gel. The resulting solution was concentrated to an oil, taken up in 25 mL benzene, and heated 10 h at reflux. By filtering the reaction mixture through silica gel, the solution was decolorized. VPC analysis at 120°C revealed the presence of two products at t_r = 3.99 min (3%) and t_r = 4.35 min (97%). Infrared analysis showed the strong presence of an ester carbonyl (1732 cm^{-1}) that was not α,β-unsaturated. ^1H NMR (400 MHz, $CDCl_3$) showed only the presence of an almost equal mixture of **20** and **21**. The cycloaddition product was not observed due to the relatively small amounts that were present with respect to **20** and **21**. ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 175.7, 150.6, 148.6, 133.7, 133.0, 131.9, 130.6, 125.8, 125.1, 60.31, 60.29, 51.0, 50.1, 45.8, 44.6, 42.1, 41.2, 34.0, 32.9, 31.8, 30.8, 30.7, 25.1, 24.9, 22.9, 14.5, 14.4.

(*E*)-6-[[(4-methylphenyl)sulfonyl]oxy]hex-2-enoic Acid, *t*-Butyl Ester (16b). A suspension of 0.473 g oil-free NaH (19.7 mmol) in 12 mL dry, deoxygenated benzene was cooled to 0°C through the use of an ice bath. To this suspension, a solution of 4.97 g (19.7 mmol) of $(EtO)_2POCH_2CO_2C(CH_3)_3$ in 5 mL of benzene was slowly added. Upon completion of addition, the reaction mixture was stirred for an additional 15 min, warmed to room temperature, and then stirred at ambient temperature for 1 h. A solution of **14b** (3.09 g, 17.9 mmol) in 17 mL benzene was slowly added to the mixture so as not to exceed a reaction temperature of 35°C. After the addition was complete, the reaction mixture was stirred an additional 4 h at room temperature. The reaction mixture was quenched by the addition of H_2O and extracted three times with Et_2O. The organics were

washed with H_2O, saturated aqueous NaCl, and dried over $MgSO_4$. The organics were filtered through a pad of silica gel, washed through with ether and concentrated *in vacuo* to yield a colorless oil. The oil was dissolved in 100 mL EtOH and 0.500 g pyridinium *p*-toluenesulfonate and heated to 60°C for 2 h. After the solution was cooled to room temperature, $NaHCO_3$ was added and the mixture concentrated *in vacuo* at ambient temperature. The mixture was diluted with Et_2O, filtered through a pad of silica gel, and thoroughly washed through with Et_2O. The solution was concentrated *in vacuo*. The ester was purified by flash chromatography on silica gel with ether/petroleum ether (1:1) to give 3.16 g (95%) of the impure alcohol **15b**. The alcohol was taken up in 40 mL of dry pyridine and cooled to 0°C. To this pyridine solution was added 6.14 g (32.2 mmol) *p*-toluenesulfonyl chloride. The reaction mixture was stirred at 0°C for 24 h and then was quenched with H_2O. The combined organics were washed with 1*N* HCl until the washings were acidic, then washed with H_2O, followed by washing with saturated aqueous $NaHCO_3$, and then a saturated solution of NaCl. The organics were then dried over $MgSO_4$. Once dry, the mixture was concentrated *in vacuo* and purified by flash chromatography. The tosylate eluted with an R_f of 0.22 with petroleum ether/ether (2:1) to give 4.50 g (78% overall) of the tosylate **16b** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br d, J=8.2 Hz, 2H, aromatic *H*'s), 7.35 (br d, J=8.2 Hz, 2H, aromatic *H*'s), 6.72 (td, J=6.8, 15.6 Hz, 1H C*H*CHCO$_2$R), 5.67 (td, J=1.6, 15.6 Hz, 1H, CHC*H*CO$_2$R), 4.04 (t, J=6.2 Hz, 2H, OCH_2), 2.45 (s, 3H, CH_3C$_6$H$_4$), 2.21 (dtd, J=1.6, 6.6, 6.8 Hz, 2H, CH$_2$CH_2CH), 1.78 (tt, J=6.2, 6.6 Hz, 2H, CH$_2$CH_2CH$_2$), 1.47 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 164.8, 144.6, 144.2, 132.5, 129.3, 127.2, 123.7, 79.8, 69.1, 28.0, 27.6, 27.3, 21.5. IR (neat) 2980, 1711, 1658, 1601 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11. Found: C, 59.87; H, 6.99.

Reaction of CpMgCl with 16b. To 170 mg (0.500 mmol) **16b** in 3.0 mL dry THF at room temperature was added a solution of 227 mg (0.540 mmol) CpMgCl in 3.0 mL THF. The reaction mixture was stirred at room temperature for 15 min, diluted with petroleum ether, and filtered through a pad of silica gel. The solution was concentrated to an oil, taken up in 25 mL benzene, and heated at reflux for 12 h. VPC analysis at 120°C revealed the presence of two products at t_r = 3.48 min (4%) and t_r= 4.19 min (96%). ^{1}H NMR (400 MHz, $CDCl_3$) showed the major VPC peak to result from two isomers of a monosubstituted cyclopentadiene. The minor compound appeared to be **26** by the characteristic peaks at δ 6.20 (d, J=5.6 Hz, 1H) and 5.91 (dd, J=2.7, 5.6 Hz, 1H). There was no tosylate functionality observed. The reaction of one-half of the reaction mixture with 0.250 mmol maleic anhydride caused the disappearance of only the peak at t_r = 4.19 min by VPC analysis.

(*E*)-7-[[(4-methylphenyl)sulfonyl]oxy]hept-2-enoic Acid, *t*-Butyl Ester (16c). Following a procedure only slightly modified from that for **16b, 16c** was prepared starting with 3.50 g (18.8 mmol) **14c**. The aldehyde was added to the phosphonate anion as previously described and allowed to react 8 h at room temperature before standard workup. Removal of the tetrahydropyran protecting group was achieved as before and the alcohol was purified by flash chromatography. Elution on silica gel with petroleum ether/ether (1:1) produced 3.34 g (89%) of a colorless oil with R_f = 0.35. Transformation of the alcohol to the tosylate was complete within 20 h and standard workup produced crude **16c**. Isolation was achieved through the use of flash chromatography. The tosylate eluted with an R_f = 0.31 with petroleum ether/ether (3:1) to give 4.87 g (73% overall) of **16c** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br d, J=7.8 Hz, 2H, aromatic *H*'s), 7.36

(br d, J=7.8 Hz, 2H, aromatic *H*'s), 6.76 (td, J=6.8, 15.6 Hz, 1H, C*H*CHCO$_2$R), 5.69 (td, J=1.6, 15.6 Hz, 1H, CHC*H*CO$_2$R), 4.03 (t, J=6.4 Hz, 2H, OCH_2), 2.45 (s, 3H, CH_3C$_6$H$_4$), 2.12 (ddt, J=1.6, 6.8, 6.8 Hz, 2H, CH$_2$CH_2CHCH), 1.62-1.72 (m, 2H, OCH$_2$CH_2), 1.42-1.52 (m, 2H, OCH$_2$CH$_2$CH_2), 1.48 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100.4 MHz, CDCl$_3$) δ 165.0, 145.9, 144.1, 132.5, 129.3, 127.2, 123.1, 79.7, 69.7, 31.0, 28.1, 28.0, 23.8, 21.5. IR (neat) 2980, 2935, 1710, 1655, 1600 cm^{-1}.

Anal. Calcd for C$_{18}$H$_{26}$O$_5$S: C, 60.99; H, 7.39. Found: C, 60.96; H, 7.30.

(*E*)-5[[(4-methylphenyl)sulfonyl]oxy]pent-2-enoic Acid *t*-Butyl Ester (16d). Following a procedure only slightly modified from that for **16b, 16d** was prepared starting with 1.41 g (8.9 mmol) **14d**. The aldehyde was added to the phosphonate anion as previously described and allowed to react 1 h at room temperature before standard workup. Removal of the tetrahydropyranyl protecting group was achieved as before and the alcohol was purified by flash chromatography. Elution on silica gel with ether/petroleum ether (3:2) produced 1.26 g (82%) of a colorless oil with R_f = 0.25. Transformation of the alcohol to the tosylate was complete within 20 h and standard workup produced crude **16d**. Isolation was achieved through the use of flash chromatography. The tosylate eluted with an R_f = 0.23 it petroleum ether/ether (2:1) to give 1.86 g (64% overall) of **16d** as a colorless oil which solidified over several days. Crystals were obtained using ether/pentane: mp 76.0 – 77.0°C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (br d, J=8.3 Hz, 2H, aromatic *H*'s), 7.32 (br d, J=8.3 Hz, 2H, aromatic *H*'s), 6.62 (td, J=6.8, 15.9 Hz, 1H, C*H*CHCO$_2$R), 5.72 (td, J=1.5, 15.9 Hz, 1H, CHC*H*CO$_2$R), 4.07 (t, J=6.5 Hz, 2H, OCH$_2$), 2.48 (dtd, J=1.5, 6.5, 6.8 Hz, 2H, OCH$_2$CH_2), 2.42 (s, 3H, CH_3C$_6$H$_4$), 1.44 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100.4 MHz, CDCl$_3$) δ 164.7, 144.6, 140.4, 132.6, 129.6, 127.6, 125.9, 80.4, 68.1, 31.6, 28.3, 21.9. IR

(neat) 2975, 2925, 1713, 1658, 1601 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_5S$: C, 58.88; H, 6.79. Found: C, 59.13; H, 7.03.

(*E*)-6-Iodohex-2-enoic Acid, *t*-Butyl Ester (17b). A solution of 1.66 g **16b** (4.9 mmol) and 2.19 g NaI (14.6 mmol) in dry acetone was heated to 45°C under argon atmosphere and allowed to stir for 2 h. After the mixture had cooled to room temperature, the mixture was concentrated *in vacuo*. The resulting slush was taken up in ether, filtered through a pad of silica gel, and washed through with ether. Concentration of the organics produced a yellow oil. Distillation of this oil (Kugelrohr, 65–70°C, 0.1 mmHg) produced 1.40 g **17b** (97%) of a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (td, J=7.1, 15.6 Hz, 1H, C*H*CHCO$_2$R), 5.80 (td, J=1.7, 15.6 Hz, 1H, CHC*H*CO$_2$R), 3.19 (t, J=6.8 Hz, 2H, IC*H*$_2$) 2.30 (ddt, J=1.7, 7.1, 7.1 Hz, 2H, ICH$_2$CH$_2$C*H*$_2$), 1.97 (m, 2H, ICH$_2$C*H*$_2$), 1.48 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 164.9, 144.5, 123.7, 79.8, 32.4, 31.4, 28.0, 5.4. IR (neat) 2980, 2935, 1720, 1660 1370, 1165 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79. Found: C, 40.28; H, 5.71.

(*E*)-7-Iodohept-2-enoic Acid, *t*-Butyl Ester (17c). Using the same procedure as that outlined for the preparation of **17b**, 2.98 g **16c** (8.42 mmol) was transformed into the crude iodide **17c**. Distillation of this oil (Kugelrohr, 80 – 85°C, 0.1 mmHg) produced 2.51 g **17c** (96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (td, J=6.9, 15.5 Hz, 1H, C*H*CHCO$_2$R), 5.75 (td, J=1.6, 15.5 Hz, 1H, CHC*H*CO$_2$R), 3.19 (t, J=7.1 Hz, 2H, IC*H*$_2$), 2.20 (ddt, J=1.6, 6.9, 6.9 Hz, 2H, CH$_2$C*H*$_2$CHCH), 1.80-1.90 (m, 2H, ICH$_2$C*H*$_2$), 1.44-1.64 (m, 2H, ICH$_2$CH$_2$C*H*$_2$), 1.48 (s, 9H, C(C*H*$_3$)$_3$). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 165.1, 146.1, 123.0, 79.8, 32.6, 30.7, 28.8, 28.0, 6.1. IR (neat) 2980, 2935, 1712, 1658, 1370, 1165 cm^{-1}.

Anal. Calcd. for $C_{11}H_{19}IO_2$: C, 42.60; H, 6.17. Found: C, 42.41; H, 6.12.

(*E*)-5-Iodopent-2-enoic Acid, *t*-Butyl Ester (17d). Using the same procedure as that outlined for the preparation of **17b**, 1.19 g **16d** (3.6 mmol) was transformed into the crude iodide **17d**. Distillation of this oil (Kugelrohr, 55 – 60°C, 0.1 mmHg) produced 0.98 g **17d** (95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (td, J=6.8, 15.6 Hz, 1H, C*H*CHCO$_2$R), 5.77 (td, J=1.5, 15.6 Hz, 1H, CHC*H*CO$_2$R), 3.16 (t, J=7.1 Hz, 2H, ICH_2), 2.73 (ddt, J=1.5, 7.1, 6.8 Hz, 2H, ICH$_2$CH_2), 1.45 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 164.9, 144.4 124.7, 80.4, 36.0, 28.3, 1.9. IR (neat) 2980, 2935, 1715, 1655, 1370, 1160 cm^{-1}.

Anal. Calcd for $C_9H_{15}IO_2$: C, 38.32; H, 5.36. Found: C, 38.38; H, 5.60.

(1R*,5S*,6R*,7S*)-Tricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic Acid, *t*-Butyl Ester (26), and (1S*,7R*,8R*,10R*) -Tricyclo-[5.2.1.0^{3,8}]dec-2-ene-10-carboxylic Acid, *t*-Butyl Ester (27). To 296 mg **17b** (1.00 mmol) in 5.0 mL dry THF at 0°C was slowly added 4.0 mL of 0.25*M* CpMgCl (1.00 mmol) in THF. The reaction was stirred at 0°C for 1 h and then allowed to warm to room temperature over the period of 1.5 h. The reaction mixture was diluted with 40 mL hexane, filtered through a silica gel pad and then washed through with petroleum ether/ether (4:1). After concentration of the solution, the nonvolatile compounds were taken up in 60 mL benzene and 5 mg hydroquinone and heated to reflux. Reflux was maintained for 2 h. VPC analysis at 120°C revealed the presence of three products with t_r = 4.07 min (75%), 4.84 min (14%), and 5.10 min (12%). The solution was concentrated with reduced pressure to a volume of 5 mL, and 20 mg maleic anhydride (0.20 mmol) was added with stirring. The mixture was allowed to react for 2 h at ambient temperature at which time the product of t_r = 4.84 min was absent. The reaction mixture was concentrated *in vacuo* and isolation of the two products was achieved by flash chromatography. Elution on silica gel with petroleum ether/ether (40:1) produced 160 mg **26** (68%) of R_f = 0.23 and

14 mg **27** (6%) of $R_f = 0.26$.

26: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, J=5.6 Hz, 1H), 5.91 (dd, J=2.7, 5.6 Hz, 1H), 3.13 (br s, 1H), 2.63 (dd, J=3.8, 3.8 Hz, 1H), 2.00-2.10 (m, 1H), 1.78-1.96 (m, 4H), 1.60-1.72 (m, 1H), 1.35-1.44 (m, 1H), 1.38 (s, 9H), 1.20-1.30 (m, 2H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 173.5, 141.6, 132.0, 79.6, 63.8, 52.4, 52.1, 50.3, 49.4, 31.2, 28.3, 27.1, 27.0. IR (neat) 3060, 2980, 2880, 1730, 1565, 1460, 1370, 1150 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.72; H, 9.33.

27: ^{1}H NMR (400 MHz, $CDCl_3$) assignment as in Figure 2: δ 5.55 (br, s 1H, H_1), 3.00 (br s, 1H, H_2), 2.57-2.62 (m, 1H, H_3), 2.50-2.54 (m, 1H, H_4), 2.32 (ddd, J=2.0, 5.9, 11.5 Hz, 1H, H_5), 2.03 (ddd, J=4.6, 11.4 Hz, 11.4, 1H, H_6), 1.69-1.79 (m, 1H, H_7), 1.71 (dd, J=1.2, 3.7 Hz, 1H, H_8), 1.35-1.65 (m, 3H, H_9,H_{10},H_{11}), 1.42 (s, 9H, H_{12}), 1.14-1.32 (m, 2H, H_{13}, H_{14}). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 174.4, 149.1, 128.7, 79.8, 51.9, 50.3, 50.2, 43.8 40.3, 30.3, 30.0, 28.4, 27.1. IR (neat) 2940, 2860, 1728, 1600, 1370, 1165, 1150 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.45; H, 9.70.

Cycloaddition of 22 at 23°C. To 296 mg **17b** (1.00 mmol) in 5.0 mL dry THF at 0°C was added 4.0 mL of 0.25*M* CpMgCl (1.00 mmol) in THF. After being stirred for 1 h at 0°C, the reaction mixture was diluted with 50 mL petroleum ether. The mixture was filtered through a silica gel pad and washed through with petroleum ether/ether (4:1). The concentration of the solution to a colorless oil was achieved *in vacuo* at or below room temperature. The mixture was then taken up in 100 mL benzene and 5 mg hydroquinone and allowed to stand 4 day at room temperature. An aliquot of the solution was concentrated *in vacuo*, and taken up in C_6D_6. ^{1}H NMR showed the cycloaddition to be greater than 95% complete. By integration of the olefin resonances, the ratio of **26** to **27** was

established as greater than 98:2. After the addition of 3 mg maleic anhydride, the sample was allowed to stand for 2 h. Analysis of the sample by capillary gas chromatography revealed a 98.5:1.5 ratio of **26** to **27**.

Cycloaddition of 23 catalyzed by Et_2AlCl at -15°C. To 296 mg **17b** (1.00 mmol) in 5.0 mL dry THF at 0°C were slowly added 4.0 mL of 0.25*M* CpMgCl (1.00 mmol) in THF. After stirring for 1 h at 0°C, the reaction mixture was diluted with 50 mL petroleum ether. The mixture was filtered through a silica gel pad and washed through with petroleum ether/ether (4:1). Concentration of the solution to a colorless oil was achieved *in vacuo* at or below room temperature. The mixture was taken up in 15 mL ether and allowed to stand 4 h at room temperature. The ether was then removed *in vacuo* and replaced with 15 mL dry, deoxygenated methylene chloride. After cooling to −78°C, 78 μL of 1.8*M* Et_2AlCl (1.4 mmol) were added slowly via syringe and stirred 15 min at −78°C. The reaction mixture was warmed to −15°C (ethylene glycol, CO_2) and stirred for 5 h. Over an additional 10 h, the solution was allowed to warm to 15°C. The reaction was quenched with saturated aqueous ammonium chloride, and extracted with ether. Analysis by capillary gas chromatography revealed the only cycloaddition product to be **26**; **27** was not detected.

(1R*,6S*,7R*,8S*)-Tricyclo[6.2.1.0^{1,6}]undec-9-ene-7-carboxylic Acid, *t*-Butyl Ester (34), and (1R*,6R*,7S*,8S*)-Tricyclo[6.2.1.0 ^{1,6}]undec-9-ene-7-carboxylic Acid, *t*-Butyl Ester (35). To 310 mg **17c** (1.00 mmol) in 5.0 mL dry THF at 0°C was slowly added 4.0 mL at 0.25*M* CpMgCl (1.00 mmol) in THF. After being stirred for 1 hr at 0°C, the reaction was diluted with 50 mL petroleum ether. The mixture was filtered through a silica gel pad and washed through with petroleum ether/ether (4:1). Concentration of the solution *in vacuo* produced a colorless oil. Cycloaddition was accomplished by dissolving the mixture in

50 mL benzene and 5 mg hydroquinone. The solution was brought to reflux, maintained at reflux for 4 h, and then cooled to room temperature. Analysis of the mixture by capillary gas chromatography at 125°C revealed the presence of three products with t_r = 4.83 min (28%) 5.21 min (63%), and 5.34 min (9%). The solution was concentrated *in vacuo* to a volume of 5 mL and 20 mg maleic anhydride (0.20 mmol) was added with stirring. The mixture was allowed to react for 3 h at ambient temperature at which time the product of t_r = 5.34 was absent. The reaction mixture was concentrated *in vacuo* and isolation of the two products was achieved by flash chromatography. Elution on silica gel with petroleum ether/ether (40:1) produced 43 mg **35** (17%) of R_f = 0.29 and 99 mg **34** (40%) of R_f = 0.24.

34: ^{1}H NMR (400 MHz, $CDCl_3$) assignments as in Figure 3: δ 5.99 (dd, J=2.9, 5.6 Hz, 1H, H_1), 5.85 (d, J=5.6 Hz, 1H, H_2), 2.99 (br s, 1H, H_3), 2.36 (dd, J=3.8, 3.8 Hz, 1H, H_4), 2.05-2.13 (m, 1H, H_5), 1.88 (br d, J=12.2 Hz, 1H, H_6), 1.62-1.78 (m, 4H, H_7, H_8, H_9, H_{10}), 1.30-1.46 (m, 1H, H_{11}), 1.38 (s, 9H, H_{12}), 1.16-1.30 (m, 2H, H_{13},H_{14}), 1.12-1.16 (m, 2H, H_{15},H_{16}). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 173.4, 143.0, 133.5, 79.5, 54.8, 53.0, 48.3, 46.4, 41.9, 33.4, 30.0, 28.4, 26.5, 23.6. IR (neat) 2980, 2925, 2860, 1726, 1370, 1255, 1160, 1150 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.44; H, 10.00.

35: ^{1}H NMR (400 MHz, $CDCl_3$) assignments as in Figure 4: δ 6.23 (dd, J=3.2, 5.6 Hz, 1H, H_1), 6.01 (d, J=5.6 Hz, 1H, H_2), 2.77-2.81 (m, 1H, H_3), 1.92-1.99 (m, 1H, H_4), 1.65-1.80 (m, 6H), 1.43 (s, 9H, $C(CH_3)_3$), 1.34 (br d, J=8.30 Hz, 1H, H_7), 1.20-1.53 (m, 3H), 0.75 (m, 1H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 175.2, 137.1, 137.0, 79.7, 53.3, 52.6, 52.2, 48.5, 46.7, 30.8, 30.7, 28.4, 27.1, 24.0. IR (neat) 2975, 2920, 2850, 1730, 1365, 1150, 1125 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.34; H, 9.67.

Cycloaddition of 31 catalyzed by Et_2AlCl at -15°C. The coupling of CpMgCl and **17c** was performed as before. The mixture of substituted cyclopentadienes was taken up in 15 mL ether and allowed to stand 4 h at room temperature. The ether was then removed *in vacuo* and replaced with 15 mL dry, deoxygenated methylene chloride. After cooling to −78°C, 78 μL of 1.8*M* Et_2AlCl (1.4 mmol) were added slowly via syringe and stirred for 15 min at −78°C. The reaction was warmed to −15°C (ethylene glycol, CO_2) and stirred for 12 h at −15°C. The reaction was quenched with saturated ammonium chloride, and extracted with ether. VPC analysis revealed the ratio of **34** to **35** to be 73:27.

(1R*,2S*,3R*,6S*)-Tricyclo[4.3.0.0^{3,7}]non-4-ene-2-carboxylic Acid, *t*-Butyl Ester (40). To 282 mg **17d** (1.00 mmol) in 5.0 mL dry THF at 0°C was slowly added 4.0 mL of 0.25 M CpMgCl (1.00 mmol) in THF. After being stirred for 1 h at 0°C, the reaction mixture was diluted with 50 mL petroleum ether. The mixture was filtered through a silica gel pad and washed through with petroleum ether/ether (4:1). Concentration of the solution *in vacuo* produced a colorless oil. Cycloaddition was accomplished by dissolving the mixture in 120 mL dry, deoxygenated toluene and 5 mg hydroquinone. The reaction mixture was heated to reflux under an argon atmosphere and maintained at reflux for 18 h. Analysis of the mixture by capillary gas chromatography at 120°C revealed the presence of two products with t_r = 3.10 min (78%) and 3.41 min (22%). The solution was concentrated to a volume of 5 mL and 40 mg maleic anhydride (0.40 mmol) was added with stirring. The mixture was allowed to react for 2 h at ambient temperature at which time the product of t_r = 3.41 min was absent. The reaction mixture was concentrated *in vacuo* and isolation of the product was achieved by flash chromatography. Elution on silica gel with petroleum ether/ether (40:1) produced 116 mg **40** (53%) of R_f = 0.18 as a colorless oil: ^{1}H NMR (400 MHz,

$CDCl_3$) assignments as in Figure 5: δ 6.04 (dd, J=2.9, 5.6 Hz, 1H, H_1), 5.86 (dd, J=2.7, 5.6 Hz, 1H, H_2), 2.83-2.88 (m, 1H, H_3), 2.57 (br s, 1H, H_4), 2.37 (d, J=4.9 Hz, 1H, H_5), 2.18-2.26 (m, 2H, H_6, H_7), 1.65-1.80 (m, 2H, H_8, H_9), 1.33-1.48 (m, 1H, H_{10}), 1.37 (s, 9H, H_{11}), 1.13-1.23 (m, 1H, H_{12}). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 172.6, 133.7, 132.9, 79.6, 63.1, 53.1, 50.8, 50.2, 38.9, 34.4, 28.4, 22.1. IR (neat) 3060, 2975, 2870, 1733, 1370, 1240, 1160, 1120 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.12; H, 9.16.

References and Notes

(1) For recent reviews on the intramolecular Diels-Alder reaction see: (a) Brieger, G.; Bennett, J.N. *Chem. Rev.* **1980**, *80*, 63. (b) Ciganek, E. *Org. React.* **1984**, *32*, 1. (c) Fallis, A.G. *Can.J.Chem.* **1984**, *62*, 183.

(2) (a) Breitholle, E.G.; Fallis, A.G. *Ibid.* **1976**, 54, 1991. (b) Breitholle, E.G.; Fallis, A.G. *J. Org. Chem.* **1978**, *43*, 1964.

(3) Landry, D.W. *Tetrahedron* **1983**, *39*, 2761.

(4) (a) Snowden, R.L. *Tetrahedron Lett.* **1981**, 97. (b) Snowden, R.L. *Ibid.* 101.

(5) (a) Attah-Poku, S.K.; Gallacher, G.; Ng, A.S.; Taylor, L.E.B.; Alward, S.J.; Fallis, A.G. *Tetrahedron Lett.* **1983**, 677. (b) Attah-Poku, S.K.; Alward, S.J.; Fallis, A.G. *Ibid.* 681. (c) Gallacher, G.; Ng, A.S.; Attah-Poku, S.K.; Antczak, K.; Alward, S.J.; Kingston, J.F.; Fallis, A.G. *Can. J. Chem.* **1984**, *62*, 1709. (d) Attah-Poku, S.K.; Antczak, K.; Alward, S.J.; Fallis, A.G. *Ibid.* 1717.

(6) For a review of polyquinanes, naturally occurring or of general synthetic interest, see: Paquette, L.A. *Top. Curr. Chem.* **1984**, *119*, 1.

(7) Sternbach, D.D.; Hughes, J.W.; Burdi, D.F.; Banks, B.A. *J. Am.Chem. Soc.* **1985**, *107*, 2149.

(8) (a) Stille, J.R.; Grubbs, R.H., unpublished results. (b) Sternbach, D.D.; Hughes, J.W.; Burdi, D.F.; Forstot, R.M. *Tetrahedron Lett.* **1983**, 3295. (c) Sternbach, D.D., unpublished results.

(9) An alternate route to capnellene is also in progress: Hellou, J.; Kingston, J.F.; Fallis, A.G., unpublished results.

(10) For a review on asymmetric Diels-Alder reactions see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876.

(11) (a) Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* **1984**, 4071.

(b) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (c) Oppolzer, W.; Chapuis, C.; Kelly, M.J. *Helv. Chim. Acta* **1983**, *66*, 2358. (d) Roush, W.R., Gillis, H.R.; Ko, A.I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (e) Ensley, H.E.; Parnell, C.A.; Corey, E.J. *J. Org. Chem.* **1978**, *43*. 1610.

(12) Wallquist, O.; Rey, M; Dreiding, A.S. *Helv. Chim. Acta* **1983**, *66*, 1891.

(13) McLean, S.; Haynes, P. *Tetrahedron* **1965**, *21*, 2329.

(14) Sternbach, D.D.; Hughes, J.W.; Burdi, D.F. *J. Org. Chem.* **1984**, *49*, 201, and unpublished results.

(15) Mironov, V.A.; Sobolev, E.V.; Elizarova, A.N. *Tetrahedron* **1963**, *19*, 1939.

(16) Smith, A.B., III,; Malamas, M.S. *J. Org. Chem.* **1982**, *47*, 3442.

(17) Baas, J.L.; Davies-Fidder, A.; Huisman, H.O. *Tetrahedron* **1966**, *22*, 285.

(18) Kraus, G.A.; Frazier, K.A.; Roth, B.D.; Taschner, M.J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.

(19) Castonguay, A.; Brassard, P. *Can. J. Chem.* **1977**, *55*, 1324.

(20) Both CpMgBr and CpMgCl are interchangeable in these reactions. For synthetic purposes, however, CpMgCl is easier to prepare.

(21) For ^{1}H NMR information on bicyclo[2.2.1]heptene compounds see: (a) Mellor, J.M.; Webb, C.F. *J. Chem. Soc. Perkin Trans. II* **1974**, 26. (b) Davis, J.C., Jr.; Van Auken, T. *J.Am.Chem.Soc.* **1965**, *87*, 3900.

(22) (a) For n=2: Vesato, S.; Kobayashi, K.; Inouye, H. *Chem. Pharm. Bull.* **1982**, *30*, 927. (b) For n=3: Vig, O.P.; Sharma, M.L.; Gakhar, M.; Malik, N. *Ind. J. Chem. Sect. B* **1980**, *19*, 755. (c) For n=1: Danieli, B.; Lesma, G.; Palmisano, G.; Tollari, S. *J. Chem. Soc. Perkin Trans. I* **1984**, 1237.

(23) For examples of magnesium enolates generated by conjugate addition to α,β-unsaturated carbonyls see: (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.*

1981, 913. (b) Munch-Peterson, J. *Org. Synth. Coll.* **1973**, *5*, 762.

(24) (a) Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Chem. Soc. Chem. Commun.* **1979**, 82. (b) Shea, K.J.; Wise, S.; Burke, L.D.; Davis, P.D.; Gilman, J.W.; Greeley, A.C. *J. Am. Chem. Soc.* **1982**, *104*, 5708.

(25) Bridges, A.J.; Whitham, G.H. *J. Chem. Soc. Perkin Trans I* **1975**, 2264.

(26) For information on two-dimensional NMR see: Bax, A. *Two-Dimensional Nuclear Magnetic Resonance in Liquids.* D. Reidel Pub. Co.: Boston, 1982.

(27) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(28) Touchstone, J.C.; Dobbins, M.F. *Practice of Thin Layer Chromatography.* John Wiley & Sons: New York, 1978, p. 207.

(29) Miyashita, N.; Yoshikoshi, A.; Grieco, P.A. *J. Org. Chem.* **1977**, *42*, 3772.

(30) Griffiths, G.F.; Kenner, G.W.; McCombie, S.W.; Smith, K.M.; Sutton, M.J. *Tetrahedron* **1976**, *32*, 275.

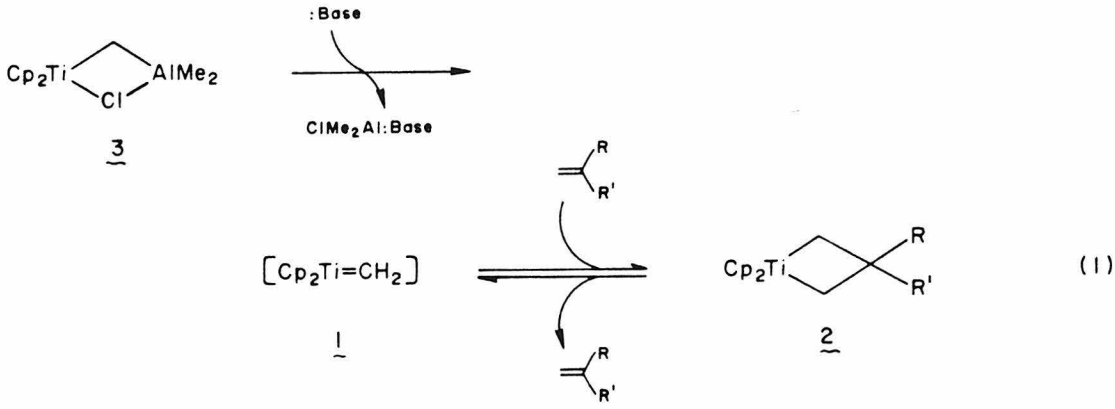
(31) (a) Hall, L.D.; Sanders, J.K.M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. (b) Sanders, J.K.; Mersh, J.D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982** *15*, 353.

CHAPTER 5

The Ring-Opening Metathesis of Bicyclo[2.2.1]heptene Ring Systems by Titanocene Alkylidene Complexes and Subsequent Intramolecular Trapping by an Ester Substituent to Form Bicyclo[3.2.0]heptene Enol Ethers

Introduction

In recent years, titanium catalyzed olefin metathesis has become a very well-understood process. Titanium complexes capable of generating the titanocene methylidene species (**1**, eq 1) have been shown to display catalytic metathesis activity. Initially, the dimethyl aluminum chloride adduct **3** was isolated by Tebbe and coworkers and found to slowly catalyze the selective exchange of terminal methylene groups of isobutene and methylene cyclohexane.[1] Addition



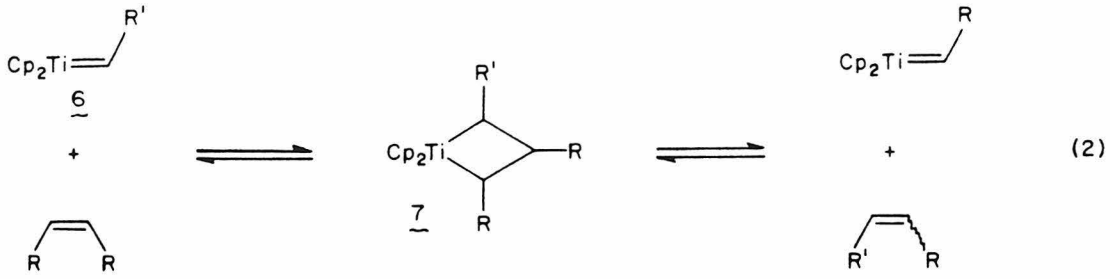
(1)

of a stronger Lewis base cocatalyst to this titanium complex produced a rapid and efficient metathesis catalyst.[2] Intermediates in this process were isolated and structurally characterized as titanacyclobutanes.[3] These olefin adducts (**2**), which can regenerate the olefin and **1**, also exhibited the ability to catalyze the degenerate metathesis of terminal olefins.[4] Even in the absence of cocatalyst, the intermediate titanacyclobutanes were found to be efficient catalysts of methylene exchange.

Despite the ability of **1** to catalyze degenerate metathesis, the productive metathesis of 1,2-disubstituted olefins was a very inefficient process.[5] Thermolysis of the α,β-disubstituted metallacycle derived from the cycloaddition of **1** to cyclopentene, quantitatively regenerated cyclopentene.[6] Thus, the prevalent pathway for the dissociation of this intermediate α,β-disubstituted metallacycle

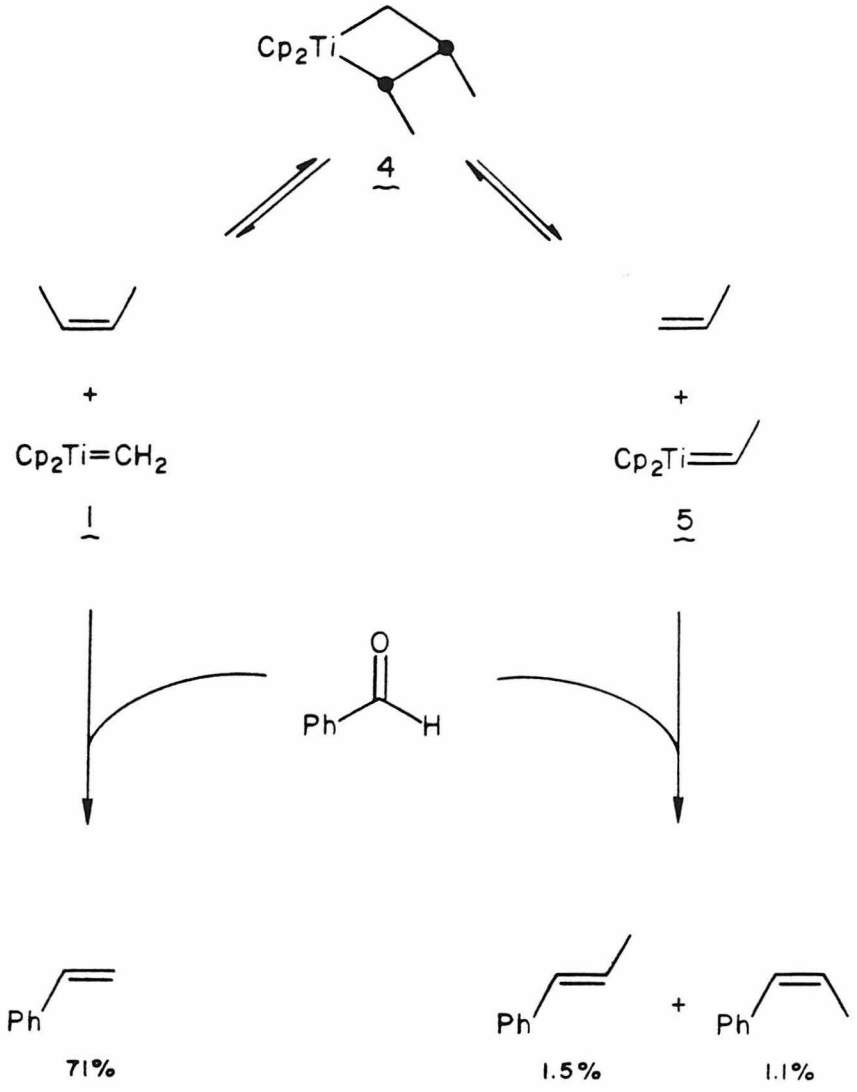
was the reverse of its formation. The extent to which **4** productively dissociated to give **5** was determined by the addition of 2.00 equivalents of benzaldehyde and subsequent thermal cleavage of the metallacycle (Scheme I).[7] Products resulting from the non-degenerate metathesis of *cis*-2-butene accounted for less than 4% of the reaction mixture. This product distribution was attributed to the lesser stability of the titanocene ethylidene (**5**), resulting from the non-degenerate pathway, than **1**. Due to the orientation of available orbitals around the titanocene unit,[8] the bonding scheme of an alkylidene ligand is such that all four substituents on the titanium carbon double bond, as on an organic olefin, lie in the same plane.[9] This arrangement of substituents results in severe steric interactions between the alkylidene substituent and the bulky cyclopentadienyl ligand. As the size of the substituent increases, these interactions become even less favorable. Thus, productive metathesis of 1,2-disubstituted olefins has been thwarted mostly by the lesser stability of the resulting alkyl substituted titanaolefin and, to a lesser extent, the greater stability of the more substituted organic olefin.

There are two methods which would be expected to enhance 1,2-disubstituted olefin metathesis. The first involves the generation of a substituted titanocene alkylidene **6**, and subsequent olefin trapping to form the intermediate trisubstituted metallacyclobutane (**7**, eq 2). In these systems where R′ is more sterically bulky than R, dissociation of the intermediate metallacycle would then favor the productive metathesis pathway. Until recently, the major obstacle in this process

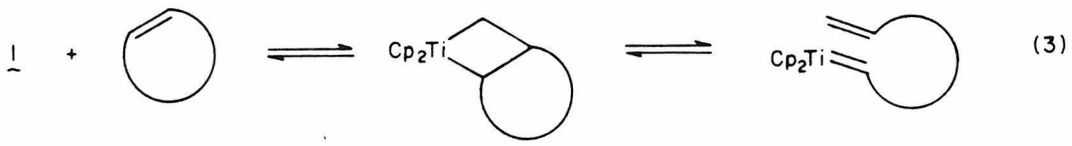


(2)

Scheme I. Productive Metathesis of 2-Butene by Thermolysis of Metallacycle **4**.



was the lack of a way in which to cleanly generate an alkyl-substituted titanocene alkylidene. The need for a general, high-yield method of producing these species has received much attention lately.[10] A general process has not yet been discovered; however, the clean generation of a titanocene alkylidene has recently been reported.[10c] The second method for the enhancement of 1,2-disubstituted olefin metathesis involves the utilization of an alternate driving force such as ring strain. Metathesis of a strained, cyclic olefin would involve ring-opening with concomitant release of the intrinsic strain energy (eq 3). If the strain turned out to be large enough, the energetics of the system would overcome the relative instability of the organometallic intermediate and favor the ring-opening metathesis. In the process, the elusive substituted alkylidene is generated in a manner similar to that recently reported.[10c]



(3)

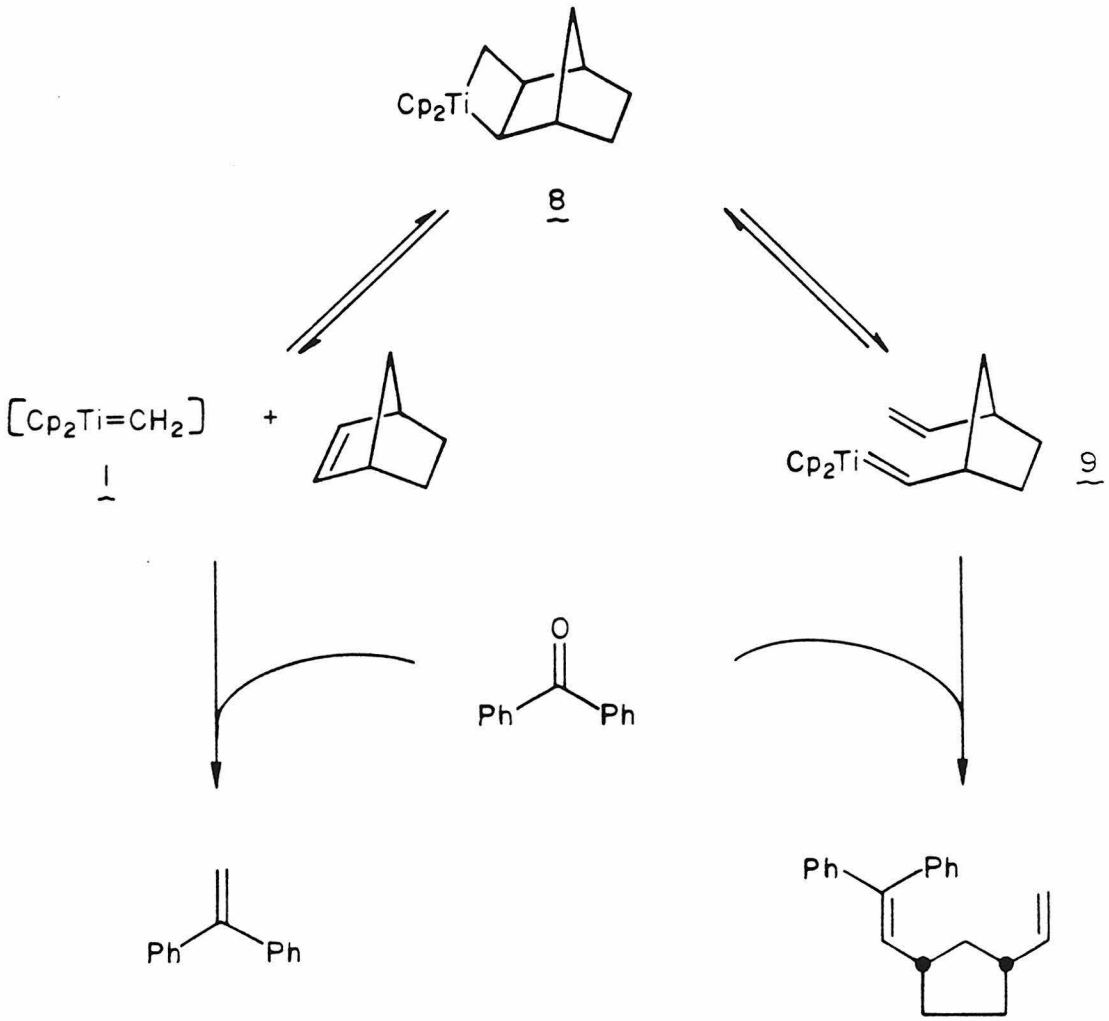
Norbornene is an extensively studied and readily available strained cyclic olefin. The compound itself has an inherent strain energy of 27.2 kcal/mol, whereas the saturated system, bicyclo[2.2.1]heptane, has a somewhat smaller value of 17.6 kcal/mol.[11] Metallacyclobutanes containing a bicyclo[2.2.1]heptane framework are possible intermediates in the structural rearrangement of tricyclo-[3.2.1.$0^{2,4}$]oct-6-ene species,[12,13] though, until recently, they had not been ob-

served. Waddington and Jennings were able to isolate several norbornene platinacyclobutanes and fully characterize these elusive intermediates.[13] Investigation of an iridium-catalyzed system further suggested that ring-opening metathesis, through an iridium alkylidene, occurred in the rearrangement of a norbornene iridacyclobutane.[14]

Generation of **1** in the presence of this strained olefin was found to produce an unusually stable metallacycle.[15] Unstrained *cis*-1,2-disubstituted olefins form metallacycles which normally exhibit dissociation at temperatures exceeding 0°C.[5] With the formation of metallacycle **8**, the strain due to the presence of the olefin in the bicyclic system (9.6 kcal/mol) was eliminated and not easily regenerated (Scheme II). In contrast to other α,β-disubstituted metallacyclobutanes, **8** showed no signs of thermal instability at temperatures up to 55°C. In the presence of benzophenone[7] at 65°C, thermal decomposition gave rise to a product distribution containing 69% of the ring-opened product **10**, resulting from the substituted alkylidene **9**, and 29% 1,1-diphenylethylene.[16]

The achievement of a substantial amount of ring-opened product provided a means of studying the intricacies of the reaction. The focus of our attention was to further accentuate the ring-opening process and to develop the synthetic utility of the metathesis process.It became apparent that there existed a possibility for additional enhancement of the metathesis product. If the substituted alkylidene could be selectively removed from the equilibrium process illustrated in Scheme II, in preference to titanocene methylidene, the reaction would be drawn toward the ring-opened product. The most efficient way to attain selective trapping would be to involve a carbonyl substituent on the norbornene. In such a system, trapping of the substituted alkylidene is an intramolecular process and entropically favored over the intermolecular reaction of the carbonyl with **1**.

Scheme II. Productive Metathesis of Norbornene by Thermolysis of Metallacycle **8**.



This intramolecular trapping process involves not only the formation of a carbon-carbon double bond, but also has the added attraction of ring formation. The structural rearrangement by the ring-opening metathesis and subsequent ring forming processes has obvious synthetic interest.

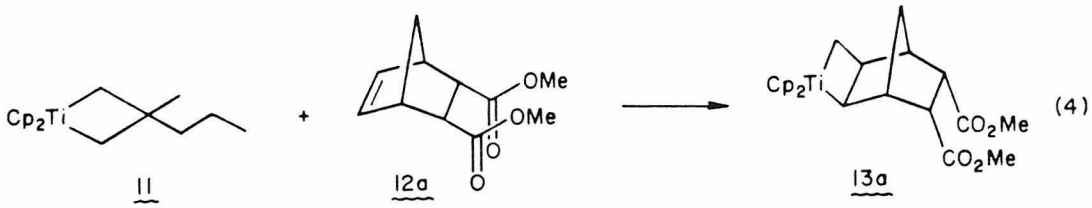
The versatility of the titanium system, in addition to the metathesis activity, lies in the variety of carbonyl trapping agents which can be employed.[7] Reaction of the ring-opened alkylidene with an attached ketone or aldehyde would give the same ring closure as an intramolecular Wittig reaction, which has found extensive application in organic synthesis.[17] The unique advantage of the use of the titanium system is that alkylidene trapping can also be performed by esters[7] and amides,[7] producing the expected enol ethers and enamines, respectively. This "Wittig-type" alkylidene transfer chemistry has only been performed on esters by the transition metal ylides of titanium,[7] zirconium,[18], niobium [19], and tantalum,[19] and there have been no reports of an intramolecular process of this type. Our investigations focused on the ring-opening metathesis and intramolecular trapping of ester-substituted bicyclo[2.2.1]heptene substrates. Through the use of ^{1}H-^{1}H correlated NMR, the products of the structural rearrangement were unequivocally identified.[20]

Because titanocene methylidene (**1**), used in the formation of metallacycle **8**, also reacts readily with the esters to form enol ethers, substrate design had to produce selective initial reaction at the olefin functionality. To accommodate this need, the ester was strategically situated as an *endo* substituent of the norbornene framework, making the reaction of the hindered ester with the sterically bulky titanocene unit highly unfavorable. An added advantage to the use of these *endo* ester substrates is their synthetic availability. A variety of *endo* ester-substituted bicyclo[2.2.1]heptene compounds are easily prepared from read-

ily accessible starting materials using the Diels-Alder cycloaddition. The value of all ester-substituted bicyclo[2.2.1]heptene compounds as intermediates in natural product synthesis is magnified by the ability to diastereoselectively perform the Diels-Alder reaction using chiral auxiliaries.[21] The use of these synthetic intermediates allows the preparation of optically pure natural products.

Results and Discussion

Initial investigation of the reaction between ester-substituted norbornene substrates and titanocene methylidene sources was performed with the dimethyl ester of *endo,endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid (**12a**). This substrate was readily prepared from the Diels-Alder adduct of maleic anhydride and cyclopentadiene using established methods.[22] Using **11** as the source of **1**, observation of the reaction by ^{1}H NMR revealed nearly quantitative conversion to a single metallacycle, as was evidenced by the appearance of two inequivalent cyclopentadienyl signals at 5.46 ppm and 5.41 ppm (eq 4). On a preparative scale, the product was isolated in high yield (84%) as a deep red powder using either **2** or **11** as the source of titanocene methylidene.



The ^{1}H NMR spectrum of this single isomer is shown in Figure 1. The presence of the two ester groups was evident from the methyl resonances at 3.46 ppm and 3.40 ppm. Proton H_3 (Figure 1) had a chemical shift characteristic of a hydrogen on the tertiary carbon α to the titanium in the metallacycle ring. Signals due to protons H_9 and H_{10} had narrow peak shapes typical for bicyclo[2.2.1]heptene bridgehead hydrogen resonances which normally exhibit very small coupling, if any, to vicinal protons[23]. Resonances H_{12} and H_{14} had the

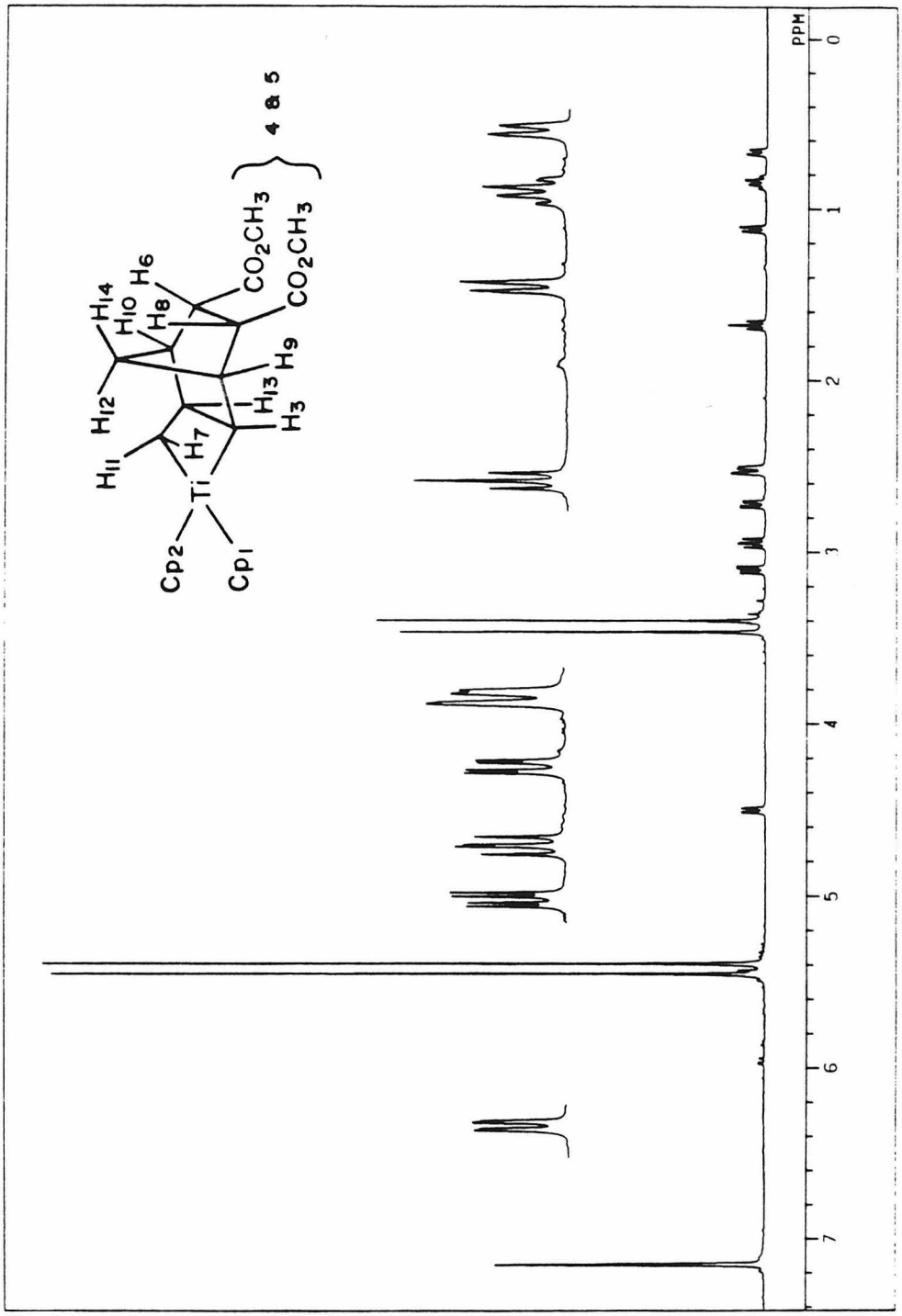


Figure 1. 400 MHz ^{1}H NMR Spectrum and Proton Resonance Assignments of **13a** in C_6D_6.

characteristic shape and pattern of protons on the methylene bridge of the norbornene substrate. From these distinctive patterns, partial assignment of proton resonances was made through the use of ^1H-^1H correlated two-dimensional NMR[20]. The crosspeaks that occur off the diagonal, as a result of J-coupling between two protons, were used to trace the carbon framework of the molecule. The resulting spectral map of **13a** is shown in Figure 2. The β-proton of the metallacyclobutane, H_{13}, which coupled to the metallacycle proton H_3, was found at a typically high field resonance. The two methylene protons in the metallacycle ring, H_7 and H_{11}, both displayed vicinal J-coupling to H_{13}. Protons H_9 and H_{10}, which tend not to display coupling to *endo*-substituted protons, showed no coupling to protons H_3 or H_{13}. The bridgehead proton H_9 exhibited coupling to *exo* substituted proton H_8 and a crosspeak surfaced as the result of vicinal coupling of H_{10} and H_6. Protons H_6 and H_8 also coupled to one another. On the methylene bridge, protons H_{12} and H_{14} coupled to each other, and both H_9 and H_{10} showed J-coupling to H_{12}. Also observed by two-dimensional NMR, was the occurrence of a weak four-bond coupling of H_3 to the bridge proton H_{14}. Difference Nuclear Overhauser Enhancement (NOE) experiments allowed the complete assignment of **13a**. Saturation of the downfield cyclopentadienyl resonance (Cp_1) produced enhancement of protons H_3, H_7, and H_{13}. The enhancement of protons H_9, H_{11}, and H_{12} resulted from the saturation of the upfield cyclopentadiene resonance (Cp_2). As a result of these experiments, proton H_9 was shown to be close to the metal center and, thus, vicinal to H_3. Another important feature of metallacycle **13a** was determined by the difference NOE experiments. The enhancement of H_{12}, upon saturation of the upfield Cp, confirmed metallacycle **13a** as the isomer resulting from cycloaddition to the less hindered *exo* face of the strained olefin.

There were three conceivable routes of thermolysis available to the metal-

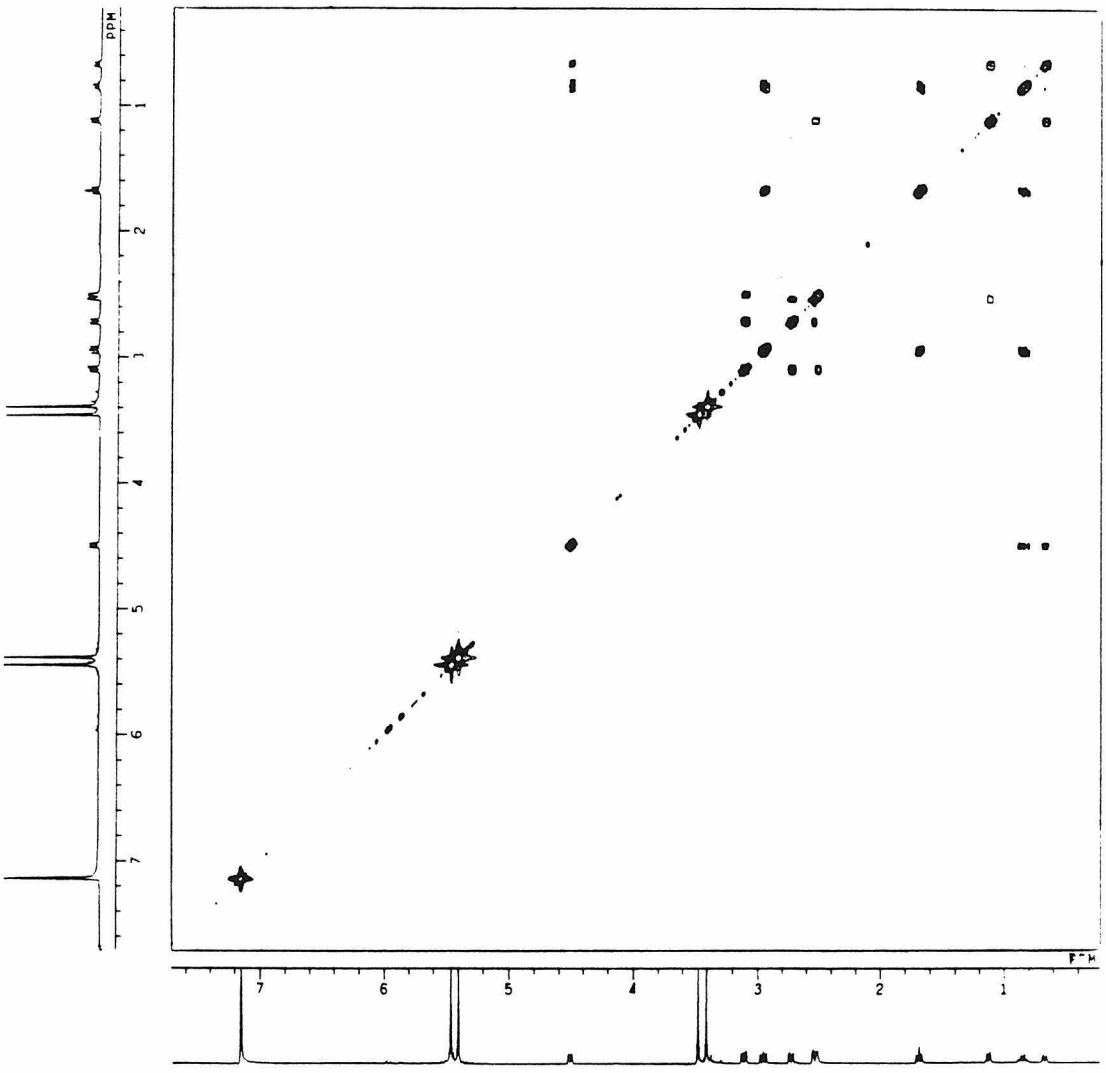
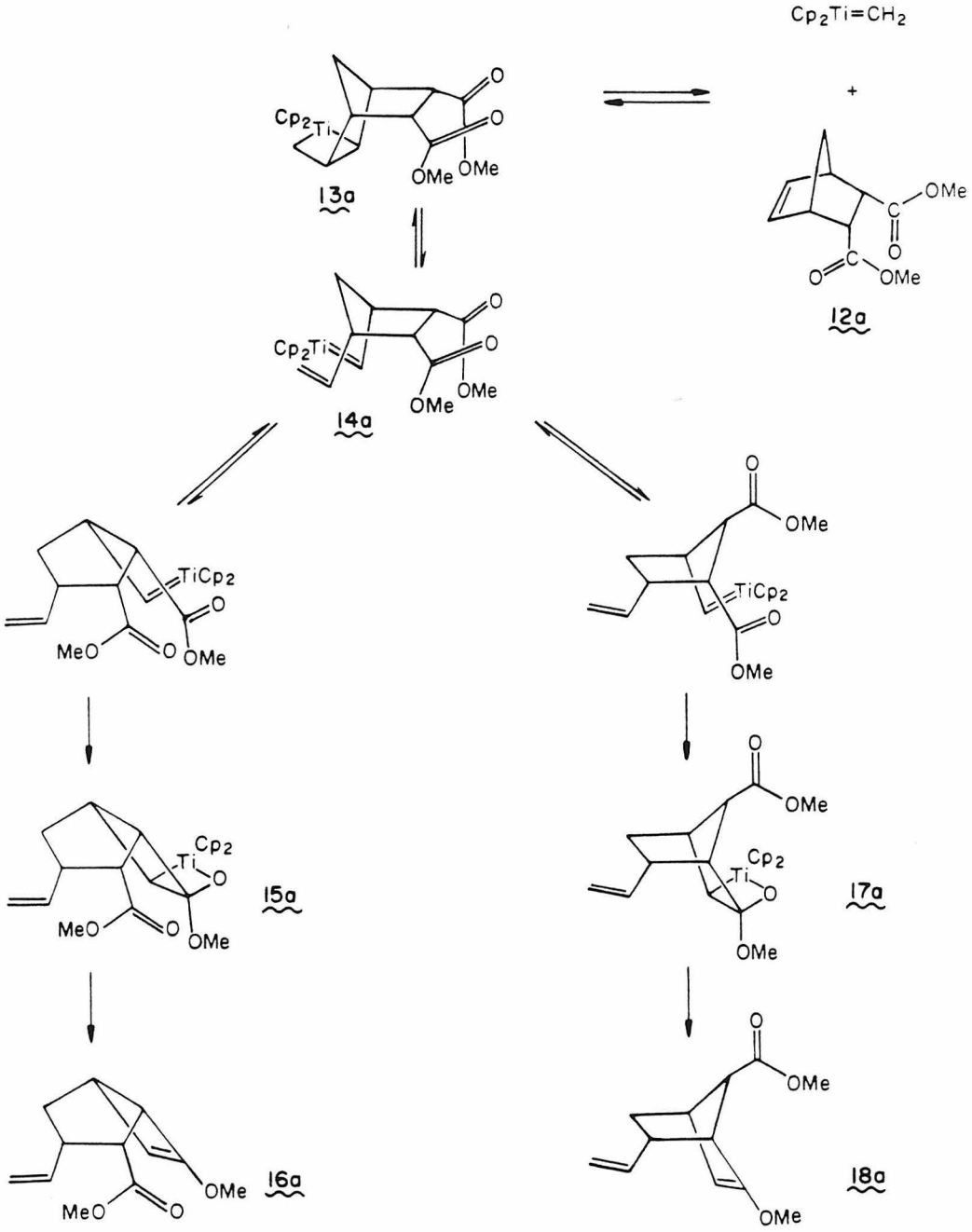


Figure 2. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum of **13a** in C_6D_6.

lacycle (Scheme III). Because metallacycle formation is reversible, it was likely that starting olefin and **1** would be regenerated. If, on the other hand, ring-opening metathesis occurred to form intermediate **14a**, then the substituted alkylidene would have two carbonyls with which it could react and, thus, two additional reaction pathways. Trapping of the alkylidene intermediate with the nearest carbonyl would result in the proposed intermediate oxametallacycle **15a**, which would then rapidly dissociate to the bicyclo[3.2.0]heptene ring system product **16a**. Alternately, the ester carbonyl across the cyclopentane ring could trap the alkylidene to produce **17a**, which would ultimately lead to the bicyclo[2.2.1]heptene ring system **18a**. Due to the elevated reaction temperatures and the regeneration of **1**, products resulting from intermolecular methylenation of **12a, 16a,** and **18a** were possible as well. Thermolysis of a benzene solution of **13a** for 11 h at 70°C produced four distinct organic products as evidenced by capillary gas chromatography. The decomposition required temperatures of at least 65°C to proceed at a reasonable rate; product distribution showed no change in relative peak integration at reaction temperatures up to 90°C. Varying the concentration of **13a** from 0.071M to 0.57M similarly had no measurable effect on product distribution. Under the reaction conditions, there was no depletion of the products over an additional 5-day period at 85°C.

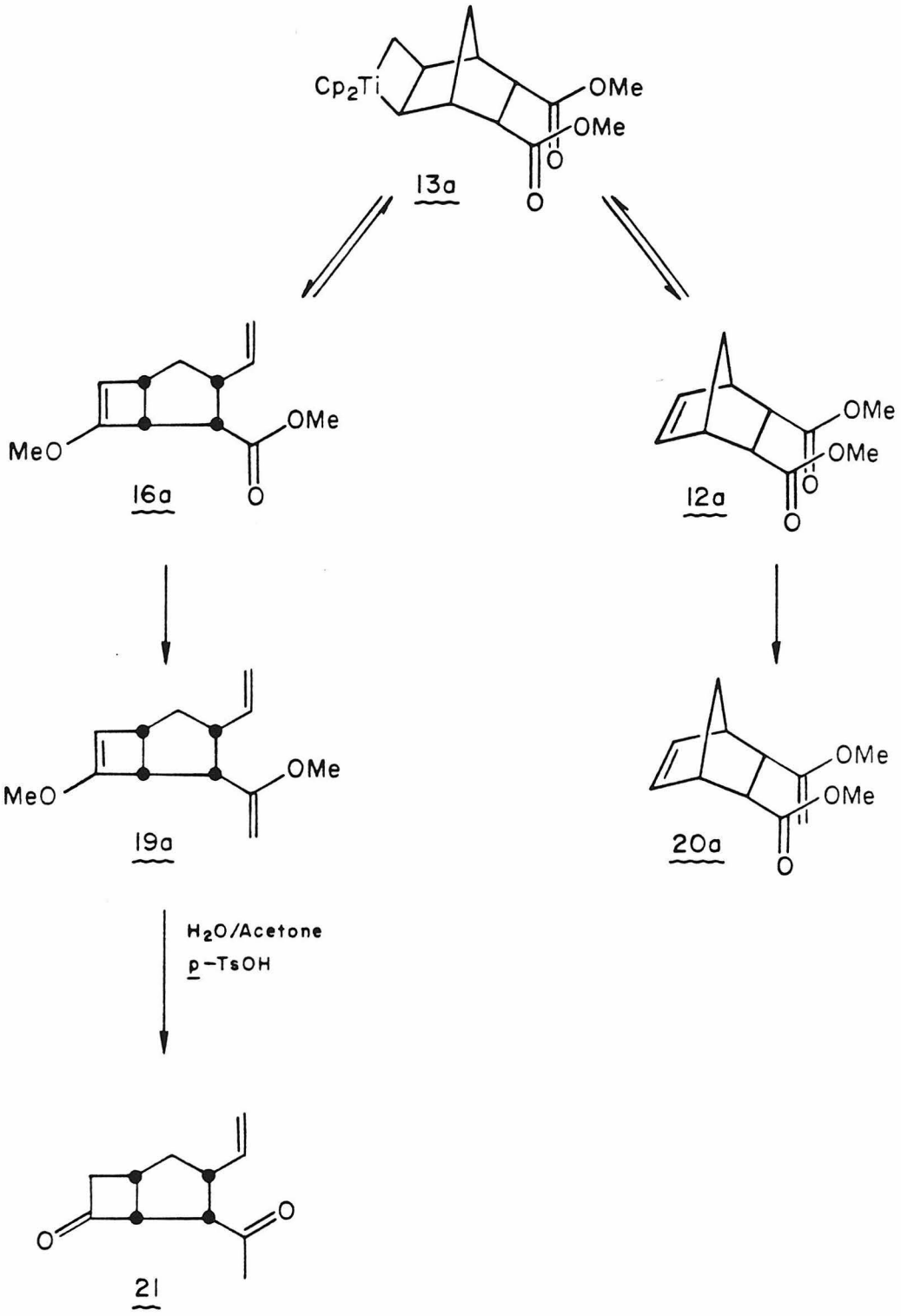
Isolation of two products from the mixture of four was accomplished using silica gel flash chromatography. The least mobile compound was found to be identical in every respect to a sample of the starting olefin **12a**. The fraction with the highest R_f value was found to be a single compound that showed extensive structural rearrangement from the original norbornene substrate. This compound was very sensitive to hydrolytic conditions and decomposed slowly upon contact with silica gel. 500 MHz ^{1}H NMR revealed the presence of a termi-

Scheme III. Pathways of Thermolysis Available to Metallacycle **13a**.



nal vinyl group by resonances at 6.30 ppm, 5.00 ppm, and 4.95 ppm, as well as a trisubstituted vinyl ether singlet at 4.45 ppm. This information suggested that ring-opening metathesis had occurred to produce a substituted alkylidene, which had then been intramolecularly trapped by an ester group. A terminal, monosubstituted vinyl ether functional group, resulting from methylenation of the second ester group, was also present by observation of the two proton resonances at 4.84 ppm and 4.20 ppm. The absence of characteristic bicyclo[2.2.1]heptene peaks, such as those due to the bridgehead protons, suggested a methylenated derivative (**19a**, Scheme IV) of **16a** rather than **18a**. The remaining chromatography fraction was examined by ^{1}H NMR and found to contain a 3:1 mixture of two compounds. The major component displayed two inequivalent norbornene olefin protons at 6.50 ppm and 6.15 ppm, terminal vinyl ether protons at 3.95 ppm and 3.82 ppm, and bridgehead protons at 2.93 ppm and 2.78 ppm. This compound was the methylenated product, **20a**, from the reaction of **12a** and **1**, which were both regenerated in the nonproductive dissociation of the metallacycle (Scheme IV). The elevated temperature at which the cycloreversion took place allowed intermolecular trapping to be a much more favorable process than during the formation of **13a**. The spectra of the minor component of the binary mixture resembled that of the other ring-opened product **19a** in every way except for one – the terminal vinyl ether resonances were absent and a downfield methyl ester singlet at 3.43 ppm was observed instead of the methyl ether singlet at 3.27 ppm. From this information, the minor component of this mixture was determined to be a product that had occurred as a result of ring opening and subsequent intramolecular trapping consistent with the structure of **16a**. Compound **16a** was also very sensitive to hydrolytic conditions such as extended contact with silica gel. Acid-catalyzed hydrolysis of the methylenated, ring-opened compound **19a**

Scheme IV. Product Map of the Thermolysis of Metallacycle **13a**.



with acetone/water produced the corresponding dione **21**, which was then characterized. Carbonyl stretching frequencies of 1777 cm^{-1} and 1710 cm^{-1} suggested the presence of both a cyclobutanone and an unstrained ketone, respectively.[24]

The structural skeleton of this derivative was determined by the decoupling of each individual proton resonance. Irradiation of the vinyl proton H_1 caused collapse of the methylene proton signals H_2 and H_3 in addition to affecting proton H_8 (Figure 3). The diastereotopic methylene protons H_{11} and H_{12} were both affected by irradiation of H_8 as was the α -carbonyl proton H_7. Proton H_4 was found to be vicinal to H_7 in a similar manner. Irradiation of H_4 affected H_9, and subsequent action on H_9 produced similar results on both H_{11} and H_{12}. Once the course around the cyclopentane ring was complete, the second ring structure was determined. Irradiation of H_9 also caused partial collapse of both α-carbonyl protons H_5 and H_6. These two diastereotopic methylene protons were also affected by irradiation of H_4 as a result of J-coupling across the cyclobutanone ring.

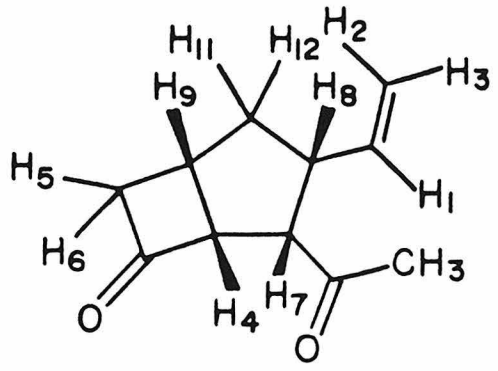


Figure 3. Structure and Proton Assignments of **21**.

From these experiments, it was shown that **21** contained a bicyclo[3.2.0]heptane skeleton. The preference for the formation of **16a** over that of **18a** was the direct result of the intermediates involved in their formation. Intermediate **15a**, although never observed, was favored with respect to **17a**. The origin of this preference was mostly the result of the unfavorable *syn* ester substituent on **17a**. The steric interaction of the ester with the titanocene unit proved to be severe by the absence of **18a** in the product mixture. The effect of similar interactions on metallacycle formation has been observed by Gilliom using a *syn* methyl substituent.[25] Due to the interactions between the methyl substituent and the cyclopentadienyl ligands of **1**, metallacycle formation does not occur.

Once the products had been identified and their specific proton resonances assigned, they were quantified by ^{1}H NMR integration against an internal standard of mesitylene. Results of this quantification are shown in Table I. Ring

Table I. Dependence of Product Distribution on the Steric Properties of the Ester Group.

Substrate		Product Yield(%)				Conversion(%)
	R	**19**	**16**	**12**	**20**	$\left(\frac{(16+19)}{(12+20+16+19)}\right)$
a	Me	12	7	40	22	23
b	Et	7	22	42	11	35
c	iPr		39	46		46

opening of the norbornene unit by the metallacycle accounted for 19% of the products – 12% due to the methylenation of **16a**. Nonproductive metallacycle decomposition was responsible for 62% of the products; 22%, due to the side-product produced from methylenation of **12b**. It became apparent from the product analysis that side products resulting from intermolecular methylenation by **1** must be minimized to selectively generate a single product. This increased selectivity was accomplished by modifying the substrate properties.

The effect of increasing the steric bulk of the ester group, thereby reducing the accessibility of the carbonyl, was investigated using the diethyl ester substrate **12b**.[22] After formation and isolation of the diethyl ester norbornene metallacycle, it was allowed to thermally rearrange under conditions similar to those used for **13a**. Products which resulted from the reaction were analyzed by capillary gas chromatography and ^{1}H NMR and quantified as shown in Table I. By changing the ester groups from methyl to ethyl, dramatic changes in the product distribution were observed. Side products, resulting from the methylenation of both **16** and the norbornene diester, were both markedly reduced and the desired product, **16**, was being selected for. Further steric bulk at the ester groups was anticipated to continue this trend.

The ester carbonyl groups were made even less accessible through the synthesis of the more hindered diisopropyl ester **12c**. Reaction of the isopropyl ester substrate with **11** formed the expected metallacycle, which was isolated in 58% yield. The reduced yield with respect to **13a** was due to the high solubility of **13c** in nonprotic solvents. Heating a benzene solution of the metallacycle at 80°C for 12 h produced only two organic products. Quantification of these products using ^{1}H NMR integration, versus the internal standard mesitylene, revealed 39% of the rearranged product **16c** and 46% of the regenerated diester **12c**. Side

products which resulted from methylene transfer to the carbonyls of the products were not observed. On a preparative scale, the product and diester were easily separated through the use of flash chromatography, although recovery of **16c** was greatly reduced due to the sensitivity of this compound toward silica gel. The product of productive metathesis, **16c**, was isolated as a clear, colorless liquid. The 400 MHz ^{1}H NMR spectrum of compound **16c** is shown in Figure 4. The terminal olefin resonances at 6.36 ppm, 5.05 ppm, and 4.97 ppm were quite diagnostic of the ring-opening metathesis process. Subsequent intramolecular trapping of the ring-opened alkylidene was evident by the cyclobutene enol ether formation. The presence of this functional group was verified by the olefinic enol ether singlet at 4.33 ppm and the isopropyl ether proton resonance at 3.94 ppm, which differed substantially from the isopropyl ester proton signal at 5.05 ppm. The individual decoupling of each proton resonance allowed the assignment of all proton resonances.

Irradiation of the distinctive secondary olefin proton H_1 resulted in the collapse of the methylene protons H_3 and H_4. In addition, H_8 was affected during this process, allowing access into the ring system. Irradiation of the allylic proton H_8 then revealed the positions of the α-carbonyl proton H_{10} and the diastereomeric methylene protons H_{11} and H_{12}. A similar collapse of resonance H_1 also occurred. Tracing the protons around the ring, irradiation of H_{10} produced partial collapse of H_8 and the next proton on the ring, H_7. Proton H_9 was subsequently affected by the irradiation of H_7, and irradiation of H_9 then resulted in partial collapse of H_{11} and H_{12}. To further confirm the proton assignments, separate irradiation of H_{11} and H_{12} affected both H_8 and H_9 as well as each other. Tracing the carbon skeleton in this manner allowed the assignment of protons, but verification of the bicyclo[3.2.0]heptene ring system analogous to

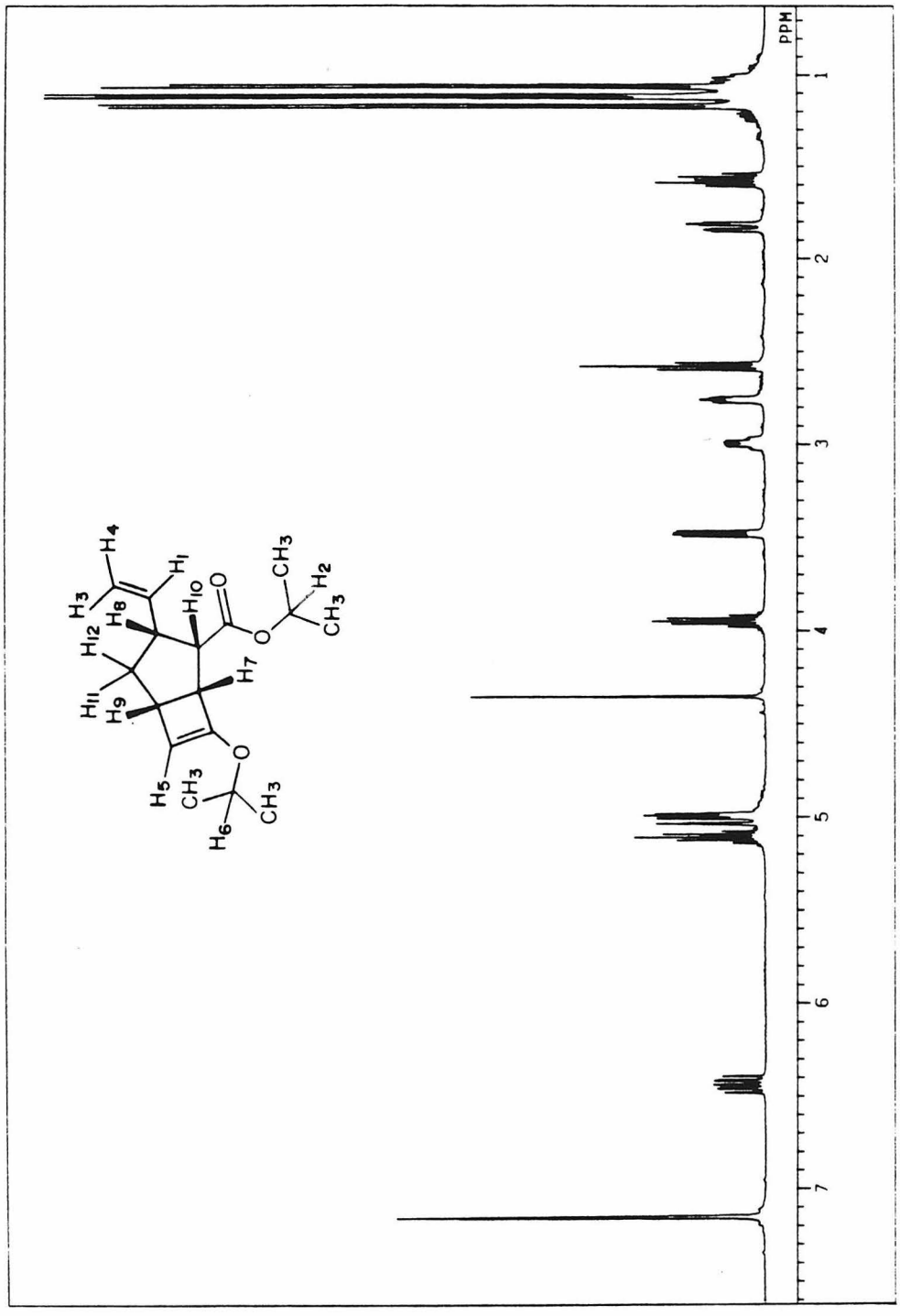


Figure 4. 400 MHz ^{1}H NMR Spectrum and Proton Resonance Assignments of **16c** in C_6D_6.

16, as opposed to the bicyclo[2.2.1]heptene system such as **18**, could not be made for this molecule. Absence of coupling to the enol ether proton prevented the distinction between the two different carbon skeletons.

Hydrolysis of **16c** with a catalytic amount of *p*-toluenesulfonic acid produced the corresponding cyclobutanone **22**, which was then used to reveal the skeletal structure as that of a bicyclo[3.2.0]heptane ring system. Carbonyl stretches characteristic of a cyclobutanone and an ester were observed by infrared spectroscopy at 1780 cm^{-1} and 1724 cm^{-1}, respectively. Assignment of each individual ^1H NMR proton resonance was made through the use of ^1H-^1H correlated NMR (Figure 5). Analysis of the spectrum crosspeaks that resulted from vicinal J-coupling allowed the verification of the bicyclo[3.2.0]heptane ring skeleton. In addition to the coupling that occurred with H_3 and H_4, H_1 displayed a crosspeak as a result of coupling with H_9. Again, the allylic proton H_9 allowed access into the ring system. Proton H_9 was found to couple to each of the cyclopentane methylene protons H_{11} and H_{12} and to the α-carbonyl proton H_6. Continuing to follow the vicinal coupling around the cyclopentane ring, H_6 was found to couple to H_5. Proton H_5 coupled to H_{10} which then coupled to H_{11} and H_{12}. Once the cyclopentane ring protons were identified, distinction between a bicyclo[3.2.0]heptane or bicyclo[2.2.1]heptane skeleton was made. The second ring was required to start from the bridgehead carbon, upon which proton H_{10} was a substituent. From there, H_{10} coupled to the diastereomeric α-carbonyl cyclobutanone protons H_7 and H_8, which also coupled to each other. Coupling across the cyclobutanone ring from H_5 to H_7 and H_8 also surfaced. This coupling pattern confirmed that **22** had the bicyclo[3.2.0]heptane ring skeleton.

The effect of increasing the size of the ester alkyl group was quite apparent from the data in Table I. As the substituent became more bulky, two important

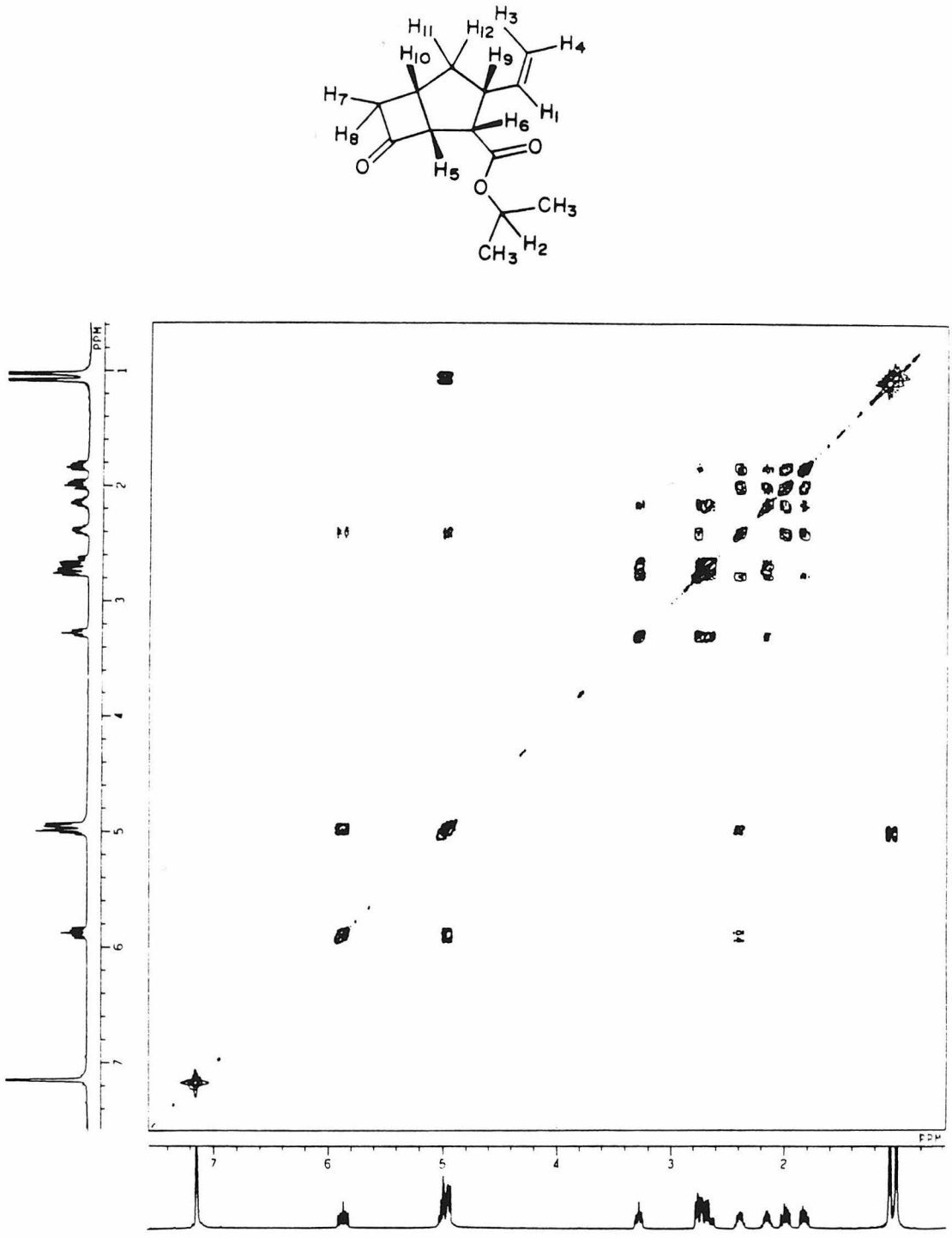


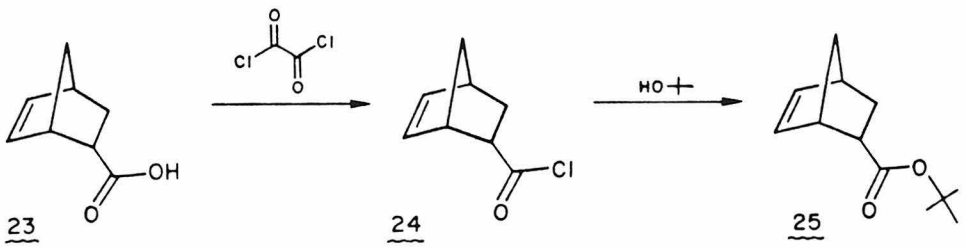
Figure 5. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum and Proton Resonance Assignments of **22** in C_6D_6.

changes occurred. The most obvious change was the reduction and ultimate elimination of the side products due to intermolecular methylenation. A more subtle change was the affect on the delicate equilibrium of this system. As the ester group changed from methyl to isopropyl, the ratio of ring-opened products to nonproductive metathesis products doubled. This was observed by examining the conversion of **12** to the rearranged products **16** and **19**. With the methyl ester, only a 23% conversion was obtained. Besides reducing the quantities of side products, the ethyl group enhanced the conversion of the ring-opening process to 35%. Through the use of the bulky isopropyl ester, the side products were finally eliminated and conversion was further enhanced to a value of 46%.

From the diester series of substrates, it was learned that the product distribution was highly dependent upon the steric properties of the ester group. The size of the O-alkyl substituent on the ester had two effects on the homologation process that altered the composition of the product mixture. Because ester substituents adopt the greatly favored *s-cis* conformation,[26] in which the substituent eclipses the carbonyl, an increase in size of the alkyl group had a dramatic effect on the steric protection of the carbonyl. In addition to the shelter provided by the alkyl substituents, the vicinal *s-cis* ester substituents also protect each other from methylenation. In order for the unfavorable interactions between the two ester alkyl groups to be minimized, the orientation of the ester groups was such that the less bulky carbonyl oxygens were directed under the norbornene framework. As a result, the carbonyl groups were further sheltered by the bicyclic skelton from the intermolecular attack of **1**. Although the increased size of ester substituents affected both homologation processes, intermolecular methylenation was reduced and ultimately eliminated with respect to the intramolecular cyclization process. The observed increase in selectivity was also due, in part,

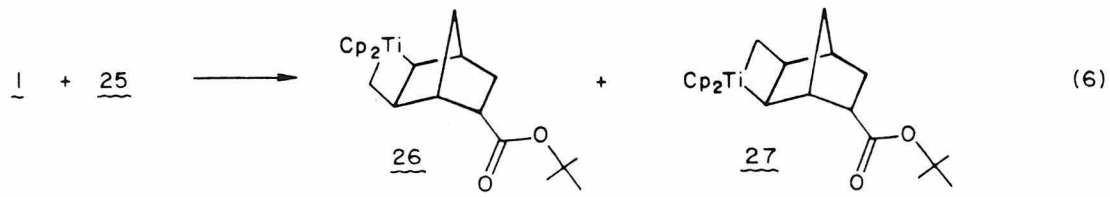
to the promotion of the ring-opening process. Because of the increased size of the ester substituents, the vicinal steric interactions of the ester groups became accentuated. The only way in which these eclipsing interactions could be reduced was through the metathesis of the norbornene ring system.

In the absence of one of the ester groups, it was anticipated that the bulk of the ester would still direct the carbonyl toward the norbornene framework, though the single carbonyl would be more subject to the intermolecular attack. In this case, however, a problem concerning the regiochemical cycloaddition of **1** to the unsymmetrical olefin substrate arose. An unsymmetrical strained olefin was prepared through the Diels-Alder reaction of acrylic acid and cyclopentadiene. The resulting acid was obtained as pure *endo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**23**) and was easily transformed to the *t*-butyl ester through the synthesis of the intermediate acid chloride (**24**, eq 5). The reaction of **1** with



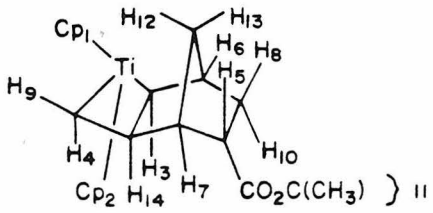
23 24 25 (5)

25 produced a nearly statistical mixture of regiochemical metallacycle isomers (eq 6). By ^{1}H NMR of the crude reaction mixture, the ratio of **26** to **27** was determined to be 53:47. There was also no evidence for methylene transfer to the carbonyl of **25**. Thus, the *t*-butyl ester had sufficient steric bulk to prevent intermolecular methylenation from occurring, but did not regiochemically direct the metallacycle formation to any appreciable extent. On a larger re-



action scale, each of the regioisomers could be isolated for characterization by repeated fractional crystallization. Configuration of the two isomers was determined through the use of ^1H-^1H correlated NMR and difference NOE studies on the isomerically pure samples. The regiochemistry of **26** was found to be that shown in eq 6 by the skeletal mapping of those protons displaying crosspeaks in the ^1H-^1H correlated spectrum. Crosspeaks which resulted from J-coupling to the bridgehead protons made possible the detection of vicinal coupling which, in the normal proton spectrum, could not be extracted from the broad bridgehead proton resonances.

The major isomer, **26**, was studied by two-dimensional ^1H NMR and the resulting spectral map is shown in Figure 6. The protons in the metallacycle ring were easily assigned by tracing the coupling from the α-proton H_3 to proton H_{14}, and from H_{14} to the inequivalent methylene protons H_4 and H_9. As previously observed for metallacycle **13a**, neither bridgehead proton H_6 or H_7 displayed coupling to the *endo* protons H_3 or H_{14}. The bridgehead proton H_6, however, showed coupling to the α-carbonyl proton H_5 while proton H_7 displayed coupling to protons H_8 and H_{10}. Assignment of H_8 as an *exo* proton and H_{10} as an *endo* proton were made based on the observed coupling constants and NMR studies of analogous compounds.[23] Protons H_{12} and H_{13} coupled to



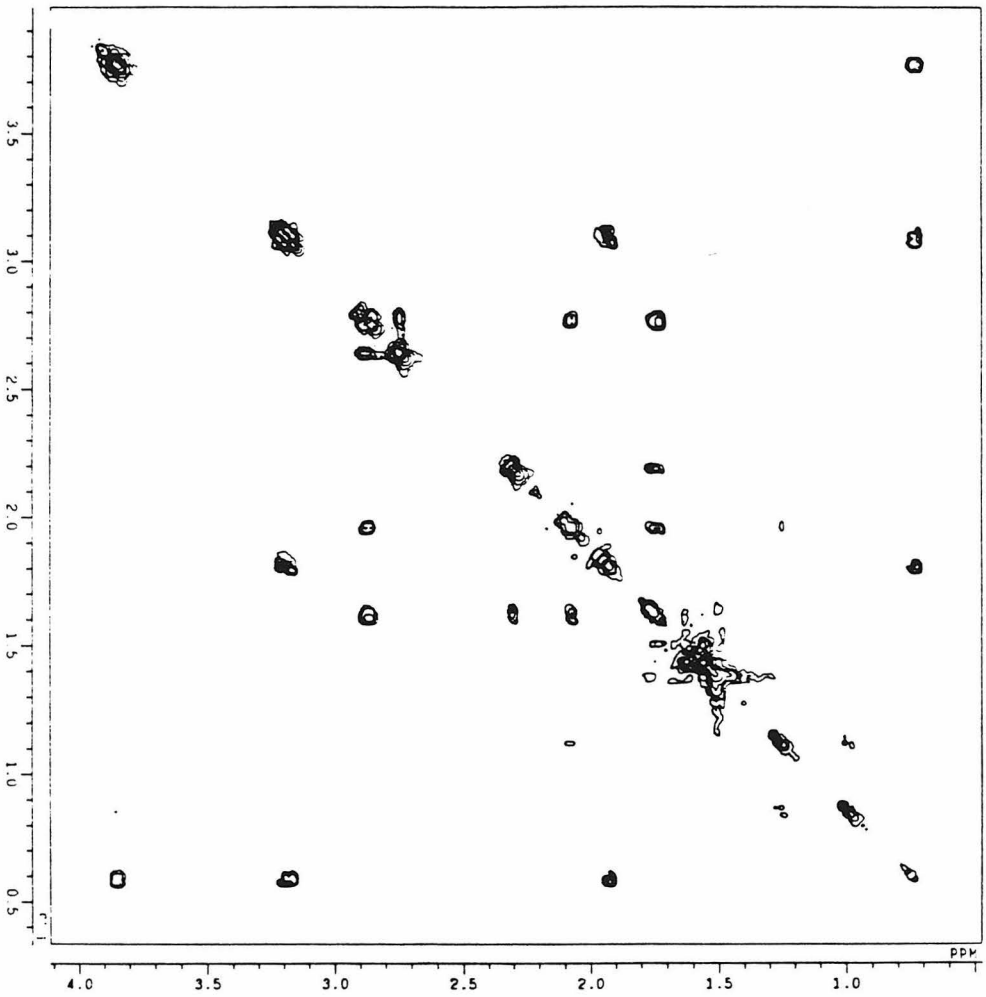


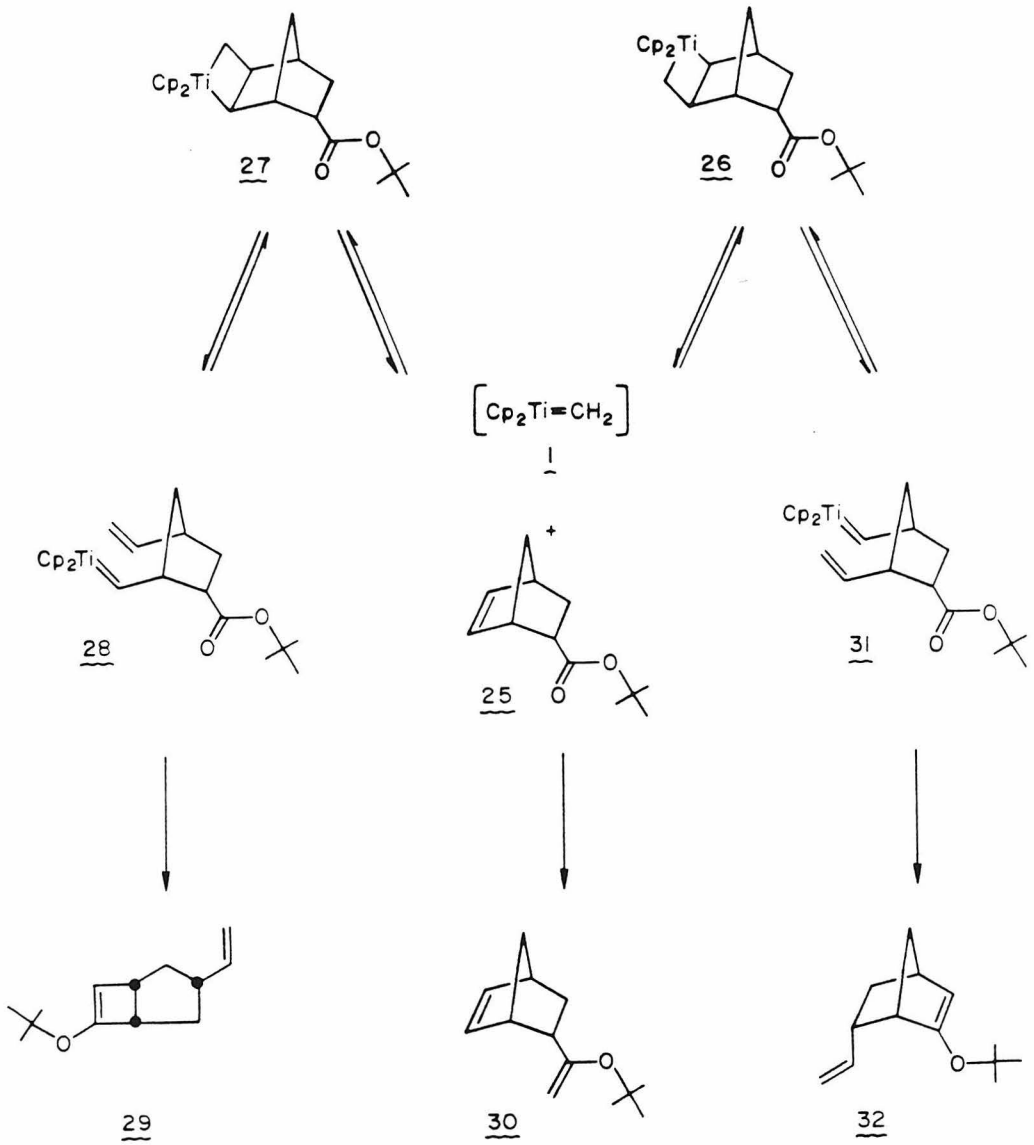
Figure 6. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum Expansion and Proton Resonance Assignments of **26** in C_6D_6.

each other, but displayed no J-coupling to the vicinal bridgehead protons. The assignment of protons was completed by utilizing information obtained through difference NOE studies of isomer **26**. Upon saturation of Cp_1, the bridgehead proton H_7 and the bridge proton H_{12} were enhanced along with the metallacycle ring proton H_9. The remaining three metallacycle ring protons H_3, H_4, and H_{14} were enhanced upon saturation of the upfield Cp_2. With the information obtained from both the ^1H-^1H correlated NMR and the difference NOE studies, the structural details of **26** were verified. Isomer **26** had proton H_7 closer to the titanium metal center and, thus, the *t*-butyl ester functionality was located on the opposite side of the norbornene framework. Due to the enhancement of H_{12}, it was also determined that this isomer resulted from addition to the *exo* face of the strained olefin.

Difference NOE experiments on the minor regioisomer **27** allowed confirmation of its structure. Saturation of Cp_1 produced enhancement of protons H_6, H_9, and H_{12}. This information allowed the similar assignment of **27** as an *exo*-metallacycle. With **26** and **27** shown to be *exo* regioisomers of one another, the remaining proton assignments of **26** were made by analogy to **27** and by the proximity of H_6 to the metal center. Saturation of the upfield Cp_2 produced the expected enhancement of protons H_3, H_4, and H_{14}.

Exposure of each separate isomer to a temperature of 80°C for 12 h resulted in two very different product distributions. Regioisomer **27** generated a mixture of two organic products, which was determined by capillary gas chromatography, ^1H NMR, and ^{13}C NMR to be an 86:14 combination of **29** and **25**, respectively (Scheme V). The abundance of the terminal vinyl group confirmed that the ring- opening process had occurred to a large extent, and the proton singlet at 4.34 ppm verified the subsequent intramolecular trapping of the alkylidene

Scheme V. Metathesis Equilibrium of **25** at 80°C.



and formation of **29**. Upon thermolysis of the other metallacycle isomer, **26**, an organic product mixture of five compounds was generated. Of this mixture, **25** contributed to 9% of the products and 33% was due to the presence of **29**. Two more major products were also detected in amounts of 29% and 22%. Although separation and full characterization of these two compounds was not achieved, it was suggested by ^{1}H NMR that 29% of the product mixture resulted from the intermolecular trapping of **1** by **25** to form **30**. The other product was thought to have arisen from the intramolecular trapping of the productive metathesis intermediate **31** to form the norbornene enol ether **32**. The fifth compound detected constituted only 7% of the product mixture; its structure and nature of origin were undetermined.

From the product distributions observed for these two monosubstituted ester metallacycle regioisomers (**26** and **27**), as well as for that of the diisopropyl ester metallacycle (**13c**), a greater understanding of the metathesis process was acquired. Efforts to enhance the ring-opening were somewhat successful compared to the parent metallacycle of norbornene (Scheme 1). As a result of the intramolecular process, the amount of the ring-opened product was increased from 67% to 86% of the product mixture. This enhancement occurred only when there was a single carbonyl in the position required to form the cyclobutene enol ether. If the carbonyl was situated in the adjacent position, such as in **26**, the ring-opening to **31** would occur, but the trapping process to form **32** was less favorable than the cyclobutene enol ether formation. Because of the less favorable pathway, the reversible recombination of the olefin to form **26** became competitive with the intramolecular carbonyl trapping of **31**. Thus, the equilibrium was shifted toward the intermolecular dissociation process and to the regeneration of **1** and **25**. These two species accounted for the presence of the other two

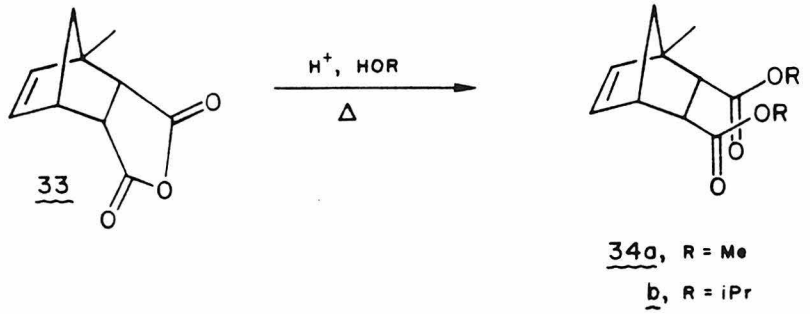
major products by intermolecular reaction at the carbonyl to produce **30**, and through the regioisomeric recombination with the strained olefin to form **27**, and ultimately, **29**.

In the presence of a second, nonparticipating ester substituent, the ratio of the ring-opened product to the nonproductive product was greatly reduced. The effect of the spectator ester substituent was believed to arise from restricting the freedom of movement of the trapping ester. As a result, the correct orientation of the trapping carbonyl was more difficult to attain, thus making the trapping process less favorable. With the intramolecular carbonyl trapping process less favorable, the delicate metathesis equilibrium was tipped toward intramolecular metallacycle formation and nonproductive dissociation to **1** and the norbornene substrate.

In the equilibrium process where an unsymmetrical substrate was more involved, and more than one metallacycle intermediate was possible, such as the case observed for **26** and **27**, the path of entry into the equilibrium was crucial to the resulting product distribution. The initial metallacycle formation became important because the transformation of **26** to **27** required the dissociation of **1** and substrate. At the temperatures required for this intermolecular isomerization to occur, the lifetime of the uncomplexed **1** was relatively short and, if recombination with the norbornene olefin did not occur, the titanocene methylidene irreversibly decomposed. This instability limited the equilibrium crossing from one metallacycle regioisomer to another. It became apparent that a method of directing the methylidene addition with the olefin, in order to selectively form one of the regioisomeric metallacycles, had to be established. With the ability to regioselectively form the metallacycle, the orientation of a single ester substituent could be controlled. The most effective place to position a substituent

was thought to be on a site as close as possible to the olefin, without actually being on the double bond. With a substituent on the olefin itself, the thermal stability of the metallacycle would be greatly modified if, in fact, metallacyclobutane formation could occur. From earlier work with 1-methylnorbornene, it was found that placing a methyl group at the bridgehead position of the norbornene framework was an effective way in which to direct metallacycle formation in these systems.[25]

Synthesis of the norbornene diesters with a 1-methyl substituent was accomplished from the corresponding anhydride **33** as shown in eq 7. To prepare the anhydride, 1-methylcyclopentadiene was selectively prepared using a slight modification of the procedure of Mironov and coworkers[27] and was subsequently trapped with maleic anhydride to form the Diels-Alder adduct **33**. The resulting anhydride was then used to prepare the desired ester substrates by acid-catalyzed esterification (eq 7). Reaction of **34b** with **11** was observed by 500 MHz ^{1}H

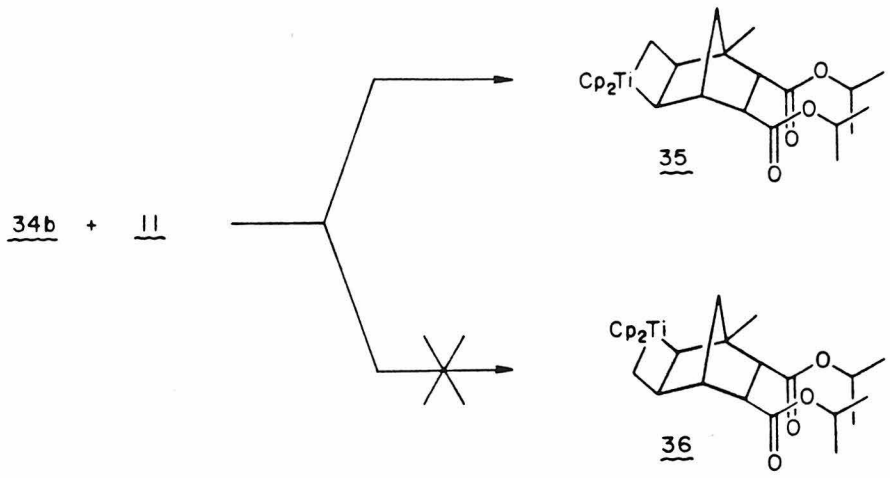


33

34a, R = Me
b, R = iPr

(7)

NMR to form only one metallacycle isomer (eq 8). Isolation of this product was achieved on a larger scale by crystallization from ether to produce a 72% yield of red crystals. Through a difference NOE experiment, the single isomer was found to have the configuration of **35**. Saturation of the upfield cyclopenta-



(8)

dienyl ligand produced enhancement of the metallacycle ring proton *cis* to the norbornene skeleton. The norbornene bridge proton *syn* to the metallacycle was also enhanced as expected. In addition to these two protons, the bridgehead proton was enhanced in these studies. The effect upon the bridgehead proton verified the proximity of the bridgehead proton to the Cp ligand as in isomer **35**. In the case of **36**, the methyl group resonance would have displayed enhancement rather than the bridgehead proton.

Slow crystallization of **35** from an ether/toluene mixture produced single crystals satisfactory for X-ray crystallographic analysis. Refinement of the structure led to a final R value of 0.058. Information acquired from the resulting crystal structure revealed many interesting features of this norbornene metallacycle. The most obvious feature was the confirmation of the structure **35**, in which the metallacycle had formed on the *exo* face of the olefin with the regiochemical addi-

tion of the titanocene unit away from the methyl substituent (Figure 7). A summary of important bond distances and angles, compared with previously reported titanacyclobutane structures, is shown in Table II. A more complete tabulation of structural information is reported in Appendix I. Compared with reported X-ray crystal structures of titanacyclobutanes,[3,25] this norbornene metallacycle displayed some unique characteristics. In addition to being a disubstituted metallacycle, the norbornene framework locked both ring substituents in place and forced the bridge carbon toward the cyclopentadienyl ligand. As a result, the *syn* bridge proton interacted directly with the cyclopentadienyl hydrogens. To relieve these steric interactions, the norbornene skeleton twisted away from the titanium ligand, causing a puckering of the normally planar metallacyclobutane ring. The metallacycle settled into a confirmation where the C(1)-Ti-C(3) plane puckered from the C(1)-C(2)-C(3) plane to an extent of 0.37 Å (25°). The twisting of the norbornene framework and puckering of the metallacycle allowed the *syn* hydrogen on the norbornene bridge to maintain an interatomic distance of 2.02 Å from the closest cyclopentadienyl hydrogen. This value is well within the sum of the van der Waals radii (2.40 Å) and is smaller than the 2.2 Å value found in the metallacycle of dicyclopentadiene. The inability of metallacyclobutanes such as **8** to accommodate a *syn* ester substituent, such as intermediate **17**, or a *syn* methyl group,[25] was quite evident from this structure.

With regard to the metathesis process, there was no apparent distortion of the metallacycle toward a metal alkylidene-olefin complex analogous to **14** (Figure 8). Both metal-carbon bonds were equal within the limits of their error. The only metallacycle distortion that was observed was the greater length of C(2)-C(3) (1.596 Å) than that of the C(1)-C(2) bond (1.560 Å). This difference in bond lengths was not significantly greater than

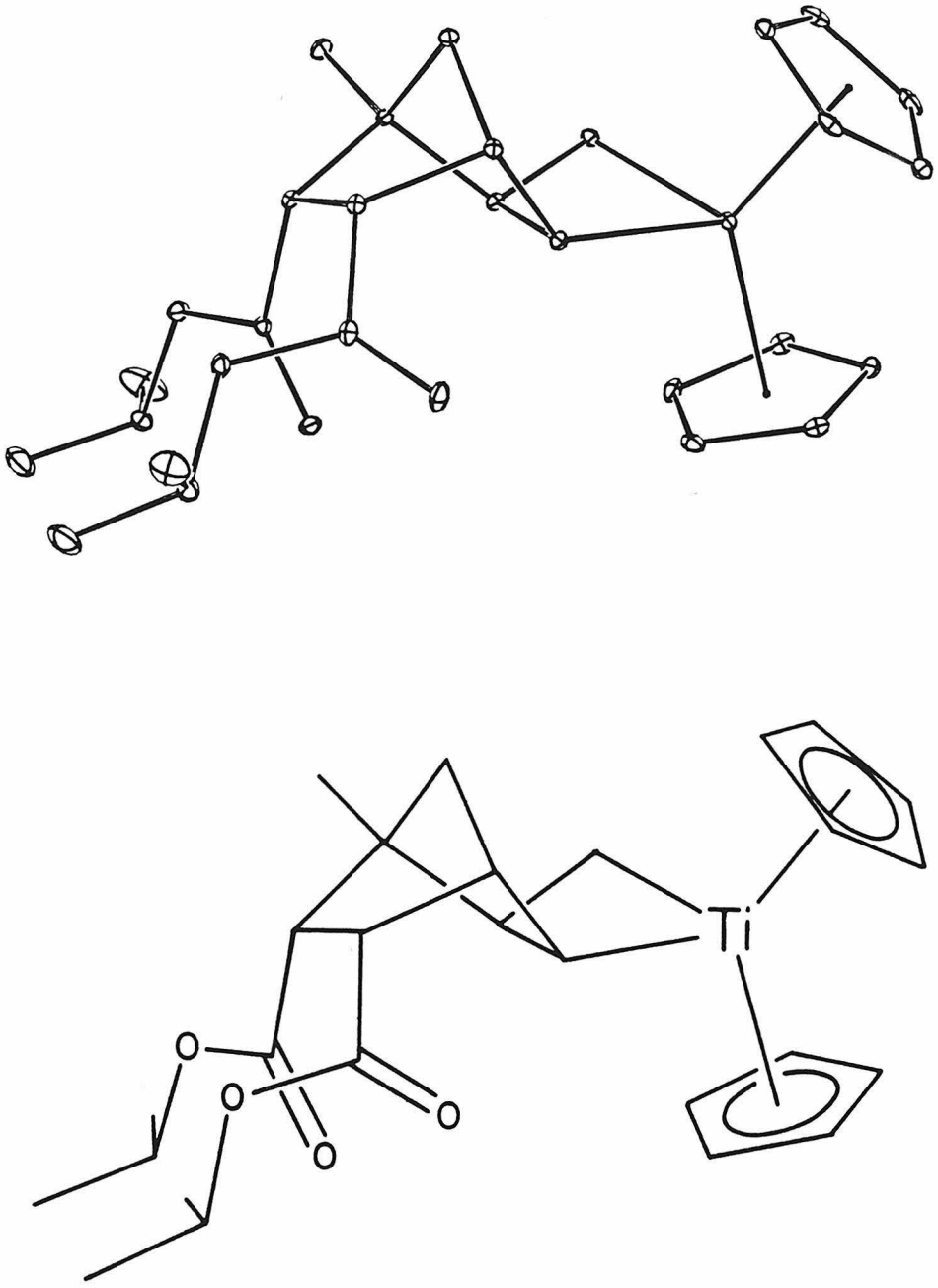
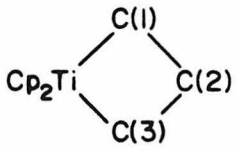
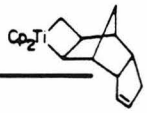
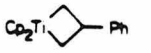


Figure 7. ORTEP Drawing of the Molecular Structure of Metallacycle **35**.

Table II. Selected Structural Parameters of Titanacyclobutanes.



Metallacycle	**35**			
Bond Lengths[a]				
Ti-C(1)	2.130(4)	2.124(2)	2.16	2.127(3)
Ti-C(3)	2.133(4)	2.141(2)	2.14	2.113(4)
C(1)-C(2)	1.560(6)	1.555(3)	1.55	1.546(5)
C(2)-C(3)	1.596(6)	1.607(3)	1.53	1.579(5)
Bond Angles[b]				
C(1)-Ti-C(3)	75.1(2)	76.9(1)	75	75.3(1)
C(1)-C(2)-C(3)	110.8(3)	113.9(2)	116	112.0(3)
Ti-C(1)-C(2)	85.2(2)	84.2(1)	84	86.0(2)
Ti-C(3)-C(2)	84.3(2)	82.5(1)	85	85.7(2)
Displacement[c]	0.37	0.27	0.09	0.05
Pucker Angle[d]	25	18	6	3
Reference		25	3	3

[a] In Å.
[b] In degrees (°).
[c] The displacement of C(2) from the plane defined by C(1)-Ti-C(3). In Å.
[d] The angle between the plane containing C(1)-Ti-C(2) and the plane containing C(1)-C(2)-C(3). In degrees (°).

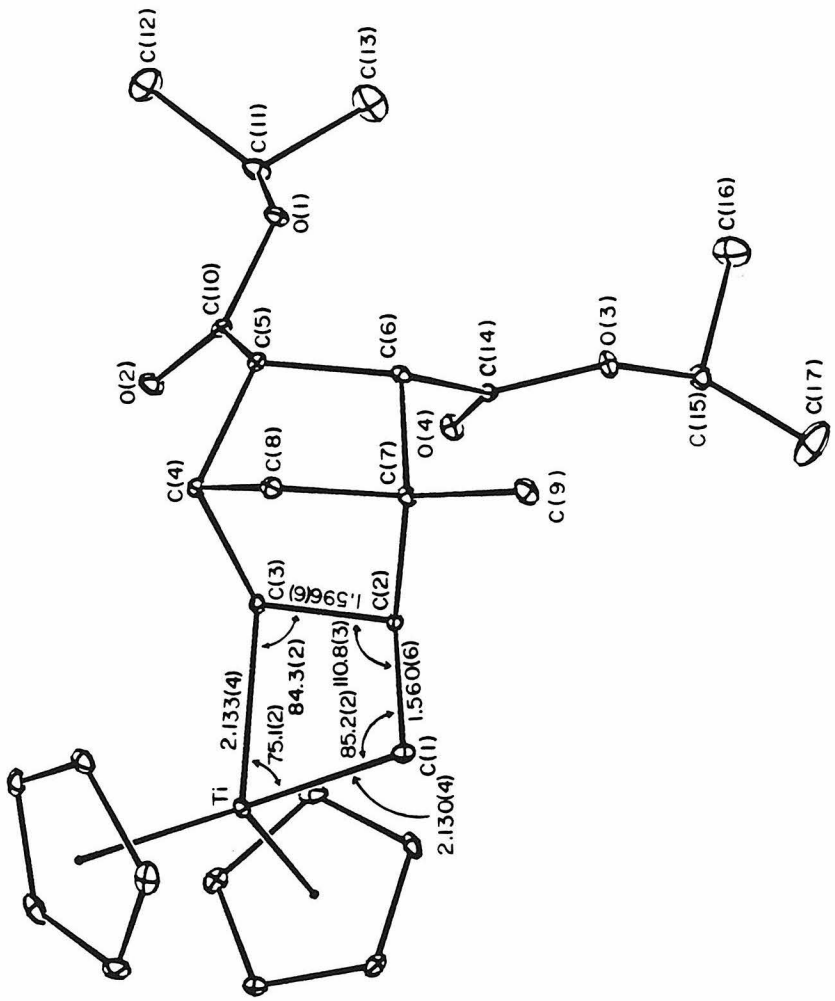
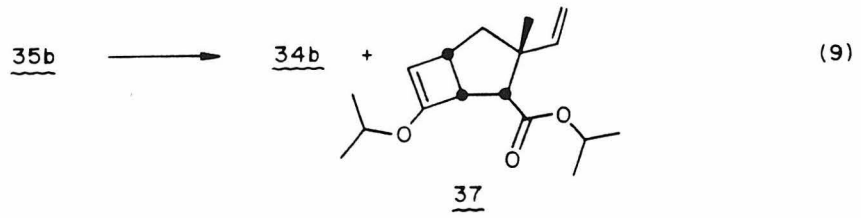


Figure 8. Selected Bond Lengths and Angles of Metallacycle **35**.

those which were previously reported for the β-substituted metallacycles.[3]

As had been expected, the carbonyl of the ester was directed under the norbornene skeleton due to the sterics of the O-alkyl substituents. As viewed from the ORTEP projection, the effect of these two substituents on each other resulted in an orientation in which the ester groups aligned in order to minimize steric interactions. Alignment of the carbonyl that would ultimately trap the alkylidene resulted in the correct orientation for the trapping process. The O-alkyl substituents were also observed in their more stable *s-cis* conformation in which the carbonyl eclipses O-alkyl group. The O(2)-C(10)-O(1)-C(11) and O(4)-C(14)-O(3)-C(15) torsion angles were found to be 4.2° and 0.4°, respectively. The preference for this conformation, as previously discussed, helped accentuate the effect of varying the bulk of the ester substituent with respect to the intermolecular side reactions.

The methyl substituted norbornene metallacycle **35** showed greater resistance to thermolysis than that without the substituent.[13c] Although thermolysis required temperatures of 90°C to attain reaction completion within 12 h, the product distribution showed no difference than a sample decomposed at 80°C for 24 h. With the methyl group present on the norbornene framework, the ring-opening was significantly reduced compared to the thermolysis of **13c**. Quantification of the products by comparison to a ^{1}H NMR internal standard, revealed that only 13% of the productive metathesis product **37** was formed while 52% of the diester was regenerated (eq 9). By incorporating a methyl group at the bridgehead position of the norbornene, the regiochemistry could be completely controlled; however, the presence of the substituent caused the ring-opening pathway to become less favorable for substrates with two vicinal *endo* ester substituents. The effect that the methyl group had on this process did not appear to arise



(9)

from the hindered intramolecular trapping of the ring-opened product as a result of conformational effects. Instead, it was believed that the inhibition of the rearrangement process was caused by the more favorable intramolecular recombination of the alkylidene intermediate with the terminal olefin, thus shifting the metathesis equilibrium toward the nonproductive intermolecular dissociation of the norbornene substrate. The prominence of diester regeneration was thought to have risen from steric interaction of the methyl group with the metallacycle ring. From these results, it became apparent that the inherent strain in the norbornene ring was not enough to enhance productive metathesis in the presence of the spectator carbonyl, and was even less effective with a 1-methyl substituent present. Thus, additional means of promoting ring-opening were explored, in conjunction with the norbornene ring strain, to further encourage metathesis in these systems. As previously discussed, there was a second means by which the ring-opened goal could be enhanced - the use of a substituted alkylidene (eq 2).

A means of cleanly generating a substituted titanocene alkylidene was recently reported.[10c] Similar to the strategy employed to ring-open strained norbornene olefins, this method used the strain of a cyclopropane ring to induce complete metathesis of a cyclopropene substrate. The thermal decay of metallacycle **38** at room temperature, formed by cycloaddition of **1** to 3,3-

38 39 (10)

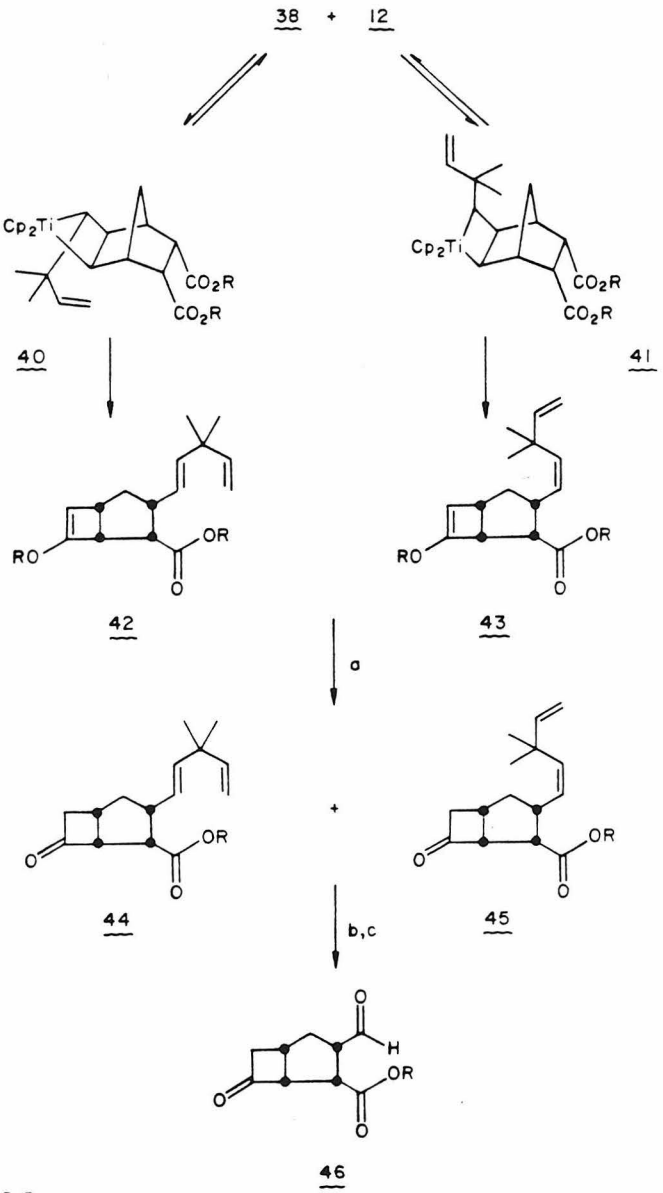
dimethylcyclopropene, has been shown to cleanly generate the titanocene alkylidene fragment **39** (eq 10). Through the use of the substituted alkylidene **39** in the formation of an α,β,α'-trisubstituted norbornene metallacycle (**7**), ring strain was expected to cause ring opening to be the dominant metathesis pathway.

With the use of the dimethyl ester **12a** as a trapping agent, **38** was completely consumed within the period of 1 h. Observation of the reaction mixture by ^{1}H NMR at ambient temperature revealed the formation of a new metallacycle with inequivalent cyclopentadienyl ligands at 5.66 ppm and 5.39 ppm, and a single cyclobutene enol ether product resonance at 4.57 ppm. The ratio of metallacycle to enol ether remained constant over a 4 h period of time. Complete metallacycle thermolysis was accomplished by heating of the mixture at 55°C for 15 h. ^{1}H NMR established the absence of a metallacyclobutane species and revealed the presence of a second cyclobutene enol ether peak. The new product peak was generated in three times the amount of the initial enol ether peak. On a larger scale, separation of the two organic decomposition products was not accomplished, but the mixture was purified to exclude all other contaminants. Examination of the product mixture by 500 MHz ^{1}H NMR showed extensive similarities in the two compounds with the major differences arising in the olefinic

region. It was evident that both products were the result of the ring-opening process and subsequent ring closure to the cyclobutene enol ether **42a** and **43a** (Scheme VI). The differences in the olefinic region resulted from the formation of two different conformations of metallacyclobutanes. Two *exo* metallacycle isomers resulted from the reaction of the substituted alkylidene with the strained olefin. The cycloaddition of the titanocene alkylidene to the strained olefin resulted in formation of metallacycle **40a** with the alkylidene substituent in a *trans* orientation to the norbornene substrate and, to a lesser extent, a titanacyclobutane with the substituent *cis* to the norbornene substrate (**41a**). Assuming that this stereochemistry was retained during the ring-opening process, two product isomers would be formed differing only in their *E* (**42a**) or *Z* (**43a**) configuration of the disubstituted olefin.

This postulate was easily substantiated by the chemical severing of the carbon-carbon double bonds. Hydrolysis of the two enol ether products generated the two respective ketones, **44a** and **45a**, with an unchanged product ratio (Scheme VI). Ozonolysis, followed by a reductive workup, produced a single aldehyde product, **46a**. Characterization of this compound was achieved through the use of two-dimensional ^{1}H-^{1}H correlated NMR (Figure 9). The aldehyde proton, H_1, displayed coupling to proton resonance H_6. Vicinal J-coupling was also evident by crosspeaks between H_6 and the diastereomeric methylene protons H_9 and H_{10} as well as H_4, the proton α to the carbonyl. Proton H_3 was found to be vicinal to both H_4 and H_8. Coupling was also observed between H_8 and both H_9 and H_{10}. As in the studies of the other bicyclo[3.2.0]heptane skeletons, cyclobutanone protons α to the carbonyl both displayed coupling to the adjacent proton H_8 and to the proton across the ring (H_3). This study confirmed the bicyclo[3.2.0]heptanone skeletal framework for aldehyde **46a**. This assignment was

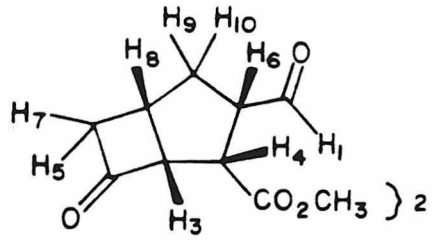
Scheme VI. Product Map of the Reaction Between **38** and **12**.



a R=Me

c R=iPr

[a](a) H_2O/Acetone, *p*-TsOH, 25°C; (b) O_3, CH_2Cl_2/MeOH, -78°C; (c) Me_2S, -78 to 25°C (86%).



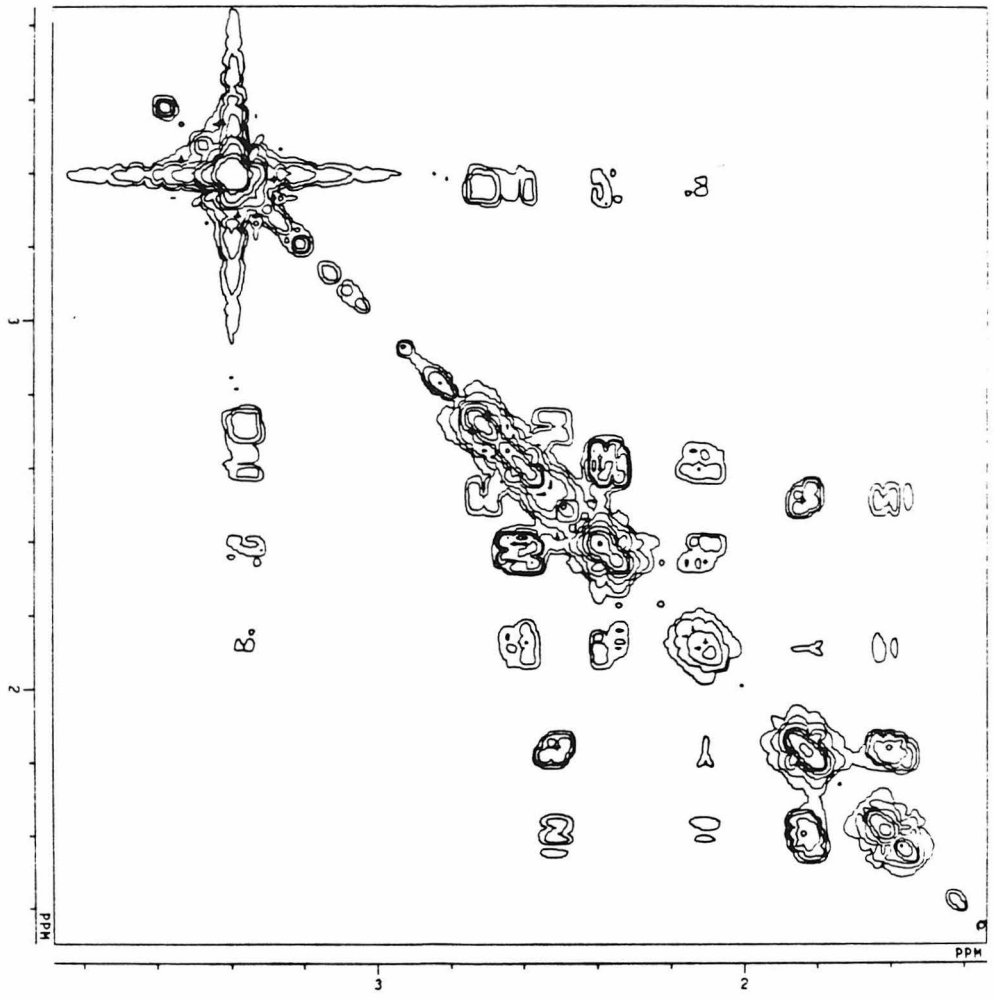


Figure 9. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum Expansion and Proton Resonance Assignments of **46a** in C_6D_6.

supported by infrared carbonyl stretches at 1718 cm^{-1} (aldehyde), 1728 cm^{-1} (ester), and 1777 cm^{-1} (cyclobutanone).

On a preparative scale, a single metallacycle product was isolated from the reaction of **38** and **12a**. Again, the use of NMR was found invaluable in the verification of metallacycle conformation. In addition to the normal resonances observed for the dimethyl ester metallacycle **13a**, a ^1H NMR spectrum of this compound (Figure 10) revealed the presence of a terminal olefin group and two methyl groups. Assignment of proton resonances was possible through coupling constants, chemical shifts and resonance patterns analogous to those found for compound **13a**. Difference NOE experiments were then used to determine the configuration of the substituents on the metallacycle ring. Saturation of the upfield cyclopentadienyl ligand resulted in the enhancement of the nearest bridge proton H_{14}, the closest bridgehead proton H_{12}, and one ring proton (H_{13}). This cyclopentadienyl ligand was therefore *cis* to the norbornene framework on the metallacyclobutane ring. Enhancement of two metallacycle ring protons, as well as the slight enhancement of the internal vinyl proton H_1 was observed by the saturation of the downfield cyclopentadienyl ligand. This series of spectroscopic experiments allowed the metallacycle to be assigned as the *trans* isomer **40a**. Decomposition of this single isomer at 55°C in C_6D_6 produced only the *E* cyclobutene enol ether product **42a** and regenerated **12a** in an 86:14 ratio. The assignment as the *E* isomer was substantiated by the magnitude of the coupling between the two protons on the disubstituted olefin (15 Hz). This product was found to be the major isomer produced from the thermolysis of the mixture of **40a** and **41a**.

Reflecting upon the information acquired from the reaction outlined in Scheme VI, several important features of this process were noted. Addition

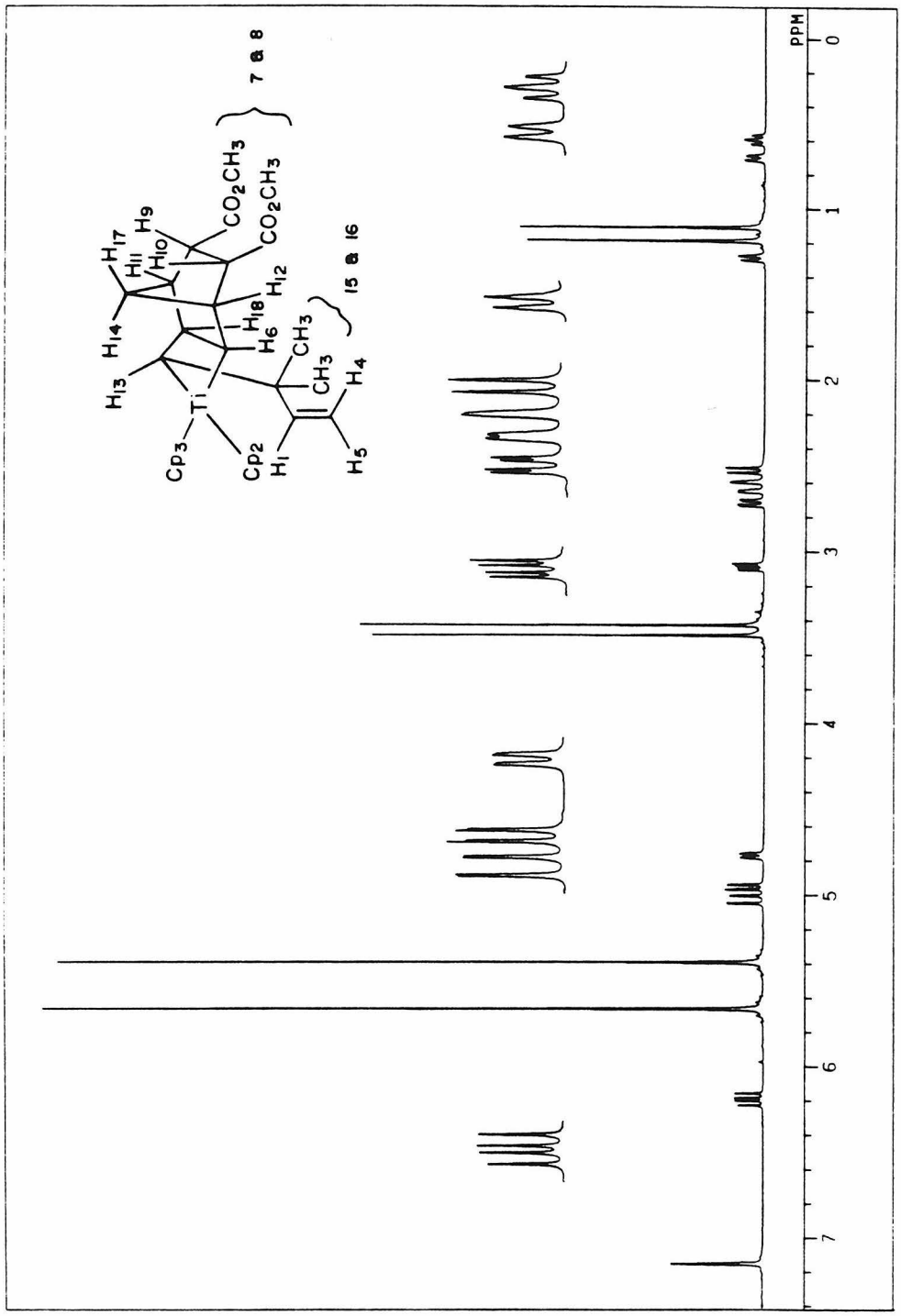


Figure 10. 400 MHz ^{1}H NMR Spectrum and Proton Resonance Assignments of **40** in C_6D_6.

of the substituted alkylidene **39a** to the norbornene substrate proceeded with two different orientations. These different reaction pathways resulted in the formation of the two diastereomeric trisubstituted metallacyclobutanes **40a** and **41a**. The metallacycle with the substituent *cis* to the norbornene framework (**41a**) rapidly regenerated **12a**, or produced the *cis* cyclobutene enol ether **43a** at room temperature and was not observed as an intermediate in the reaction. The relative instability of this intermediate was undoubtedly due to the steric interactions that resulted from the bulkyl substituent in a configuration *cis* to the norbornene. Models showed highly unfavorable interactions between the substituent and both the bridge and bridgehead portions of the norbornene skeleton. Relief of this strain was accomplished only by metallacycle cycloreversion. Thus, in the reaction mixture at 25°C, only the *trans* metallacycle **40a** and the organic product **43a**, resulting from the *cis* metallacycle, were observed. Upon heating to 55°C, thermolysis of the less sterically strained **40a** occurred, producing the second and major product of the reaction (**42a**). It was also observed that, in spite of the use of the dimethyl ester, side products resulting from intermolecular trapping were not detected.

To determine the amounts of products that were formed from the intermediate trisubstituted metallacycles **40** and **41**, ^{1}H NMR integration versus an internal standard was used. ^{1}H NMR integration was the method of choice due to the sensitivity of the cyclobutene enol ether functionality during the process of isolation. The use of 1.30 equivalents of metallacycle **38** insured complete metallacycle formation with the diester substrate **12**. After thermal decomposition, the products were compared to an internal standard of mesitylene. The results can be seen in Table III. The separate reaction of both the dimethyl and diisopropyl esters produced similar overall product yields, but the distribution of the

Table III. Product Distribution upon Reaction of **12** with **38**.

Substrate		Product Yield(%)				Conversion $\left(\frac{42+43}{12+42+43}\right)$	
	R	42(%)	43(%)	12(%)	42/43		Overall Yield(%)
a	Me	46	15	30	3.1	67	91
b	iPr	57	23	10	2.5	89	90

products differed for the two substrates. The conversion of the norbornene substrate to ring-opened metathesis products for **12c** (89%) was much higher than that for **12a** (67%). This trend was similar to that observed for the ring-opening metathesis by the titanocene methylidene fragment. As previously discussed, the *cis* substituent interactions of the ester groups are relieved somewhat upon ring-opening to a substituted cyclopentane moiety. The increased size of the isopropyl groups could have caused an increase in these steric interactions by inducing a less favorable orientation of these carbonyl substituents. As a result, ring opening became enhanced for the diisopropyl ester substrate.

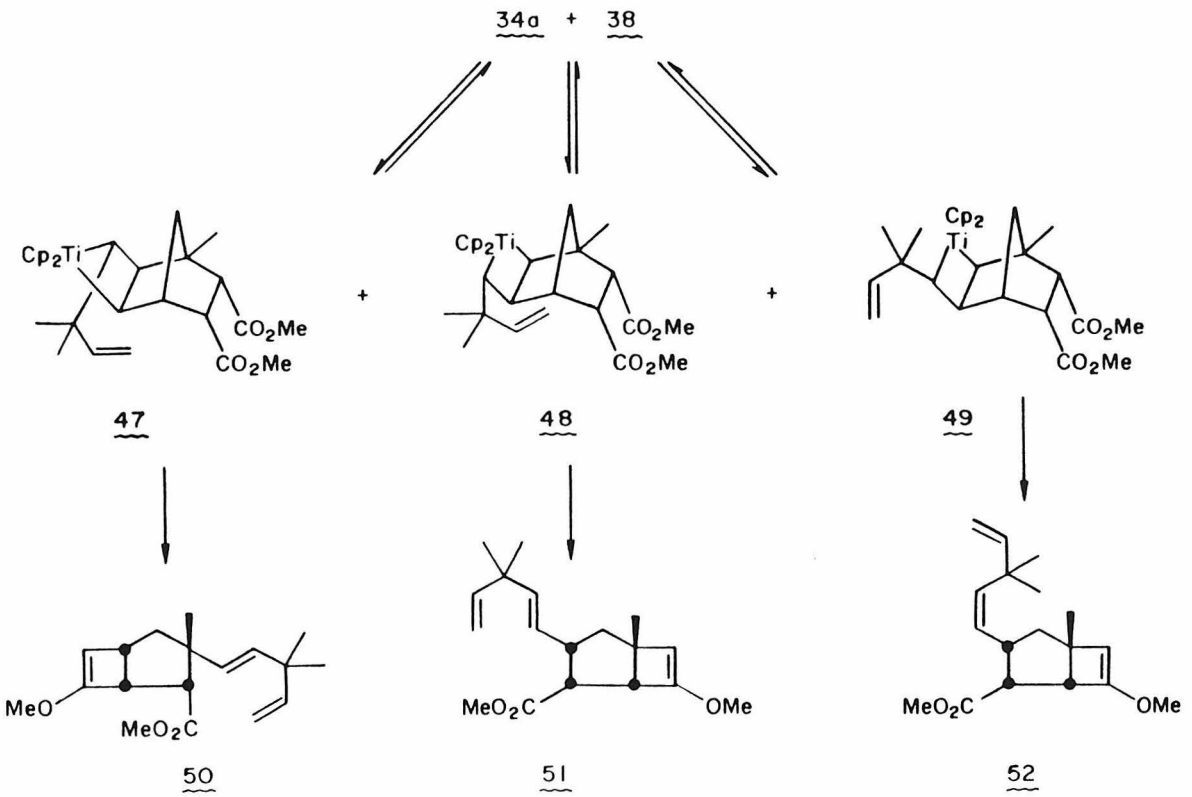
From the observation that the isolated *trans* substituted metallacycle **40a** decomposed to produce an 86% conversion of **12a**, it was deduced that productive metathesis was more prevalent for the *trans* metallacycle **40** than the *cis* metallacycle **41**. Added steric interactions between the *cis* quaternary substituent and the norbornene framework were thought to cause the increased intermolecular dissociation of the titanocene methylidene fragment from **12a**. Also of note from Table III were the differing ratios of *trans* to *cis* products. The origin of the larger ratio of 3.1:1.0 for **12a**, in comparison to that of 2.5:1.0 for **12c**, was undetermined.

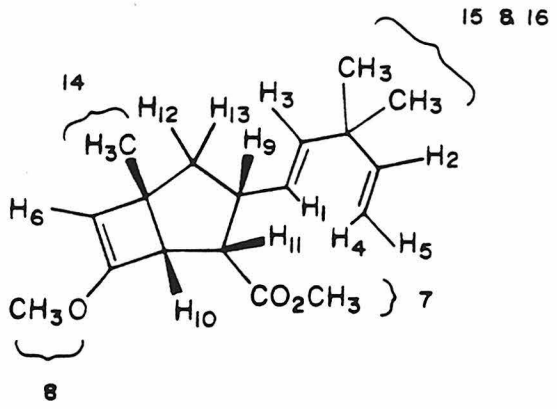
With the use of the substituted alkylidene, the ring opening of the strained olefin was greatly enhanced with respect to the metathesis induced by titanocene methylidene. In spite of the fact that minor complications had occurred by the formation of *cis* and *trans* product isomers, the development and utility of this process began to show promise. As previously noted, it was observed that ring-opening metathesis was further enhanced by the absence of the second, nonparticipating ester group. The increase in substrate conversion was observed only for the metallacycle regioisomer with the correct orientation for intramolecular

trapping to occur. Similar results were obtained for the reaction of **38** with **25**. Thermolysis of this metallacycle mixture produced six organic products, as determined by capillary gas chromatography, of which the major isomer contributed only 40% toward the total product mixture. The need for a substrate substituent to direct the regiochemical addition of the alkylidene to the strained olefin was obvious. Although difficult to predict, it was thought that the presence of a 1-methyl substituent would again direct the regiochemical addition of the substituted alkylidene. Due to increased steric interaction with the alkylidene substituent, the methyl directing group was also expected to reduce, if not eliminate, the amount of *cis* metallacycle formed.

Reaction of **38** with the 1-methyl dimethyl ester **34a** at room temperature, followed by heating at 65°C for 12 h, produced three cyclobutene enol ether peaks in a ratio of 65:32:4 as observed by ^{1}H NMR. Thin layer silica gel chromatography produced two distinct spots upon elution with petroleum ether/ether (9:1). The products of R_f 0.19 and 0.25 were separated by flash chromatography and spectroscopically characterized. The more rapidly eluted compound was found to be **50**, the expected product of the ring-opening process, and was the major product of the reaction (Scheme VII). The remaining elutant was shown to be an 8:1 mixture of inseparable isomers which both resulted from the ring-opening process. Determination of the structure of the major isomer was accomplished by two-dimensional NMR (Figure 11). Proton H_1 coupled to H_3 and a ring proton H_9. The allylic proton also coupled to the α-carbonyl proton H_{11} as well as the diastereotopic methylene protons H_{12} and H_{13}. Proton H_{10} coupled only to H_{11}; H_{12} and H_{13} coupled only to one another and to H_9. The methyl directing group on the substrate was therefore on the ring carbon between H_{10} and both H_{12} and H_{13}. Due to the large vicinal coupling between H_1 and H_3 (16 Hz),

Scheme VII. Product Map of the Reaction Between **38** and **34a**.





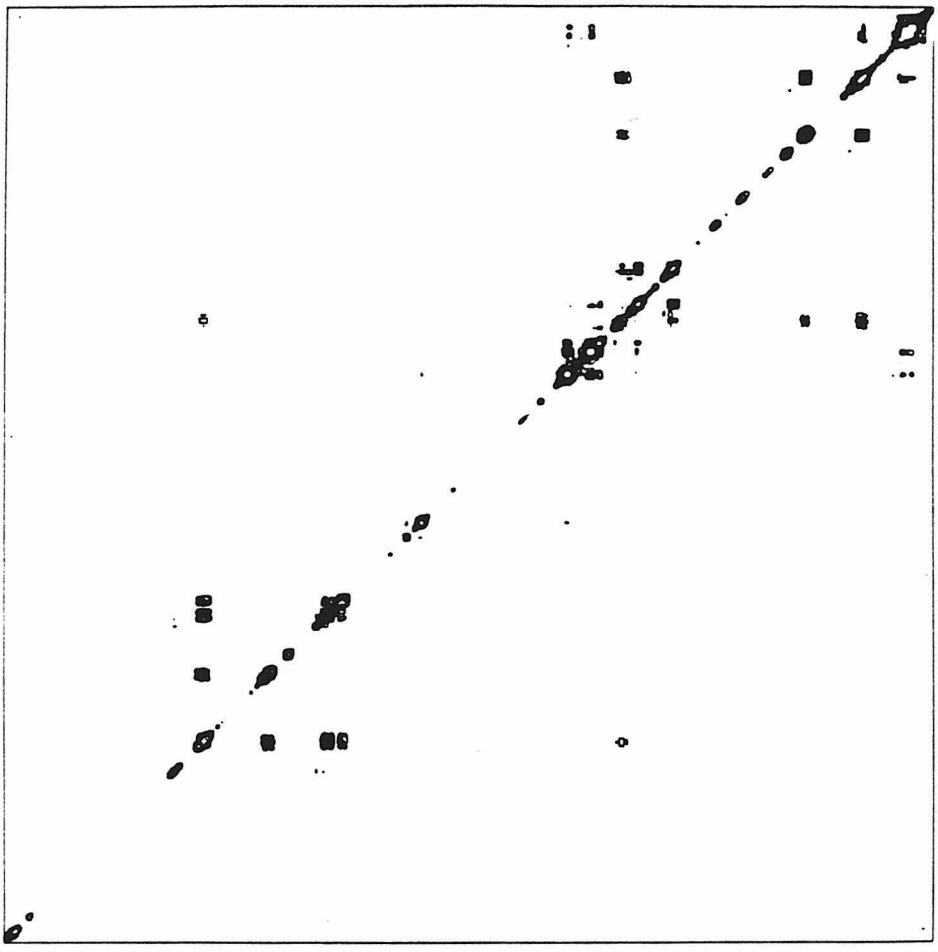
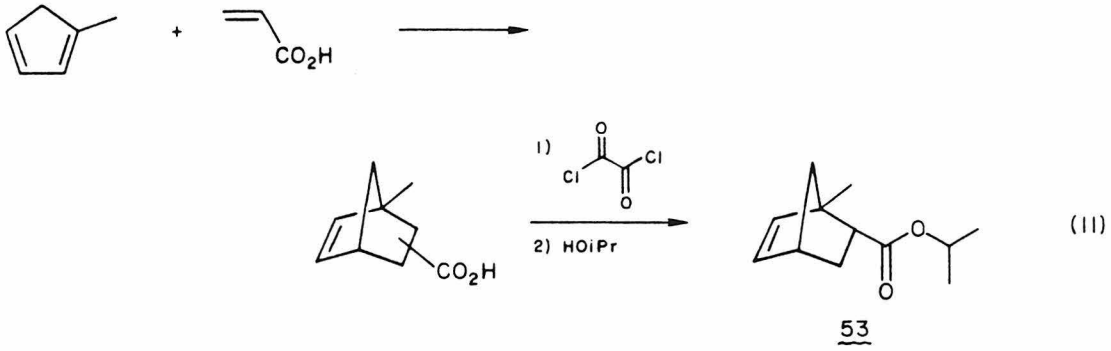


Figure 11. 400 MHz ^1H-^1H Correlated NMR Spectrum and Proton Resonance Assignments of **52** in C_6D_6.

product **51** was found to have a *trans* geometry about the disubstituted olefin. The minor isomer was determined to be the *cis* isomer (**52**) of the same methyl substituted bicyclo[3.2.0]heptene skelton, due to spectroscopic similarities and negligible differences in elutant polarity. This 8:1 ratio of *trans* to *cis* isomers, in which the titanium metal center added to the strained olefin on the same side as the methyl directing group, was the result of the opposite regiochemical addition that produced **50**. Of the observed organic products, the expected product **50** accounted for 44% of the mixture. The products resulting from the opposite regiochemical addition were found to be 22% (**51**) and roughly 2% (**52**) of the reaction mixture. The remaining 32% was accounted for by the regeneration of **34a**. Thus, with this substrate, 68% conversion was achieved.

In the cycloaddition of the substituted alkylidene with **34a**, the 1-methyl substituent on the norbornene had a lesser directing effect on the regiochemical metallacycle formation. The inability of the methyl substituent to direct the cycloaddition of **39** as efficiently as observed for the addition of **1**, was due to the increased steric interaction between the added alkylidene substituent and the methyl group. Because this interaction had reached a magnitude comparable to that of the cyclopentadienyl ligand interactions with the methyl substituent, both pathways were represented by product formation. The effect of the increased alkylidene substituent interactions with the methyl substituent were also evident by the absence of the corresponding *Z* isomer of **50**. The larger ratio of the *trans*:*cis* products **51** and **52**, 8:1, as compared to 3:1 for the titanocene methylidene source, was most likely due to the differing conformational preferences of this metallacycle ring for a *trans* substituent as a result of the methyl group. Unlike the relationship between **34b** and **12c**, conversion of **12a** was not dramatically different than that for the methyl substituted **34a**.

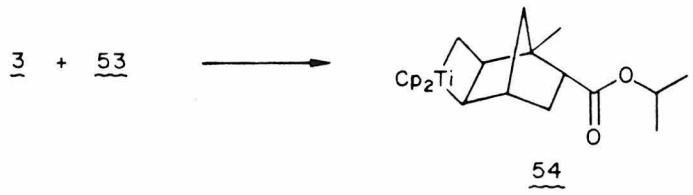
Because of the delicate balance of product formation caused by the third substituent on the metallacycle, we were interested in further observation of additional competing pathways of reaction. Our attention turned toward determining the extent to which the process of trapping an intermediate such as **14** to form a bicyclo[2.2.1]heptene system (**18**) would occur. A process such as this was suspected in the thermolysis of **27**, but was never verified. The substrate chosen for this study was that which would use a methyl substituent to help direct the metallacycle formation, so that the trapping ester would be situated across the substrate ring from the titanium. The synthesis of substrate **53** was accomplished through the Diels-Alder reaction of 1-methylcyclopentadiene and acrylic acid, followed by the formation of the isopropyl ester **53** from the corresponding acid chloride (eq 11). This isomer was isolated in 92% isomeric purity through the use of silica gel chromatography in 48% yield.



(11)

53

Generation the of titanocene methylidene fragment (**1**) in the presence of **53** resulted in the formation of the expected metallacycle (eq 12). Crystallization of a solution of the organometallic products produced a single metallacycle isomer **54**. Difference NOE experiments verified the regiochemistry of the methyl substituent with respect to the titanium by observed enhancement of the bridge-



(12)

head proton upon saturation of the *cis*, downfield cyclopentadienyl ligand. The regiochemistry of the Diels-Alder reaction was confirmed as the saturation of the methyl substituent resulted in the enhancement of the adjacent proton α to the carbonyl, H_6. Thermolysis of this compound was much cleaner than that observed for metallacycle **27**. Three organic products were observed by capillary gas chromatography. The major products resulted from the regeneration of **53**. Presence of the starting ester was confirmed by ^{1}H NMR and capillary gas chromatography. Intermolecular methylenation of ester **53** was found to be the second most prominent organic product by NMR. ^{1}H NMR detection of a trisubstituted cyclic enol ether proton at 4.32 ppm led us to believe that the third product resulted from ring opening and subsequent carbonyl trapping to form the bicyclo[2.2.1]heptene ring system. Isolation of this product was not acheived due to its limited contribution to the product mixture. Increasing the abundance of this product required more productive metathesis of the norbornene substrate.

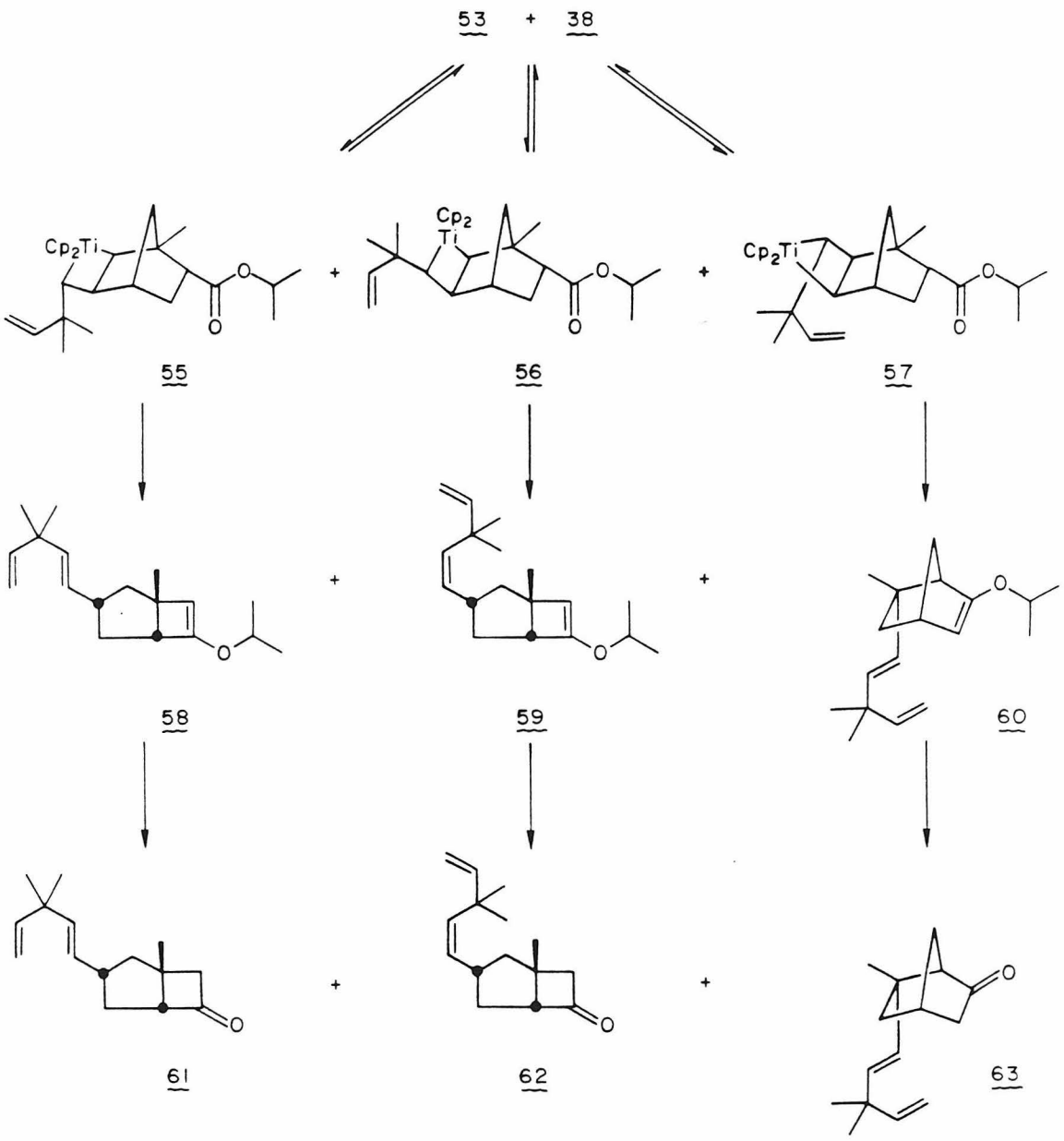
Allowing the substituted alkylidene **39** to react with **53**, three productive organic products were formed in a ratio of 2.6:1.1:1.0, and **53** was regenerated to an extent of only 6%. This mixture of products was inseparable by silica gel chromatography and was subjected to hydrolysis conditions. The resulting mixture of ketones produced two elutants of R_f=0.48 and 0.32 in petroleum ether/ether

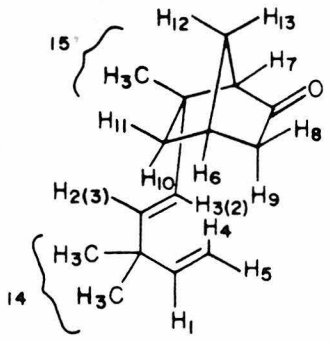
(4:1). Separation of these elutants produced a mixture of two isomeric compounds as the more mobile elutant and a single product as the compound with the lower R_f. By 400 MHz ^{1}H NMR, the mixture of compounds was a 2.5:1.0 ratio of *trans* to *cis* cyclobutanones that did not contain isolated disubstituted double bonds. Thus, it was assumed that this mixture had resulted from the regiochemical addition of the titanium on the same side as the methyl substituent to form **55** and **56**, followed by the ring opening and alkylidene trapping process to produce **58** and **59** (Scheme VIII). By ^{1}H NMR, the remaining product was found to have the isolated disubstituted double bond of the expected product **63**, as well as the very characteristic bridgehead protons of the bicyclo[2.2.1]heptane ring system.

^{1}H-^{1}H correlated NMR confirmed the skeleton and found the regiochemistry of the substituents consistent with the structure **63**. The olefinic region displayed the expected crosspeaks, thus, the aliphatic region was closely inspected to determine the skeletal framework of the bicyclic system (Figure 12). The bridgehead proton H_6 coupled to both H_{12} and H_{13}. These bridge protons coupled to the other bridgehead proton H_7. Proton H_7 coupled to both H_8 and H_{11}, which were assigned as the *exo* protons based on the appearance of crosspeaks. Each of these *exo* protons coupled to their geminal, *endo* proton; H_8 to H_9; H_{11} to H_{10}. As a result of these findings, the topology and regiochemistry of **63** were confirmed. This molecule also exhibited a carbonyl stretching frequency of 1750 cm^{-1} and a ^{13}C NMR resonance of 212 ppm. The additional spectral evidence supported this structural assignment.

The product distributions shown in Scheme VIII differed significantly from those observed for the other 1-methyl directing system investigated (Scheme VII). In the system involving the diester **34a**, it was found that the methyl substituent

Scheme VIII. Product Map of the Reaction Between **38** and **53**.





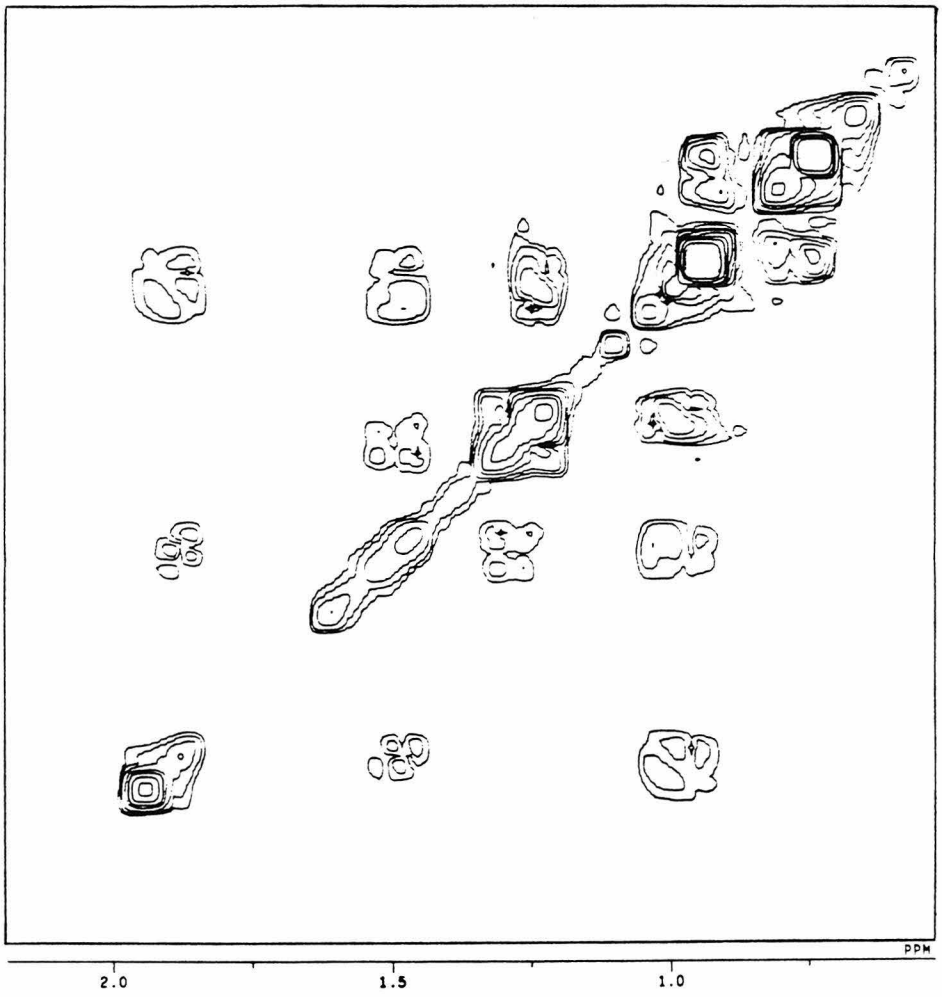
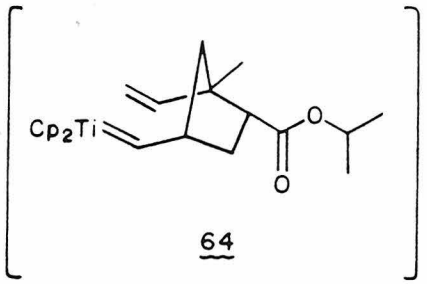


Figure 12. 400 MHz ^{1}H-^{1}H Correlated NMR Spectrum Expansion and Proton Resonance Assignments of **63** in C_6D_6.

had a somewhat reduced directing effect on the regiochemical addition of the substituted alkylidene. Nevertheless, it did display a positive directing effect, 65:35, in the favor of metallacycle formation with the titanocene unit directed away from the methyl substituent. A different distribution was found using the ester **53**. In this case, products resulting from metallacycle formation with the titanocene unit close to the methyl substituent accounted for the major portion of the ring-opened product mixture. In fact, **63**, the product expected from the directing effect of the methyl group, contributed only 22% to the productive metathesis mixture.

The delicate balance of the metathesis equilibrium again comes into effect. It was unlikely that the addition of a single methyl ester substituent had a large enough effect to completely reverse the kinetic regiochemical addition of the substituted alkylidene to the two substrates **34a** and **53** - especially in light of the negligible regiochemical preference for kinetic metallacycle formation observed with **25**. Instead, it was more probable that the metallacycle **57**, leading to the formation of **60**, was actually formed to a greater extent than indicated by the product distribution. The low conversion of this metallacycle to **60** could result from a number of factors. This metallacycle could have a much greater propensity than that of **34a** to nonproductively dissociate, but this difference was unlikely since all previous observations indicate that the ring opening of the mono substituted norbornene substrates occurred to an equal or greater extent than the diester substrates. The fate of metallacycle **57** was thus believed to involve ring opening to the substituted alkylidene **64**. From this intermediate, two intramolecular reactions could occur. The productive trapping of the alkylidene to form **60** appeared to be unfavorable relative to other available pathways, and **60** was formed to only a small extent. Intramolecular cycloaddition to the



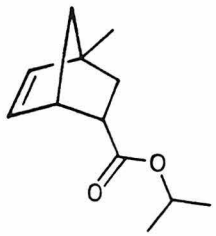
64

olefin again regenerated the same metallacycle intermediate **57**. Intermolecular dissociation to **53** and **39**, followed by recombination to form the opposite regioisomers, **55** and **56**, allowed the more favorable cyclobutene enol ether formation. Thus, the unfavorable trapping process to form the bicyclo[2.2.1]heptene enol ether allowed the equilibrium to be drawn against the directing effect of the methyl substituent toward the more facile formation of **59** and **60**. Again, as in the separate thermolysis of **26** and **27**, evidence for the equilibrium of metallacycles through the intermediate titanocene alkylidene was observed. During the regeneration of **39**, which appeared to be less subject to decomposition than **1**, conversion to productive metathesis products was high (94%), and products resulting from the intermolecular olefination of the ester group were not observed. The increased stability of alkylidene **39**, during the dissociation of **57** and the recombination to **55** and **56**, was expected to result from intramolecular formation of the intermediate metallacycle **38**.

From the results that were obtained from the variety of substrates and metallacycles studied, the optimal substrate for this synthetic transformation was conceived. The substrate had to possess a single *endo* ester substituent such as **25**, but also required a bridgehead substituent to regiochemically direct metallacycle formation. The relationship between the alkyl directing group and the

ester substituent was required to be *"meta."* Such a substrate was expected to specifically form the alkyl-substituted isomer of **27** upon reaction with titanocene methylidene. Reaction with **38** was expected to increase the conversion of substrate with respect to the use of fragment **1**. The strategic positioning of the alkyl group, relative to the ester substituent, was expected to further reduce the favorability of the bicyclo[2.2.1]heptene formation and tip the balance of the equilibrium toward the desired product. With the presence of the alkyl group, the *E*:*Z* ratio of products was also expected to be greatly increased.

The simplest substrate for this study would have been **65**, the Diels-Alder regioisomer of **53**. Due to the stronger interaction of carbon atoms with the large coefficients in the frontier orbitals of the diene and dienophile, the cycloaddition

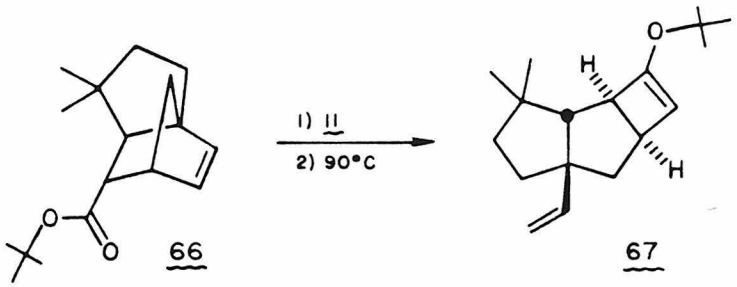


65

of 1-methyl cyclopentadiene **65** and an acrylate ester produced a mixture of four isomers that consisted of only 13% **65**.[23a] To overcome the effect of the orbital coefficients, the use of a three-carbon tether was employed to restrict regiochemical addition and ensure *endo* cycloaddition. The preparation of the tricyclic strained olefin **66** was accomplished as previously reported.[28] Incorporation of the geminal dimethyl substituents into this substrate were desired for subsequent transformation of the molecule into the natural product capnellene.[29a] The substituents were not expected to alter the course of the metathesis rearrangement

in any way.

Reaction of **66** with 1.15 equivalents **11** was found to proceed as expected (eq 13). Thermolysis of the mixture produced the desired tricyclic product **67** and regenerated **66** in a 84:16 ratio, respectively. ^{1}H NMR comparison of the products with an internal standard revealed a total quantitative yield (100%) of the two

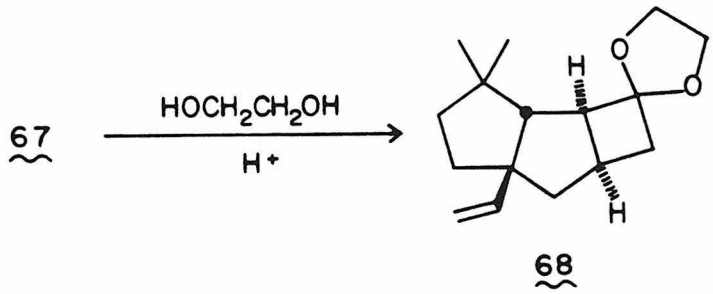


(13)

products. Conversion of this substrate showed essentially no difference from the 86% conversion of the non-bridgehead-substituted metallacycle **27**. Unlike the relationship between the thermolysis of **12c** and **34b**, the methyl directing group did not substantially reduce conversion. The reaction of **66** with **38**, on the other hand, did not produce the expected results. Instead of reacting in a selective manner, as with **53**, thermolysis of the mixture produced six products. These results were similar to those observed for **25**, which also contained a *t*-butyl ester carbonyl. Different results were observed for the reaction of **53**, which had an isopropyl ester substituent.

For the generation of **1** on a larger scale, the use of the commercially available Tebbe reagent (**3**), or its *in situ* preparation,[30] was preferable to the use of **11**. Metallacycle formation using **3** as the source, followed by removal of the aluminum adduct, produced results similar to the reaction with **11** upon thermolysis. The drawback to this procedure was the need to remove the

$Me_2AlCl{\cdot}DMAP$ adduct from the metallacycle solution. The removal process not only required special inert atmosphere techniques, but also was very costly to overall product yield. In an attempt to avoid this purification step, the reaction mixture containing the aluminum adduct was exposed to thermolysis conditions. In the presence of the aluminum adduct, complete conversion of the substrate to **67** was achieved. The ability of the aluminum adduct to produce complete conversion of the substrate was believed to have arisen from an ability either to stabilize **1** and prevent its decomposition in solution, to promote ring-opening of the intermediate metallacycle through interaction with the metallacycle itself, and/or to activate the ester carbonyl toward intramolecular olefination. Because **1** was not removed from the equilibrium mixture by decomposition, the equilibrium was driven toward the formation of **67**. Due to the sensitive nature of the cyclobutene enol ether, as previously discussed, **67** was transformed into the corresponding 1,3-dioxolane **68**. As **68**, the product was isolated in 81% isolated yield based on substrate **66** (eq 14).



(14)

The ring-opening metathesis and intramolecular carbonyl trapping rearrangement of *endo,endo*-diesterbicyclo[2.2.1]heptene substrates have been accomplished with titanocene alkylidene reagents. Conversion of the substrate to the

bicyclo[3.2.0]heptene product using sources titanocene methylidene (**1**) was optimized by increasing the steric bulk of the ester substituent. Rearrangement of the diisopropyl ester **12c** was achieved in 46% conversion. Use of a substituted alkylidene, generated from **38**, further enhanced the conversion of **12c** to the rearranged product. Thermolysis of the mixture resulting from the reaction of **38** and **12c** transformed the substrate with 89% conversion into a mixture of *E* and *Z* isomeric products, which, after hydrolysis of the enol ether and removal of the auxiliary alkyl substituent, produced a single bicyclo[3.2.0]heptane product. Cleavage of the cyclobutene ring could also provide a method of preparing multiple substituted cyclopentane substrates containing a variety of functionality upon which to elaborate. This strategy had been used before to transform bicyclo[3.2.0]heptene enol ether substrates into natural products. A prostanoid, a modified prostaglandin, was prepared in this way.[31] The synthesis of brefeldin A, a fungal metabolite similar in structure to a prostaglandin,[32] was also achieved through the use of this methodology. As a precursor to a substituted cyclopentane, the use of bicyclo[3.2.0]heptene enol ethers could also be incorporated into the synthetic preparation of prostaglandin compounds. There are many other naturally occurring cyclopentane and polyquinane products[33] toward which this methodology may be applied.

The use of a substrate with a single *endo*-ester required a substituent on the bridgehead carbon "*meta*" to the ester substituent. Due to the unsymmetrical nature of the substrate, the substituent functioned to direct the regiochemical addition of the titanocene methylidene in metallacycle formation. Thermolysis of the metallacycle proceeded with an 84% conversion of the substrate to the rearranged product. Through the use of **3** to generate **1**, which is a more convenient reagent, complete conversion of the substrate occurred with high yield.

The requirement of a substituent "*meta*" to the carbonyl was ideal for tricyclic substrates formed from the intramolecular cycloaddition of a cyclopentadiene, tethered to an α,β-unsaturated ester. Through the ring-opening metathesis and intramolecular ring formation of bridged tricyclic species, an efficient synthetic route to several of the naturally occurring polyquinane products,[33] that have received much synthetic interest lately, was made available. The synthesis of one of these natural products, $\Delta^{(9,12)}$-capnellene, required only the functional group modification of **68**.[29]

Experimental Section

General Procedures. All manipulations of air and/or moisture sensitive compounds were carried out with use of standard Schlenk or vacuum line techniques. Argon was purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4Å molecular sieves. Solids were transferred in a nitrogen-filled Vacuum Atmospheres Dri-Lab equipped with an MO-40-1 purification train and a DK-3E Dri-Kool. Measurement of weight was conducted after minimizing static interference through the use of a Staticmaster ionizing unit (Nuclear Products Co.). Flash chromatography was performed according to general procedure of Still and coworkers[34] employing Silica Woelm 32-63 (32-63 μm). Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates and visualized by iodine vapor or phosphomolybdic acid dip.[35] All reaction temperatures were measured externally.

Materials. *t*-Butyl alcohol was distilled from CaH_2 before use. Mesitylene (MCB Reagents) was stored over 4Å molecular sieves under argon. Acrylic acid was distilled immediately prior to use. Preparation of metallacycle reagents **11**[33] and **38**[10c] was performed according to reported procedure. Tebbe reagent (**2**) was prepared according to literature procedure.[4] The norbornene substrates *endo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid[37] and the dimethyl and diethyl esters of *endo,endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid[22] were prepared using reported methods. 4-Dimethylaminopyridine (DMAP) was obtained from Aldrich Chemical Company, decolorized with activated charcoal, and recrystallized from hot toluene. With the exception of *p*-toluenesulfonic acid monohydrate, maleic anhydride, and 4-dimethylaniline, which were purchased from MCB Reagents, all chemicals were obtained from the Aldrich Chemical Company and were used without further purification.

$CDCl_3$ was stored over 4Å molecular sieves and filtered through Activity I alumina immediately prior to use. Dichloromethane (CH_2Cl_2) was dried over P_2O_5 and degassed on a vacuum line. Pentane was stirred over H_2SO_4, dried over CaH_2, and vacuum-transferred onto sodium-benzophenone ketyl. Benzene and tetrahydrofuran (THF) were dried over CaH_2 and vacuum-transferred onto sodium-benzophenone ketyl. Diethyl ether (ether), and toluene, benzene-d_6 (Cambridge Isotope Laboratories), and toluene-d_8 (Cambridge Isotope Laboratories) were degassed and stirred over sodium-benzophenone ketyl. The dried and degassed solvents were vacuum-transferred into dry vessels equipped with Teflon valve closures and stored under argon. Reagent grade petroleum ether (35-60°C) was used without further purification. In the cases where the rigid exclusion of oxygen was not required, anhydrous ether was used without further purification.

Instrumentation. NMR spectra were recorded on a JEOL FX-90Q (89.60 MHz ^1H; 22.53 MHz ^{13}C), a JEOL GX-400 (399.65 MHz ^1H; 100.40 MHz ^{13}C), or a Bruker WM-500 (500.13 MHz ^1H). Chemical shifts were reported versus residual solvent signals on the δ scale. Data were reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad), coupling constant (Hz), integration, and interpretation. Difference NOE experiments were performed according to published procedures and were described fully in the text of this paper.[38] Analytical gas chromatographic analyses (VPC) were performed on a Shimadzu GE-Mini 2 flame ionization instrument modified for capillary use and equipped with a Hewlett-Packard Model 339A integrator (column: 0.24 mm x 15 m DB1). The detector and injector temperature were 250°C. Column temperature and retention times (t_r) were reported. Preparative gas chromatography was performed on a Varian Aerograph

Model 920 instrument using a 5′ x 1/4″ 15% SE-30 on Chromosorb W column (column a) or a 5′ x 1/4″ Hallcomid M-18-01 60/80 on Chromosorb W (column b). Infrared analyses utilized a Beckman 4210 spectrophotometer and were reported in reciprocal centimeters cm^{-1}). Melting points were determined on a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected. Ozone was obtained using a Welsbach generator.

Combustion analyses were performed by Galbraith Laboratories, Inc. (Knoxville, Tennessee) or by Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory.

Two-Dimensional ^1H-^1H Correlated NMR Spectra.[20] The data were acquired using a JEOL GX-400 NMR spectrometer operating at 399.65 MHz proton frequency. The pulse sequence was 90°-t_1-45°-Acquisition-Relaxation Delay and the phases of the pulses and receiver were cycled to provide quadrature detection in f_1 and selection of "P-type" peaks. The 90° ^1H pulse width on the 5 mm $^1H/^{13}C$ probe was 15.0 μs. The f_2 spectral width was 3201.0 Hz and the pulse delay (PD) was 3.0 sec. Two dummy scans were taken before each slice to eliminate non-equilibrium magnetization. Eight transients of 1 K data points were collected for 384 increments of t_1. The total acquisition time was 3.5 h. The data were zero-filled to 512 points in t_1, apodized with a sine-ball window function in both dimensions and Fourier-transformed in both dimensions. The absolute value spectrum was calculated and the entire data set symmetrized.

General Procedure for NMR Tube Reactions. An NMR tube was first weighed under static-free conditions in a nitrogen atmosphere. Solids were loaded into the tube, static was removed, and weight was recorded. A latex septum was fitted onto the NMR tube and sealed with Parafilm. Solvent (400 μL) and liquid substrates were added via syringe. Reactions were conducted following the

same conditions as described for preparative reactions. To quantify the resulting products, mesitylene was added via syringe and the compounds assayed by integration of peak areas. Paramagnetic titanium products were quenched by exposure to oxygen so that NMR spectra could be obtained. Results of these reactions are described fully in the text of this paper.

Preparation of 13a from 11. To a solution of **11** (1.14 g, 4.13 mmol) in 8 mL toluene at -50°C, was added a precooled solution of **12a** (1.48 g, 7.1 mmol) in 7 mL toluene. The mixture was warmed to -10°C and then slowly allowed to reach ambient temperature over the period of 1 h. After being stirred at room temperature for 30 min, the mixture was concentrated to a red slush *in vacuo*. The reaction mixture was suspended in 50 mL pentane and stirred for 30 min. The precipitate was removed by filtration, washed with 2 x 10 mL pentane, and dried *in vacuo*. After dissolving this solid in a minimum amount of CH_2Cl_2 at -40°C, the product was slowly precipitated from solution with 20 mL pentane, and stirred at -40°C for 15 min. The precipitate was isolated by filtration and residual solvent was removed *in vacuo* to produce 1.41 g (85% yield) of a red powder. ^{1}H NMR (400 MHz, C_6D_6), proton assignments as shown in Figure 1: δ 5.46 (s, 5H, Cp_1), 5.41 (s, 5H, Cp_2), 4.48 (d, J=8.3 Hz, 1H, H_3), 3.46 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 3.09 (dd, J=4.4, 11.4 Hz, 1H, H_6), 2.94 (dd, J=9.0, 10.8 Hz, 1H, H_7), 2.72 (dd, J=3.0, 11.4 Hz, 1H, H_8), 2.53 (br s, 1H, H_9), 2.49 (br s, 1H, H_{10}), 1.67 (dd, J=9.0, 9.4 Hz, 1H, H_{11}), 1.12 (d, J=10.1 Hz, 1H, H_{12}), 0.83 (ddd, J=8.3, 9.4, 10.8 Hz, 1H, H_{13}), 0.68 (d, J=10.1 Hz, 1H, H_{14}). ^{13}C NMR (22.5 MHz, C_6D_6) δ 173.1, 172.4, 109.9, 108.8, 96.3, 73.0, 51.8, 51.0, 50.7, 49.8, 47.1, 46.2, 35.9, 15.8. IR (CH_2Cl_2) 2950, 1740, 1433, 1200, 1170, 815 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}O_4Ti$: C, 65.68; H, 6.51. Found: C, 65.53; H, 6.46.

Preparation of 13a from 3. To a solution of **3** (2.27 g, 8 mmol) in 15 mL

THF at -50°C was added a precooled solution of **12a** (2.10 g, 10 mmol) in 15 mL THF. The reaction mixture was allowed to warm to ambient temperature over the period of 5 min and then was stirred at room temperature for 15 min. After concentration of the mixture *in vacuo* to a thick oil, the products were suspended in 50 mL pentane. The solid was isolated by filtration, washed with 2 x 15 mL ether, and finally with 1 x 20 mL pentane. Residual solvent was removed *in vacuo* to give 2.70 g **13a** (84%) as a red powder. This powder was identical to the product obtained from the reaction of **12a** with **11**.

Thermolysis of 13a. A solution of **13a** (1.00 g, 2.49 mmol) in 7 mL benzene was heated at 80°C for 22 h. The reaction mixture was then cooled to room temperature and quenched by pouring into 100 mL vigorously stirring pentane. After being stirred for 1 h, the solution was filtered and concentrated to an oil. The oil was redissolved in pentane and stirred for 1 day. Following removal of insoluble products by filtration, the solution was concentrated to an oil. Partial separation of this mixture was achieved through flash chromatography using petroleum ether/ether (1:1). The elutant of R_f=0.77 (28 mg, 1.4%) was found to be **19a**. The next elutant was identified as a mixture of **16a** and **20a** of R_f=0.56 (74 mg, 14%). Isolation of **16a** was achieved by preparative gas chromatography (column b). Compound **18a** was unstable to the conditions of preparative gas chromatography. The remaining organic product had R_f=0.41 (168 mg, 32%) and was spectroscopically identical to **12a**.

19a: ^{1}H NMR (500 MHz, C_6D_6) δ 6.30 (ddd, J=9.0, 10.5, 17.5 Hz, 1H), 5.00 (ddd, J=1.5, 2.0, 17.5 Hz, 1H), 4.95 (ddd, J=1.5, 2.0, 10.5 Hz, 1H), 4.84 (dd, J=1.5, 2.0, Hz, 1H), 4.45 (s, 1H), 4.20 (d, J=2.0 Hz, 1H), 3.55 (dd, J=3.8, 6.5 Hz, 1H), 3.28 (s, 3H), 3.18 (s, 3H), 3.10=3.20 (m, 1H), 2.85 (dd, J=7.0, 3.5 Hz, 1H), 2.75 (dd, J=6.8, 6.8 Hz, 1H), 1.85 (d, J=13.5 Hz, 1H), 1.75 (ddd, J=7.5,

7.5, 13.5, Hz, 1H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 162.4, 155.9, 143.3, 113.1, 100.8, 83.2, 55.0, 54.1, 51.1, 50.0, 46.6, 38.1, 35.5.

16a: ^1H NMR (500 MHz, C_6D_6) δ 6.30 (ddd, J=8.8, 10.5, 17.0 Hz, 1H), 4.99 (dd, J=2.0, 17.0 Hz, 1H), 4.96 (dd, J=2.0, 10.5 Hz, 1H), 4.40 (s, 1H), 3.45 (dd, J=3.6, 7.5 Hz, 1H), 2.95 (br ddd, J=3.2, 7.5, 15.5 Hz, 1H), 2.68-2.72 (m, 1H), 2.55 (dd, J=7.5, 7.5 Hz, 1H), 1.80 (ddd, J=2.8, 2.8, 13.0 Hz, 1H), 1.55 (ddd, J=7.5, 7.5, 13.0 Hz, 1H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 171.4, 155.6, 142.1, 114.0, 100.9, 55.4, 51.1, 51.0, 48.6, 48.5, 38.9, 35.7.

20a: ^1H NMR (500 MHz, C_6D_6) δ 6.51 (dd, J=3.0, 5.5 Hz, 1H), 6.15 (dd, J=3.0, 5.5 Hz, 1H), 3.94 (d, J=2.0 Hz, 1H), 3.81 (d, J=2.0 Hz, 1H), 3.34 (s, 3H), 3.09 (s, 3H), 3.05 (dd, J=3.1, 10.5 Hz, 1H), 2.98 (dd, J=3.3, 10.5 Hz, 1H), 2.91 (br s, 1H), 2.76 (br s, 1H), 1.27 (ddd, J=2.0, 2.0, 8.3 Hz, 1H), 0.92 (ddd, J=0.6, 0.6, 8.3 Hz, 1H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 172.6, 163.6, 135.7, 134.2, 82.3, 54.4, 51.5, 44.94, 49.91, 48.9, 48.8, 46.6.

Hydrolysis of 19a. To a solution of **19a** (28 mg, 0.14 mmol) in 5 mL acetone was added a solution of 5 mg *p*-toluenesulfonic acid in 3 mL H_2O. The reaction mixture was first allowed to be stirred for 24 h at room temperature, and then the acetone was removed at reduced pressure. The aqueous layer was extracted with 3 x 10 mL ether and the combined organics were washed with 1 x 5 mL saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Concentration *in vacuo* produced **21**: ^1H NMR (500 MHz, C_6D_6), protons assigned as in Figure 3: δ 5.65 (ddd, J=8.0, 10.5, 17.0 Hz, 1H, H_1), 4.88 (ddd, J=2.0, 3.0, 17.0 Hz, 1H, H_2), 4.83 (ddd, J=1.0, 2.0, 10.5 Hz, 1H, H_3), 3.18 (dddd, J=3.0, 3.5, 9.0, 9.5 1H, H_4), 2.75 (ddd, J=3.0, 4.8, 18.0 Hz, 1H, H_5), 2.66 (ddd, J=3.5, 8.5, 18.0 Hz, 1H, H_6), 2.57 (dd, J=7.5, 9.5 Hz, 1H, H_7), 2.38-2.45 (m, 1H, H_8), 2.18 (ddddd, J=4.8, 6.5, 8.5, 8.5, 9.0 Hz, 1H, H_9), 1.80 (s, 3H, CH_3), 1.71-1.82 (m, 2H, CH_2). ^{13}C NMR (22.5

MHz, C_6D_6) δ 207.9, 207.2, 137.6, 116.2, 67.1, 58.7, 52.4, 52.2, 38.2, 32.3, 29.3. IR(neat) 1778, 1710, 1640, 1364, 1172 cm^{-1}.

Preparation and Thermolysis of 13b. To a solution of **11** (276 mg, 1 mmol) in 2 mL toluene at -50°C, was added a precooled solution of **12b** (238 mg, 1 mmol) in 2 mL toluene. The mixture was warmed to -10°C and then slowly allowed to reach ambient temperature over the period of 1 h. After being stirred at room temperature for 20 min, the mixture was concentrated *in vacuo* to an oil. The oil was taken up in a minimum amount of pentane and then cooled to -50°C. The resulting precipitate was isolated by filtration and residual solvent was removed *in vacuo*. After dissolving the red powder in 2 mL benzene, the solution was heated at 80°C for 12 h. The reaction mixture was cooled to room temperature, diluted with petroleum ether, and allowed to stir in contact with air for 1 h. Filtration of this mixture produced a clear solution of products which was analyzed by capillary gas chromatography. Analysis at 120°C revealed four products with t_r= 9.18 min (**19b**, 7%), 10.10 min (**20b**, 11%), 10.26 min (**16b**, 22%), and 11.42 min (**12b**, 42%).

Preparation of 12c. A solution of 10.00 g bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride and 0.20 g *p*-toluenesulfonic acid monohydrate in 30 mL dry isopropanol was heated to reflux. The mixture was maintained at reflux for 16 h and then the condenser was removed to allow 20 mL of isopropanol to boil off. An additional 20 mL of isopropanol were added and subsequently allowed to boil from the reaction vessel. This procedure was repeated two times with a total of 40 mL of isopropanol. Next, the reaction mixture was redissolved in 20 mL isopropanol and heated at reflux for an additional 22 h. After cooling to room temperature, the mixture was concentrated *in vacuo*. The resulting oil was taken up in 150 mL diethyl ether and washed with 6 x 50 mL saturated aque-

ous $NaHCO_3$, 3 x 50 mL H_2O, 1 x 50 mL saturated NaCl solution, and dried over $MgSO_4$. After concentration of the product, it was redissolved in petroleum ether/ether (4:1) and filtered through a pad of silica gel. Concentration of the elutant gave 12.3 g **12c** (76% yield). ^1H NMR (90 MHz, C_6D_6) δ 6.22 (dd, J=1.5, 1.5 Hz, 2H), 4.89 (qq, J=6.3, 6.3 Hz, 2H), 2.80-3.05 (m, 4H), 1.06 (d, J=6.3 Hz, 6H), 1.04 (d, J=6.3 Hz, 6H), 0.70-1.30 (m, 2H), ^{13}C NMR (22.5 MHz, C_6D_6) δ 171.2, 135.0, 67.1, 48.5, 46.7, 22.0, 21.9. IR (neat) 2980, 2940, 1740, 1375, 1255, 1200, 1175, 1110 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.59; H, 8.37.

Preparation of 13c from 11. To a solution of **11** (276 mg, 1 mmol) in 2 mL toluene at -50°C was added a precooled solution of **12c** (266 mg, 1 mmol) in 2 mL toluene. The mixture was warmed to -10°C and then slowly allowed to reach ambient temperature over the period of 1 h. After stirring at room temperature for 1 h, the reaction mixture was concentrated *in vacuo* to a red oil. This oil was taken up in a minimum amount of pentane, filtered, and the mother liquor slowly cooled to produce red crystals. Isolation of the crystalline solid by filtration and removal of the residual solvent *in vacuo* produced 353 mg (76% yield) of **11c**. ^1H NMR (500 MHz, C_6D_6), proton assignments as in analogous compound **12a**: δ 5.48 (s, 5H, Cp_1), 5.41 (s, 5H, Cp_2), 5.18 (qq, 6.2, 6.2 Hz, 1H, $CH(CH_3)_2$), 5.06 (qq, J=6.2, 6.2 Hz, 1H, $CH(CH_3)_2$), 4.60 (d, J=9.0 Hz, 1H, H_3), 3.09 (dd, J=4.2, 11.4 Hz, 1H, H_6), 3.02 (dd, J=9.3, 9.3 Hz, 1H, H_6), 2.72 (dd, J=2.3, 11.4 Hz, 1H, H_8), 2.56 (br s, 1H, H_9), 2.54 (br s, 1H, H_{10}), 1.72 (dd, J=9.3, 9.3 Hz, 1H, H_{11}), 1.17 (d, J=6.2 Hz, 3H, CH_3), 1.15 (d, J=6.2 Hz, 3H, CH_3), 1.14 (d, J=6.2 Hz, 3H, CH_3), 1.12 (d, J=6.2 Hz, 3H, CH_3), 1.0-1.2 (m, 1H, H_{12}), 0.91 (ddd, J=9.0, 9.3, 9.3 Hz, 1H, H_{13}), 0.69 (d, J=10.0 Hz, 1H, H_{14}). ^{13}C NMR (22.5 MHz, C_6D_6) δ 172.0, 171.5, 109.8, 108.7, 97.4, 73.2, 67.1, 66.7, 52.0, 50.1,

47.3, 46.3, 35.9, 22.2, 22.0, 15.6.

Anal. Calcd for $C_{26}H_{34}O_4Ti$: C, 68.12; H, 7.48. Found: C, 68.24; H, 7.07.

Thermolysis of 13c. To a solution of **3** (5.00 g, 17.6 mmol) in 15 mL CH_2Cl_2 at -40°C was added a solution of **12c** (3.98 g, 14.9 mmol) in 15 mL CH_2Cl_2. Under a strong flow of argon, DMAP was added to the mixture through the top of the reaction vessel. The reaction mixture was allowed to warm to room temperature over the period of 10 min and stirred at room temperature for 15 min. Slow transfer of this solution into 250 mL pentane -30°C resulted in the precipitation of DMAP·Me_2AlCl from solution. The solid was removed by filtration and the solution was concentrated to a red oil *in vacuo*. The mixture was dissolved in 35 mL C_6H_6 and heated at 80°C for 15 h. After the solution cooled, it was transferred into 600 mL oxygenated pentane. The mixture was stirred for 1 h, filtered, and then concentrated to an oil. This oil was dissolved in 300 mL pentane and stirred for 1 h. After filtration, the solution was concentrated to an oil. Separation of **16c** and **12c** was achieved through silica gel flash chromatography with petroleum ether/ether (8:1). The cyclobutene enol ether **16c** (625 mg, 16%) was the more mobile (R_f=0.30) and was isolated as a colorless liquid. The diester **12c** (1.59 g, 40%), with R_f=0.12, was also recovered.

16c: ^{1}H NMR (500 MHz, C_6D_6), assignments are shown in Figure 4: δ 6.36 (ddd, J=8.2, 10.2, 17.2 Hz, 1H, H_1), 5.05 (qq, J=6.3, 6.3 Hz, 1H, H_2), 4.97 (ddd, J=1.3, 2.0, 17.2 Hz, 1H, H_3), 4.94 (ddd, J=1.3, 2.0, 10.2 Hz, 1H, H_4), 4.33 (s, 1H, H_5), 3.94 (qq, J=6.1, 6.1 Hz, 1H, H_6), 3.44 (dd, J=3.8, 7.5 Hz, 1H, H_7), 2.97 (dddddd, J=1.3, 1.3, 3.3, 7.2, 7.4, 8.2 Hz, 1H, H_8), 2.75 (ddd, J=2.0, 3.8, 7.2 hz, 1H, H_9), 2.57 (dd, J=7.4, 7.5 Hz, 1H, H_{10}), 1.79 (ddd, J=2.0, 3.3, 12.9 Hz, H_{11}), 1.58 (ddd, J=7.2, 7.2, 12.9 Hz, 1H, H_{12}), 1.14 (d, J=6.3 Hz, 3H, CH_3), 1.11 (d, J=6.1 Hz, 3H, CH_3), 1.10 (d, J=6.3 Hz, 3H, CH_3), 1.06 (d, J=6.1 Hz, 3H, CH_3).

^{13}C NMR (22.5 MHz, C_6D_6) δ 170.8, 153.7, 142.6, 113.4, 100.4, 70.7, 66.9, 51.3, 48.3, 48.1, 38.7, 35.7, 22.1, 21.8. IR (neat) 3060, 2980, 2940, 1730, 1628, 1375, 1260, 1110 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.28; H, 9.03.

Hydrolysis of 16c. To a solution of **16c** (430 mg, 1.63 mmol) in 12 mL acetone was added a solution of 30 mg *p*-toluenesulfonic acid in 6 mL H_2O. The reaction mixture was stirred for 5.5 h at room temperature. After removal of the acetone *in vacuo*, the aqueous layer was extracted with 3 x 30 mL ether. The combined organic extractions were washed with 2 x 25 mL saturated aqueous $NaHCO_3$, 1 x 20 mL saturated aqueous NaCl, and dried ($MgSO_4$). Concentration of the solution produced a colorless oil which was purified by flash chromatography. Elution on silica gel with petroleum ether/ether (1:1) produced a single compound. Distillation of this product at reduced pressure (Kugelrohr, 10 mmHg, 65°C) produced 340 mg **22** (94%).

22: ^1H NMR (500 MHz, C_6D_6), assignments are made as shown in Figure 5: δ 5.88 (ddd, J=7.4, 10.4, 17.2 Hz, 1H, H_1), 4.99 (qq, J=6.3, 6.3 Hz, 1H, H_2), 4.97 (ddd, J=1.4, 1.9, 17.2 Hz, 1H, H_3), 4.94 (ddd, J=1.0, 1.9, 10.4 Hz, 1H, H_4), 3.28 (dddd, J=2.9, 3.4, 9.5, 9.7 Hz, 1H, H_5), 2.76 (dd, J=7.7, 9.7 Hz, 1H H_6), 2.74 (ddd, J=2.9, 4.7, 17.9 Hz, 1H, H_7), 2.66 (ddd, J=3.4, 8.5, 17.9 Hz, 1H, H_8), 2.40 (dddddd, J=1.0, 1.4, 7.4, 7.4, 7.7, 11.5 Hz, 1H, H_9), 2.15 (ddddd, J=4.7, 7.2, 7.4, 8.5, 9.5 Hz, 1H, H_{10}), 1.99 (ddd, J=7.2, 11.5, 12.9 Hz, 1H, H_{11}), 1.83 (ddd, J=7.4, 7.4, 12.9 Hz, 1H, H_{12}), 1.08 (d, J=6.3 Hz, 3H, H_{13}), 1.03 (d, J=6.3 Hz, 3H, H_{14}). ^{13}C NMR (22.5 MHz, C_6D_6) δ 207.2, 171.5, 137.1, 116.3, 68.2, 67.6, 53.0, 52.4, 51.6, 38.4, 29.5, 21.9. IR (neat) 3080, 2980, 2940, 1780, 1725, 1640, 1380, 1190, 1110 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25, H, 8.16. Found: C, 70.07; H, 7.90.

Preparation of 25. To a solution of *endo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (4.44 g, 32.1 mmol) in 55 mL CH_2Cl_2 at 0°C was added oxalyl chloride (20.4 g, 16.1 mmol) via syringe. The reaction mixture was stirred at 0°C for 9 h until gas evolution had ceased. After concentration of this mixture to an oil *in vacuo*, the acid chloride was distilled (Kugelrohr, 5 mmHg, 80°C). The distillate was diluted with 10 mL $CHCl_3$ and added over a period of 45 min to a mixture of N,N-dimethylaniline (5.83 g, 48.2 mmol) and *t*-butyl alcohol (6.00 g, 80.9 mmol) at 0°C. Once addition was complete, the mixture was stirred at room temperature for 1 h and was then heated to reflux and stirred at reflux for 4 h. The reaction mixture was cooled to 0°C and quenched by the addition of 25 mL 6*N* H_2SO_4. After extracting the aqueous layer with 3 x 45 mL ether, the organic extractions were combined. The organics were washed with 25 mL 6*N* H_2SO_4, 2 x 30 mL H_2O, 2 x 30 mL 10% K_2CO_3, 1 x 15 mL saturated aqueous NaCl, and then dried (Na_2SO_4, K_2CO_3). After concentration of the mixture, the product was distilled from MgO under reduced pressure (Kugelrohr, 5 mmHg, 85°C). Distillation produced 4.44 g **25** (71%) as a colorless oil.

25: ^{1}H NMR (400 MHz, C_6D_6) δ 6.08 (dd, J=3.1, 5.5 Hz, 1H), 6.03 (dd, J=2.7, 5.6 Hz, 1H), 3.10 (br s, 1H), 2.69 (ddd, J=4.3, 4.3, 8.6 Hz, 1H), 2.61 (br s, 1H), 1.55-1.66 (m, 2H), 1.34 (s, 9H), 1.28-1.36 (m, 1H), 0.95 (d, J=8.3 Hz, 1H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 173.0, 137.6, 132.5, 79.0, 49.8, 46.1, 44.4, 42.9, 29.2, 28.2.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.04; H, 9.21.

Preparation and Isolation of 26 and 27. To a solution of **3** (1.17 g, 4.12 mmol) in 4 mL CH_2Cl_2 at -40°C was added a precooled solution of **25** in 4 mL CH_2Cl_2. To this mixture was added DMAP (0.74 g, 6.1 mmol) through a rapid flow of argon. The reaction mixture was allowed to warm to ambient temperature over

the period of 15 min and then stirred for 3 h at room temperature. This mixture was then slowly added to 75 mL vigorously stirred pentane at -30°C. After the resulting precipitate (DMAP·Me_2AlCl) was removed by filtration, the solution was concentrated *in vacuo* to an oil. Repeated fractional crystallization from pentane/toluene (3:1) produced 250 mg **26** (16%) as the least soluble isomer and 250 mg **27** (16%) as the more soluble isomer. Although further crystallization of remaining fractions would have produced increased yields of **26** and **27**, a sufficient amount had been isolated to examine the properties of each individual isomer.

26: ^{1}H NMR (400 MHz, C_6D_6) δ 5.43 (s, 5H, Cp_1), 5.41 (s, 5H, Cp_2), 3.77 (d, J=9.0 Hz, 1H, H_3), 3.10 (dd, J=8.8, 11.0 Hz, 1H, H_4), 2.78 (ddd, J=3.6, 4.0, 11.0 Hz, 1H, H_5), 2.64 (d, J=4.0 Hz, 1H, H_6), 2.20 (br s, 1H, H_7), 1.97 (ddd, J=1.4, 3.2, 3.6 Hz, 1H, H_8), 1.82 (dd, J=8.8, 8.8 Hz, 1H, H_9), 1.64 (ddd, J=3.7, 11.0, 11.4 Hz, 1H, H_{10}), 1.43 (s, 9H, H_{11}), 1.14 (dd, J=1.2, 9.5 Hz, 1H, H_{12}), 0.87 (dd, J=2.4, 9.5 Hz, 1H, H_{13}), 0.61 (ddd, J=8.8, 9.0, 11.0 Hz, 1H, H_{14}). ^{13}C NMR (100.4 MHz, C_6D_6) δ 174.0, 109.7, 108.8, 105.2, 79.3, 74.2, 48.7, 47.1, 46.5, 37.7, 37.0, 28.8, 16.6.

27: ^{1}H NMR (400 MHz, C_6D_6), δ 5.39 (s, 5H, Cp_1), 5.36 (s, 5H, Cp_2), 3.85 (d, J=9.3 Hz, 1H, H_3), 3.11 (dd, J=9.3, 11.2 Hz, 1H, H_4), 2.73 (ddd, J=3.9, 5.1, 12.5 Hz, 1H, H_5), 2.67 (br s, 1H, H_6), 2.18 (br d, J=3.9 Hz, 1H, H_7), 1.90 (ddd, J=2.2, 5.1, 10.8 Hz, 1H, H_8), 1.85 (dd, J=8.8, 9.3 Hz, 1H, H_9), 1.70 (ddd, J=4.5, 10.8, 12.5 Hz, 1H, H_{10}), 1.45 (s, 9H, H_{11}), 1.10 (d, J=9.9 Hz, 1H, H_{12}), 0.86 (d, J=9.9 Hz, 1H, H_{13}), 0.29 (ddd, J=8.8, 9.3, 11.2 Hz, 1H, H_{14}). ^{13}C NMR (100.4 MHz, C_6D_6) δ 173.5, 109.5, 108.6, 98.4, 79.0, 77.0, 51.5, 43.5, 36.7, 32.6, 28.8, 20.8.

Anal. Calcd for $C_{23}H_{30}O_2Ti$: C, 71.50; H, 7.83. Found: C, 71.84; H, 7.82.

Preparation of 1-Methylcyclopentadiene. A 2.8*M* solution of MeMgBr in ether (97 mL, 271 mmol) was concentrated *in vacuo* to a white solid and then redissolved in 100 mL THF. After cooling this solution to 0°C, freshly distilled cyclopentadiene (12.4 g, 187 mmol) was added via syringe. The mixture was allowed to stir at 0°C for 30 min and then at room temperature for 2 h. At this time, the gas evolution had slowed and the reaction mixture was heated to 85°C for 3 h until gas evolution had ceased. After being cooled to room temperature, all volatiles were removed *in vacuo*. The resulting mixture was dissolved in 550 mL THF and cooled to 0°C. As methyl iodide (53.1 g, 374 mmol) was slowly added over the period of 20 min, the internal temperature of the exothermic reaction mixture was carefully maintained between 15°C and 30°C through the use of an ice bath. Once addition was complete, the solution was stirred for 1 h. The reaction mixture was degassed by two freeze-pump-thaw cycles and the volatiles were subsequently vacuum-transferred into a 78°K flask. The solution containing volatile products was stirred for 4 h at room temperature. This solution was used for the preparation of **34** and **53** without further purification.

Preparation of 33. To a solution of 1-methylcyclopentadiene at 0°C, prepared from 290 mmol cyclopentadiene, was added maleic anhydride (17.06 g, 174 mmol). The reaction was stirred at 0°C for 1 h and then for 12 h at room temperature. Concentration of the mixture *in vacuo* produced a white solid. Crystallization from ether produced 21.7 g (70%) of the isomerically pure anhydride **33**: mp 87.5-88.5°C (lit. 88.5-89.0°C).[27]

Preparation of 34a. A solution of anhydride **33** (3.0 g, 16.8 mmol) and 30 mg *p*-toluenesulfonic acid monohydrate in 10 mL methanol was heated at reflux for 15 h. The reaction mixture was concentrated to a volume of 4 mL by allowing methanol to boil off in the absence of a reflux condenser. An additional

10 mL of methanol were added and the reaction was heated at reflux for 12 h. The reaction mixture was again concentrated to a volume of 4 mL, 10 mL of methanol were added, and the reaction heated at reflux for 3 h. After cooling to room temperature, the solvent was removed *in vacuo*. The resulting liquid was taken up 50 mL ether, washed with 3 x 50 mL saturated aqueous $NaHCO_3$, 1 x 10 mL saturated aqueous NaCl, and then dried ($MgSO_4$). The solution was concentrated to a liquid *in vacuo* and subsequently distilled at reduced pressure (Kugelrohr, 0.1 mm, 80°C) to give 3.27 g **34a** (87%) as a colorless liquid. Cooling of this liquid induced solidification. Recrystallization from ether/pentane gave white crystalline **34a**: mp=34.8-35.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, J=3.2, 5.6 Hz, 1H), 6.04 (d, J=5.6, 1H), 3.61 (s, 3H), 3.58 (s, 3H), 3.44 (dd, J=3.5, 10.3 Hz, 1H), 3.09 (br s 1H), 3.05 (d, J=10.3 Hz, 1H), 1.37 (s, 3H), 1.31-1.43 (m, 1H), 1.29 (d, J=8.6 Hz, 1H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 171.61, 171.58, 138.5, 133.8, 54.6, 53.7, 53.0, 51.0, 50.94, 50.91, 49.9, 17.4.

Preparation of 34b. A flask containing a solution of anhydride **33** (5.00 g, 28.1 mmol) and 0.50 g *p*-toluenesulfonic acid monohydrate in isopropanol was equipped with a soxhlet extraction apparatus. The extraction thimble was filled with 4Å molecular sieves for the purpose of removing water from the esterification process. The volume of isopropanol was adjusted so that the minimum volume of the mixture of the reaction vessel was 10-15 mL and then was heated to reflux for 4 days. After cooling to room temperature, the isopropanol was removed *in vacuo*. The resulting liquid was purified by flash chromatography. Eluting with petroleum ether/ether (4:1) on silica gel, followed by distillation at reduced pressure (Kugelrohr, 0.1 mmHg, 90°C), produced 4.83 g **34b** (62%) as a colorless oil.

34b: ^{1}H NMR (90 MHz, C_6D_6) δ 6.40 (dd, J=3.0, 5.4 Hz, 1H), 6.16 (d,

J=5.4 Hz, 1H), 5.05 (qq, J=6.3, 6.3 Hz, 1H), 5.00 (qq, J=6.3, 6.3 Hz, 1H), 3.11 (dd, J=3.5, 10.2 Hz, 1H), 2.91 (br s, 1H), 2.77 (d, J=10.2 Hz, 1H), 1.29 (s, 3H), 1.16 (dd, J=1.7, 8.3 Hz, 1H), 1.15 (d, J=6.3 Hz, 3H), 1.09 (d, J=6.3Hz, 3H), 1.08 (d, J=6.3 Hz, 3H), 1.06 (d, J=6.3 Hz, 3H), 0.79 (d, J=8.3 Hz, 1H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 171.0, 139.0, 135.1, 67.2, 54.8, 54.4, 53.8, 51.9, 46.6, 22.1, 21.9, 17.8.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.31; H. 8.42.

Preparation of 35. To a solution of metallacycle **11** (382 mg, 1.38 mmol) in 4 mL toluene at -50°C was added a precooled solution of **34b** (507 mg, 1.81 mmol) in 4 mL toluene. The mixture was then placed in a -10°C bath and allowed to slowly warm to room temperature over the period of 45 min. After removal of solvent from the reaction mixture *in vacuo*, the metallacycle product was taken up in a minimal amount of ether, filtered, and then slowly cooled to -50°C. Crystallization from ether produced 470 mg **35** (72%) of red crystals: ^{1}H NMR (500 MHz, C_6D_6) δ 5.53 (s, 5H), 5.47 (s, 5H), 5.20 (qq, J=6.3, 6.3 Hz, 1H), 5.07 (qq, J=6.3, 6.3 Hz, 1H), 4.64 (d, J=8.7 Hz, 1H), 2.95 (d, J=11.3 Hz, 1H), 2.76 (dd, J=2.8, 11.3 Hz, 1H), 2.66 (dd, J=9.3, 9.3 Hz, 1H), 2.51 (br s, 1H), 1.67 (dd, J=9.3, 9.3 Hz, 1H), 1.40 (s, 3H), 1.18 (d, J=6.3 Hz, 3H), 1.15 (d, J=6.3 Hz, 3H), 1.14 (d, J=6.3 Hz, 3H), 1.10 (d, J=6.3 Hz, 3H), 1.05-1.20 (m, 1H), 0.67 (ddd, J=8.7, 9.3, 9.3 Hz, 1H), 0.59 (d, J=10.0 Hz, 1H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 171.7, 171.5, 110.0, 109.1, 9.77, 68.3, 67.0, 66.5, 53.9, 53.5, 51.4, 49.7, 42.5, 22.3, 22.1, 21.9, 21.0, 20.8.

Anal. Calcd for $C_{27}H_{36}O_4Ti$: C, 68.64; H, 7.68. Found: C, 68.89; H, 7.73.

Isolation of 40. To a solution of **38** (260 mg, 1.00 mmol) in 1 mL toluene at -20°C was added **12a** (210 mg, 1.00 mmol) via syringe. The reaction mixture was warmed to -5°C and then allowed to warm slowly to ambient temperature over

the period of 1 h. After being stirred at room temperature for 3 h, the reaction mixture was diluted with 10 mL pentane and cooled to -40°C. The solution was filtered, warmed to room temperature, and then concentrated *in vacuo* to an oil. This oil was dissolved in 5 mL pentane/ether (4:1) and slowly cooled to -50°C. The mixture was filtered and the solution concentrated to a volume of 1 mL *in vacuo*. After allowing the solution to cool slowly to -50°C, the resulting solid was isolated by filtration and washed with 3 x 4 mL cold pentane. Removal of residual solvent *in vacuo* produced 201 mg **40** (43%) as a purple powder: ^{1}H NMR (400 MHz, C_6D_6), assignments are shown in Figure 8: δ 6.19 (dd, J=10.8, 17.6 Hz, 1H, H_1), 5.66 (s, 5H, Cp_2), 5.39 (s, 5H, Cp_3), 5.03 (dd, J=1.4, 17.6 Hz, 1H, H_4), 4.95 (dd, J=1.4, 10.8 Hz, 1H, H_5), 4.77 (d, J=9.2 Hz, 1H, H_6), 3.49 (s, 3H, H_7), 3.43 (s, 3H, H_8), 3.09 (dd, J=4.6, 11.3 Hz, 1H, H_9), 2.72 (dd, J=3.0, 11.3 Hz, 1H, H_{10}), 2.65 (br d, J=3.7 Hz, 1H, H_{11}), 2.60 (br s, 1H, H_{12}), 2.53 (d, J=11.6 Hz, 1H, H_{13}), 1.29 (br d, J=10.3 Hz, 1H, H_{14}), 1.19 (s, 3H, H_{15}), 1.11 (s, 3H, H_{16}), 0.71 (br d, J=10.3 Hz, 1H, H_{17}), 0.60 (dd, J=9.2, 11.6 Hz, 1H, H_{18}). ^{13}C NMR (22.5 MHz, C_6D_6) δ 173.0, 172.5, 149.8, 109.2, 108.7, 101.6, 99.9, 51.4, 50.9, 50.7, 49.9, 47.2, 45.9, 45.7, 35.5, 32.5, 30.2, 18.9.

Anal. Calcd for $C_{27}H_{34}O_4Ti$: C, 68.93; H, 7.28. Found: C, 68.78; H, 7.28.

Preparation of 42 and 43. To a solution of **12a** (210 mg, 1.0 mmol) in 2 mL toluene at room temperature, was added a solution of **38** (416 mg, 1.6 mmol) in 2 mL toluene. After being stirred for 4 h at room temperature, the reaction mixture was heated to 55°C and maintained at that temperature for 15 h. Upon cooling to ambient temperature, the reaction mixture was added to 125 mL petroleum ether. This mixture was stirred for 4 h with exposure to oxygen and then filtered. The solution was concentrated to an oil and purified by silica gel flash chromatography. An inseparable mixture of **42** and **43** (R_f=0.44) could

be isolated by elution on silica gel with petroleum ether/ether (3:1). Separation from **12a** (R_f=0.22) was accomplished to give 146 mg of a 3.9:1.0 mixture of **42** and **43** (53%).

Preparation of 46. A 3.9:1.0 mixture of **42:43** (100 mg, 0.362 mmol) was dissolved in 4 mL acetone/water (4:1) and 5 mg *p*-toluenesulfonic acid monohydrate was added. After being stirred for 4 h at 25°C, the acetone was removed *in vacuo* and the acqueous solution extracted with 5 mL ether. The ether solution was washed with 2 x 1 mL saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Concentration of this solution gave 95 mg of an oil. This oil was dissolved in 3 mL methanol/CH_2Cl_2 (5:1). A solution of Sudan IV indicator[39] in CH_2Cl_2 was added until the reaction mixture became a detectable tint of red. The mixture was cooled to -78°C and treated with ozone until the red tint of indicator was absent. After flushing the reaction vessel with nitrogen for 20 min at -78°C, methyl sulfide (3 mL) was added. Over the period of 8 h, the reaction mixture was allowed to warm to ambient temperature. The mixture was then concentrated to an oil *in vacuo* and purified by flash chromatography. Elution on silica gel with ether produced 61 mg **46** (86%) as a colorless oil with R_f = 0.26: ^{1}H NMR (400 MHz, C_6D_6), assignments as in Figure 8: δ 9.67 (d, J=1.5 Hz, 1H, H_1), 3.41 (s, 3H, H_2), 3.38 (dddd, J=3.4, 3.5, 8.2, 9.5 Hz, 1H, H_3), 2.73 (dd, J=7.9, 9.5 Hz, 1H, H_4), 2.63 (ddd, J=3.4, 9.2, 18.3 Hz, 1H, H_5), 2.54 (dddd, J=1.5, 8.2, 7.9, 8.2 Hz, 1H, H_6), 2.38 (ddd, J=3.5, 3.5, 18.3 Hz, 1H, H_7), 2.13 (ddddd, J=3.5, 3.7, 8.2, 8.2, 9.2 Hz, 1H H_8), 1.85 (ddd, J=3.7, 5.2, 13.7 Hz, 1H, H_9), 1.61 (ddd, J=8.2, 8.2, 13.7 Hz, 1H, H_{10}). ^{13}C NMR (100.4 MHz, C_6D_6) δ 206.3, 200.3, 170.9, 66.5, 56.3, 52.8, 52.0, 49.0, 33.5, 29.6. IR (neat) 2950, 2865, 2840, 2730, 1777, 1728, 1718, 1435, 1200 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.84; H, 6.29.

Reaction of 34a with 38. A solution of **34a** (224 mg, 1 mmol) and **38** (286 mg, 1.1 mmol) in 3 mL toluene was stirred at room temperature for 30 min and then heated at 65°C for 18 h. Upon cooling, the reaction mixture was diluted with petroleum ether and exposed to oxygen. After being stirred for 1 h, the mixture was filtered and the resulting solution was concentrated *in vacuo*. The product mixture was purified by flash chromatography. Elution on silica gel with petroleum ether/ether (9:1) produced two separate fractions containing products of the metathesis rearrangement. The more mobile fraction, R_f=0.38, contained 64 mg **50** (22%) as a colorless oil. The fraction of R_f=0.33 contained 41 mg (14%) of an inseparable mixture of **51** and **52** (9.3:1.0).

50: ^{1}H NMR (500 MHz, C_6D_6) δ 6.07 (d, J=16.1 Hz, 1H), 5.87 (dd, J=10.5, 17.5 Hz, 1H), 5.41 (d, J=16.1 Hz, 1H), 5.01 (dd, J=15, 17.5 Hz, 1H), 4.92 (dd, J=1.5, 10.5 Hz, 1H), 4.40 (s, 1H), 3.56 (dd, J=3.7, 7.6 Hz, 1H), 3.42 (s, 3H), 3.27 (s, 3H), 2.76 (ddd, J=2.1, 3.7, 7.2 Hz, 1H), 2.30 (d, J=7.6 Hz, 1H), 1.98 (dd, J=2.1, 12.8 Hz, 1H), 1.32 (dd, J=7.2, 12.8 Hz, 1H), 1.22 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 171.8, 155.0, 148.1, 134.9, 134.8, 110.5, 100.3, 55.0, 54.2, 52.0, 50.6, 49.1, 42.9, 39.2, 37.5, 29.3, 27.5, 27.3.

51: ^{1}H NMR (500 MHz, C_6D_6), assignments shown in Figure 9: δ 5.89 (dd, J=8.6, 15.6 Hz, 1H, H_1), 5.87 (dd, J=10.5, 17.3 Hz, 1H, H_2), 5.43 (d, J=15.6 Hz, 1H, H_3), 5.04 (dd, J=1.5, 17.3 Hz, 1H, H_4), 4.94 (dd, J=1.5, 10.5 Hz, 1H, H_5), 4.42 (s, 1H, H_6), 3.43 (s, 3H, H_7), 3.28 (s, 3H, H_8), 3.07 (dddd, J=3.2, 7.2, 7.3, 8.6 Hz, 1H, H_9), 2.96 (d, J=7.1 Hz, 1H, H_{10}), 2.73 (dd, J=7.1, 7.2 Hz, 1H, H_{11}), 1.83 (dd, J=3.2, 12.7 Hz, 1H, H_{12}), 1.45 (dd, J=7.3, 12.7 Hz, 1H, H_{13}), 1.16 (s, 3H, H_{14}), 1.12 (s, 3H, H_{15}), 1.11 (s, 3H, H_{16}). ^{13}C NMR (22.5 MHz, C_6D_6) δ 171.6, 155.0, 147.9, 138.5, 130.0, 110.6, 104.3, 56.7, 55.1, 50.6, 48.8, 47.7, 45.5, 41.9, 39.2, 27.5, 27.3, 24.5.

Preparation of 53. A solution of 1-methylcyclopentadiene, prepared from 72.4 mmol cyclopentadiene, was diluted to a volume of 45 mL with ether. Acrylic acid (5.22 g, 72.4 mmol) was added to this solution and the reaction allowed to stir for 48 h. After concentration of the mixture *in vacuo*, the cycloaddition products were distilled at reduced pressure (Kugelrohr, 2 mmHg, 100°C) to give 5.65 g (37.1 mmol, 51%) of a colorless oil. The oil was dissolved in 20 mL CH_2Cl_2, cooled to 0°C, and oxalyl chloride (14.15 g, 111.4 mmol) was added via syringe. After being stirred for 5 h at 0°C, the mixture was concentrated *in vacuo* at 0°C. The residual oil was distilled at reduced pressure (Kugelrohr, 5 mmHg, 90°C) to produce 4.30 g (23.0 mmol, 62% from acid) of the mixture of acid chlorides. A solution of the acid chloride mixture in 5.0 mL $CHCl_3$ was slowly added to a mixture of N,N-dimethylaniline (4.19 g, 34.5 mmol) and 35 mL isopropanol. After the mixture had been stirred for 1 h at 0°C, the reaction mixture was heated to 65°C and then stirred for 5 h at that temperature. Removal of the isopropanol was achieved *in vacuo* and then the reaction quenched with 25 mL 6*N* H_2SO_4. The aqueous solution was extracted with 3 x 40 mL ether. The combined organics were subsequently washed with 1 x 25 mL 6*N* H_2SO_4, 2 x 50 mL H_2O, 2 x 50 mL 10% aqueous K_2CO_3, 1 x 20 mL saturated aqueous NaCl, and then dried (Na_2SO_4). Concentration of the mixture *in vacuo* followed by distillation at reduced pressure (Kugelrohr, 10 mmHg, 100°C) produced 3.23 gm (16.6 mmol, 72% from acid chloride) of a mixture of esters. The mixture was purified by flash chromatography with petroleum ether/ether (25:1). Concentration of the R_f=0.23 elutant gave 1.55 g of an inseparable mixture of two isomeric esters. The mixture was shown to consist of **53** (92%) and an isomeric impurity (8%).

53: ^{1}H NMR (400 MHz, C_6H_6) δ 6.09 (dd, J=3.1, 5.6 Hz, 1H), 5.87 (d, J=5.6 Hz, 1H), 4.97 (qq, J=6.1, 6.4 Hz, 1H), 2.55 (br s, 1H), 2.47 (dd, J=4.4,

9.3 Hz, 1H), 1.85 (ddd, J=3.7, 9.3, 11.7 Hz, 1H), 1.70 (ddd, J=3.1, 3.5, 11.7 Hz, 1H), 1.48 (s, 3H), 1.23 (ddd, J=2.0, 2.7, 8.1 Hz, 1H), 1.02 (d, J=6.1 Hz, 3H), 1.01 (d, J=6.1 Hz, 3H), 0.96 (br d, J=8.1 Hz, 1H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 173.2, 137.4, 137.0, 66.9, 56.6, 55.5, 53.8, 48.7, 42.9, 31.2, 21.9, 18.4.

Preparation of 54. To a solution of **3** (1.30 g, 4.78 mmol) in 5 mL CH_2Cl_2 at -40°C was added a precooled solution of **53** (1.00 g, 5.15 mmol) in 5 mL CH_2Cl_2. Under a strong flow of argon, DMAP was slowly added to the reaction mixture. The mixture was allowed to warm to room temperature over the period of 15 min, and then was stirred at room temperature for 15 min. This solution was then slowly added to 80 mL pentane at -30°C. After being stirred 10 min at -30°C, the solution was rapidly filtered and then concentrated to a deep red oil. The metallacycle products were dissolved in 50 mL pentane, filtered, concentrated to a volume of 5 mL, and cooled to -50°C. The resulting precipitate was isolated by filtration and residual solvent was removed *in vacuo*. This powder was dissolved in a minimum amount of hexane, filtered and cooled to -50°C. Isolation of the resulting crystals gave 1.06 g **54** (57%): ^{1}H NMR (500 MHz, C_6D_6) δ 5.48 (s, 5H), 5.44 (s, 5H), 5.07 (qq, J=6.3, 6.3 Hz, 1H), 3.88 (d, J=9.0 Hz, 1H), 2.73 dd, J=9.1, 10.6 Hz, 1H), 2.63 (dd, J=3.6, 11.0 Hz, 1H), 2.14 (br s, 1H), 2.06 (ddd, J=3.6, 3.6, 11.3 Hz, 1H), 1.80 (ddd, J=0.8, 11.0, 11.3 Hz, 1H), 1.78 (dd, J=9.1, 9.1 Hz, 1H), 1.53 (s, 3H), 1.10-1.15 (m, 1H), 1.11 (d, J=6.3 Hz, 3H), 1.09 (d, J=6.3 Hz, 3H), 0.79 (dd, J=1.4, 9.9 Hz, 1H), 0.52 (dddd, J=1.4, 9.0, 9.1, 10.6 Hz, 1H). ^{13}C NMR (22.5 MHz, C_6D_6) δ 174.2, 109.9, 109.0, 104.3, 69.3, 67.0, 52.2, 50.9, 48.1, 43.7, 39.6, 22.2, 22.0, 21.0, 20.8.

Anal. Calcd for $C_{23}H_{30}O_2Ti$: C, 71.50; H, 7.83. Found: C, 71.20; H, 8.11.

Reaction of 53 with 38. To a solution of **38** (265 mg, 1.02 mmol) in 1.0 mL benzene was added a solution of **53** (152 mg, 0.78 mmol) in 1.5 mL benzene. The

mixture was allowed to stir 2 h at ambient temperature and was then heated at 60°C for 26 h. Once the reaction mixture had cooled to room temperature, the mixture was added to 100 mL petroleum ether and stirred for 1 h. The mixture was filtered and the resulting solution concentrated to an oil. This oil was dissolved in 15 mL acetone/water (5:1) and 5 mg *p*-toluenesulfone acid monohydrate was added. After being stirred for 5 h, the acetone was removed *in vacuo* and the aqueous layer washed with 3 x 5 mL ether. The combined organic extractions were washed with 1 x 5 mL saturated aqueous $NaHCO_3$, 1 x 5 mL saturated aqueous NaCl, and dried $MgSO_4$. Concentration *in vacuo* produced an oil. Flash chromatography allowed the separation of two eluting fractions of R_f=0.48 and R_f=0.32. The more mobile elutant was found by ^{1}H NMR to be an inseparable 2.3:1.0 mixture of **61** and **62** (90 mg, 53%), respectively. The major isomer **61** was identified by the olefin region of the ^{1}H NMR (400 MHz, C_6D_6) δ 5.81 (dd, J=10.6, 17.2 Hz, 1H), 5.40 (d, J=16.5 Hz, 1H), 5.27 (dd, J=6.6, 16.5 Hz, 1H), 4.98 (d, J=17.2 Hz, 1H), 4.94 (d, J=10.6 Hz, 1H). Identification of the *cis* minor isomer **62** was also accomplished by ^{1}H NMR (400 MHz, C_6D_6) δ 5.91 (dd, J=10.5, 17.3 Hz, 1H), 5.22 (d, J=10.4 Hz, 1H), 5.05 (dd, J=10.4, 10.4 Hz, 1H), 4.97 (d, J=17.3 Hz, 1H), 4.87 (d, J=10.5 Hz, 1H). The resonances at 5.27 ppm and 5.05 ppm were not only coupled to the resonances at 5.40 ppm and 5.22 ppm, respectively, but each was also coupled to a vicinal allyl proton. This information confirmed the position of the methyl group as that of isomers **61** and **62**. The elutant of R_f=0.32 was further purified by preparative chromatography to give 24 mg **63** (14%): ^{1}H NMR (400 MHz, C_6D_6), assignments as shown in Figure 10: δ 5.85 (dd, J=10.6, 17.5 Hz, 1H, H_1), 5.51 (d, J=16.0 Hz, 1H, H_2), 5.43 (d, J=16.0 Hz, 1H, H_3), 5.01 (dd, J=1.3, 17.5 Hz, 1H, H_4), 4.95 (dd, J=1.3, 10.6 Hz, 1H, H_5), 2.09 (s, 1H, H_6), 2.04 (br s, 1H, H_7), 1.64 (ddd, J=2.9, 4.8,

17.3 Hz, 1H, H_8), 1.44 (dd, J=4.4, 17.3 Hz, 1H, H_9), 1.40 (dd, J=2.0, 12.2 Hz, 1H H_{10}), 1.18 (ddd, J=2.9, 4.3, 12.2 Hz, 1H, H_{11}), 1.05-1.40 (m, 2H, H_{12},H_{13}), 1.09 (s, 6H, H_{14}), 0.89 (s, 3H, H_{15}). ^{13}C NMR (100.4 MHz, C_6D_6) δ 212.1, 147.4, 136.5, 134.3, 111.0, 62.2, 44.1, 41.9, 41.7, 39.6, 36.4, 36.3, 28.6, 27.8, 27.7. IR (CCl_4) 2860, 1750, 1640, 1410 cm^{-1}.

(1S*,2S*,5R*,7S*)-10,10-Dimethyl-7-vinyltricyclo[5.3.0.0^{2,5}]decane-3,3′-[1,3]-dioxolane (68). To a solution of DMAP (1.56 g, 12.8mmol) and **66** (1.68 g, 6.4 mmol) in 13 mL benzene was slowly added a solution of **3** 92.73 g, 9.6 mmol) in 6 mL benzene. The reaction temperature was maintained below 30°C through the use of an ice bath. Once addition was complete, the reaction mixture was stirred for 1.5 h at room temperature. The solvent volume was reduced *in vacuo* by 1 mL, the reaction vessel sealed, and then placed in a 90°C oil bath for 4 h. After allowing the reaction to cool to room temperature, the mixture was slowly added to 1 L petroleum ether. The mixture was allowed to stir in contact with oxygen for 72 h at room temperature. The mixture was cooled to -30°C, the precipitate was removed by filtration and the solution was concentrated to a slushy solid. The precipitate that was removed from the solution was further extracted by suspension in 20 mL benzene, stirring for 3 h, and was subsequently diluted with 1 L petroleum ether. This mixture was cooled to -30°C, filtered, and the resulting solution was combined with the previously obtained slushy solid. After concentration of the mixture, the solid was brought up in 800 mL petroleum ether, the mixture was cooled to -30°C, and filtered. The resulting solution was concentrated *in vacuo* to an oil and then dissolved in 150 mL benzene and 20 mL ethylene glycol. To this mixture was added *p*-toluenesulfonic acid monohydrate (500 mg). The reaction flash was equipped with a Dean-Stark trap containing 4Å molecular sieves, and heated to reflux for 20 h. Once the reaction mixture

had cooled to room temperature, the reaction mixture was poured into saturated aqueous 100 mL $NaHCO_3$, diluted with 150 mL benzene, and separated. The aqueous layer was extracted with 2 x 100 mL benzene. The organic extractions were combined, washed with saturated aqueous $NaHCO_3$, and then dried ($MgSO_4$). After filtration through a silica gel pad, which was washed thoroughly with benzene, the solution was concentrated to give 1.30 g **68** (81%) as an oil: ^1H NMR (400 MHz, C_6D_6) δ 6.41 (dd, J=10.7, 17.3 Hz, 1H), 5.18 (dd, J=1.2, 17.3 Hz, 1H), 4.98 (dd, J=1.2, 10.7 Hz, 1H), 3.38-3.48 (m, 4H), 2.94-2.99 (m, 1H), 2.44-2.54 (m, 2H), 2.44 (d, J=2.4 Hz, 1H), 2.20-2.28 (m, 1H), 1.88-1.98 (m, 2H), 1.72 (dd, J=7.7, 13.6 Hz, 1H), 1.34-1.56 (m, 4H), 1.02 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 150.2, 109.2, 108.6, 64.5, 63.5, 62.9, 61.8, 55.9, 48.0, 42.4, 42.1, 40.6, 38.9, 33.7, 30.9, 26.6. IR (neat) 3080, 2940, 2860, 1630, 1460, 1365, 1280, 1145, 1040 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.26; H, 9.72.

References and Notes

(1) (a) Tebbe, F.N.; Parshall, G.W.; Overall, D.W. *J. Am. Chem. Soc.* **1979** *101*, 5074. (b) Klabunde, U.; Tebbe, F.N.; Parshall, G.W.; Harlow, R.L. *J. Mol. Catal.* **1980**, *8*, 37.

(2) Howard, T.R.; Lee, J.B.; Grubbs, R.H. *J. Am. Chem. Soc.* **1980**, *102*, 6876.

(3) Lee, J.B.; Gajda, G.J.; Schaefer, W.P.; Howard, T.R.; Ikariya, T.; Straus, D.A.; Grubbs, R.H. *J. Am. Chem. Soc.* **1981**, *103*, 7358.

(4) Lee, J.B.; Ott, K.C.; Grubbs, R.H., *J. Am. Chem. Soc.* **1982**, *104*, 7491.

(5) Straus, D.A.; Grubbs, R.H. *J. Mol. Catal.* **1985**, *28*, 9.

(6) Ikariya, T.; Grubbs, R.H., unpublished results.

(7) Organic carbonyls irreversibly trap titanocene alkylidenes producing the "Wittig-type" alkylidene transfer product. See: (a) Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* **1984**, *25*, 5733. (b) Pine, S.H.; Zahler R.; Evans, D.A.; Grubbs, R.H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (c) Pine, S.H.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.*, **1985**, *50*, 1212. (d) Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem.* **1985**, *50*, 2316.

(8) Lauher, J.W.; Hoffmann, R. *J. Am. Chem. Soc.* **1976**, *98*, 1729.

(9) Francl, M.M.; Pietro, W.J.; Hout, R.F., Jr.,; Hehre, W.J. *Organometallics* **1983**, *2*, 815.

(10) (a) Hartner, F.W.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4979. (b) Yoshida, T. *Chem. Lett.* **1982**, 429. (c) Gilliom, L.; Grubbs, R.H. *Organometallics* **1986**, *5*, 0000.

(11) Schleyer, P.v.R.; Williams, J.E.; Blanchard, K.R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.

(12) (a) Volger, H.C.; Hogeveen, H.; Gaasbeek, M.M.P. *J. Am. Chem. Soc.*

1969, *91*, 218, 2137. (b) Katz, T.J.; Cerefice, S.A. *J. Am. Chem. Soc.* **1969**, *91*, 2405. (c) Katz, T.J.; Cerefice, S.A. *J. Am. Chem. Soc.* **1971** *93*, 1049. (d) Johnson, T.H.; Cheng, S.S. *Synth. Commun.* **1980**, *10*, 381.

(13) (a) Waddington, M.D.; Jennings, P.W. *Organometallics* **1982**, *1*, 385. (b) Waddington, M.D.; Jennings P.W. *Organometallics* **1982** *1*, 1370.

(14) Campbell, W.H.; Jennings, P.W. *Organometallics* **1983**, *2*, 1460.

(15) (a) Marchand, A.P.; Grubbs; R.H., unpublished results. (b) Howard, T.H.; Grubbs, R.H.; Marchand, A.P. Southeast/Southwest Regional ACS Meeting, New Orleans, LA, December 1980, paper 262 (c) Hentges, S.; Grubbs, R.H., unpublished results.

(16) Gilliom, L.R.; Grubbs, R.H. *J. Am. Chem. Soc.* **1986**, *108*, 0000.

(17) For a review of the intramolecular Wittig reaction see: Becker, K.B. *Tetrahedron* **1980**, *36*, 1717.

(18) (a) Hartner, F.W., Jr.; Schwartz, J.; Clift, S.M. *J. Am. Chem. Soc.* **1983** *105*, 640. (b) Clift, S.M.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 8300.

(19) Schrock, R.R. *J. Am. Chem. Soc.* **1976**, *98*, 5399.

(20) For information on two-dimensional NMR see: Bax, A. *Two-Dimensional Nuclear Magnetic Resonance in Liquids.* D. Reidel Pub. Co.: Boston, 1982.

(21) (a) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.*, **1984**, *106*, 4261. (b) For a recent review on asymmetric Diels-Alder reactions see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876.

(22) Morgan, M.S.; Tipson, R.S.; Lowry, A.; Baldwin, W.E. *J. Am. Chem. Soc.* **1944**, *66*, 404.

(23) For ^{1}H NMR information on bicyclo[2.2.1]heptene compounds see: (a) Mellor, J.M.; Webb, C.F. *J. Chem. Soc. Perkin Trans. II* **1974**, 26. (b) Davis, J.C.; Van Auken, T. *J. Am. Chem. Soc.* **1965**, *87*, 3900.

(24) Silverstein, R.M.; Bassler, G.C.; Morrill, T.C. *Spectrometric Identification of Organic Compounds.* John Wiley & Sons: New York, 4th ed., 1981.

(25) Gilliom, L.R., Ph.D thesis, California Institute of Technology (1986).

(26) For methyl acetate, the $\Delta H(s\text{-}cis - s\text{-}trans)$ is 4.20 kcal/mol. For a review on the conformations of esters see: Jones, G.I.L.; Owen, N.L. *J. Mol. Struct.* **1973**, *18*, 1.

(27) Mironov, V.A.; Sobolev, E.V.; Elizarova, A.N. *Tetrahedron* **1963**, *19*, 1939.

(28) Chapter 4, this thesis.

(29) Chapter 6, this thesis.

(30) (a) Cannizzo, L.F.; Grubbs, R.H. *J. Org. Chem* **1985**, *50*, 2386. (b) Chou, T.S.; Huang, S.B.; Hsu, W.H. *J. Chin. Chem. Soc. (Taipei)*, **1982**, *30*, 277.

(31) Greene, A.; Crabbe, P. *Tetrahedron Lett.* **1975**, 2215.

(32) Baudouy, R.; Crabbe, P.; Greene, A.E.; Drian, C.L.; Orr, A.F. *Tetrahedron Lett.* **1977**, 2973.

(33) Paquette, L.A. *Top. Curr. Chem.* **1984**, *119*, 1.

(34) Still, W.D.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(35) Touchstone, J.C.; Dobbins, M.F. *Practice of Thin Layer Chromatography.* John Wiley & Sons: New York, 1978, p. 207.

(36) Chapter 1, this thesis.

(37) (a) Alder, K., Stein, G.; Liebmann, M.; Rolland, E. *Ann.* **1934** *514*, 197. (b) Roberts, J.D.; Trumbull, E.R., Jr.; Bennett, W.; Armstrong, R. *J. Am. Chem. Soc.* **1950**, *72*, 3116.

(38) (a) Hall, L.D.; Sanders, J.K.M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. (b) Sanders, J.K.M.; Mersh, J.D. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 353.

(39) Veysoglu, T.; Mitscher, L.A.; Swayze, J.K. *Synthesis* **1980**, 807.

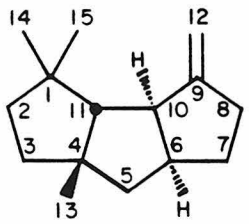
CHAPTER 6

The Total Synthesis of (±)$\Delta^{(9,12)}$-Capnellene

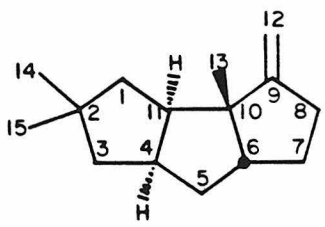
Introduction

The soft coral *Capnella imbricata*, isolated off the coasts of both Sewaru, Leti Island, Indonesia, and of Liang Island of New Guinea, was found to be an excellent source of a novel family of natural products.[1] This family of non-isoprenoid sesquiterpenes has in common a linear triquinane ring system with a very specific pattern of methyl substituents.[2] The *cis-anti-cis* tricyclo[6.3.0.$0^{2,6}$]undecane ring system of these marine natural products, known as the capnellanes, is exemplified by the presumed biosynthetic precursor to this family $\Delta^{(9,12)}$-capnellene (**1**).[3] The capnellanes are found in various stages of oxidation ranging from entirely hydrocarbon[1a,3] to the polyhydride metabolites of capnellene,[1b,4] the capnellenols. Because of the pattern of methyl substituents on the tricylic ring, the capnellanes differ from their terrestrial counterparts, the hirsutanes.[5] This diference is readily seen by comparison of **1** with hirsutene (**2**). Instead of a geminal dimethyl unit at C-2 and an angular methyl group at C-10, the marine natural products possess the dimethyl unit at C-1 and the angular methyl group at C-4.

In spite of the slight differences in structure found in the capnellanes and their terrestrial counterparts, these families seem to display similar biological effects. The promising antibacterial and antitumor properties of the hirsutanes,[6]



1



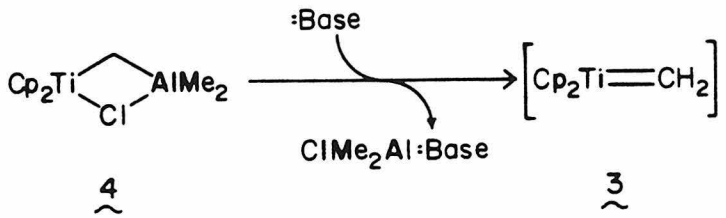
2

in addition to the challenging skeletal framework, has led to substantial interest in the synthesis of this family of natural products.[7] Although the details of the biological function of the capnellanes are not known, these molecules appear to act as chemical defense agents against infestation by algae, microbial growth,[8] and larvae[9] within the coral reef biomass. The importance of **1** as the possible biosynthetic precursor to the capnellanes has caused it to be a "focal point" of substantial synthetic efforts directed toward the construction of the capnellane skeletal framework.[10]

The most popular route to the synthesis of **1** has been through the sequential formation of each additional ring. One of the first synthetic preparations of **1** was achieved on a cyclopentene substrate through ring annulation involving the Rupe rearrangement to form the second ring.[10,11] Formation of the third ring was then accomplished through intramolecular aldol condensation. This strategy was also demonstrated by two successive α-alkynone cyclization steps on a cyclopentanone substrate.[12] Most recently, the palladium-catalyzed carbonylative coupling of vinyl triflates with vinyl stannanes, followed by the silicon-directed Nazarov reaction, was shown to be an effective method of sequential cyclopentenone ring annulation. An alternate route to annulate three carbons in a repetitive manner by two successive synthetic operations was through the insightful use of the intramolecular "magnesium-ene" reaction.[14] The use of conjugate addition and subsequent intramolecular alkylation as a method of ring annulation has also been employed in the total synthesis of **1**.[15] Straying from this strategy, involving the sequential formation of two cyclopentane rings on an initial five-membered ring, the biogenetically patterned synthesis of $\Delta^{8(9)}$-capnellene, an isomer of **1**, utilized a trans annular cyclization of a bicyclo[6.3.0^{1,5}]undecadiene substrate to simultaneously form both additional rings.[16] Using methods of se-

quential ring formation, up to two of the four total asymmetric centers in **1** could be formed with each individual step. A synthesis involving the formation of four asymmetric centers involved the Diels-Alder cycloaddition with an unsymmetrical cyclopentadiene.[17] Unfortunately, the epimerization of two of the asymmetric centers was required to obtain the desired *cis-anti-cis* triquinane ring system. Only one reported synthesis of capnellene has involved the simultaneous formation of two additional rings on an existing five-membered ring, as well as the generation of three of the four asymmetric centers. This method involved the elegant use of an intramolecular 1,3-diyl trapping reaction.[18] Due to the formation of large amounts of the *cis-syn-cis* isomer, the yields obtained in the process were substantially reduced. In spite of this difficulty, ring formation by 1,3-diyl trapping showed promise for the asymmetric synthesis of **1** through the uses of chiral auxiliaries. Preliminary investigation has produced only 5% *de* for the capnellene precursor, but efforts toward asymmetric induction in this system are being continued.[19]

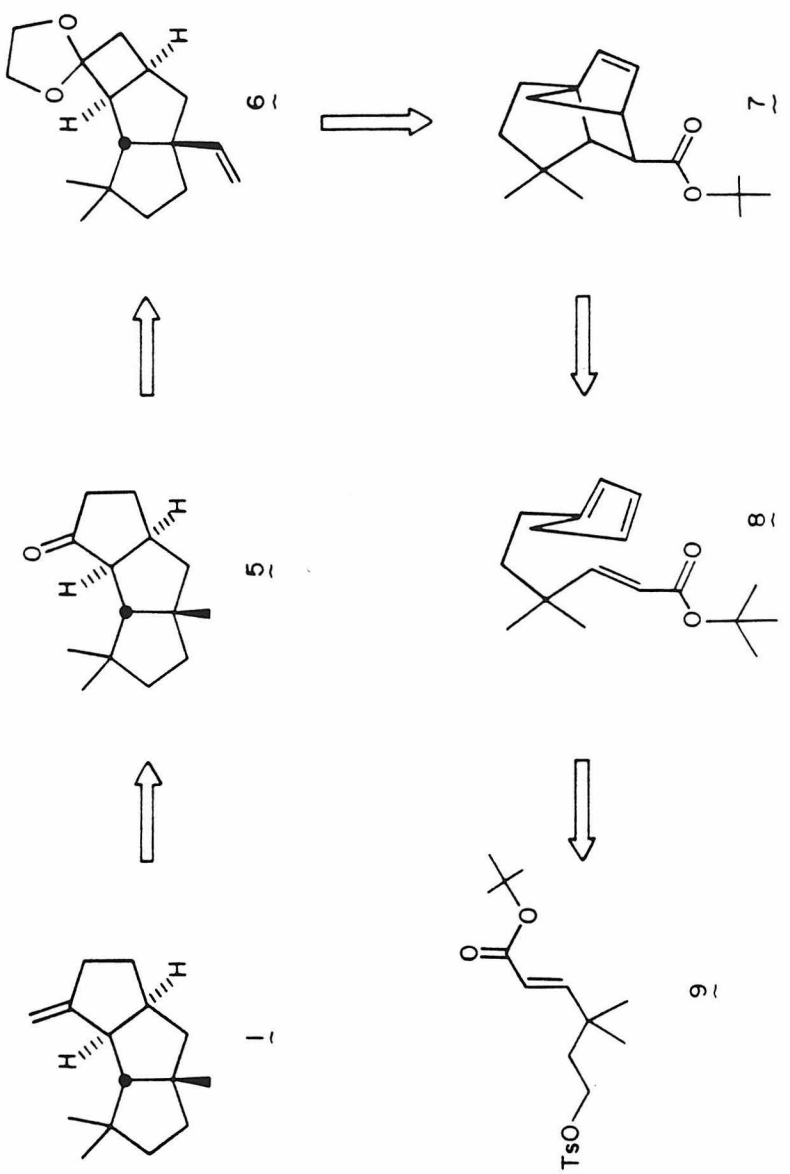
In designing a synthesis of **1**, it was our goal to incorporate several important features. Both the efficiency and the versatility of the titanocene methylidene **3**, generated from the Tebbe reagent (**4**, eq 1),[20] were to be demonstrated. The demonstration of versatility included three different modes of reac-



4 3 (1)

tivity: metathesis of a strained olefin,[21] intramolecular alkylidenation of an ester,[22] and methylenation of a ketone.[22c] In addition to exhibiting the synthetic capabilities of **4**, it was our intent to form all four centers of the natural product in a single reaction. Another requirement of the ring-forming reaction was the effectiveness and possible application of asymmetric induction by chiral auxiliaries during the cyclization process.

The retrosynthetic analysis of **1**, as seen in Scheme I, reveals an obvious application of **4** in the last step of the total synthesis. Previous methylenation of the known precursor to **1**, ketone **5**, has been accomplished with the corresponding Wittig reagent.[10–14,18] Access to the tricyclic ketone required only the functional group modification of the protected cyclobutanone **6**. Altering the substituent at C-4 to an angular methyl group, and ring expansion of the cyclobutanone to a cyclopentanone were needed for this modification sequence. As a key transformation in the reaction sequence, we wished to include the olefin metathesis intramolecular alkylidenation rearrangement for the formation of **6**.[21a] The strained olefin required for this structural rearrangement was the tricyclic compound **7**. As previously discussed, **8** was efficiently prepared by the coupling of **9** with cyclopentadienyl magnesium chloride, and the subsequent intramolecular cycloaddition provided an excellent source of **7**.[23] Because **7** can be formed through the intramolecular $4\pi + 2\pi$ cycloaddition of **8**, it is of great importance to this synthetic scheme. During the cycloaddition of **8**, all four asymmetric centers of capnellene were established. The importance of the cycloaddition in this reaction sequence has become magnified with the recent advances in asymmetric induction of the Diels-Alder reaction.[24] With the presence of the carboxylic acid group, comes the possible future application of chiral ester groups,[25] or oxazolidones[26] toward the first asymmetric synthesis of capnellene.



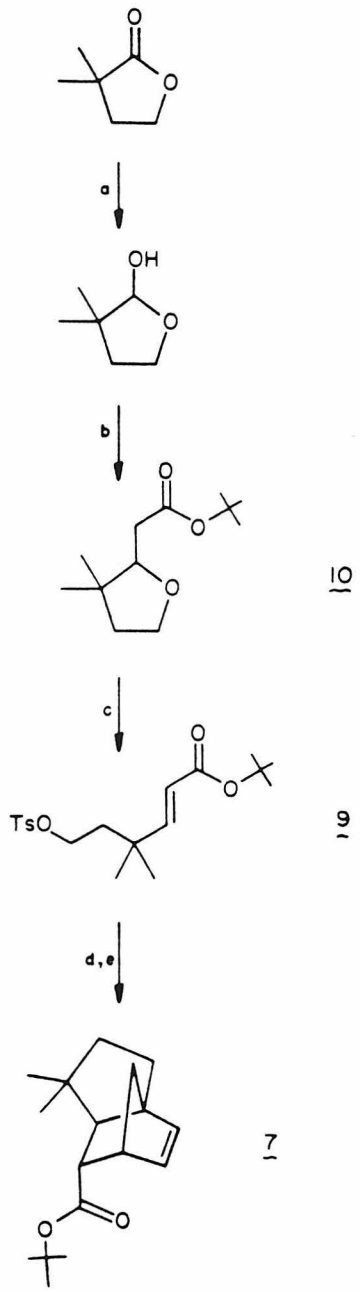
Scheme I. Retrosynthetic Analysis of **1**.

Results and Discussion

As previously reported,[23] the preparation of **6** proceeded in good yield. Reduction of α,α-dimethyl-γ-butyrolactone with diisobutylaluminum hydride, followed by Simmons-Horner homologation, produced **10** in 89% yield (Scheme II). Treatment of **10** with lithium diisopropylamide and subsequent trapping with *p*-toluenesulfonyl chloride resulted in an 81% yield of tosylate **9**. Coupling with cyclopentadienyl magnesium chloride generated the functionalized, substituted cyclopentadiene **8**, and upon heating, the intramolecular cycloaddition produced **7**, which was isolated in 81% yield. Metathesis of the strained olefin and subsequent intramolecular trapping of the titanocene alkylidene proceeded smoothly using the Tebbe reagent. Protection of the resulting cyclobutene enol ether as the ethylene ketal allowed the isolation of **6** in 81% yield based on **7**. From **6**, preparation of the ketone **5** required the modification of two separate functional groups. The vinyl substituent at C-4 had to be trimmed to a methyl group, and ring expansion of the cyclobutanone to a cyclopentanone was also necessary.

Removal of the excess carbon on the C-4 substituent was accomplished through ozonolysis (Scheme III). Reductive workup of the methoxy hydroperoxide with sodium borohydride[27] produced the alcohol **6** in 91% isolated yield. Further reduction of the neopentyl-like alcohol was accomplished by reported methods.[28] Following established procedure,[29] the bis(dimethylamino)phosphorodiamidate ester **12** was prepared, and could be isolated in 88% yield; however, use of crude **12** proved more efficient in the overall transformation of **11** to **13** than using flash chromatography to isolate **12**. Reductive cleavage of **12** was accomplished with 20 equivalents of lithium in ethylamine. Under normal conditions (0°C), the deep-blue solvated lithium solution became colorless within 30 min, signifying the unusual consumption of all solvated electrons. After standard

Scheme II[a] Synthetic Approach to the Preparation of **7**.



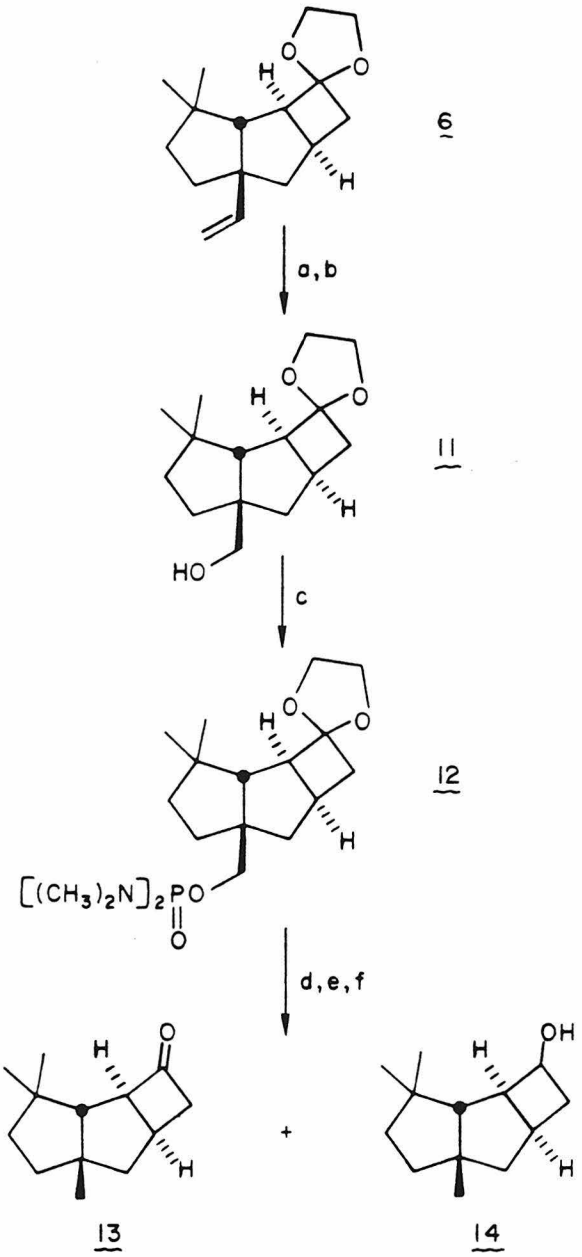
10

9

7

[a](a) DIBAL, -78°C, Toluene; (b) $(EtO)_2POCH_2CO_2C(CH_3)_3$, NaH, Benzene, 25°C (89%); (c) LDA, *p*-TsCl, THF, -78°C to 25°C (83%); (d) CpMgCl, THF, 25°C; (e) Benzene, 75°C (81%).

Scheme III[a] Synthetic Modification of the Angular C-4 Substituent.

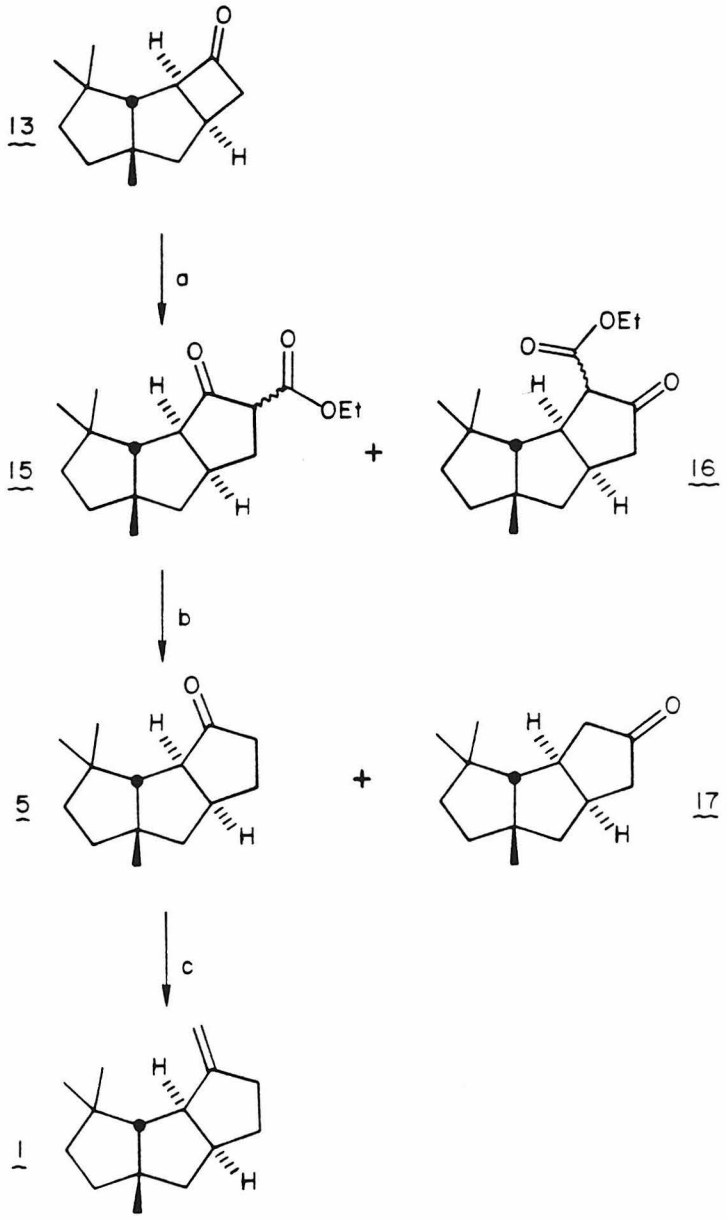


[a](a) O_3, $MeOH/CH_2Cl_2$, -78°C; (b) $NaBH_4$, -78 to 25°C (91%); (c) *n*-BuLi, $((CH_3)_2N)_2POCl$, NEt_3, DME, 25°C; (d) Li, *t*-BuOH, $EtNH_2$, THF, -50 to -40°C; (e) H_2O/Acetone, *p*-TsOH·H_2O, Benzene, reflux; (f) 0.15 eq. PDC, CH_2Cl_2, 25°C (68%).

workup, the protecting group was removed by acid-catalyzed exchange dioxolanation to acetone with acid catalyst. Analysis of the mixture revealed the presence of two compounds. Isolation was achieved by flash chromatography to yield the desired cyclobutanone **13** (30%) and a single cyclobutanol isomer **14** (51%).[30] The ethylene glycol ketal of this cyclobutanone was found to be much more sensitive to these reaction conditions than the reported ketals of cyclohexanones.[28] As a result of the overreduction of substrate **12**, less severe conditions were sought. At -78°C, the reaction proceeded very slowly with little conversion occurring over a 4 h period. Analysis of products that were formed after 4 h at -78°C, showed mostly the ketal of **13**, but reduction to the alcohol **14** was also observed to an extent of about 5%. Because the formation of **14** could not be eliminated, the reduction was performed at -50°C to -40°C and followed closely by thin layer chromatography. After 1 h, the reaction was quenched and, following removal of the ketal protecting group, produced $\approx$ 9:1 mixture of **13**:**14**. The slight overreduction of **13** was easily remedied by the addition of 0.15 equivalents of pyridinium dichromate. This procedure completely oxidized **14** to **13**. Isolation of the cyclobutanone **13** from this solution was achieved in 68% overall yield from the alcohol **11**.

Once the transformation of the vinyl substituent to the methyl group had been accomplished, the ring expansion of the cyclobutanone to the cyclopentanone was examined. A similar system, a cyclobutanone fused to a six-membered ring, showed complete regiospecificity of the boron trifluoride etherate catalyzed ring expansion with ethyl diazoacetate at room temperature.[31] The expansion of **13** proved somewhat different. At room temperature, the reaction produced a mixture of four isomeric β-keto esters **15** and **16** (Scheme IV). Decarboxylation of the β-keto esters, according to established procedure,[32]

Scheme IV[a] Ring Expansion of **13**.



[a](a) $BF_3 \cdot Et_2O$, N_2CHCO_2Et, Et_2O, -28°C; (b) NaCl, DMSO, H_2O, 150°C (73%); (c) **4**, Pyridine, Et_2O, -40 to 25°C (93%).

produced a 2.9:1.0 ratio of ketones **5** and **17**. The use of Lewis acid catalysts $AlCl_3$[33] and $TiCl_4$ at -40°C proved even less selective, producing **5:17** product ratios of 2.0:1.0 and 2.1:1.0, respectively. To investigate the use of an alternate methylene source, the boron trifluoride etherate catalytic ring expansion with trimethylsilydiazomethane,[34] found to be highly regiospecific with cyclohexanones,[35] was examined. Following reported procedure, the ring expansion catalyzed by boron trifluoride etherate produced many products as a result of repeated methylene insertion. Returning to the original ethyl diazoacetate reaction, the product selectivity was optimized by lowering the reaction temperature. At -28°C, the boron trifluoride etherate catalyzed ring expansion of **13** with ethyl diazoacetate produced a mixture of β-keto esters which, after decarboxylation, gave a 5.0:1.0 ratio of **5:17**. Separation of these isomers was achieved through flash chromatography to give a single ketone in 73% isolated yield. By comparison to spectra of independently synthesized **5**,[36] the major ketone product was verified as **5** by NMR and IR. The ^1H NMR spectra are compared in Figure 1 and the ^{13}C NMR spectra are compared in Figure 2.

The final transformation of **5** to the natural product **1** has been reported for most syntheses of **1**.[10–14,17,18] Usually, the α,β-unsaturated analog of **5** is hydrogenated in high yield and then taken on to **1** without isolation. The yields of this two-step process have been reported to vary from 36%[11,17] to 84%[12] due to the sensitive nature of the methylene Wittig reagent. The use of Tebbe reagent (**4**) for the methylenation process proved to be a highly efficient method for the transformation of **5** to $\Delta^{(9,12)}$-capnellene. Workup of the reaction mixture required only dilution with pentane and filtration through silica gel. The only eluting product was isolated in 93% yield. Compared to spectra of $\Delta^{(9,12)}$-capnellene prepared by another route,[37] the product was confirmed by NMR

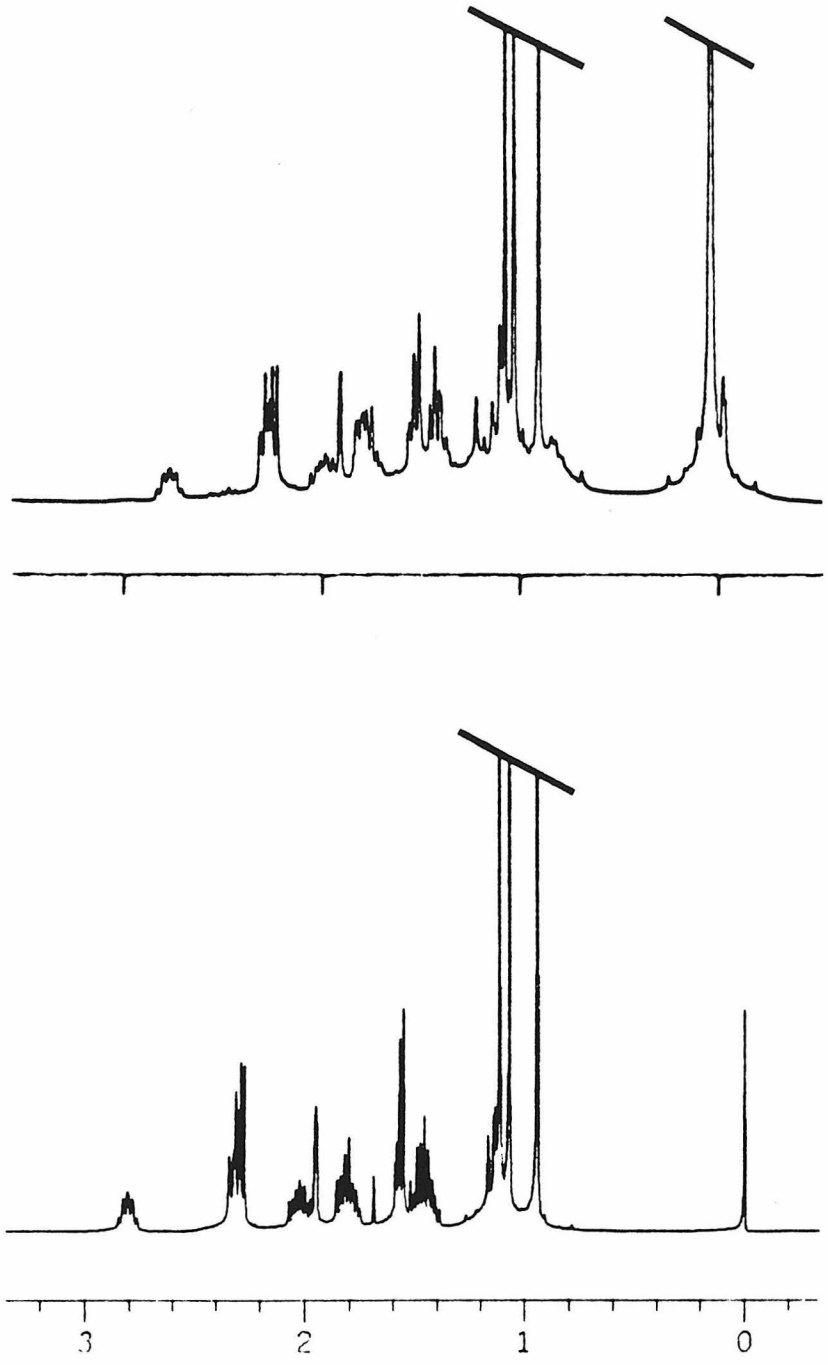


Figure 1. ^{1}H NMR Spectra of **5** in $CDCl_3$: (a) 270 MHz ^{1}H NMR Spectrum of an Independently Prepared Sample,[36] (b) 400 MHz ^{1}H NMR Spectrum of **5**.

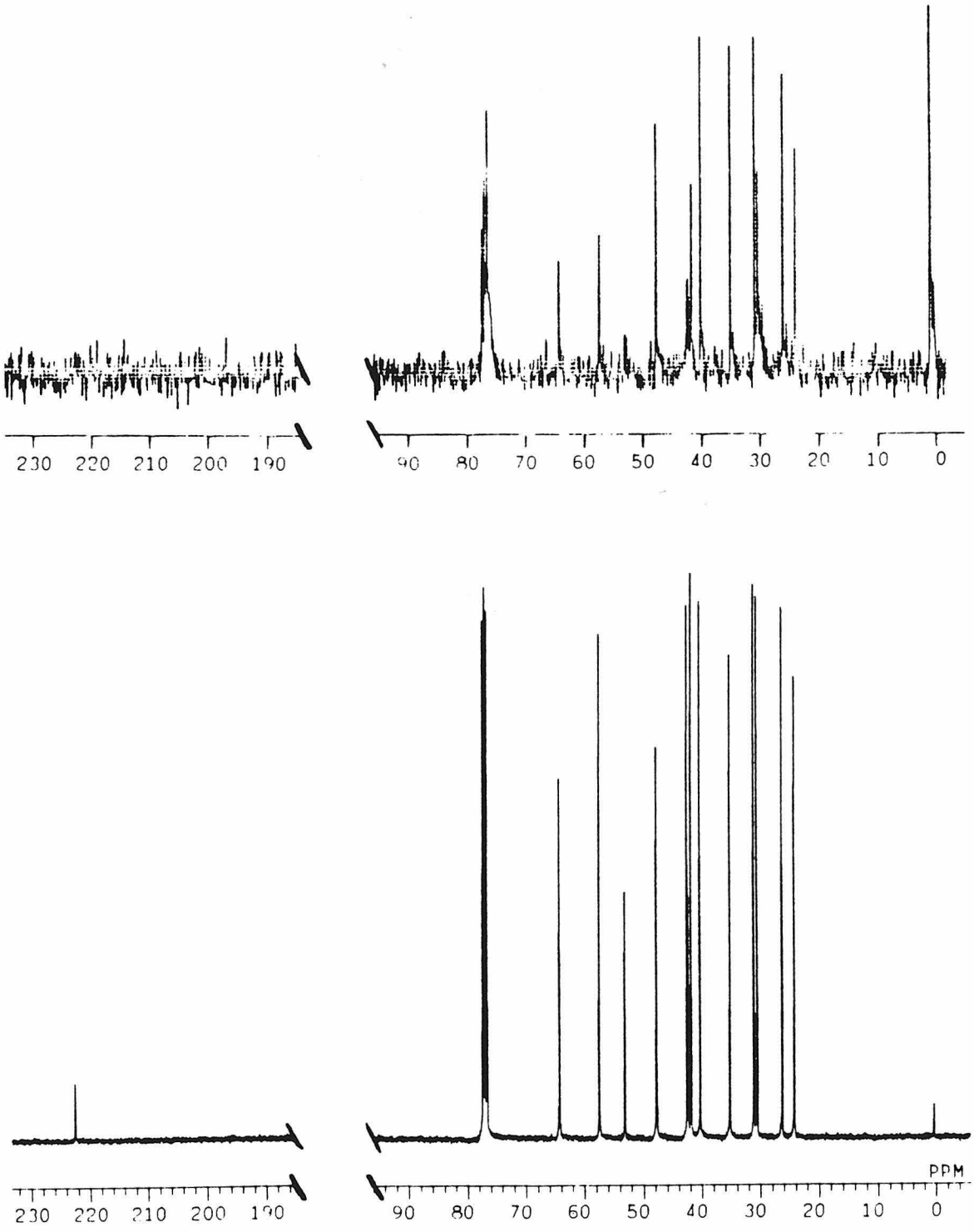


Figure 2. ^{13}C NMR Spectra of **5** in $CDCl_3$: (a) 67 MHz ^{13}C NMR Spectrum of an Independently Prepared Sample,[36] (b) 100 MHz ^{13}C NMR Spectrum of **5**.

and IR to be **1**. The ^{1}H NMR spectra are compared in Figure 3; the ^{13}C NMR spectra are compared in Figure 4.

This synthesis of $\Delta^{(9,12)}$-capnellene is the first to achieve the formation of all four asymmetric centers in a single step. By using the intramolecular cycloaddition for this purpose, a promising route to enantiomerically pure **1** has been opened. Through the use of chiral auxiliaries,[25,26] asymmetric induction in the cycloaddition process appears encouraging. Use of the versatile Tebbe reagent provided a novel way in which to rearrange the bridged cycloaddition product to the required linear skeleton. This rearrangement was achieved through the ring-opening metathesis of the strained olefin and subsequent intramolecular trapping of the substituted alkylidene. After functional group modification using established methods, the ketone precursor to **1** was obtained. Final methylenation using **4** proved to be very efficient in the transformation of the ketone to **1**. Overall, the yield of **1** obtained through this synthetic route was 20%.

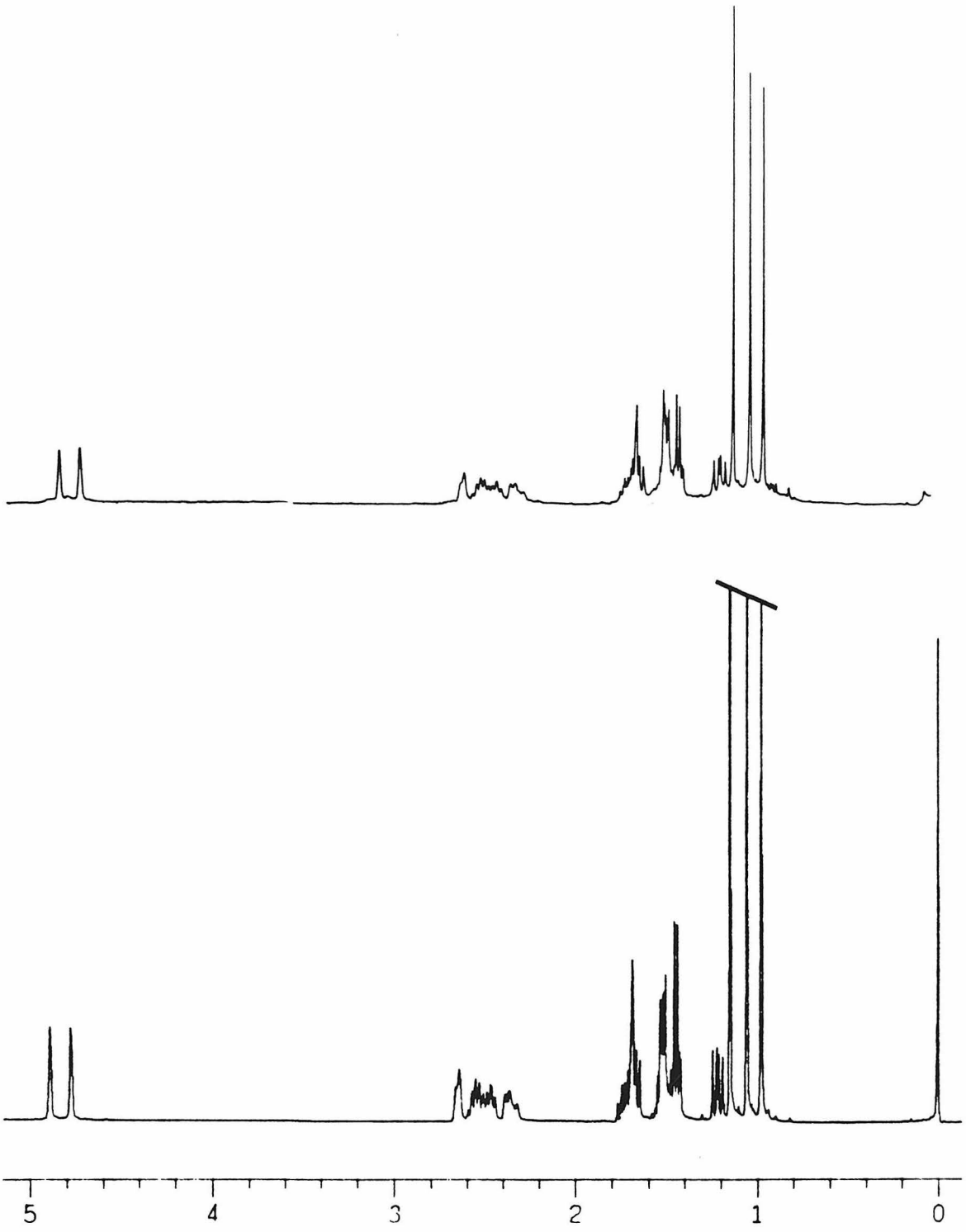


Figure 3. ^{1}H NMR Spectra of $\Delta^{(9,12)}$-Capnellene in $CDCl_3$: (a) 360 MHz ^{1}H NMR Spectrum of Natural Product Isolated from *Capnella imbricata*,[37] (b) 400 MHz ^{1}H NMR Spectrum of **1**.

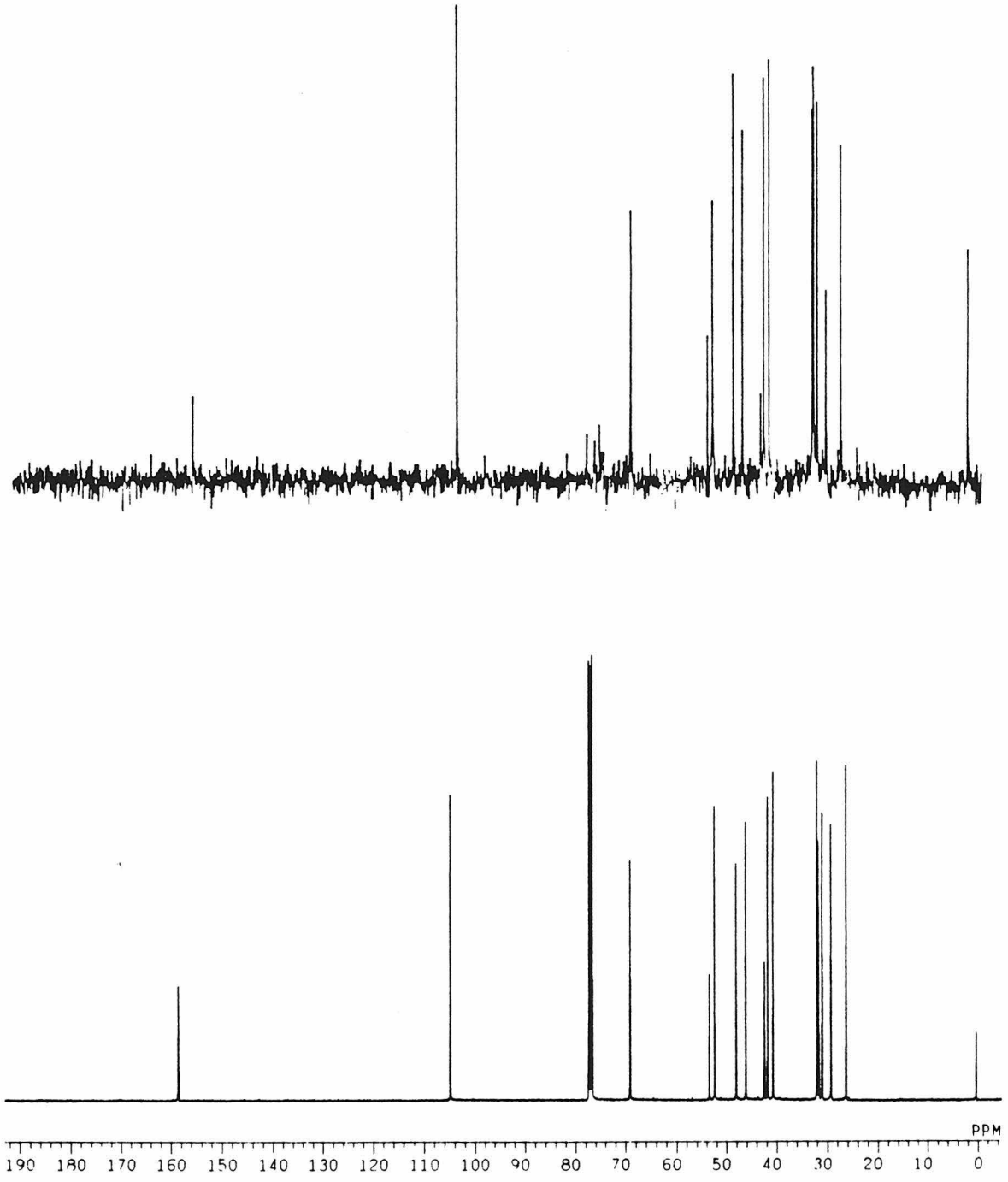


Figure 4. ^{13}C NMR Spectra of $\Delta^{(9,12)}$-Capnellene in $CDCl_3$: (a) 90 MHz ^{13}C NMR Spectrum of Natural Product Isolated from *Capnella imbricata*,[37] (b) 100 MHz ^{13}C NMR Spectrum of **1**.

Experimental Section

General Procedures. All manipulations of air and/or moisture sensitive compounds were carried out with use of standard Schlenk or vacuum line techniques. Argon was purified by passage through columns of BASF RS-11 (Chemalog) and Linde 4Å molecular sieves. Solids were transferred in a nitrogen-filled Vacuum Atmosphere Dri-lab equipped with an MO-40-1 purification train and a DK-3E Dri-Kool. Measurement of weight was conducted after minimizing static interference through the use of Staticmaster ionizing unit (Nuclear Products Company). Flash chromatography was performed according to general procedure of Still and coworkers,[38] employing Silica Woelm 32-63 (32-63 μm). Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates and visualized by phosphomolybdic acid dip.[39] All reaction temperatures were measured externally.

Materials. Boron trifluoride etherate (Aldrich Chemical Company) was treated with small amounts of diethyl ether and then distilled at reduced pressure (10 mmHg, 46°C). Bis(dimethylamino)phosphorochloridate (Aldrich Chemical Company) was distilled prior to use. Ethylamine ($EtNH_2$, Matheson) was passed through a tower of KOH immediately before use. Triethylamine (MCB Reagents) was distilled from CaH_2 under argon. *t*-Butyl alcohol (Aldrich Chemical Company) was dried over $MgSO_4$, filtered, and degassed through two freeze-pump-thaw cycles. Tebbe reagent (**4**) was prepared according to reported procedure.[40] Lithium wire was cleaned by washing with pentane, methanol and then pentane. Ethyldiazoacetate ($N_2CHCO_2CH_2CH_3$), Sudan IV, *n*-butyllithium, and pyridinium dichromate were obtained from Aldrich Chemical Company and used without further purification. *p*-Toluenesulfonic acid monohydrate was obtained from MCB Reagents.

$CDCl_3$ was stored over 4Å molecular sieves and filtered through Activity I alumina immediately prior to use. Pyridine was stored over 4Å molecular sieves. Dichloromethane (CH_2Cl_2) was dried over P_2O_5 and degassed on a vacuum line. Tetrahydrofuran (THF) was dried over CaH_2 and vacuum-transferred onto sodium-benzophenone ketyl. Diethyl ether (ether), dimethoxyethane (DME), and benzene-d_6 (Cambridge Isotope Laboratories) were degassed and stirred over sodium-benzophenone ketyl. The dried and degassed solvents were vacuum-transferred into dry vessels equipped with Teflon valve closures and stored under argon. Reagent grade petroleum ether (35-60°C) was used without further purification. In the cases where the rigid exclusion of oxygen was not required, anhydrous ether and reagent pentane were used without further purification.

Instrumentation. NMR spectra were recorded on a JEOL GX-400 (399.65 MHz ^1H; 100.40 MHz ^{13}C). Chemical shifts are reported versus residual solvent signals on the δ scale. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, m=multiplet, and br=broad), coupling constant (Hz), integration, and interpretation. Analytical gas chromatographic analyses (VPC) were performed on a Shimadzu GE-Mini 2 flame ionization instrument modified for capillary use and equipped with a Hewlett-Packard Model 339A integrator (column: 0.24 mm x 15 m DB1). The detector and injector temperatures were 250°C. Infrared analyses utilized a Beckman 4210 spectrophotometer and were reported in reciprocal centimeters (cm^{-1}). Melting points were determined on a Thomas Hoover Unimelt capillary melting point apparatus and were uncorrected. Ozone was obtained using a Welsbach generator.

Combustion analyses were performed by Mr. Lawrence Henling at the California Institute of Technology Microanalytical Laboratory.

(1S*, 2S*, 5R*,7R*)-10,10-Dimethyl-7-hydroxymethyltricyclo[5.3.0.0^{2,5}]dec-

ane-3,3′-[1,3]dioxolane (11). Olefin **6** (1.37 g, 5.48 mmol) was dissolved in 85 mL CH_2Cl_2/methanol (3:1) and a solution of indicator Sudan IV in CH_2Cl_2 was added until a faint red tint to the solution was detectable.[41] The solution was cooled to -78°C, and O_3 was bubbled through the mixture until the color of the indicator was replaced with a blue tint. After bubbling dry nitrogen through the solution for 20 min, the mixture was treated with sodium borohydride (0.622 g, 16.4 mmol) and stirred an additional 3 h at -78°C. The reaction mixture was warmed to room temperature, stirred 15 min, and then quenched by the addition of 50 mL water. After separation of the mixture, the aqueous layer was extracted with 3 x 50 mL ether. The combined organic fractions were combined and dried ($MgSO_4$). Concentration of the solution produced an oil that was purified by flash chromatography. Elution on silica gel with ether/petroleum ether (3:1) gave 1.25 g **11** (91%) with R_f=0.36: ^{1}H NMR (400 MHz, C_6D_6) δ 3.72 (d, J=10.7 Hz, 1H), 3.64 (br d, J=10.7 Hz, 1H, pattern sharpens upon addition of D_2O), 3.23-3.40 (m, 4H), 2.92-2.96 (br m, 1H), 2.48-2.63 (m, 2H), 2.46 (br s, 1H, exchanged with D_2O), 2.29 (dd, J=2.8, 12.5 Hz, 1H), 2.11 (d, J=1.0 Hz, 1H), 1.98 (dd, J=2.3, 14.0 Hz, 1H), 1.59-1.74 (m, 2H), 1.32-1.48 (m, 3H), 0.93 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 108.7, 71.4, 64.4, 63.4, 63.1, 59.7, 55.3, 45.6, 43.2, 42.7, 41.8, 38.6, 34.1, 30.1, 25.1. IR (neat) 3420, 2940, 2860, 1460, 1040, 1010 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.07; ;H, 9.46.

Esterification of bis(dimethylamino)phosphorchloridate with 11. To a solution of alcohol **11** (1.17 g, 4.64 mmol) in 48 mL DME at room temperature was added a solution of 1.6*M* *n*-butyllithium in hexanes (3.3 mL, 5.3 mmol). After stirring for 1 h, a solution of bis(dimethylamino)phosphorochloride (2.5 mL, $\approx$ 14 mmol) in 4.8 mL triethylamine was added and the reaction mixture stirred for 5

h at room temperature. The mixture was treated with 100 mL water, separated, and the aqueous layer extracted with 3 x 100 mL ether. The combined organics were washed with 2 x 50 mL water, 1 x 30 mL saturated aqueous NaCl, and dried over $MgSO_4$. Following removal of solvent, the crude ester was isolated by flash chromatography. Elution down a short silica gel column with ethyl acetate produce 1.58 g of ester **12** (88%) with R_f = 0.11. ^{1}H NMR (400 MHz, C_6D_6) δ 4.34 (dd, J=5.1, 9.8 Hz, 1H), 4.17 (dd, J=4.4, 9.5 Hz, 1H), 3.32-3.45 (m, 4H), 2.93-2.99 (m, 1H), 2.55 (d, J=9.3 Hz, 6H), 2.53 (d, J=9.3 Hz, 6H), 2.44-2.66 (m, 2H), 2.10-2.22 (m, 3H), 1.96-2.00 (m, 1H), 1.63 (d, J=8.7, 14.3 Hz, 1H), 1.41-1.58 (m, 3H), 0.95 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 108.3, 72.1 (d, J=5.1 Hz), 64.5, 63.5, 61.5 (d, J=7.3 Hz), 59.3, 55.0, 45.3, 43.2, 42.3, 42.2, 38.1, 37.1 (d, J=3.7 Hz), 34.0, 30.1, 25.0.

Reduction of 12 at 0°C. To a 0°C solution of lithium (0.54 g, 78 mmol) in 200 mL $EtNH_2$ was slowly added a solution of **12** (1.51 g, 3.90 mmol) and *t*-butyl alcohol (0.39 g, 5.3 mmol) in 60 mL THF. After stirring for 30 min at 0°C, the reaction mixture became clear and colorless. The reaction was quenched after 1 h by the addition of saturated aqueous NH_4Cl. Following concentration of the solution at reduced pressure and temperature (aspirator, 0°C), saturated aqueous $NaHCO_3$ was added. The aqueous solution was extracted with 3 x 200 mL pentane; the combined organic fractions were dried ($MgSO_4$), and concentrated to an oil. The oil was dissolved in 50 mL acetone/water (20:1) and *p*-toluenesulfonic acid monohydrate (100 mg) was added. After heating the mixture at reflux for 20 h, the solution was cooled, quenched with saturated aqueous $NaHCO_3$ and the acetone was removed *in vacuo*. The aqueous solution was extracted with 3 x 50 mL pentane and the combined organics were dried ($MgSO_4$). TLC revealed two compounds with R_f = 0.38 and R_f = 0.06 upon elution with petroleum

ether/ether (9:1). Separation of these compounds was achieved through the use of flash chromatography. Elution with petroleum ether/ether (9:1) produced 225 mg **13** (30%) as a colorless oil. Subsequent elution with ether produced an oil that was crystallized from pentane to give 387 mg **14** (51%) as white crystalline solid.

13: ^{1}H NMR (400 MHz, C_6D_6) δ 3.15-3.20 (m, 1H), 2.78-2.90 (m, 1H), 2.33-2.45 (m, 2H), 1.95 (s, 1H), 1.73 (dd, J=8.9, 14.1 Hz, 1H), 1.28-1.48 (m, 5H), 1.06 (s, 3H), 0.84 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 211.8, 68.7, 66.7, 55.5, 54.3, 48.9, 42.3, 42.1, 41.1, 33.5, 31.8, 30.6, 25.4. IR (neat) 2950, 2830, 1780, 1470, 1460, 1075 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48 Found: C, 81.12; H, 10.47.

14: mp = 66.0-67.0°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (dd, J=6.6, 12.2 Hz, 1H), 2.55-2.65 (m, 1H), 2.45 (dd, J=5.4, 8.1 Hz, 1H), 1.84-2.05 (m, 4H), 1.61 (s, 1H), 1.49-1.54 (m, 2H), 1.30-1.45 (m, 2H), 1.30-1.45 (m, 3H), 1.25 (s, 3H), 0.96 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100.4 MHz, C_6D_6) δ 73.2, 68.5, 56.9, 55.9, 50.7, 42.8, 42.5, 42.2, 38.0, 35.0, 31.9, 31.1, 25.7. IR (CCl_4) 3620, 2950, 2870, 1460, 1110 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.15; H, 11.25.

(1R*, 2S*, 5R*, 7S*)-7,10,10-Trimethyltricyclo[5.3.0.^{2,5}]decan-3-one. To a solution of **11** (1.08 g, 4.27 mmol) in 48 mL DME at room temperature was added a solution of 2.5*M* *n*-butyllithium in hexanes (2.0 mL, 4.9 mmol). After being stirred 1 h, a solution of bis(dimethylamino)phosphorochloridate (2.5 mL, $\approx$ 14 mmol) in 4.8 mL triethylamine was added and the reaction mixture stirred for 10 h at room temperature. The mixture was treated with 100 mL water, separated, and the aqueous layer extracted with 3 x 100 mL ether. The combined organics were washed with 2 x 50 mL water, 1 x 30 mL saturated aqueous NaCl, and dried

($MgSO_4$). Concentration of this solution produced 1.56 g of crude **12** (95% mass balance). A -78°C mixture of crude **12** (1.50 g, 3.88 mmol) and *t*-butyl alcohol (0.39 g, 5.3 mmol) in 60 mL THF was added to a -78°C solution of lithium (0.54 g, 78 mmol) in 200 mL $EtNH_2$. The mixture was warmed to -50°C and was allowed to stir for 1 h between -50°C and -40°C. After cooling the mixture to -78°C, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl. The colorless solution was warmed to 0°C, and the mixture concentrated via aspirator. Once concentrated, saturated aqueous $NaHCO_3$ was added, and the mixture extracted with 3 x 200 mL pentane. The organic fractions were combined and dried ($MgSO_4$). The resulting oil was dissolved in 50 mL acetone/water (20:1) and *p*-toluenesulfonic acid monohydrate (50 mg) was added. After heating this mixture at reflux for 20 h, the solution was cooled, quenched with saturated aqueous $NaHCO_3$ and the acetone was removed *in vacuo*. The aqueous solution was extracted with 3 x 50 mL pentane and the combined organics were dried ($MgSO_4$). After concentration of this solution, the mixture was dissolved in 10 mL CH_2Cl_2 and 219 mg pyridinium dichromate (0.58 mmol) was added. After being stirred for 3 h, the reaction mixture was diluted with ether and then filtered. Flash chromatography with petroleum ether/ether (9:1) was employed to give 537 mg **13** (68%).

(1S*, 2S*, 6S*, 8S*)-8,11,11-trimethyltricyclo[6.3.0.0.^{2,6}]undecan-3-one. To a 0°C solution of **13** (372 mg, 1.94 mmol) in 25 mL ether was added boron trifluoride etherate (667 mg, 4.84 mmol) via syringe. After being stirred for 30 min at 0°C, the reaction mixture was cooled to -28°C (*o*-xylene/CO_2), and $N_2CHCO_2CH_2CH_3$ (4.84 mmol) was added. The reaction was stirred for 5 h at -28°C and then quenched with saturated aqueous $NaHCO_3$. After being stirred for 1 h, the mixture was extracted with 3 x 50 mL ether. The combined organics

were concentrated to an oil and dissolved in 35 mL DMSO. To this solution were added NaCl (124 mg, 2.13 mmol) and H_2O (105 mg, 5.82 mmol). The mixture was heated to 150°C and maintained at that temperature for 5 h. After cooling to room temperature, 40 mL water were added and the mixture was extracted with 3 x 50 mL ether. The combined organics were dried ($MgSO_4$) and then concentrated to an oil. VPC analysis revealed a 5.0:1.0 mixture of two products. Separation of the products was achieved through flash chromatography. Elution on silica gel with petroleum ether/ether (9:1) produced 293 mg **5** (73%) with R_f = 0.29 and 52 mg **17** (13%) with R_f = 0.21.

5: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75-2.85 (m, 1H), 2.25-2.35 (m, 3H), 1.96-2.08 (m, 1H), 1.94-1.98 (m, 1H), 1.75-1.87 (m, 2H), 1.54-1.59 (m, 2H), 1.38-1.54 (m, 2H), 0.99-1.17 (m, 1H), 1.11 (s, 3H), 1.07 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 222.2, 64.0, 57.1, 52.8, 47.5, 42.2, 42.0, 41.5, 40.0, 34.8, 30.8, 30.2, 26.0, 23.9. IR (neat) 2950, 2860, 1740, 1460, 1170 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.42; H, 10.66.

17: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60-2.72 (m, 1H), 2.46-2.59 (m, 1H), 2.23-2.42 (m, 2H), 2.19 (dd, J=3.3, 18.8 Hz, 1H), 1.99 (dd, J=7.6, 18.8 Hz, 1H), 1.99 (dd, J=7.6, 13.6 Hz, 1H), 1.36-1.58 (m, 6H), 1.22 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 220.0, 67.7, 53.2, 48.2, 45.1, 44.3, 44.1, 42.6, 42.0, 41.3, 41.2, 32.7, 30.8, 25.7. IR (neat) 2950, 2870, 1740, 1460, 1410, 1150 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.24; H, 10.66.

$\Delta^{(9,12)}$-Capnellene. A precooled solution of ketone **5** (179 mg, 0.87 mmol) in 3 mL ether was added to a solution of **4** (342 mg, 1.20 mmol) in 3 mL ether at -40°C. To this mixture was added pyridine (123 mg, 1.56 mmol) via syringe. The reaction was maintained at -40°C for 30 min and then allowed to warm to

ambient temperature over the period of 1 h. The reaction was then quenched by the addition of 50 mL pentane and exposure to oxygen. After being stirred for 3 h, the mixture was filtered through a silica gel pad, and washed through with pentane. The solution was concentrated under aspirator (30 mmHg) at 0°C. The resulting oil was taken up in 20 mL pentane and filtered through a pad of silica gel, washed through with pentane, and concentrated under reduced pressure and temperature to produce 165 mg **1** (93%) as a colorless liquid: R_f (TLC, pentane) = 0.71. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (s, 1H), 4.78 (s, 1H), 2.62-2.68 (m, 1H), 2.42-2.60 (m, 2H), 2.30-2.40 (m, 1H), 1.64-1.77 (m, 3H), 1.42-1.56 (m, ,5H), 1.21 (dd, J=9.5, 13.2 Hz, 1H), 1.15 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 158.2, 104.5, 68.8, 53.1, 52.0, 47.7, 45.8, 42.1, 41.5, 40.4, 31.7, 31.4, 30.7, 28.9, 25.9. IR (neat) 3070, 2940, 2860, 1650, 1460, 1385, 1370, 1365, 875 cm^{-1}. Exact mass calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1880.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.12; H, 11.72.

References and Notes

(1) (a) Kaisin, M.; Sheikh, Y.M.; Durham, L.J.; Djerassi, C.; Tursch, B.; Daloze, D.; Braekman, J.C.; Losman, D.; Karlsson, R. *Tetrahedron Lett* **1974**, 2239. (b) Sheikh, Y.M.; Singy, G.; Kaisin, M.; Eggert, H.; Djerassi, C.; Tursch, B.; Daloze, D.; Braekman, J.C. *Tetrahedron* **1976**, *32*, 1171.

(2) Paquette, L.A. *Top. Curr. Chem.* **1984**, *119*, 1.

(3) Ayanoglu, E.; Gebreyesus, T.; Beechan, C.M.; Djerassi, C.; Kaisin, M. *Tetrahedron Lett.* **1978**, 1671.

(4) (a) Sheikh, Y.M.; Djerassi, C.; Braekman, J.C.; Daloze, D.; Kaisin, M.; Tursch, B.; Karlsson, R. *Tetrahedron* **1977**, *33*, 2115. (b) Karlsson, R. *Acta Crystallogr. Sect B.* **1976**, *32*, 2609. (c) Kaisin, M.; Tursch, B.; Declercq, J.P.; Germain, G.; van Meerssche, M. *Bull. Soc. Chim. Belg.* **1979**, *88*, 253.

(5) For a review on this family of compounds see: Ayer, W.A.; Browne, L.M. *Tetrahedron* **1981**, *37*, 2199.

(6) (a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (b) Takeuchi, T.; Takahashi, S.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Ibid.* **1971**, *24*, 631.

(7) (a) For a discussion of the synthetic achievements in this family of molecules see: (a) Reference 2, pp 108-120. (b) Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448 and references cited therein.

(8) (a) Cierzsko, L.S. *N.Y. Acad. Sci.* **1962**, *24*, 502. (b) Burkolder, P.R.; Burkolder, L.M. *Science* **1958**, *127*, 1174.

9) Cierzsko, L.S.; Karns, T.K.B. *Biology and Geology of Coral Reefs.* Jones, O.A.; Eudean, R., ed.; Vol. II, Chap 6; Academic Press: New York, 1972.

(10) Paquette, L.A.; Stevens, K.E. *Can. J. Chem.* **1984**, *62*, 2415.

(11) Paquette, L.A.; Stevens, K.E. *Tetrahedron Lett.* **1981**, 4393.

(12) Huguet, J.; Karpf, M.; Dreiding, A.S. *Helv. Chim. Acta* **1982** *65*, 2413.

(13) Crisp, G.T.; Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.

(14) Oppolzer, W.; Battig, K. *Tetrahedron Lett.* **1982**, 4669.

(15) Piers, E.; Karunaratne, V. *Can. J. Chem.* **1984**, *62*, 629.

(16) (a) Birch, A.M.; Pattenden, G. *Tetrahedron Lett.* **1982**, 991. (b) Birch, A.M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. I* **1983**, 1913.

(17) Mehta, G.; Reddy, D.S.; Murty, A.N. *J. Chem. Soc., Chem. Commun.* **1983**, 824.

(18) (a) Little, R.D.; Carroll, G.L. *Tetrahedron Lett.* **1981**, 4389. (b) Little, R.D.; Carroll, G.L.; Peterson, J.L. *J. Am. Chem. Soc.* **1983**, *105*, 928.

(19) (a) Little, R.D.; Moeller, K.D. *J. Org. Chem.* **1983**, *48*, 4487. (b) Stone, K.J.; Little, R.D. *J. Am. Chem. Soc.* **1985**, *107*, 2495.

(20) Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(21) (a) Chapter 5, this thesis. (b) Gilliom, L.R.; Grubbs, R.H. *Organometallics* **1986**, *5*, 0000. (c) Gilliom, L.R.; Grubbs, R.H. *J. Am. Chem. Soc.* **1986**, *108*, 0000.

(22) For intermolecular methylenation of ester groups see: (a) Pine, S.H.; Zahler, R.; Evans, D.A.; Grubbs, R.H. *J. Am. Chem. Soc.* **1980**, *102*, 3270. (b) Stevenson, J.W.S.; Bryson, T.A. *Tetrahedron Lett.* **1982**, 3143. (c) Clawson, L.; Buchwald, S.L.; Grubbs, R.H. *Tetrahedron Lett.* **1984**, 5733. (d) Pine S.H.; Pettit, R.J.; Geib, G.D.; Cruz, S.G.; Gallego, C.H.; Tijerina, T.; Pine, R.D. *J. Org. Chem.* **1985**, *50*, 1212.

(23) Chapter 4, this thesis.

(24) For a review on asymmetric Diels-Alder reactions see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876.

(25) (a) Oppolzer, W.; Chapuis, C.; Kelley, M.J. *Helv. Chim. Acta* **1983**, *66*, 2358. (b) Rousch, W.R.; Gillis, H.R.; Ko, A.I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (c) Ensley, H.E.; Parnell, C.A.; Corey, E.J. *J. Org. Chem.* **1978**, *43*, 1610.

(26) (a) Evans, D.A.; Chapman, K.T.; Bisaha, J. *Tetrahedron Lett.* **1984**, 25. (b) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.

(27) Becker, D.; Kalo, J.; Brodsky, N.C. *J. Org. Chem.* **1978**, *43*, 2562.

(28) Ireland, R.E.; Muchmore, D.C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

(29) Muchmore, D.C., Ph.D. thesis, California Institute of Technology (1971).

(30) The stereochemistry of this single isomeric alcohol was not determined. Oxidation of **14** with pyridinium dichromate produced **13** as confirmed by capillary gas chromatography and 400 MHz ^{1}H NMR.

(31) Liu, H.J.; Ogino, T. *Tetrahedron Lett.* **1973**, 4937.

(32) (a) Krapcho, A.P.; Lovey, A.J. *Tetrahedron Lett.* **1973**, 957. (b) Krapcho, A.P.; Jahngen, E.G.E.; Lovey, A.J. *Tetrahedron Lett.* **1974**, 1091.

(33) Muller, E.; Lurken, W.; Bauer, M. *Tetrahedron Lett.* **1962**, 775.

(34) Mori, S.; Sakai, I.; Aoyama, T.; Shiori, T. *Chem. Pharm. Bull.* **1982**, *30*, 3380.

(35) (a) Hashimoto, N.; Aoyama, T.; Shiori, T. *Tetrahedron Lett.* **1980**, 4619. (b) Hashimoto, N.; Aoyama, T.; Shiori, T. *Chem. Pharm. Bull.* **1982**, *30*, 119.

(36) Copies of spectra were generously provided by Professor J.K. Stille (Colorado State University).

(37) Copies of spectra obtained from Professor C. Djerassi (Stanford University)

were generously provided by Professor J.K. Stille (Colorado State University).

(38) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(39) Touchstone, J.C.; Dobbins, M.F. *Practice of Thin Layer Chromatography.* John Wiley & Sons: New York, 1978, p. 207.

(40) Lee, J.B.; Ott, K.C.; Grubbs, R.H. *J. Am. Chem. Soc.* **1982**, *104*, 7491.

(41) Veysoglu, T.; Mitscher, L.A.; Swayze, J.K. *Synthesis* **1980**, 807.

APPENDIX I

X-ray Diffraction Structral Data

X-Ray Structure Determination of Metallacycle 35

Single crystals of the metallacycle (**35**) were grown from a toluene/diethyl ether solution slowly cooled from 25° to -45°. A single crystal was mounted approximately along **a** in a glass capillary under N_2. A series of oscillation and Weissenberg photographs indicated symmetry no higher than $\bar{1}$. The intensity data were collected on an Enraf-Nonius CAD4 diffractometer (graphite monochromator and Mo$K\alpha$ radiation λ = 0.7107Å). The entire Ewald sphere was collected to $\theta = 13°$ and hemisphere $(+h, \pm k, \pm \ell)$ from $\theta = 13°$ to 25°. The unit cell parameters (Table I) were obtained by least-squares refinement of 25 reflections centered at $\pm 2\theta$. The total, 5742 reflections, yielded an averaged data set of 4339 reflections; 3727 had $I > 0$ and 2058 had $I > 3\sigma_I$. The three check reflections indicated no decomposition, and the data were reduced to F^2. Additional details of the data collection are given in Table I.

The position of the Ti atom was derived from the Patterson map, and the subsequent Fourier map phased on the Ti atom revealed the remainder of the structure. The hydrogen atoms were located from difference maps and were introduced into the model with fixed coordinates at idealized positions with isotropic U = 0.063Å^2. Least-squares refinement of the atomic coordinates and U's (anisotropic for all non-H atoms) minimizing $\Sigma w \Delta^2$, $\Delta = F_o^2 - (F_c/k)^2$, with weights $w = \sigma_{F^2}^{-2}$ led to $R_F = \sum ||F_o| - |F_c|| / \sum |F_o|$ = 0.1160 for $I > 0$, R_F = 0.0584 for $I > 3\sigma_I$, and the goodness–of-fit S = $[\sum w\Delta^2/(n-v)]^{1/2}$ = 1.54 (n = 4339 reflections, p = 289 parameters); the maximum shift/error ratio < 0.1, the average < 0.1, and the maximum deviations in the $\Delta\rho$ map are near the isopropyl groups and are less than 0.9 e Å^{-3}. All calculations were carried out on a VAX 11/750 computer using the CRYM system of programs. The form factors for all atoms were taken from Table 2.2B, *International Tables for X-Ray Crystallography* (1974).

Table I — Summary of Crystal Data and Intensity Collection Information.

Formula	$C_{27}H_{36}O_4Ti$
Formula weight	472.49
Space group	$P\bar{1}$
a	8.942(1)Å
b	11.576(2)Å
c	13.577(2)Å
α	64.749(12)°
β	78.571(11)°
γ	82.157(10)°
V	1243.7(3)Å^3
Z	2
λ	0.7107 Å
Scan range	1.2°(θ)
Scan	$\theta - 2\theta$
Scan speed	2.55°min^{-1}

Table II. Atom Coordinates ($\times 10^5$) and U's (Å^2, $\times 10^4$).

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}	U_{eq}
Ti	3899(9)	11372(7)	15845(7)	364(5)	289(5)	355(5)	−22(4)	−36(4)	−98(4)	351(2)
$C(1)$	10389(47)	8281(37)	31088(34)	464(30)	331(27)	542(33)	9(22)	−108(24)	−252(25)	419(12)
$C(2)$	16734(44)	−5150(37)	31553(31)	302(27)	417(29)	248(26)	−50(21)	−20(20)	−141(23)	321(12)
$C(3)$	19274(45)	−5189(35)	19598(31)	400(30)	361(27)	263(26)	−30(22)	−56(21)	−138(21)	336(11)
$C(4)$	36987(46)	−6523(38)	16764(33)	312(28)	399(29)	332(28)	−21(22)	−1(21)	−101(24)	372(13)
$C(5)$	42131(45)	−20658(41)	22884(34)	322(28)	447(30)	343(29)	15(22)	10(22)	−164(25)	383(12)
$C(6)$	37414(46)	−23089(39)	35206(34)	329(28)	379(29)	393(30)	4(22)	−150(22)	−131(24)	365(12)
$C(7)$	32907(46)	−9201(39)	34734(35)	329(29)	395(29)	357(29)	−51(22)	−103(22)	−141(24)	355(12)
$C(8)$	42807(47)	−1384(39)	23955(37)	348(30)	411(30)	504(34)	−64(22)	−61(24)	−110(26)	445(14)
$C(9)$	35162(53)	−7931(42)	45092(38)	667(37)	620(35)	543(35)	−34(28)	−278(29)	−256(29)	577(14)
$C(10)$	37609(51)	−30175(46)	19293(40)	370(32)	504(34)	432(34)	92(25)	−9(25)	−226(29)	444(14)
$C(11)$	40520(61)	−52515(50)	23206(47)	772(42)	455(36)	774(46)	83(30)	−366(35)	−291(35)	629(17)
$C(12)$	52802(78)	−54333(56)	14802(54)	1377(63)	1021(52)	1294(61)	33(46)	−98(51)	−850(49)	1126(22)
$C(13)$	39608(81)	−63853(55)	33899(58)	1887(77)	568(45)	1322(62)	−247(47)	−422(57)	−359(44)	1226(28)
$C(14)$	24644(51)	−32172(39)	41542(38)	327(31)	342(29)	385(32)	30(22)	−55(24)	−109(25)	371(13)
$C(15)$	13018(56)	−45323(48)	59679(40)	529(35)	503(36)	483(36)	−137(28)	−27(27)	−99(30)	538(16)
$C(16)$	20108(70)	−58207(54)	63902(54)	993(53)	586(42)	1509(64)	−164(38)	−7(47)	−56(42)	1178(27)
$C(17)$	6525(86)	−41138(65)	68471(63)	1643(75)	1297(64)	1703(78)	−716(56)	1008(62)	−780(60)	1617(31)
$O(1)$	43556(33)	−41959(28)	25283(24)	641(23)	388(21)	610(24)	147(17)	−300(18)	−232(19)	525(9)
$O(2)$	30642(39)	−28012(29)	11949(26)	813(27)	688(25)	566(26)	240(20)	−402(22)	−333(21)	647(10)
$O(3)$	24615(34)	−36550(27)	52351(24)	556(22)	587(23)	332(21)	−199(17)	−104(17)	−72(18)	511(10)
$O(4)$	15797(34)	−35036(28)	37481(24)	505(23)	600(23)	495(23)	−187(18)	−155(18)	−163(18)	528(9)
$C(21A)$	16097(85)	31237(52)	9123(44)	1031(54)	447(38)	612(41)	−386(36)	109(38)	−228(31)	694(19)
$C(22A)$	3019(69)	33531(45)	4499(55)	708(46)	242(32)	861(51)	34(29)	110(38)	−34(31)	713(25)
$C(23A)$	4985(72)	27390(57)	−2477(45)	712(47)	605(42)	518(40)	−294(35)	−187(33)	90(31)	685(20)
$C(24A)$	19180(74)	21204(45)	−1998(41)	835(47)	409(34)	367(34)	−201(32)	167(31)	−69(27)	591(19)
$C(25A)$	26102(55)	23590(48)	5032(46)	479(37)	454(35)	545(39)	−124(28)	−65(30)	24(29)	566(17)
$C(21B)$	−13533(50)	−5031(44)	20328(54)	271(30)	392(34)	999(50)	−37(24)	−2(31)	−240(35)	583(20)
$C(22B)$	−16909(52)	5174(53)	10776(41)	422(33)	689(39)	570(37)	−125(28)	−20(27)	−376(33)	518(14)
$C(23B)$	−22750(50)	15392(43)	13324(42)	398(32)	482(33)	589(38)	58(25)	−129(27)	−215(30)	492(14)
$C(24B)$	−22548(50)	11876(50)	24328(44)	364(31)	729(40)	564(37)	2(27)	8(26)	−420(33)	514(14)
$C(25B)$	−17024(53)	−914(55)	28796(40)	334(33)	810(44)	363(33)	−140(30)	−72(25)	72(32)	599(20)

282

Table III. Hydrogen Atom Coordinates ($\times 10^4$) and B's ($Å^2$, $\times 10^4$).

	x	y	z	B
H(1A)	199	798	3690	5.0
H(1B)	1772	1359	3078	5.0
H(2)	918	−1068	3679	5.0
H(3)	1710	−1030	1840	5.0
H(4)	4003	−288	892	5.0
H(5)	5293	−2208	2102	5.0
H(6)	4595	−2713	3928	5.0
H(8A)	4065	755	2165	5.0
H(8B)	5342	−340	2422	5.0
H(9A)	4492	−1053	4670	5.0
H(9B)	2771	−1277	5141	5.0
H(9C)	3319	106	4369	5.0
H(11)	3068	−5196	2033	5.0
H(12A)	5970	−4659	1186	5.0
H(12B)	5929	−6142	1727	5.0
H(12C)	4901	−5327	833	5.0
H(13A)	4658	−7030	3293	5.0
H(13B)	2949	−6661	3666	5.0
H(13C)	4224	−6124	3914	5.0
H(15)	499	−4541	5596	5.0
H(16A)	2398	−5937	7035	5.0
H(16B)	2861	−5922	5876	5.0
H(16C)	1359	−6482	6590	5.0
H(17A)	449	−3228	6532	5.0
H(17B)	−260	−4546	7226	5.0
H(17C)	1356	−4338	7353	5.0
H(21A)	1778	3445	1413	5.0
H(22A)	−595	3843	618	5.0
H(23A)	−238	2753	−679	5.0
H(24A)	2319	1615	−610	5.0
H(25A)	3622	2057	672	5.0
H(21B)	−940	−1334	2097	5.0
H(22B)	−1547	516	354	5.0
H(23B)	−2629	2365	826	5.0
H(24B)	−2567	1739	2824	5.0
H(25B)	−1600	−587	3638	5.0