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Synthetic approaches to I. The D-ring of oridonin, and II. The A-ring of taxol

Wilson, Phyllis Joy, Ph.D.

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SYNTHETIC APPROACHES TO

I. THE D-RING OF ORIDONIN AND

II. THE A-RING OF TAXOL

BY

PHYLLIS J. WILSON

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of the Doctor of Philosophy, The City of University of New York.

1991

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This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

Nov. 15, 1990
Date

W F Blakemore
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Nov. 15, 1990
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ABSTRACT

Synthetic Approaches to I. the D-ring of Oridonin and II. the A-ring of taxol.

by

Phyllis J. Wilson

Advisor: Professor William F. Berkowitz

This study was directed towards the synthesis of the natural products oridonin and taxol. Methodologies for construction of the bicyclo[3.2.1]octane fragment of the C/D subunit of oridonin were investigated. Towards this end, palladium coupling reactions and free radical carbocyclization reactions were explored.

In designing a synthesis based on free radical cyclization, a major consideration is the regioselectivity of the reaction. When both 5-exo-trig and 6-endo-trig modes of cyclization are possible, five membered ring formation predominates. The results of our

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studies indicate equal formation of both 5 and 6 membered rings following vinyl radical carbocyclization. Factors affecting this unexpected regiochemical outcome were investigated.

The A-ring of taxol was the next synthetic target. This was approached by the electrophilic cyclization of an epoxy olefin for construction of the 6-membered ring.

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Acknowledgements

I am indebted to a number of people who have been instrumental in making completion of this work possible. I would like to thank professor William F. Berkowitz for his constant guidance and assistance. My sincere appreciation to professors R. W. Franck, R. E. Engel, and A. D. Baker for their continued interest in my progress. I would like to thank Dr. K. G. Grohmann for agreeing to read my thesis at such short notice. I am also grateful to Dr. Hoe-Sup Byun for his valuable discussions and suggestions. I would especially like to thank Dr. D. C. Locke who most graciously performed all of the GC/MS analyses which facilitated interpretation of the experimental results. The assistance offered by my fellow graduate students is also gratefully acknowledged. I would also like to thank the Chemistry Department of Queens College which allowed me the use of the chemicals and facilities. The secretaries and stockroom personnel were also especially helpful and for this I am grateful.

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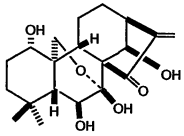
PART I - SYNTHETIC APPROACHES TO THE D-RING OF ORIDONIN

INTRODUCTION

Oridonin[1] **1** is a member of a class of diterpenoids isolated from various Rabdosia (Labiatae) species growing China and Japan. The ent-kaurane structure **2** is common to a large number of these diterpenoids.



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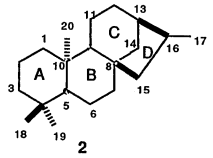

2

"In Japan, the leaves of Rabdosia japonica and R. trichocarpa are used as a common household medicine for gastrointestinal disorders. The drug is called 'enmei-so', which means 'grass effective for prolongation of human life.' In China, some Rabdosia species are used as antitumor and antiphlogistic agents."[1]

Oridonin exhibits a wide variety of anti-tumor activity[1,2] and a preliminary report of clinical trials has been published.[3] Oridonin also shows activity as an antimutagen[4], insecticide[5] and anti-

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bacterial.[1] It's biological activity coupled with it's highly oxygenated framework makes Oridonin an attractive synthetic target.

Although the ent-kaurane structure has incited some synthetic activity,[6] the vast majority of the work on kauranes has been for the purposes of structure elucidation or functional group interconversions[7]. Our model studies involved the investigation of methodologies for the construction of the bicyclo[3.2.1]octane fragment of the C/D subunit of Oridonin. A successful strategy would be applicable to other members possessing the ent-kaurane structure. The synthetic strategies researched included:

A. Free Radical Carbocyclization Reactions
   1. Vinyl radical cyclizations
   2. Radical cyclization reactions of alkynes
   3. Atom transfer cyclization reactions

B. The use of palladium to form carbon-carbon bonds.

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CHAPTER 1

FREE RADICAL CARBOCYCLIZATIONS

Free radical reactions are increasingly being used in Organic synthesis to form carbon-carbon bonds.[8-11] The mildness of the reaction conditions and the (normally) high levels of their chemo-, regio-, and stereoselectivity allow radical reactions to serve as powerful synthetic tools especially in the synthesis of carbocyclic compounds.

Aspects of Organic Free Radical Chemistry

Most organic free radical chain reactions may be divided into three phases outlined below and illustrated in Figure 1 in which A, B, C, and D represent atoms.

1. **Initiation:** Free radicals are generated from neutral species by homolytic bond cleavage.

2. **Propagation:** A new radical is produced by intra- or intermolecular abstraction, addition, or fragmentation.

3. **Termination:** Termination of the chain reaction occurs by recombination or disproportionation of two radicals.

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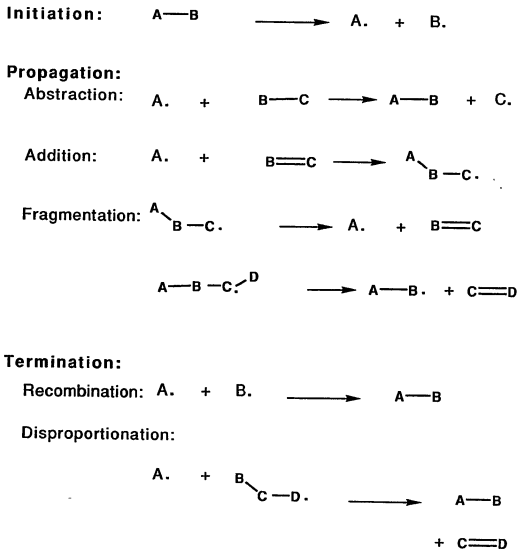

Figure 1. Possible modes of reaction for organic free radicals.

Radical Philicity. The electronic nature of a free radical controls its subsequent reaction(s).[11a] Nucleophilic radicals prefer

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addition to electron-poor alkenes, while electrophilic radicals react with electron-rich olefins. Radicals centered on atoms more electronegative than carbon are considered electrophilic; conversely, atoms less electronegnative than carbon form nucleophilic radicals.[9] The philicity of carbon-centered radicals depends upon substitution. Alkyl, acyl, aryl, and vinyl radicals and those substituted with electron-releasing groups are nucleophilic, while carbon radicals with electron-withdrawing groups are electrophilic.[11a]

Free Radical Addition Reactions

Free radical addition reactions serve as powerful means for inter- and intramolecular carbon-carbon bond formation. Addition to carbon-carbon multiple bonds is favorable energetically since a carbon-carbon σ bond (ca. 88 kcal/mol) is formed at the expense of a carbon-carbon π bond (π CC = 54-59 kcal/mol).[11a] Radical additions are subject to both steric and electronic effects; the relative impact of these factors is dependent upon whether the addition is inter- or intramolecular.

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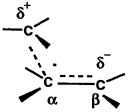
a. Intermolecular Additions: The rate and regioselectivity of addition reactions are affected by substituents on both the attacking radical and on the α- and β-positions of the multiple bond.[11a] The addition of alkyl radicals to alkenes is exothermic and is expected to have an early transition state according to the Hammond Postulate. Calculations have suggested a dipolar complex.[11b] The incoming radical behaves as a nucleophile and assumes a fractional positive charge whereas the olefin becomes fractionally negative.[11c]



The addition rates are determined by the relative energy gaps between the singly occupied molecular orbital (SOMO) of the attacking radical and the highest occupied or lowest unoccupied molecular orbitals (HOMO and LUMO, respectively) of the olefin (Fig.2).[9,11]

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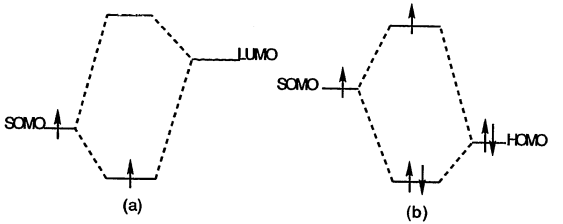

Fig. 2. Dominant orbital interactions for (a) nucleophilic radicals and electron-deficient alkenes and for (b) electrophilic radicals and electron-rich alkenes.

b. Intramolecular Additions: In the intramolecular additons of radicals, there is a marked preference for exo ring closure.[12]

The preferred formation of a less stable primary radical is due to a chairlike transition state[13] and indicates that radical ring closures are subject to stereoelectronic and kinetic rather than thermodynamic control.[11] This transition state permits favorable

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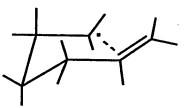
overlap between the radical SOMO and the LUMO of the alkene. The ideal SOMO-LUMO overlap (attack angle ca.109^{o}) is accomodated much better in the 5-exo transition state than in the 6-endo.[10]



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CHAPTER 2

VINYL RADICAL CYCLIZATIONS

Intramolecular addition of a vinyl radical to a double bond is a useful synthetic tool as it affords rings with a double bond at a predictable position. The synthetic utility of vinyl radical cyclization has been demonstrated by Stork[14,15] and others.[16,17]

$Bu_3SnH/AIBN$
C_6H_6, reflux

(1)
ref 14

The regiochemical preference in the cyclization of vinyl radicals parallels that of the alkyl analogues.[14] When both 5-exo-trig and 6-endo-trig modes of cyclization are possible, five membered ring formation predominates.

Our model studies involved the free radical cyclization of a vinyl halide for construction of the bicyclo[3.2.1]octanol derivative of the C/D subunit of oridonin. Synthesis of the required substrate is outlined in Scheme 1.

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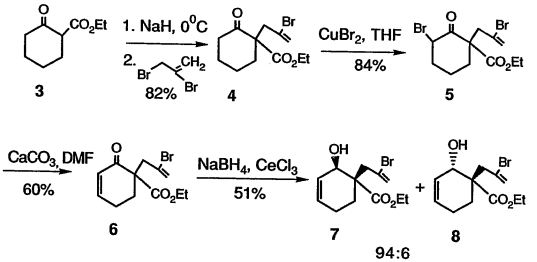
Scheme I



Cyclization results are outlined in Scheme 2. A benzene solution of tributyltin hydride (0.044 M), and a catalytic amount of AIBN were added slowly to a refluxing solution of allylic alcohol **7** (0.025 M) in benzene. Cyclization produced a mixture of products **9** and **10** in a 1:1 ratio (determined by HPLC and GCMS using a carbowax column, on a non-polar methyl silicone column, one component was observed).

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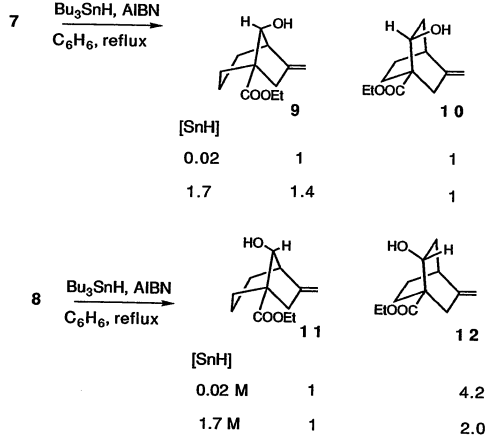
Scheme II



A combination of methods was used to assign the structures of **9** and **10**. Gross structures were determined on the basis of ^1H NMR data including 2D-COSY NMR splitting assignments. The IR spectra indicated hydroxyl (3554 and 3544 cm^{-1}) and exo-methylene functionalities (1654 and 1662 cm^{-1}) for **9** and **10**, respectively.

To obtain further structural evidence, the alcohols were oxidized to the corresponding ketones **13** and **14**.

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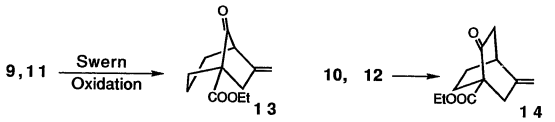

The infrared spectrum of **13** was characteristic of an ester and a 5-membered ring ketone (1760, 1730 cm^{-1}), whereas **14** showed a single carbonyl stretch at 1740 cm^{-1}. ^{13}C NMR DEPT (distortionless enhancement by polarization transfer) spectra were determined to assign carbon multiplicities. A major structural difference between ketones **13** and **14** is the presence of a CHC=O subunit in **13** and a CH_2C=O subunit in **14.** Methine carbons appear in the DEPT spectra of **13** at 54 ppm and of **14** at 38 ppm. Conversely, the methylene carbons of **13** are at 39, 38, 37, and 18 ppm, whereas those of **14** are at 44, 34, 26, and 25 ppm. The methine of **13** at 54 ppm and the methylene of **14** at 44 ppm are considered to be adjacent to carbonyl carbons, which cause a downfield shift of 10 - 14 ppm.[18] Based on these and the X-ray data discussed below, we assigned the bicyclo[3.2.1] and [2.2.2] octanol structures to **9** and **10** respectively.

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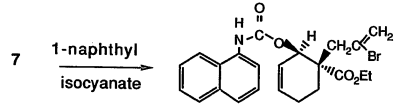
We were interested in determining if the stereochemistry of the OH groups in the allylic alcohols affected the ratio of cyclization products. Consequently, the absolute configuration of alcohol **7** was determined by a single crystal X-ray structure of its urethane derivative **15**. This revealed the OH group of the of the major alcohol epimer (**7**) to be cis to the allyl group.



15

Free radical cyclization of (minor) alcohol **8** produced bicyclo [3.2.1]octanol **11** and bicyclo[2.2.2]octanol **12** in the ratio of 1 : 4.2 (determined by HPLC and GCMS). Oxidation of [3.2.1] alcohol epimers **9** and **11** provided the same ketone **13** as evidenced by IR and GCMS data. Similarly, both [2.2.2] alcohols **10** and **12** afforded ketone **14**.

We considered the pathways by which the bicyclo[3.2.1] and [2.2.2] alcohols could arise (Schemes III, IV).

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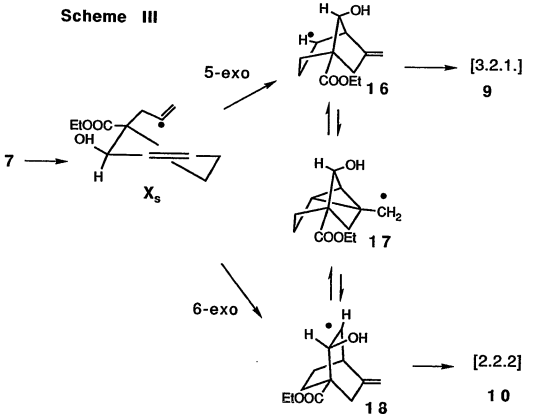
Scheme III



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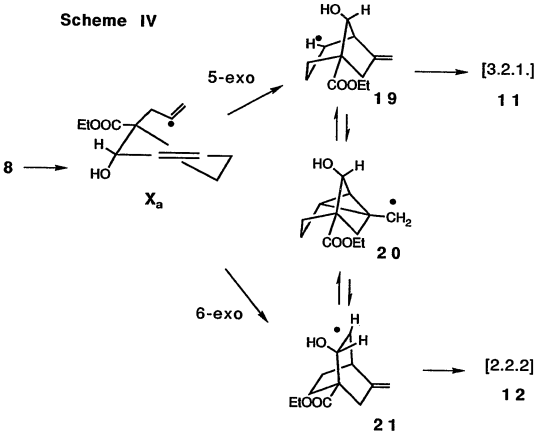
Scheme IV



There are four possiblities: 1) 5-exo-trig ring closure of radical X_s from **7** can generate radical **16**, which could be trapped by a hydrogen atom donor to give [3.2.1] product **9**, or rearrange via the cyclopropylcarbinyl radical **17** to [2.2.2] radical **18**, and lead to a mixture of [3.2.1] and [2.2.2] products. 2) Similarly, cyclization by a 6-exo-trig pathway can also produce a mixture of products via radical **18**. Alternatively, there may be competition between 5-exo-trig and 6-exo-trig modes of cyclization 3) with or 4)

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without cyclopropylcarbinyl rearrangement. The ratio of products could be a reflection of the extent of each mode of cyclization, the ratio of the two intermediate radicals,**16** and **18**, their rate of equilibration, and their relative rates of hydrogen atom capture.

In order to determine if rearrangement were taking place, the reaction was examined using varying concentrations of tributyltin hydride and the product ratios were determined by GCMS using a carbowax column. An increase in the concentration of stannane is expected to result in the capture of the initially formed bicyclic radical, thereby minimizing any rearrangement to **17**. (This procedure was suggested to us by Prof. D. Curran). At concentrations of tin hydride between 0.017 M and 0.028 M, the ratio of products **9** (3.2.1) and **10** (2.2.2) from allylic alcohol **7** remained at 1 : 1. Even use of 1.7 M tin hydride resulted in a ratio of only 1.4 : 1 (plus 50% of the reduced starting material). This contrasts with the results of Stork[19a] (eq 2) in which the ratio of 5-exo to 6-endo product for formation of monocyclic products was found to increase with stannane concentration.

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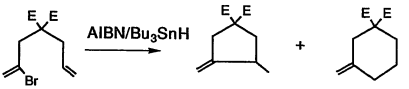

(2)

At 1.7 M stannane concentration, allylic alcohol **8** gave cyclized products in the ratio of 2 : 1 ([3.2.1] : [2.2.2]), with 75% of the reduced starting material.

These data are consistent with the first alternative mechanism, if interpreted as follows. Rules summarizing the regiochemistry of radical reactions[8] illustrate that 5-exo-trig ring closures predominate over the 6-endo- (or 6-exo-) mode. Vinyl radical additions to alkenes result in the formation of homoallylic radicals which may rearrange unimolecularly at very rapid rates (10^5 - 10^8)[19] via cyclopropylcarbinyl radicals.[19a,20] Hydrogen atom transfer to alkyl radicals by tin hydrides is a second order reaction and occurs at 0.74×10^6 for cyclohexyl radicals.[21] Thus, 1.7 M Bu_3SnH is sufficient to capture the initial radicals at a rate which may be competitive with rearrangement, but 0.025 M Bu_3SnH is not.

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One may then assume: 1) All bicyclic radicals, once formed, rearrange rapidly via a cyclopropylcarbinyl intermediate (eg. **17**). 2) At equilibrium (low Bu_3SnH concentration), the concentrations of **16** and **18** (from **7**) are equal, as are those of **19** and **21** (from **8** via X_a, Scheme III). The calculated[22] enthalpies of formation of **9-12** vary by no more than 1 Kcal. 3) Tin hydride capture of radicals **16, 18** proceed at similar rates, but the reaction of **19** is slower than that of **21** due to steric congestion caused by the **syn**-hydroxyl group in **19**. Thus the ratio of **9** to **10** would close to 1, while that of **12/11** should be greater than 1. 4) The rate of equilibration of **19** and **21** (via **20**) is slower than the rate of equilibration of **16** and **18** (via **17**). If this were true, then a change to a high Bu_3SnH concentration could increase the ratio of the former pair (eg. from 1/4.2 to 1/2), but not the latter, due to competitive capture of the radical (**19**) initially formed by 5-exo-trig ring closure. This data is also consistent with formation of <u>only</u> **16** (and **19**), <u>both</u> **16** and **18** (**19** and **21**), but <u>not</u> **18** (**21**) alone.

If the ratio of products were determined only by the relative

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rates of formation (and capture) of **16** and **18** (or **19** and **21**), with no intervening rearrangement, then the product ratios should not vary with tin hydride concentration. The rate constant for cyclization of a vinyl radical is the same order of magnitude as that for hydrogen abstraction from stannane by a vinyl radical (3×10^8).[8] At high tin hydride concentrations (1.7 M), cyclization is therefore accompanied by reduction.

The influence of the nature of the halide on the efficiency of carbocyclization was investigated. Both the ease of abstraction of the halogen and the energies of the HOMO of the carbon-halogen bond fall in the order I>Br>Cl.[23] Preparation of the vinyl iodide used in this study is outlined below.

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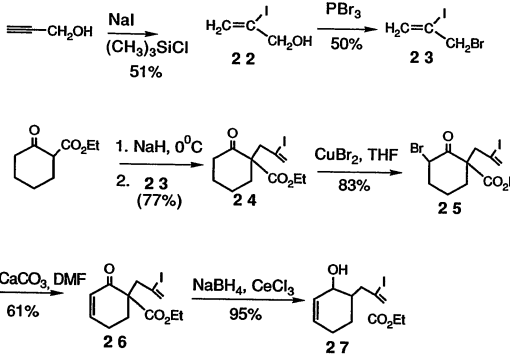
Scheme 5



Radical cyclization of vinyl iodide **27** afforded two products each possessing a mass of 210 with fragmentation patterns similar to those of the [3.2.1] and [2.2.2] bicyclo alcohols **9** and **10** respectively. The products were in the ratio of 1 : 1 as determined by HPLC analysis. These results are identical to those obtained for the cyclization of the vinyl bromide.

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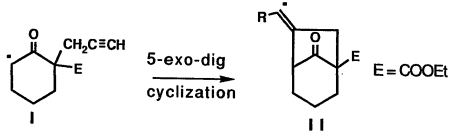
CHAPTER 3

RADICAL CYCLIZATION OF ALKYNES

Vinyl radical cyclization of allylic alcohol **7** afforded a mixture the desired bicyclo[3.2.2]octanol **9** and bicyclo[2.2.2]octanol **10**. The formation of five-membered rings predominates when CC-triple bonds are used as intramolecular traps.[9] Several groups have utilized the addition of alkyl radical onto alkynes to construct functionalized five membered rings.[24] It occured to us that formation of the [3.2.1] system could be achieved by the intramolecular addition of a radical to a CC-triple bond. The α-bromoketone **29** would serve as the precursor to the radical required for cyclization (scheme 6).

Scheme 6



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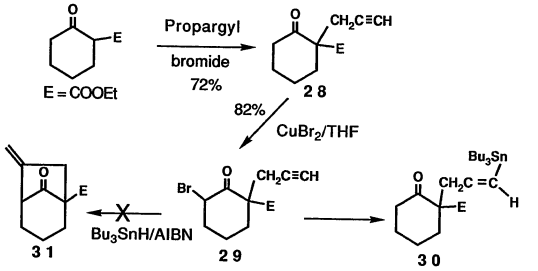

The IR data of the cyclization product indicated disappearance of the CC-triple bond and GCMS analysis showed incorporation of tin in the molecule. We concluded that the tributyltin hydride had added across the CC-triple bond.

In order to minimize the addition of tributyltin hydride to the CC-triple bond, and to facilitate ring closure, the trimethylsilyl group was introduced at the terminal position of the alkyne (scheme 7).

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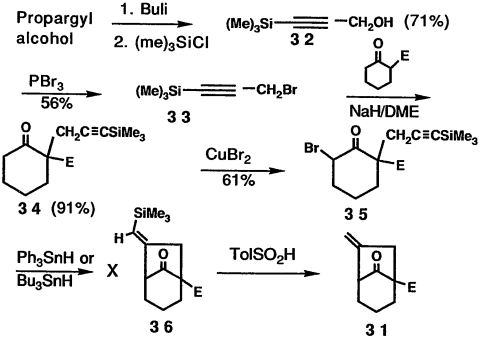
Scheme 7



Desilylation[24c] of the vinylsilane **36** resulting from radical cyclization of **35** would produce the desired product **31**. However, radical reaction of bromoketone **35** using either tributyltin hydride or triphenyltin hydride resulted in reduction of the bromide and regeneration of compound **34** in 60% and 72% yield, respectively. This was evidenced by the NMR, IR, GCMS and analysis data.

Similar to the intramolecular addition of radicals to CC-double bonds, the addition to alkynes is subject to stereoelectronic

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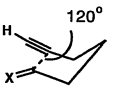
control.[25] A criteria for cyclization onto an alkyne is that the incoming radical must approach along the correct vector, ie at an angle of ca 120° with the axis of the single bond from the alkyne.[26]



III

IV

Failure of radical I to cyclize may be due to the strain involved in achieving the correct geometry.

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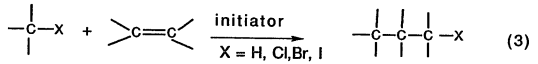
CHAPTER 4

ATOM TRANSFER CYCLIZATION REACTIONS

The results of our studies on the radical cyclization reactions of alkynes **29** and **35** indicated that the radical generated α to the carbonyl group was reduced by the tin hydride rather than cyclized. The trapping of stabilized radicals by hydrogen abstraction from the reagent before cyclization is a common problem encountered with organotin hydrides. To avoid the presence of a hydrogen atom donor, an alternative method of initiation was investigated. The atom transfer addition of a C-X bond (where X is a univalent atom) across a double bond (eq 3) is a fundamental reaction of free radicals which results in the formation of C-C bonds.[10]



(3)

Curran[10, 27] has demonstrated the synthetic utility of this method. The free radical isomerization of unsaturated α-iodo carbonyls resulted in the formation of cyclic γ-iodo carbonyls (eq 4).[27a]

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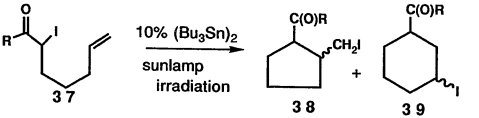
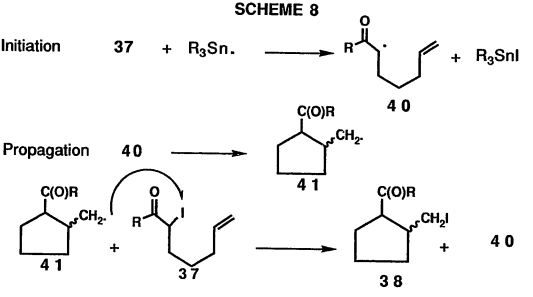


(4)

37a	R = OMe	93	:	7
b	R = OMe, I = Br	90	:	10
c	R = t-Bu	74	:	26

A standard free radical chain reaction (outlined below) is proposed for the isomerization.[28]

SCHEME 8



Abstraction of an iodine atom by a tri-n-butyltin radical initiates the chain. Cyclization is followed by iodine atom transfer from a

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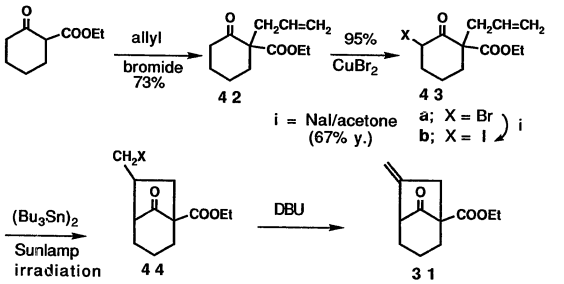
molecule of the starting iodide to the intermediate cyclic radical.

In order to investigate the feasibility of this methodology in construction of the bicyclo[3.2.1]octanone system the following model study was carried out (Scheme 9).

Scheme 9



Isomerization of the α-halo ketone followed by dehydrohalogenation would constitute a facile entry to the bicyclo[3.2.1]octanone **31**. Sunlamp irradiation[27a] of a benzene solution of α-bromo ketone **43a** and hexabutylditin produced no change in the molecule (78% recovery) as evidenced by the ^{1}H NMR and IR data. Atom transfer is

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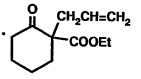
a key step in the free radical chain reaction (scheme 8). Since bromine transfer is slower than iodine transfer,[29] the corresponding α-iodo ketone was prepared and subjected to the above isomerization conditions. The α-iodo ketone was similarly unaffected following sunlamp irradiation (54% recovery).



V

Failure of compounds **43a** and **43b** to cyclize can be understood if one assumes that the α-keto radical is delocalized into the carbonyl[30] and thus delocalization prevents the radical **V** from assuming the favored transition state for 5-exo cyclization. The ·C-CO bond has partial double bond character which is incorporated into the 5-membered ring on cyclization.

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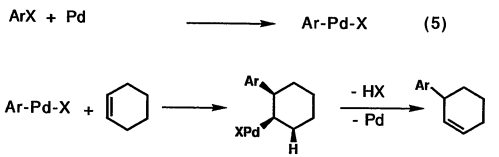
CHAPTER 5

PALLADIUM MEDIATED CARBON-CARBON BOND FORMATION

The Heck reaction[31] which involves addition of an aryl- or alkenyl-palladium bond to alkenes followed by dehydropalladation (eq 5) is a well established method for carbon-carbon bond formation.



Palladium catalysed reactions are increasingly being used in organic synthesis[32] due to the mildness of the reaction conditions and the potential for generating carbon-carbon bonds in a single step.

Similar to aryl or vinyl halides, alkyl halides can oxidatively add to palladium to afford an alkyl metal complex. Mori and Ban[33] have shown that α-halo carbonyl compounds possessing an internal double bond undergo cyclization in the presence of a palladium

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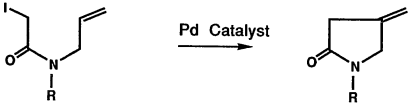
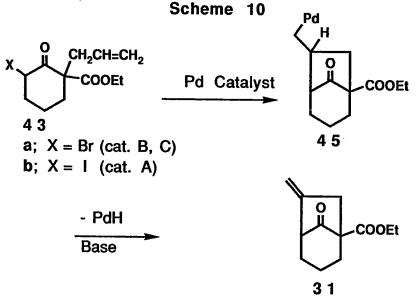
catalyst (eq 6).



(6)

These results prompted us to develop palladium catalyzed cyclization procedures for preparing the bicyclo[3.2.1] octanone system (scheme 10).

Scheme 10



Catalyst system:

(A) $Pd(PPh_3)_4$, proton sponge (bis(1,8-dimethylamino)-naphthalene), HMPA. (B) $Pd(OAc)_2$, Ag_2CO_3, PPh_3, CH_3CN. (C) $Pd(OAc)_2$, CH_3CN,

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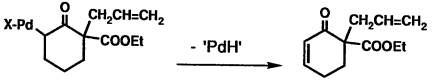
P(o-tolyl)$_3$, Et_3N, sealed tube, 110°C.

Catalyst A[33]

To regenerate the metal catalyst from the hydride metal complex, a base is required. Since Et_3N should afford the ammonium salts of the starting material, the reaction was carried out in the presence of bis(1,8-dimethylamino)-naphthalene (proton sponge) as the base. The α-iodo ketone **43b** (40% recovery) remained unchanged following the reaction using catalyst system A.

Catalyst B[34, 35]

Use of catalyst system B gave a mixture of several components as shown by HPLC analysis. Formation of the enone is a possible side reaction due to β- hydride elimination.



Catalyst C[36]

Treatment of the α-bromo ketone with catalyst C resulted in reduction of the carbon-halogen bond, affording the starting ketone

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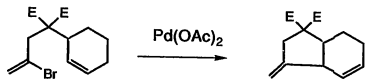
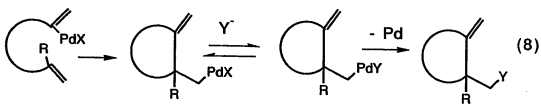
42 (in 45% yield) as evidenced by the NMR, IR and GCMS data.

The intramolecular version of the Heck reaction has been utilized to produce carbocycles.[37] This reaction is frequently accompanied by migration of the olefin double bond following 'PdH' elimination (eq 7, ref. 37c).



E = COOEt (7)

Introduction of an external hydride ion source has been found to prevent regeneration of the olefin[38] (eq 8).



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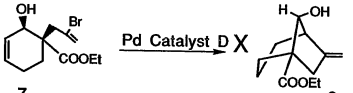
Scheme 11

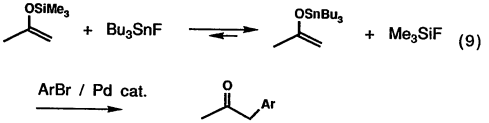


7 9

Catalyst D: $Pd(OAc)_2$, PPh_3, pyrrolidine, HCOOH, CH_3CN, 80°C.

Intramolecular Heck reaction of **7** in the presence of HCOOH as a hydride source was expected to produce the bicyclo[3.2.1] alcohol **9** (scheme 11). Alcohol **7** was unaffected (60% recovery) by treatment with catalyst D as evidenced by the ^1H NMR and IR spectral data of the product.

Kuwajima and Urabe[39] have demonstrated that reaction of silyl enol ethers with aryl bromides in the presence of a palladium catalyst results in coupling. The mechanism of the reaction is postulated to involve in situ generation of an α-stannyl ketone via silyl/stannyl exchange followed by arylation with the aryl bromide.



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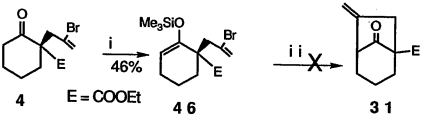
It was expected that vinyl bromides would react in a similar manner to aryl bromides by adding oxidatively to palladium. The simplicity of the procedure prompted us to consider an intramolecular version of this coupling reaction (scheme 12).

Scheme 12



4 E = COOEt 46 31

(i) Et_3N, Me_3SiCl; (ii) Bu_3SnF, $PdCl_2(P(o\text{-}MeC_6H_4)_3)_2$ benzene, reflux.

Silyl enol ether **46** survived the reaction conditions to be recovered in 58% yield. The unreactivity of the silyl enol ether may arise from steric repulsion between the olefinic moiety and the tributyltin fluoride. Kuwajima successfully applied this procedure to acyclic silyl enol ethers while the cyclic analogues gave low yields of coupled products.

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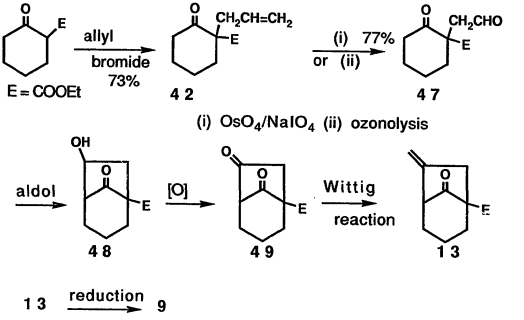
CHAPTER 6

INTRAMOLECULAR ALDOL CONDENSATION - AN ALTERNATE APPROACH TO THE BICYCLO[3.2.1]OCTANOL SYSTEM

Vinyl radical cyclization of allylic alcohol **7** afforded two products which originally were tentatively assigned as bicyclo[3.2.1] octanol **9** and bicyclo[2.2.2]octanol **10**. In order to confirm the structure of **9**, its synthesis by an alternate procedure (outlined in scheme 13) was attempted. Comparison of the spectral data would assist in confirming its structure.

Scheme 13



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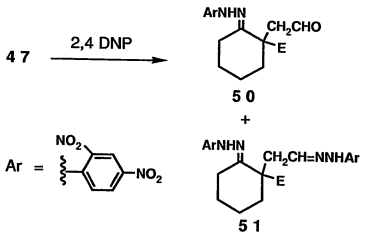

The IR spectrum (CCl_4, 5%) of keto aldehyde **47** showed the presence of an hydroxyl group. However, at lower concentrations (1%) the hydroxyl group was not observed. This was attributed to equilibration between **47** and the bicyclic compound **48**. Under acidic conditions (conc. HCl), the aldol condensation was not successful. When NaOEt/EtOH was used to perform the aldol condensation, the NMR of the product indicated disappearance of the aldehydic proton. The infrared spectrum was characteristic of a 5-membered ring ketone (1753), suggesting that cyclization had taken place. However, examination of the GC/MS revealed that the product contained a mixture of eight components. The major component constituted 49% of the mixture and showed a m/z of 212

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which would correspond to the desired product. The masses of the other components were all in excess of this value. All attempts at performing the aldol condensation resulted in a mixture of products and the synthesis was subsequently abandoned.

Due to its instability, the elemental analysis of ketoaldehyde **47** was performed on the 2,4 dinitrophenylhydrazone derivative. The NMR data of the product showed that the aldehydic and aromatic protons were in the ratio of 1 : 3 indicating formation of the mono hydrazone derivative **50**. However, GC/MS analysis indicated the presence of the bis hydrazone derivative **51** (m/z 572). The elemental analysis results did not correspond to either **50** or **51**. We concluded that the product contained **50** with a trace amount of compound **51**.

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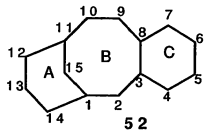
CHAPTER 7

PART II - SYNTHETIC STUDIES DIRECTED TOWARD THE A-RING OF TAXOL

INTRODUCTION

Taxanes[40-44] are a class of diterpenoids isolated from the bark of several species of the evergreen, yew (genus Taxus, family taxaceae).[43,45] A common structural feature of these diterpenoids is the taxane skeleton **52** (tricyclo[9,3,1,0]pentadecane.[42]



52

The structures of representative members of this class of diterpenoids are shown below.

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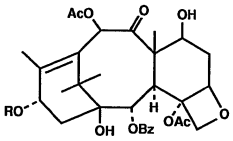


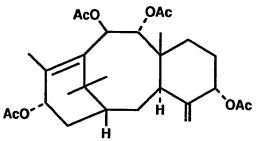
53 R = $C_6H_5CONHCH(C_6H_5)CHCO-OH$

Taxol

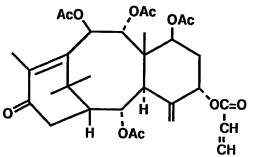
54 R = $CH_3CH{=}C(CH_3)CONHCH(C_6H_5)CHCO-OH$

Cephalomannine

55 R = H - Baccatin III



56 Taxusin



57 Taxinin B

Additional structural features which are common to this class of compounds include: 1). methyl groups at C-8 and C-12. 2). the gem-dimethyl group at the C-15 bridge. 3). the bridgehead double bond at C-11,12. 4). the trans ring fusion stereochemistry of the bicyclo[6.4.0] B/C subunit. 5). oxygenation at C-2, 9, 10 and 13 (the

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only exception is Taxusin which bears no functionality at C-2).

Several members of the taxane diterpenoids (eg. Taxol **53** and Cephalomanine **54**) exhibit anti-leukemic and anti-tumor activities and have shown potential as chemotherapeutic agents.[41-49] The taxanes have incited much synthetic activity [50a-m] due to their biological significance and the challenges presented by the stereochemical complexity of the taxane framework.

A structural feature of the Taxol A-ring is a cyclohexane ring possessing a gem-dimethyl group. A search of the literature revealed that several groups have successfully constructed this type of system (schemes 14 - 23). Electrophilic polyolefin cyclization[51] serves as the basis of many of these syntheses.

1. Bromonium ion induced cyclization of geranyl derivatives have been investigated by J. Faulkner[52] and Y. Kitahara.[53] Treatment of geranyl acetate with a mixture of Br_2 and $SnBr_4$[52] afforded the cyclized bromoacetate **59** in modest yield (scheme 14). Competitive addition of Br_2 to the carbon-carbon double bond was also observed.

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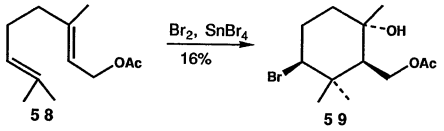
Scheme 14



58 59

2. T. R. Hoye[54] has demonstrated the feasibility of mercuric ion initiated cyclization of 1,5 dienes (Schene 15). An intramolecular nucleophile serves to stabilize and capture the intermediate carbocation. It was found that carboxylic acids, ketones, and alcohols are effective trapping nucleophiles whereas acetate esters gave complex mixtures of products. Cyclization of homogeranic acid was accomplished by treatment of the diene with mercuric trifluoroacetate. The resulting organomercury trifluoroacetate was subsequently transformed to the alkyl bromide **63** or the hydrocarbon **64**.

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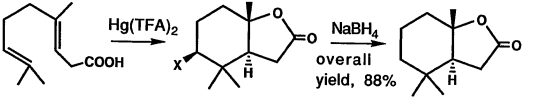
Scheme 15



60 64

61 X = HgTFA
62 X = HgBr } KBr
63 X = Br } Br2

3. Initiation of ring closure by a carbonium allows for the simultaneous introduction of a functional group at the electrophilic terminus of cyclization (Y. Kitahara[55]). The reaction of geranyl acetate with an equimolar mixture of a $AlCl_3$-AcCl complex in methylene chloride at 0 °C gave the acylation product **65** which was quantitatively converted to the unsaturated compound **66** by dehydrohalogenation. The use of a $SnCl_4$-AcCl complex in nitromethane provided direct entry to the unsaturated product **66** (scheme 16). Extensive experimentation in the laboratory of W. F. Berkowitz have failed to reproduce this reaction.

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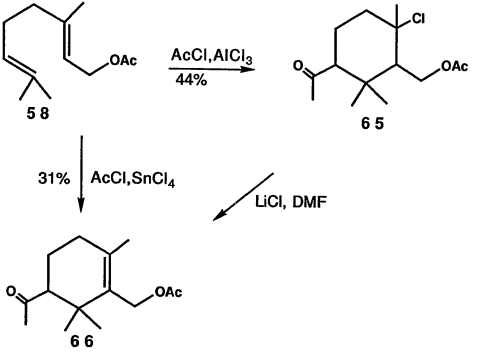
Scheme 16



4. The use of ogranoselenium reagents to induce cyclization 0f 1,5 dienes has been demonstrated by F. Rouessac.[56] Treatment of homogeranic acid with phenyl selenyl chloride followed by trifluoroacetic acid afforded the selenolactone **67** (scheme 17). The unsaturated lactone **68** was obtained by subsequent oxidative elimination.

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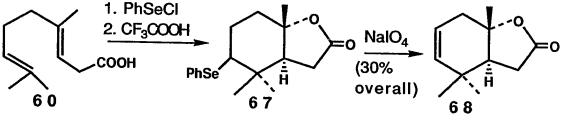
Scheme 17



5. L. Weiler et al[57] have shown that unsaturated β-keto esters undergo electrophilic cyclization in the presence of sulfenylating or selenylating reagents (scheme 18). Treatment of β-keto ester **69** with a complex of benzeneselenyl chloride and $AlCl_3$ afforded the cyclized product **71a**. Alternatively, the reaction of **69** with benzenesulphenyl chloride and $AlCl_3$ provided the addition product **70** which on refluxing in silica gel/CH_2Cl_2 underwent cyclization to **71b**. The cyclized products were further elaborated to the unsaturated ester **73**.

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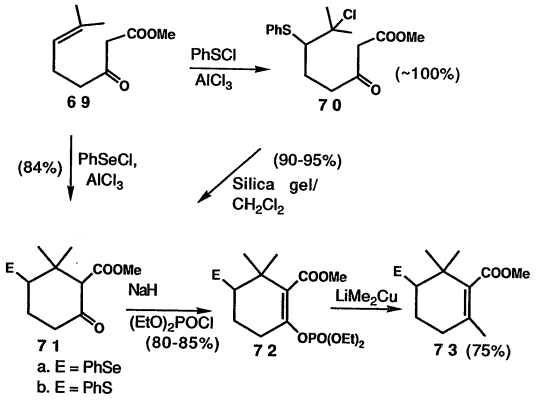
Scheme 18



6. Selenium-assisted carbocyclization reactions have been investigated T. Kametani et al[58] (scheme 19). Their results demonstrate that it is possible to convert unsaturated selenyl derivatives to the cyclic isomers under acidic conditions. The β-hydroxy selenyl compound **75** required for cyclization was prepared by epoxidation of geranyl acetate followed by treatment with phenylselenium anion. Cyclizaton of **75** to produce the selenyl alcohol **77** was accomplished in the presence of trifluoroacetic

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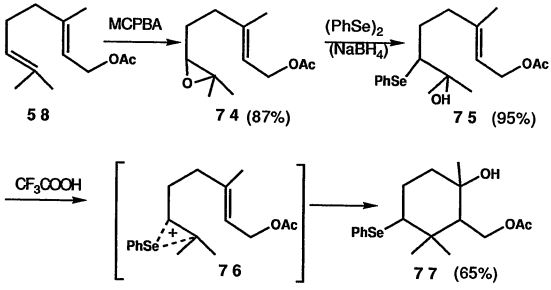
acid. Success of the cyclization was attributed to stabilization of the carbocation (generated by acid treatment of **75**) via a seleniranium intermediate **76**.

Scheme 19



58 **74** (87%) **75** (95%)

76 **77** (65%)

7. Initiation of ring closure is also possible by the electrophilic opening of a terminal epoxide. L. Weiler et al[59] have demonstrated that epoxy allylsilanes undergo stereoselective cyclization on treatment with Lewis acids to give cyclic alcohols (Scheme 20). They found that the allylsilane has a pronounced effect on activating

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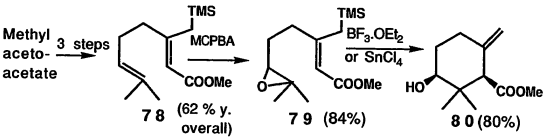
the olefin to undergo cyclization and produce the exomethylene regioselectively. Starting from methyl acetoacetate, the allylsilane **78** was prepared in three steps with an overall yield of 62%. Selective epoxidation of **78** with MCPBA afforded the epoxy allylsilane **79** which was cyclized with either stannic chloride or boron trifluoride etherate.

Scheme 20



8. The electrophilic cyclization of epoxy allylsilanes was applied by T. Frejd et al[60] to the synthesis of of an optically active A-ring synthon of Taxol (scheme 21). The required epoxy allylsilane, prepared from L-arabinose, was cyclized on treatment with $BF_3.OET_2$. The exomethylene functionality generated on cyclization was isomerized to produce the α,β–unsaturated ester **84** on heating in DBU.

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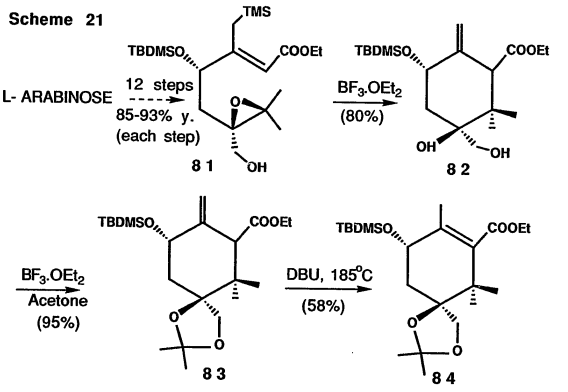
Scheme 21



9. Studies performed by F. Rouessac et al[61a] (Scheme 22) illustrated that electrophilic cyclization of epoxy olefins can lead to epoxide rearrangement. Starting from geraniol, epoxide **86** was prepared by selective epoxidation of geraniol pivalate with MCPBA. Treatment of a solution of **86** in CH_2Cl_2 with $SnCl_4$ at 0 °C afforded the bicyclic ether **87** which was deprotected to produce the alcohol **88**. In this paper, Rouessac made reference to an alternate method described by Y. Yamada et al [61b] for generating the

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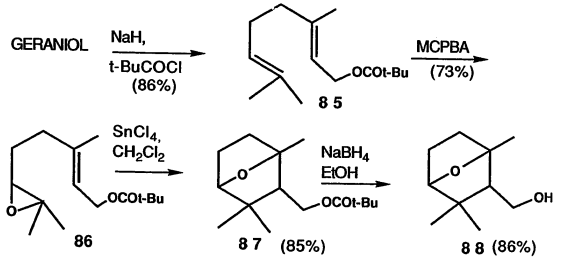
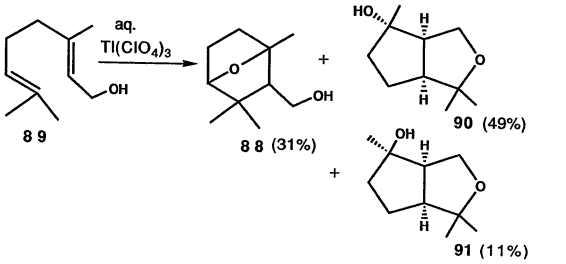
bicylic alcohol **88**. The reaction of thallium (III) perchlorate with geraniol afforded the bicyclic ether **88** together with two other carbocyclic products (scheme 23).

Scheme 22



Scheme 23



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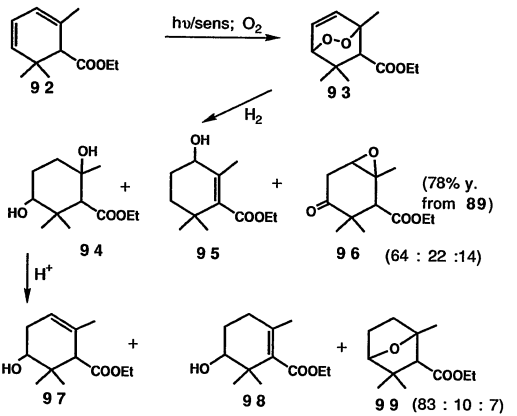
10. An alternate approach to this type of substituted cyclohexane system has been reported by R. Kaiser et al[62] (scheme 24). Photooxidation of ethyl safranate produced the peroxide **93** which on reduction afforded the dihydroxy ester **94** as the major product. Dehydration of **94** with p-toluene sulfonic acid provided the unsaturated hydroxy ester **97**.

Scheme 24



A major consideration in designing the synthesis of the Taxol

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A-ring is the presence of a tertiary hydroxyl group at C-1. As the preceding examples illustrate, cyclization of an epoxy olefin leads to the formation of a ring bearing an OH functionality. This protocol is suitable for construction the A-ring of Taxol as the resulting alcohol would be available for further elaboration to the B, C and D-rings.

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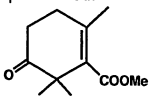
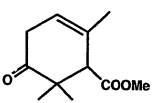
CHAPTER 8

RESULTS AND DISCUSSION

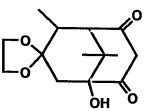
Our strategy for assembling the taxane skeleton requires synthesis of the substituted cyclohexenone **100** or **101** with the double bond in either position as the A-ring synthon. This would be further elaborated to provide the A/B ring synthon **103** via compound **102**.



100



101



102

Condensation of **103** with the C-ring synthon **104** would form the cyclic carbamate **105**. Intramolecular photocycloaddition would give the intermediate **106** which on hydrolysis would undergo fragmentation and ring expansion to provide **107** as the tricyclic carbon skeleton of taxol. The rationale for formation of the cyclic carbamate is to provide an anchor for the intramolecular photocycloaddition of **105** and to enolize the diketone of **102** in the required direction.

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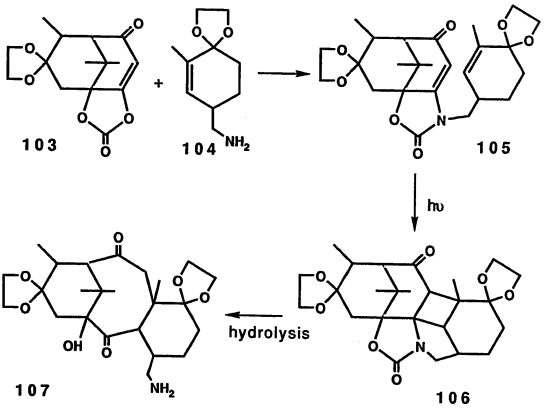

The next required step of the synthesis would be construction of the oxetane D-ring. Elimination of the aminomethyl group should afford an exocyclic double bond which could be converted to the allylic alcohol **109** by treatment with singlet oxygen[63] or by epoxidation followed by base catalyzed rearrangement.[64] The allylic alcohol **109** can be converted to the diol-acetate **111** and subsequently to the desired oxetane **112** according to the procedure reported by our laboratory[65] as shown in scheme 25.

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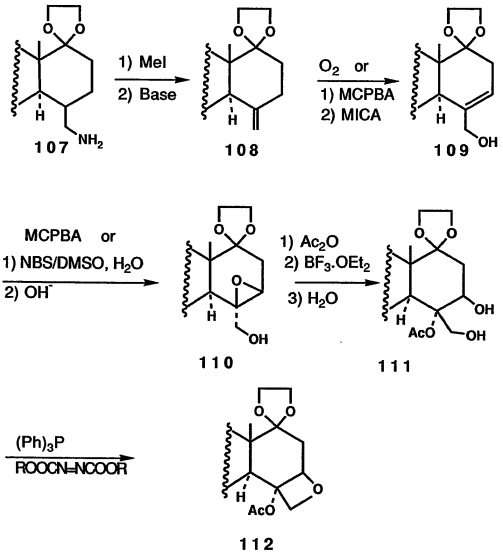
Scheme 25



Construction of the A-ring Synthon **101**.

Our approach to the A-ring synthon was based on the electrophilic cyclization of an unsaturated epoxide for construction of the 6-membered ring (examples of this were shown in the previous

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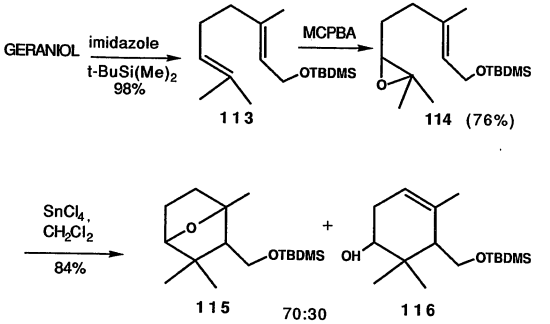
section). Starting from geraniol, the epoxy olefin **114** was prepared by selective epoxidation of the t-butyldimethylsilyl protected alcohol **113** (scheme 26). Lewis acid catalysed cyclization[66] afforded two products which were separated by HPLC and identified as the bridged epoxide **115** and the unsaturated alcohol **116** in a ratio of 70:30, respectively. Complete separation of the two isomers by column chromatography could not be achieved.

Scheme 26



The results of F. Rouessac[61a] indicated that cyclization of epoxy geranyl pivalate **86** resulted in exclusive formation of the bridged

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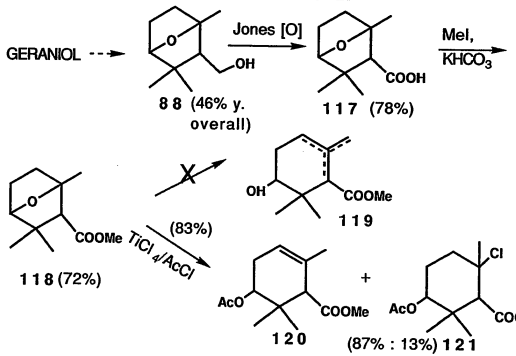
epoxide **87** (scheme 22). This was of interest to us as we expected to be able to open the bridged epoxide at a later stage in the synthesis to generate an unsaturated alcohol of the structure **119** (scheme 27). Consequently, the epoxy alcohol **88** was prepared according to the procedure outlined by Rouessac[61a] (scheme 22) and further elaborated as shown in scheme 27.

Scheme 27



Precedent for cleavage of an oxide bridge is provided by the conversion of compound **122** to **123** with lithium hexamethyl-

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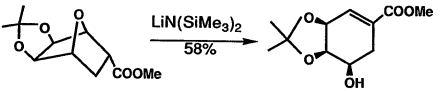
disilazide.[67]



122 123

We tried, unsuccessfully to open the epoxide **118** under both basic ($LiN(SiMe)_2$[67], LDA[68] or NaOMe) and acidic ($BF_3.OEt_2$)[66] conditions. In each case the starting material remained unchanged following the reaction. Studies performed previously in our laboratory illustrated that the cleavage of an acetal was acheived with a mixture of titanium tetrachloride and acetyl chloride.[69] Applicaton of this protocol to the epoxide **118** afforded two compounds determined by GC/MS to be in a ratio of 87:13. The minor product, which was not isolated, showed a m/z value of 241 consistent with loss of Cl from structure **121**. A value of 209 corresponding to a loss of OCH_3 from **120** was observed for the major product which was isolated by HPLC and characterized. Examination of the ^1H NMR indicated an olefinic resonance (1 H) at 5.50 ppm. In addition, methine protons appeared as a singlet at 3.00

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ppm and as a double doublet at 4.73 ppm. Methyl singlets appeared at 0.99, 1.02, 1.66, 2.05 and 3.72 ppm. The signal at 1.66 was indicative af a vinylic methyl group. A multiplet (2 H) corresponding to allylic methylene protons appeared between 2.10 and 2.40 ppm. The IR spectrum showed a carbonyl absorption at 1740 cm^{-1}. The HRMS gave a mass of 239.1267 $(M-H)^+$ (calcd. 239.1283) while the GC/MS analysis showed a peak at m/z 209 consistent with (M^+ - OCH_3). Based on the above data, the major product was assigned the structure **120**.

At this stage, we considered two options, we could convert compound **120** to ketone **101** by hydrolysis of the acetoxy group followed by oxidation (scheme 28). Oxidation of the olefin would result in formation of the diketone **124**. Selective ketalization of the less hindered ketone should afford **125** which would provide entry to the A/B ring synthon. Alternatively, we could first oxidize the olefin to a carbonyl group which would be protected as the ketal **127** (scheme 29) and subsequently transformed to the A/B ring synthon.

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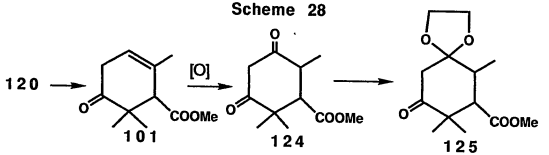
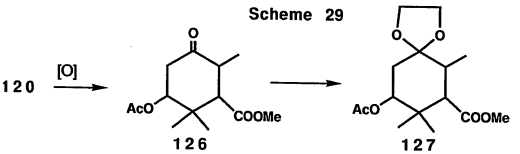
Scheme 28



Scheme 29



We proceeded with the second option as this would afford a single carbonyl group available for ketalization. This required finding a procedure for conversion of an olefin to a carbonyl. Our model studies were performed on 2-methylcyclohexene. We explored the following reactions:

(1). The Wacker oxidation.[70] This gave a mixture of unidentifiable products.

(2). Epoxidation/rearrangement. Alkenes have been converted to carbonyls in a single step by the in situ generation of an epoxide

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followed by rearrangement.[71,72] However, our results on treatment of 1-methylcyclohexene with H_2O_2/HCOOH[72] indicated that the epoxide was opened by the addition of HCOOH. Both an hydroxyl group (3500) and a carbonyl group (1725 cm^{-1}) were present in the IR spectrum. The ^1H NMR data indicated a methyl singlet at 1.3 and an aldehydic proton at 8.2 ppm. The GC/MS showed a m/z value of 158. These data were in accord with the proposed structure **128**.

128

(3). Epoxidation followed by rearrangement. Epoxides have been known to undergo rearrangement to the carbonyl on treatment with a variety of salts.[73] The epoxide of 1-methylcyclohexene was prepared by reaction with MCPBA and treated with $MgBr_2$.[73a,b] The IR spectrum of the product showed an hydroxyl absorption and no carbonyl. Without further characterization, it was assumed that the epoxide had opened to form the bromohydrin or diol. By refluxing the

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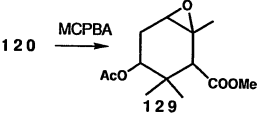
isolated epoxide with anhydrous $LiClO_4$ in benzene[73c] 2-methylcyclohexanone was obtained. The GC/MS gave the correct m/z value of 112, the IR spectrum showed a carbonyl at 1715 cm^{-1} and the methyl group appeared as a doublet at 1.1 ppm in the ^1H NMR.

Encouraged by the above results for the $LiClO_4$ induced epoxide rearrangement, we proceeded to convert **120** to the epoxide **129**. The reaction of **120** with MCPBA gave a mixture of products of which compound **129** constituted 17% (determined by GC/MS analysis). There were no vinylic protons in the ^1H NMR indicating that no starting material remained, however, this was not a clean reaction. In search of a more efficient epoxidation procedure, we considered the use of magnesium monoperphthalate (MMPP),[81] a mild oxidizing agent. As a model study, 1-methylcyclohexene was treated with MMPP. However, only the starting material was recovered following this reaction and this route was consequently abandoned.



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Next, we explored the use of hydroboration/oxidation in order to transform the C-C double bond of **120** to a carbonyl. Since boranes are known to react much faster with C-C double bonds than with esters,[74] we did not anticipate reduction of the methyl ester or the acetoxy group of **120**. Hydroboration of **120** using BH_3.DMS[75] was followed by pyridinium chlorochromate oxidation[76] of the organoborane. The ^1H NMR of the product indicated that a mixture was obtained. There were two signals for the methoxy group appearing at 3.4 and 3.5 ppm. In addition, the signal at 2.1 ppm corresponding to the acetoxy group was not very prominent suggesting it was affected during the reaction. The appearance of vinylic protons as doublets at 5.8 and 6.8 ppm indicated the presence of an enone. GC/MS analysis indicated a mixture of which two components, constituting 73% and 9% of the mixture, gave the same m/z value of 196. This value is consistent with either enone **130** or loss of HOAc from **131**.

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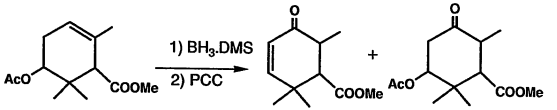
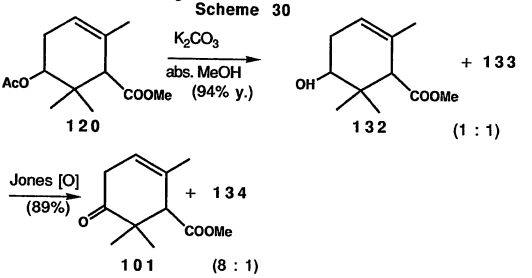


120 130 131

It was evident from these data that hydroboration/oxidation of **120** was accompanied by the loss of HOAc. As no method appeared to affect the double bond cleanly, it was therefore decided to convert compound **120** instead to **101** (scheme 30) and proceed with the synthesis of the A/B ring synthon **102**. The alkene would be oxidized at a later stage.

Scheme 30



120 132 (1 : 1) 101 (8 : 1)

Hydrolysis of the acetoxy group was performed with a mixture of K_2CO_3 in absolute methanol to afford approximately equal amounts

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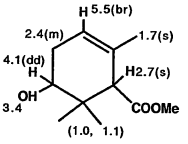
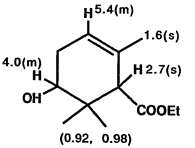
of compound **132** and an unknown compound **133** which were isolated by HPLC. The ^{1}H NMR data of compound **132** and the known ethyl ester analog **97** were compared. Assignments are shown below.



132



97

A carbonyl and an hydroxyl absorption at 1720 and 3490 cm^{-1} respectively, appear in the IR spectrum of **132**. Similar absorptions appear at 1730 and 3460 cm^{-1} for compound **97**. The above data and an M^+ peak at m/z 198 in the GC/MS spectrum are in accord with the proposed structure of **132**. However, the structure of **133** was not evident. The ^{1}H NMR spectrum indicates the absence of any vinylic protons, however it also showed a methine singlet at 2.9 ppm corresponding to a proton α to the COOMe group. This would suggest that the double bond had not isomerized to form the α,β unsaturated ester. In addition to an hydroxyl group, there were two carbonyl

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absorptions at 1715 and 1740 cm^{-1} in the IR spectrum. Similar to compound **132**, the GC/MS analysis of **133** showed a m/z value of 198.

Jones oxidation[77] of the mixture of alcohols **132** and **133** provided ketones **101** and **134** which were separated by HPLC in a ratio of approximately 8:1, respectively. The fact that **101** was obtained as the major product would suggest that both alcohols **132** and **133** were oxidized by Jones reagent to produce **101**. Compound **101** showed a vinylic proton at 5.7 ppm in its ^1H NMR spectrum and two carbonyl absorptions at 1720 and 1735 cm^{-1} in the IR spectrum. In addition, the GC/MS gave the expected M^+ value of 196. The minor product **134** also showed two carbonyl absorptions at 1720 and 1740 cm^{-1}. However, the ^1H NMR showed no vinylic protons and the m/z value obtained by the GC/MS was 250. The identity of this minor product is unknown.

Proposed strategy for construction of the A/B ring synthon **103**.

A strategy for transforming ketone **101** to the A/B ring synthon is outlined in scheme 31.

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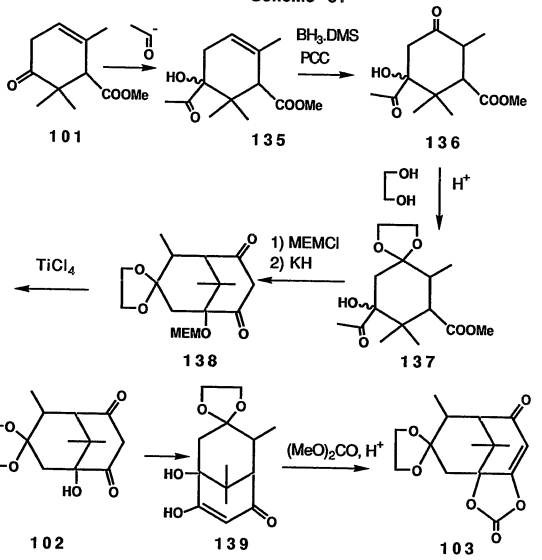
Scheme 31



101 135 136 137 138 102 139 103

Addition of an acetyl anion functional group to the carbonyl carbon of **101** should afford the α-hydroxy-keto ester **135**. The stereochemistry of **135** is not crucial, the ester group is expected to epimerize prior to cyclization. Hydroboration/oxidation could be

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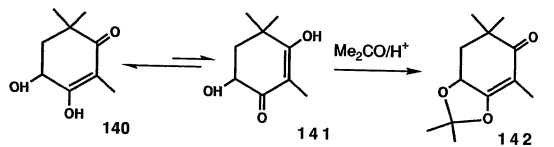
performed at this stage to produce the diketone **136**. Since the acetyl group would be hindered by the gem-dimethyl group, selective ketalization should give the ketal **137**. Protection of the hydroxyl group as the MEM ether, base catalyzed cyclization and deprotection of the hydroxyl group would provide the 1-hydroxybicyclo[3.3.1] nonane-2,4-dione **102**. The next required step would be formation of the cyclic carbonate. The diketone **102** can enolize in two directions, however, it is expected that the hydroxyl group might influence the formation of enol **139**. Hence **102** on treatment with $(MeO)_2CO/H^+$ should afford the desired carbonate **103** as the A/B ring synthon. Formation of a cyclic carbonate involving an α-hydroxy ketone is supported by the formation of the cyclic ketal **142** as shown by E. Widmer et al.[78]



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Experimental Section

General Methods. Proton NMR spectra were recorded on a Varian EM360 (60 MHz) or an IBM Bruker WP 200 SY (200 MHz) spectrometer in $CDCl_3$ with Me_4Si as the internal standard. ^1H NMR (300 MHz) and ^{13}C NMR were acquired using a GE-QE-300 spectrometer at Hunter College by Dr. Mike Blumenstein. Chemical shifts are reported in parts per million downfield from Me_4Si. J values are reported in Hz. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared spectra were recorded on a Perkin-Elmer IR 598, or a Perkin Elmer 1600 series FTIR instrument. Melting points were determined in open capillaries by using a Thomas-Hoover Uni-melt apparatus and are uncorrected. GCMS analyses were performed by Dr. D.C. Locke at Queens College on a Hewlett Packard 5988A GCMS instrument with a cross linked methyl silicone column. For separation of polar compounds, a carbowax column was used. High Resolution MS analyses were performed at the Rockefeller University by Dr. Steven Cohen. Microanalyses were performed by Galbraith Laboratories,

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Knoxville, TN. X-ray crystal structures were determined at Hunter College by Prof. G. Quigley. Analytical HPLC was conducted with a Waters Associates system consisting of two 4 mm X 30cm μ-Porasil silica columns in series, a 6000 SDS pump, U6K injector, and model 401 differential refractomerer. Preparative HPLC separations were performed using a Waters RCM 8mm X 10cm column with a microporasil radial PAK 8mm cartridge.

Flash chromatography was performed according to the method described by W.C. Still[82] using silica gel 60 (230-400 mesh) and eluted with 5:1 hexane/ethyl acetate unless otherwise stated. THF was distilled from a sodium benzophenone ketyl. Methylene chloride, benzene, acetonitrile, DME and DMF were distilled over calcium hydride and stored over molecular sieves. HMPA was distilled under reduced pressure prior to use. Most chemicals (eg. propargyl bromide and 2,3 -dibromopropene) were purified by distillation prior to use. Other solvents and chemicals were used as purchased. Palladium catalysts were purchased from Aldrich except for dichlorobis(tri-o-tolylphosphine)palladium which was prepared

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according to Heck's[31b] procedure. After work up, organic solvents were usually washed with water and brine, dried over anhydrous $MgSO_4$ (unless otherwise stated) and concentrated under reduced pressure using a rotary evaporator.

Ethyl 1-(2-bromo-2-propenyl)-2-oxocyclohexanecarboxylate (4). To a suspension of sodium hydride (4.8g of 97% solid, 0.20 mol) in dry DMF[83] at 0°C was added a solution of of ethyl 2-oxocyclohexanecarboxylate (34.0g, 0.200 mol) in DMF under a nitrogen atmosphere. After the mixture was stirred for 1 h, 40g (0.20 mol) of 2,3-dibromopropene in DMF was added and stirring was continued at room temperature overnight. The mixture was poured into ice-water and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation of the residue afforded 47.34g (82%) of a colorless liquid **4**: bp. 115 °C / 0.5 torr; FTIR (CCl_4) 2981, 2942, 2867, 1718, 1656, 1624 cm^{-1}; ^1H NMR (200 MHz) 1.30 (t, 3 H,

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$CH_2\underline{CH_3}$), 1.40-1.94 (m, 5 H, CH_2CH_2CH), 2.00-2.14 (m, 1 H), 2.42-2.48 (t, 2 H, $CH_2\underline{CH_2}C{=}O$), 2.74-3.36 (AB q, $\underline{CH_2}C(Br){=}CH_2$), 4.44 (q, 2 H, $\underline{CH_2}CH_3$), 5.60 (d, 2 H, $C(Br){=}CH_2$); GCMS, m/z 245 (1.5), 243 (M^+ - OCH_2CH_3, 1.7), 209 (85), 163 (69), 137 (100). Anal. Calcd for $C_{12}H_{17}BrO_3$: C,49.87; H,5.88; Br,27.64. Found: C,49.52; H,5.94; Br,27.56.

Ethyl 3-bromo-1-(2-bromo-2-propenyl)-2-oxocyclohexane-carboxylate (5). A mixture of 6.0g (0.02 mol) of ketone 4 and 9.0g (0.04 mol) of $CuBr_2$[84] dissolved in 100 mL of dry THF was stirred at room temperature for 2 days, during which time a white solid precipitated. The mixture was filtered and the filtrate was diluted with water and extracted with chloroform. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation afforded 6.41g (84%) of 5 as an oil: bp 130-135 ^oC / 1.0 torr; FTIR (CCl_4) 2980,

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2940, 2871, 1731, 1624 cm^{-1}; ^1H NMR 1.2-1.5 (t, 3 H), 1.5-2.1 (m, 4 H), 2.2-2.7 (m,2 H), 2.8-3.4 (AB q, 2 H), 3.4-3.7 (t, 1 H), 4.0-4.5 (q, 2 H), 5.7 (d, 2 H); GCMS m/z (no M^+), 289 (M^+ - Br, 25), 217 (30.1), 215 (M^+ - Br -COOEt, 32.9), 135 (M^+ -2 Br -COOEt,100). Anal. Calcd for $C_{12}H_{16}Br_2O_3$: C, 39.17; H, 4.35; Found: C, 39.55; H, 4.55.

Ethyl 1-(2-bromo-2-propenyl)-2-oxo-3-cyclohexenecarboxylate (6). A mixture of bromoketone 5 (3.0g, 8.2 mmol) and $CaCO_3$[85] (2.0g, 20 mmol) in 30 mL of dry DMF was heated at 120 °C overnight (18 h). The mixture was cooled and filtered. The filtrate was diluted with 30 mL of water and extracted with ether. The ether was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by flash chromatography (5:1 hexane-ethyl acetate) provided 1.42g of 6 as an oil (60%): FTIR (CCl_4) 3036, 2981, 2930, 2869, 1734, 1686, 1624 cm^{-1}; ^1H NMR (200 MHz) 1.25 (t, 3 H, $CH_2\underline{CH_3}$), 2.06 (m, 1 H), 2.45 (m, 1 H), 2.65 (m, 2 H), 2.96-3.32 (AB

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q, 2 H, $\underline{CH_2}C(Br)=CH_2$), 4.16 (q, 2 H, $\underline{CH_2}CH_3$), 5.57-5.69 (d, 2 H, $C(Br)=CH_2$), 6.08 (d, 1 H, CH=$\underline{CH}$-C=O), 6.96 (m, 1 H, $\underline{CH}$=CH-C=O); GCMS m/z (no M^+), 243 (3.17), 241 (M^+ - OEt, 3.15), 207 (M^+ - Br, 71.94), 133 (M^+ - Br -COOEt, 53.44), 68 (100). Anal. Calcd for $C_{12}H_{15}BrO_3$: C, 50.22; H, 5.23; Found: C, 50.25; H, 5.43.

Ethyl 2-hydroxy-1-(2-bromo-2-propenyl)-3-cyclohexene-carboxylate (7, 8). To a solution of enone **6** (12.0g, 42.0 mmol) and $CeCl_3.7H_2O$[86] (15.7g, 42.0 mmol) in absolute methanol was added $NaBH_4$ (1.59g, 42.0 mmol) in methanol at 0 °C. The mixture was stirred for 2 h at room temperature, then diluted with ice-water, acidified with 1.0 N HCl and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford 10.55g of an oil. Flash chromatography (5:1 hexane-ethyl acetate) provided 5.38 g of **7** (44.9%) and 0.73 g of **8** (6.1%) (51%overall yield). GCMS analysis of the crude product on a carbowax column showed that the alcohols

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were in the ratio of 94% : 6%. **7:** FTIR (CCl_4) 3529, 3033, 2981, 2935, 2870, 1731,1624 cm^{-1}; ^1H NMR (200 MHz) 1.25-1.32 (t, J = 7.18, 3 H, CH_2CH_3), 1.83-2.16 (m, 4 H, CH_2CH_2), 2.58-2.67 (br s, 1 H, OH), 2.70-3.13 (AB q, J = 14.90,2H, $\underline{CH_2}CBr=CH_2$), 4.13-4.24 (q, J = 7.19, 2 H, CH_2CH_3), 4.46-4.47 (d, J = 1.841, 1 H, $\underline{CH}OH$), 5.55-5.66 (d, J = 14.38, 2 H, CH=CH); 5.74-5.79 (d, J = 1.94, 2 H, $CBr=CH_2$); GCMS m/z (no M^+), 270 ($M^+ - H_2O$, 0.1), 221(14.14), 219 (14.50), 209 (M^+ - Br, 100), 163 (M^+ - Br - EtOH, 47), 135 (35), 111 (68), 91 (34), 79 (45). Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.87; H, 5.88; Found: C, 49.07; H, 6.05. **8:** FTIR (CCl_4) 3603, 3516, 3032, 2980, 2927, 2848, 1739, 1624 cm^{-1}; ^1H NMR (200 MHz) 1.26-1.33 (t, J = 7.07, 3 H, CH_2CH_3), 1.85-1.97 (m, 1 H, H-6ax), 2.09-2.21 (m, 3 H, H-5a,b, H-6eq), 2.68-2.99 (AB q, J = 14.73, 3 H, H-7a,b, OH), 4.11 (br s, 1 H, $\underline{CH}OH$), 4.15-4.26 (q, J = 7.18, 2 H, CH_2CH_3), 5.56-5.65 (d, J = 15.57, 2 H, CH=CH); 5.79 - 5.80 (d, J = 2.44, 2 H, $CBr=CH_2$); GCMS m/z (no M^+), 221(21.91), 219 (21.20), 209 (50.5), 163 (44), 135 (31), 111

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(100), 91 (50), 79 (57). Anal. Calcd for $C_{12}H_{17}BrO_3$: C,49.87; H,5.88; Br,27.64. Found: C,49.37; H,5.64; Br,27.46.

Radical Cyclization[16] of allylic alcohol (7). To a refluxing solution of allylic alcohol **7** (0.28g, 1 mmol) in 40 mL of dry benzene was added during 1 h, tributyltin hydride (0.25 mL, 1.1 mmol) and AIBN (10 mg) dissolved in 25 mL of benzene. Heating was continued for an additional 1 h. After removal of the solvent under reduced pressure, the residue was dissolved in ether and stirred with saturated aqueous potassium fluoride for 2 h, and the white precipitate of tributyltin fluoride was filtered. The filtrate was extracted with ether, washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexane - EtOAc) to afford 0.16g of a mixture of **9** and **10** (80%) as an oil. HPLC analysis of the product showed two components, which were separated to give **9** (17.3 mg) and **10** (18.7 mg). The approximate 1: 1 ratio of products was confirmed by GCMS analysis of the crude

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product using a carbowax column. The ratio found was **9 : 10** (47.8 : 48.0). **9:** FTIR (CCl_4) 3544, 3073, 2982, 2941, 2860, 1735, 1662 cm^{-1}; ^1H NMR (300 MHz) 1.29-1.34 (t, J = 7.06, 3 H, $CH_2\underline{CH}_3$), 1.52-1.79 (m, 5 H) 1.90-1.95 (m, H-2ax), 2.43-2.49 (d, J = 17.0, H-7b), 2.73 (s, H-5), 2.86-2.91 (d, J = 17.02, H-7a), 2.99 (2, 1 H, OH), 3.95 (s, 1 H, C<u>H</u>OH), 4.18-4.26 (q, J = 6.99, 2 H, $\underline{CH}_2CH_3$), 5.03 (d, J = 1.10, 2 H, $C=CH_2$); GCMS m/z 210 (M^+,8.4), 119 ($M^+ - CO_2Et - H_2O$, 100), 91 (58.5), 79 (35.4). HRMS calcd for $C_{12}H_{17}O_3$ (M - H) 209.1178, found 209.1140. **10:** FTIR (CCl_4) 3554, 3072, 2982, 2939, 2869, 1734, 1654 cm^{-1}; ^1H NMR (300 MHz) 1.29 - 1.33 (t, J = 7.03,3 H, $CH_2\underline{CH}_3$), 1.53-1.73 (m, 4 H, CH_2CH_2), 1.87-1.94 (m, H-7b), 2.13-2.31 (ddd, J = 13.39, 9.76, 2.87, H-7a), 2.34-2.36 (t, J = 2.72, H-4), 2.44-2.50 (dd, J = 16.8, 1.57, H-6b), 2.86-2.92 (dd, J = 16.59, 2.21, H-6a), 2.90-2.91 (d, J = 2.56, 1 H, OH), 4.17-4.24 (q, J = 7.04, 2 H, $\underline{CH}_2CH_3$), 4.28 (d, J = 1.32, 1 H, C<u>H</u>OH), 4.72-4.73 (d, J = 1.53, 1 H, $C=CH_2$), 4.84 (d, J = 1.35, 1 H, $C=CH_2$); GCMS m/z 210 (M^+,4.9), 119

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(M^+ - CO_2Et - H_2O, 70.1), 91 (100), 79 (21.7). HRMS calcd for $C_{12}H_{17}O_3$ (M - H) 209.1178, found 209.1172.

Radical cyclization of alcohol 7 under high tributyltin hydride concentration. To a refluxing solution **7** (0.10g, 0.347 mmol) in 8 mL of benzene was added tributyltin hydride (4.5 mL, 0.017 mol) and AIBN (10 mg) dissolved in 2 mL of benzene. Heating was continued for an additional 1 h. Excess tributyltin hydride was distilled off under reduced pressure. GCMS analysis of the residue showed that the products **9** and **10** were in the ratio of 1 : 1.4.

Preparation of a urethane derivative of allylic alcohol 7. The allylic alcohol **7** (0.2g, 0.69 mmol) and freshly distilled 1-naphthyl isocyanate[87] (0.12 mL, 0.868 mmol) were heated under a nitrogen atmosphere at 60 - 70 ^oC for 2.5 h. After the mixture was cooled to room temperature, 4 mL of petroleum ether (30 - 60) were added and the mixture was boiled for l min., then filtered. The filtrate was cooled in ice to allow crystallization to take place,

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affording 0.12g of **15** (37%) as white crystals. Recrystallization from CCl_4 / hexane afforded crystalline needles (mp 106-107 ^oC) which were suitable for X-ray analysis. FTIR (CCl_4) 3444, 3045, 2984, 2932, 1738, 1625, 1531 cm^{-1}; ^1H NMR 1.1-1.4 (t, 3 H), 1.9-2.3 (m, 4 H), 2.8-3.2 (AB q, 2 H), 4.0-4.4 (q, 2 H), 5.4 (s, 1 H), 5.6 (d, 1 H, $C=CH_2$); 6.0 (d, 1 H, $C=CH_2$); 6.9 (br s, 1 H, NH), 7.4-7.8 (m, 7 H) GCMS m/z 378 (M^+ - Br, 1.9), 334 (9.5), 143 (100), 91 (4.6), 79 (44.5). HRMS calcd for $C_{23}H_{23}BrNO_4$ (M - H) 456.0889, found 456.0810.

X-ray Analysis of 15. The crystals were triclinic, space group P21/C with a = 21.596 (20) A^o, b = 11.169 (0) A^o, c = 9.405 (0) A^o for $C_{23}H_{24}BrNO_4$. A crystal measuring 0.20 x 0.20 x 6.0 mm was used for data collection. The structure was solved by direct methods using 3767 reflections. The N-naphthylcarbamoyloxy group proved to be cis to the 2-bromo-2-propenyl group.

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Swern oxidation[88] of the mixture of 9 and 10. To a solution of oxalyl chloride (0.18 mL, 2.34 mmol) in 5 mL of dry methylene chloride maintained at - 78 °C was added a solution of DMSO (0.3 mL, 3.9 mmol) in methylene chloride and and the mixture was stirred for 2 min. The mixture of alcohols **9 and 10** (0.4g, 1.90 mmol) in 10 mL of methylene chloride was added during 5 min. Stirring was continued for 45 min., then triethylamine (1.2 mL, 9.4 mmol) was added. After 5 min., the mixture was allowed to warm to room temperature, water was added and the aqueous layer was extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the crude product (5:1 hexane - ethyl acetate) gave **13** (0.1568 g) and **14** (0.1400 g) as pale yellow oils. **13: Ethyl 8-oxo-6-methylene bicyclo[3.2.1.]octanecarboxylate.** FTIR (CCl_4) 3070, 2950, 1758, 1729, 1661, 1447, 1367, 1290 cm^{-1}; ^1H NMR (300 MHz) 1.26-1.30 (t, J = 7.17, 3 H, $CH_2\underline{CH_3}$), 1.62-1.71 (m, H-3_{eq}), 1.78-1.92 (m, H-4_{eq}), 2.00-2.21 (m, 3 H,

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H-2_{eq},3_{ax},4_{ax}), 2.31-2.42 (m, H-2_{ax}), 2.70-2.77 (dd, J = 17.38, 2.14, H-7b), 2.96-2.98 (m, H-5), 3.24-3.32 (dd, J = 17.36, 2.52, H-7a), 4.18-4.25 (q, J = 7.09, 2 H, $\underline{CH_2}CH_3$), 5.05 (d, J = 0.49, 2 H, $C=CH_2$); ^{13}C NMR (300 MHz) DEPT 14 (CH_3), 18 (CH_2), 37 (CH_2), 39 (CH_2), 40 (CH_2), 54 (CH), 59 (quaternary C), 61 (OCH_2), 108 ($=CH_2$), 143 ($\underline{C}=CH_2$), 171 (C=OO), 213 (C=O); GCMS m/z 208 (M^+,5.5), 163 (M^+ - OEt, 25.9), 162 (M^+ - HOEt, 100), 135 (M^+ - COOEt,4.8), 107 (43.7), 91 (43.1), 79 (36.0). HRMS calcd for $C_{12}H_{17}O_3$ (M + H) 209.1178, found 209.1169. **14: Ethyl 2-oxo-5-methylenebicyclo [2.2.2.] octanecarboxylate.** FTIR (CCl_4) 3073, 2940, 1741, 1660, 1467, cm^{-1}; ^1H NMR (300 MHz) 1.26-1.31 (t, J = 7.14, 3 H, $CH_2\underline{CH_3}$), 1.80-.97 (m, 3 H, H-2_b,3), 2.30-2.39 (m, H-2_a), 2.40-2.41(d, J = 2.82, 2 H, H-7), 2.62-2.70 (dd, J = 17.76, 2.15, H-6_b), 2.72-2.74 (t, J = 2.82, H-4), 2.98-3.05 (dd, J = 17.76, 2.59, H-6_a), 4.19-4.26 (q, J = 7.17, 2 H, $\underline{CH_2}CH_3$), 4.81(d, J = 1.1, 1 H, $C=CH_2$), 4.96 (d, J = 0.82, 1 H, $C=CH_2$); ^{13}C NMR (300 MHz) DEPT 15

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(CH_3), 25 (CH_2), 26 (CH_2), 34 (CH_2), 38 (CH) 44 (CH_2), 56 (quaternary C), 61 (OCH_2), 108 (=CH_2), 145 (C=CH_2), 170 (C=OO), 210 (C=O); GCMS m/z 208 (M^+, 27), 163 (M^+ - OEt, 45), 162 (M^+ - HOEt, 56), 135 (M^+ - COOEt, 58), 107 (76), 93 (100), 91 (99), 79 (48). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; Found: C, 69.30; H, 7.77.

Oxidation of alcohols (9) and (10). Alcohol **9**, (3.5 mg, 0.016 mmol) and alcohol **10**, (6.7 mg, 0.032 mmol) were oxidized separately according to the Swern[84] procedure described above by using oxalyl chloride (59 μL, 0.63 mmol), dimethylsulfoxide (100 μL, 1.3 mmol) and triethylamine (0.42 mL, 2.9 mmol). The GCMS and IR data of the corresponding ketones were identical to those obtained for **13** and **14** respectively.

Cyclization[16] of allylic alcohol (8). A solution of alcohol **8** (0.1214 g, 0.4215 mmol) in 20 mL of dry benzene and a solution of tributyltin hydride (0.12 mL, 0.4637 mmol) and 10 mg AIBN in 10 ml

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of benzene were combined as above for alcohol **7**. After removal of the solvent, GCMS analysis of the crude reaction product mixture showed two components with M^+ of 210 in the ratio of 4.2 : 1. The crude product was purified by flash chromatography (5:1 hexane-EtOAc) to remove excess tributyltin hydride. The products were separated by HPLC to give **11** (2.9 mg) and **12** (11.7 mg). **11:** FTIR (CCl_4) 3568, 3072, 2981, 2940, 2869, 1714, 1661, 1464, cm^{-1}; ^1H NMR (200 MHz) 1.26 (t, J = 7.08, 3 H, $CH_2\underline{CH_3}$), 1.61 (m, 4 H, CH_2CH_2), 1.73 (s, 2 H, CH_2), 2.10 (m, H-5), 2.56 (d, J = 1.94, 2 H,H-7a,b), 2.69 (br s, 1 H, OH), 4.12 (q, J = 7.23, 3 H, $\underline{CH_2}CH_3$, $\underline{CH}OH$), 4.88 (br s, 1 H, $C=CH_2$), 4.94 (br s, 1 H, $C=CH_2$) ; GCMS m/z 210 (M^+,8.2), 119 ($M^+ - CO_2Et - H_2O$, 100), 91 (51.7), 79 (35.2). **12:** FTIR (CCl_4) 3468, 3069, 2938, 2869, 1715, 1653, 1447 cm^{-1}; ^1H NMR (200 MHz) 1.51 (t, J = 7.13, 3 H, $CH_2\underline{CH_3}$), 1.90 (m, 4 H, CH_2CH_2), 2.30 (m, 2 H, $\underline{CH_2}CHOH$), 2.46 (dt, J = 18.14, 2.75, H-6a), 2.56 (m, H-4), 2.87, (dt, J = 18.14, 2.75, H-6b), 3.49 (br s, OH), 4.36 (s, 1 H,

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CHOH), 4.40 (q, J = 7.18, 2 H, CH_2CH_3), 4.90 (d, J = 1.68, 1 H, $C=CH_2$), 5.04 (d, J = 1.68, 1 H, $C=CH_2$); GCMS m/z 210 (M^+,5.5), 119 (M^+ - CO_2Et - H_2O, 71.1), 93 (100), 91(88.7), 79 (35). HRMS calcd for $C_{12}H_{17}O_3$ $(M - H)^+$ 209.1178, found 209.1188.

Radical cyclization of alcohol 8 under high tributyltin hydride concentration. Alcohol **8** (100 mg, 0.347 mmol) in 8 ml of benzene was reacted with tributyltin hydride (4.5 mL, 0.017 mol) and AIBN (10 Mg) in 2 mL of benzene according to the procedure described for **7**. After removal of the solvent, GCMS analysis of the residue showed that **11** and **12** were in the ratio of 1 : 2.

Oxidation of the mixture of alcohols 11 and 12. The mixture of alcohols **11** and **12** (30 mg, 0.1428 mmol) was oxidized by the Swern[88] procedure using oxalyl chloride (59 µl, 0.65 mmol), dimethylsulfoxide (100 µl, 1.30 mmol) and triethylamine (0.42 mL, 3.0 mmol). The products were separated by HPLC to give **13** (1.5

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mg) and **14** (3.2 mg). These products were identical to those obtained by the oxidation of alcohols **9** and **10** as shown by the identity of IR and GCMS spectra.

Oxidation of alcohol (12). Alcohol **12**, (11.7 mg, 0.057 mmol) was oxidized by Swern's[88] method using oxalyl chloride (11.2 μL, 0.12 mmol), dimethylsulfoxide (19 μL, 0.25 mmol) and triethylamine (80 μL, 0.56 mmol). The GCMS and IR data of the isolated ketone were identical to those of ketone **14**.

2-iodo-2-propene-1-ol (22).[89a] Under a nitrogen atmosphere, trimethyl chlorosilane (32.6 mL, 0.25 mol) was added dropwise at 0°C to a mixture of propargyl alcohol (10.0 mL, 0.16 mol) and sodium iodide (77.0 g, 0.48 mol) in acetonitrile.[89b] The mixture was stirred at room temperature for 1 h, filtered and the filtrate was extracted with ether. The combined extracts were washed with sodium thiosulfate and brine then dried and concentrated. Distillation afforded 16.0 g (51%) of 22 as an oil: bp 75-80 °C/8.0

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torr; IR (CCl_4) 3400 (br), 3020, 1620 cm^{-1}; ^1H NMR (60 MHz) 3.0 (br.s, 1 H), 4.1 (br. s, 2 H), 5.9 (s, 1 H), 6.5 (s, 1 H).

3-bromo-2-iodopropene (23).[90] To a solution of alcohol **22** (7.5 g, 0.04 mol) and pyridine (1.0 mL, 12.4 mmol) in ether at 0 °C was added dropwise PBr_3 (1.6 mL, 16.7 mmol) dissolved in ether.[90] The mixture was refluxed for 2 h then cooled. The cooled mixture was poured cautiously onto ice and extracted with ether. The combined extracts were washed with saturated sodium bicarbonate and brine, dried (K_2CO_3) and concentrated to afford 5.0 g (50%) of **23**: IR (CCl_4) 3080, 2940, 1620 cm^{-1}; ^1H NMR (60 MHz) 4.2 (s, 2 H), 5.8 (s, 1 H), 6.4 (s, 1 H).

Ethyl 1-(2-iodo-2-propenyl)-2-oxocyclohexanecarboxylate (24). To a suspension of sodium hydride (0.88 g of 55% solid in mineral oil, 0.02 mol) in dry DMF[83] at 0 °C was added a solution of ethyl 2-oxocyclohexanecarboxylate (3.45 g, 0.02 mol) in DMF under a

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nitrogen atmosphere. After 1 h, bromide **23** (5.0 g, 0.02 mol) in DMF was added dropwise and stirring was continued at room temperature overnight. After work up according to the procedure described for **4**, the crude product was purified by column chromatography (5:1 Hexane-EtOAc) to afford 5.16 g (77%) of an oil, **24**: IR (CCl_4) 2980, 1715, 1650 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.4 -1.8 (m, 6 H), 2.5 (m, 2 H), 2.8-3.5(AB q, 2 H), 4.3 (q, 2 H), 6.1 (d, 2 H); GC/MS, m/z 291 (M^+ - OEt), 209 (M^+ - I).

Ethyl 3-bromo-1-(2-iodo-2-propenyl)-2-oxocyclohexane-carboxylate (25). A mixture of ketone **24** (25.0 g, 0.074 mol) and $CuBr_2$[84] (33.0 g, 0.14 mol) dissolved in dry THF was stirred at room temperature for 2 days. After work up according to the procedure described for compound **5**, and purification by column chromatography (5:1 Hexane-EtOAc) 25.56 g (83%) of an oil, **25** was obtained: IR (CCl_4) 2980, 1731, 1624 cm^{-1}; ^1H NMR (60 MHz) 1.2-1.5 (t, 3 H), 1.5-2.1 (m, 4 H), 2.2-2.7 (m,2 H), 2.8-3.4 (AB q, 2 H), 3.4-3.7 (t, 1 H), 4.0-4.5 (q, 2 H), 5.7 (d, 2 H).

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Ethyl 1-(2-iodo-2-propenyl)-2-oxo-3-cyclohexenecarboxylate (26). A mixture of bromoketone **25** (37 g, 0.089 mol) and $CaCO_3$[85] (17.8 g, 0.18 mol) in dry DMF were heated at 120 °C overnight. The mixture was worked up according to the procedure described for compound **6.** Purification of the crude product by column chromatography (5:1 Hexane-EtOAc) afforded 29.85 g (61.38%) of **26** as an oil: FTIR (CCl_4) 3036, 2981, 1734, 1686, 1624 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 2.3-2.7 (m, 4 H), 3.0-3.5 (AB q, 2 H), 4.2 (q, 2 H), 5.4-5.8 (d, 2 H), 5.9-6.3 (d, 1 H), 6.7-6.9 (m, 1 H).

Ethyl 2-hydroxy-1-(2-iodo-2-propenyl)-3-cyclohexenecarboxylate (27). To a solution of enone **26** (16.14 g, 0.048 mol) and $CeCl_3.7H_2O$[86] (27.0 g, 0.048 mol) in absolute methanol was added $NaBH_4$ (1.80g, 0.048 mol) in methanol at 0 °C. The mixture was stirred for 2 h at room temperature, then worked up following the procedure described for compound **7** to afford 15.27 g (95%) of the

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crude product. 3.0 g of the crude product was purified by column chromatography (5:1 Hexane-EtOAc) to afford 1.13 g of **27** as an oil: IR (CCl_4) 3530, 3030, 2980, 1731,1624 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.8-2.1(m, 4 H), 2.6 (br s, 1 H), 2.7-3.0 (AB q, 2 H), 4.2 (q, 2 H), 4.4 (d, 1 H), 5.6 (d, 2 H); 5.7 (d, 2 H); GCMS m/z 270 (M^+ - I).

Radical Cyclization[16] of allylic alcohol (27). To a refluxing solution of allylic alcohol **27** (0.80 g, 2.4 mmol) in 40 mL of dry benzene was added during 1 h, tributyltin hydride (0.72 mL, 2.62 mmol) and AIBN (10 mg) dissolved in 20 mL of benzene. Heating was continued for an additional 1 h, then the mixture was worked up following the procedure described for cyclization of allylic alcohol **7**. HPLC analysis of the product showed two components with peaks of equal intensity. GC/MS m/z 210 (M^+). The GCMS data of the products were identical to those of the bicyclo[3.2.1] and [2.2.2] octanols **9** and **10**, respectively.

Ethyl 1-[2-propynyl]-2-oxocyclohexanecarboxylate (28). To

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a suspension of sodium hydride (1.45 g of 97% solid, 58.8 mmol) in dry DMF[83] at 0 °C was added a solution of of ethyl 2-oxocyclohexanecarboxylate (10.0 g, 58.8 mmol) in DMF under a nitrogen atmosphere. After the mixture was stirred for 1 h, 4.37g (58.8 mmol) of propargyl chloride in DMF was added and stirring was continued at room temperature overnight. The mixture was poured into ice-water and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation of the residue afforded 8.80 g (72%) of a liquid **28**: bp. 104-107 °C / 1.0 torr; IR (CCl_4) 3300, 2940, 2120, 1720 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.5-1.9 (s, 6 H), 1.9-2.4 (AB q, 2 H), 2.6 (m, 3 H), 4.2 (q, 2 H); GC/MS 208 (M^+), 135 (M^+ - COOEt).

Ethyl 3-bromo-1-(2-propynyl)-2-oxocyclohexanecarboxylate (29). A mixture of 12.0 g (57.6 mmol) of ketone **28** and 25.8 g (0.12 mol) of $CuBr_2$[84] dissolved in 100 mL of dry THF was stirred at room temperature for 2 days. The mixture was worked up

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according to the procedure described for preparing bromo ketone **5**. Distillation afforded 13.6 g (82%) of **29** as an oil: bp 110 °C / 0.7 torr; IR (CCl_4) 3310, 2940, 2120, 1720 cm^{-1}; ^1H NMR 1.3 (t, 3 H), 1.6-2.1 (m, 4 H), 2.2 (s, 2 H), 2.3 (s, 1 H), 3.5 (t, 1 H), 4.2 (q, 2 H); GCMS 289 (M + 2), 287 (M^+).

Radical cyclization[16] reaction of alkyne 29. A refluxing solution of ketone **29** (0.20 g, 0.69 mmol) in benzene was reacted with a solution of tributyltin hydride (0.2 mL, 0.76 mmol) and AIBN (10 mg) as described for the radical cyclization of allylic alcohol **7**. Purification by column chromatography (5:1 hexane-EtOAc) afforded 0.15 g of **30** as an oil: IR (CCl_4) 2940,1720, 1450 cm^{-1}; ^1H NMR (60 MHz) 0.9-1.2 (t, 12 H), 1.2-1.9 (m, 26 H), 2.3-2.6 (m, 4 H), 4.2 (q, 2 H) 5.9 (m, 2 H); GC/MS 372 (incorporation of Sn was indicated by the fragmentation pattern).

3-Trimethylsilyl-2-propyn-1-ol (32).[90b-92] To n-butyl lithium (1.5 M, 180 mL, 0.28 mol) at -20 °C was added propargyl

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alcohol (8.1 mL, 0.14 mol) in 20 mL of dry THF under a nitrogen atmosphere.[92] After 1 h, trimethylchlorosilane (39 mL, 0.31 mol) in 20 mL of THF was added. The dry-ice bath was removed and stirring was continued overnight at room temperature. The mixture was poured into ice-cold 1.5 M HCl and stirred for 2.5 h, then extracted with ether. The combined organic extracts were washed with sodium bicarbonate, water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the crude product through a short vigreux column afforded 16.1 g (71%) of **32** as a liquid: bp 93-95 ^{o}C/23 torr (lit. bp 71 ^{o}C/15 torr) ; IR (CCl_4) 3600, 2950, 2180 cm^{-1}; ^{1}H NMR (60 MHz) 0.2 (s, 9 H), 2.4 (br s, 1 H), 4.5 (s, 2 H).

3-Bromo-1-trimethylsilyl-1-propyne (33).[90,91] To a solution of alcohol **32** (1.0 g, 7.8 mmol) and pyridine (0.1 mL,1.2 mmol) in dry ether at 0 ^{o}C was added an ether solution of PBr_3[90] (2.0 mL, 0.02 mol) under a nitrogen atmosphere. The mixture was refluxed for 2 h, then cooled, poured onto ice and extracted with ether. The combined ether extracts were washed with sodium

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bicarbonate, water and brine, dried (K_2CO_3) and concentrated to afford 0.8 g (56%) of **33** as an oil: IR (CCl_4) 2960, 2180 cm^{-1}; ^1H NMR (60 MHz) 0.0 (s, 9 H), 3.8 (d, 2 H). lit bp. 71-73 °C/26 torr.

Ethyl 1-(3-trimethylsilyl-2-propynyl)-2-oxocyclohexanecarboxylate (34). Under a nitrogen atmosphere, a solution of 2-oxocyclohexanecarboxylate (2.7 g, 15 mmol) in DME[93] was added dropwise to a suspension of NaH (0.66 g of 57% solid, 15 mmol) in dry DME at 0 °C. After the mixture was stirred for 30 min., bromide **33** (3.0 g, 15 mmol) was added and stirring was continued at room temperature overnight. The mixture was washed with ice-cold water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude product by column chromatography (5:1 hexane-EtOAc) afforded 4.0 g (91%) of an oil, **34**: IR (CCl_4) 2940, 2180, 1720, cm^{-1}; ^1H NMR (60 MHz) 0.0 (s, 9 H), 1.1 (t, 3 H), 1.9 (s, 2 H), 2.0-2.5 (s, 6 H), 2.6 (m, 2 H), 4.0 (q, 2 H); GC/MS 280 (M^+), 207 (M^+ - COOEt). Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.28;

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H, 8.57. Found: C, 64.22; H, 8.31.

Ethyl 3-bromo-1-(3-trimethylsilyl-2-propynyl)-2-oxo-cyclo hexanecarboxylate (35). A mixture of ketone **34** (3.5 g, 12.5 mmol) and $CuBr_2$[84] (5.6 g, 25 mmol) dissolved in 50 mL of dry THF was stirred at room temperature for 2 days. The reaction mixture was worked up following the procedure described for preparing α-bromo ketone **5**. Purification of the crude product by column chromatography (5:1 hexane-EtOAc) afforded 2.73 g (61%) of **35** as an oil: IR (CCl_4) 2940, 2180, 1720, cm^{-1}; ^1H NMR (60 MHz) 0.0 (s, 9 H), 1.1 (t, 3 H), 1.9 (s, 2 H), 2.0-2.5 (s, 6 H), 3.5 (t, 1 H), 4.0 (q, 2 H); GC/MS 345 (M^+ - CH_3). Anal. Calcd for $C_{15}H_{23}BrO_3Si$: C, 50.14; H, 6.40; Br, 22.28; Found: C, 50.51; H, 6.40; Br, 23.94.

Radical cyclization of alkyne (35)

Method A: tributyltin hydride.[24c] To a refluxing solution of alkyne **35** (0.7 g, 1.95 mmol) in 40 mL of dry benzene was added

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during 4.5 h, tributyltin hydride (0.55 mL, 2.1 mmol) and AIBN (10 mg) dissolved in 20 mL of benzene. Heating was continued for an additional 2 h. After removal of the solvent under reduced pressure, the residue was dissolved in ether and stirred with saturated aqueous potassium fluoride for 2 h, and the white precipitate of tributyltin fluoride was filtered. The filtrate was extracted with ether, washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The oil obtained on purification by flash chromatography (5:1 hexane-EtOAc) showed ^1H NMR, IR, and GC/MS data identical to those of ketone **34** (0.33 g, 60%) indicating that reduction of the bromide had taken place.

Method B: triphenyltin hydride.[24a] To a refluxing solution of alkyne **35** (0.5 g, 1.4 mmol) and AIBN (10 mg) in 30 mL of dry benzene was added during 6 h, triphenyltin hydride (0.7 g, 2.1 mmol) dissolved in 20 mL of benzene. Heating was continued overnight. The reaction mixture was then worked up as described for method A. Flash chromatography (5:1 hexane-EtOAc) of the crude product afforded an oil with NMR, IR, and GC/MS data identical to those of

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ketone **34** (0.28 g, 72%).

Ethyl 1-(2-propenyl)-2-oxocyclohexanecarboxylate (42). To a suspension of sodium hydride (2.8g of 55% solid, 65 mmol) in dry DMF[83] at 0 °C was added a solution of of ethyl 2-oxocyclohexanecarboxylate (10.0g, 65 mmol) in DMF under a nitrogen atmosphere. After the mixture was stirred for 1 h, 7.8 g (0.20 mol) of allyl bromide in DMF was added and stirring was continued at room temperature overnight. The mixture was poured into ice-water and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation of the residue afforded 10.0 g (73%) of a liquid **42**: bp. 85-90 °C/0.25 torr; FTIR (CCl_4) 3076, 2940, 1716 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.5-1.9 (s, 6 H), 2.3-2.5 (m, 4 H), 4.2 (q, 2 H), 5.0 (m, 1 H), 5.2 (s, 2 H); GC/MS 210 (M^+).

Ethyl 3-bromo-1-(2-propenyl)-2-oxocyclohexanecarboxylate (43a). A mixture of 7.0 g (33 mmol) of ketone **42** and 14.8 g

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(66 mmol) of $CuBr_2$[84] dissolved in 50 mL of dry THF was stirred at room temperature for 2 days. Work up according to the procedure described for preparation of α-bromo ketone **5** followed by distillation afforded 9.0 g (95%) of a liquid **43a**: bp 120-122 °C / 0.25 torr; FTIR (CCl_4) 3076, 2940, 1716 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.5-1.9 (s, 6 H), 2.3-2.5 (m, 2 H), 3.5-3.7 (t, 1 H), 4.2 (q, 2 H), 5.0 (m, 1 H), 5.2 (s, 2 H); GC/MS 247 (M^+ - allyl), 217, 215 (M^+ - COOEt), 209 (M^+ - Br).

Ethyl 3-iodo-1-(2-propenyl)-2-oxocyclohexanecarboxylate (43b). A mixture of α-bromo ketone **43a** (3.2 g, 0.11 mol) and sodium iodide[94] (4.8 g, 0.32 mol) in 50 mL of acetone was refluxed under a nitrogen atmosphere for 6 h. The mixture was cooled filtered and the solvent was evaporated. The residue was dissolved in water and extracted with hexane. The combined organic layers were washed with saturated $Na_2S_2O_3$, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford 2.5 g

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(67%) of an oil. GC/MS analysis of the product indicated it contained 22% of ketone **42** (M^+ 210) and 78% of α-iodo ketone **43b** m/z 291 (M^+- OEt) 263, (M^+- COOEt), 209 (M^+- I). Purification by flash chromatography (5:1 hexane-EtOAc) afforded **43b**: FTIR (CCl_4) 3075, 2940, 1716 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.5-1.9 (s, 6 H), 2.3-2.5 (m, 2 H), 3.5-3.7 (t, 1 H), 4.2 (q, 2 H), 5.0 (m, 1 H), 5.2 (s, 2 H).

Atom transfer cyclization reactions of (43a) and (43b).[27a] A mixture of α-bromo ketone **43a** (0.5 g, 1.74 mmol), hexabutylditin (15 μL, 0.17 mmol) and AIBN (10 mg) dissolved in 10 mL of dry benzene was irradiated with a 275W sunlamp for 2 h. Removal of the solvent followed by purification by column chromatography (5:1 hexane-EtOAc) afforded 0.39 g (78% recovery) of an oil. The NMR and IR data of the product were identical to those of the starting material. Similar treatment of a benzene solution of α-iodo ketone **43b** (0.5 g, 1.45 mmol), Bu_6Sn_2 (15 μL, 0.17 mmol) and AIBN (10

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mg) resulted in recovery of the starting material (0.27 g, 54%) as evidenced by the NMR data.

Palladium coupling reactions of α-bromo ketone (43a) and α-iodo ketone (43b).

Catalyst system A:[33] A solution of α-iodo ketone **43b** (0.5 g, 1.5 mmol), $Pd(PPh_3)_4$ (172 mg, 0.015 mmol), "proton sponge" (0.32 g, 4.47 mmol) dissolved in 3 mL of HMPA was heated at 50 °C under a nitrogen atmosphere for 3 h. Ethyl acetate was added to the reaction mixture and the organic layer was washed with 10% HCl, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (5:1 hexane-EtOAc) to afford 0.20 g (40% recovery) of an oil which showed NMR and IR spectral data identical to those of the starting material.

Catalyst system B: [34, 35] A mixture of α-bromo ketone **43a** (0.5 g, 1.7 mmol), Ag_2CO_3 (0.94 g, 3.4 mmol), $Pd(OAc)_2$ (19 mg, 0.085

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mmol), triphenylphosphine (66.8 mg, 0.25 mmol), and 10 mL of dry CH_3CN was flushed with nitrogen and then heated at 80 °C for 24 h. The inorganic salts were removed by filtration and the filtrate was concentrated and passed through a short column of silica gel eluting with 40 - 60° petroleum ether to remove dissolved salts. Concentration of the solvent and purification of the residue by column chromatography (5:1 hexane-EtOAc) afforded 0.13 g of an oil. GC/MS analysis of the product indicated that it contained the starting material (10%) and several other components, none of which corresponded to the desired product.

Catalyst system C:[36] A mixture of α-bromo ketone **43a** (0.5 g, 1.7 mmol) , distilled Et_3N (0.29 mL, 2.1 mmol), $Pd(OAc)_2$ (19 mg, 0.085 mmol), tri-o-tolylphosphine (104 mg, 0.34 mmol), and 2 mL of dry CH_3CN was flushed with nitrogen and then heated in a sealed tube at 110 °C for 24 h. After being cooled to room temperature, the mixture was taken up in 50 mL of CH_2Cl_2, washed with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oil

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obtained following column chromatography (5:1 hexane-EtOAc) showed ^1H NMR, IR, and GC/MS data identical to those of ketone **42** (0.17 g, 45%) indicating that the halogen had been reduced.

Intramolecular Heck reaction of allylic alcohol (7).[38a] A mixture of allylic acohol **7** (0.5 g, 1.7 mmol), $Pd(OAc)_2$ (20 mg, 0.087 mmol), triphenylphosphine (46 mg, 0.17 mmol), pyrrolidine (0.15 mL, 1.7 mmol), formic acid (66 μL, 1.7 mmol) and 10 mL of dry CH_3CN was heated at 80 ^oC for 2 h. After removal of the solvent, 40 - 60^o petroleum ether was added to the residue to remove dissolved salts. Concentration of the solvent and purification of the residue by column chromatography (5:1 hexane-EtOAc) afforded 0.3 g (60% recovery) of an oil which was identical to the allylic alcohol as determined by the NMR, and IR data.

Ethyl 1-(2-bromo-2propenyl)-2-trimethylsilyloxycyclo-hex-2-enecarboxylate (46). To a solution of ketone **4** (5.0 g, 17 mmol) and triethylamine (10 mL, 76 mmol) in 20 mL of dry DMF was

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added trimethylchlorosilane (5.0 mL, 38 mmol) and the mixture was refluxed overnight.[95] The mixture was cooled, diluted with hexane then washed with ice-cold saturated sodium bicarbonate, 10% HCl, water and brine, dried ($MgSO_4$) and concentrated. Distillation of the crude product afforded 2.8 g (46%) of **46** as an oil: bp 120-125 °C /0.7 torr; IR 2960, 2870, 1720, 1620 cm^{-1}; ^1H NMR (60 MHz) 0.0 (s, 9 H), 1.1 (t, 3 H), 1.5-2.0 (m, 6 H), 2.9 (s, 2 H), 4.0 (q, 2 H), 4.8 (t, 1 H), 5.5 (d, 2 H).

Palladium coupling reaction of silyl enol ether (46).[39] A mixture of the silyl enol ether **46** (0.5 g, 1.4 mmol), tributyltin fluoride (433 mg, 1.4 mmol) and $PdCl_2(P(o\text{-}CH_3C_6H_4)_3)_2$ (33 mg, 42 mmol) in 10 mL of benzene was heated at reflux for 3 h under nitrogen. The reaction mixture was then cooled, diluted with ether and washed with 1N NaOH. Drying ($MgSO_4$) and removal of the solvent followed by column chromatography afforded (5:1 hexane /EtOAc) 0.29 g (58% recovery) of an oil which showed NMR and IR data identical to those of the starting silyl enol ether.

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Preparation of dichlorobis(tri-o-tolylphosphine)palladium catalyst, $PdCl_2(P(o\text{-}CH_3C_6H_4)_3)_2$.[31b] A mixture of $PdCl_2$ (0.55 g, 3.1 mmol), LiCl (dried overnight at 100 °C/1 torr) (0.26 g, 6.2 mmol) and tri-o-tolylphosphine (2.0 g, 6.5 mmol) in 50 mL of absolute ethanol was refluxed for 1.5 h. A yellow solid precipitated within 0.5 h. The mixture was cooled, filtered and the solid was washed with methanol and allowed to dry affording, 2.24 g (91%) of a yellow powder with mp > 250 °C.

Preparation of keto aldehyde (47). To a mixture of alkene **42** (1.0 g, 4.8 mmol) and OsO_4[96] (65 mg, 0.25 mmol) in 15 mL of water and 15 mL of ether was added dropwise a solution of $NaIO_4$ (2.1 g, 9.9 mmol) in 10 mL of water. The temperature was maintained at 25 °C during the addition. Stirring was continued for an additional 2 h, then the mixture was extracted with EtOAc. The combined extracts were washed with sodium thiosulfate, dried (Na_2SO_4) and concentrated. After purification by column chromatography (5:1

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hexane-EtOAc), 0.77 g (77 %) of **47** was obtained as an oil: FTIR (CCl_4, 5%) 3500, 2940, 2867, 1728 cm^{-1}; FTIR (CCl_4, 1%) 2940, 2868, 1729 cm^{-1}; ^1H NMR (60 MHz) 1.2 (t, 3 H), 1.8 (s, 6 H), 2.4 (m, 2 H), 2.5 (s, 2 H), 4.2 (q, 2 H) 9.8 (s, 1 H); GC/MS 194 ($M^+ - H_2O$).

Ozonolysis[97] of alkene (42). Ozone was bubbled into a solution of alkene **42** (1.0 g, 4.8 mmol) in 10 mL of methanol and 15 mL of methylene chloride at -78 °C until a blue color persisted (0.5 h). After being purged with nitrogen, 5 mL (68 mmol) of dimethyl sulfide was added at -78 °C and stirring was continued for 0.5 h. The mixture was allowed to to warm to room temperature then water was added and the mixture was extracted with methylene chloride. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. After purification of the residue by column chromatography (5:1 hexane-EtOAc), 0.70 g of an oil was obtained. GC/MS analysis of the product indicated that the desired aldehyde **47**, m/z 184 (M^+ - CO), constituted 43% of a mixture of six

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components. The ^1H NMR data also suggested that a mixture of products was obtained: 1.3 (t, 3 H), 1.4-1.6 (m, 6H), 2.2 (m, 2 H), 2.7 (s, 2 H), 3.2 (s, 3 H), 4.2 (q, 2 H), 4.8 (m, 2 H), 5.9 (br, 2 H), 9.7 (s, 1 H). FTIR (CCl_4) 3466, 2937, 2868, 1734 cm^{-1}.

Attempted aldol condensation of keto aldehyde (47).

1. Acidic Conditions:[98] A mixture of 0.77 g (3.6 mmol) of keto aldehyde **47** (obtained by OsO_4 oxidation of alkene **42**), glacial acetic acid (3.5 mL), conc. HCl (0.8 mL), and water (1.74 mL) was heated at 100 ^oC for 15 min. then stirred at room temperature overnight. The mixture was diluted with water and extracted with ether. The combined extracts were washed with saturated sodium bicarbonate, water, and brine, dried ($MgSO_4$), and concentrated. The ^1H NMR spectral data of the residue was identical to that of keto aldehyde **47**.

2. Using NaOEt/EtOH:[99] Sodium metal (0.18 g, 7.8 mmol) was allowed to dissolve in 60 mL of absolute ethanol. This solution of NaOEt was added dropwise during 2 h, to a solution of keto aldehyde

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47 (1.94 g, 9.2 mmol) in 30 mL of ethanol at room temperature. After the mixture was stirred for an additional 0.5 h, it was neutralized with 1.5 N HCl and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, then dried ($MgSO_4$). After removal of the solvent and column chromatography (5:1 hexane-EtOAc), 1.81 g of an oil remained: FTIR (CCl_4,) 3444, 2937, 1753 1734 cm^{-1}; ^1H NMR (60 MHz) 1.3 (t, 3 H), 1.6 (s, 6 H), 2.3-2.5 (m, 3 H), 3.7 (m, 1 H), 4.2 (q, 2 H) 5.9 (br, 1 H); GC/MS showed eight components, two of which constituted (1) 49% and (2) 22% of the mixture. (1) m/z 212 (with a different fragment pattern from keto aldehyde **47**). (2) m/z 228.

Preparation of a 2,4 DNP derivative of keto aldehyde (47). To a solution of 2,4 DNP[100] (0.75 g, 3.8 mmol) in 30 mL of DME was added keto aldehyde **47** (0.5 g, 2.4 mmol) and 3 drops of conc. HCl. After the mixture was heated at 50-60 ^oC for 2 h, it was allowed to cool and cold water (12 mL) was added until turbidity persisted. The mixture was cooled in ice, the crystals were collected by suction

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filtration and washed with ethanol. Recrystallization (twice) from $CHCl_3$/hexane afforded 0.2 g (11%) of **50** as orange colored crystals: mp 175-176 ^oC; IR (KBr pellet) 3300 (d), 2940, 1740, 1620, 1580 (C=N) cm^{-1}; NMR (60 MHz) 1.3 (t, 3 H), 1.6 -1.8 (m, 8 H), 3.1 (s, 2 H), 4.3 (q, 2 H), 7.7-7.9 (m, 3 H), 8.3 (br, 1 H), 9.2 (s, 1 H); GC/MS m/z 572 (M^+ of bis derivative **51**). Anal. Calcd for $C_{17}H_{20}N_4O_7$ (mono derivative **50**): C, 52.04; H, 5.14; N, 14.28. $C_{23}H_{24}N_8C_{10}$ (bis derivative **51**): C, 48.25; H, 4.23; N, 19.57. Found: C,42.45; H, 3.70; N, 16.44.

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Geraniol pivalate (85).[61a] Under a nitrogen atmosphere, a suspension of sodium hydride (2.8 g of 55% solid in mineral oil, 65 mmol) in dry ether was cooled in an ice bath. An ether solution of geraniol (10.0 g, 65 mmol) was then added dropwise during 1 h. After the mixture was stirred for an additional 1 h, a solution of pivaloyl chloride (8.6 g, 71 mmol) in ether was added dropwise and the mixture was allowed to stir at room temperature overnight. The reaction mixture was filtered and the ether phase was washed with saturated sodium bicarbonate, water and brine, then dried ($MgSO_4$). Evaporation of the solvent left a residue which was purified by column chromatography (5:1 hexane/EtOAc) to afford 14.0 g (90%) of **85** as a liquid: IR (CCl_4) 2960, 1730, 1620 cm^{-1}; ^1H NMR (60 MHz) 1.2 (s, 9 H), 1.6 (s, 9 H), 2.0 (s, 4 H), 4.5 (d, 2 H), 4.9-5.2 (m, 2 H); GC/MS 137 (M^+ - OC(O)t-Bu).

(2E) 6,7-epoxy-3,7-dimethyloct-2-enol pivalate (86).[61a] To a solution of MCPBA (9.4 g of 80-85% solid, 54 mmol) in 200 mL of dry CH_2Cl_2 cooled to 0 °C (ice-salt) was added a solution of **85**

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(10.0 g, 42 mmol) during 1.5 h. Stirring was continued for an additional 1 h, then the mixture was filtered and the filtrate washed with 10% Na_2SO_3, 10% Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated. After column chromatography (5:1 hexane/EtOAc), 6.7 g (63%) of a liquid, **86** was obtained: IR (CCl_4) 2960, 1730, 1660 cm^{-1}; ^1H NMR (60 MHz) 1.2 (s, 9 H), 1.3 (d, 6 H), 1.8 (s, 3 H), 2.1-2.3 (m, 4 H), 2.8 (t, 1 H), 4.6 (d, 2 H), 5.4 (t, 1 H); GC/MS 153 (M^+ - OC(O)t-Bu).

Exo-1,3,3-trimethyl-2-pivaloyloxymethyl-7-oxabicyclo [2.2.1]heptane (87).[61a] Under a nitrogen atmosphere, a solution of epoxide **86** (4.0 g, 15.7 mmol) in 850 mL of dry CH_2Cl_2 was allowed to cool to O ^oC. With the aid of a syringe, $SnCl_4$ (0.55 mL, 4.77 mmol) was introduced and the mixture was allowed to stir at 0 ^oC for 15 min. After hydrolysis with 10% Na_2CO_3, the organic layer was separated, washed with saturated Na_2CO_3, and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column

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chromatography (5:1 hexane/EtOAc) to provide 3.5 g (86%) of **87** as an oil: IR (CCl_4) 2960, 1725 cm^{-1}; ^1H NMR (60 MHz) 1.0 (s, 3 H), 1.1 (s, 3H), 1.2 (s, 9 H), 1.4 (s, 3 H), 1.5-1.7 (m, 4 H), 2.1 (s, 1 H), 3.8 (m, 1 H), 4.0-4.2 (m, 2 H); GC/MS 254 (M^+).

Exo-1,3,3-trimethyl-2-hydroxymethyl-7-oxabicyclo[2.2.1] heptane (88). [61a] To a solution of $NaBH_4$ (12.0 g, 315 mmol) in 150 mL of absolute ethanol was added dropwise a solution of pivalate **87** (4.0 g, 15.7 mmol) in 30 mL of ethanol at 0 °C. The solution was then warmed to room temperature and stirred overnight. The reaction mixture was diluted with 100 mL of CH_2Cl_2, washed with brine and dried ($MgSO_4$). After evaporation of the solvent, 2.3 g (85%) of **88** remained as an oil: IR (CCl_4) 3500, 2960, 1380 cm^{-1}; ^1H NMR (60 MHz) 1.1 (d, 6 H), 1.4 (s, 3H), 1.5-1.7 (m, 4 H), 2.1 (s, 1 H), 3.7-3.8 (d, 3 H), 5.3 (s, 1 H); GC/MS 170 (M^+).

(2E)1-t-Butyldimethylsilyloxy-3,7-dimethyl-2,6-octadiene

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(113). To a mixture of geraniol (1.0 g, 6.5 mmol) and imidazole (1.1 g, 16 mmol) in dry CH_2Cl_2 was added a solution of t-butyldimethylchlorosilane (1.2 g, 7.8 mmol) in CH_2Cl_2 at 0 °C.[79] After being stirred at room temperature overnight, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Column chromatography purification of the residue afforded 1.7 g (98%) of **113** as a liquid: IR (CCl_4) 2940, 1660 cm^{-1}; ^1H NMR (60 MHz) 0.3 (s, 6 H), 1.1 (s, 9 H), 1.8 (s, 9 H), 2.2-2.4 (s, 4 H), 4.4-4.6 (d, 2 H), 5.4-5.6 (m, 2 H); GC/MS 268 (M^+). HRMS calcd for $C_{16}H_{31}OSi$ $(M - H)^+$ 267.2144, found 267.1923.

(2E)1-t-Butyldimethylsilyloxy-6,7-epoxy-3,7-dimethyloct-2-ene (114). To a mixture of **113** (15.0 g, 56 mmol) in CH_2Cl_2 (200 mL) and saturated sodium bicarbonate solution (170 mL) cooled to 0 °C, was added solid m-chloroperbenzoic acid[80] (10.6 g of 80-85% solid, 62 mmol) in portions. After being stirred at room

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temperature for 3.5 h, the organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. Purification by column chromatography (12:1 hexane/ethyl acetate) afforded 12.2 g (76%) of **114** as a liquid: IR (CCl_4) 2960, 1620 cm^{-1}; ^1H NMR (60 MHz) 0.2 (s, 6 H), 1.0 (s, 9 H), 1.4 (d, 9 H), 1.7 (s, 4 H), 2.8 (t, 1 H), 4.2 (d, 2 H), 5.4 (t, 1 H); GC/MS 227 (M^+ - t-Bu). HRMS calcd for $C_{16}H_{31}O_2Si$ $(M - H)^+$ 283.2093, found 283.2019.

Cyclization of (2E)1-t-Butyldimethylsilyloxy-6,7-epoxy-3,7-dimethyloct-2-ene (114). To a solution of epoxide **114** (0.5 g, 1.8 mmol) in 50 mL of dry benzene was added $SnCl_4$ (41 µL, 0.36 mmol) at O ^oC 66. The ice bath was removed and stirring was continued for 0.5 h then the mixture was diluted with water and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated. Purification by column chromatography (5:1 hexane/EtOAc) afforded 0.42 g (84 %) of a liquid: GC/MS analysis

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indicated two major components in the ratio of 72% : 22%. The products were separated by HPLC (20 : 1 hexane/ethyl acetate) to afford compounds **115** and **116**. **115**: IR (CCl_4) 2960, 1260 cm^{-1}; ^1H NMR (200 MHz) 0.02 (s, 6 H), 0.85 (s, 9 H), 1.00 (s, 6 H), 1.30 (s, 3 H), 1.40-1.44 (m, 5 H), 3.50 (m, 2 H), 3.68 (m, 1 H); GC/MS 269 (M^+ - CH_3). HRMS calcd for $C_{16}H_{33}O_2Si$ $(M + H)^+$ 285.2250, found 285.2229. **116** : IR (CCl_4) 3400, 2960 cm^{-1}; ^1H NMR (200 MHz) 0.00 (s, 6 H), 0.82 (s, 9 H), 1.03 (s, 6 H), 1.61 (s, 3 H), 2.09-2.21 (m, 3 H), 3.18 (br, 1 H), 3.71 (m, 3 H), 4.72 (m, 1 H); GC/MS 227 (M^+ - t-Bu). HRMS calcd for $C_{16}H_{33}O_2Si$ $(M + H)^+$ 285.2250, found 285.2221.

1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (117). Jones reagent was added dropwise to a solution of alcohol **88** (2.0 g, 12 mmol) in 60 mL of acetone at 0 °C until the orange color of the reagent persisted (6.0 mL).[77] After being stirred at room temperature for 2.5 h, the reaction mixture was

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diluted with ether, washed with 1.5 N HCl, water and brine and dried ($MgSO_4$). Evaporation of the solvent afforded 1.70 g (78%) of **117** as a viscous oil: IR (CCl_4) 2500-3300 (br), 1710 cm^{-1}; ^1H NMR (60 MHz) 1.1 (s, 3 H), 1.2 (s, 3H), 1.6 (s, 3 H), 1.7-1.8 (m, 4 H), 2.3 (s, 1 H), 4.0-4.2 (d, 1 H), 10.9 (br s, 1 H); GC/MS 169 (M^+- CH_3).

Methyl 1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylate (118). To a mixture of the acid **117** (1.94 g, 10.5 mmol) and $KHCO_3$ (1.58 g, 15.4 mmol) in dry DMF was added MeI (0.72 mL, 11.5 mmol) at room temperature. After being stirred overnight, the mixture was diluted with water and extracted with ether. The ether extracts were washed with water and brine, dried ($MgSO_4$) and concentrated. After purification by column chromatography (5:1 hexane/EtOAc) 1.5 g (72 %) of **118** as a yellow oil was obtained: IR (CCl_4) 2940, 1740 cm^{-1}; ^1H NMR (60 MHz) 1.0 (s, 3 H), 1.1 (s, 3 H) 1.5 (s, 3H), 1.7-1.9 (m, 4 H), 2.3 (s, 1 H), 3.7 (s, 3 H), 3.8 (m, 1 H); GC/MS 198 (M^+). ^1H NMR data is in accord with the known ethyl ester

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analog **99**: 0.98 (s, 3 H), 1.21 (s, 3 H), 1.24 (t, 3 H), 1.45 (s, 3 H), 2.29 (s, 1 H), 3.90 (d, 1 H), 4.11 (q, 2 H).

Attempts at opening the epoxide 118.

(1) $LiN(Si(Me)_3)_2$.[67] To a solution of hexamethyldisilazide (0.63 mL, 3.0 mmol) in 15 mL of dry THF was added n-BuLi (2.5 M in hexane, 1.2 mL, 2.9 mmol)) at -78 °C. After 1 h, a solution of the epoxide **118** (0.5 g, 2.5 mmol) in 15 mL of dry THF was added dropwise and the mixture was stirred for an additional 1.5 h before being allowed to warm to 0 °C. The solvent was evaporated and the residue was dissolved in methylene chloride. The organic phase was washed with 1N HCl and brine, dried ($MgSO_4$) and concentrated. The oil remaining (0.49g, 98% recovery) showed ^1H NMR and IR spectral data identical to those of the starting material.

(2). LDA.[68] Under a nitrogen atmosphere, n-BuLi (0.82 mL of a 2.5 M solution in hexane, 2.0 mmol) was added to a solution of diisopropyl amine (0.57 mL, 2.0 mmol) in 10 mL of THF at -78 °C. After 0.5 h, the epoxide (200 mg, 1.0 mmol) was added and the temperature was

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maintained at -78 °C for 1 h. The mixture was allowed to warm to room temperature then heated at 75-80 °C overnight. The mixture was cooled, then poured into cold saturated NH_4Cl and extracted with ether. The combined ether extracts were washed with 1.5 N HCl and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The NMR and IR spectra of the residue (120 mg, 60% recovery) were identical to those of the starting material.

(3). NaOME/MeOH. Sodium methoxide (50 μL of a 30% solution in methanol, 0.50 mmol) was added to a soiution of the epoxide (37.6 mg, 0.19 mmol) in 5 mL of absolute methanol and the mixture was stirred at room temperature overnight. The reaction mixture was cooled in ice, hydrolysed with 1.5 N HCl and extracted with ether. The ether extracts were washed with water and brine, then dried ($MgSO_4$). Evaporation of the solvent resulted in recovery of the starting material (25.7 mg, 68% recovery) as evidenced by the NMR and IR data.

(4). $BF_3.Et_2O$[66]. To a solution of epoxide **118** (100 mg, 0.51 mmol)

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in 10 mL of dry benzene was added $BF_3.Et_2O$ (20 μL, 0.15 mmol) at 0 °C. After the mixture was stirred at room temperature for 4 h, it was diluted with water and extracted with ether. The organic phase was washed with water and brine, then dried ($MgSO_4$). The starting material (72 mg, 72%) was recovered on evaporation of the solvent.

Methyl 2,2,6-trimethyl-3-acetoxycyclohex-5-enecarboxylate (120). To an ice-cooled solution of epoxide **118** (1.2 g, 6.1 mmol) in 80 mL of dry methylene chloride under a nitrogen atmosphere was added a solution of acetyl chloride (1.1 mL, 15 mmol) in CH_2Cl_2.[69] This was followed by titanium tetrachloride (0.8 mL, 7.6 mmol) dissolved in 20 mL of CH_2Cl_2, added dropwise during 10 min. The mixture was stirred cold for an additional 45 min and then quenched by addition of 6.0 g of solid potassium carbonate followed by 100 mL of methylene chloride and 2 mL of water. Stirring was continued for 2 h while a precipitate of titanium dioxide formed and carbon dioxide evolved. The organic

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layer was decanted and washed with water, saturated Na_2CO_3 and brine, dried ($MgSO_4$) and concentrated. After purification of the residue by column chromatography (5:1 hexane/EtOAc), 1.2 g (83 %) of a yellow oil was obtained. GC/MS analysis of the product indicated two components in the ratio of 87:13. The major component, **120** was isolated by HPLC (20 : 1 hexane/ethyl acetate). IR (CCl_4) 2960, 1740 cm^{-1}; ^1H NMR (200 MHz) 0.99 (s, 3 H), 1.02 (s, 3 H) 1.66 (s, 3H), 2.05 (s, 3 H), 2.10-2.40 (m, 2 H), 3.00 (s, 1 H), 3.72 (s, 3 H), 4.73 (dd, 1 H), 5.50 (br s, 1 H); GC/MS 209 (M^+ - OCH_3). HRMS calcd for $C_{13}H_{19}O_4$ $(M - H)^+$ 239.1283, found 239.1267.

Attempted oxidation of 2-methylcyclohexene.

(1). Wacker Oxidation.[70] A 50 mL flask containing a mixture of 2-methyl cyclohexene (0.48 g, 5 mmol), cuprous chloride (0.5 g, 5 mmol) and palladium chloride (0.18 g, 1 mmol) suspended in DMF (10 mL) and water (1.2 mL)[70a] was connected to an apparatus used for catalytic hydrogenation filled with oxygen at atmospheric

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pressure.[70d] The stirred mixture was heated at 65 °C under an oxygen atmosphere until the uptake of oxygen ceased (344 mL 0_2, 7 h). The reaction mixture was cooled, filtered, poured into 3N HCl and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. GC/MS analysis of the product indicated several components none of which showed a M^+ corresponding to the desired product.

(2). Epoxidation/rearrangement using H_2O_2/HCOOH.[72]

In a 3 neck flask was placed a mixture of 2-methyl cyclohexene (0.5 g, 5.2 mmol), 88% formic acid (0.16 mL, 4.4 mmol), p-toluenesulfonic acid (.05 equiv., 49 mg, .26 mmol) and toluene (25% by wt of olefin, 0.14 mL). Hydrogen peroxide (0.46 mL of a 50% solution, 6.8 mmol) was added slowly and the temperature was allowed to rise to 50 °C. The temperature was maintained at 50 °C with cooling. (CAUTION: If there is no exotherm after 10% of the hydrogen peroxide is added, the addition must be discontinued and the reaction mixture heated to 50 °C. If this is not done a dangerous

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reaction can occur). After stirring at 50 °C for an additional 2 h, the reaction mixture was cooled, diluted with water and extracted with CH_2Cl_2. The organic layer was washed with 10% sodium bisulfite and tested with peroxide test paper until complete destruction of peroxide was indicated. The organic layer was then washed with brine, dried ($MgSO_4$) and concentrated to afford (0.25 g, 31%) an oil, **128**: IR (CCl_4) 3500, 2920, 2870, 1725 cm^{-1}; ^1H NMR (60 MHz) 1.3 (s, 3 H), 1.5-1.8 (br, 8 H), 4.1 (s, 1 H), 4.8 (br, 1 H), 8.2 (s, 1 H); GC/MS 158. These data indicate that the epoxide formed by H_2O_2 was opened by the addition of HCOOH.

(3). Epoxidation followed by rearrangement.

(A) (i) Epoxidation of 2-methylcyclohexene.[80] A solution of 2-methyl- cyclohexene (0.48 g, 5 mmol) in dry methylene chloride was added to a solution of MCPBA (1.3 g, 7.5 mmol) at 0 °C. Usual work-up followed by column chromatography (5:1 hexane/EtOAc) afforded 0.4 g (78%) of the epoxide. IR (CCl_4) 2940, 1380 cm^{-1}; ^1H NMR 1.3 (s, 3 H) 1.6-1.8 (br, 8H), 3.1 (s, 1 H); GC/MS 112 (M^+).

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(ii) Attempted epoxidation of 2-methylcyclohexene using MMPP.[81] A solution of magnesium monoperphthalate (MMPP) hexahydrate (0.92 g, 1.9 mmol) in 20 mL of water was added to a solution of 2-methylcyclohexene (0.24 g, 2.5 mmol) in 20 mL of 2-propanol and the temperature was maintained 50 ^{o}C for 4 h. The mixture was then cooled, extracted with ether and the combined extracts were washed with water and dried ($MgSO_4$). Concentration of the solvents (rotary evaporator, no heating) gave an oil (83 mg, 35% recovery) with ^{1}H NMR spectral properties identical to those of the starting alkene.

(B) Rearrangement

(i) Rearrangement using $MgBr_2$ etherate.[73a] Magnesium bromide etherate was prepared by the dropwise addition of bromine (1 mL, 2.9 g, 18.4 mmol) to 1.5 g (62.5 mmol) of magnesium covered with 75 mL of anhydrous ether. An exothermic reaction ensued and the mixture was cooled in ice then allowed to stir at room temperature for 2 h. The resulting suspension was decanted from the excess magnesium, chilled and the etheral mother liquor was decanted from

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the white crystalline etherate. The salt was dissolved in a mixture of 50 mL of dry benzene and 50 mL of anhydrous ether. A solution of methyl-1,2-epoxycyclohexane (0.3 g, 2.7 mmol) in 10 mL of ether was treated with the above freshly prepared $MgBr_2$ etherate and the mixture was heated at reflux for 2 h. The mixture was allowed to cool then diluted with ether and poured into an aqueous solution of ammonium chloride. After the organic layer was separated and washed twice with water, the combined solvents were dried ($MgSO_4$) to afford 0.14 g of an oil. The IR spectrum of the product showed an hydroxyl absorption and no carbonyl. Without further characterization, the product was assumed to be the bromohydrin or the diol.

(ii) Rearrangement using anhydorus $LiClO_4$.[73c] A mixture of methyl-1,2-epoxycyclohexane (0.3 g, 2.7 mmol) and $LiClO_4$ (0.28 g, 2.7 mmol) in 10 mL of dry benzene was refluxed for 4 h. After the mixture was cooled, it was diluted with water extracted with ether and the combined extracts were washed with water and brine. Drying ($MgSO_4$) and removal of the solvent (rotary evaporator, no

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heating) afforded 0.11 g (37%) of an oil: IR (CCl_4) 2940, 1715 cm^{-1}; ^1H NMR 1.3 (d, 3 H), 1.6-1.8 (m, 6H), 2.1-2.2 (m, 3 H); GC/MS 212 (M^+)

Epoxidation of compound 120. To a mixture of **120** (1.0 g, 4.2 mmol) dissolved in 30 ml of CH_2Cl_2 and saturated $NaHCO_3$ (15 mL) cooled to 0 °C was added MCPBA (1.9 g of 50-60% solid, 5.5 mmol) was added in portions. After complete addition, the mixture was allowed to stir at room temperature for 3 h. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Removal of the solvent provided 1.0 g of an oil: GC/MS analysis indicated that the product was a mixture of several components. One component, present in 17%, showed m/z 197 (M^+ - COOMe) which could correspond to the desired product.

Hydroboration Oxidation of compound 120. To a solution of **120** (0.74 g, 3.1 mmol) in 10 mL of dry CH_2Cl_2 was added 10.0 M

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BH_3.DMS[75] (0.11 mL, 1.1 mmol) at ^oC under a nitrogen atmosphere. After the mixture was stirred at room temperature for 3 h, it was cooled to ^oC and pyridinium chlorochromate[76] (3.0 g, 13 mmol) was added during 5 min. Stirring was continued for 10 h (overnight) at room temperature. Following the addition of anhydrous ether, the mixture was filtered through a pad of anhydrous $MgSO_4$ and neutral alumina eluting with ether. Concentration of the solvent and purification by column chromatography (5:1 hexane/EtOAc) afforded 0.50 g of an oil. The ^1H NMR (60 MHz) spectrum indicated a mixture of products: 1.1 (br s, 6 H), 1.4-1.6 (m, 2 H), 1.7 (s, 3 H), 2.1 (s, 3 H), 2.7 (m, 1 H), 2.8 (s, 1 H), 3.4 (s, ?H), 3.5 (s, 3 H), 5.8 (d, 1 H), 6.6 (d, 1 H); IR (CCl_4) 2940, 1740, 1690 cm^{-1}; GC/MS: two components assigned as **130** and **131** showing m/z 196 (M^+ - HOAc).

Hydrolysis of compound 120. A mixture of compound **120** (0.25 g, 1.0 mmol) and K_2CO_3 (0.16 g, 1.1 mmol) in 10 mL of anhydrous methanol was stirred at room temperature for 1 h. The mixture was

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diluted with water, neutralized with 1.5 N HCl and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$) and concentrated to provide 0.19 g (94% combined yield) of an oil. HPLC analysis of the residue showed two components in an approximate 1 : 1 ratio which were separated by HPLC using 10 : 1 hexane/ethyl acetate affording compounds **132** and **133**. **132:** IR (CCl_4) 3490, 3010, 2960, 1720 cm^{-1}; ^1H NMR (200 MHz) 1.0 (s, 3 H), 1.1 (s, 3 H) 1.7 (s, 3H), 2.4 (m, 2 H), 2.7 (s, 1 H), 3.4 (br, 1 H), 3.8 (s, 3 H), 4.1 (br, 1 H) 5.5 (br, 1 H); GC/MS 198 (M^+). HRMS calcd for $C_{11}H_{17}O_3$ $(M-H)^+$ 197.1178, found 197.1158. **133:** IR (CCl_4) 3500, 2960, 1740, 1715 cm^{-1}; ^1H NMR (60 MHz) 0.9 (s, 3 H), 1.1 (s, 3 H), 1.3 (s, 3H), 1.4 (s, 3 H), 1.8 (s, 3H), 2.1 (m, 4 H), 2.9 (s, 1 H), 3.5(br, 1 H), 3.9 (s, 3 H), 4.4 (s, 1 H); GC/MS 198. HRMS calcd for $C_{11}H_{19}O_3$ $(M+H)^+$ 199.1334, found 199.1325. In addition there was a peak at 247.

Oxidation of the mixture of 132 and 133. Jones reagent was

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added to the mixture of alcohols **132** and **133** (0.21 g, 1.1 mmol) in acetone at 0 °C until an orange color persisted (1 mL).[77] After the mixture was stirred at room temperature for 3 h, it was diluted with ether then washed with 1.5 N HCl, water and brine. Drying and removal of the organic layer afforded 0.19 g (89%) of an oil. Purification by HPLC (10 : 1 hexane/ethyl acetate) provided **101** and **134** in an approximate ratio of 8 : 1, respectively. **101:** IR (CCl_4) 3010, 2980, 1735, 1720 cm^{-1}; ^1H NMR (200 MHz) 1.1 (s, 3 H), 1.3 (s, 3 H) 1.9 (s, 3H), 3.0 (d, 3 H), 3.7 (s, 3 H), 5.7(br, 1 H); GC/MS 196 (M^+). HRMS calcd for $C_{11}H_{15}O_3$ $(M-H)^+$ 195.1021, found 195.1031. **134:** IR (CCl_4) 2940, 1740, 1720 cm^{-1}; ^1H NMR (60 MHz) 1.1 (s, 3 H), 1.5 (s, 3 H) 1.6 (s, 3H), 1.8 (s, 3 H), 2.0 (s, 1 H), 2.4 (s, 1 H), 3.4 (d, 1 H), 3.8 (s, 3 H), 3.9 (s, 1 H), 4.2 (s, 1 H); GC/MS 250. HRMS calcd for $C_{11}H_{15}O_3$ $(M-H)^+$ 195.1021, found 195.1013. There were also peaks at 247 and 301.

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APPENDIX

^{1}H NMR (300 MHz) of compounds 9, 10, 13, and 14.

2D-COSY of compounds 9, 10, and 13.

DEPT of compounds 13 and 14.

X-ray structure of compound 15.

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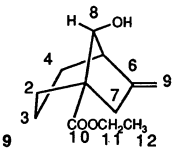

X = exo

N = endo

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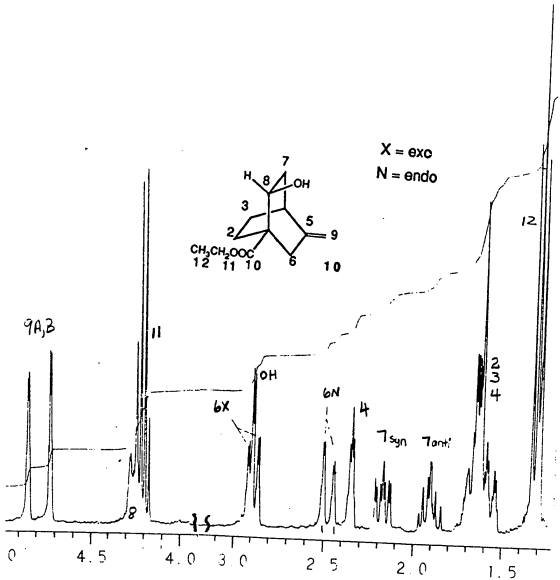

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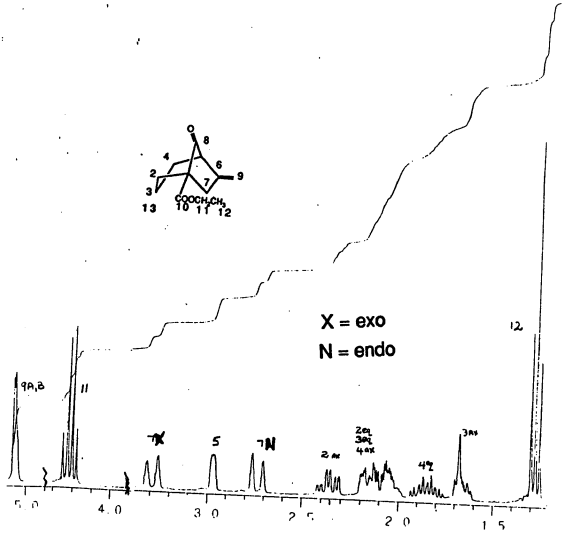

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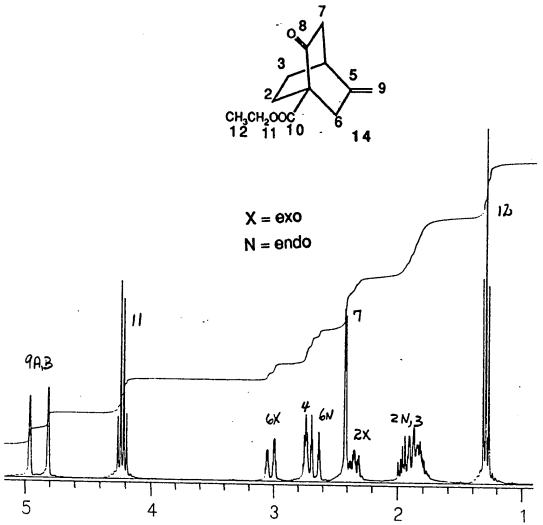

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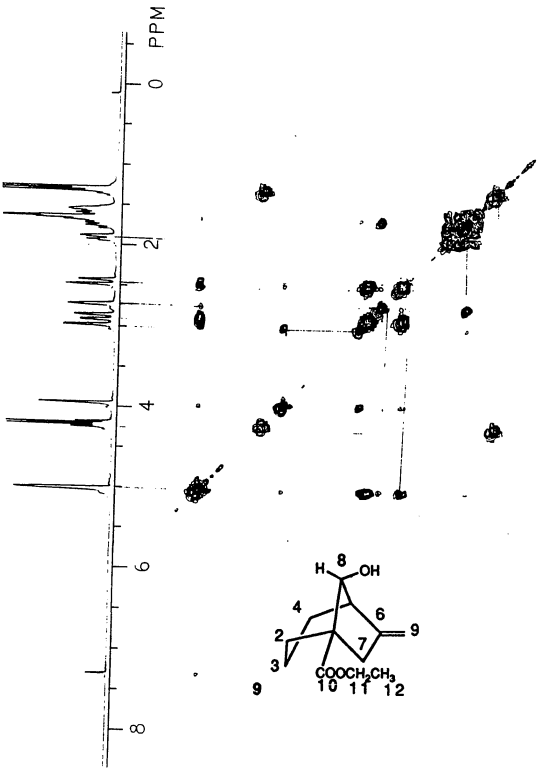

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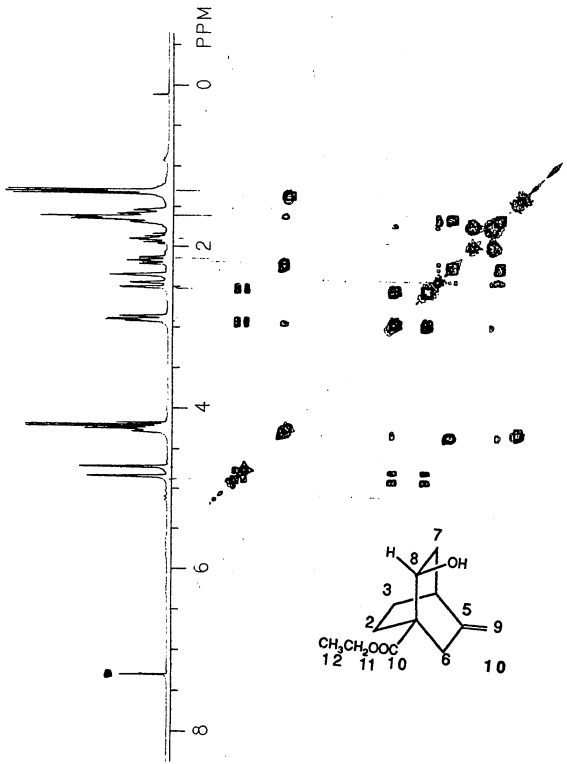

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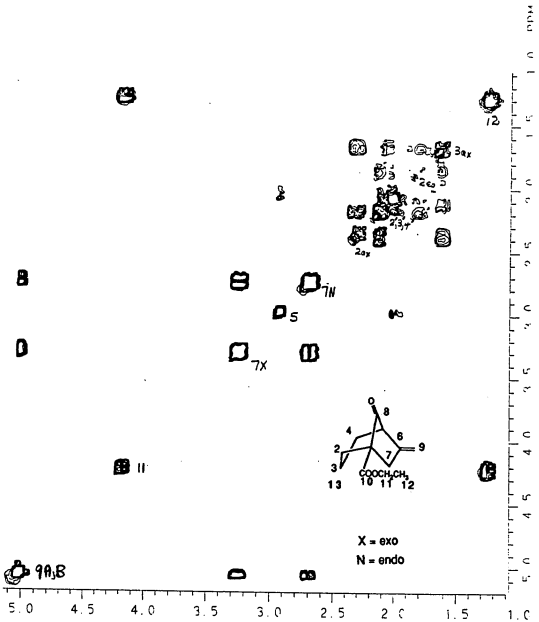

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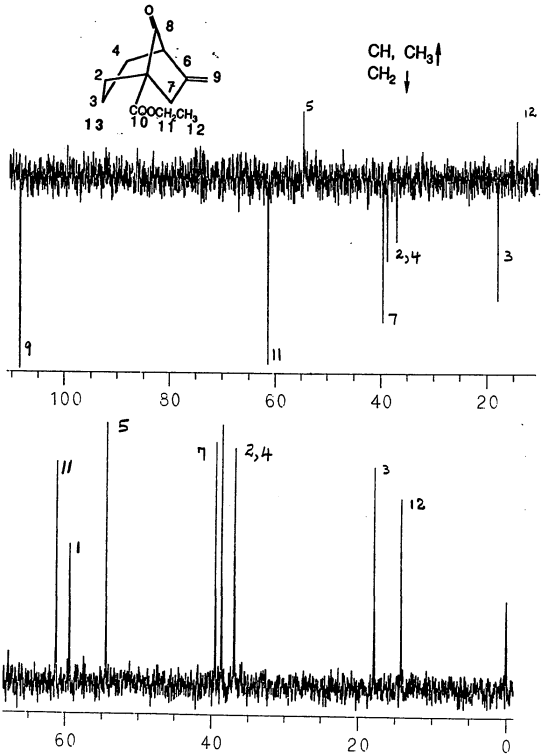

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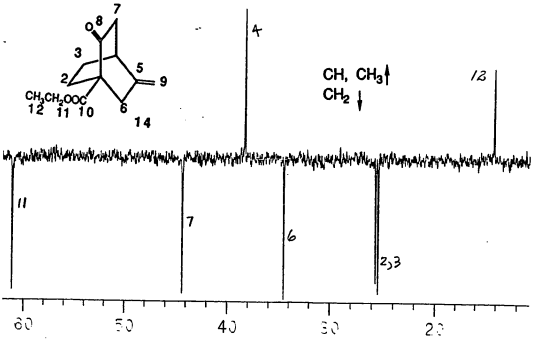

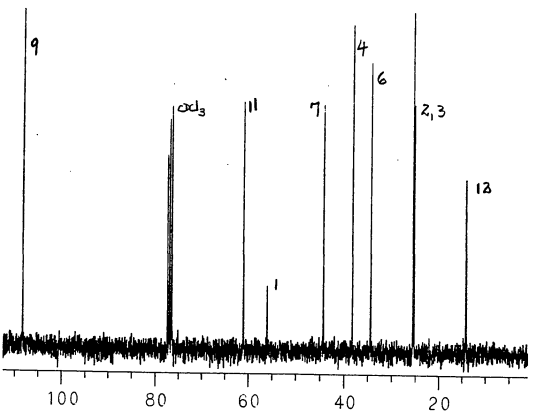

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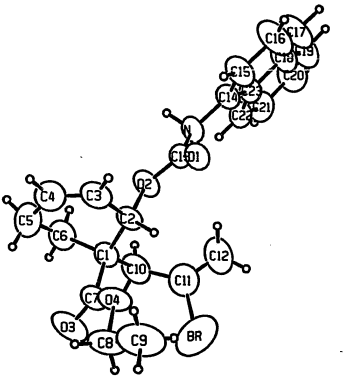

X-ray structure of compound **15**.

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