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The synthesis of the A-ring of taxol

Gao, Zhongli, Ph.D.

City University of New York, 1994

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The Synthesis of the A-ring of Taxol

By

Zhongli Gao

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

1994

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.

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Date

William Frost Perkonitz
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THE CITY UNIVERSITY OF NEW YORK

Abstract**The Synthesis of the A-ring of Taxol**

By

Zhongli GaoAdvisor: Professor **W.F. Berkowitz**

Synthesis of the tetracyclic portion of taxol from simple precursors has the potential not only for providing an alternative source of this drug, and a second generation of drugs with enhanced attributes, but also for defining the portions of molecule responsible for its biological activity. In our attempts at total synthesis of taxol via a photochemical approach, eg. connecting an A-ring synthon with a CD-ring portion, we needed a useful A-ring synthon. The focus of this investigation was directed toward the synthesis of an A-ring synthon for taxol.

The synthesis started from the Johnson-Claisen rearrangement reaction of 3-methyl-2-buten-1-ol to afford, after hydrolysis, 3,3-dimethyl-4-pentenoic acid. This acid was esterified with 2-methyl-2-buten-1-ol. The resulting

ester was subjected to the Ireland-Claisen rearrangement conditions and esterification to form a diene ester. This diene ester and its derivatives have also been synthesized via two other routes. Ozonolysis of the diene ester yielded a ketoaldehyde. This ketoaldehyde underwent an intramolecular aldol reaction catalyzed by (L)-proline to yield an *A*-ring synthon with the proper functionalities for further transformation. The further transformation was attempted by protection of the keto functionality as a ketal and oxidation of the hydroxyl group into a keto group to obtain a key intermediate keto ester. Addition of an acetyl equivalent was attempted by acetylene addition-hydration.

Meanwhile, the diene ester was reduced into an alcohol and protected as a silyl ether. After ozonolysis and aldol cyclization, another *A*-ring synthon was obtained successfully. This and the intermediate obtained above are both suitable for the further transformation and will be employed in the construction of the *A*-ring synthon of taxol.

Acknowledgements

I wish to express my deepest gratitude to my advisor Professor William F. Berkowitz, for giving me the opportunity to be a member of his group, and for teaching me how to appreciate the art of organic synthesis. His insightful guidance, continuous support and intellectual discussions made the years of my graduate career pleasant and fruitful.

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Special thanks go to Professor David C. Locke at Queens College, CUNY, who did all the GC / MS analysis reported in this manuscripts.

I would also like to acknowledge my colleagues, and all members of the Department of Chemistry at Queens College, for the warm and caring work environment that they shared with me. Thanks to the Department of Chemistry for providing financial support through teaching assistantship throughout my stay at CUNY.

Finally, I would like to dedicate this thesis to my wife who supported me in every way throughout the years of my studies.

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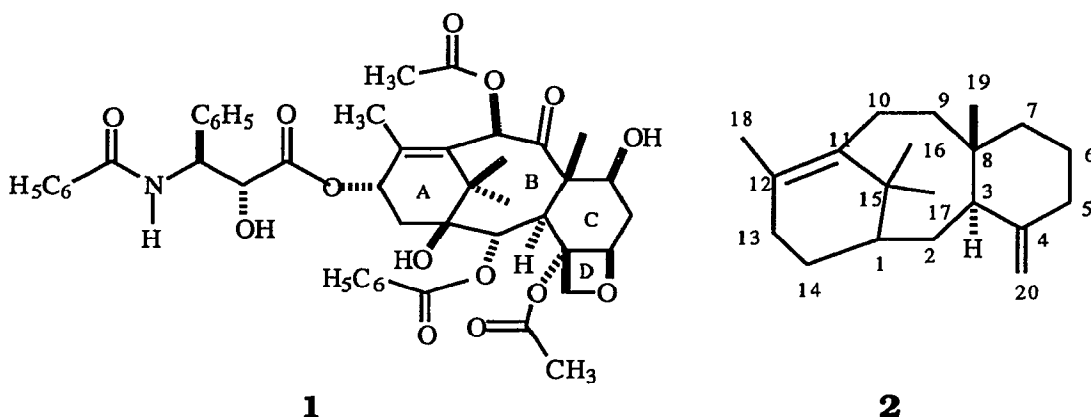
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Chapter 1. Introduction

1.1 Background

Taxol (**1**) is a novel polyoxygenated diterpenoid isolated from the western yew tree, *Taxus brevifolia*. It has shown promising results in fighting advanced cases of ovarian, breast, and other cancers.¹ Structurally, this drug shares a common carbon skeleton² **2** with the group of taxane diterpenes isolated from various yew (*Taxus*) species.



Taxol was discovered as part of an NCI sponsored program in which extracts of over 35,000 plant species were tested for anticancer activities between 1958-1980.³ M. E. Wall and M. C. Wani first isolated a crude taxol concentrate from yew tree bark and wood samples in 1963. Initial screening tests showed the extract to be a potential anti-

cancer agent which was very active against an unusually wide range of rodent cancers. The isolation of the active agent, a process that took several years because the agent was present at very low concentrations in the plants, led to the determination of its structure by X-ray analysis.³

1.2 Mechanism of Action

Investigation found a unique mechanism for taxol's anti-tumor activity involving cell microtubules. Microtubules are ubiquitous cellular constituents that consist of a and b tubulin protein subunits. They are the primary constituents of mitotic spindles (the rod-like material that is responsible for the equal partitioning of chromosomes to daughter cells). Microtubules play a key role in mitosis, maintenance of cell shape, cell motility, and intracellular transport. They are self-assembling and self-disassembling structures that are in dynamic equilibrium with tubulin dimers, the protein subunits of which they are composed. A substance that interferes with microtubules can disrupt cell growth and function.

The first report of taxol's novel mechanism of action was by Horwitz⁴ who in 1979 indicated that taxol was an antimicrotubule agent whose mechanism of action differed

from existing antimicrotubule agents such as colchicin.⁵ Binding of taxol to tubulin acts to stabilize cell microtubules and to prevent their depolymerization. Other drugs were known to bind tubulin, but they all enhanced disassembly of microtubules. Taxol's mechanism was unique. Cells treated with taxol (0.1-10 $\mu\text{mol} / \text{L}$) form disorganized microtubules and formed abnormal spindles during mitotic cell division. This disrupts the substructure of cancer cells and somehow prevents their rapid division and spread. The exact mechanism of this anticancer action is not yet known but it has been speculated that taxol acts as an alkylating agent.⁶ According to Horwitz, the binding of taxol is reversible.

1.3 Therapeutic Demand and Availability of Taxol

In phase II clinical trials,⁷ taxol has caused full or partial tumor shrinkage in 22 to 50% of patients with refractory cases of ovarian cancer (cases unresponsive to conventional therapy), with an average response rate of about 30%. And in phase II clinical trials of the drug in metastatic breast cancer patients who had not received very much prior therapy, full or partial responses have been seen in 56% to 62% of patients. Additional clinical trials, including

some phase III trials are currently being conducted to evaluate taxol's effectiveness against various forms of cancer.⁸

The effectiveness of taxol in these studies has heightened public awareness and led to increased demand for this drug. In addition, the FDA^{9a} has approved taxol for use in treating ovarian cancer patients who have failed to respond to standard chemotherapy or platinum-based drugs such as cisplatin. Taxol is currently available in the quantities necessary for US patients. The major source is semisynthesis from baccatin III obtained by extraction from the English yew by Bristol Myers Squibb. The bark of the Pacific yew tree which grows in forests of the western US and Canada is another source for obtaining taxol.^{9b} Yews are slow-growing evergreens, and the isolation procedure required to obtain taxol is difficult, low-yielding and expensive. Based on current bark-extraction procedures,¹⁰ it is estimated that it takes about three trees to provide enough drug to treat one cancer patient. In addition, the trees must be killed to harvest the bark. This has promoted concerns by ecologists about survival of the tree and its habitats.¹¹

Strategies being investigated^{9b} to increase the availability of taxol include total synthesis from simple starting

materials, partial synthesis from readily available taxol precursors, extraction from taxus bark and/or needles, cultivation of taxus plants, identification of simpler drug analog and cell culture production. Although, for the short term, extraction from the natural resources is the most viable way to obtain taxol, chemical synthesis, especially total synthesis, in the long term, would be of great scientific value. Chemical synthesis could not only be an alternative supply of the drug on a commercial basis, but could also supply taxol mimics, taxol surrogates, or second-round drug candidates. This is because taxol may not prove to be the best anticancer drug due to its toxicity and poor aqueous solubility. Taxol analogs could also have greater therapeutic effect with fewer drawbacks. It is believed that chemical synthesis may play its biggest role in making these analogs of taxol.

1.4 Semisynthesis of Taxol

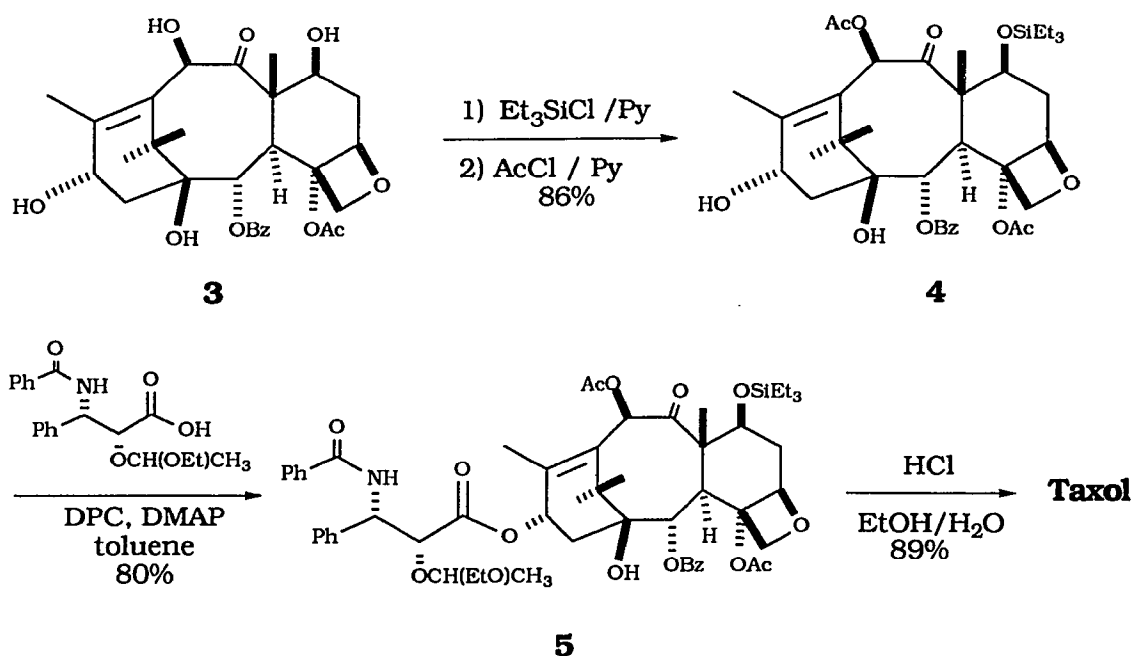
Owing to the growing demand for taxol and the structural challenge, the synthesis of taxol has attracted great attention all over the world. There are more than 35 research groups worldwide that have worked on the synthesis of taxol and related compounds.¹² It is believed that

taxol is one of the most important targets for synthetic chemistry today.

Although the total synthesis of taxol remains as yet an unattained goal, the partial synthesis from naturally occurring 10-deacetyl Baccatin III (**3**) has already achieved¹³ (Scheme 1), and is an important commercial source of the drug.

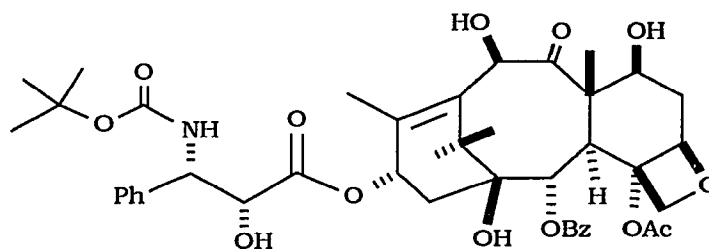
There have also been reports of very efficient synthesis of the taxol side chain.¹⁴

Scheme 1. Green's Semisynthesis of taxol



In addition to the partial synthesis of taxol, there are

several reports of semisynthesis of closely related analogs of taxol.¹⁵ To date, the most interesting analog is taxotere (**6**), a very potent anticancer agent also prepared from naturally occurring 10-deacetyl Baccatin III in the manner similar to Scheme 1. Taxotere differs from taxol only in the C13 ester chain and at C10 where a hydroxyl group is in place of the acetoxy group. Taxotere shows greater aqueous solubility and may be more potent than taxol.¹⁶

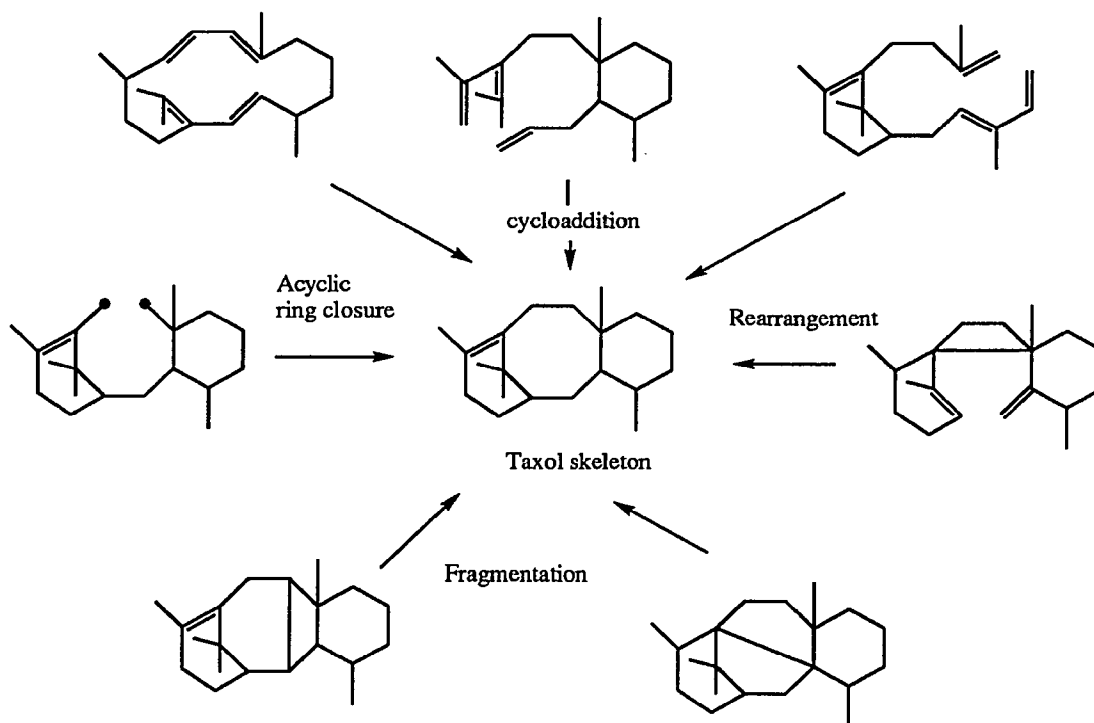
**6**

1.5 Strategies of the Total Synthesis of Taxol, a Brief Review

The semisynthesis of taxol and its analogs discussed above all start from the naturally occurring taxane skeleton. Intense efforts directed towards the total synthesis of taxol have been made.^{12,17} In consideration of the complexity of taxol, the most challenging parts of the molecule include the 8-membered ring, C1 hydroxyl, oxetane-acetoxy

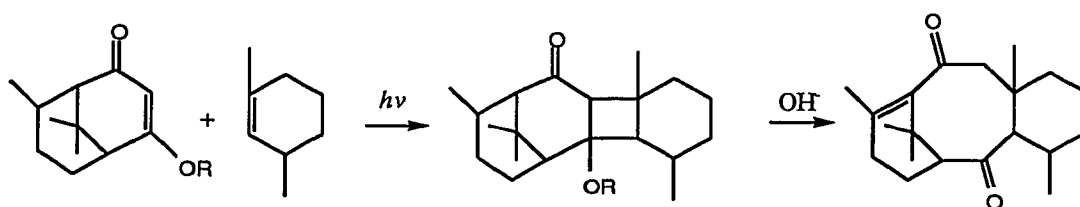
groups and general stereochemical problems. Several synthetic strategies have been documented, which include, as a key step various forms of intramolecular Diels-Alder reaction,^{17a-e} intramolecular carbocation-induced cyclization,^{17f-g} the Claisen and other rearrangements,^{17h-k} photochemical cyclization,^{17l-q} nickel catalyzed cycloaddition,^{17r,s} and N(II) / Cr (II) mediated coupling^{17t} (Scheme 2).

Scheme 2. Strategies for construction of taxane skeleton



Among these strategies, the de Mayo sequence ([2+2] photoaddition followed by base initiated fragmentation as shown in Scheme 3) is primarily noteworthy for the construction of the eight membered ring at the same time as the A ring and C/D ring units are connected.

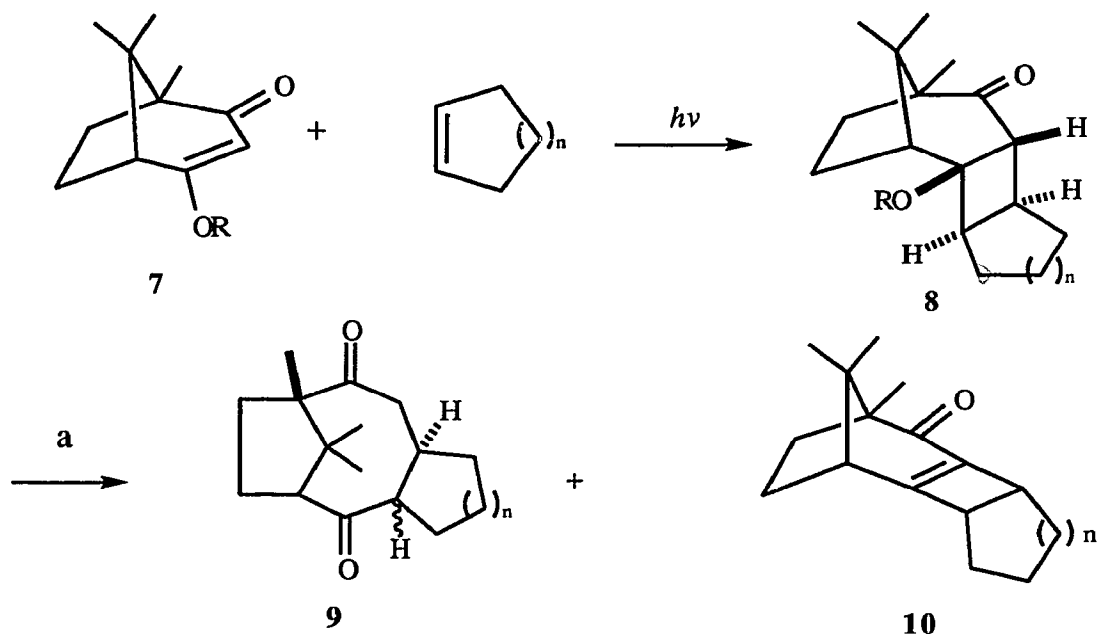
Scheme 3. de Mayo sequence



The potential of de Mayo sequence in construction of the taxane skeleton can be clarified with the following well documented examples (Schemes 4-8).

Scheme 4¹⁸ illustrates a series of intermolecular photoaddition reactions between homocamphor derivatives **7** and cyclopentene and cyclohexene. The interesting stereochemical feature of these reactions is the facial selectivity imposed by the homocamphor geminal dimethyl moiety. Berkowitz subjected **8** to a variety of fragmentation protocols, which were complicated in some instance by elimination product **10**.

Scheme 4. Berkowitz's Model Study



R = Me, Ac

a. conditions tested:

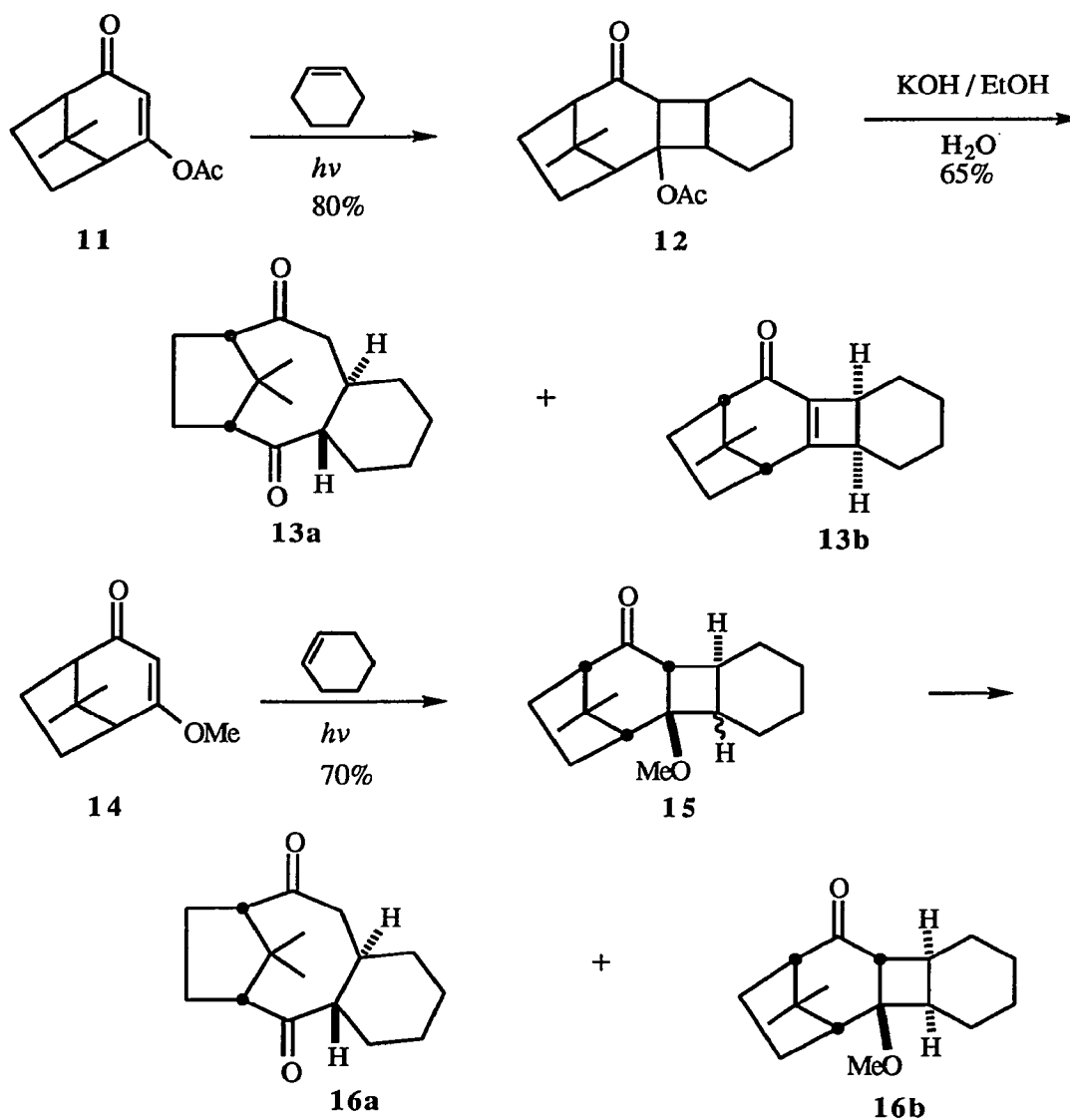
(1) H_2SO_4 / MeOH (30%); (2) K_2CO_3 / MeOH (60%)

(3) KOH / EtOH (60%); (4) TMSI (90%)

$n=1, 2$.

A quite similar result was observed by Fetizon¹⁹ (Scheme 5). Again, the fragmentation of **12** with KOH in aqueous ethanol afforded **13a** (48%) and **13b** (32%), while **15** afforded **16a** and recovered diastereomer of **15**. Scheme 6¹⁸ shows another similar result.

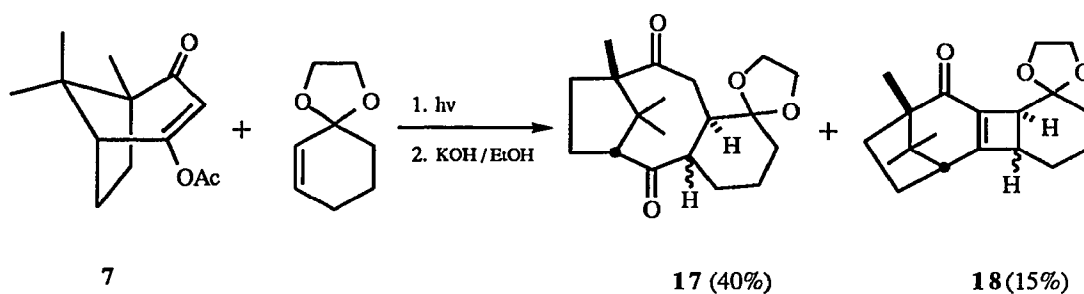
Scheme 5. Fetizon's approach



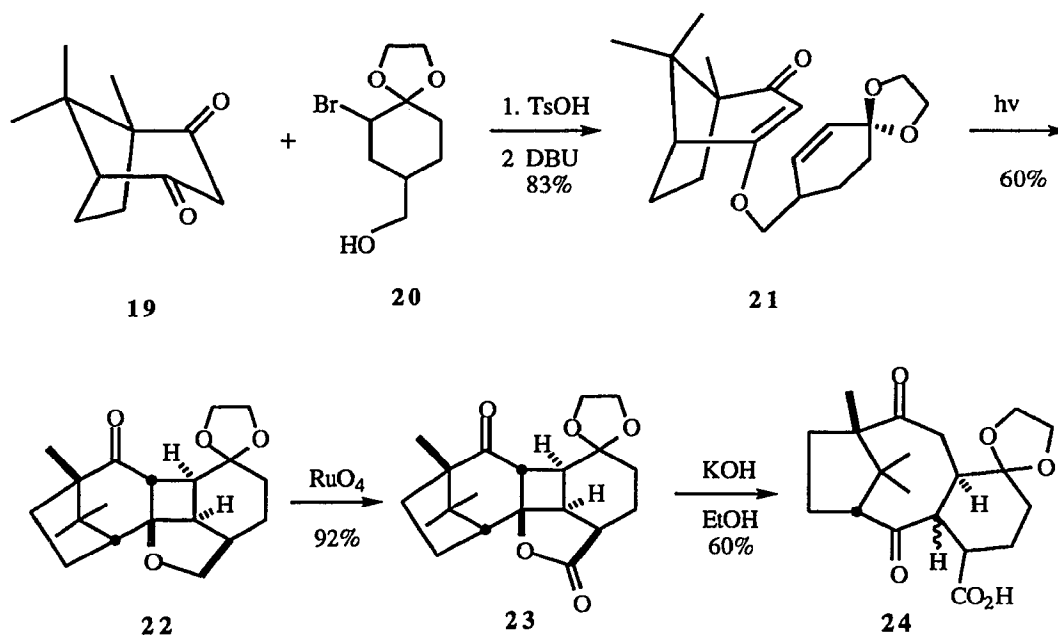
The intramolecular de Mayo sequence was also tested. Scheme 7^{18a} illustrates the preparation of a homocamphor-derived vinylogous ether **21** which underwent a pho-

tochemical transformation to **22** whose stereochemical details were postulated on the basis of the observed intermolecular cycloaddition reaction mentioned above in Schemes 5 and 6. The subsequent transformations completed the preparation of taxane model **24**.

Scheme 6. Berkowitz's intermolecular Approach



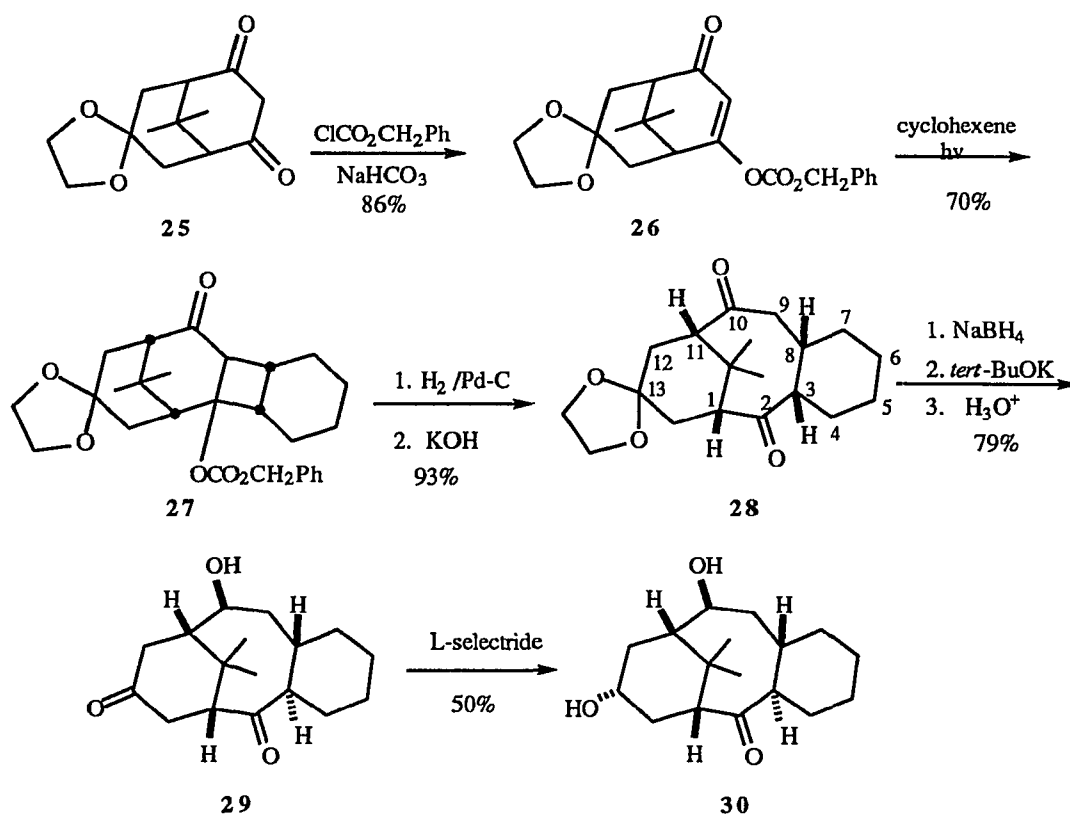
Scheme 7. Berkowitz's Intramolecular Approach



Blechert's similar intermolecular approach, Scheme 8,²⁰ differed by the introduction of a ketal moiety to control the C1-C8 relative stereochemistry. Consequently, the sequence shown in Scheme 8 yielded the *correct* C1-C8 relative stereochemistry.

Indeed, the C1-C8 relative stereochemistry is one of the fundamental issues that any taxane synthesis strategy must take into account. Blechert (Scheme 8) succeeded in fixing photochemically the C1 and C8 stereochemistry and then adjusted stereochemistry at C3 through a late

Scheme 8. Blechert's approach



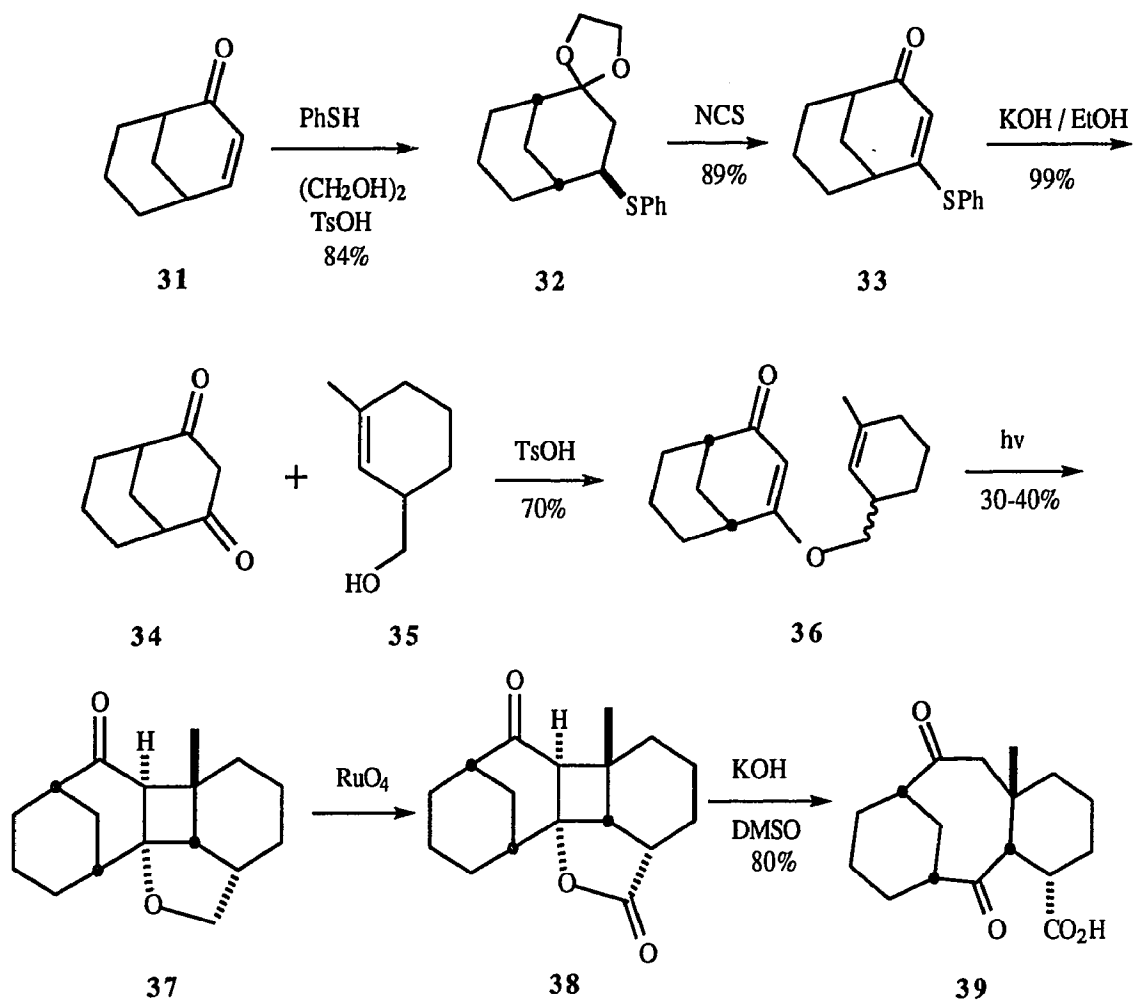
epimerization. The important stereochemical control device in Blechert's approach was the ketal. This may be appreciated by considering the results shown in Schemes 4-7. It was postulated¹⁸ that the *gem*-dimethyl of the homocamphor-derived substrates (Scheme 7) prohibited *exo* approach of the olefin with the result that the C1- C8 relative stereochemistry was incorrectly introduced. The problem was solved by using the ketal moiety which overcame the control imposed by the geminal dimethyl feature by sterically hindering *endo* approach.

On the other hand, Inouye's²¹ unadorned system (Scheme 9) underwent cycloaddition on the *exo* face of the vinylogous ether chromophore through a process that correctly established C1-C8 relative stereochemistry; this again presumably because of the absence of the geminal dimethyl group.

All these examples strongly demonstrated that the strategy studied ([2+2] photoaddition followed by fragmentation) is a relatively efficient way for construction of the taxane skeleton. It is worth noting that the relative stereochemistry at C1 and C8 was efficiently controlled by the ketal (Scheme 8). Without the ketal, the stereochemistry would be controlled by the geminal dimethyl group

which gave the incorrect stereochemistry (Schemes 5-7).

Scheme 9. Inouye's approach



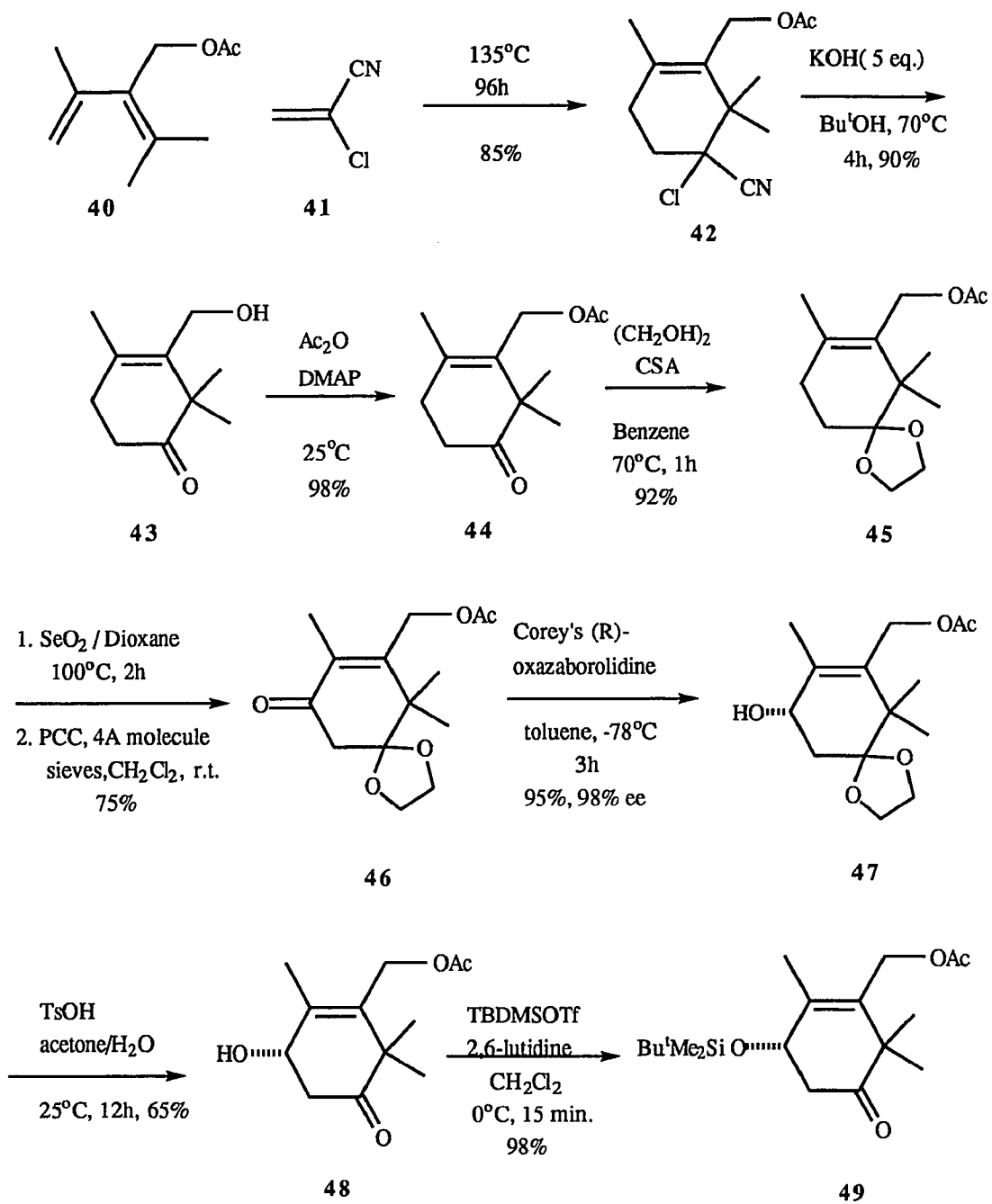
1.6 Approaches to the A-ring Synthon of Taxol

The A-ring of taxol with its *gem*-dimethyl and oxygen functionalities at C1 and C13 presents a considerable synthetic challenge. It is not surprising that the emphasis of many investigations have been on the synthesis of the A-ring,²² either by itself or as part of an ABC-ring framework. In convergent synthesis, especially the de Mayo sequence mentioned in Section 1.5, the A-ring is one of the starting points for construction of the ABC-ring skeleton. In this section, some approaches to the A-ring synthon will be briefly reviewed.

1.6.1 Cyclization

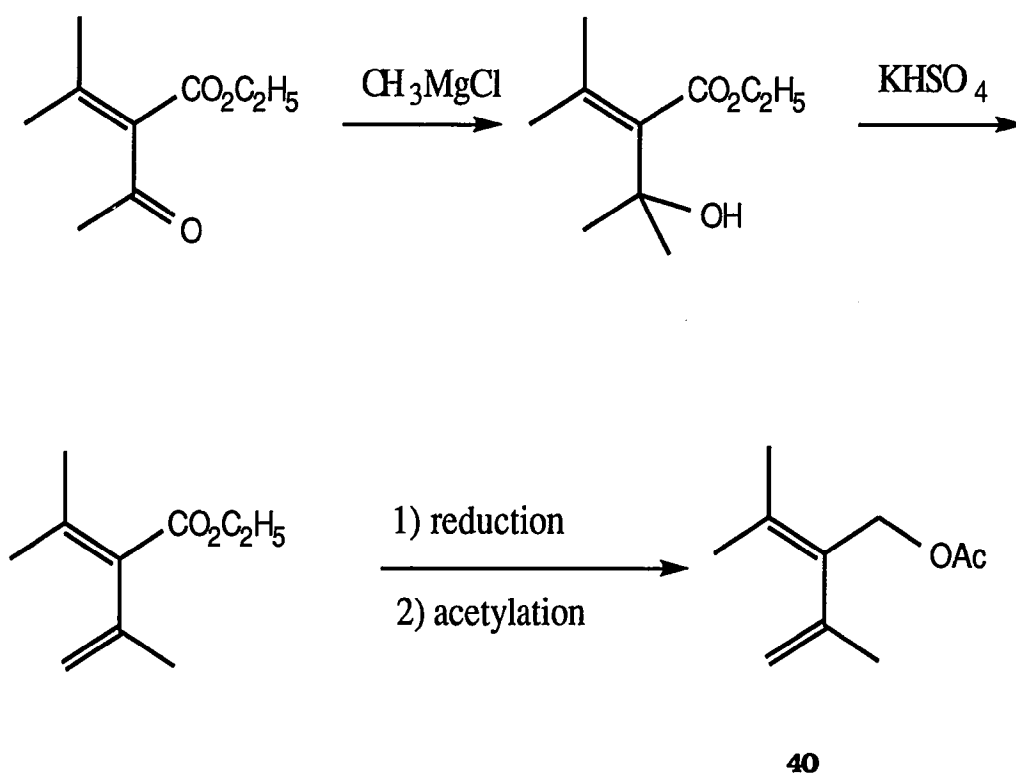
Very recently, Nicolaou^{22a} reported a stereocontrolled construction of A-ring synthon by employing the Diels-Alder reaction to construct a substituted cyclohexane ring (Scheme 10). The key step, reaction of diene **40** with ketene equivalent **41**, established the major features of the A-ring in one step. The C13 hydroxyl group of taxol was successfully introduced through an allylic oxidation (SeO₂), followed by an enantioselective reduction with Corey's (R)-oxazaborolidine.

Scheme 10. Nicolaou's approach



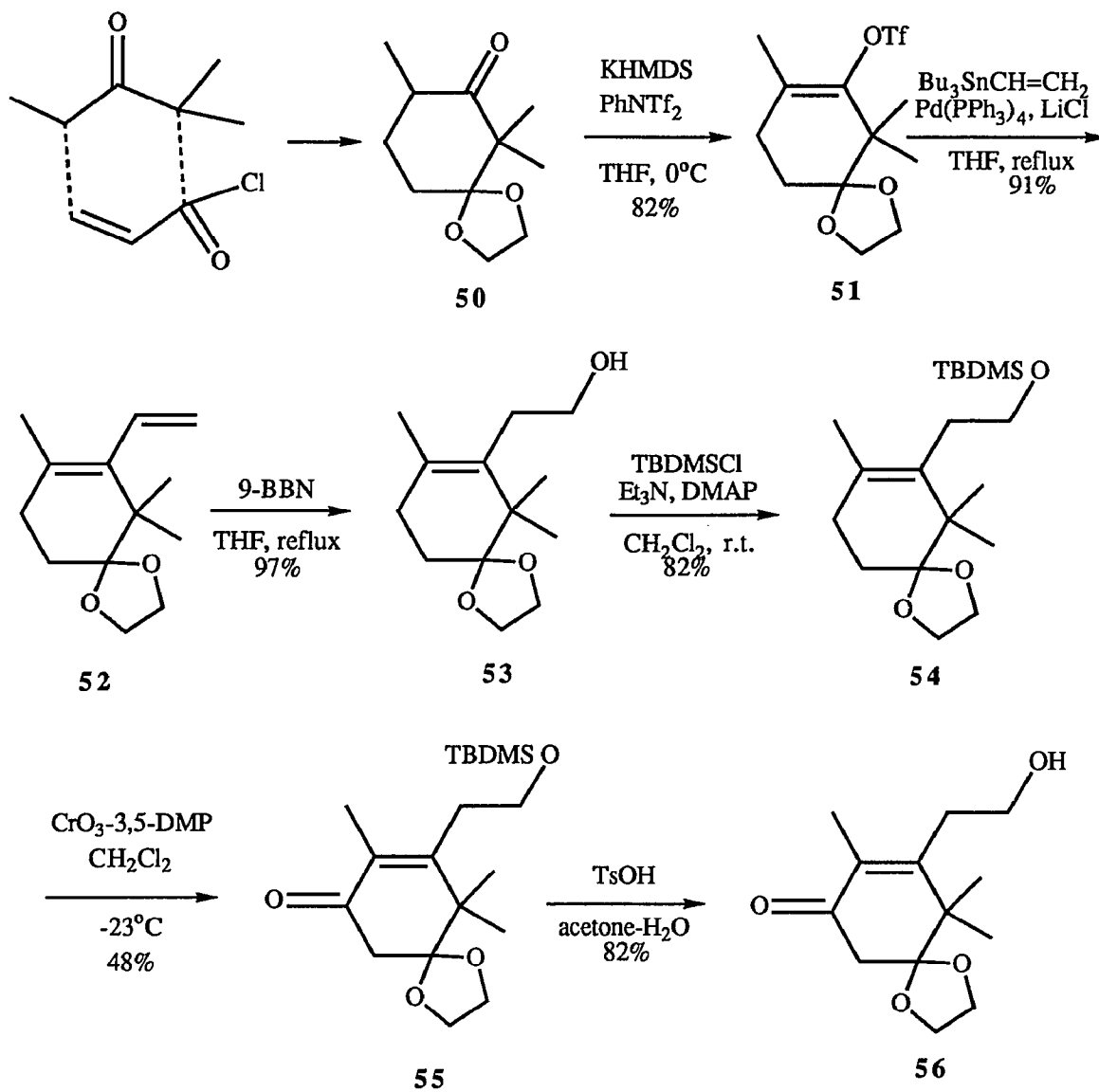
The starting material diene **40** in Nicolaou's approach was prepared by the following known sequence (Scheme 11):^{22b}

Scheme 11. Preparation of **40** in Nicolaou's Approach



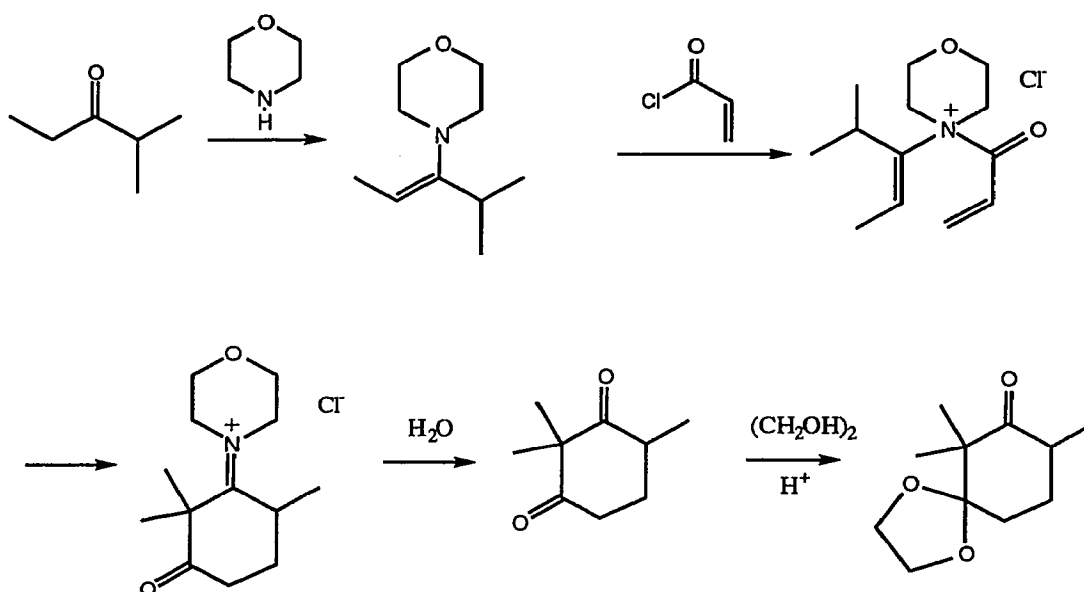
Another approach was reported by Danishefsky^{22c} as shown in Scheme 12. The C13 oxygen was introduced by allylic oxidation (CrO_3 -3, 5-DMP).

Scheme 12. Danishefsky's approach



Ketone **50** was prepared by the following known five-step sequence (Scheme 13):^{22d}

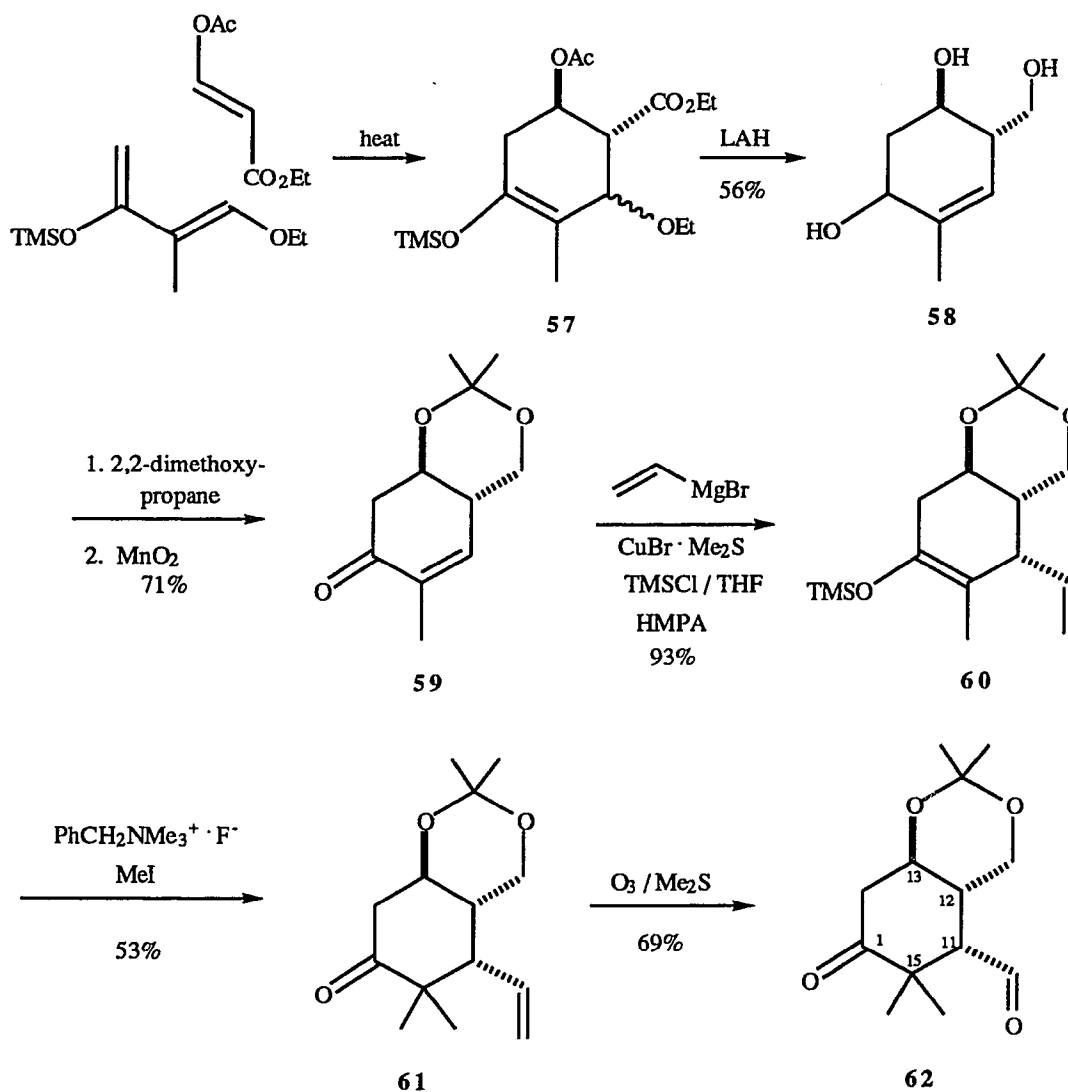
Scheme 13. Preparation of **50** in Danishefsky's approach



Clark^{22e} has also investigated the preparation of A-ring precursor of taxol, **62** (Scheme 14) using the Diels-Alder reaction. By choosing a different diene and dienophile, the C1 and C13 oxygen functionalities were incorporated in the Diels-Alder reaction step, while the C11

carbon functionality was introduced subsequently by Michael addition.

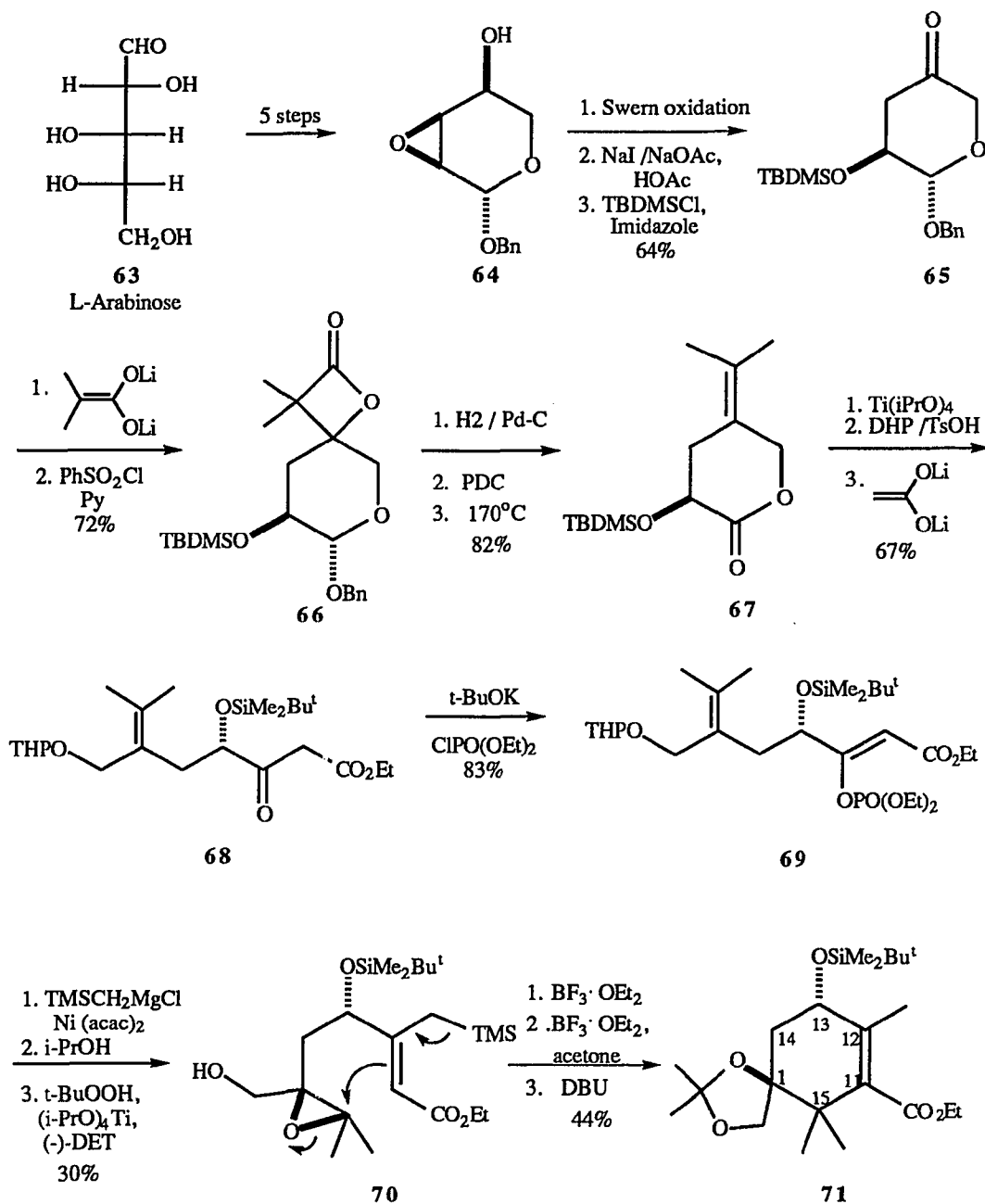
Scheme 14. Clark's Approach



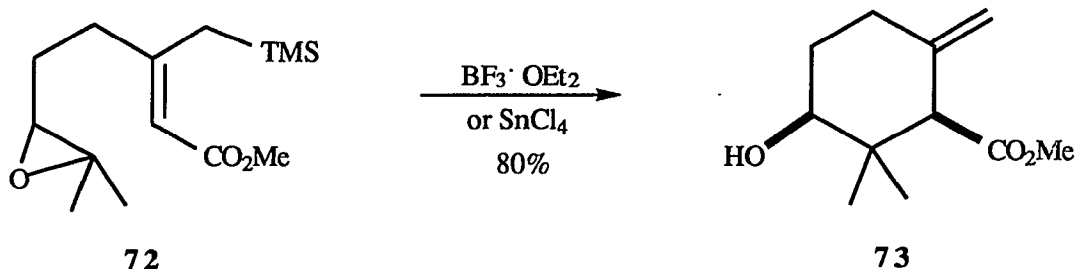
All of the approaches reviewed above can be classified as a "two-molecule" strategy: the cyclohexane ring was assembled from two fragments. The following examples are classified as "one-molecule" strategies.

Frejd's^{22f} work is illustrated in Scheme 15. The sequence started from L-arabinose and **71** was prepared via a 23-step transformation. The key step is the Lewis acid catalyzed cyclization of trimethyl silyl epoxide **70**. The feature of this sequence is that the C13 hydroxyl group comes from the C2 of L-arabinose, with the correct absolute stereochemistry being transferred to the end of synthesis. Sharpless epoxidation created another chiral center which was kept intact during the cyclization step. The final cyclization was secured by the trimethyl silyl group control element. This type of cyclization would not give the desired cyclic product unless the trimethylsilyl group is present. Another similar example^{22g} is shown in Scheme 16.

Scheme 15. Frejd's Approach



Scheme 16. Armstrong's approach

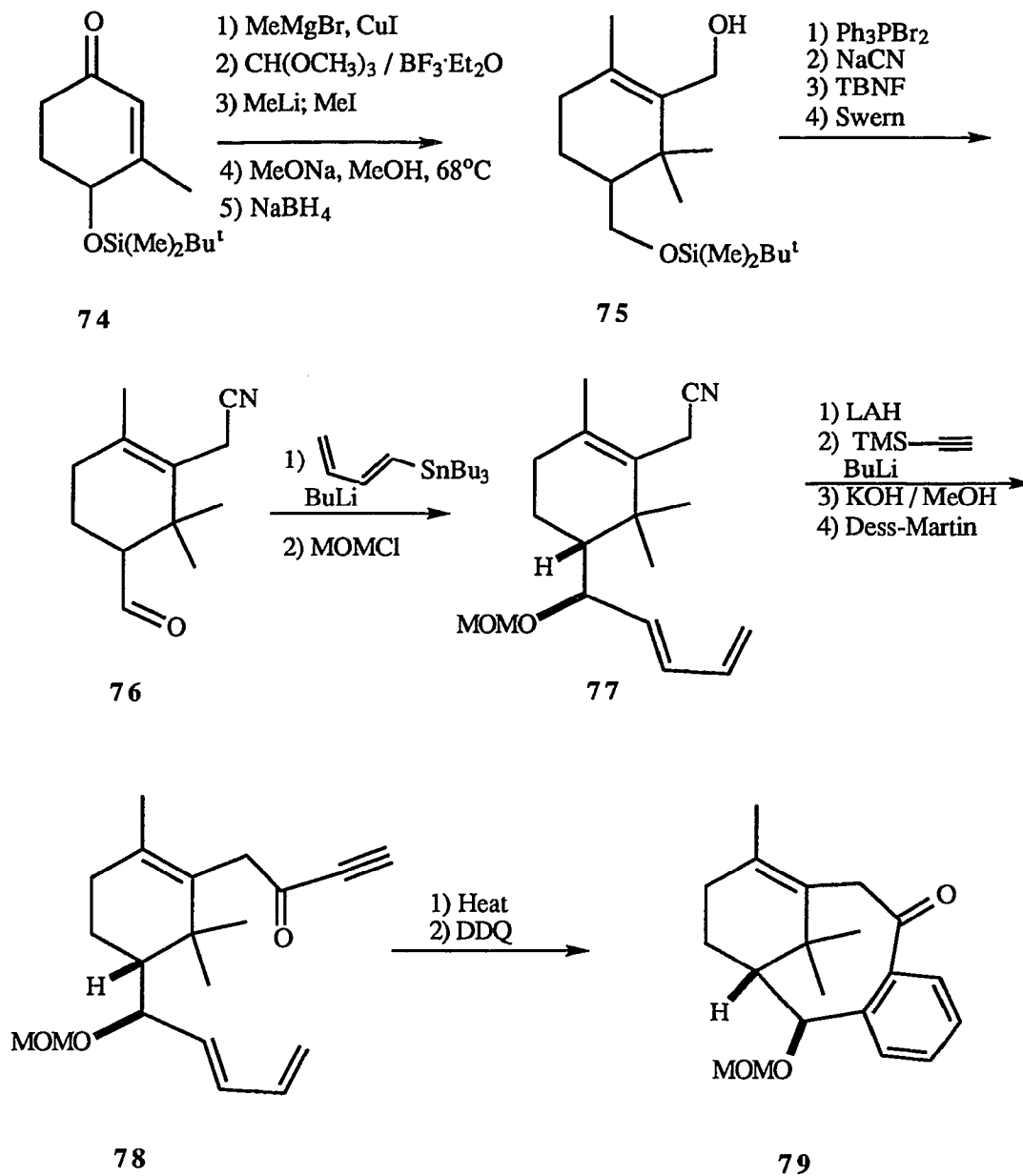


1.6.2 Modification of cyclic system

In this section, some approaches to the A-ring synthesis for taxol involving the modification of an existing cyclohexane ring system will be briefly mentioned.

In 1993, Fallis^{17e} reported the synthesis of a taxane skeleton via an intramolecular Diels-Alder reaction. The sequence started from a known enone **74** and after a series of manipulations, a key precursor **78** was obtained. The Diels-Alder reaction was effected by heating and the stereochemistry of addition was found to be controlled by the C2 epimer (Scheme 17).

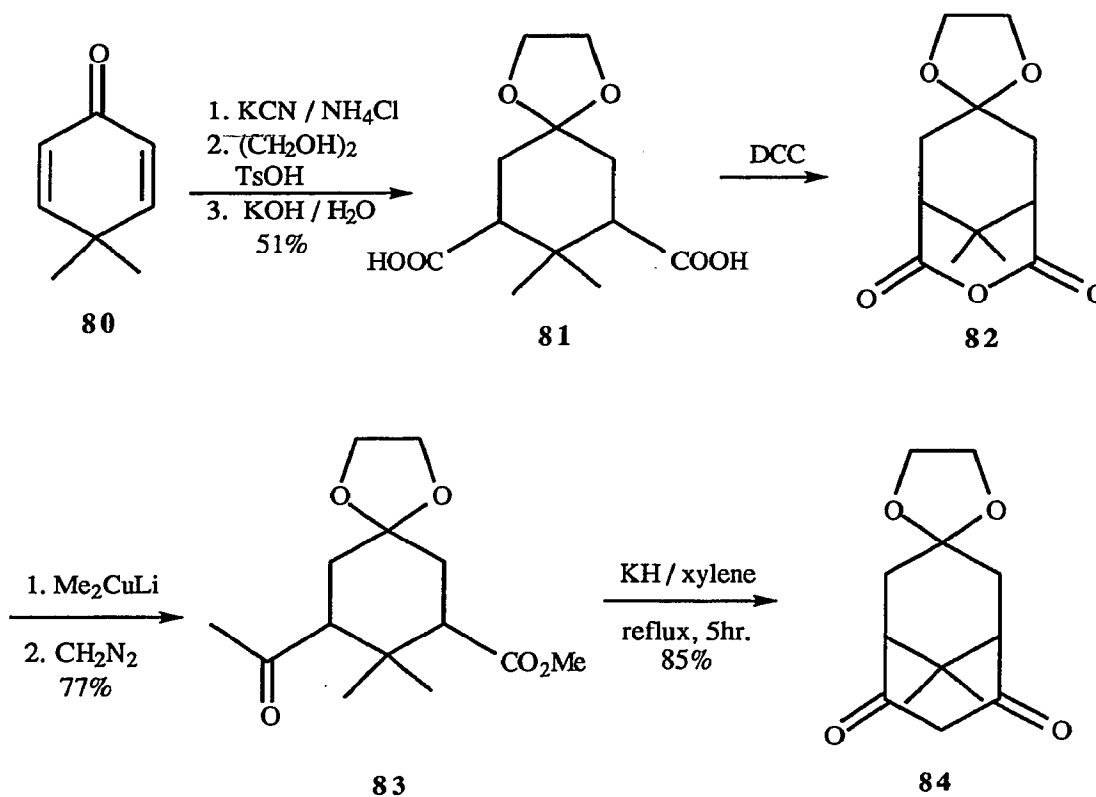
Scheme 17. Fallis' Approach



Blechert²⁰ assembled **84** through the seven-step process depicted in Scheme 18. The sequence created a [3, 3, 1]

ring system successfully, but the hydroxyl group at C1 was not incorporated.

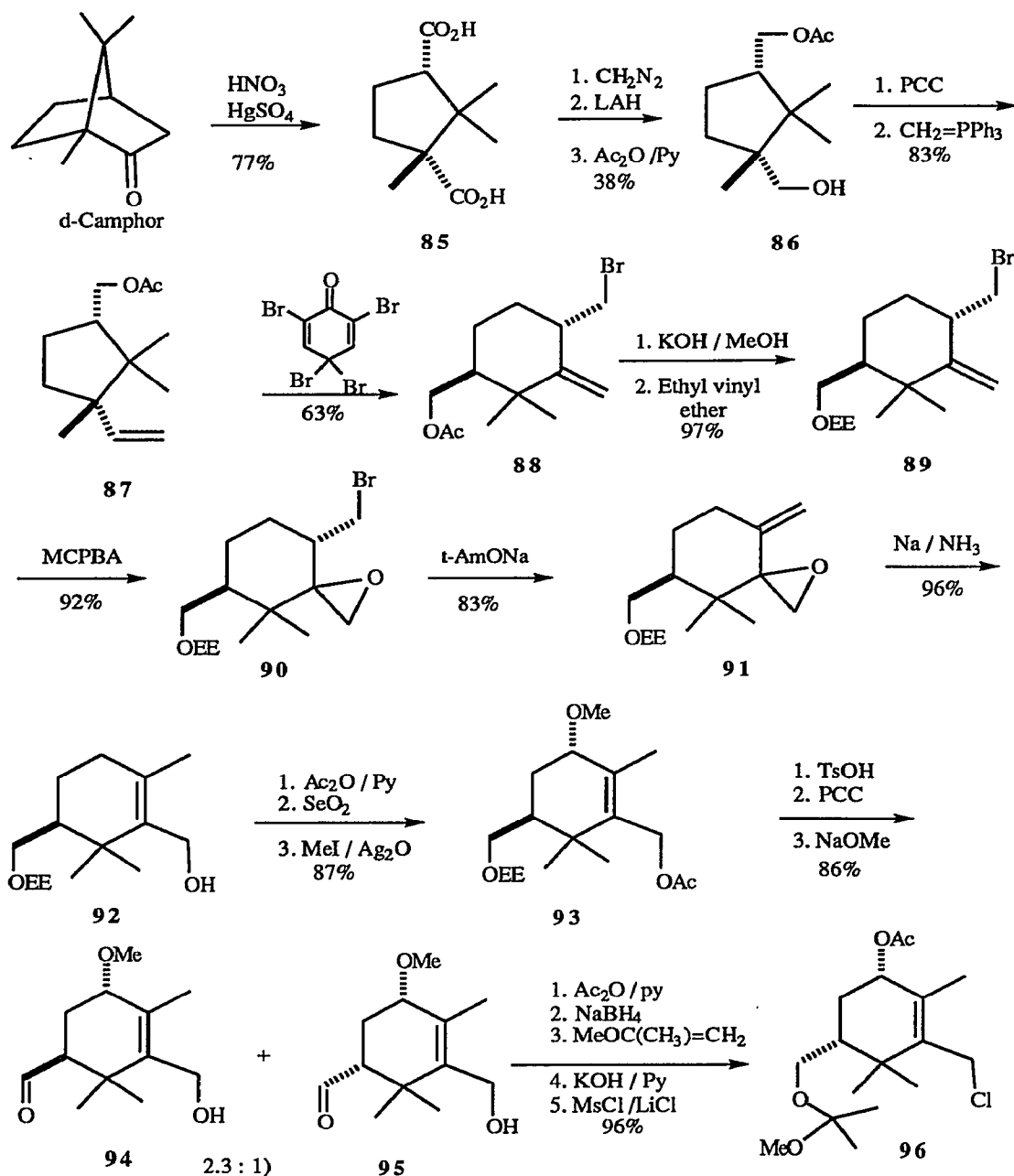
Scheme 18. Blechert's approach



In Kitagawa's^{22h, 1} synthesis (Scheme 19), d-camphor was chosen as a starting point, and after a 23-step manipulation, **96** was prepared. The key step is the ring expansion of **87** by bromination-dehydrobromination with rearrangement to deliver **88**. In the rearrangement process,

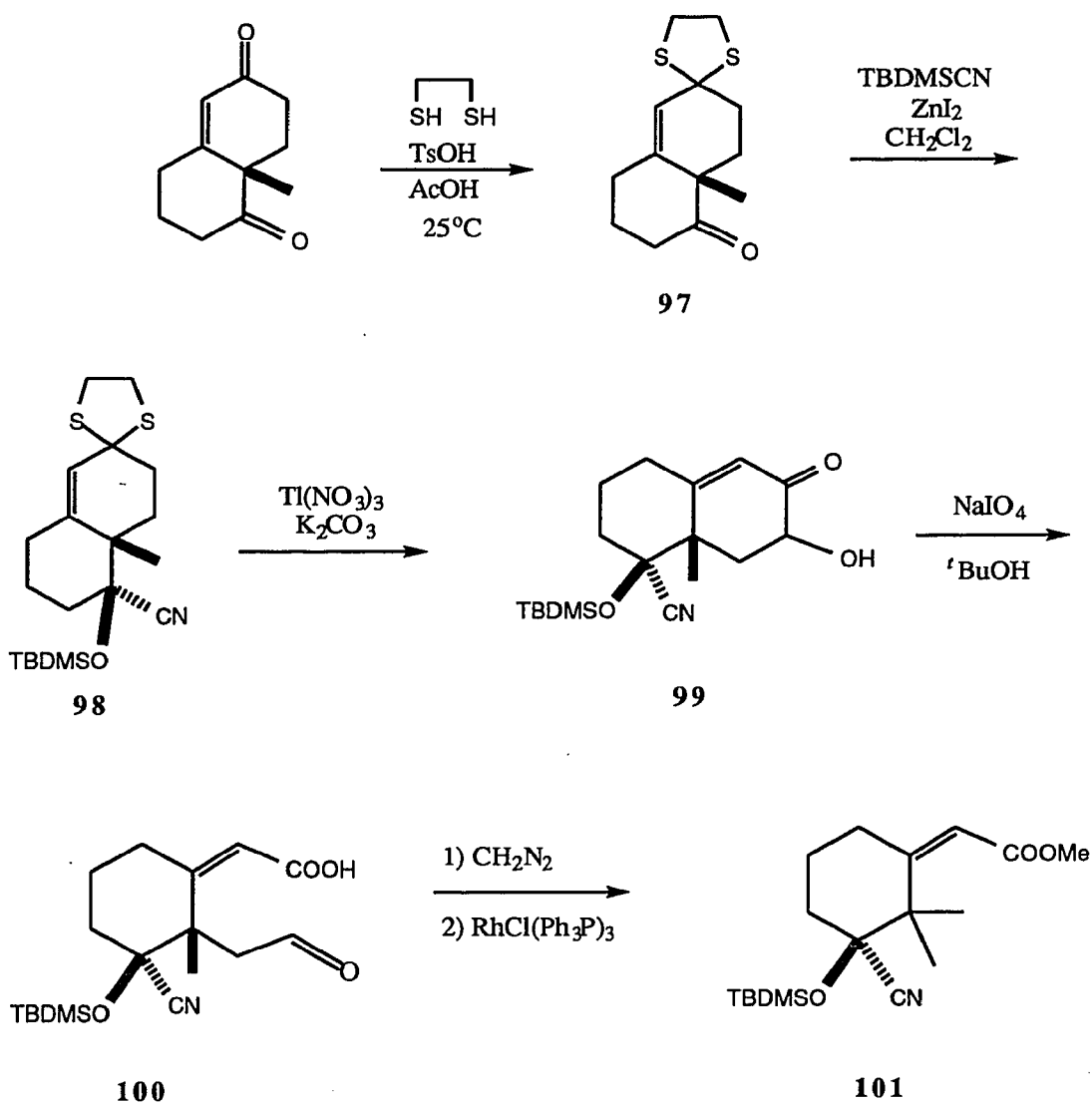
migration of the less substituted homoallylic cyclopentane carbon in **87** created the carbon skeleton associated with **88**.

Scheme 19. Kitagawa's Approach



Another sequence started from the (S)-(+)-enantiomer of the Wieland Miescher ketone was reported by Watt,^{22j} as shown in Scheme 20.

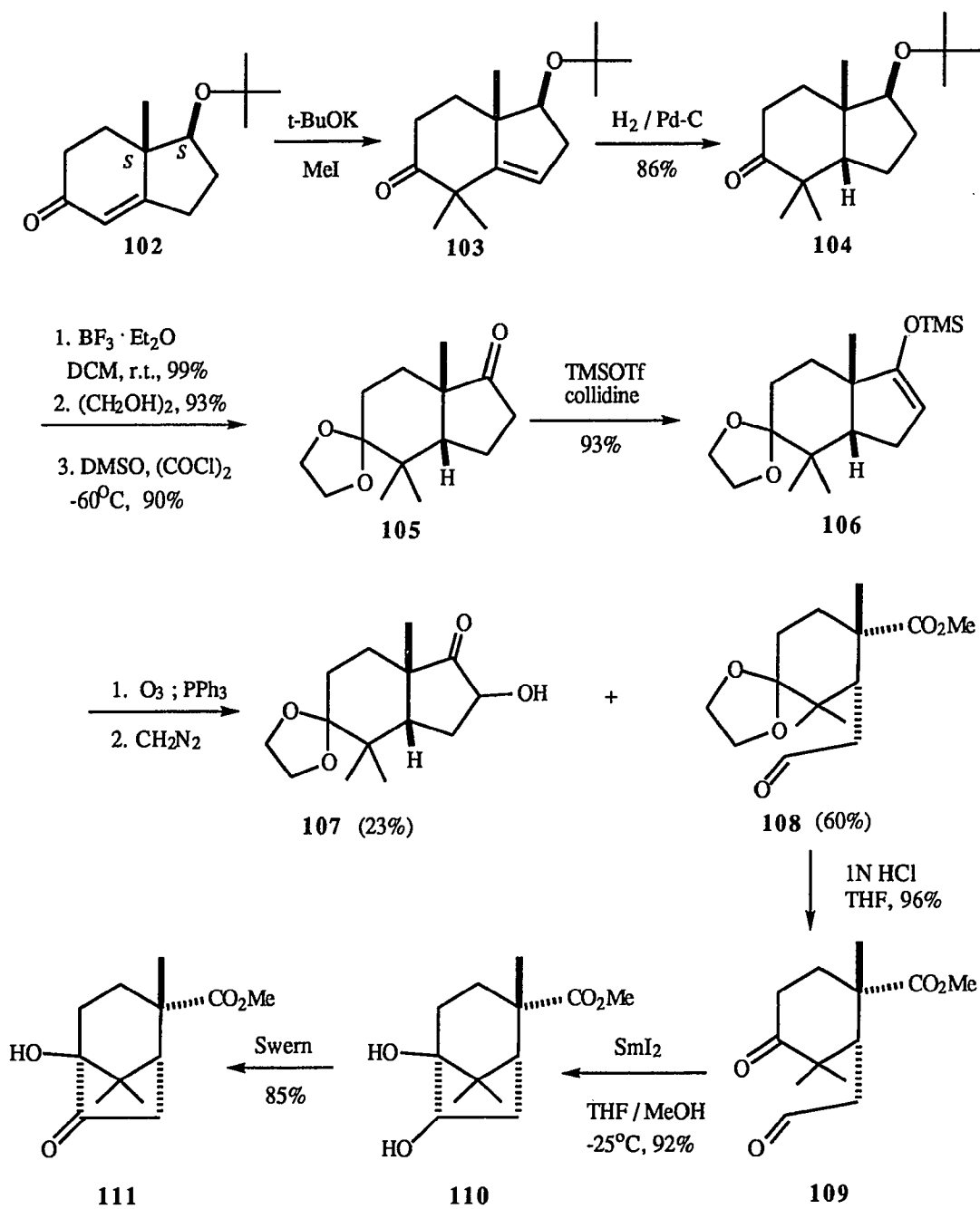
Scheme 20. Watt's Approach



One of the most recent synthesis of taxol A-ring ana-

log was documented by Potier and coworkers.^{22k} as shown in Scheme 21.

Scheme 21. Potier's Approach

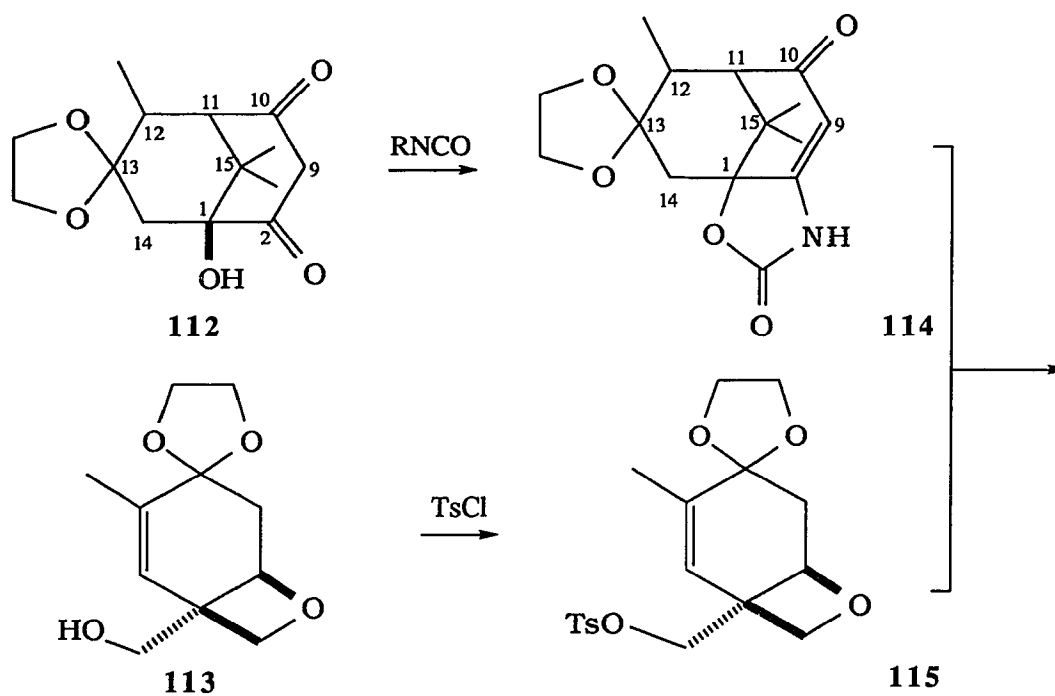


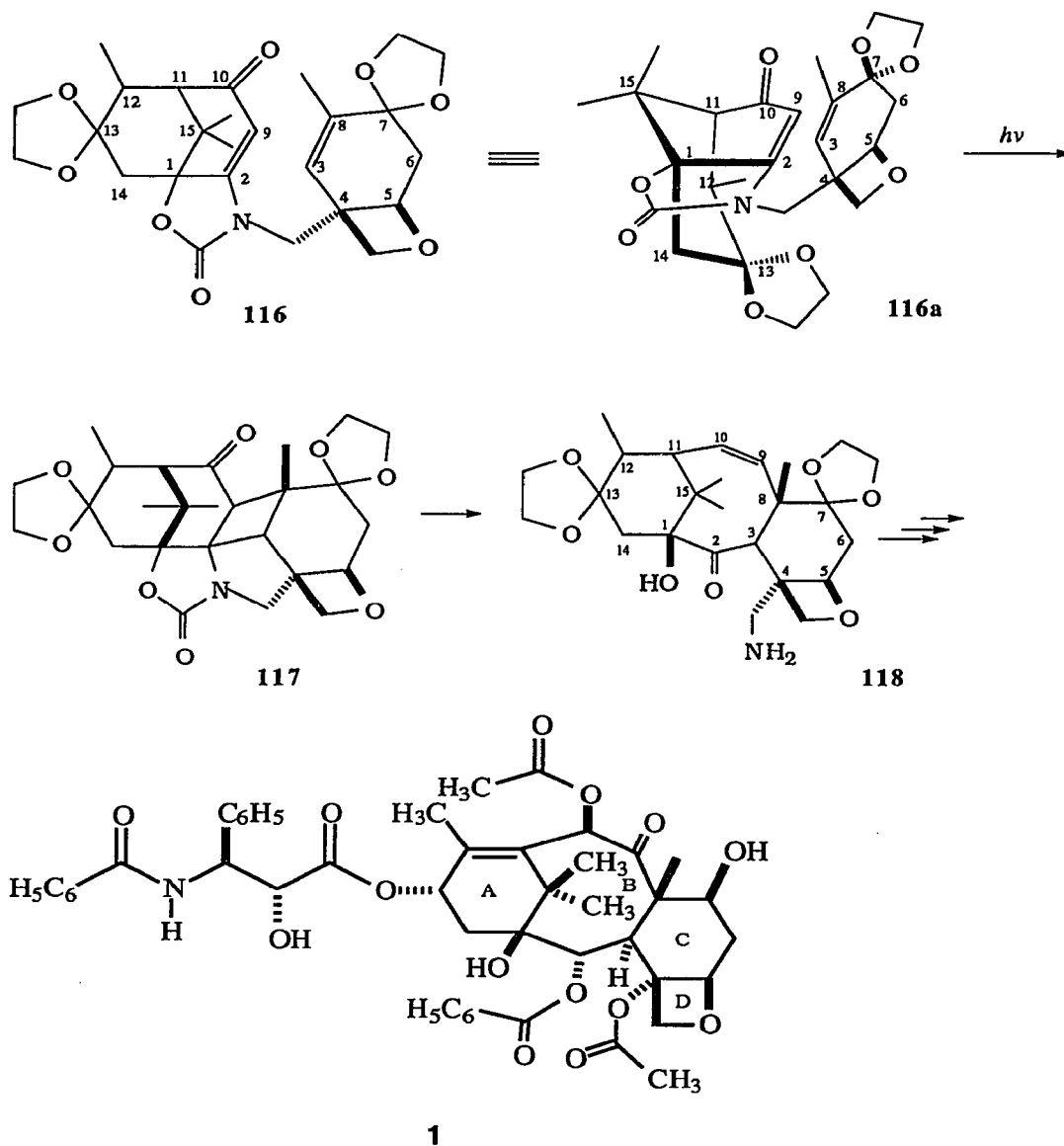
The synthesis started from the known lower analog of Wieland-Miescher ketone **102** via a 11-step sequence (Scheme 21). The key step was the construction of the C1-C2 bond by an intramolecular SmI_2 mediated reductive pinacolic coupling reaction. Although the C1 hydroxyl group in A-ring of taxol was incorporated in this synthesis, the C13 hydroxyl functionality still needs to be introduced. In addition, the C12 ester group needs to be removed at a proper stage.

Chapter 2. Results and Discussion

As indicated in section 1.5, the de Mayo sequence is one of the noteworthy approaches for the assembly of the taxol framework. The synthesis of taxol can be envisioned as shown in Scheme 22.

Scheme 22. Proposal for the total synthesis of taxol





Diketone **112** is to be converted into **114** which will be combined with **115** to give de Mayo precursor **116**. Molecule **116** should adopt a conformation like **116a**. The facial selectivity will be directed by the C13 ketal group

which ensures the photoaddition will occur from the exo side and that the correct stereochemistry of the C8 angular methyl group will be achieved. Furthermore, if **112** is optically active with the correct stereochemistry at C1, the photoadduct **117** would be optically active with the correct stereochemistry at C8. Subsequent transformation of **117** will finally complete the total synthesis of taxol possibly enantioselectively. Thus, molecule **112** is the starting point, and its stereochemistry at C1 is also the fundamental element for the total enantioselective synthesis based on the de Mayo strategy (the stereochemistry at C11 and C12 is not important because they will eventually be joined by a double bond).

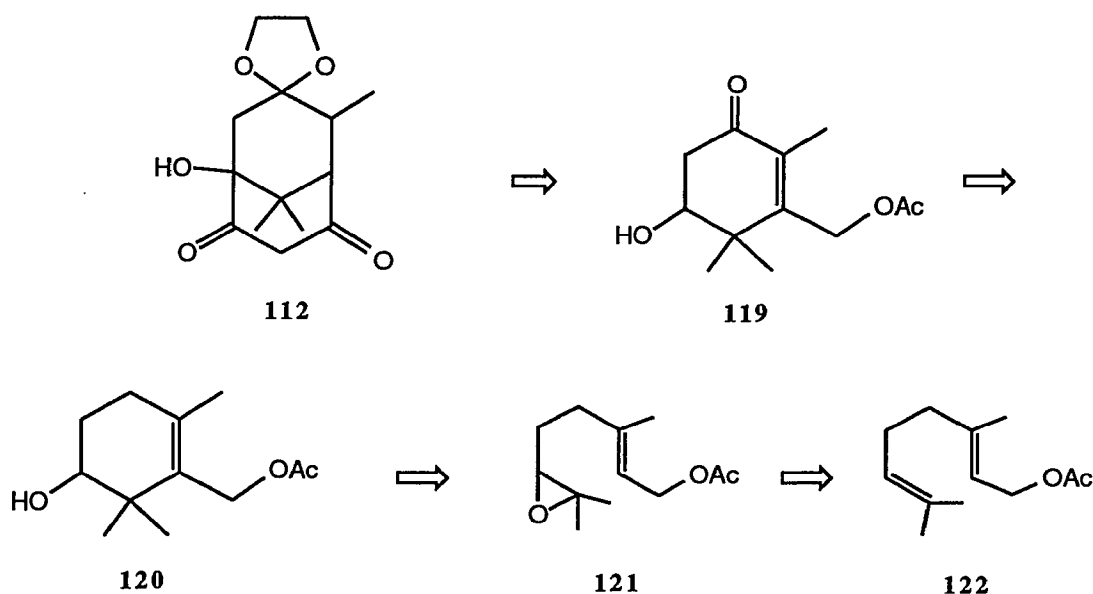
Although there have been several successful approaches toward the synthesis of an A-ring synthon for taxol (Section 1.6), no one has yet made an A-ring synthon that can be easily transformed into a fully functionalized taxol A-ring that can be incorporated in our proposed total synthesis, except that of Frejd, which is too long. The focus of this investigation is directed towards the efficient synthesis of diketone **112**.

2.1 Initial attempts

In construction of molecule **112**, there are several ret-

rosynthetic approaches available. Initially, geraniol derivatives attracted our attention due to the similarity of its cyclized form with the A-ring of taxol, as shown in Scheme 23.

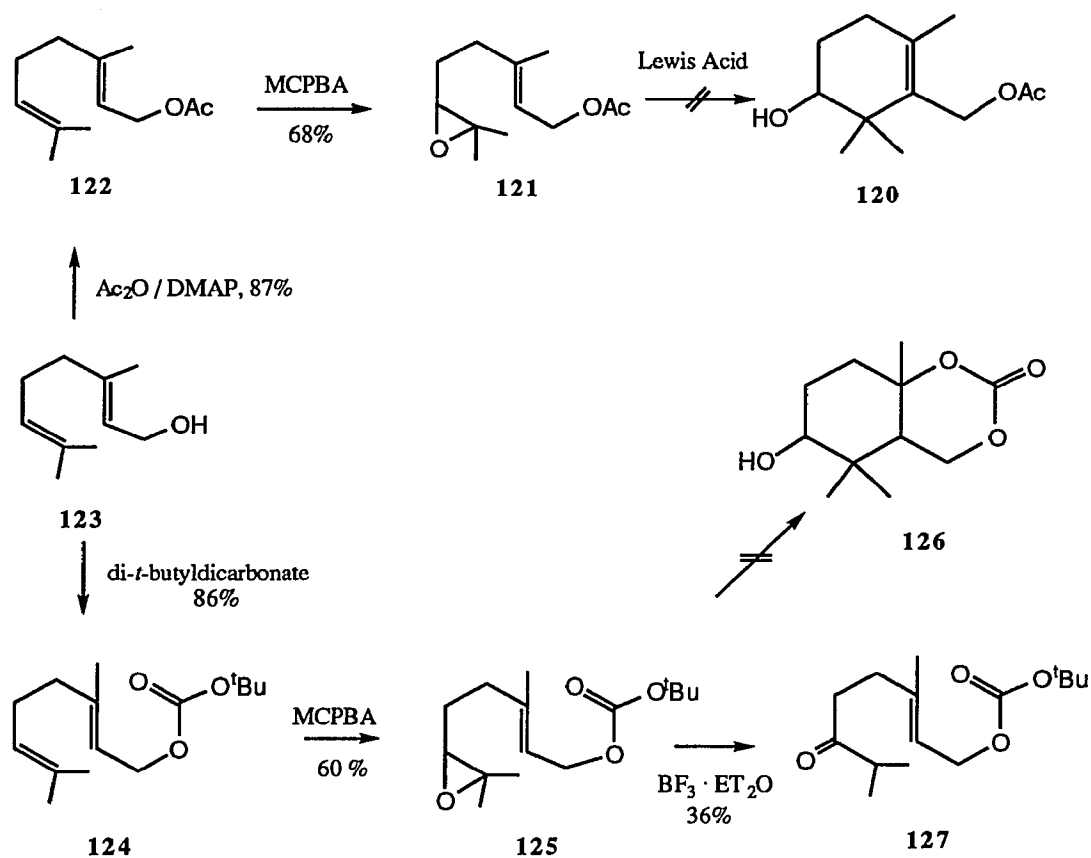
Scheme 23 Initial retrosynthesis



Thus, geraniol (**123**) was protected as an acetate **122** which was epoxidized to afford **121**. A similar sequence yielded carbonate **125**. Cyclization reactions of **122** and **125** to give **120** or **126** were unsuccessful, with all conditions tested: $\text{BF}_3 \cdot \text{Et}_2\text{O}$,^{22g, 23a} SnCl_4 ,^{23b} AlCl_3 , $\text{HCl} \cdot \text{Et}_2\text{O}$,

H_3PO_4 ,^{23c} H_2SO_4 / THF, Al_2O_3 / xylene, $\text{F}_3\text{CCO}_2\text{H}$,^{23d,e} and Cp_2TiCl .^{23f} In all cases, a very complicated tar-like mixture resulted, with the exception of **125** which gave **127** in 36% isolated yield upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Scheme 24).

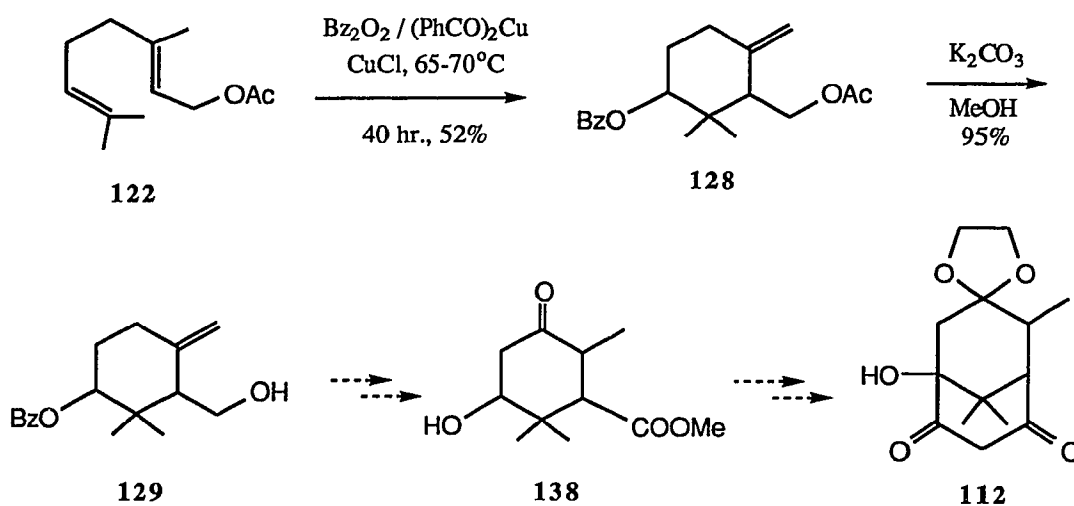
Scheme 24. Cyclization of geraniol derivatives



We then thought to employ a free radical cyclization

condition. When **122** was subjected to the free radical cyclization conditions,²³ **128** was obtained in 52% yield. Although this result encouraged us greatly, there still appeared to be a long way to go before reaching target molecule **112** and we looked for more advanced intermediates.

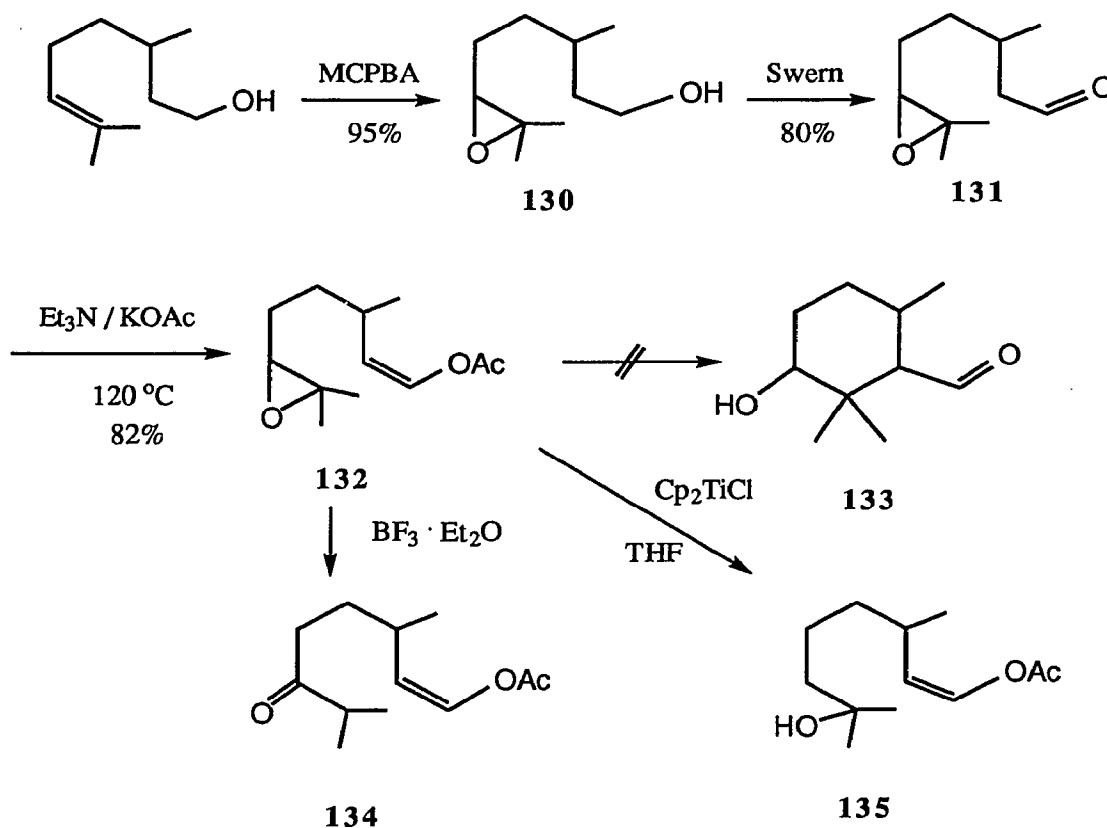
Scheme 25. Free radical cyclization



The cyclization of citronellol derivatives was then tested (Scheme 26). Citronellol was epoxidized to afford **130** in 95% yield. Swern oxidation, followed by enolization afford-

ed **132**. When **132** was subjected to cyclization, neither cationic ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) nor free radical conditions (Cp_2TiCl) produced a desired product **133**. A noncyclized product resulted in all cases.

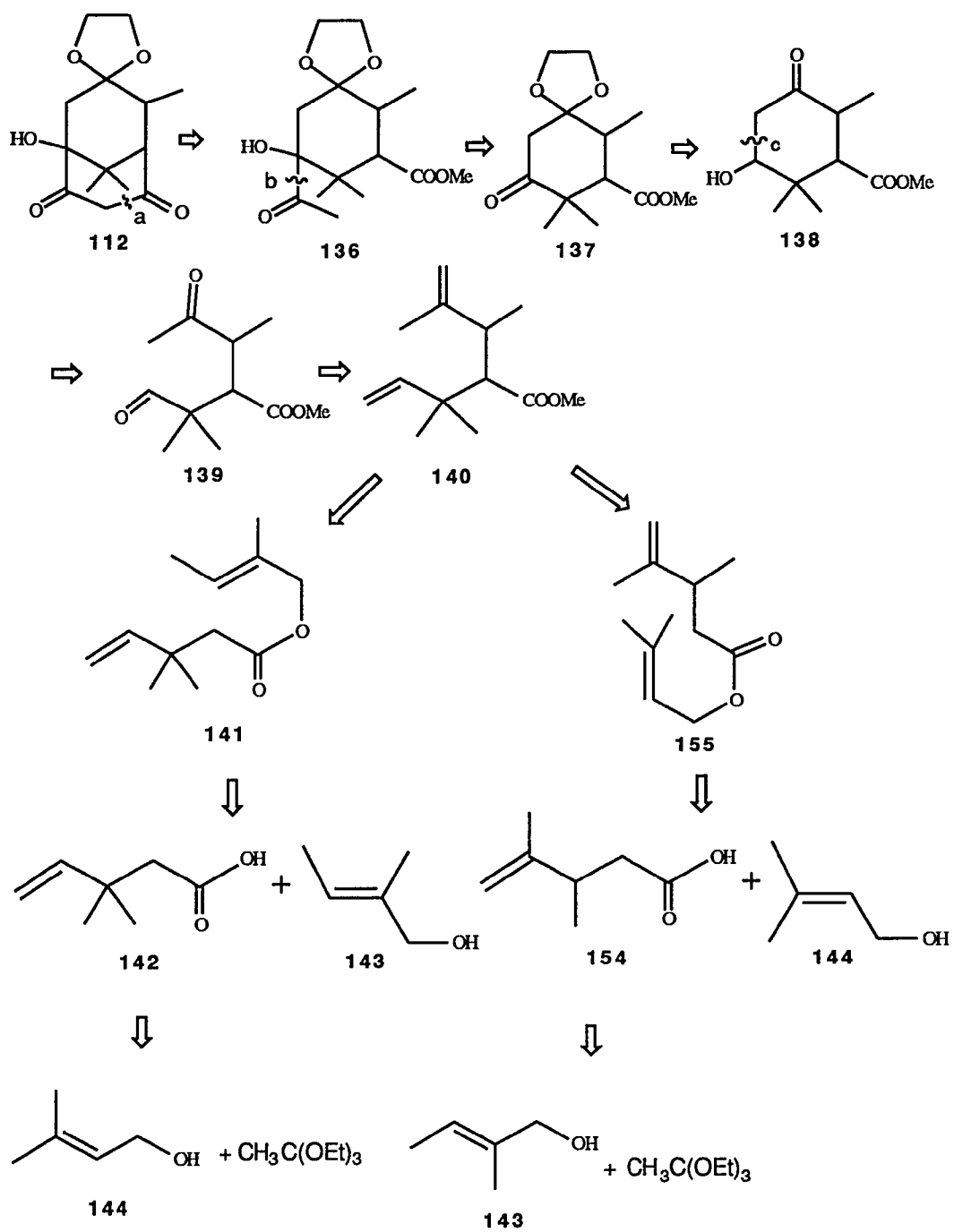
Scheme 26. Cyclization of citrnellol derivative



At this junction, we conceived of retrosynthetic Scheme

27. The precursor of **112** could be **136** which may be derived by disconnection of bond b leading to precursor **137**. Molecule **137** could be obtained from **138**. Molecule **138** is densely substituted and the choice of the disconnection (**138**) leading to acyclic precursor **139** will be the key step in the synthesis. Strategically, disconnection of the bond c of **138** would lead to an aldol condensation reaction. Construction of a 1,5-keto-aldehyde **139** presents a problem until we conceived the idea of generating each carbonyl by ozonolysis of the corresponding alkene. If both carbonyl groups are substituted by methylene groups, molecule **140** can be derived. In the synthetic direction, this can be effected by ozonolysis. The substitution pattern of **140** is a diallyl substituted acetic acid. Each allyl group may be installed via an Claisen rearrangement --- a Johnson orthoester Claisen followed by an Ireland enolate-Claisen rearrangement. This analysis leads to **141**. The ester **141** can be obtained by combination of **142** and **143**. The acid **142** could be obtained by a Johnson-Claisen rearrangement reaction. The similar analysis for another sequence of installment of **140** through **155** and **154** would lead to **143**.

Scheme 27. Retrosynthetic Analysis



2.2 Synthesis of Diene Ester 140.

Preparation of acid fragment 142

The synthesis started from the Johnson-Claisen rearrangement reaction shown in Scheme 28. As we know, Claisen rearrangement reactions are concerted,²⁴ and are greatly effected by steric hindrance. Preparation of **146** requires creation of a quaternary center via this reaction. The reaction was investigated thoroughly under various conditions (Scheme 28)²⁵ using two different alcohols, 3-methyl-2-buten-1-ol (**144**) and 4-methyl-3-penten-2-ol (**145**). **144** is commercially available. **145** was obtained in 94% yield by the reduction of mesityl oxide with sodium boronhydride²⁶ in the presence of cerium chloride. The results of the rearrangement reactions are collected in Table 1. The optimum reaction conditions (Entry 6) were established as heating (143-145°C) the mixture of the corresponding allylic alcohol with 3.0 equiv. of triethyl orthoacetate catalyzed by 0.066 equiv. of propionic acid over 3 days with continuous removal of ethanol formed by distillation. The ester **146** thus obtained was saponified with potassium hydroxide in methanol²⁷ to give an acid **142** in 95% yield. The corresponding rearrangement of alcohol **144** with trimethyl orthoacetate gave inferior results.

Scheme 28. Johnson-Claisen rearrangement

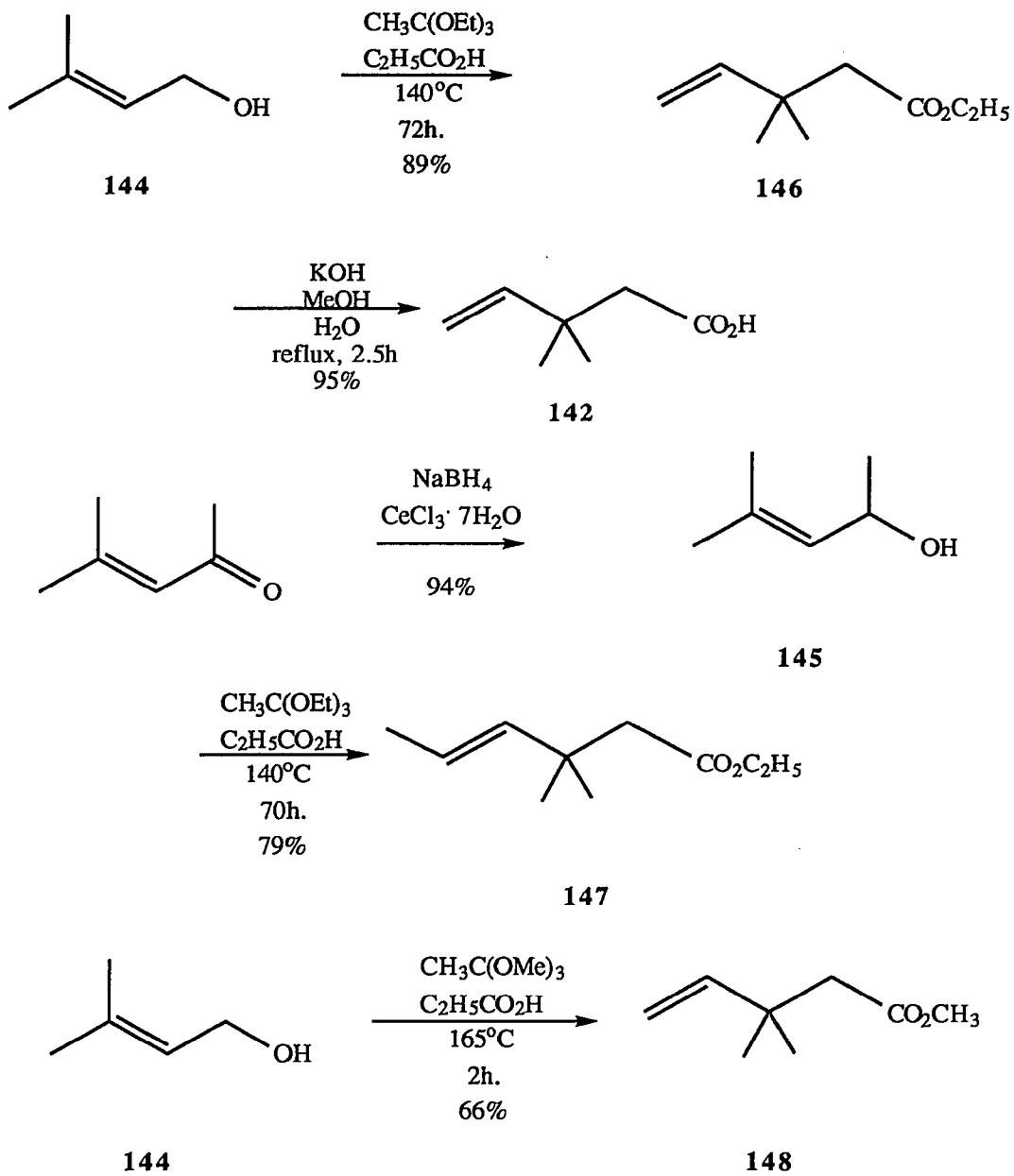
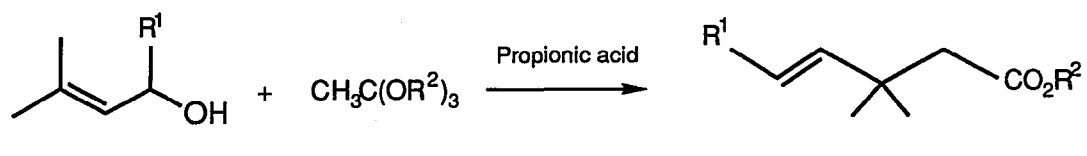


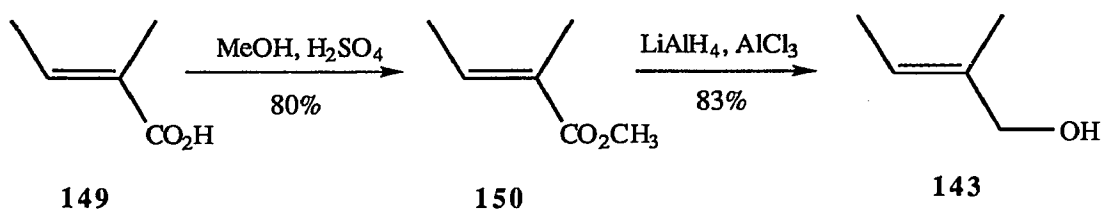
Table 1. Optimization of Johnson-Claisen rearrangement reaction

Entry	Substrate		Reagent acid		Solvent	Temperature (°C)	Time (h)	product	yield (%)
	R ¹	R ²	(equiv.)						
1	H	Me	2.5	0.05	<i>o</i> -xylene	132-133	3h	148	48
2	H	Me	4.0	0.05	mesitylene	163-165	2h	148	66
3	Me	Et	5.78	0.047	no	158-162	2h	147	79
4	H	Et	5.75	0.047	no	143-145	5h	146	31
5	H	Et	5.75	0.057	no	143-145	10h	146	43
6	H	Et	3.0	0.066	no	143-145	72h	146	89
7	Me	Et	4.0	0.072	no	143-145	70h	147	79

Synthesis of Alcohol 143

The next synthetic task was preparation of alcohol **143**. Alcohol **143** was obtained by the route outlined in Scheme 29. Methyl tiglate (**150**), prepared by esterification of tiglic acid (**149**) with methanol catalyzed by concentrated sulfuric acid²⁸ (yield 80%), was reduced by lithium aluminum hydride in presence of aluminum chloride in ether²⁹ in 83% yield.

Scheme 29. Preparation of alcohol **143**

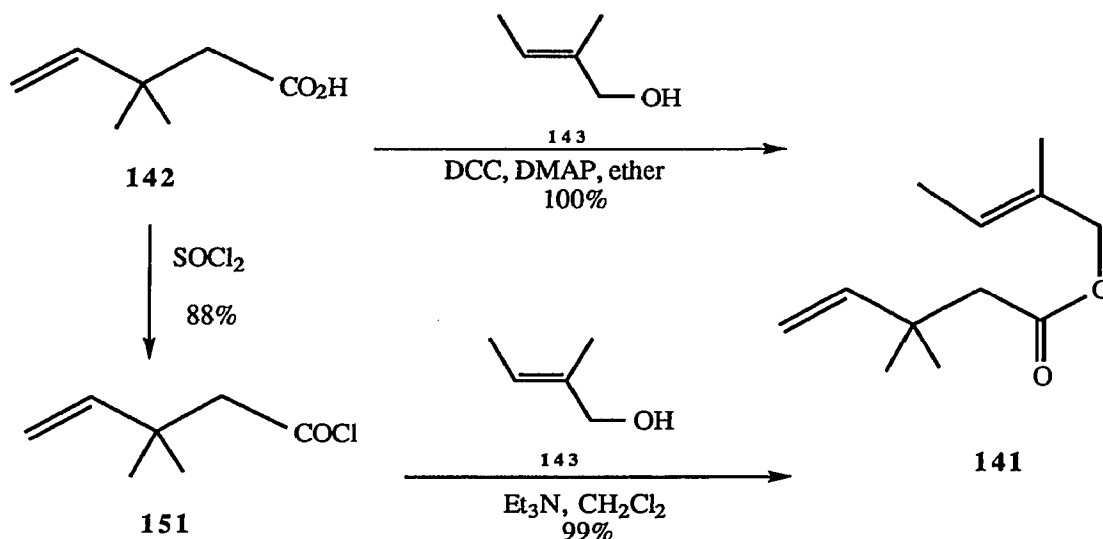


Synthesis of ester 141

The ester **141** was synthesized in 100% yield by the reaction of the acid **142** with alcohol **143** in anhydrous ether catalyzed by DMAP with dicyclohexyl carbodiimide (DCC) as the dehydration reagent.³⁰ Alternately, acid **142** was converted into acid chloride **151** with thionyl chloride³¹ in 88% yield, and esterified smoothly with alcohol

143 in methylene chloride in the presence of triethylamine³² in 99% yield (Scheme 30).

Scheme 30. Synthesis of the ester **141**

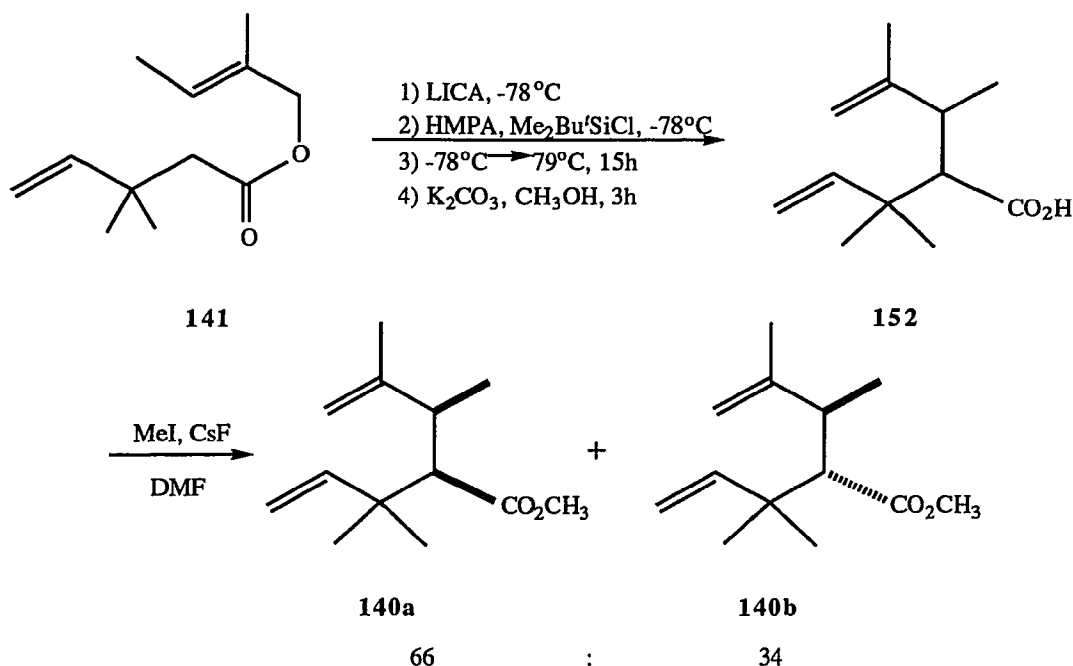


Synthesis of 152 via Ireland-Claisen Rearrangement

With ester **141** in hand, we were ready to investigate the Ireland-Claisen rearrangement reaction which was the key part of the synthetic plan. It was expected that this rearrangement reaction would be difficult because the alkyl group would be introduced into the position adjacent to a quaternary center. The reaction conditions were explored thoroughly through several experiments involving

variation of the reaction time, base, and the temperature .
The results of these experiments are summarized in Table
2.

Scheme 31. Synthesis of diene ester **140**



As shown in Table 2, the standard procedure³³ first examined produced recovered starting material along with some unidentified impurities (Entry 1). The literature³⁴ was searched thoroughly and the reaction conditions were then modified as shown in entry 2. The reaction mixture was heated for 3 h at 70 °C instead of quenching at

Table 2. Optimization of The Ireland-Claisen Rearrangement Reaction

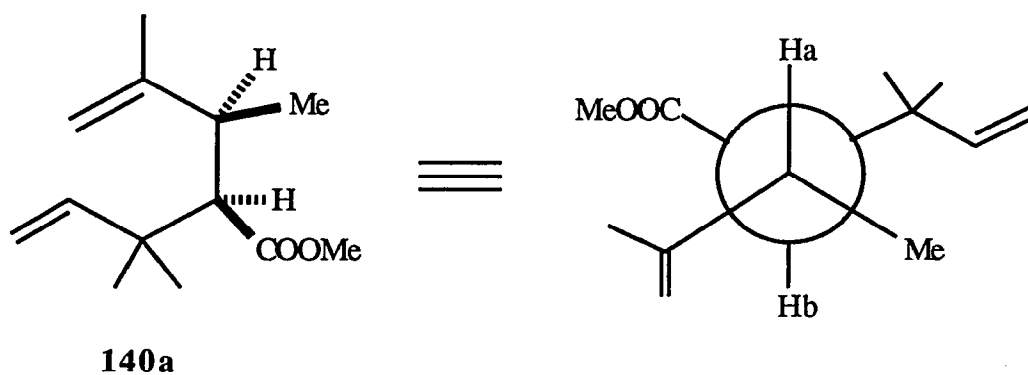
Entry	ester conc. (M)	base (equiv.)	time (min.)	HMPA (equiv.)	TBDMSCl (equiv.)	time (min.) (h.)	heating time (h)	Temp. (°C)	Yield (%)
1	0.50	LDA (1.10)	10	0.60	1.00	5	15min.	0	0
2	0.90	LCIA (1.10)	10	0.80	1.05	5	3	70	35
3	0.45	LCIA (1.10)	15	0.80	1.05	15	16	70	25
4	0.40	LCIA (2.50)	15	5.75	1.10	5	1.0	25	0
5	0.40	LCIA (2.50)	15	5.75	1.10	3	3.5	88	0
6	0.90	LCIA (1.10)	10	0.80	1.05	5	6	70	61
7	0.40	LCIA (1.10)	60	1.40	1.05	40	15	79	85*

* total yield of **140** from **141**.

0°C, giving a 35% yield of **152** and some recovered starting material. These results suggested that the reaction might need a longer heating time, and therefore, as shown in Entry 3, the reaction mixture was heated for 16 h. However, a very complicated mixture resulted and no starting material was recovered. Acid **152** was isolated in only 25% yield. The effect of more base was investigated next (Entries 4 and 5), but 2.5 molar equivalents of base afforded no product after isolation. Besides this, the reaction products were extremely complicated, and no starting material was recovered. In Entry 6, other conditions were the same as Entry 2, except the mixture was heated longer. The yield was 61%, along with recovered starting material. It was then recognized that the enolization procedure might present problems. In Entry 7, the enolization period was lengthened to 1h. and the quenching of the enolate with tert-butylchlorodimethylsilane was lengthened to 40 min. The yield of **140** reached 85% from **141**. Thus, the optimum conditions established were as follows: **141** was enolated with 1.10 equiv. of LICA over 1h; protected the enolate which formed with tert-butylchlorodimethyl silane in the presence of 1.40 equiv. of HMPA at -78°C over 40 min.; raised the temperature slowly and heated at 78-79°C for 15h. Another important im-

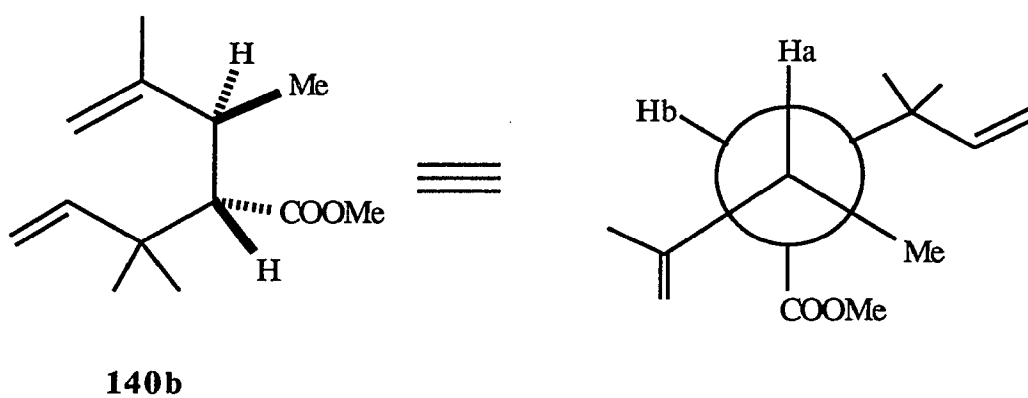
provement for the reaction conditions was that the hydrolysis of the rearrangement product, the silyl ester, was carried out under the basic conditions (potassium carbonate^{35a}) and a longer reaction time, instead of the acidic conditions (acetic acid in THF^{35b}) adopted previously. Using acidic conditions, the product acid was contaminated by acetic acid and the separation was not achieved very readily.

Once the acid **152** was obtained, esterification was effected by the reaction of iodomethane in dry DMF catalyzed by cesium fluoride.³⁶ The diene ester **140** obtained this way was rather pure. Separation was needed only for removal of a trace of the solvent DMF, using hexane and ethyl acetate (15 : 1) as eluent on a short silica gel column. Diene ester **140** is a colorless oily liquid with a somewhat pleasant smell. There are two diastereomers, *erythro* and *threo*, present in diene ester **140**. The two isomers **140a** and **140b** were separated cleanly by preparative HPLC and the ratio was determined to be ca. 66:34. The relative stereochemistry for these two isomers was assigned tentatively based on ¹H NMR of the individual isomers (Scheme 32).³⁷

Scheme 32. Stereochemistry of **140**

$$J_{ab} = 11.2 \text{ Hz}$$

Erythro



$$J_{ab} = 8.4 \text{ Hz}$$

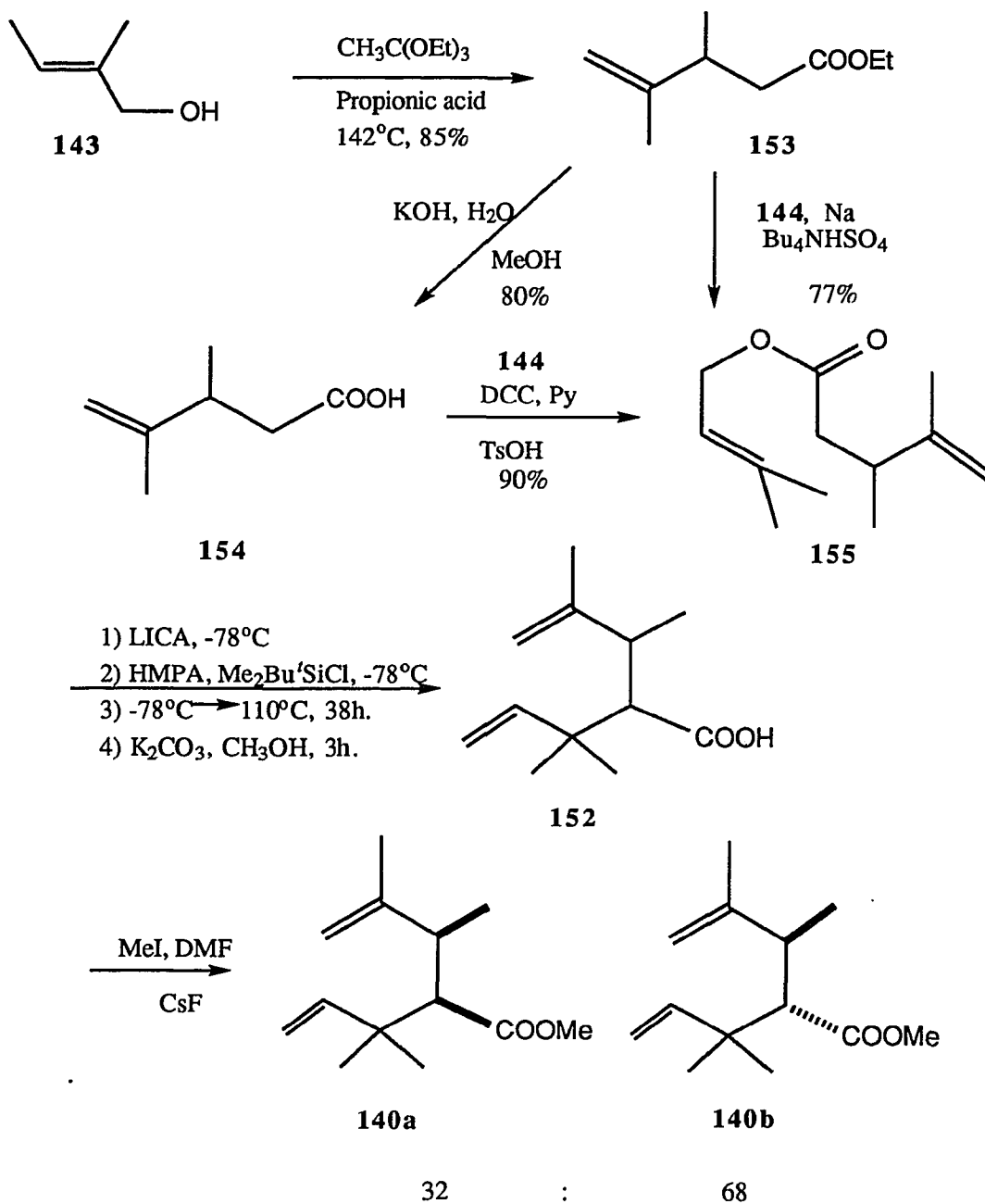
Threo

2.3 An Alternative Route to Diene Ester 140.

As we realized earlier, Scheme 27, the allyl substituents may be installed in either order. Therefore, **140**

may be also derived from an ester **155** available from **144** and **154**. As shown in Scheme 33, the second route to **140** started from alcohol **143**. The mixture of **143** and triethyl orthoacetate was heated at 142°C for 4h, with propionic acid^{25a} as a catalyst, and an ester **153** was obtained in 85% yield. If the reaction mixture was heated for a shorter time (1.5h), the yield decreased somewhat (81%). The next step was preparation of ester **155**. The shortest route from ester **153** to **155** was transesterification, which was first performed based on a literature procedure³⁸ using potassium carbonate as the base. Unfortunately, the method did not work in the system studied. Reaction conditions were then modified to employ sodium metal to produce the alkoxide anion and a higher temperature (bath temperature: 105°C). In this way, ester **155** was obtained in 77% isolated yield. Alternately, ethyl ester **153** was hydrolyzed with aqueous potassium hydroxide in methanol²⁷ to acid **154** in 80% yield. Esterification with **144** was then effected by toluenesulfonic acid and DCC³⁹ in pyridine in 90% yield.

The Ireland-Claisen rearrangement reaction was then tried and, after several tries, it was found that the longer

Scheme 33. An alternate route to diene ester **140**

heating time and higher temperature were crucial for the success of the reaction. The results were collected in Table 3.

Table 3. Optimization of the Claisen Rearrangement Reaction

Entry	Ester conc. (M)	base (equiv.)	time (min.)	HMPA (equiv.)	TBDMSCl (equiv.)	time (min.)	heating time(h)	temp. (°C)	yield (%)
1	0.14	LDA (1.26)	15	0	2.90	10	2.5	70	0
2	0.20	LCIA (1.05)	10	0.60	1.05	10	15 min.	0	0
3	1.00	LCIA (1.10)	30	1.00	1.05	5	2.5	80	34
4	0.75	LCIA (1.10)	15	4.00	1.05	10	38	79	49
5	0.40	LCIA (1.10)	60	1.40	1.05	40	38	110	64*

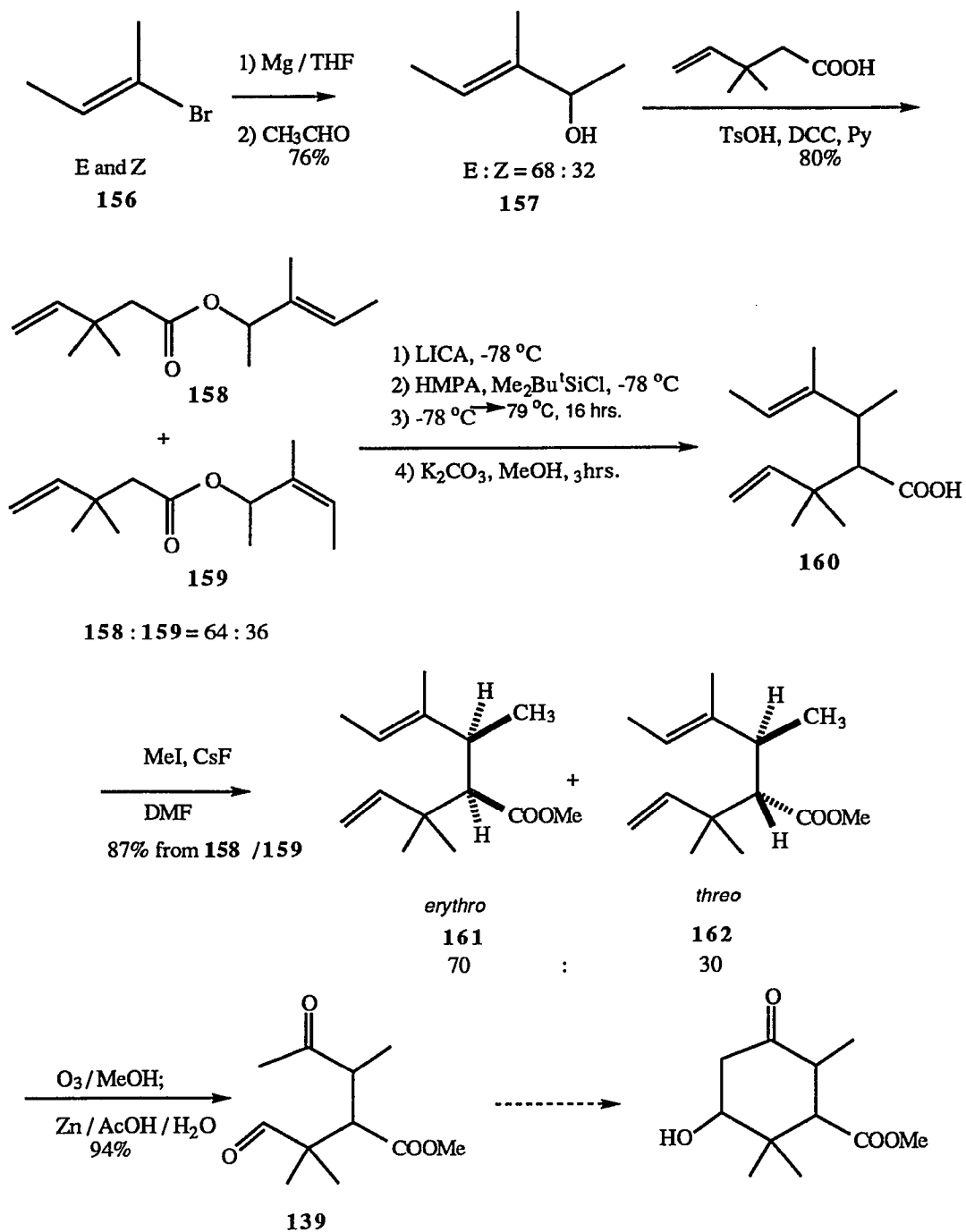
* total yield of **140** from **155**.

The esterification was carried out in the same way as in Scheme 31 and the two isomers, **140a** and **140b**, were also separated by HPLC in the same way. The ratio of **140a** to **140b** was determined to be 32 : 68. The individual spectra of **140a** and **140b** were identical with those obtained in

Scheme 31. It was interesting to note that the stereoselectivity, though not important, for these two ways of Claisen rearrangement (Scheme 31 and Scheme 33) was opposite. The ratio shown in Scheme 31 is 66 : 34; while the ratio shown in Scheme 33 is 32 : 68.

2.4 A Route to the Derivative of Diene Ester 140

In order to get additional insight into the transition state of the Claisen rearrangement, the reaction of **158/159** were investigated as shown in Scheme 34. The sequence started from vinyl bromide **156**. The Grignard reagent was prepared and reacted with acetaldehyde to obtain an alcohol **157**. The E/Z ratio was found to be 68: 32 (NMR). Alcohol **157** was then combined with acid **142** to give **158** and **159** in 80% yield. The two isomers, **158** and **159** were separated carefully by preparative MPLC and their structures were fully characterized. The ratio of **158** : **159** was found to be 64 : 36 (isolated). The Ireland-Claisen rearrangement started from the mixture of **158** and **159**, and the acid **160** was obtained. After esterification (MeI, CsF, 87%), **160** gave a diastereomeric mixture of esters which was separated by HPLC and the structures of the individual isomers **161** and **162** were fully characterized.

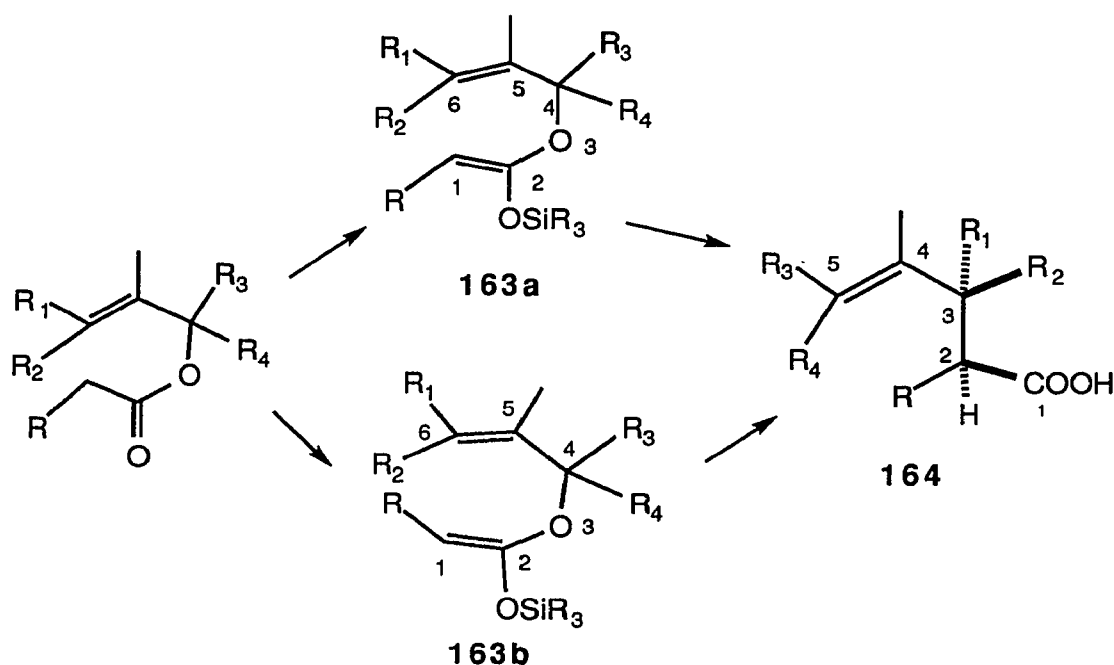
Scheme 34. Synthesis of a derivative of diene ester **140**

The ratio of **161** to **162** was found to be 2:1 (both NMR and HPLC).

It is interesting to note that only E isomer was obtained. The Z isomer was not detected by NMR or HPLC. The ratio of *erythro* **161** to *threo* **162** was approximately the same as that of *erythro* **140a** to *threo* **140b**. These results can be argued rationally in terms of the relative stability of the transition states.

The Claisen rearrangement is a suprafacial, concerted, nonsynchronous pericyclic process that may be considered phenomenologically as an intramolecular S_N2' alkylation.²⁴ When the sp^2 -hybridized C1- and C6-positions of allyl O-silyl ketene acetals (**163**) are substituted (R_1, R_2, R are not H) to provide enantiotopic faces at both termini, the rearrangement can proceed through two pairs of achiral transition states to provide two diastereomers (*threo* and *erythro*) bearing newly created centers of asymmetry at C2 and C3 of the product **164** (Scheme 35). On the other hand, when the C4-position is substituted (R_3 and R_4 are not the same), the issue of Z/E selectivity arises. Generally speaking, the erosion of diastereoselectivity can be attributed to two factors: the geometric integrity of the allylic double bond and the silyl ketene acetals and the selectivity of the chair-like transition states *vs.* boat-like transition

Scheme 35. Stereochemistry of the Ireland-Claisen rearrangement



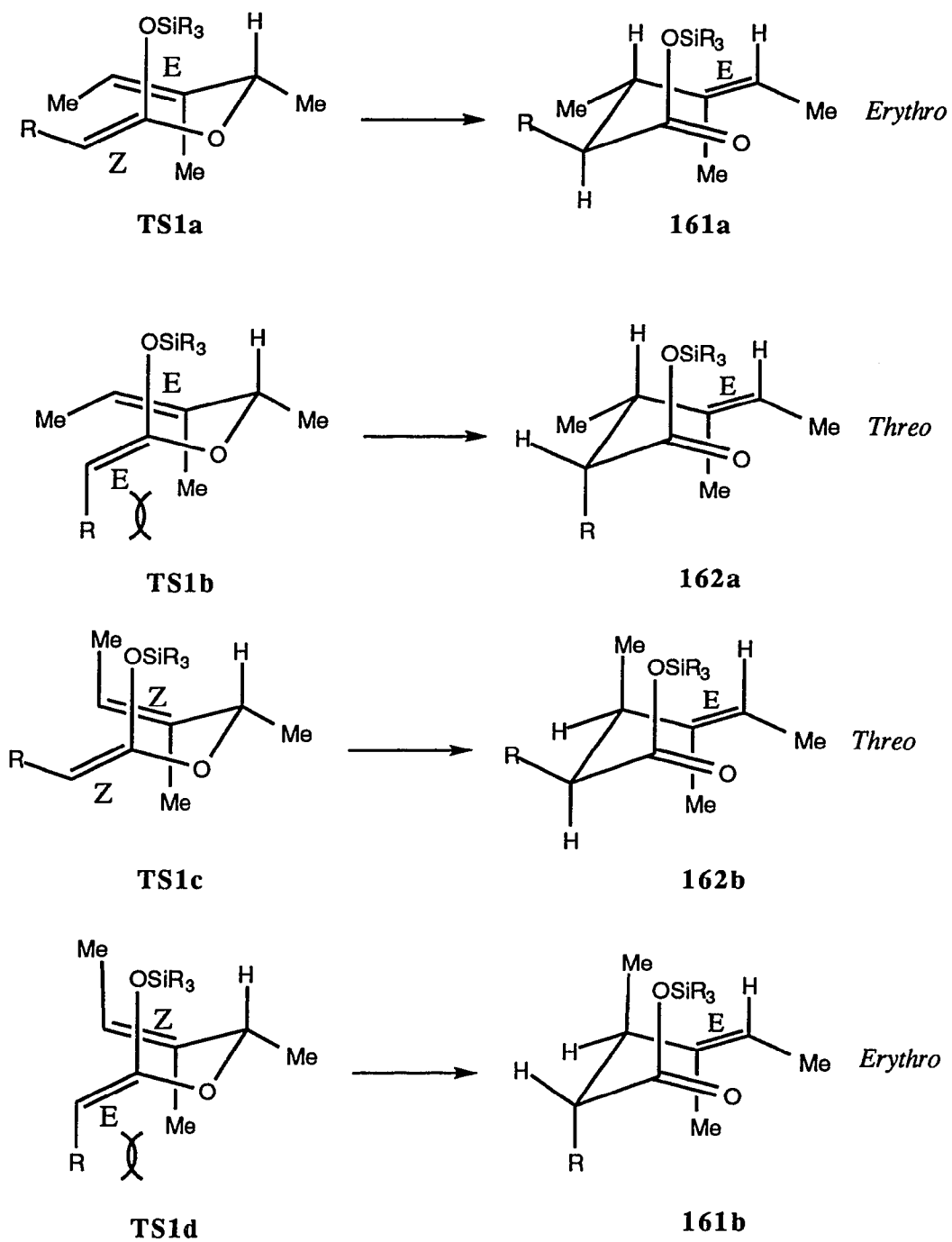
R1	R2	R3	R4	Product	Alkene geometry	stereo-chemistry
CH ₃	H	H	H	140a	-	<i>Erythro</i>
H	CH ₃	H	H	140b	-	<i>Threo</i>
CH ₃	H	CH ₃	H	161	E	<i>Erythro</i>
H	CH ₃	CH ₃	H	162	E	<i>Threo</i>

states. While the geometry of the double bond in the product can be attributed to the orientation of R₃ and R₄ in the transition states. If the chair-like transition states are

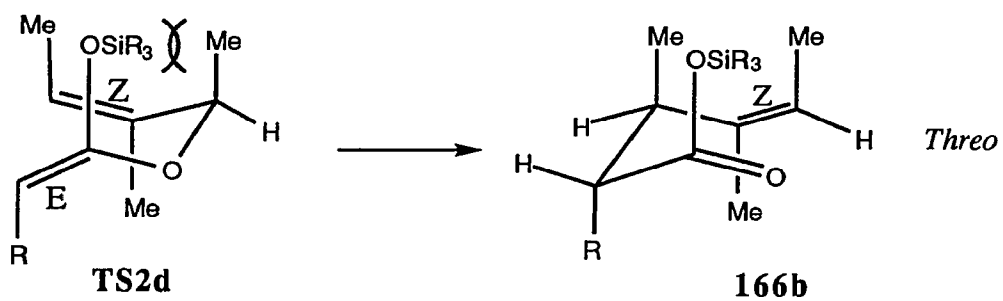
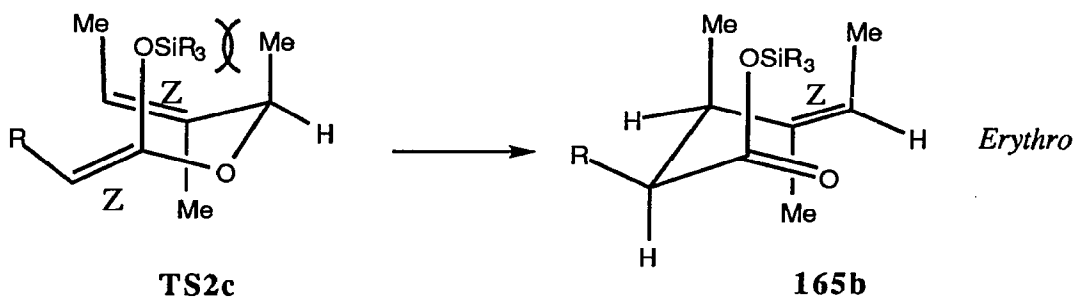
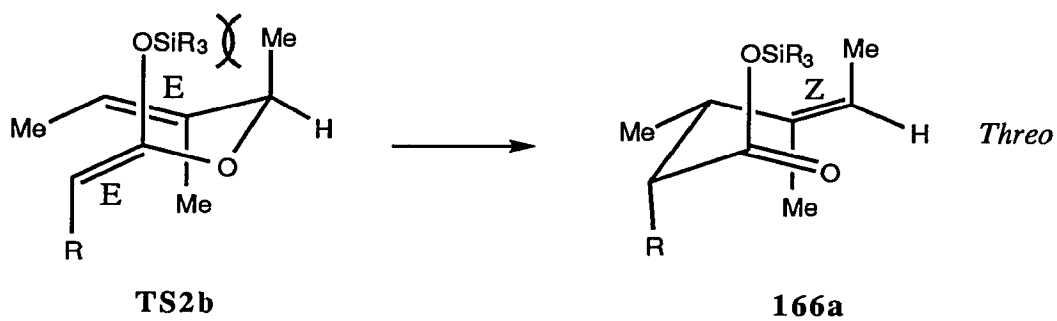
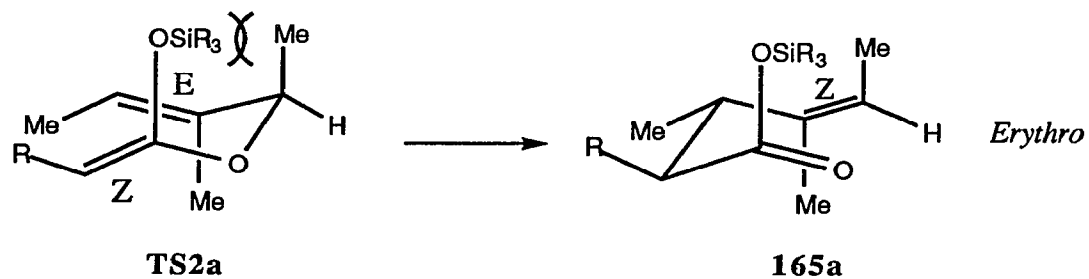
predominant, a change in the geometry of a only one of the two double bond of the starting material exchanges the enantiotopicity of the faces of the double bond and leads to the opposite stereoisomer; any pairwise change in olefin geometry results in the formation of the same diastereomer.

The Ireland variant of the Claisen rearrangement characterizes the typical Claisen rearrangement mechanistically. The deprotonation of esters by lithium dialkylamine base has proved amenable to the generation of specific enolates. It was reported⁴⁰ that E-lithium enolate ((Z)-O-silyl ketene acetals) were predominantly generated in THF in the presence of HMPA. In our system, we added HMPA in THF when deprotonation of ester **158/159** was effected. So we can assume that the production of the (Z)-O-silyl ketene acetyl is predominant over the (E)-O-silyl ketene acetal. In Doering's⁴¹ studies, it was revealed the chair-like transition state is preferred. If we only consider the chair-like transition states (Scheme 36), we would find that **TS1a** is favored over **TS1b**; similarly, **TS1c** is favored over **TS1d** (Scheme 36). On the other hand, **TS1a** is favored over **TS1c** because one methyl group in **TS1c** occupies an axial position. So, **TS1a** would provide a major product, *erythro* isomer. It was worth to point out that the (E)-O-

Scheme 36. Rationale of the rearrangement reaction



Scheme 36. Rationale of the rearrangement reaction (continued)



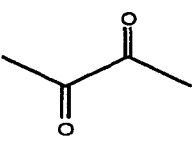
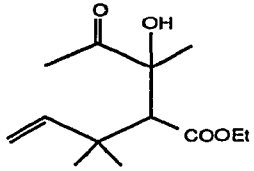

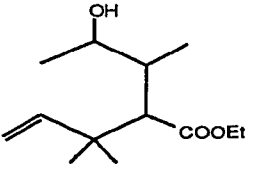
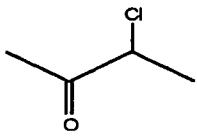
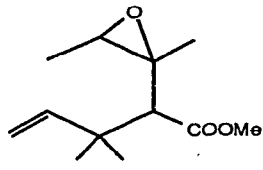
silyl ketene acetal could not be ruled out completely because **141** (E alkene only) gave *erythro* and *threo* in a ratio of 66 : 34, not pure *erythro*. On the other hand, the discussion above is not very conclusive because the rearrangement of **158/159** was started from the cis/trans mixture. The further investigation is under way.

Analysis of **TS1** and **TS2** reveals that all **TS1s** are favored over all **TS2s**. This explained the observed results in which only E alkene products were observed and Z-alkenes were not detected.

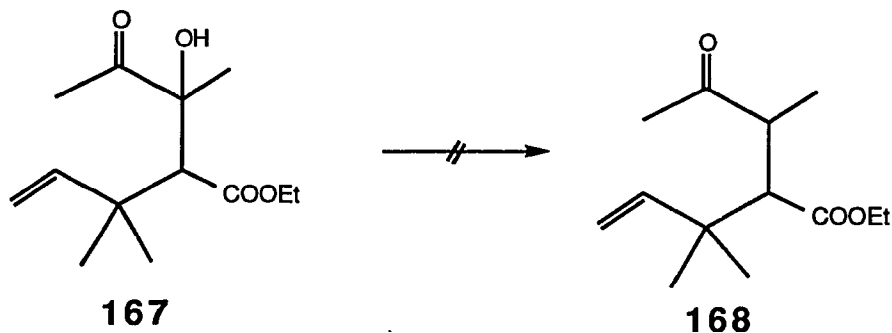
2.5 Miscellaneous Pathways toward the Derivatives of Diene Ester 140

As our ongoing project, we are still looking for an even shorter route to diene ester **140** or its equivalents. Alkylation can be one of the possibilities. Some results are collected in Table 4. It was worth noting that the reaction of Entry 1 is very neat and the work up and the separation were very easy. Only the mono-addition product **167** was isolated. Product **167** contains two diastereoisomers, corresponding to *erythro* and *threo* isomers. The ratio was 75 : 25 based on NMR, although structures were not assigned.

Table 4. Alkylation of Ethyl 3,3-dimethyl-4-pentenoate

Entry	Alkylating reagent	Product	Yield (%)
1		 167	84%
2		 169	20%
3		 170	39%

Dehydroxylation of **167** to yield ethyl 2-(1, 1-dimethyl-2-propenyl)-3-methyl-4-oxopentenoate (**168**) is unsuccessful (Scheme 37).

Scheme 37 Dehydration of **167**

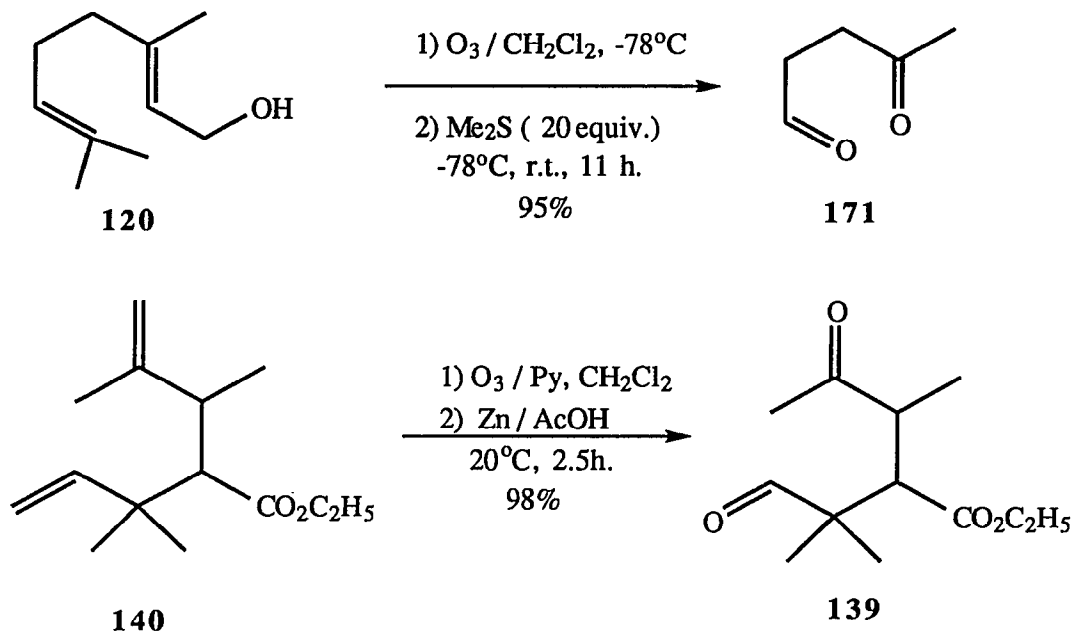
The reaction in Entry 2 was not very successful, the yield was only ca 20%. The product shown in Entry 3 was not what we desired. We were going to prepare the ketone **168**, but unfortunately we obtained **170** in low yield instead.

2.6 Ozonolysis of the Dienes

As outlined in Scheme 38, ozonolysis of diene ester **140** afforded keto aldehyde **139**. The reaction proved to be troublesome, even though ozonolysis is such a typical organic transformation. The procedure for a diene system reported in the literature⁴² (O_3 , methanol; dimethyl sulfide as reducing reagent) was first tried on a small scale (0.48 mmol) and found to be adequate (81 % yield), but the product mixture was very complicated and difficult to sep-

arate. When the reaction was scaled up, the reaction actually failed. There were three major products, one of them was the desired keto aldehyde **139** (<40%). The others, with molecular weights 186 and 228 (GC/MS), respectively, did not contain an aldehyde group (^1H NMR). Various procedures from the literature⁴³ (yields range from 34% to 100%) were collected and compared, and reaction conditions were explored further using geraniol as a model molecule. The optimum conditions for ozonolysis of geraniol to yield 4-oxo-pentanal (**171**) were established to be passing ozone into a cold (-78 °C) solution of geraniol in methylene chloride (0.10 m M) until the blue color persisted and the color of the test solution of potassium iodide in 1% acetic acid (used for absorbing unreacted ozone) changed its color from yellow to orange suddenly; passing argon into the reaction solution for at least 5 min. to remove excess O_3 ; adding dimethyl sulfide (20 equiv.) at -78°C and stirring for 30 min., then at room temperature for 11 h (see Experimental). The yield was good (95%) and the separation was easy. Unfortunately, under exactly the same conditions, diene ester **140** only afforded a trace of the component which showed an aldehyde peak in NMR;

Scheme 38. Ozonolysis of the dienes



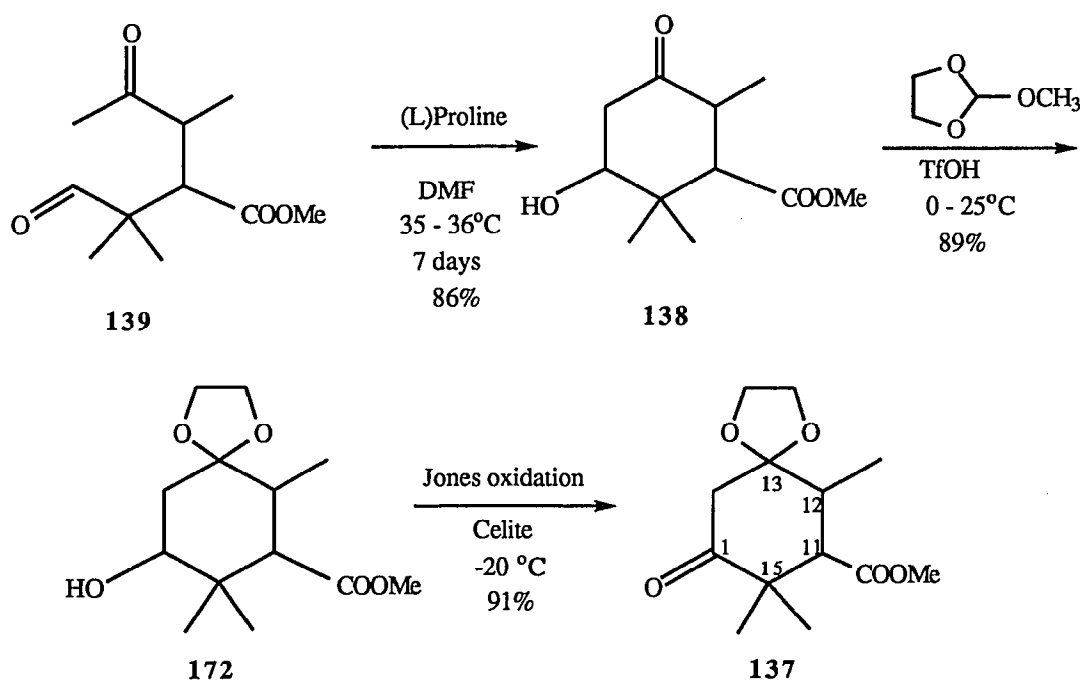
most of the components did not contain an aldehyde group. It was found that without methanol, the reduction of the ozonide took quite a long time; when methanol was added as a co-solvent, the reduction took only a few hours, but dimethyl acetal components were observed which caused extra work to hydrolyze. In order to avoid using methanol as a co-solvent, we tried to find some other solvents. In our attempts, we tried a condition⁴⁴ in which pyridine was employed as a co-solvent. These conditions turned out to be good, and we obtained **139** in 98% yield.

2.7 Synthesis of 137

With ketoaldehyde **139** in hand, the next synthetic task was to explore cyclization conditions (Scheme 39).

The aldol condensation was effected by treatment of keto aldehyde **139** with (L)-proline⁴⁵ in dry DMF to obtain **138** in 86% yield. Attempted aldol condensations with potassium hydroxide in methanol (1%)⁴⁶ and zirconium tert-butoxide⁴⁷ in THF were not successful.

Scheme 39. Synthesis of **137**



The conversion of hydroxy-keto-ester **138** into ketal **172** was first attempted with a conventional method using ethylene glycol as reagent and toluenesulfonic acid as catalyst.⁴⁸ The reaction was successful but the yield was low (65%). We continued to search for an even milder set of conditions because the β -hydroxy-ketone, is likely to be sensitive to the acidic conditions required, which may also lead to dehydration. Fortunately, the literature⁴⁹ referred us to 2-methoxy-1, 3-dioxolane as a reagent and TfOH as a catalyst. Using this procedure we obtained **172** in 89% yield. The oxidation of **172** was effected by Jones reagent.^{48b} It was found that the presence of celite⁵⁰ was helpful in the workup and increased the yield. Without celite, the green, muddy precipitate was difficult to filter. Celite adsorbs the precipitate and forms a green powder.

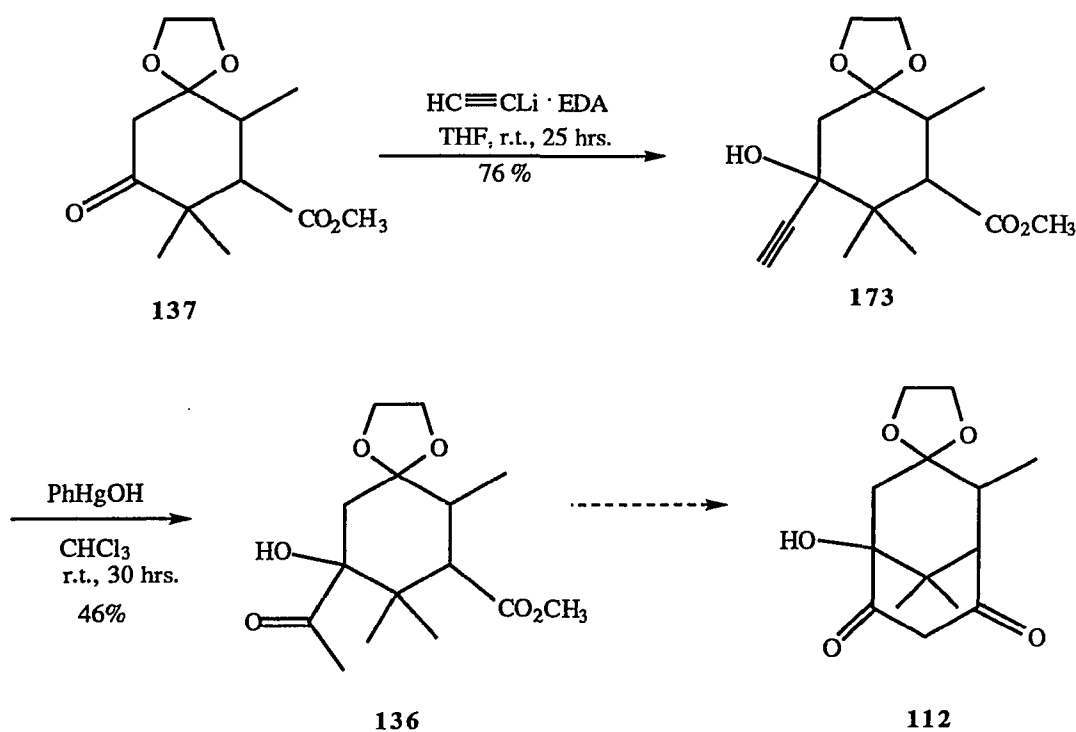
Keto-ester **137** contains two diastereomers, *cis* and *trans*. In taxol, these two centers (C11 and C12) will be connected by a double bond. We still separated the two isomers with preparative HPLC for structural characterization. The structural assignment (see Experimental) is tentative in nature.

2.8 Attempt at the Synthesis of Target Molecule 112

The next synthetic task is to add an acetyl equivalent

to molecule **137**. Although a lot of acetyl equivalents are known, one which meet our needs is still very limited. If we use a too strong nucleophile, both ketone and ester would be attacked; if we use a too weak nucleophile, there would be no reaction because this ketone is extremely crowded. We have already tried to use 2-trimethylsilyloxypropionitrile⁵¹ as an acetyl equivalent to add to keto-ester **137**, but the reaction was unsuccessful. Finally, we found lithium acetylide⁵² was good for this reaction. After addition, the acetylene was converted into an α -hydroxy ketone. The conventional method,⁵³ which use mercuric sulfate in hot

Scheme 40. Attempt at the synthesis of molecule **112**



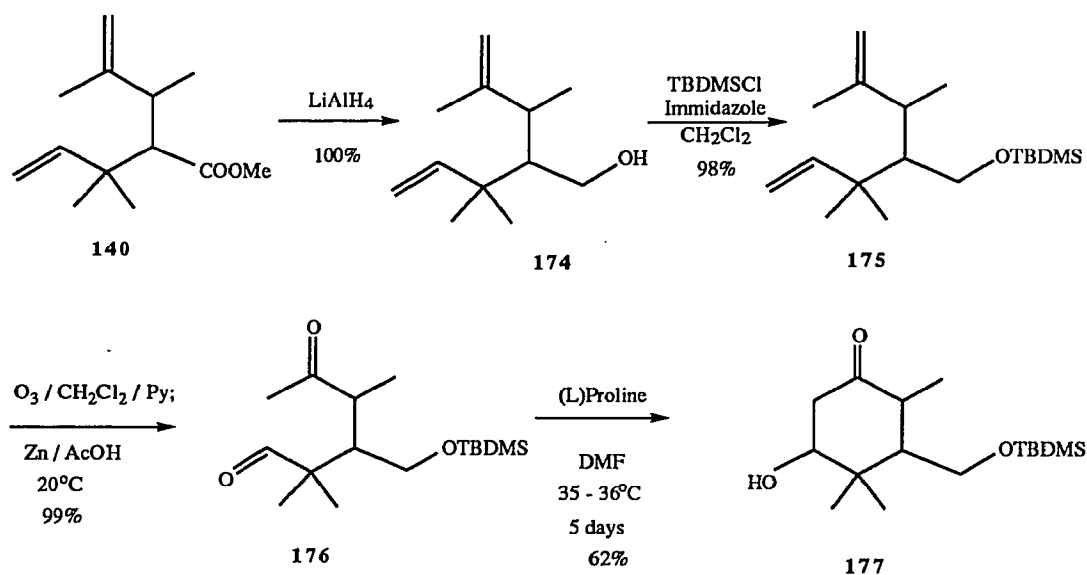
dilute sulfuric acid, is not adequate to this system because the protection group ketal is intolerant to these conditions. Fortunately, the literature⁵⁴ led us to phenylmercuric hydroxide (commercially available). The reaction was tried in chloroform under the reflux conditions employed by the literature. The yield was very poor(46%). After two trials we found the conditions must be modified. We use CDCl_3 as solvent and run the reaction in an NMR tube at room temperature, monitoring the reaction directly with ^1H NMR. So far, this condition was still not satisfactory because the yield was very low and the reproducibility was poor. Hydroxy ketone **136** was isolated and identified. The investigation of cyclization of **136** to produce **112** under Claisen condensation conditions is under way.

2.9 An Alternative Route to Derivative of **138**

As discussed in section 2.8, the keto group in keto-ester **137** was inactive towards weaker nucleophiles due to the steric hindrance. The ester group excludes the possibility of using stronger nucleophiles, such as Grignard and lithium reagent to introduce a two-carbon unit. In order to overcome this difficulty, we developed another parallel route starting from **140**. Reduction of **140** with diisobuty-

luminum hydride (DIBALH),⁵⁶ followed by protection with tert-butylchlorodimethylsilane catalyzed by imidazole⁵⁷ to afford **175** in 98% yield. Ozonolysis of **175** yielded **176** in almost quantitative yield (99%). Intramolecular aldol condensation of **176** catalyzed by (L)-proline afforded **177** in 62% yield. This route not only provided the way to prepare hydroxy-ketone **177**, but also tested the applicability of the approach in another similar system.

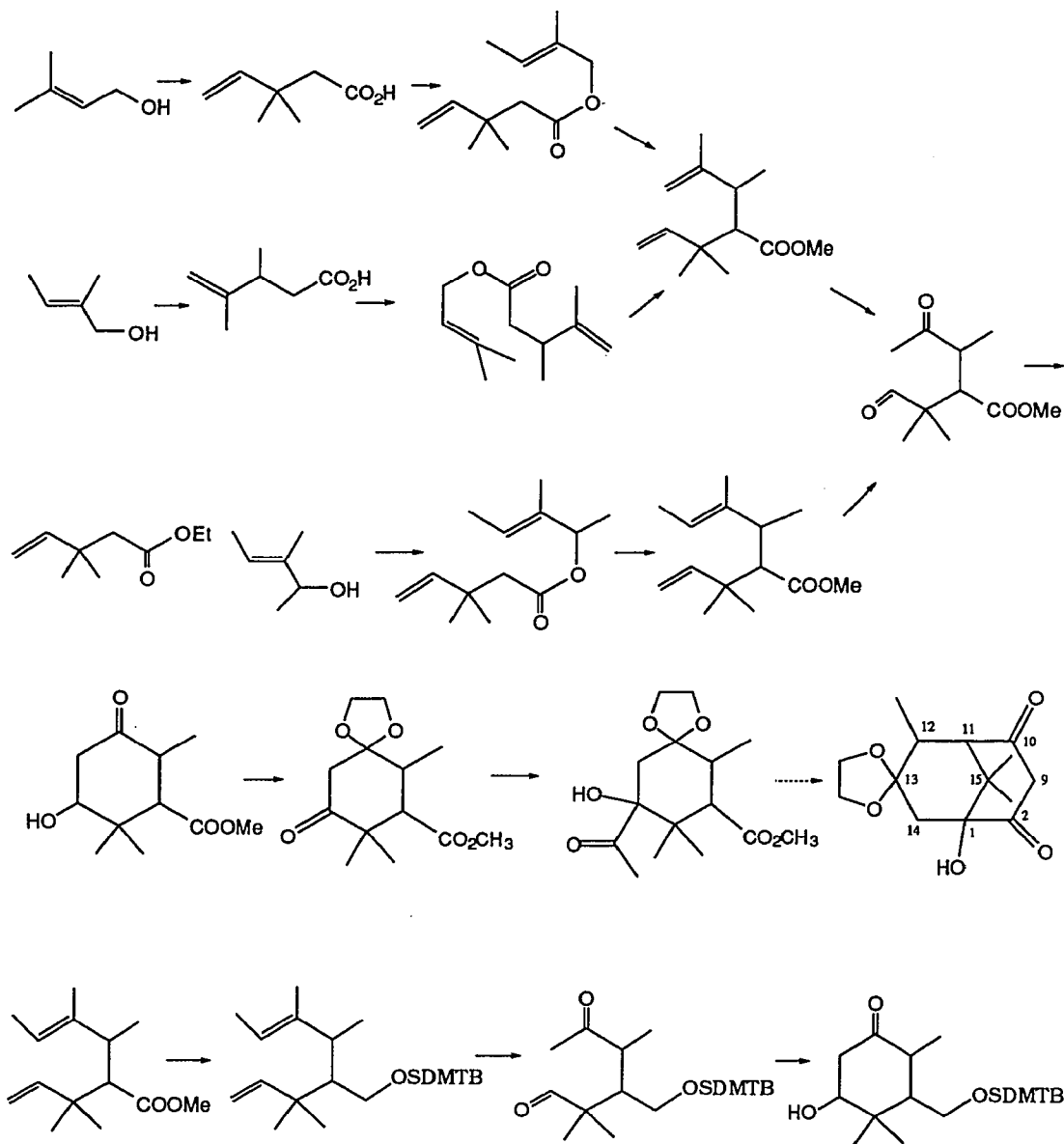
Scheme 36. Synthesis of **177**



2.10 Conclusion and Future Plan

In summary, we have completed the synthesis of a taxol A-ring synthon **138** in two similar systems and attempted the further transformation of **138**. The sequence started with the tandem Johnson-Claisen and the Ireland-Claisen rearrangements. These two reactions allow us to construct a chain rapidly and efficiently. After ozonolysis and aldol condensation, we obtained an A-ring synthon of taxol with all substituents required for further transformations(see Scheme 41).

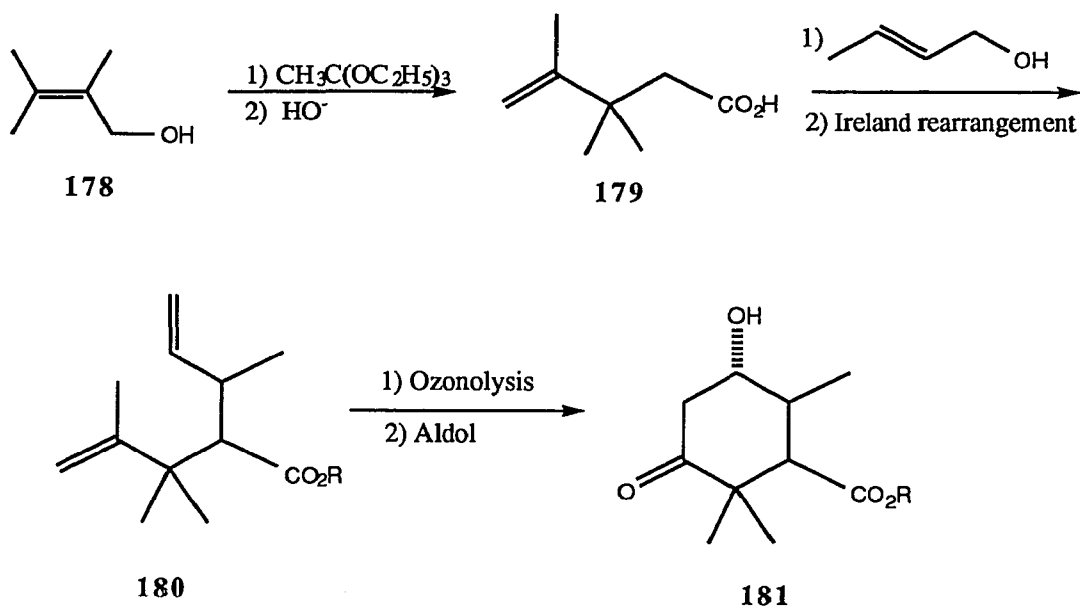
Scheme 42. Summary



Our future plans are depicted in Schemes 43 and 45.

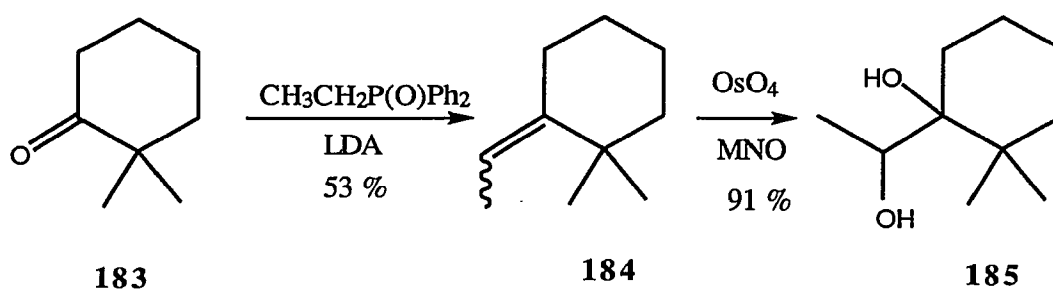
Scheme 43 is based on the same idea as Scheme 27, but introduces the possibility of synthesizing **181** enantioselectively by specifying the absolute configuration at C13 through enantioselective aldol reaction.⁵⁸ Scheme 45 shows the future plans for manipulation of **137**. Wittig reaction of **137** would afford **182**, which could possibly be converted enantioselectively into **136** via asymmetric dihydroxylation reaction by using a proper chiral catalyst,⁵⁹ followed by oxidation.

Scheme 43 Proposal for synthesis of taxol A-ring synthon A variation



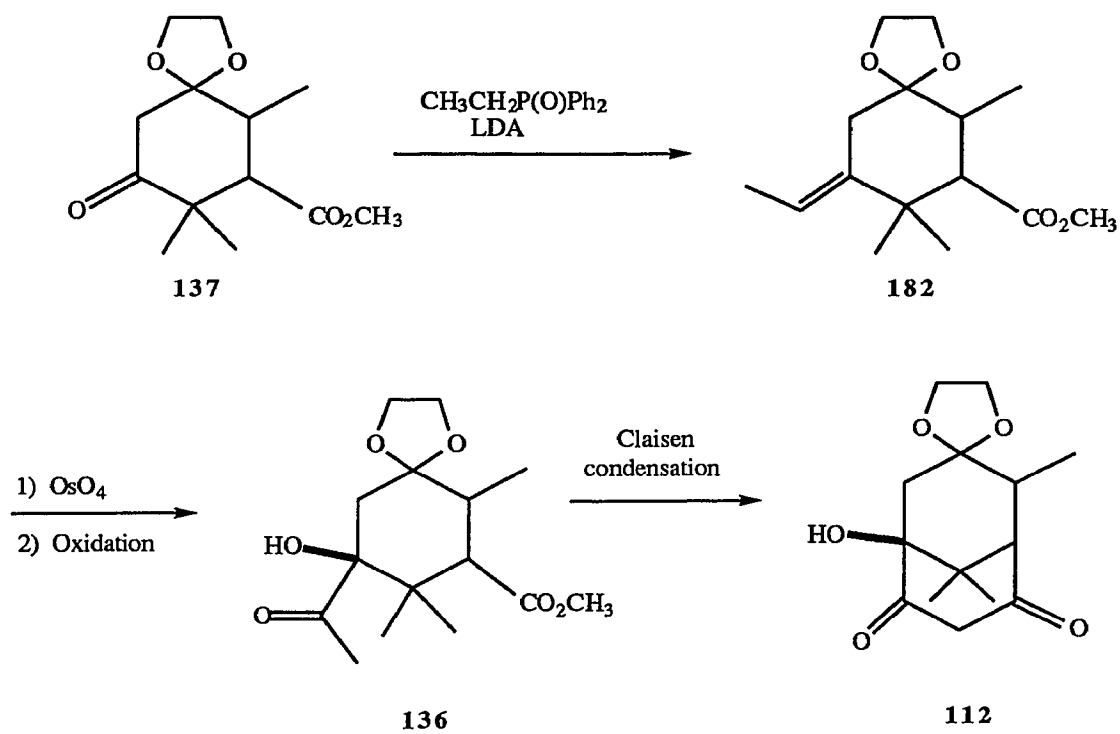
The Wittig reaction and dihydroxylation reaction have already been tested in a model (achiral) system as shown in Scheme 44.

Scheme 44. A model study



In Scheme 44, Wittig reaction⁶⁰ of 2,2-dimethylcyclohexanone (commercially available) with ethyl diphenyl phosphate using LDA as a base afforded **184** in 53% yield. Dihydroxylation^{22c} of **183** yielded diol **185** in 91% yield.

As shown in Scheme 45, the final cyclization (the Claisen condensation) is anticipated to be initiated by a base. This reaction has been proved to be successful in a model system, lacking the C1 hydroxyl group, by Blechert.²⁰

Scheme 45 Proposal for future manipulation of **137**

Chapter 3 Experimental Section

General All starting materials were obtained from commercial supplies and purified by distillation or recrystallization before use except as mentioned. THF, ether, benzene and dimethoxy ethane (DME) were distilled from sodium with benzophenone as indicator. The solvents were distilled immediately prior to use and the solvent was transferred directly into the reaction flask through a stainless steel tube. Triethylamine, diisopropylamine, cyclohexyl-isopropylamine, methylene chloride, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and hexamethyl phosphoramide (HMPA) were distilled from calcium hydride prior to use. ^1H NMR spectra were measured in deuteriochloroform using a Bruker/ IBM 200MHz NMR spectrometer or Varian Anaspect EM 360 (60MHz) NMR spectrometer. IR spectra were taken with a Perkin-Elmer 598 Infrared Spectrophotometer or Perkin Elmer 1600 FT-IR spectrophotometer. GC/MS were kindly obtained by Dr. Locke at the Queens College Department of Chemistry using a Hewlett Packard 5988A GC/ MS. Elemental analysis were performed by Galbraith Labs., Knoxville, Tenn.

Ethyl 3,3-dimethyl-4-pentenoate (146)⁶¹ A mixture of 3-methyl-2-buten-1-ol (**144**) (27.65 g, 322 mmol), triethyl orthoacetate (156.28 g, 965 mmol, 3.0 equiv.),^{25c} and propionic acid (1.43 g, 19.3 mmol, 0.06 equiv.) was heated at 144 °C for three days with continuous removal of ethanol by distillation. Additional propionic acid (0.08 g, 1.0 mmol, 0.003 equiv.) was added^{25c} every 24 h. After the reaction was complete, the excess of triethyl orthoacetate was distilled out under reduced pressure (56°C / 18 mmHg). The remaining trace of triethyl orthoacetate was removed by washing the ether solution of the crude product with 1.0 % of sulfuric acid (3 X 50 mL), brine (50 mL), sodium bicarbonate (50 mL) and brine (50 mL), successively. The ether solution was dried over magnesium sulfate and concentrated to yield the crude product as an oil. this was distilled at 62-63 °C / 18 mmHg (lit 34-35 °C / 0.1 mmHg ^{61a}, 81-83 °C / 47 mmHg^{61b}, 94-98 °C/ 72 mmHg^{61d}) to obtain 44.81 g (yield: 89%) of colorless oily liquid **146**. ¹H NMR δ 1.11 (s, 6H, gem-dimethyl), 1.22 (t, J=7.1 Hz, 3H, OCH₂CH₃), 2.26 (s, 2H, CH₂CO₂), 4.08 (q, J=7.1Hz, 2H, OCH₂), 4.91 (dd, J₁=10.6 Hz, J₂=1.0 Hz, 1H, CH₂=CH), 4.95 (dd, J₁=17.5 Hz, J₂=1.0Hz, 1H, CH₂=CH), 5.88 (dd, J₁ = 17.5 Hz, J₂ = 10.6 Hz, 1H, CH₂=CH) (lit ^{61c, 25c}). IR (cm⁻¹, CCl₄):

2960 (s), 1730 (s), 1640, 1230, 1120 (lit ^{61a, 61b}); MS (m/z): 156 (M⁺), 141, 127, 113, 111, 110, 99, 88, 85, 83, 82, 71, 70, 69(100 %), 55 (lit ^{61e}); Anal. Calcd for C₉H₁₆O₂ : C, 69.19, H, 10.33; Found: C, 69.43, H, 10.56.

Ethyl 3,3-dimethyl-4-hexenoate (147)⁶² The procedure used for preparation of **146** was applied to the homolog. A mixture of 4-methyl-3-penten-2-ol (**145**) (20.00 g, 199.7 mmol), triethyl orthoacetate (129.40 g, 798.8 mmol, 4.0 equiv.), and propionic acid (0.70 g, 9.4 mmol, 0.047 equiv.) was heated at the temperature of 144 °C for 70 h. with continuous removal of ethanol by distillation. Additional propionic acid (0.08 g, 1.0 mmol, 0.003 equiv.) was added every 12 h. After the reaction was complete, the excess of triethyl orthoacetate was removed by distillation under reduced pressure (56 °C/ 18 mmHg). The remaining liquid was fractionally distilled and the sample collected at 70-71 °C / 23 mmHg (lit.^{62b} 100-105°C / 57 mmHg) afforded 26.77g (79%) of colorless oily liquid **147**. ¹H NMR δ: 1.07 (s, 6H, *gem*-dimethyl), 1.20 (t, J =7.1 Hz, 3H, OCH₂CH₃), 1.61 (d, J= 6.0 Hz, CH₃C=), 2.21 (s, 2H, CH₂CO₂), 4.07 (q, J=7.1 Hz, 2H, OCH₂), 5.51-5.28 (m, 2H, vinyl) (lit ^{62a}). IR (cm⁻¹, CCl₄): 3080, 2970, 2949, 2877, 1736, 1643, 1458, 1433,

1414, 1379, 1345, 1266, 1191, 1146, 1068, 1009, 915, 894.

Methyl 3,3-dimethyl-4-pentenoate (148) A modification of the procedure of Beckwith⁶³ was employed. A solution of 4.66 g (54.1 mmol) of 3-methyl-2-buten-1-ol (**144**), 16.25 g (135 mmol, 2.5 equiv.) of trimethyl orthoacetate, and 0.215 g (2.90 mmol, 0.055 equiv.) of propionic acid in 50 mL of *o*-xylene was heated to reflux with stirring (bath temperature: 132-133°C). Methanol was removed continuously by distillation. Heating and stirring was continued for a total of 3 h. The reaction mixture was cooled to room temperature and distilled under reduced pressure (20 mmHg) using spinning band distillation equipment. After the reagent trimethyl orthoacetate was removed (b.p. 47-48 °C / 20 mmHg), the product **148** was distilled as a colorless liquid (b.p. 51-52 °C / 20 mmHg, (lit.⁶³ 59°C / 33 mmHg), 3.69 g (48%). ¹H NMR δ: 1.13 (s, 6H, *gem*-dimethyl), 2.31 (s, 2H, CH₂CO₂), 3.64 (s, 3H, OCH₃), 4.93 (dd, J₁ = 10.6 Hz, J₂ = 1.0 Hz, 1H, CH₂=CH), 5.01 (dd, J₁ = 17.5 Hz, J₂ = 1.0 Hz, 1H, CH₂=CH), 5.90 (dd, J₁ = 17.5 Hz, J₂ = 10.6 Hz, 1H, CH₂=CH); IR (cm⁻¹, CCl₄): 3080, 2980 (s), 1740 (s), 1640, 1460, 1435, 1380, 1325, 1230, 1205, 1130, 1015, 915; MS (m/z): 142 (M⁺), 127, 120, 111, 110,

85, 82, 74, 69(100 %), 59, 55. The NMR spectrum is identical with that reported in the literature for this compound.⁶³

3,3-Dimethyl-4-pentenoic acid (142)^{61c, 61d, 64} The hydrolysis method of Bartlett²⁷ was used. Ethyl 3,3-dimethyl-4-pentenoate (**146**) (31.375 g, 0.200 mol) was dissolved in a solution of 20.875 g (0.4728 mol, 1.86 equiv.) of potassium hydroxide in 26 mL of water and 78 mL of methanol. The solution was deaerated by three cycles of vacuum / argon exchange, and then heated in an oil bath (bath temperature: 103-105°C) under reflux with stirring for 1.5 h. The reaction mixture was then cooled to room temperature and extracted with ether (3 X 20 mL). The aqueous solution was cooled in an ice bath, diluted with 40 mL of water and acidified with precooled 3 N hydrochloric acid to pH 2. The cloudy solution which formed was extracted with ether (5 X 100 mL). The combined ether extracts were washed with brine (20 mL) and dried over magnesium sulfate. Removal of solvent afforded a crude product of **142** as a colorless liquid. This was distilled at 100 °C / 13 mmHg (lit. 100-102 °C / 14 mmHg;^{61c} 83-85 °C / 4 mmHg;^{61d} 65-70 °C / 3 mmHg⁶⁴) to give 22.36 g (87%) of pure **142**. ¹H NMR δ: 1.14 (s, 6H, *gem*-dimethyl), 2.32 (s, 2H,

CH₂CO₂), 4.95 (dd, J₁=10.6 Hz, J₂=1.0 Hz, 1H, CH₂=CH), 4.98 (dd, J₁=17.5 Hz, J₂=1.0 Hz, 1H, CH₂=CH), 5.92 (dd, J₁=10.6 Hz, J₂=17.5 Hz, 1H, CH₂=CH), 10.8 (broad, 1H, COOH) (lit. ^{61c, 61d, 64}); IR (cm⁻¹, CCl₄): 3400 (broad, strong), 2980 (s), 1720 (s), 1640 (w), 1420, 1240 (s), 915 (lit. ^{61c, 61d, 64}); MS (m/z): 128 (M⁺), 113, 110, 95, 85, 83, 82, 71, 69 (100), 68, 67, 65, 60, 59, 55, 53, 45, 41 (lit. ^{61c, 64}). Anal. Calcd for C₇H₁₂O₂ : C, 65.59, H, 9.44; found: C, 65.61, H, 9.36.

2-Methyl-2-butenyl 3,3-dimethyl-4-pentenoate (141)

Esterification Method A : Paquette's³⁰ esterification method was employed. 3, 3-dimethyl-4-pentenoic acid (**142**: 11.10 g, 86.7 mmol, 1.35 equiv.) and 5.54 g (64.40 mmol) of 2-methyl-2-buten-1-ol (**143**) were dissolved in 250 mL of anhydrous ether (distilled over sodium with benzophenone ketyl as indicator immediately before use). To this cooled (0 °C) solution was added 17.90 g (86.6 mmol, 1.35 equiv.) of DCC in 50 mL of anhydrous ether dropwise, followed by 1.18 g (9.7 mmol, 0.15 equiv.) of DMAP in one portion. After addition was complete, the ice bath was removed and the solution was stirred at room temperature for 22 h. The reaction mixture was diluted with 400 mL of hexane and the white precipitate which

formed was filtered through a silica gel pad and the pad was washed with hexane and ethyl acetate (20 : 1). the filtrate was concentrated to yield a crude product which was purified further by flash chromatography with hexane and ethyl acetate (20 : 1) as eluent (TLC Rf=0.78, hexane/ethyl acetate, 20 :1) to yield 12.60 g (100%) of **141** as a colorless liquid. ^1H NMR δ : 1.10 (s, 6H, *gem*-dimethyl), 1.57-1.61 (m, 6H, 2 X $\text{CH}_3\text{C}=\text{}$), 2.29 (s, 2H, CH_2CO_2), 4.39 (s, broad, 2H, OCH_2), 4.87 (dd, $J_1=17.5$ Hz, $J_2=1.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}$), 4.91 (dd, $J_1 = 10.6$ Hz, $J_2 = 1.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}$), vinyl, 5.53 (m, 1H, $\text{CH}_3\text{CH}=\text{}$). 5.91 (dd, $J_1 = 17.5$ Hz, $J_2 = 10.6$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}$); IR (cm^{-1} , CCl_4): 2960 (s), 1730 (s), 1640, 1450, 1355, 1320, 1230, 1120, 918, 906. MS (m/z): 196 (M^+), 136, 128, 113, 111, 110, 95, 86, 85, 83, 82, 71, 70, 69 (100%), 68, 55, 41; Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43, H, 10.27; Found: C, 73.45, H, 10.30.

Method B : Holmberg's³⁹ esterification protocol was employed in the preparation of ester **141**. 3,3-dimethyl-4-pentenoic acid (**142**) (9.06 g, 70.78 mmol), 6.66 g (77.41 mmol, 1.09 equiv.) of 2-methyl-2-buten-1-ol (**143**), and 0.64 g of *p*-toluene sulfonic acid were dissolved in 72 mL of pyridine. The solution was cooled in an ice bath. To this mixture was added 17.4 g (84.33 mmol, 1.20 equiv.) of

DCC. The ice bath was removed and the mixture was stirred at room temperature for 24 h. A voluminous white precipitate formed. The mixture was then cooled in an ice bath and 10 mL of acetic acid was added and the mixture was stirred overnight. The reaction mixture was diluted with 300 mL of pentane and cooled thoroughly in an ice bath. The precipitate which formed were filtered and washed with cold pentane (3 X 30 mL). The combined organic layers were washed with sodium bicarbonate (50mL) and brine (50mL) and dried over magnesium sulfate. Removal of the solvent yielded a colorless liquid. The crude product was separated by flash column chromatography using hexane and ethyl acetate (20:1) as eluent. Fractions with TLC $R_f=0.78$ (hexane and ethyl acetate, 20 : 1) were collected. The solvent was removed and 13.03 g (93%) of colorless liquid **141** was obtained. This sample is identical in TLC R_f ^1H NMR, IR, and MS with that obtained via method A.

Method C: 3,3-dimethyl-4-pentenoyl chloride (151) The acid chloride was prepared based on a typical procedure.³¹ 3,3-dimethyl-4-pentenoic acid **142** (4.79 g, 37.4 mmol) was cooled in an ice-acetone bath at -11 °C. To this was slowly added, by syringe with stirring during 5 min., 20

mL of freshly distilled thionyl chloride. After addition was complete, the ice bath was removed and the mixture was heated in an oil bath for 50 min. at 80 - 82 °C and finally distilled under reduced pressure to yield 4.80 g (88 %) of colorless liquid acid chloride, b.p. 54 °C / 16mmHg. ^1H NMR δ : 1.14 (s, 6H, *gem*-dimethyl), 2.32 (s, 2H, $\text{CH}_2\text{CO}_2\text{Cl}$), 5.01 (dd, $J_1=11.0$ Hz, $J_2=1.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}$), 5.05 (dd, $J_1=17.0$ Hz, $J_2=1.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}$), 5.88 (dd, $J_1=17.0$ Hz, $J_2=11.0$ Hz, 1H, $\text{H}_2\text{C}=\text{CH}$); IR (cm^{-1} , CCl_4): 3040 (w), 2980 (s), 1804 (vs), 1640 (w), 990, 660(s).

Esterification: The ester was prepared from the acid chloride obtained above based on the known procedure.³² A solution of 3,3-dimethyl-4-pentenoyl chloride **151** (3.80 g, 25.9 mmol) in 70 mL methylene chloride was cooled in an ice bath while 2-methyl-2-buten-1-ol (**143**) (2.23 g, 25.9 mmol) was added. To this cold mixture, a solution of triethylamine (5.3 g, 52.5 mmol) in 17 mL of methylene chloride was added during 20 min. As the triethylamine solution was added, white smoke appeared briefly on the top of the colorless reaction solution. After about 25 min., a white precipitate formed. Stirring was continued for an additional hour at 0 °C. The reaction mixture was then poured into 25 mL of cold water, the layers were separated, and the aqueous layer was extracted with methylene

chloride (3 X 25 mL). The combined organic layers were washed with sodium bicarbonate (10 mL) and brine (10 mL), and dried over magnesium sulfate. After filtration and concentration, a light yellow liquid remained. The crude product was passed through a short column packed with 50 g of silica gel using hexane and ethyl acetate (20 :1) as eluent. The eluate afforded 5.01 g (99%) of colorless oily liquid **141**. This sample shows the identical TLC R_f, IR and NMR spectra as the sample obtained by Method A.

2-(1,2-Dimethyl-2-propenyl)-3,3-dimethyl-4-pentenoic acid (152) from 141: A variety of Ireland-Claisen rearrangement conditions^{34a-f} proved unsatisfactory. The Ireland-Claisen rearrangement was performed as the following modified procedure. A solution of 3.45 g (24.42 mmol, 1.10 equiv.) of dry cyclohexyl-isopropylamine in 25 mL of THF was cooled to -15°C in a carefully adjusted acetone-dry ice bath. Butyl lithium (2.50 M, 9.1 mL, 22.69 mmol, 1.10 equiv.) was added dropwise by syringe to this solution during 15 min. with stirring. The mixture was stirred for an additional 15 min. at -15 °C, then cooled to -78°C during 40 min. Then, 2-methyl-2-butenyl 3,3-dimethyl-4-pentenoate (**141**: 4.05 g, 20.66 mmol) in 5 mL

of THF was added with stirring during 8 min. When the addition was complete, the mixture was stirred at -78°C for an additional 1h. HMPA (5.0 mL, 5.15 g, 28.77 mmol, 1.40 equiv.) was added at -78°C , followed by a solution of tert-butyl chlorodimethylsilane (3.30 g, 21.89 mmol, 1.05 equiv.) in 3 mL of THF, and stirring was continued at -78°C for 40 min. The dry ice-acetone bath was removed and the reaction mixture was kept at room temperature for 5 min. and then, immersed in an ice-water bath for 15 min. The ice-water bath was replaced with an oil bath and the temperature was slowly raised to 70°C during 45 min. This temperature was maintained for 30 min., then raised to $78\text{-}79^{\circ}\text{C}$ and stabilized (shorter times and lower temperatures gave inferior yields). The solution was refluxed gently for 15 h., then cooled in an ice-water bath. To this cold solution, a solution of 3.00 g of potassium carbonate in 30 mL of water and 60 mL of methanol was added. The mixture was stirred at room temperature for 3 h, then transferred to a separatory funnel and diluted with 150 mL of ether. The two layers which formed were separated. The organic layer was extracted with 5% aqueous potassium hydroxide (5 X 50 mL). The combined aqueous layers were cooled in an ice-water bath and acidified with cold 3 N hydrochloric acid to pH 2. The solution became milky

white, and was then extracted with ether (6 X 50 mL). The combined ether solutions were washed with brine (20 mL) and dried over magnesium sulfate. Concentration of the solution yielded 3.61 g (89%) of acid **152** (a mixture of two diastereoisomers) as a colorless oily liquid. ^1H NMR (mixture of two isomers) δ : 11.01 (s, broad, COOH), 5.95 (dd, $J_1 = 17.2$ Hz, $J_2 = 10.7$ Hz), 4.94 (dd, $J_1 = 17.2$ Hz, $J_2 = 1.5$ Hz), 4.86 (dd, $J_1 = 10.7$ Hz, $J_2 = 1.5$ Hz), 4.68-4.61 (m), 2.52-2.34 (m), 1.66 (s, broad), 1.65 (s, broad), 1.19 (s), 1.12 (s), 1.11 (s), 1.10 (s), 1.02 (d, $J = 6.7$ Hz), 1.00 (d, $J = 6.8$ Hz); IR (cm^{-1} , CCl_4): 3500-3100 (s, broad, COOH), 2990, 1705 (s), 1640, 1405, 1280, 905; MS (m/e): 179 (M-OH), 168, 153, 135, 127, 113, 109, 95, 81, 69, 44, 41 (100%).

152 from 155 Acid-**152** was also obtained by the rearrangement of **155**. A solution of 1.46 g (10.3 mmol, 1.10 equiv.) of cyclohexyl-isopropylamine in 20 mL of THF was cooled to -15°C in an acetone-dry ice bath. Butyl lithium (2.50 M, 3.8 mL, 9.58 mmol, 1.10 equiv.) was added dropwise by syringe to this solution during 15 min. with stirring. The stirring was continued for 15 min. and the mixture was then cooled to -78°C during 40 min. 3-methyl-2-butenyl 3,4-dimethyl-4-pentenoate (**155**: 1.71 g, 8.72 mmol) in 4.2 mL of THF was then added with stirring dur-

ing 5 min. and the mixture was stirred at -78°C for an additional hour. HMPA (2.1 mL, 2.21 g, 12.25 mmol, 1.42 equiv.) was added at -78°C , followed by a solution of tert-butylchlorodimethylsilane (1.39 g, 9.24 mmol, 1.05 equiv.) in 2.5 mL of THF. Stirring was continued at -78°C for 40 min. The dry ice-acetone bath was removed and the reaction solution was kept at room temperature for 5 min. and then, immersed in an ice-water bath for 15 min. The ice-water bath was replaced with an oil bath and start to heat slowly to raise the temperature to room temperature. The solvent was removed at room temperature under vacuum as 25 mL of toluene (distilled over sodium with benzophenone ketyl as indicator) was added portionwise. The total volume was ca. 35 mL. The solution was heated to 70°C during 25 min. and kept at 70°C for 10 min., then heated to $109-110^{\circ}\text{C}$ and refluxed gently at this temperature for 38 h. The reaction mixture was then cooled in an ice-water bath and to this cold solution was added a solution of 1.50 g (10.87 mmol) of potassium carbonate in 15 mL of water and 30 mL of methanol. The mixture was stirred at room temperature for 3.5 h., then transferred to a separatory funnel and diluted with 100 mL of ether. Two layers was separated and the organic layer was extracted with 5 % aqueous potassium hydroxide (5 X 15 mL). The combined

aqueous layers were cooled in an ice-water bath and acidified with cold 3 N hydrochloric acid to pH 2. The solution became milky white. The solution was then extracted with ether (6 X 15 mL). and the combined ether layers were washed with brine (2 X 5 mL) and dried over magnesium sulfate. Concentration of the solution yielded 1.10 g (64%) of crude **152** (a mixture of two diastereomers) as a colorless oily liquid. ^1H NMR (mixture of two isomers) δ : 10.5 (s, broad, COOH), 5.98 (dd, $J_1 = 17.5$ Hz, $J_2 = 10.7$ Hz), 4.96 (dd, $J_1 = 17.5$ Hz, $J_2 = 1.5$ Hz), 4.89 (dd, $J_1 = 10.7$ Hz, $J_2 = 1.5$ Hz), 4.70-4.61 (m), 2.54-2.35 (m), 1.66 (s, broad), 1.64 (s, broad), 1.21 (s), 1.13 (s), 1.10 (s), 1.09 (s), 1.01 (d, $J=6.7$ Hz), 1.00 (d, $J=6.8\text{Hz}$); IR (cm^{-1} , CCl_4): 3500-3082 (s, broad, COOH), 2972, 2935, 1702, 1643, 1459, 1415, 1380, 1365, 1298, 1197, 1046, 988, 924.

Methyl 2-(1, 2-dimethyl-2-propenyl)-3,3-dimethyl-4-pentenoate (140) from **141** The esterification procedure of Otera³⁷ was employed. Acid **152** (from **141**) (3.61 g, 18.4 mmol) and iodomethane (4.38 g, 30.8 mmol) were dissolved in 70 mL of dry DMF. To this solution was added carefully powdered dry cesium fluoride (5.00 g, 30.96 mmol) portionwise with exclusion of moisture. The mixture was stirred at room temperature for 24 h. At the end

of the reaction, the reaction solution, which was yellowish with a little precipitate, was cooled in an ice water bath and diluted with cold saturated aqueous sodium bicarbonate (20 mL) and then extracted with ether (4 X 100 mL). The combined ether layers were dried (magnesium sulfate) and concentrated in vacuum to yield 5.61 g of a colorless liquid. The crude product thus obtained was separated by flash chromatography (eluent: hexane : ethyl acetate, 20:1) to obtain 3.68 g (95 %) of **140** as a colorless liquid with a pleasant smell. Two diastereomers, *threo* and *erythro*, were present in the sample in a ratio of 34 : 66 (HPLC and NMR). The two pure isomers were isolated by preparative HPLC with hexane: ethyl acetate (200:1) as eluent. The NMR of these two isomers were tentatively assigned as follows: *threo* (t_R 28 sec., 34%): 1H NMR δ : 0.93 (d, $J = 6.8$ Hz, 3H, $CHCH_3$), 1.08 (s, 6H, *gem*-dimethyl), 1.64 (m, 3H, $CH_3C=$), 2.46 (d, $J = 8.4$ Hz, 1H, $CHCO_2$), 2.59 (m, 1H, CH_3CH), 3.61 (s, 3H, OCH_3), 4.67 (s, broad, 1H, $CH_2=C(Me)$), 4.79 (s, broad, 1H, $CH_2=C(Me)$), 4.88 (dd, $J_1 = 2.3$ Hz, $J_2 = 17.8$ Hz, 1H, $CH_2=CH$), 4.94 (dd, $J_1=2.3$ Hz, $J_2=10.5$ Hz, 1H, $CH_2=CH$), 5.98 (dd, $J_1 = 10.5$ Hz, $J_2 = 17.8$ Hz, 1H, $CH_2=CH$). IR (cm^{-1} , CCl_4): 3082 (w), 2971, 2948, 1736, 1643, 1461, 1431, 1378, 1267, 1190, 1167, 1146, 1009, 1001, 916, 894; MS (m/z): 210, 195, 182, 167, 151,

141, 127, 109, 95, 83, 69 (100 %), 55, 41; Anal. Calcd. for $C_{13}H_{22}O_2$ (mixture of two isomers): C, 74.24, H, 10.55; Found: C, 74.43, H, 10.56.

erythro (t_R 32 sec., 66%): 1H NMR δ : 1.02 (d, $J = 6.9$ Hz, 3H, $CHCH_3$), 1.08 (s, 6H, *gem*-dimethyl), 1.64 (m, 3H, $CH_3C=$), 2.43 (d, $J = 11.2$ Hz, 1H, CH_2CO_2), 2.59 (dq, $J_1 = 6.9$ Hz, $J_2 = 11.2$ Hz, 1H, CH_3CH), 3.54 (s, 3H, OCH_3), 4.62 (s, broad, 1H, $CH_2=C(Me)$), 4.65 (s, broad, 1H, $CH_2=C(Me)$), 4.92 (dd, $J_1 = 10.8$ Hz, $J_2 = 1.1$ Hz, 1H, $CH_2=CH$), 5.01 (dd, $J_1 = 1.1$ Hz, $J_2 = 17.5$ Hz, 1H, $CH_2=CH$), 5.98 (dd, $J_1 = 10.8$ Hz, $J_2 = 17.5$ Hz, 1H, $CH_2=CH$); IR (cm^{-1} , CCl_4): 3082, 2969, 2949, 2877, 1737, 1643, 1461, 1431, 1378, 1343, 1299, 1190, 1149, 1067, 1008, 913, 898. MS (m/e): 210, 195, 178, 167, 151, 141, 127, 121, 109, 95, 81, 69(100%), 55, 41.

140 from 155 The rearrangement product of **155** was similarly esterified. The crude acid 2-(2-dimethyl-3-butenyl)-3,3-dimethyl-4-pentenoic acid (1.10 g, 5.60 mmol) and iodomethane (1.03 g, 7.24 mmol) were dissolved in 13 mL of dry DMF. To this solution was added carefully powdered dry cesium fluoride (0.90 g, 5.57 mmol) portionwise under the condition of exclusion of moisture. The mixture was stirred at room temperature for 20 h. At the end of the reaction, the reaction mixture

was yellowish. This solution was cooled in an ice water bath and diluted with cold saturated aqueous sodium bicarbonate (15 mL) and then extracted with ether (4 X 15 mL). The combined ether layers were dried (magnesium sulfate) and concentrated to yield a colorless liquid. The crude product thus obtained was separated by flash chromatography (eluent: hexane : ethyl acetate, 10:1) to obtain 1.17 g (99 %) of **140** as a colorless liquid. The sample contains the same two diastereomers in a ratio of 68 : 32 (NMR). The individual spectra were identical with those of products obtained from **141**.

Methyl 2-methyl-2-butenolate (150) Tiglic acid was esterified by a standard procedure.²⁸ Tiglic acid (60.00 g, 0.60 mol) was dissolved with stirring in 480 mL of methanol. To this clear, slightly yellow solution, 24 mL of concentrated sulfuric acid was added dropwise at room temperature with stirring during 15 min. The acidic reaction mixture was heated to reflux during 20 min. and kept at reflux temperature for 2.5 h. (bath temperature: 78-81 °C). The bright yellow solution which resulted was cooled in an ice bath to room temperature and then poured into 1200 mL of ice-water with stirring. Powdered sodium bicarbonate was added portionwise with stirring until the pH reached

8.0 (no bubbles evolved). The organic layer which formed was separated and the aqueous layer was extracted with ether (3 X 100 mL). The combined ether layers were washed with brine, saturated sodium bicarbonate and brine (50 mL each), successively, then dried over magnesium sulfate. The mixture was filtered and the solvent was removed to obtain 67.94 g of yellow liquid. The crude product **150**, was distilled at 140-141 °C / 760 mmHg (lit.⁶⁵ 139.4-139.6 °C / 766 mmHg) to give 54.91 g (80.2 %) of colorless liquid **150**. ¹H NMR δ : 1.77 -1.84 (m, 6H, 2 X CH₃C=), 3.73 (s, 3H, OCH₃), 6.68 (dq, J₁ = 1.4 Hz, J₂ = 7.01 Hz, 1H, =CH) (lit.⁶⁶); IR (cm⁻¹, CCl₄): 3010, 2995, 2975, 1720 (C=O), 1655, 1435, 1260, 1190, 1135, 1080; MS (m / z): 114 (M⁺), 99, 83, 82, 59, 55 (100, M⁺-CO₂Me); Anal. Calcd for C₆H₁₀O₂: C, 63.13, H, 8.83; Found: C, 63.28, H, 8.80.

(E)-2-Methyl-2-buten-1-ol (143) Methyl 2-methyl-2-butenolate (**150**) was reduced by the procedure of Gastaminza.²⁹ A suspension of lithium aluminum hydride (17.10 g, 450 mmol) in 450 mL of sodium dried ether was prepared in a well dried round bottomed flask equipped with a pressure equalizing dropping funnel and a condenser to whose top was attached a drying tube. The suspension was stirred at room temperature for 30 min. and

cooled in an ice water bath for 30 min. A solution of aluminum trichloride (20.04g, 150 mmol) in 750 mL of ether was added to the suspension of lithium aluminum hydride with ice-water bath cooling and stirring during 25 min. After addition was complete, stirring was continued at room temperature for 35 min. A solution of 27.36 g (240 mmol) of **150** (obtained above) in 150 mL of ether was then added dropwise during 40 min. at 5-10 °C. Immediately after the addition was complete, the ice water bath was replaced with one at 20 °C, and stirring was continued at 20 °C for 50 min. Then, 75 mL of 20% sulfuric acid was added through a dropping funnel with ice-water bath cooling and stirring during 20 min. to insure all precipitate dissolved. Cooling was required, otherwise the addition caused vigorous refluxing. The mixture was stirred for an additional 45 min. The clear ether solution appeared on the top of the muddy gray precipitate. This solution was decanted into a separatory funnel. The muddy precipitate was washed with three 100 mL portions of ether. The combined ether solutions were washed with sodium bicarbonate (50 mL) and brine (50 mL), and dried over magnesium sulfate. Evaporation of the solvent yielded 30.61 g of a colorless liquid. The crude product was distilled at 66-68°C / 33 mmHg (lit.⁶⁶ 66-68 °C / 33 mmHg), to obtain

17.05 g (83 %) of **143** as a colorless liquid. No *Z* isomer⁶⁷ was detected by NMR. ¹H NMR δ : 1.51 (s, 1H, D₂O labile, OH), 1.61 (m, 6H, 2 X MeC=), 3.96 (s, broad, 2H, CH₂O), 5.47, (q, J = 5.3 Hz, 1H, CH=). IR (cm⁻¹, CCl₄): 3620 (sharp), 3350 (strong and broad), 2990, 2920, 2880, 1670, 1440, 1380, 1050, 1005; MS (m/z): 86 (M⁺), 71 (100, M⁺-Me), 68 (M⁺-H₂O), 67, 57, 55, 53, 43, 41; Anal. Calcd for C₅H₁₀O: C, 69.72, H, 11.70; Found: C, 69.80, H, 11.69. The NMR and IR are comparable with those reported in the literature.⁶⁸

4-Methyl-3-penten-2-ol (145) CeCl₃ · 7H₂O²⁶ (96.12 g, 0.258 mol) was dissolved in 240 mL of dry methanol to form a clear, colorless solution. To this solution, 25.14 g (0.258 mol) of mesityl oxide was added in one portion. A solution of 10.20 g (0.271 mol) of sodium borohydride in 150 mL of methanol was added dropwise during 8 min. After addition was complete, the solution was stirred for 8 min., then poured into a beaker containing 300 g of ice. To this solution was added 60 mL of 3 N hydrochloric acid. The solution became cloudy and milky white. The mixture was extracted with ether (5 X 100 mL). The combined ether extracts were washed with brine (30 mL), sodium bicarbonate (30 mL), and brine (30 mL), successively, and dried

over magnesium sulfate. The crude product was obtained by evaporation of the ether solution. Distillation of the residue at 131-133 °C / 760 mmHg (lit.^{69a}, 131-133 °C) afforded 24.25 g (94%) of **145** as a colorless liquid. ¹H NMR δ : 1.21 (d, J = 6.2 Hz, 3H, CH₃CH), 1.68 (d, J = 1.2 Hz, 3H, CH₃C=), 1.71 (d, J = 1.3 Hz, 3 H, CH₃C=), 1.75 (s, broad, 1H, OH), 4.56 (m, 1H, CH₃CH), 5.19 (m, 1H, CH=) (lit. ^{62a 69b}); IR (cm⁻¹, CCl₄): 3620 (sharp), 3400 (strong and broad), 2990, 2920, 1445, 1375, 1070, 1030 (lit. ^{62a 69b}).

Ethyl 3,4-dimethyl-4-pentenoate (153) A mixture of 2-methyl-2-buten-1-ol (**143**) (11.65 g, 140 mmol), triethyl orthoacetate (125.95 g, 778 mmol, 5.5 equiv.), and propionic acid (0.4725 g, 0.0064 mol, 0.06 equiv.) was heated to 144 °C for 4 h with continuous removal of ethanol by distillation. The excess of triethyl orthoacetate was then distilled under reduced pressure (56°C / 18 mmHg). The remainder trace of triethyl orthoacetate was removed by washing an ether solution of the crude product with 1.0 % sulfuric acid (3 X 50 mL), brine (50 mL), sodium bicarbonate (50 mL) and brine (50 mL), successively. The ether solution was dried over magnesium sulfate, and concentrated to yield the crude product. This was distilled at 80-82 °C / 26 mmHg (lit.⁷⁰ 50-70 °C / 15 mmHg) to obtain

18.21 g (85%) of **153** as a colorless oily liquid. ^1H NMR δ : 1.04 (d, $J = 6.8$ Hz, 3 H, CH_3CH), 1.24 (t, $J=7.1$ Hz, 3H, OCH_2CH_3), 1.72 (s, broad, 3H, $\text{CH}_3\text{C}=\text{}$), 2.28 (dd, $J_1 = 14.7$ Hz, $J_2 = 8.0$ Hz, 1H, $\text{C}_2\text{-H}_a$), 2.43 (dd, $J_1 = 14.7$ Hz, $J_2 = 7.0$ Hz, $\text{C}_2\text{-H}_b$), 2.67 (m, 1H, CH_3CH), 4.14 (q, $J = 7.1$ Hz, 2H, OCH_2), 4.70 (s), 4.72 (s), total 2H, $\text{CH}_2=\text{}$) (lit. ⁷⁰); IR (cm^{-1} , CCl_4): 3060, 2960 (s), 1730 (s), 1640, 1440, 1370, 1270, 1165, 1030, 892; MS (m/z): 156 (M^+), 141, 111, 110, 85, 83 (100%), 82, 81, 70, 69, 68, 67, 55, 41; Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}_2$: C, 69.19, H, 10.33; Found, C, 69.09, H, 10.03.

3,4-dimethyl-4-pentenoic acid (154) The ester was hydrolyzed as before.²⁷ Ethyl 3,4-dimethyl-4-pentenoate (**153**) (12.55 g, 80.0 mmol) was dissolved in a solution of 8.35 g (149.0 mmol) of potassium hydroxide in 10.5 mL of water and 31 mL of methanol. The solution was deaerated by three cycles of vacuum/argon exchange, and then heated in an oil bath (bath temperature: 103-105°C) under reflux with stirring for 2.0 h. The reaction solution was cooled to room temperature and diluted with 20 mL of water, then extracted with ether (3 X 20mL). The aqueous layer was separated and cooled in an ice-water bath and then acidified with precooled 3 N hydrochloric acid to pH 2. At the neutralization point, the solution became cloudy.

The solution was then extracted with ether (5 X 35 mL). The combined ether layers were washed with brine (20 mL) and dried over magnesium sulfate. Removal of solvent afforded 8.16 g (80 %) of **154** as a colorless liquid. ^1H NMR δ : 1.09 (d, $J = 6.8$ Hz, 3 H, CH_3CH), 1.70 (s, broad, 3H, $\text{CH}_3\text{C}=\text{}$), 2.23-2.34 (m, 2H, CH_2CO), 2.70 (m, 1H, CH_3CH), 4.72 (s, broad, 2H, $\text{CH}_2=\text{}$), 9.10 (s, broad, 1H, carboxyl) (lit.⁷¹); IR (cm^{-1} , CCl_4): 3550-3000 (strong and broad, carboxyl), 3060, 2990 (s), 1720 (s), 1650, 1440, 1410, 1290, 1240, 1190; MS (m/z): 128 (M^+), 113, 110, 87, 83, 82, 71, 69, 67, 59, 55, 41 (100%).

3-methyl-2-butenyl 3, 4-dimethyl-4-pentenoate (155)

Method A: Bram's solid-liquid PTC transesterification procedure³⁸ was attempted with some modifications. Ethyl 3,4-dimethyl-4-pentenoate (**153**: 1.56 g, 10 mmol) was mixed with 2.43 g (28.23 mmol, 2.8 equiv.) of 3-methyl 2-buten-1-ol (**144**), and 67.9 mg (0.2 mmol) of tetrabutyl ammonium hydrogen sulfate with stirring. To this mixture was added 30 mg (1.3 mmol) of sodium metal in small portions. The reaction mixture was then heated in an oil bath (110°C) for 21 h. with stirring. After the reaction was complete (TLC), the reaction mixture was cooled to room

temperature and diluted with 10 mL of water and 100 mL of ether. The ether layer was washed with brine (8 mL), 0.1N hydrochloric acid (8 mL), and brine (8mL), successively, then dried over magnesium sulfate, and concentrated to yield 3.54 g of yellow liquid. This liquid was purified by flash chromatography (hexane and ethyl acetate, 20 :1) to give 1.51 g (77%) of colorless liquid **155**.

Method B: The esterification was carried out as preparation of **141**.³⁹ 3,4-dimethyl-4-pentenoic acid **154** (7.99 g, 62.4 mmol), 5.86 g (67.98 mmol) of 3-methyl-2-buten-1-ol (**144**), and 0.561 g of *p*-toluene sulfonic acid were dissolved in 63 mL of pyridine, and the solution was cooled in an ice bath. To this mixture was added 15.40 g (74.64 mmol, 1.20 equiv.) of DCC. The ice bath was removed and the mixture was stirred at room temperature for 24 h. The mixture was cooled in an ice bath and 10 mL of acetic acid was added and the mixture was stirred overnight. The reaction solution was then diluted with 250 mL of pentane and cooled thoroughly in an ice bath. The precipitate which formed was filtered through a glass funnel and the filtrate cake was washed with cold pentane (3 X 30mL). The combined pentane filtrates were washed with sodium bicarbonate (40 mL) and brine (30 mL) and dried over

magnesium sulfate. Removal of the solvent yielded a colorless liquid which was separated by flash column chromatography using hexane and ethyl acetate (20:1) as eluent giving 11.01 g (90%) of a colorless liquid **155**. ^1H NMR δ : 1.04 (d, $J = 6.8$ Hz, 3H, CH_3CH), 1.70-1.76 (m, 9H, 3 X $\text{CH}_3\text{C}=\text{}$), 2.01-2.50 (m, 2H, CH_2CO), 2.32 (m, 1H, CH_3CH), 4.54 (d, $J = 7.2$ Hz, OCH_2), 4.72 (s, broad, 2H, $\text{CH}_2\text{C}=\text{}$), 5.33 (m, 1H, $\text{CH}_2\text{CH}=\text{}$); IR (cm^{-1} , CCl_4): 3060 (w), 2980 (s), 2975, 1734 (s), 1440, 1370, 1270, 1155; MS (m/z) 196 (M^+), 181 (M^+-Me), 167, 153, 141, 136, 128, 109, 86, 83, 69 (100), 55, 41; Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43, H, 10.27; Found: C, 73.72, H, 10.73. TLC and spectral data proved that the samples of ester **155** prepared by method A and B were identical.

3-Methyl-3-penten-2-ol (157) Salomon's⁷² procedure for preparation of a vinyl Grignard reagent was employed. A mixture of 17.0 g (0.70 g-atom) of magnesium turnings and a crystal of iodine in a 1.0 L three necked round bottomed flask purged with argon, was added 50 mL of a solution of 87.75 g of 2-bromo-2-butene (cis / trans mixture) in 400 mL of dry THF from a pressure-equalized dropping funnel. The reaction was initiated by gentle heating and after the reaction was initiated, the remaining solution

was added at such a rate to keep the solution refluxing gently. After the addition was complete, the solution was stirred at room temperature for 14h under argon. The solution was cooled in an ice bath, and a solution of acetaldehyde in 50 mL of THF was added dropwise at 0°C over 24 min. After addition was complete, the mixture was stirred at room temperature for 2 h. The mixture was poured with stirring into a beaker containing 1.0 kg ice, 200 mL concentrated hydrochloric acid, and 400 mL water. Stirring was continued until the ice melted. The solution was extracted with ether (6 X 200 mL). The combined ether solutions were washed with sodium bicarbonate (100 mL), brine (100 mL), and dried over magnesium sulfate. Evaporation yielded 53.94 g of light yellow liquid. The crude product was distilled under reduced pressure (87 - 88 °C / 95 mmHg, lit.⁷³ Z isomer b.p. 87-88 °C / 90 mmHg) to obtain 41.87 (76%) of an alcohol. The sample contains *E* and *Z* isomers in a ratio of 68 : 32 (NMR).

***E*-isomer:** ¹H NMR δ: 5.46 (m, 1 H, CH₃CH=), 4.16 (q, J = 6.6 Hz, 1H, CH₃CH₂OH), 1.58 (m, 6H, 2 X CH₃C=), 1.54 (s, D₂O labile, 1H, OH), 1.20 (d, J = 6.6 Hz, 3H, CH₃CH₂OH).

***Z*-isomer:** ¹H NMR (lit.⁷³) δ: 5.23 (qq, J₁ = 6.4 Hz, J₂ = 0.6 Hz, CH₃CH=), 4.78 (dq, J₁ = 0.6 Hz, J₂ = 6.4 Hz, 1H, CH₃CH₂OH), 1.66 (m, 6H, 2 X CH₃C=), 1.56 (s, 1H, OH), 1.20 (m, 3H,

CH_3CHOH). The NMR was assigned based on the literature.⁷³⁻⁷⁴ IR (cm^{-1} , CCl_4): 3618, 3363, 2976, 2922, 2863, 1456, 1377, 1315, 1252, 1070, 1032, 940, 883, 829; MS (m/z): 100 (M^+), 85 (100%), 82, 83, 72, 67, 65, 57, 53, 43. Anal. (mixture of isomers) Calcd for $\text{C}_6\text{H}_{12}\text{O}$: C, 71.94, H, 12.08. Found: C, 71.80, H, 11.98.

1,2-Dimethyl-2-butenyl 3,3-dimethyl-4-pentenoate

(158/159) The ester was prepared by Method B used for preparation of **155**. A mixture of 3,3-dimethyl-4-pentenoic acid (**142**) (9.06 g, 70.78 mmol), 7.74 g (77.41 mmol, 1.09 equiv.) of 2-methyl-2-buten-1-ol (**157**), and 0.64 g of *p*-toluene sulfonic acid were dissolved in 72 mL of pyridine. The solution was cooled in an ice bath. To this mixture was added 17.4 g (84.33 mmol, 1.20 equiv.) of DCC. The ice bath was removed and the mixture was stirred at room temperature for 24 h. The mixture was then cooled in an ice bath and 10 mL of acetic acid was added and the mixture was stirred overnight. The reaction mixture was diluted with 300 mL of pentane and cooled thoroughly in an ice bath. The precipitate formed were filtered and washed with cold pentane (3 X 30 mL). The pentane solution was washed with sodium bicarbonate (50 mL) and brine (50 mL) and dried over magnesium sulfate. Removal

of the solvent yielded a colorless liquid. The sample thus obtained was separated by flash column chromatography using hexane and ethyl acetate (20:1) as eluent. Fractions with TLC $R_f=0.81$ (hexane and ethyl acetate, 20 : 1) were collected, the solvent was removed and 11.67g (80%) of colorless liquid **158/159** was obtained. 60 mg of sample of the isomeric mixture was chromatographed using MPLC (Lobar size B; eluted with hexane / ethyl, 120 : 1) to give 34.9 mg of E-isomer and 19.6 mg of Z-isomer.

E-isomer: (GC/MS t_R 10.6 min., 65%) 1H NMR δ : 1.10 (s, 6H, *gem*-dimethyl), 1.25 (d, $J = 6.5$ Hz, 3H, CH_3CH), 1.59 (m, 6H, 2 X $CH_3C=$), 2.25 (s, 2H, CH_2CO_2), 4.90 (dd, $J_1 = 1.2$ Hz, $J_2 = 10.6$ Hz, 1H, $CH_2=CH$), 4.94 (dd, $J_1 = 17.5$ Hz, $J_2 = 1.2$ Hz, 1H, $CH_2=CH$), 5.24 (q, $J = 6.5$ Hz, 1H, $CH_3CH=$), 5.50 (m, 1H, $CH_3CH=$), 5.87 (dd, $J_1 = 10.6$ Hz, $J_2 = 17.5$ Hz, 1H, $CH_2=CH$); IR (cm^{-1} , CCl_4): 3085, 2967, 2932, 2869, 1728, 1672, 1640, 1449, 1416, 1382, 1365, 1340, 1321, 1238, 1207, 1125, 1082, 1046, 998, 955, 916. MS (m/z): 210 (M^+), 168, 153, 128, 113, 111, 100, 85, 84, 83 (100%), 82, 69, 67, 55, 41; Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24, H, 10.55; Found: C, 74.16, H, 10.49.

Z-isomer: (GC/MS t_R 11.85 min., 35%) 1H NMR δ 1.10 (s, 6H, *gem*-dimethyl), 1.24 (d, $J = 6.6$ Hz, 3H, CH_3CH), 1.65 (m, 6H, 2 X $CH_3C=$), 2.25 (s, 2H, CH_2CO_2), 4.93 (dd, $J_1 =$

10.7 Hz, $J_2 = 1.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 4.95 (dd, $J_1 = 17.4$ Hz, $J_2 = 1.2$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.50 (q, $J = 6.5$ Hz, 1H, CH_3CHO -), 5.75 (dq, $J_1 = 6.6$ Hz, $J_2 = 0.6$ Hz, 1H, $\text{CH}_3\text{CH}=\text{CH}$), 5.88 (dd, $J_1 = 10.7$ Hz, $J_2 = 17.4$ Hz, 1H, $\text{CH}_2=\text{CH}$); IR (cm^{-1} , CCl_4): 3085, 2967, 2932, 2870, 1728, 1673, 1640, 1449, 1415, 1382, 1365, 1340, 1321, 1238, 1207, 1125, 1081, 1047, 999, 955, 909; MS (m/z): 210 (M^+), 168, 150, 128, 113, 111, 100, 99, 85, 84, 83 (100%), 82, 69, 67, 55, 53, 42, 41.

3,3-Dimethyl-2-(1,2-dimethyl-2-butenyl)-4-pentenoic acid (160)

The Ireland-Claisen rearrangement was performed as before. A solution of 3.45 g (24.42 mmol, 1.10 equiv.) of cyclohexyl-isopropylamine in 25 mL of THF was cooled to -15°C in a carefully adjusted acetone-dry ice bath. Butyl lithium (2.50 M, 9.1 mL, 22.69 mmol, 1.10 equiv.) was added by syringe to this solution dropwise during 15 min. with stirring. The stirring was continued for 15 min. and the reaction mixture was then cooled to -78°C during 40 min. Then, 1, 2-dimethyl-2-butenyl 3,3-dimethyl-4-pentenoate (**158/159**) (4.34 g, 20.66 mmol) in 10 mL of THF was added with stirring during 8 min. After the addition was complete, the mixture was stirred at -78°C for 1h. 5.0 mL of HMPA (5.15 g, 28.77 mmol, 1.40 equiv.) was added at -78°C , followed by a solution of tert-

butylchlorodimethylsilane (3.30 g, 21.89 mmol, 1.05 equiv.) in 6 mL of THF, and stirring was continued at -78 °C for 40 min. The dry ice-acetone bath was removed and the reaction mixture was kept at room temperature for 5 min. and then, immersed into an ice-water bath for 15 min. The ice-water bath was replaced with an oil bath and the temperature was raised slowly to 70 °C during 45 min. This temperature was kept for 30 min., then raised to 78-79°C and stabilized. The solution was refluxed gently for 15 h. then was cooled in an ice-water bath. To this cold solution, a solution of 3.00 g of potassium carbonate in 30 mL of water and 60 mL of methanol was added. The mixture was stirred at room temperature for 3 h. After the reaction was complete, the reaction mixture was transferred to a separatory funnel and diluted with 150 mL of ether. The two layers were separated. The organic layer was extracted with 5% aqueous potassium hydroxide (5 X 50 mL). The combined aqueous layers were cooled in an ice-water bath and neutralized with cold 3 N hydrochloric acid to pH 2. The solution became milky white. Then the solution was extracted with ether (6 X 50 mL). The combined ether solutions were washed with brine (20 mL) and dried over magnesium sulfate. Concentration of the solution yielded 4.06 g of acid **160** as a colorless oily liquid, which

solidified after stand at room temperature for a while but melt when warmed slightly. IR (cm^{-1} , CCl_4): 3622, 3460, 2971, 1702, 1458, 1415, 1382, 1298, 1278, 1199, 1175, 1047, 988.

Methyl 3,3-dimethyl-2-(1,2-dimethyl-2-butenyl)--4-pentenoate (161/162) The crude acid **160** obtained above (4.06 g) and iodomethane (4.10 g, 28.88 mmol, 1.5 equiv.) were dissolved in 65 mL of dry DMF. To this solution was added carefully powdered dry cesium fluoride (4.40 g, 28.95 mmol, 1.5 equiv.) portionwise under drying conditions. The mixture was stirred at room temperature for 22 h. The reaction solution was cooled and diluted with cold saturated aqueous sodium bicarbonate (20 mL). A lot of bubbles evolved. The mixture was then extracted with ether (4 X 100 mL). The combined ether layers were washed with brine (20 mL) and dried (magnesium sulfate) and concentrated in vacuum to yield 5.90 g of a colorless liquid. The crude product thus obtained was purified by flash chromatography (eluent: hexane : ethyl acetate, 20:1) to obtain 3.77 g (87 %) of **161/162** as a colorless liquid. There are two diastereomers, *threo* and *erythro*, present in the sample in a ratio of 35 : 65 (HPLC and NMR). The two isomers were isolated by HPLC with hexane: ethyl acetate

(200:1) as eluent. The structures of the two isomers were tentatively assigned. Only E isomers were detected.

Erythro (t_R 34 sec., 65%): 1H NMR δ : 0.96 (d, $J = 6.4$ Hz, 3H, $CHCH_3$), 1.00 (s, 6H, *gem*-dimethyl), 1.46 (m, 6H, 2 X $CH_3C=$), 2.41 (d, $J=11.0$ Hz, 1H, $CHCO_2$), 2.43 (dq, $J_1 = 6.9$ Hz, $J_2 = 11.0$ Hz, 1H, $CHCH_3$), 3.47 (s, 3H, OCH_3), 4.92 (dd, $J_1 = 10.8$ Hz, $J_2 = 1.1$ Hz, 1H, $CH_2=CH$), 5.01 (dd, $J_1 = 1.1$ Hz, $J_2 = 17.5$ Hz, 1H, $CH_2=CH$), 5.19 (m, 1H, $CH_3CH=$), 5.98 (dd, $J_1 = 10.8$ Hz, $J_2 = 17.5$ Hz, 1H, $CH_2=CH$); IR (cm^{-1} , CCl_4): 3084, 2969, 2934, 1736, 1637, 1458, 1432, 1381, 1267, 912. MS (m/z): 224 (M^+), 209, 195, 192, 182, 164, 155, 149, 141, 139, 135, 123, 110, 95, 83 (100%), 69, 55, 41;

threo (t_R 27 sec., 35%): 0.85 (d, $J = 6.8$ Hz, 3H, $CHCH_3$), 1.13 (s, 6H, *gem*-dimethyl), 1.43 (m, 6H, 2 X $CH_3C=$), 2.38 (d, $J = 9.0$ Hz, 1H, $CHCO_2$), 2.52 (m, 1H, $CHCH_3$), 3.61 (s, 3H, OCH_3), 4.88 (dd, $J_1 = 2.3$ Hz, $J_2 = 17.8$ Hz, 1H, $CH_2=CH$), 4.94 (dd, $J_1 = 2.3$ Hz, $J_2 = 10.5$ Hz, 1H, $CH_2=CH$), 5.26 (m, 1H, $CH_3CH=$), 5.98 (dd, $J_1 = 10.5$ Hz, $J_2 = 17.8$ Hz, 1H, $CH_2=CH$). IR (cm^{-1} , CCl_4): 3076, 2976, 2931, 1740, 1635, 1432, 1373, 1238, 1048, 913; MS (m/z): 224 (M^+), 209, 195, 192, 182, 164, 155, 149, 141, 139, 135, 125, 123, 109, 95, 83 (100%), 81, 69, 67, 55, 41; Anal. Calcd for $C_{14}H_{24}O_2$ (mixture of two isomers): C, 74.95, H, 10.78; Found: C, 74.94, H, 10.74.

Ethyl 2-(1,1-dimethyl-2-propenyl)-3-methyl-3-hydroxy-4-oxo-pentanoate (167) A solution of 0.76 mL (549 mg, 5.42 mmol, 1.08 equiv.) of diisopropylamine in 5 mL of THF was cooled to -15 °C in an acetone-dry ice bath. Butyl lithium (2.20 mL, 2.5 M, 5.5 mmol, 1.10 equiv.) was added to this solution dropwise during 5 min. with stirring. The stirring was continued for 15 min., the mixture was cooled to -78°C, and ethyl 3,3-dimethyl-4-pentenoate (**146**) (780 mg, 5.0 mmol) in 1.5 mL of THF was then added with stirring over a period of 5 min. This mixture was stirred at -78 °C for an additional hour. A solution of 2,3-butanedione (430 mg, 5.0 mmol, 1.0 equiv.) in 5.0 mL of THF was cooled to -78 °C. To this solution was added the above enolate solution dropwise through a stainless tube with stirring during 5 min., and the resulting mixture was stirred at this temperature for an additional 4 h. The reaction was quenched by adding saturated aqueous ammonium chloride solution (10 mL) by syringe. The mixture was allowed to warm to room temperature and was extracted with ether (4 X 20 mL). The combined ether layers were washed with 5 mL portions of brine, 0.1 N hydrochloric acid, brine and sodium bicarbonate, and brine, successively, then dried over magnesium sulfate. Evaporation of the solvent gave a yellow liquid. The crude product thus obtained was

purified by MPLC (eluent: hexane : ethyl acetate, 3 : 1), giving 1.01 g (84%) of colorless liquid **167**. The preparation was repeated two more times with a 10 fold scale up and gave quite reproducible results. There are two isomers, *threo* and *terthro*, present in the sample in a ratio of ca. 3:1(NMR); We are unable to assign peaks to individual isomers. ^1H NMR δ : 6.01 (dd, $J_1 = 10.7$ Hz, $J_2 = 17.4$ Hz), 5.82 (dd, $J_1 = 1.7$ Hz, $J_2 = 17.4$ Hz), 4.85-5.05 (m), 4.20 (q, $J = 7.2$ Hz), 4.15 (q, $J = 7.2$ Hz), 3.06 (s), 2.97 (s), 2.23(s), 2.20 (s), 1.60 (s, D_2O labile, OH), 1.29-1.11 (many singlets); IR (CCl_4 , cm^{-1}): 3500, 2995, 1715, 1740, 1640, 1450, 1375, 1190, 915; MS (m/z): 243 (M^{++1}), 225 ($\text{M}^+ - \text{H}_2\text{O}$), 199, 181, 157, 131, 103, 85, 69 (100%), 43; Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_4$, C, 64.42, H, 9.16; Found: C, 64.22, H, 9.31.

2-(1,1-Dimethyl-2-propenyl)-3-methyl-3,4-epoxypentanoate (170) A solution of 134 mg (1.33 mmol) of diisopropylamine in 2 mL of dry THF was cooled in an ice-acetone bath (-15 °C) and 0.55 mL of 2.5 M butyl lithium (1.37 mmol) in hexane was added slowly during 10 min. The resulting mixture was cooled in a dry ice acetone bath for 30 min., then methyl 3,3-dimethyl-4-pentenoate (**148**: 142 mg, 1.0 mmol) in 1.0 mL of THF was added dropwise during 15 min. This solution was stirred at -78°C for 30

min. Then, 3-chloro-2-butanone (213 mg, 2.0 mmol) in 1.0 mL of THF was added rapidly (1 min.) into this solution. The mixture was stirred for 5 min., then, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of 5 mL of water. The mixture was then extracted with ether (3 X 5 mL), the combined ether extracts were washed with 5 mL 3 portions of brine, 1 N hydrochloric acid, brine, sodium bicarbonate, brine, successively, and dried over magnesium sulfate. The solvent was removed by evaporation giving 0.21 g of a yellow liquid. The crude product was separated by MPLC (eluent, hexane : ethyl acetate, 2 : 1) to yield 82.3 mg (38.8%) of **170**. There were two isomers present in the sample. We are unable to separate and assign the peaks to the individual isomers. The following NMR was taken from the isomeric mixture. ^1H NMR δ : 1.14 (s), 1.16 (s), 1.26 (d, $J = 5.5$ Hz), 1.58 (s), 2.84 (q, $J = 5.5$ Hz), 3.72 (s, OCH_3), 4.93 (dd, $J_1 = 10.6$ Hz, $J_2 = 1.0$ Hz), 5.01 (dd, $J_1 = 17.5$ Hz, $J_2 = 1.0$ Hz), 5.90 (dd, $J_1 = 17.5$ Hz, $J_2 = 10.6$ Hz, vinyl); IR (cm^{-1} , CCl_4): 3080, 2960, 1740, 1640, 1460, 1435, 1240, 1155, 905.

4-Oxo-pentanal (171) The ozonolysis method was based on the literature.⁷⁵ A solution of 3.00 g (19.48 mmol) of

geraniol in 200 mL of dry methylene chloride was cooled to $-78\text{ }^{\circ}\text{C}$ while a stream of ozone in oxygen was passed through the solution until the blue color persistent and the effluent test solution of potassium iodide in 5 % acetic acid changed color from yellow to orange. Argon was passed through the solution for at least 5 min. to drive out the remaining ozone. To this solution was added dropwise 29.3 mL (24.80 g, 0.4 mol, 20 equiv.) of dimethyl sulfide. After addition was complete, the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min. The ice bath was removed and the stirring was continued at room temperature for 11 h. The reaction mixture was diluted with 100 mL of methylene chloride, and the solution was washed with brine (3 X 20 mL), dried over magnesium sulfate, and evaporated to obtain 3.79 g of crude product. This was separated by flash chromatography using hexane and ethyl acetate (1:1) as eluent to give 1.91 g (95%) of **171** as a colorless oily liquid. ^1H NMR δ : 2.16 (s, 3H, CH_3CO), 2.70 (s, 4H, CH_2CH_2), 9.47 (s, 1H, CHO); (C_6D_6 , ppm)⁷⁶ : 1.68 (s, 4H, CH_2CH_2), 2.09 (s, 3H, CH_3CO), 9.28 (s, 1H, CHO); IR (cm^{-1} , CCl_4): 2964 (s), 2938, 1715 (s), 1549, 1458, 1373, 1187, 1160, 1009; MS (m/z): 101 (M^++1), 100 (M^+), 85, 72, 58, 57, 43 (100%), 42.

Methyl 2-(1, 1-dimethyl-2-oxoethyl)-3-methyl-4-oxopentanoate (139) Method A: (from 140) The ozonolysis procedure of Slomp and Johnson⁴⁴ was employed. A solution of methyl 2-(1, 2-dimethyl-2-propenyl)-3, 3-dimethyl-4-pentenoate (**140**: 23.4 mg, 0.11 mmol) in 5 mL methylene chloride and 17.6 mg (0.22 mmol, 2 equiv.) of pyridine was cooled to -78°C. Ozone in oxygen stream, which was dried by passing through a tube cooled to -78°C, was bubbled through the solution with stirring. The color of the solution changed sequentially into yellowish after ozone passed through the solution for a while, then colorless, then gray and finally blue. As soon as the blue color appeared, the ozone stream was replaced by nitrogen until the blue color disappeared. Zinc dust (114.4 mg, 1.74 mmol, 15.9 equiv.) was added at -78 °C, followed by 0.23 mL (0.241g, 4.01 mmol, 18.2 equiv.) of acetic acid dropwise with stirring. As soon as the addition was complete, the dry ice acetone bath was replaced by a water bath at 20°C and the suspension was stirred for 2.5 h. The mixture was filtered. The zinc powder was washed *thoroughly* with ethyl acetate. The combined filtrates were washed with cold water in the presence of crushed ice (2 X 5 mL), 5% sodium hydroxide until pH 8, then washed with saturated sodium chloride solution. Each wash was back washed

with ethyl acetate (10 mL). The combined ethyl acetate solution were dried over magnesium sulfate and concentrated to obtain a yellowish oily liquid. The liquid was immediately introduced into a short column packed with 20 g of silica gel and eluted with hexane and ethyl acetate (1.5 : 1) and collect the component with Rf 0.56 to yield a colorless liquid 23.1 mg (98%) of **139** as a colorless liquid. There were two isomers present in the sample. The two isomers, *threo* and *erythro*, were separated by preparative HPLC with hexane/ethyl acetate (9/1) as eluent (MPLC could not separate the two isomers completely with hexane and ethyl acetate (3 / 1) as eluent). The ^1H NMR were tentatively assigned as follows:

Erythro (t_{R} 78 sec., 67.5%): ^1H NMR δ : 9.49 (s, 1H, CHO), 3.65 (s, 3H, OCH_3), 3.10 (d, $J = 10.1$ Hz, 1H, CHCO_2CH_3), 3.03 (dq, $J_1 = 10.1$ Hz, $J_2 = 6.9$ Hz, 1H, CHCH_3), 2.15 (s, 3H, CH_3CO), 1.15 (s, 3H), 1.01 (s, 3H), (*gem*-dimethyl), 1.01 (d, $J = 6.9$ Hz, 3H, CHCH_3); IR (cm^{-1} , CCl_4): 2972, 2951, 1727 (vs), 1462, 1436, 1353, 1273, 1211, 1164, 1022, 1002, 895; MS (m/z): 214 (M^+), 183, 171, 155, 154, 144, 143, 142, 139, 116, 115, 114, 111, 101, 83, 71, 72, 70, 69, 59, 55, 43 (100%, CH_3CO). Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4$: C, 61.66, H, 8.46; Found C, 61.45, H, 8.35.

Threo (t_{R} 78 sec., 32.5%). ^1H NMR δ 9.41 (s, 1H, CHO),

3.68 (s, 3H, OCH₃), 3.21 (d, J = 8.9 Hz, 1H, CH-CO₂CH₃), 2.91 (dq, J₁ = 8.9 Hz, J₂ = 7.0 Hz, 1H, CHCH₃), 2.17 (s, 3H, CH₃CO), 1.13 (s, 3H), 1.01 (s, 3H) (*gem*-dimethyl), 1.10 (d, J = 7.0 Hz, 3H, CHCH₃); IR (cm⁻¹, CCl₄): 2976, 2951, 1721 (vs), 1463, 1435, 1354, 1278, 1209, 1154, 908.

Method B: Nakamura's⁷⁵ ozonolysis procedure was employed. A solution of methyl 2-(1,2-dimethyl-2-propenyl)-3,3-dimethyl-4-pentenoate (**140**: 113.0 mg, 0.538 mmol) in 20 mL of methylene chloride was cooled to -78°C while a stream of ozone in oxygen was passed through the solution until the blue color persistent and the effluent test solution of potassium iodide in 5 % acetic acid changed color from yellow to orange (ca. 8 min.). Argon was passed through the solution for at least 5 min. to drive out the remaining ozone. To this solution, 0.8 mL (668.5 mg, 0.76 mmol, 20 equiv.) of dimethyl sulfide was added dropwise by syringe. The solution was then stirred at -78°C for 30 min. The ice bath was removed and the stirring was continued at room temperature for three days. The reaction mixture was diluted with 70 mL of ether, and the solution was washed with brine (3 X 5 mL), dried over magnesium sulfate, and evaporated to obtain a crude product. This was separated on a short column

using hexane and ethyl acetate (2.5 : 1) as eluent to produce 96.7 mg (84%) of **139** as a colorless oily liquid. The sample showed the identical TLC R_f and NMR and IR with that of the sample obtained by Method A.

139 from 161/162: method A.⁴⁴ A solution of methyl 2-(1,2-dimethyl-2-butenyl)-3,3-dimethyl-4-pentenoate (**161/162**) (650 mg, 3.095 mmol) in 65 mL dry methylene chloride (distilled over calcium hydride immediately before use) and 490 mg of pyridine (6.20 mmol, 2 equiv.) was cooled to -78°C. Ozone in oxygen stream was passed through the solution with stirring. The ozone stream was dried by passing through a tube which was cooled to -78 °C. The color of the solution changed sequentially into yellowish after ozone passed through the solution for a while, then colorless, then gray and finally blue. As soon as the blue color appeared, the ozone stream was replaced by nitrogen until the blue color disappeared (ca. 5 min.). 3.18 g (48.65 mmol, 16.0 equiv.) of zinc dust was added to the reaction solution at -78 °C, followed by dropwise addition of 6.4 mL (7.00g, 0.117 mol, 37.7 equiv.) of acetic acid with stirring. As soon as the addition was finished, the dry ice acetone bath was replaced by a water bath at 20°C and the suspension was stirred for 2.5 h. The mixture was

filtered. The zinc powder was washed many times with ethyl acetate. The combined filtrate was washed with cold water in the presence of crushed ice (2 X 5 mL), 5% sodium hydroxide until pH 8, then washed with saturated sodium chloride solution (2 X 10 mL). Each wash was back washed with ethyl acetate (10 mL) and combined. The solution was dried over magnesium sulfate and the solvent was removed to obtain a yellowish oily liquid. The liquid was *immediately* separated by a short column packed with 20 g of silica gel and eluted with hexane and ethyl acetate (1.5 : 1) and collect the component with Rf 0.56 to yield a colorless liquid 647.0 mg (98%) of colorless liquid **139**. This sample shows the identical TLC Rf, IR and ¹H NMR spectra as the sample obtained via **140**.

Method B: The method was based on the literature.⁷⁷ A solution of 2.11 g (9.41 mmol) of **161/162** in 150 mL of ethanol was cooled in dry ice-acetone bath while ozone in oxygen stream was passed through with stirring until the color of the solution turned into gray blue. Nitrogen was passed through the solution for ca. 5 min. to drive the remaining ozone out. The solution was allowed to stand at room temperature for 5 min., and then put in an ice water bath. To the solution, 24.97 g (382 mmol, 40 equiv.) of zinc dust was added at 0°C with stirring, followed by a solution

of acetic acid and water (1 : 1, V / V) dropwise. After completion of the addition, the mixture was stirred at 0°C for 3 h. The mixture was filtered and the filtrate cake was washed thoroughly with ether. The combined filtrate was diluted with ether to the total volume of 750 mL. The ether solution was washed with sodium bicarbonate until pH 8 (no more bubbles evolved), then washed with brine (75 mL). After drying over magnesium sulfate and evaporation of the solvent, a yellow liquid was obtained. The crude product was purified by a short column with hexane and ethyl acetate (2 : 1) as eluent to obtain 1.89 g (94%) of a colorless liquid. TLC R_f, NMR and IR proved the identity of the sample obtained above with the sample obtained via method A.

Methyl 5-hydroxyl-3-oxo-2, 6, 6-trimethyl-cyclohexane-carboxylate (138) The aldol condensation conditions of Hajos and Parrish⁴⁵ were employed. A solution of 18 mg (0.16 mmol) of (L)-proline in 5 mL of freshly distilled dry DMF (distilled from calcium hydride immediately before use) was deaerated by three cycles of vacuum / argon exchange and stirred at room temperature for 1 hr. Then, 1.09 g (5.10 mmol) of methyl 2-(1, 2-dimethyl-2-oxoethyl)-3-methyl-4-oxo-pentanoate **139** in 1.0 mL of DMF

was added. The mixture was stirred at 36°C for 7 days. The reaction solution was yellow at the end of the reaction. The reaction solution was diluted with 200 mL of ether. The ether solution was washed with brine (2 X 20 mL) and dried over magnesium sulfate. The solvent was removed and the crude product was separated by flash chromatography using hexane and ethyl acetate (1.5 : 1) as eluent to obtain 0.94 g (86%) of **138** as a viscous colorless liquid, a mixture of several diastereoisomers. $^1\text{H NMR}$ δ : 1.20-0.95 (many singlet and doublet, 1.61 (broad, s, D_2O labile), 2.21 (s), 2.22(s), 2.95-2.25 (m), 3.74 (s), 3.76 (s), 3.79 (s), 4.07 (m); IR (cm^{-1} , CCl_4): 3616, 3436, 2984, 2950, 2885, 1739, 1460, 1435, 1374, 1240, 1149, 908, 883; MS (m/z): 214 (M^+), 196 ($\text{M}^+ - \text{H}_2\text{O}$), 183 ($\text{M}^+ - \text{OCH}_3$), 182 ($\text{M}^+ - \text{HOCH}_3$), 155 ($\text{M}^+ - \text{CO}_2\text{CH}_3$), 137 [$(\text{M}^+ - \text{H}_2\text{O}) - \text{CO}_2\text{CH}_3$], 115 (100%, $\text{C}_6\text{H}_{11}\text{O}_2$). Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4$: C, 61.66, H, 8.47; Found C, 61.45, H, 8.35.

Methyl 1, 4-dioxa-9-hydroxy-6, 8, 8-trimethyl-spiro [4, 5] decane-7-carboxylate (172) Method A the typical protocol was attempted based the known procedure.⁴⁸ A solution of methyl 5-hydroxyl-3-oxo-2, 6, 6-trimethyl-cyclohexanecarboxylate (**138**) 192.6 mg, 0.90 mmol), 540.9 mg (8.70 mmol, 9.6 equiv.) of ethylene glycol and 2.0 mg (

0.0105 mmol, 0.012 equiv.) of toluene sulfonic acid in 6 mL of benzene was heated with stirring in an oil bath with continuous removal of benzene by distillation and dry benzene was added through dropping funnel continuously to keep the volume of the benzene approximately the same. The operation was continued until the distillate no longer cloudy. (ca. 2h). The reaction flask was cooled to room temperature in a water bath. The solution was diluted with 100 mL of ether and the ether solution was washed with saturated sodium bicarbonate solution (2 X 5 mL), brine (5 mL), and dried over magnesium sulfate. Removal of the solvent yielded 208 mg of colorless liquid. The crude product was separated by flash chromatography with hexane and ethyl acetate (1:1) as eluent. Collection of the sample yielded 152.3 mg (65%) of colorless oily liquid **172**.

Method B The protection of ketone carbonyl group was done by Johnson's procedure.⁴⁹ To 1.0 mL of 2-methoxy-1,3-dioxolane was added 460 mg (2.15 mmol) of methyl 5-hydroxyl-3-oxo-2, 6, 6-trimethyl-cyclohexanecarboxylate (**138**) and the mixture was cooled to 0 °C in an ice-water bath. To this mixture, 6 µL of TfOH was added at 0 °C with stirring over 10 min. After addition was complete, the ice-water bath was removed and the mixture was stirred at room temperature for 5h. To this solution was added a

mixture of ether (50 mL) and saturated sodium bicarbonate (50 mL) with stirring. The two layers which formed were separated and the aqueous layer was extracted with ether (3 X 15 mL). The combined ether layers were washed with brine (5 mL) and dried (MgSO_4) and evaporated to yield a reddish crude product which was purified by a short column flash chromatography with hexane and ethyl acetate (1:1) as eluent to obtain 461 mg (89 %) of product **172** as a mixture of stereoisomers. ^1H NMR δ : 4.07 (m), 3.79 (s), 3.76 (s), 3.74 (s), 2.95-2.25 (m), 2.21 (m), 1.61 (br, D_2O labile), 1.20-0.95 (m); IR (cm^{-1} , CCl_4): 3616, 3523, 2981, 2950, 2883, 1736, 1459, 1446, 1434, 1380, 1321, 1193, 1156, 1095, 1035, 946, 909; MS (m/z): 258 (M^+), 257, 229, 213, 197, 181, 157, 153, 125, 111, 99, 87 (100%), 59, 43; Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}_5$: C, 60.44, H, 8.59; Found: C, 60.48, H, 8.51.

Methyl 1, 4-dioxa-9-oxo-6, 8, 8-trimethyl-spiro [4, 5] decane-7-carboxylate (137) Oxidation of hydroxy ketal was performed using Sone's^{48b} procedure. A mixture of methyl 1, 4-dioxa-9-hydroxy-6, 8, 8-trimethyl-spiro [4, 5] decane-7-carboxylate (**172**: 790 mg, 3.06 mmol) and 4.0 g of celite in 50 mL of acetone was cooled to $-20\text{ }^\circ\text{C}$ in a dry ice-acetone bath. Jones reagent (2.5 M, 1.33 mL, 0.68 mmol,

1.10 equiv.) was added dropwise over a period of 5 min. The solution was stirred at -20°C for 1.5 h. Then, 1.0 mL isopropyl alcohol was added at -20°C and stirred until the red solution turned into green (ca. 40 min.). The solution was then diluted with 10 mL of cold saturated sodium bicarbonate solution. The green precipitate formed was filtered and the filter-cake was washed with ethyl acetate (50 mL). The combined ethyl acetate solutions were dried over magnesium sulfate and evaporated to yield a light yellow liquid. This was purified on a short column using hexane and ethyl acetate (2:1) as eluent to yield 714 mg (91%) of colorless liquid **137** as a diastereomeric mixture. A portion was purified by MPLC (hexane and ethyl acetate, 3 : 1) and was separated further by HPLC, using hexane and ethyl acetate (9 : 1) as eluent. Two isomers were obtained. The structures of two isomers were tentatively assigned as follows:

trans-137 (t_{R} 69 sec., 74%): ^1H NMR δ : 0.96 (s), 0.97 (s), 1.01 (d, $J = 6.9$ Hz), (totally 9H, *gem*-dimethyl and CH_3CH), 2.19 (s, 2H, CH_2), 3.04 (m, 1H, CH_3CH), 3.15 (d, $J = 8.5$ Hz, 1H, CHCO_2CH_3), 3.62 (s, 3H, OCH_3), 3.73-3.87 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$); IR (cm^{-1} , CCl_4): 2970, 2953, 2881, 1736, 1718, 1467, 1434, 1351, 1284, 1224, 1194, 1153, 1105, 1014, 950; MS (m/z): 256, 227, 153, 144, 127, 114, 99, 87,

73 (100%), 43.

cis-137 (t_R 74 sec., 26%): ^1H NMR δ : 0.98 (s), 1.04 (s), (6H, *gem*-dimethyl), 1.21 (d, $J = 7.1$ Hz, 3H, CH_3CH), 2.16 (s, 2H, CH_2), 2.75 (d, $J = 7.9$ Hz, 1H, CHCO_2CH_3), 3.13 (m, 1H, CH_3CH), 3.59 (s, 3H, OCH_3), 3.83-3.92 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$); IR (cm^{-1} , CCl_4): 2973, 2949, 2882, 1722, 1434, 1401, 1353, 1204, 1162, 1107, 1003, 949; MS (m/z): 257 (M^++H), 256 (M^+), 227, 213, 186, 171, 153, 144, 114, 99, 87, 73 (100%), 43. Anal. Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_5$: C, 60.92, H, 7.87; Found: C, 60.88, H, 7.63.

Methyl 9-acetynyl-1,4-dioxa-9-hydroxy-6,8,8-trimethylspiro[4,5]decane-7-carboxylate (173) Schmidt's⁵² method was employed in this synthesis. 0.330 g (90%, 3.18 mmol, 6.5 equiv.) of lithium acetylide ethylenediamine complex (commercially available from Aldrich) was placed in a round bottom flask which was dried and the air was replaced by three circles of vacuum/argon exchange. 7mL of THF was added directly from the distillation apparatus to the flask. To this brown suspension was added 125.0 mg (0.488 mmol) of **137** at room temperature with stirring. The mixture was stirred at room temperature for 25 h. The reaction mixture was then poured on to 100 g of crushed ice and extracted with ether (4 X 70 mL). The com-

bined ether extracts were washed with 5% sulfuric acid (5 mL) in the presence of crushed ice, saturated sodium bicarbonate (6 mL), and brine, successively, and dried over magnesium sulfate. The solvent was removed and a reddish oily liquid was resulted. The crude product was purified by a short column chromatography using hexane and ethyl acetate (1.5 : 1) as eluent to obtain 104.7 mg (76%) of **173** as a colorless liquid of a isomeric mixture. ^1H NMR δ : 3.95-3.93 (m), 3.65 (s), 3.64 (s), 2.90-2.40 (m), 2.50 (s), 2.51 (s), (acetylene, lit.⁵² 2.50), 2.18 - 2.19 (m), 1.23-0.92 (m); IR (CCl_4 , cm^{-1}): 3650, 3450, 3310, 2980, 2948, 1735, 1471, 1434, 1372, 1285, 1193, 1142, 1107, 1049, 948; MS (m/e): 257 (M^+ -acetylene), 241, 225, 213, 197, 181, 171, 155, 129 (100%), 86, 73, 55.

Methyl 9-acetyl-1, 4-dioxa-9-hydroxy-6, 8, 8-trimethylspiro [4, 5] decane-7-carboxylate (136) Janout's⁵⁴ hydration method was used. 70.4 mg (0.25 mmol) of **173** was dissolved in 2 mL of chloroform. To this solution was added 73.7 mg (0.25 mmol, 1.0 equiv.) of phenyl mercuric hydroxide and the mixture was heated at 60°C (bath temperature) with stirring for 3.5h. After the reaction is complete (TLC), the reaction mixture was concentrated under vacuum to dryness and the residue was passed through a

short silica gel column eluted with hexane and ethyl acetate (1.5 : 1) to obtain 43.2 mg of a yellow liquid. The sample obtained above was further purified with MPLC with hexane and ethyl acetate (5 : 1) to obtain 34.5 mg (46%) of **136** as a colorless liquid of a isomeric mixture. ^1H NMR δ : 4.00-3.95 (m), 3.62 (s), 3.61 (s), 2.90-2.00 (m), 2.15 (s) and 2.16 (s), (acetyl), 1.50-1.10 (m), 1.00-0.90 (m); IR (CCl_4 , cm^{-1}): 3650, 3455, 2976, 2958, 1736, 1456, 1434, 1266, 1195, 1104, 1034; MS (m/e): 300 (M^+), 268, 253, 241, 209, 195, 172, 154, 137, 129, 99, 86, 73, 45, 43.

1, 2-dimethyl-2 (1,1-dimethyl propenyl)-4-hexen-1-ol (174) Heathcock's⁵⁶ procedure was employed. A solution of 2.50 g (11.16 mmol) of diene ester **140** in 50 mL of dry THF was cooled to -78°C . To this solution was added dropwise 45 mL of a 1.0 M solution of diisobutylaluminum hydride in hexane. The solution was allowed to warm to room temperature over 25 min. and then stirred at room temperature for 1.5 h. The solution was then cooled to an ice bath, and 15.00 g of potassium fluoride was added, followed by dropwise addition of 80 mL of water. The mixture was allowed to warm to room temperature and diluted with 100 mL of water. The solution was extracted with

ethyl acetate (5 X 40 mL). The combined ethyl acetate solutions were washed with brine (20 mL), dried over magnesium sulfate, and evaporated to yield 2.18 g (100%) of **174** as a colorless liquid. There were two isomers present in the sample. The isomers were not separated and analyzed directly. IR (mixture of two isomers, CCl_4 , cm^{-1}): 3090, 2979, 2929, 1640, 1470, 1460, 1415, 1370, 1260, 1100; Major isomer (66.5%, GC/MS t_R : 12.50 min.): ^1H NMR δ : 6.06 (dd, $J_1 = 17.6$ Hz, $J_2 = 10.7$ Hz, $\text{CH}_2=\text{CH}$), 5.58 (m, $\text{CH}_3\text{CH}=\text{}$), 4.97 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 4.94 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 3.74 (m, CH_2O), 2.53-2.49 (m, $\text{CHCH}(\text{CH}_3)$), 1.55-1.45 (m, broad, 2 X $\text{CH}_3\text{C}=\text{}$), 1.05 (s, *gem*-dimethyl), 1.01 (d, $J = 7.1$ Hz, $\text{CH}-\text{CH}_3$); GC/MS (m/e): 196 (M^+), 181 ($\text{M}-\text{CH}_3$), 165, 139, 135, 123, 121, 112, 109, 107, 100, 97, 96, 95, 84, 83 (100%), 69, 55, 41.

Minor isomer (33.5%, GC/MS t_R : 12.74 min.): ^1H NMR δ : 5.95 (dd, $J_1 = 17.9$ Hz, $J_2 = 10.3$ Hz, $\text{CH}_2=\text{CH}$), 5.27 (m, $\text{CH}_3\text{CH}=\text{}$), 4.88 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 4.86 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 3.53 (m, CH_2O), 2.33-2.49 (m, $\text{CHCH}(\text{CH}_3)$), 1.55-1.45 (m, broad, 2 X $\text{CH}_3\text{C}=\text{}$), 1.09 (s, *gem*-dimethyl), 0.95 (d, $J = 7.1$ Hz, $\text{CH}-\text{CH}_3$); MS (m/e): 196 (M^+), 181, 165, 154, 139, 123, 121, 111, 109, 97, 95, 84, 83, 69, 67, 57, 55, 41.

1,2-dimethyl-2-(1,1-dimethyl-propenyl)-4-hexen-1-oxo-tert-butyldimethylsilyl ether (175) Hori's⁵⁷ method of protection was used. To an ice bath cooled solution of **174** 2.18 g (11.16 mmol), 1.66 g (24.41 mmol, 2.2 equiv.) of imidazole in 60 mL of methylene chloride (distilled over calcium hydride immediately before use), was added 1.84 g (12.20 mmol, 1.1 equiv.) of tert-butyldimethylchlorosilane in 10 mL of methylene chloride at 0°C under argon. As half of the TBDMSCl solution was added at 0°C, white precipitate formed. Stirring was continued at 0°C and then at room temperature overnight at which time TLC showed the reaction was complete. To the reaction mixture was added 40 mL of saturated ammonium chloride solution and the resulted mixture was extracted with methylene chloride (4 X 40 mL). The extracts were washed with 5% of hydrochloric acid (20 mL), sodium bicarbonate solution (20 mL), and saturated sodium chloride solution (20 mL). The methylene chloride solution was then dried over magnesium sulfate and concentrated under vacuum on rotary evaporator to obtain 3.39 g (98%) of **175** as a colorless liquid. There were two isomers present in the sample. Major isomer: ¹H NMR δ: 5.96 (dd, J₁ = 17.6 Hz, J₂ = 10.7 Hz, CH₂=CH), 5.28 (m, CH₃CH=), 4.91 (dd, J₁ = 17.6 Hz, J₂

= 1.5 Hz, $\text{CH}_2=\text{CH}$), 4.84 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 3.63 (dd, $J_1 = 3.9$ Hz, $J_2 = 10.3$ Hz, CH_2O), 2.53-2.49 (m, $\text{CHCH}(\text{CH}_3)$), 1.55-1.45 (m, broad, 2 X $\text{CH}_3\text{C}=\text{}$), 1.05 (s, *gem*-dimethyl), 1.01 (d, $J = 7.1$ Hz, CHCH_3), 0.86 (s, *tert*-butyl), 0.01 (s, 2 X CH_3); Minor isomer: ^1H NMR δ : 5.91 (dd, $J_1 = 17.9$ Hz, $J_2 = 10.3$ Hz, $\text{CH}_2=\text{CH}$), 5.22 (m, $\text{CH}_3\text{CH}=\text{}$), 4.83 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 4.81 (dd, $J_1 = 17.6$ Hz, $J_2 = 1.5$ Hz, $\text{CH}_2=\text{CH}$), 3.48 (dd, $J_1 = 3.2$ Hz, $J_2 = 10.3$ Hz, CH_2O), 2.33-2.49 (m, $\text{CHCH}(\text{CH}_3)$), 1.55-1.45 (m, broad, 2 X $\text{CH}_3\text{C}=\text{}$), 1.09 (s, *gem*-dimethyl), 0.95 (d, $J = 7.1$ Hz, CHCH_3), 0.85 (s, *tert*-butyl), 0.02 (s, 2 X CH_3); IR (CCl_4 , cm^{-1}): 3090, 2979, 2929, 1640, 1470, 1460, 1415, 1370, 1260, 1100; MS (m/e): 310 (M^+), 295, 253, 241, 226, 211, 200, m 169, 135, 121, 115, 109, 96, 89, 83, 75 (100%), 73, 55, 41.

2,2,4-trimethyl-5-oxo-3-tertbutyldimethylsiloxy-methylhexanal (176) The ozonolysis was performed as before.⁴⁴ A solution of 1, 2-dimethyl-2 (1,1-dimethyl propenyl)-4-hexen-1-oxy tert-butyl dimethylsilyl ether (**175**) (961 mg, 3.1 mmol) in 65 mL dry methylene chloride and 490 mg (6.20 mmol, 2 equiv.) of pyridine was cooled to -78°C . Ozone in oxygen stream was passed through the solution with stirring. The ozone stream was dried by passing

through a tube which was cooled to -78°C . The color of the solution changed sequentially from colorless into yellowish after ozone passed the solution for a while, then colorless, then gray and finally blue. As soon as the blue color appeared, the ozone stream was replaced by nitrogen until the blue color disappeared (ca. 5 min.). 3.18 g (48.65 mmol, 16.0 equiv.) of zinc dust was added to the reaction solution at -78°C , followed by dropwise addition of 6.4 mL (7.00 g, 0.12 mmol, 37.8 equiv.) of acetic acid with stirring. As soon as the addition was complete, the dry ice acetone bath was replaced by a water bath at 20°C and the suspension was stirred for 2.5 h. The mixture was filtered. The zinc powder was washed many times with ethyl acetate. The combined filtrate was washed with cold water in the presence of crushed ice (2 X 5 mL), 5% sodium hydroxide until pH 8, then washed with saturated sodium chloride solution (2 X 10 mL). Each wash was back washed with ethyl acetate (10 mL) and combined. The solution was dried over magnesium sulfate and the solvent was removed to obtain a yellowish oily liquid. The liquid was *immediately* separated by a short silica gel column eluted with hexane and ethyl acetate (5 : 1) and collect the component with R_f 0.71 to yield 920 mg (98%) of **176** as a colorless liquid. There are two diastereomers present in the sample. The NMR was

taken from the mixture of the isomers and a tentative assignment was based on the ratio and the splitting constant. Major isomer (GC/MS t_R : 16.54 min., 72.6 % by GC) ^1H NMR δ : 9.44 (s, CHO), 3.63-3.58 (m, CH_2O), 2.42-2.40 (m, $\text{CH}(\text{CH}_3)\text{CH}$), 2.19 (s, CH_3CO), 1.05 (d, $J = 7.2$ Hz), 1.07 (s) and 1.05 (s), (*gem*-dimethyl), 0.85 (s, *t*-butyl), 0.01 (s, 2 X CH_3); MS (m/e): 300, 285, 267, 257, 255, 143, 229, 225, 213, 199, 171, 109, 97, 75 (100%), 43; Minor isomer (GC t_R : 16.67 min., 27.4 % by GC) ^1H NMR δ : 9.46 (s, CHO), 3.71-3.66 (m, CH_2O), 2.71-2.67 (m, $\text{CH}(\text{CH}_3)\text{CH}$), 2.17 (s, CH_3CO), 1.08 (d, $J = 7.1$ Hz), 1.03 (s) and 1.02 (s), (*gem*-dimethyl), 0.83 (s, *t*-butyl), 0.08 (s, 2 X CH_3); MS (m/e): 300, 285, 268, 267, 243, 229, 225, 213, 199, 185, 171, 97, 75 (100%), 43; IR (cm^{-1} , CCl_4): 3720, 3350, 2950, 2910, 1720, 1494, 1375, 1250, 1110, 1040, 850; Anal. Calcd for $\text{C}_{16}\text{H}_{32}\text{O}_3\text{Si}$: C, 63.94, H, 10.74; Found C, 63.96, H, 10.53.

Methyl 5-hydroxyl-3-oxo-2, 6, 6-trimethyl-cyclohexane-carboxylate (177) Aldol condensation was carried out as before.⁴⁵ A solution of 48 mg (0.16 mmol) of (L)-proline in 40 mL of freshly distilled dry DMF (distilled from calcium hydride immediately before use) was deaerated by three cycles of vacuum/argon exchange and stirred at room temperature for 1 h. Then, 450 mg (1.50 mmol) of **176** in

1.0 mL of DMF was added. The mixture was stirred at 36°C for 5 days. The reaction solution was yellow at the end of the reaction. The reaction solution was diluted with 120 mL of ethyl acetate. The ethyl acetate solution was washed with brine (2 X 20 mL) and dried over magnesium sulfate. The solvent was removed and the crude product was separated by flash chromatography using hexane and ethyl acetate (1.5 : 1) as eluent to obtain 290 mg (64%) of **177** as a colorless liquid, a mixture of diastereoisomers. ¹H NMR δ: 0.02 (s), 0.03 (s), 0.85 (s), 0.86 (s), 1.02-1.25 (m), 2.15-2.82 (m), 3.62-3.76 (m), 3.81-3.91 (m); IR (cm⁻¹, CCl₄): 3630, 3421, 2958, 2930, 1714, 1471, 1463, 1372, 1301, 1240, 1103, 1047, 981, 938, 853, 838; MS (m/z): Major isomer (GC/MS t_R: 19.00 min.): 300 (M⁺), 285, 267, 255, 245, 244, 243, 225, 215, 213, 185, 172, 171, 169, 151, 123, 121, 119, 109, 105, 81, 75 (100%), 73, 69, 55, 43. Minor isomer (GC t_R:16.28 min.) : 300, 267, 244, 243, 229, 225, 213, 172, 171, 155, 137, 129, 125, 111, 109, 97, 75, 73, 72, 69, 59, 43; Anal. Calcd for C₁₆H₃₂O₃Si: C, 63.95, H, 10.74; Found C, 63.95, H, 10.90.

3-Benzoyloxy-2,2-dimethyl-6-methylenyl-cyclohexanol methanol acetate (128)²³ A solution of geraniol acetate (16.0 g, 86.4mmol), benzoyl peroxide (purified immediately

before use; 5.50 g, 22.7 mmol), cupric benzoate (prepared by a reaction of sodium benzoate with cupric sulfate, dried at 250 °C under vacuum for 20 h; 0.500 g, 1.60 mmol), and cuprous chloride (0.080 g, 0.79 mmol) in acetonitrile (150 mL) was heated at 65°C for 20h. To this mixture, another portion of benzoyl peroxide (5.50 g, cupric benzoate (0.500 g,) and cupric chloride(0.070 g) in 40 mL of acetonitrile was added and the reaction mixture was stirred at 70 °C for another 20 h. The reaction solution was cooled and diluted with 10% sodium carbonate (150 mL), and then extracted with ether (6 X 100 mL). The ether extracts were washed with 10% sodium carbonate and water, dried over magnesium sulfate and evaporated. The crude product was distilled to get 6.50 g geraniol acetate (90-95 °C / 0.25-0.27 mmHg) (recovery=40.6%). The residue (13.87 g) was partitioned on a column of 500 g of silica gel using hexane and ethyl acetate (5:1) as eluent. The first portion of the eluent (75 mL) was found to be geraniol acetate (1.20 g, 7.5% recovery). A second portion (125 mL) gave 7.87 g of product which was found to contain phenyl group (NMR). 80.1 mg of this was separated further with MPLC (solvent: hexane/ethyl acetate, 12/1, flow rate: 4.3 mL/min.), to give 70.2 mg (51.5%, based on the grams of uncovered geraniol acetate) of pure **128**. as a colorless liquid. ¹H NMR

(200MHz, CDCl₃): 1.01 (s, 3H), 1.09 (s, 3H), *gem*-dimethyl), 1.55-2.50 (m, 6H), 2.05 (s, CH₃CO₂-), 4.30-5.00 (m, 4H, vinyl and -CH₂O-), 7.50-8.02 (m, phenyl); IR (CCl₄, cm⁻¹): 3060, 2980, 2960, 1750, 1720, 1380, 1270, 1230; MS (m/e): 316 (M⁺), 257, 194, 152, 105 (100%, PhC=O⁺), 77. The spectra are comparable with that reported in the literature.^{23h}

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