AN ABSTRACT OF THE THESIS OF

Edward D. White III for the degree of Master of Science in Chemistry presented on March 15, 1988.

Title: Synthetic Transformations on Shikimic Acid

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Abstract approved: _____ Dr. James D. White

Four strategies which involve synthetic elaboration of the shikimate nucleus are discussed. Methyl shikimate was differentially protected as the 3,4-O-cyclopentylidene ketal and as the 5-O-tert-butyldiphenylsilyl ether. The methyl ester was then reduced with diisobutylaluminum hydride and the resulting allylic alcohol was oxidized to aldehyde **47** with pyridinium chlorochromate. The cyclopentylidene protecting group of **47** was removed to liberate the 3- and 4-hydroxyl groups which were acylated with maleic anhydride and succinic anhydride. The acylated aldehydes, as well as aldehyde **47**, were converted to their respective dimethylhydrazones.

The protected shikimaldehyde **43** was treated with the anion of enamine **61**. This resulted in the formation of γ-lactone **63** by initial reaction of the enamine at the aldehyde carbon followed by intramolecular attack of the intermediate alkoxide on the fumarate ester.

The shikimate ester **54** and aldehyde **48** were selectively oxidized at the allylic position with manganese dioxide, producing **74** and **75** respectively. Ketoaldehyde **75** was reacted in a Lewis acid catalyzed Diels-Alder reaction with 3,5-dimethylfuran to give **77**.

Alcohol **46** was converted to vinyl ether **81** which was used in a Claisen rearrangement to extend the shikimate framework at the C-2 position. Subsequent α-methylenation of the resulting pair of diastereomeric aldehydes **82** and **83**, followed by intramolecular conjugate addition of a hydroxyl group to the unsaturated aldehyde system, led to acetals **86** and **87**.

Synthetic Transformations on Shikimic Acid

by

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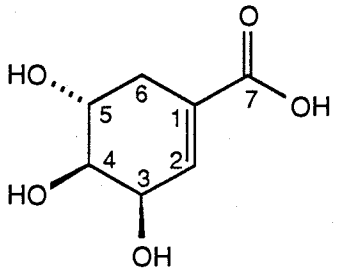
SYNTHETIC TRANSFORMATIONS ON (-)-SHIKIMIC ACID

I. INTRODUCTION

(-)-Shikimic acid (**1**) is a natural product of broad biological significance. It is known to occur in virtually all types of organisms and at all levels of the plant and animal kingdoms. Specifically, (-)-shikimic acid is a focal intermediate in the biosynthesis of a large spectrum of naturally occurring compounds including aromatic amino acids, vitamins, coenzymes, and polyaromatics.



1

The intermediacy of shikimic acid in the biosynthesis of the aromatic amino acids phenylalanine, tyrosine, and tryptophan was first discovered in studies on auxotrophic mutants of E. coli and Aerobacter aerogenes.[1] Figure 1 summarizes the known pathway to these shikimate metabolites. The occurrence and significance of this important metabolic sequence, known as the "shikimate

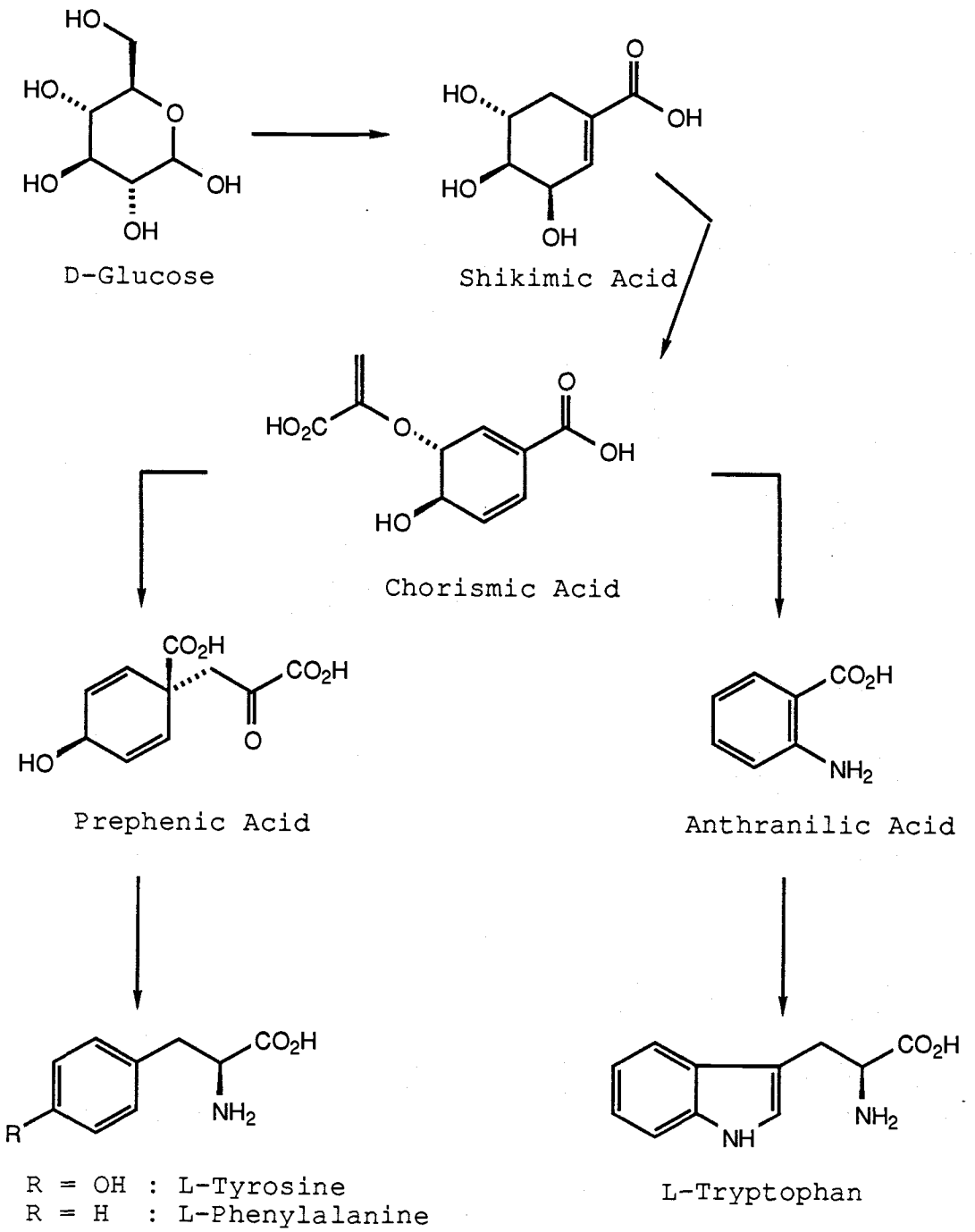
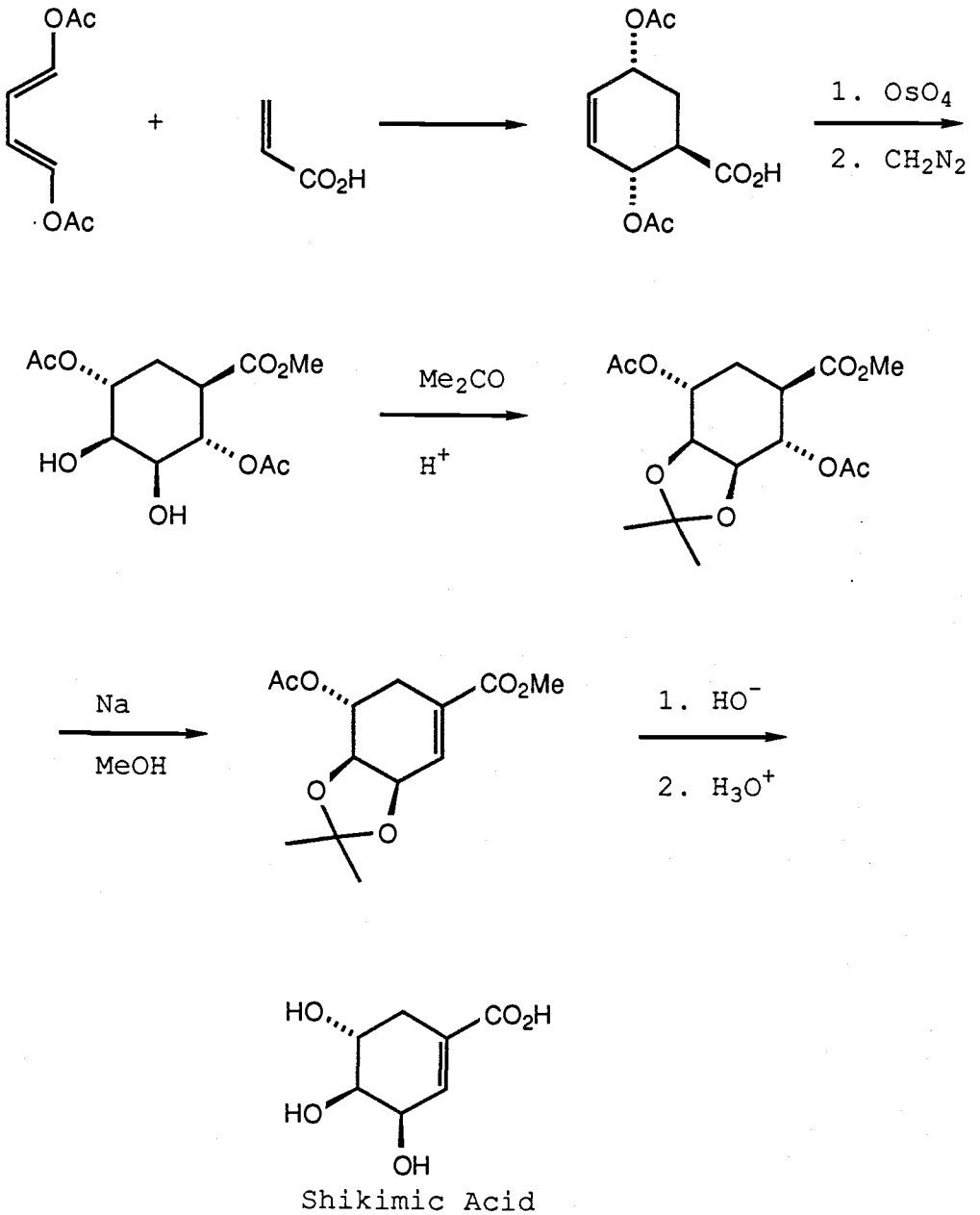


Figure 1. Biosynthesis of aromatic amino acids.

pathway", has been reviewed by E. Haslam[2] as well as by many other authors, and these critical biological processes are the subject of numerous current investigations.[3]

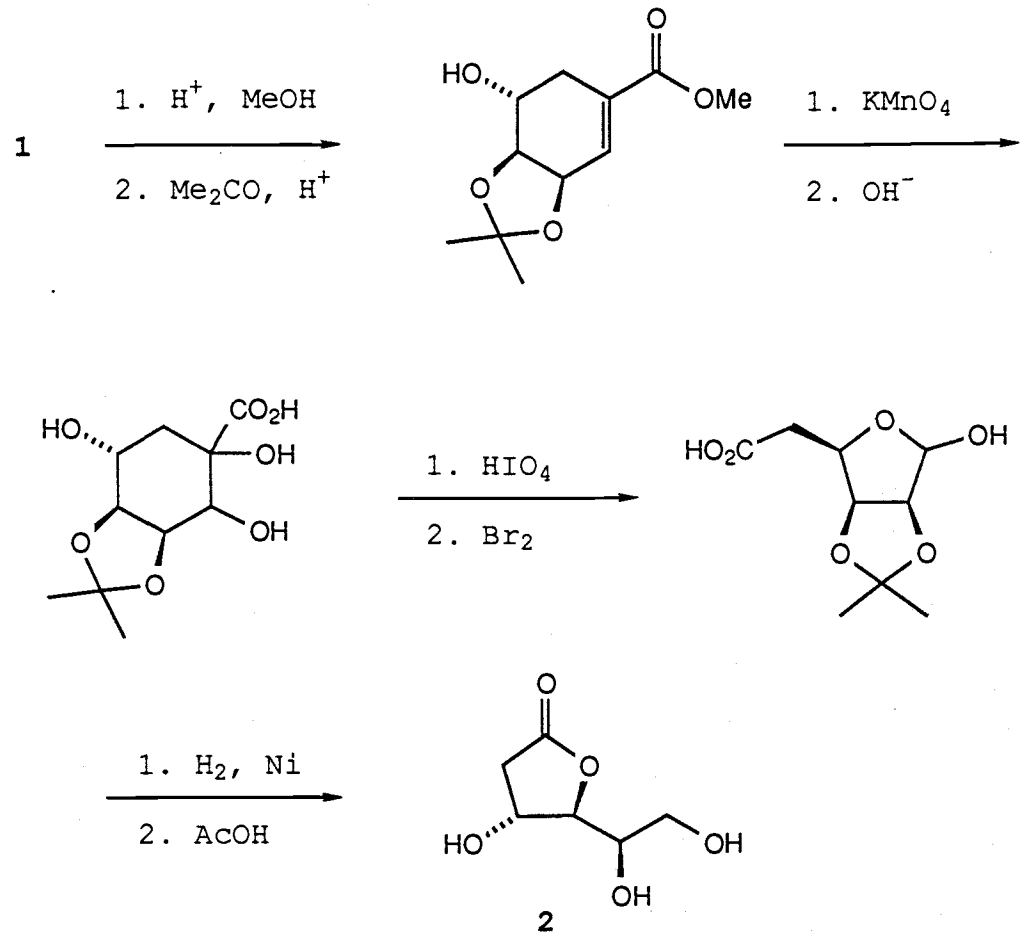
The primary focus of early studies of the chemistry of shikimic acid was on the establishment of its structure and the mechanisms by which it can be formed in the shikimate pathway. The absolute configuration of the three contiguous chiral centers and the position of the α,β-unsaturated double bond was determined in the mid 1930s by degrading (-)-shikimic acid to 2-deoxy-D-arabinohexono-γ-lactone **2**.[4]

Recently, shikimic acid has been employed as a chiral precursor in syntheses of shikimate metabolites and various other natural products. Additionally, it has itself been the target of numerous total syntheses.[5] The first total synthesis of shikimic acid was completed by McCrindle[6] in 1960. This synthetic route, summarized in figure 2, led to the preparation of racemic shikimic acid via a Diels-Alder cycloaddition which formed the six membered ring. Annulation was followed by oxidation of the double bond with osmium tetroxide which set in place the cis diol present at the 3 and 4 carbons of shikimic acid. Protection, elimination, and finally deprotection resulted in a product which was identical in all respects, except optical rotation, to natural shikimic acid.



Shikimic Acid

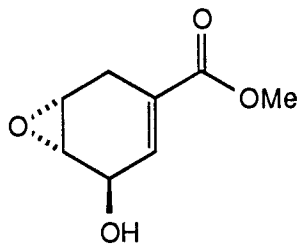
Figure 2. McCrindle synthesis of d,l-shikimic acid.



2

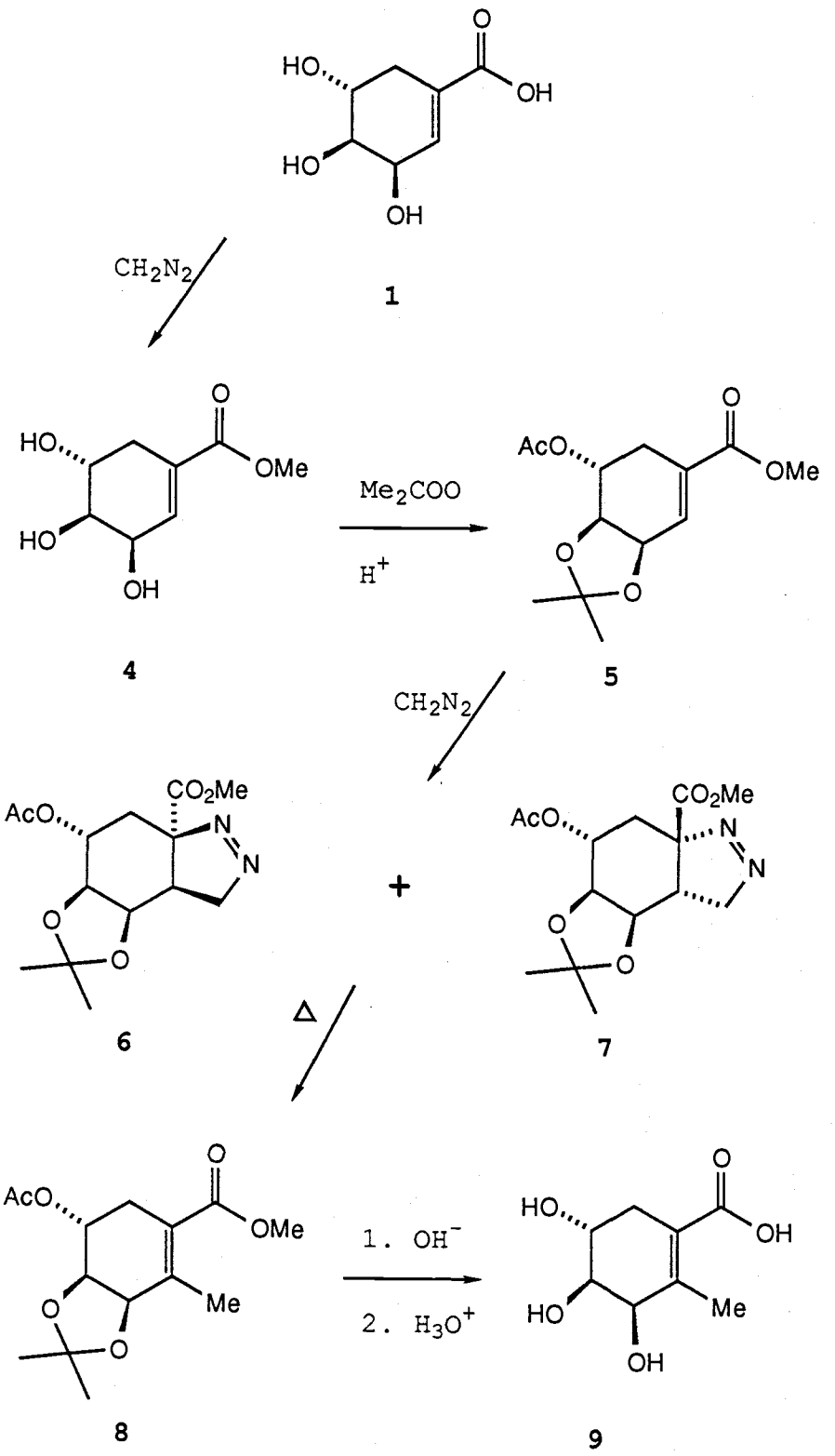
A number of subsequent syntheses of racemic shikimic acid have employed similar approaches to that used by McCrindle.[5a] Most of these incorporate a 4+2 cycloaddition using a variety of diene and dienophile combinations and an appropriate sequence of functional group conversions to arrive at the target molecule. However, it was not until the early 1980s that efficient total syntheses of enantiomerically pure shikimic acid were realized. Representative chiral syntheses of (-)-shikimic acid were accomplished using optically pure carbohydrates such as D-mannose,[7] D-ribose,[8] and D-lyxose[9] as chiral precursors.

The most recent reports describe preparative scale syntheses in which enantioselective hydrolysis of an epoxide such as **3** is accomplished enzymatically through the use of commercially available lipases.[10]



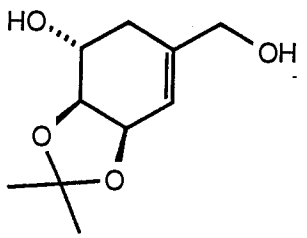
3

Much of what is now considered the most standard and useful chemistry of shikimic acid was first carried out by Grewe. Building on the basic shikimate chemistry used in early degradation work, his initial investigations in this area revealed the reactivity of shikimate derivatives toward diazomethane[11] and the differential reactivity of the three secondary alcohols. He found that treatment of shikimic acid with diazomethane at room temperature and for limited time periods resulted in the formation of methyl shikimate (**4**). However, when the shikimate derivative **5**, formed by the known ketalization of the cis hydroxyl groups and subsequent acetylation with acetic anhydride, was exposed to an excess of diazomethane for prolonged periods, the initially produced α,β-unsaturated methyl ester underwent further reaction at the carbon-carbon double bond to yield the isomeric pyrazolines **6** and **7**. Heating of


HO
OH
HO
OH
O
CH_2N_2
1
HO
OMe
HO
OH
O
4
Me_2COO
H^+
AcO
OMe
O
O
O
5
CH_2N_2
AcO
CO_2Me
N
N
O
O
6
+
AcO
CO_2Me
N
N
O
O
7
Δ
AcO
OMe
Me
O
O
8
1. OH^-
2. H_3O^+
HO
OH
HO
Me
OH
9

these two compounds resulted in a single product **8** which could be hydrolyzed to 2-methylshikimic acid **9**.

Grewe later studied the reactivity of carbon 7 in a preparation of the next two lower oxidation states of the carboxyl group. He found that treatment of the acetonide of methyl shikimate with lithium aluminum hydride cleanly gave the primary alcohol **10** with no evidence of 1,4 reduction.[12] Grewe then successfully transformed the carboxyl group to an aldehyde function by way of a reduction of the acid chloride **11** with sodium trimethoxyborohydride, resulting in a synthesis of shikimaldehyde (**12**).[13]



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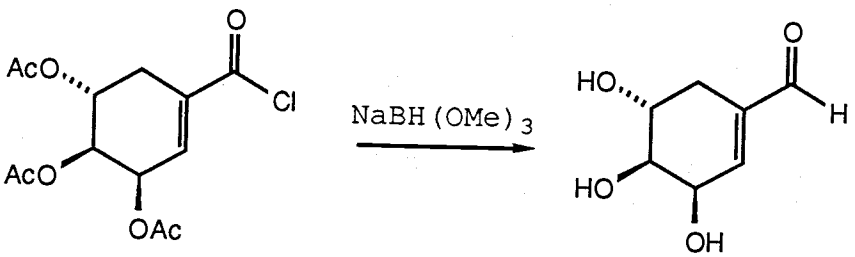
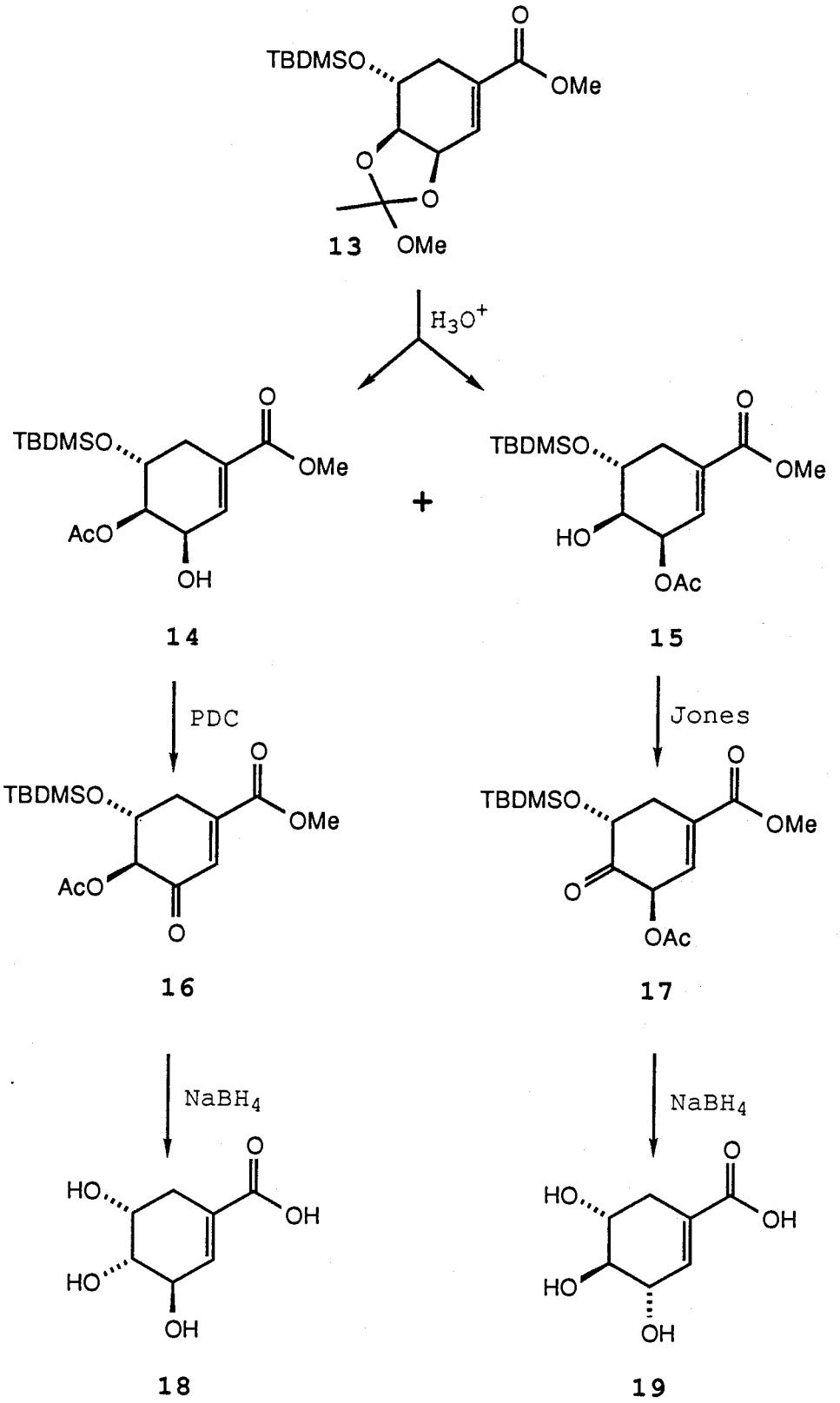


11 **12**

In an effort to produce specifically labeled (deuterium and tritium) shikimate derivatives for biochemical feeding studies, Zamir has effected chemical

transformations on shikimic acid. Her work resulted in preparations of oxidized keto variants at the C-3 and C-4 positions, as well as the C-3 and C-4 epimeric alcohols.[14] Zamir converted a C-5 silyl ether derivative of methyl shikimate to the two alcohols **14** and **15** by hydrolysis of the orthoacetate **13**. These inseparable alcohols were then oxidized and the resulting product mixture was separated as the ketoesters **16** and **17**. Both ketoesters were then independently reduced to a mixture of epimeric acetoxy alcohols by treatment with sodium borohydride. The mixture of epimers in each case could be separated by flash chromatography. Deprotection resulted in a simple route to the C-3 and C-4 epimers of shikimic acid **18** and **19**.

Berchtold examined the reactivity of methyl shikimate toward azodicarboxylates and triphenylphosphine and obtained some unique results.[15] His intent was to activate the cis 3,4-diol functionality with diethyl azodicarboxylate and triphenylphosphine to form an intermediate such as **20**. This intermediate was expected to undergo an intramolecular fragmentation and result in the anti-hydroxy epoxide **21a**. Interestingly, the only hydroxy epoxide that was produced under these conditions was the syn compound **21b**. This observation suggests that the reaction proceeds by selective activation of the 5-hydroxyl group, a selectivity without prior literature precedence.


TBDMSO
OMe
O
O
O
OMe
13
H_3O^+
TBDMSO
OMe
AcO
OH
14
+
TBDMSO
OMe
HO
OAc
15
PDC
TBDMSO
OMe
AcO
O
16
Jones
TBDMSO
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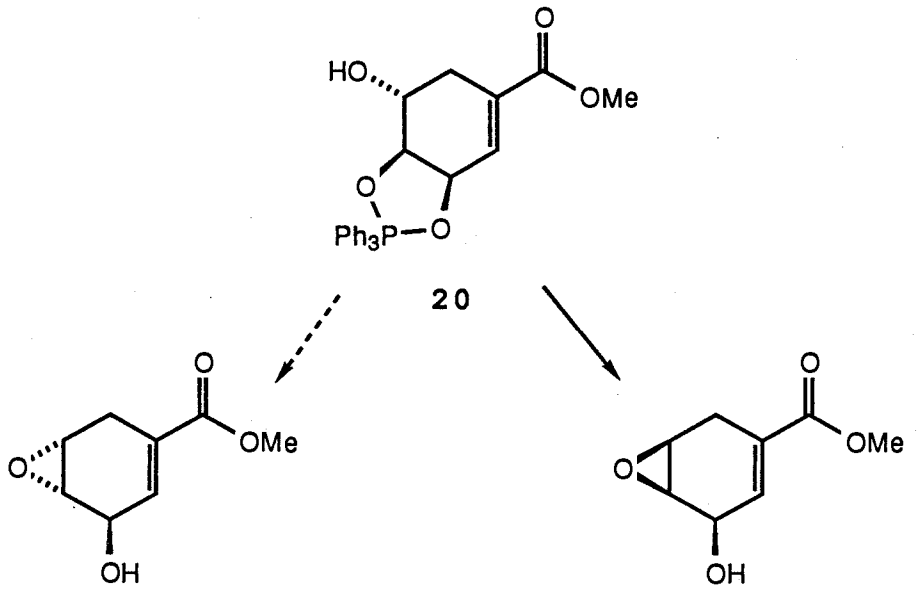
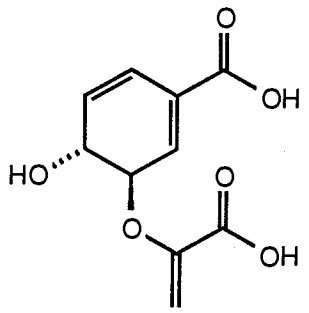


20

21a **21b**

The reactivity of the double bond of shikimic acid and its derivatives in respect to addition has been described as poor.[16] For example, attempts to effect hydroxylation of this double bond with iodine and silver acetate in wet acetic acid were unsuccessful. Other attempted addition reactions, including epoxidation using hydrogen peroxide and sodium tungstate, meta-chloroperbenzoic acid, and para-nitroperbenzoic acid, also failed.

Shikimic acid has been used as a chiron in the enantioselective syntheses of a few natural products. In most cases, syntheses using shikimic acid as the starting material have been aimed at the preparation of close relatives, particularly intermediates of the shikimate pathway. Among these endeavors are the syntheses of chorismic acid **22**,[17] (-)-5-enolpyruvyl shikimate-3-



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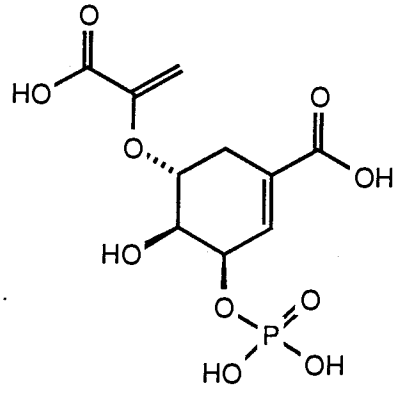

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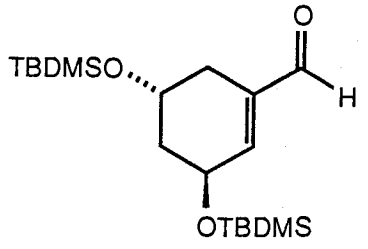


24

phosphate **23**,[18,20] and the shikimaldehyde derivative **24**.[19] It should be noted that, in all of the above syntheses, no chemical transformations significantly different from known shikimate chemistry are utilized.

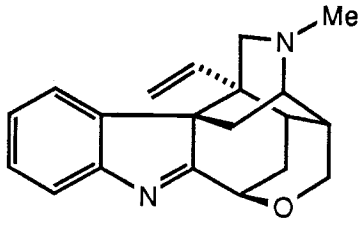
Although shikimic acid has not seen much synthetic utility outside the realm of its closely related metabolites, it does possess many structural features which make it a suitable chiral precursor for a wide variety of compounds. First, (-)-shikimic acid is commercially available in optically pure form. This attribute is an important consideration in terms of both convenience and

synthetic utility. In addition, the shikimate nucleus has an unique set of chemical properties which is not often found in commercially available precursors. Of primary significance in this regard is the recognition that shikimic acid is a highly functionalized polyhydroxy carboxylic acid.

In fact, a close analysis of the chemical constitution of shikimate will bear out the subtle differences which make it much more than a simple hydroxy acid. Every carbon atom of this compound can be chemically distinguished in one way or another. Only three of the seven carbon atoms are at the same oxidation state. Of the three secondary alcohols, two have their hydroxy group on the same face of the ring, thereby facilitating a ketalization that leaves one hydroxy group free. Hence the C-5 alcohol is easily differentiated from the other two alcohols since it can be oxidized, reduced, or otherwise transformed with the remaining oxygenated carbons protected.

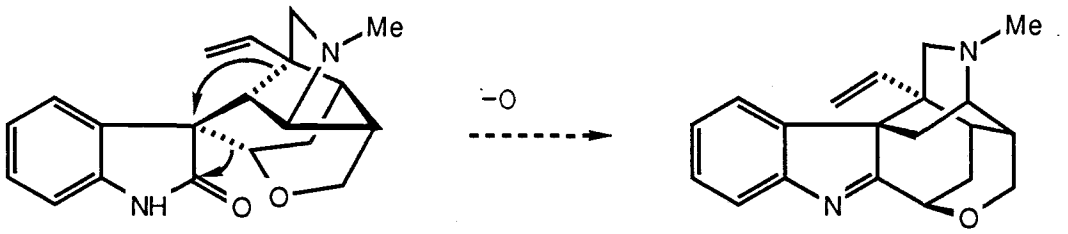
The C-3 and C-4 alcohols are also chemically distinct. Although they are both secondary alcohols and are syn to each other, the C-3 alcohol is allylic and can be selectively oxidized. In some cases, it can also be selectively acylated or alkylated. Therefore, each carbon of shikimic acid has the potential for independent chemical conversion to a different functionality.

Another important feature of shikimic acid is its chiral topology. The three contiguous stereogenic centers provide a very useful template for the elaboration of additional chirality. Furthermore, the α,β-unsaturated carbonyl system provides a functional site for the introduction of additional structure. Hence, a high degree of stereoselectivity can be expected in such processes as annulation, homologation, or functional group interchange based on shikimic acid.



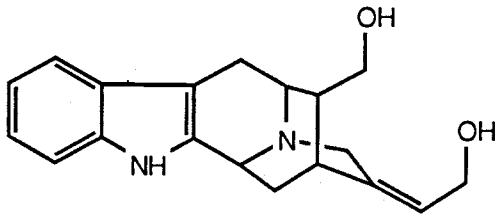
25

Koumine (**25**) is the principal alkaloid of the Chinese medicinal plant Gelsemium elegans, known locally as Kou-wen. The complex structure of koumine, as determined by Liu,[21] has its planar indolenine moiety attached to a tetracyclic array which possesses five chiral centers and two heterocyclic rings. Although structurally unique, koumine is closely related to gelsemine (**26**), an alkaloid of Gelsemium sempervirens.[22] Koumine and gelsemine are at the same overall oxidation state, and a close examination of the two alkaloids reveals that they can be interconverted by a pair of 1,2 alkyl migrations and addition or loss of oxygen.



26 **25**

A biosynthetic pathway leading to koumine from 18-hydroxy-desoxysarpagine (**27**) has been proposed by Lounasmaa and Koskinen.[23] Using a biomimetic strategy based on this route, Sakai and coworkers have synthesized 11-methoxykoumine (**29**) from the naturally occurring Gardneria nutans alkaloid 18-hydroxygardnerine (**28**).[24] However, a total synthesis of koumine from commercially available starting materials has not been reported.



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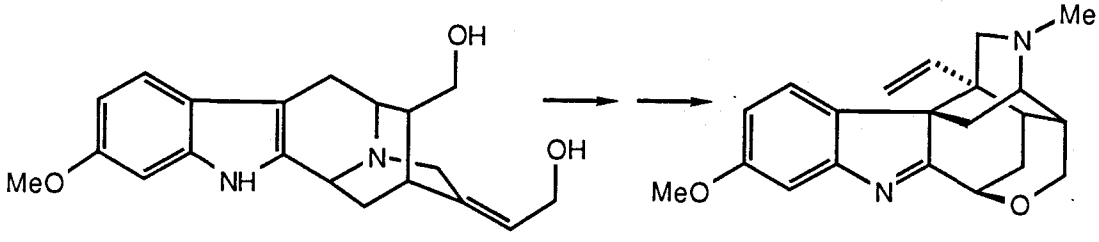


28 **29**

Of the five chiral centers found in the tetracyclic moiety of koumine, four are at carbons in a single six-membered ring. Considering this and the foregoing discussion of shikimic acid as a chiral precursor, koumine can be viewed as a reasonable candidate for an enantioselective total synthesis employing a shikimate chiron.

Figure 3 illustrates a retrosynthesis of koumine, and figure 4 depicts four possible retrosynthetic sequences terminating at (-)-shikimic acid. The final stage in all four involves elaborating the indolenine system onto the tricyclic compound **30** via a Fischer indole synthesis.[25] Thus, the focus of these routes is the enantioselective preparation of **30**. With **30** redrawn to highlight its resemblance to the shikimate framework, it becomes clear that shikimic acid is a logical choice as a koumine chiron. Accordingly, efforts were undertaken to prepare **30** enantioselectively using (-)-shikimic acid as the starting material.

Routes A, B, and C (figure 4) all share a strategy that employs an annulation across the 1,2-double bond of a shikimate derivative as the key transformation. Route A would rely on the use of an azadiene in a Diels-Alder reaction similar to that demonstrated by Ghosez.[26] Here the shikimate nucleus would serve as the diene in a highly polarized version of a 4+2 cycloaddition. In routes B and

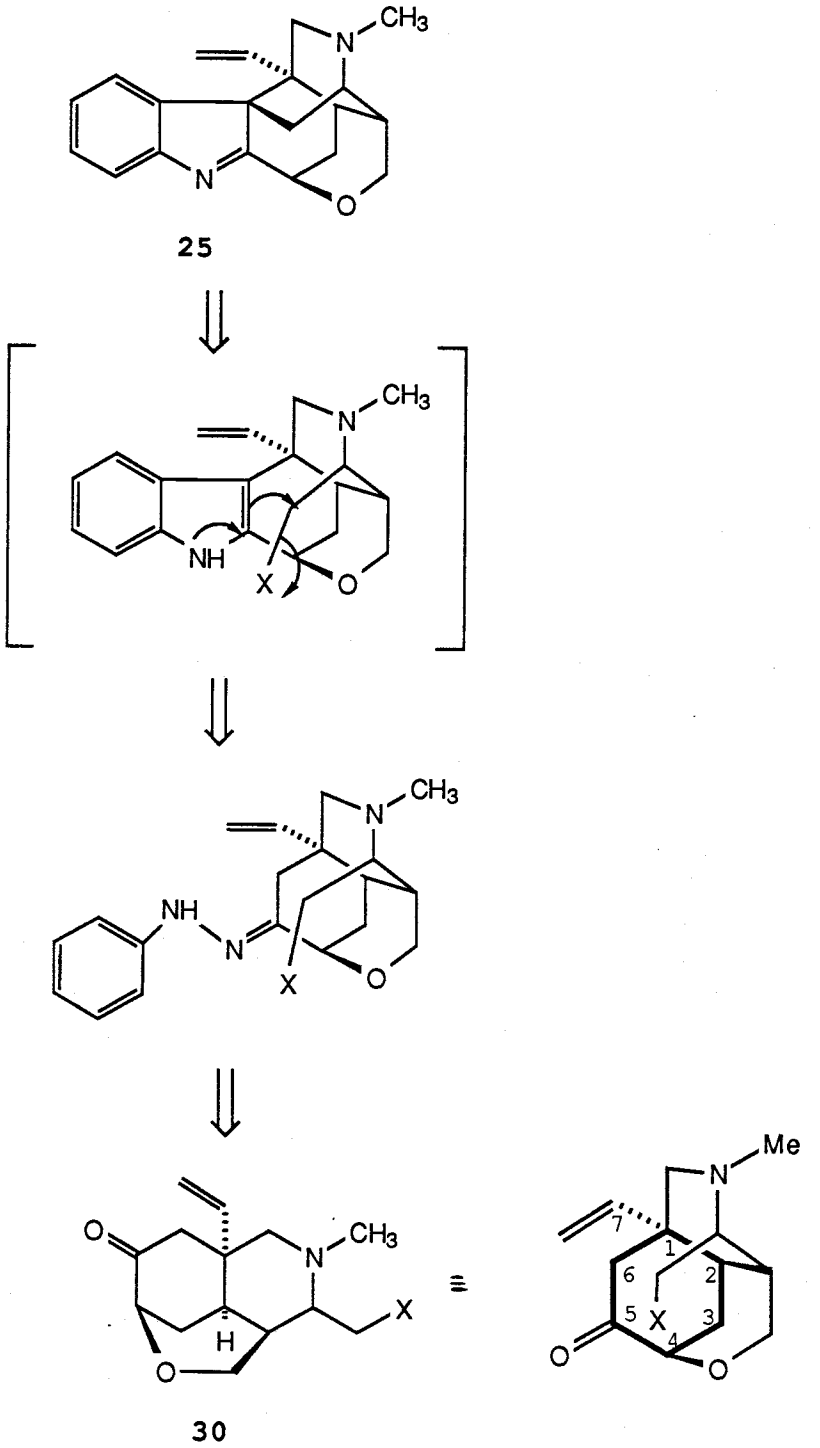


Figure 3. Schematic diagram of a retrosynthesis of koumine.

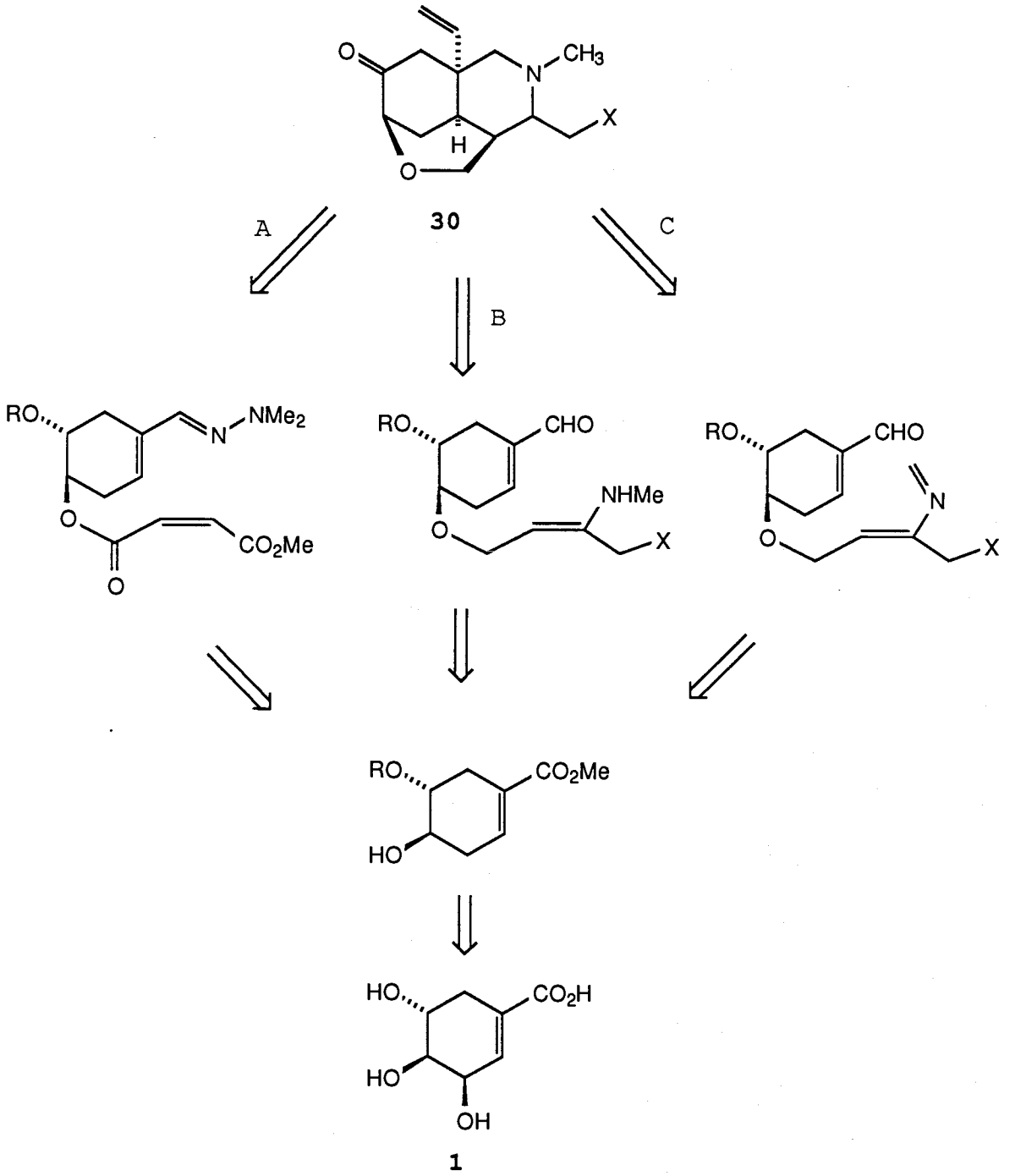


Figure 4. Schematic diagram of a retrosynthesis of **30**.

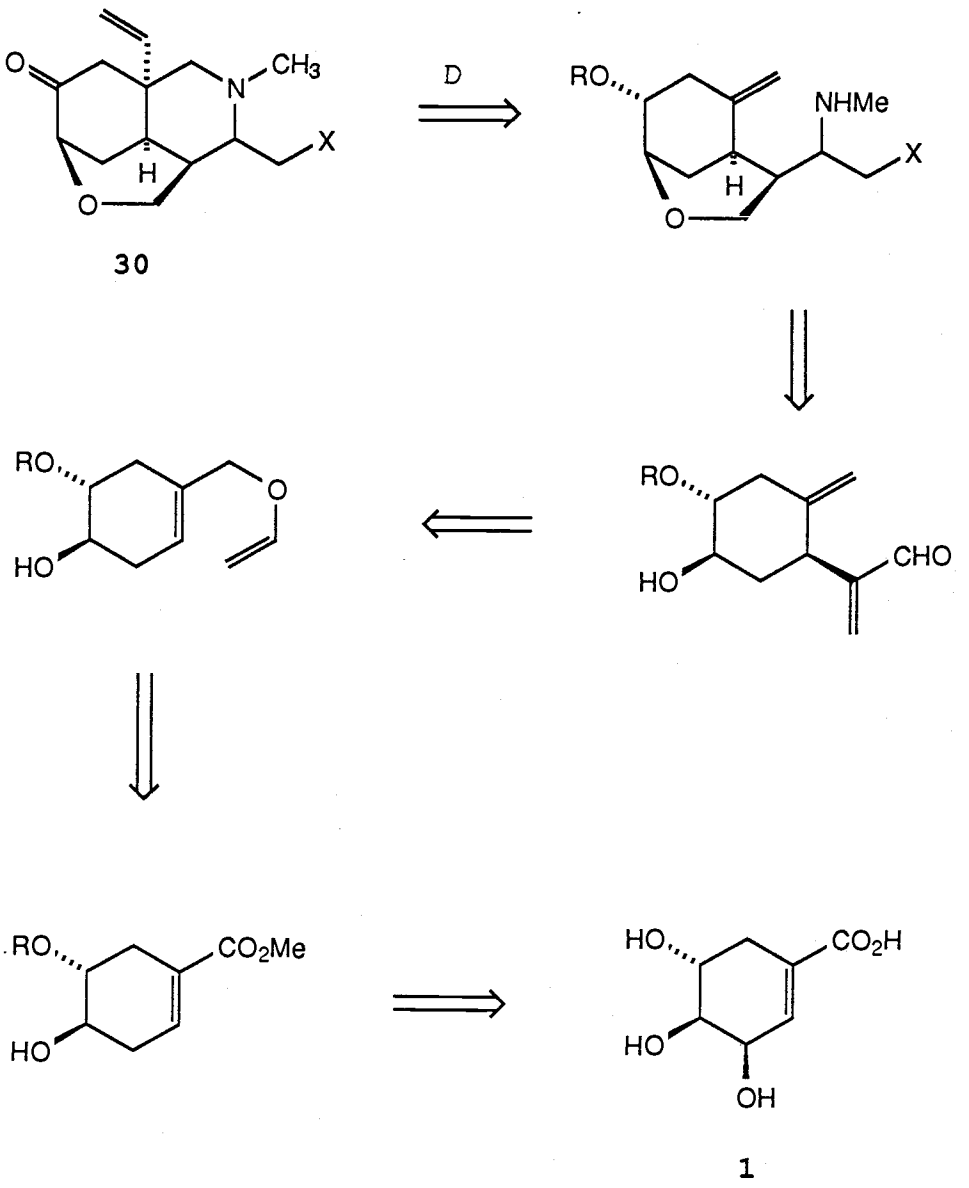
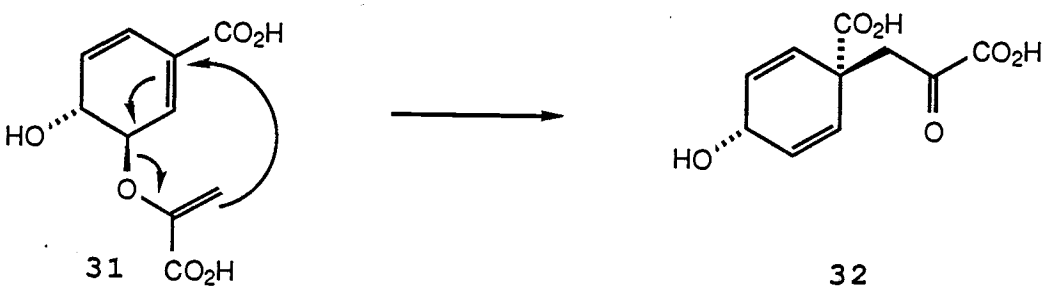


Figure 4. (cont.)

C the polarization is reversed from that of route A, with the double bond of the shikimate nucleus being electrophilic rather than electron rich. A tandem Michael addition-condensation is envisioned in route B where an enamine is postulated to add in conjugate fashion to the unsaturated aldehyde and a spontaneous condensation of the resulting secondary amine with the aldehyde carbonyl follows. This approach is similar in many ways to the known chemistry of the Hantzsch pyridine synthesis.[27] The key step of route C visualizes a different version of a Diels-Alder addition using an azadiene analogous to that explored earlier by Ghosez.[28]. In this plan, the 1,2-double bond of shikimate serves as the dienophile.

The synthetic strategy depicted in route D is fundamentally different from that portrayed in routes A, B, and C in that the second and third rings of the target **30** would be formed in a stepwise fashion rather than simultaneously. Here, a sequence of synthetic operations would transform the shikimate ring to an intermediate which is quite different from any anticipated in the previous routes. Early steps on this route would invoke a Claisen rearrangement not unlike that which is believed to occur in the biosynthetic transformation of chorismic acid **31** to prephenic acid **32**.[29] The B ring would then be formed via an ether synthesis in which the 4-hydroxyl group of the original shikimate ring adds conjugately to an α,β-



31 32

unsaturated aldehyde system. Closure of the C ring may then be envisioned through an intramolecular nucleophilic addition of an amine to a carbon-carbon double bond.

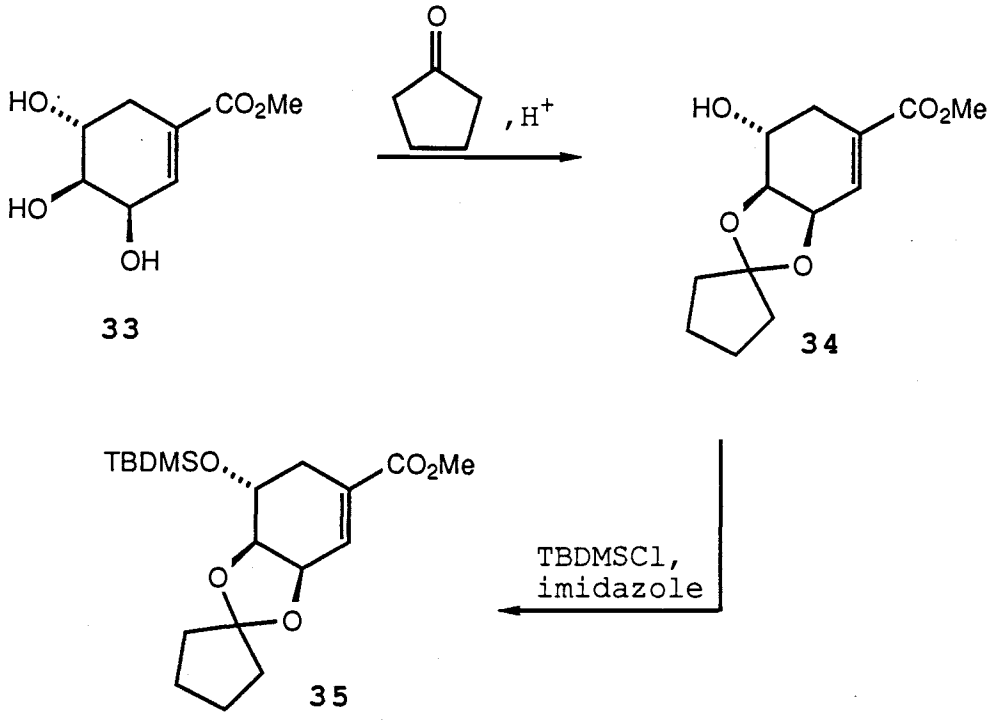
Each of the synthetic pathways outlined above would have in common a few early steps which would involve known shikimate chemistry. Specifically, the three secondary alcohols must be differentiated and that at C-3 would ultimately require removal by reduction to a methylene group. With these options in mind, the synthesis of koumine was pursued via the four routes in turn.

II. SYNTHETIC STUDIES USING SHIKIMIC ACID

The initial moves in any plan to synthesize **30** from shikimic acid must include esterification of the carboxyl group and differential protection of the three secondary alcohols. In addition to the obvious strategic importance attached to masking the free hydroxyl groups with appropriate protecting groups, this maneuver is also of practical convenience. Shikimic acid can be difficult to work with as the free acid or the free polyol due to poor solubility in organic solvents, whereas the decreased polarity resulting from ether and acetal derivatives renders the system much more tractable.

Esterification of commercially obtained (-)-shikimic acid was accomplished using diazomethane. On small to moderate scales this method is more convenient than the same conversion with methanol and sulfuric acid. Accordingly, a methanolic solution of shikimic acid was treated with an etheral solution of diazomethane producing methyl shikimate (**33**) in quantitative yield. Methyl shikimate obtained in this manner did not require purification.

Of the large variety of protecting groups available for alcohols, the ketal and silyl ether seemed the most logical choices for preparing shikimate derivatives. A



single protecting function for all three hydroxyl groups would clearly not suffice since these alcohols must be chemically differentiated. By taking advantage of the cis relationship of the 3- and 4-hydroxy groups, this pair of alcohols can be protected as an acetal or ketal. This leaves the 5-position free for attachment of a suitable ether linkage.

Many different and perhaps equally convenient reagents are available for the ketalization of a cis-diol. In this case, cyclopentanone was chosen based partly on the known propensity for cyclopentylidene derivatives to be crystalline solids and partly on their ease of hydrolysis. Hence, methyl shikimate was subjected to acid catalyzed treatment with cyclopentanone in benzene as solvent. This

solvent allowed azeotropic removal of water by a Dean-Stark trap. Following chromatographic purification, the cyclopentylidene **34** was obtained in 94% yield. All attempts to crystallize this substance from ethanol, methanol, ethyl acetate, hexane, toluene, and benzene failed.

The remaining C-5 hydroxyl group could now be protected as an ether. The protecting group at this site must be inert to the acidic conditions which will be required to remove the cyclopentylidene unit. This requirement ruled out many of the smaller, less sterically demanding groups such as trimethylsilyl, methoxymethyl, and methoxyethoxymethyl ethers, as well as acid-labile groups like the tetrahydropyranyl ether. These considerations ultimately led to the use of a tert-butyldiphenylsilyl ether as the 5-hydroxy protecting group which remained in place through most of the synthetic transformations described herein. Initially, however, the C-5 hydroxyl group was protected as its tert-butyldimethylsilyl ether. Later it was ascertained that this function was not sufficiently inert to acidic conditions and it was abandoned in favor of the more acid stable tert-butyldiphenylsilyl ether. Thus, alcohol **34** was treated with tert-butyldimethylsilyl chloride and imidazole in dimethylformamide to give the silyl ether **35** in 97% yield.

The Diels-Alder reaction of azadienes is an important and versatile tool for the synthesis of heterocyclic compounds.[30] Ghosez has demonstrated its applicability in the preparation of tetrahydropyridines from hydrazone **36**, as shown in figure 5.[26] Our plan at this point was to convert **35** to an azadiene eg **44** and test its reactivity with a variety of dienophiles. However, as a model for

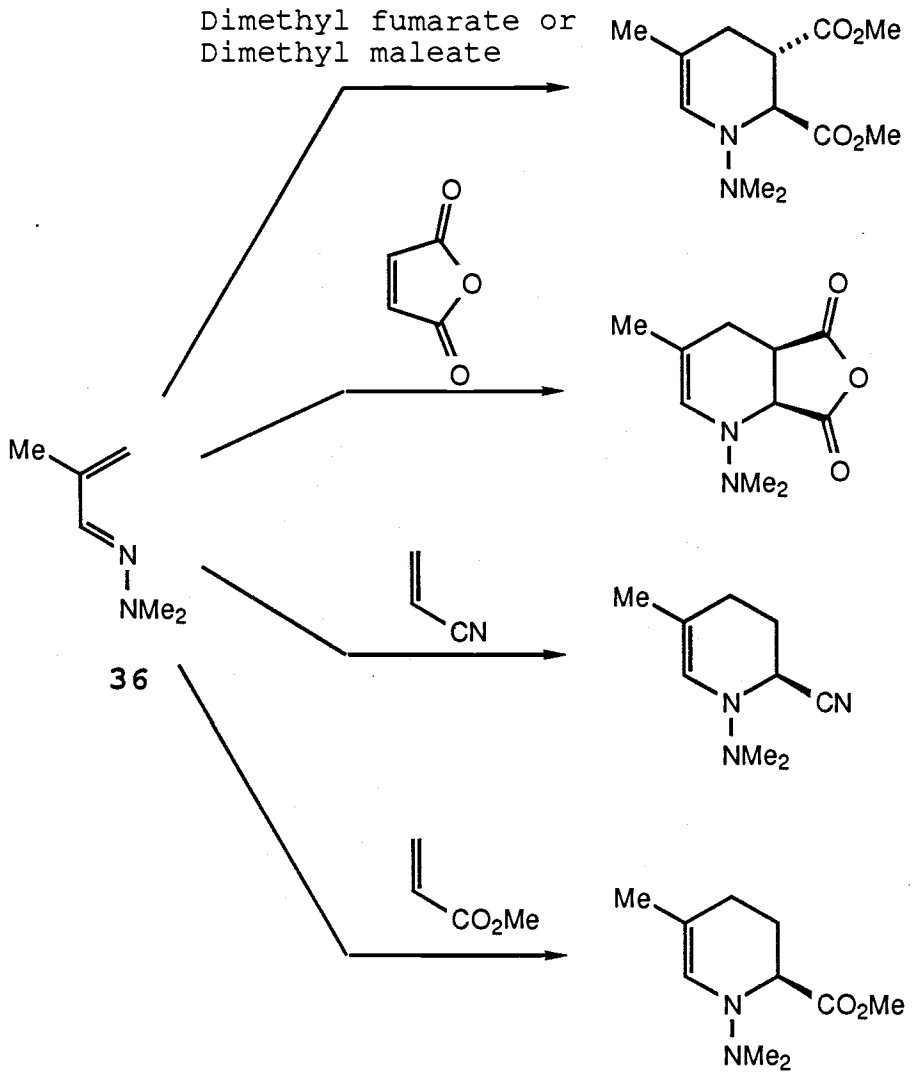
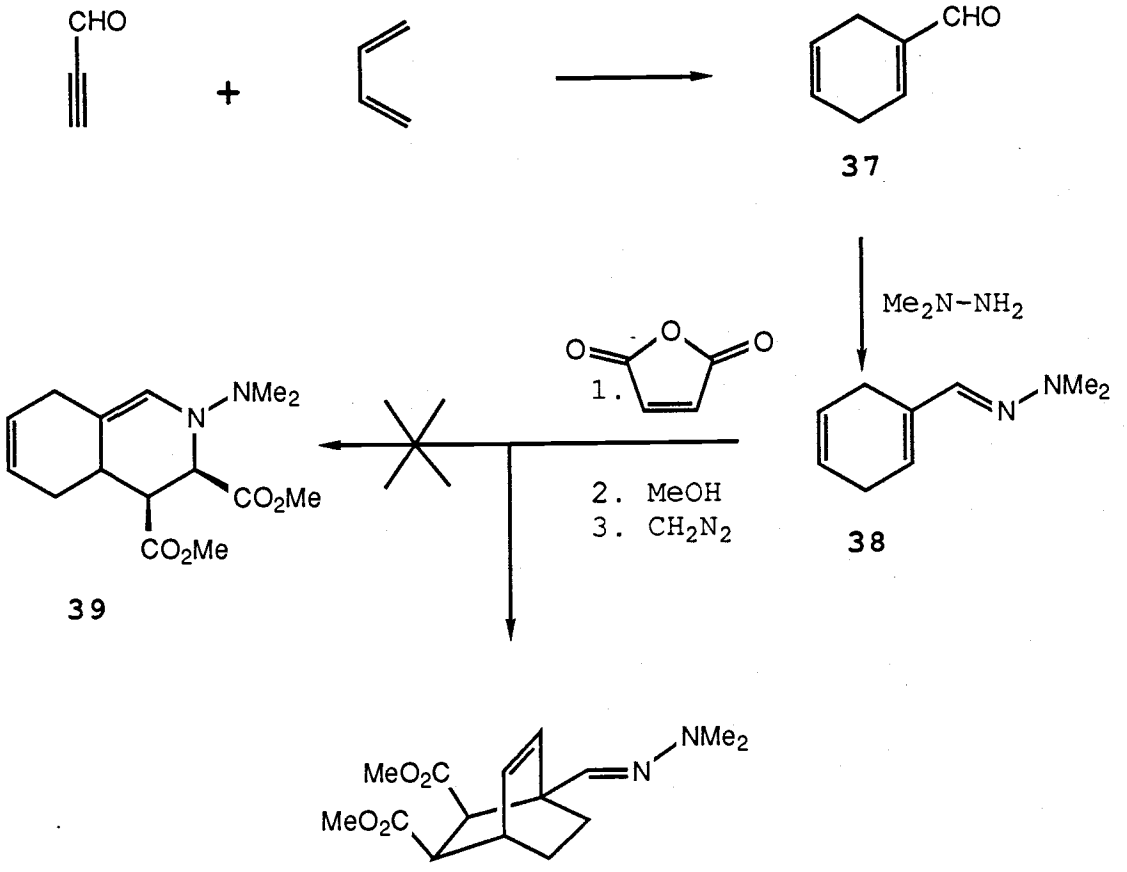


Figure 5. Tetrahydropyridines prepared via hetero Diels-Alder reactions of an azadiene.

this hetero Diels-Alder reaction, we first decided to investigate the cycloaddition of **38** with maleic anhydride, ethyl acetylenedicarboxylate, and methyl 2-butynoate. Hydrazone **38** was readily available in 78% yield as a yellow oil via the condensation of aldehyde **37**[31] with dimethylhydrazine in methanol. Aldehyde **37** was itself easily prepared by the cycloaddition of 1,3-butadiene and propargyl aldehyde (**36**).[31,32]

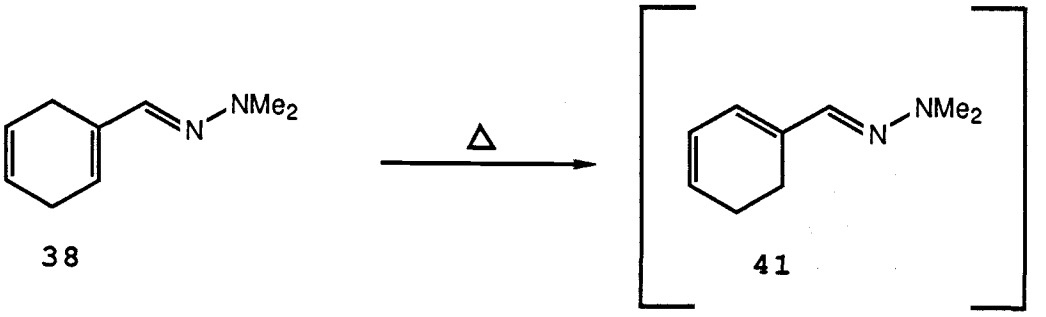


Attempts to bring about the reaction of **38** with various dienophiles, such as maleic anhydride, dimethyl maleate, dimethyl fumarate, dimethyl acetylenedicarboxyl-

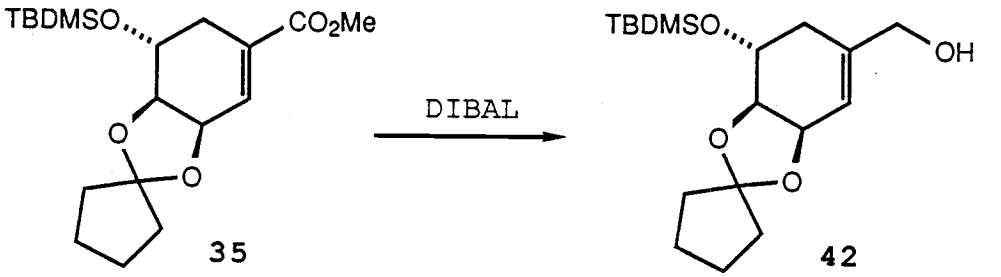
ate, methyl 2-butynoate, and 2-[5H]-furanone, at room temperature met with no success. At 110°C in toluene, however, **38** formed a one-to-one adduct with maleic anhydride. After methanolysis of the anhydride and methylation of the remaining carboxylic acid with diazomethane, the compound which was isolated was found to be not the expected adduct **39**, but the bridged product **40**. The cycloaddition achieved in this reaction was apparently preceded by isomerization of the 1,2-double bond of the cyclohexadiene into conjugation with both the second double bond and the hydrazone. A 4+2 addition then proceeded through conjugated diene **41** leading to the observed product.

The apparent lack of reactivity of the 1-aminoazadiene **38** toward dienophiles was a disappointment, but it was nevertheless decided to pursue this route with a shikimate derivative. The rationale for this lay in the fact that the problem of double bond isomerization would not be a factor in the shikimate system and, thus, more vigorous conditions could be applied to the cycloaddition.

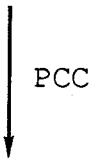
In order to transform **35** to a 1-dimethyaminoazadiene analogous to **38**, the reduction of the carboxylic ester to an aldehyde and condensation with 1,1-dimethylhydrazine was necessary. Attempts to reduce the methyl ester of **35** directly to the aldehyde with one equivalent of diisobutylaluminum hydride[33] yielded instead a 1:1 mixture

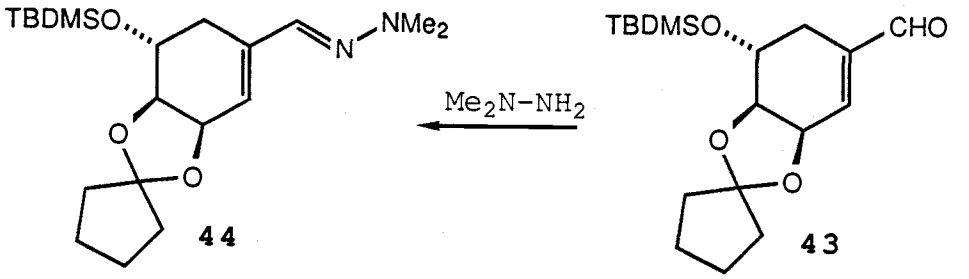


38 41



35 42





44 43

of starting material and the primary alcohol **42**. In view of our failure to stop the reduction of **35** at the aldehyde stage, the reaction was carried out with two equivalents of the hydride which yielded **42** as a colorless oil in 97% yield after purification. Aldehyde **43** was then obtained in 97% yield by treatment of **42** with pyridinium chlorochromate in dichloromethane at room temperature. Condensation of **43** with one equivalent of 1,1-dimethylhydrazine in methanol produced the desired hydrazone **44** in 86% yield as a gummy yellow solid.

With the stage now set for a test of azadiene **44** as a Diels-Alder partner, this hydrazone was exposed to a variety of dienophiles at a range of temperatures and in different solvents. Unfortunately, none gave any trace of a cycloadduct.

Clearly there is a significant difference between the cyclic hydrazone **44** and the acyclic azadienes used successfully by Ghosez.[26] The diene **36**, being unsubstituted at the terminal carbon of the unsaturated hydrazone, lacks the inductive effect of the alkyl group that is present in our cyclic examples. The acyclic hydrazone **36** is therefore more highly polarized and perhaps for this reason more reactive in cycloaddition. There was one avenue left open, however, which could conceivably overcome the reluctance of **44** to undergo cycloaddition. This approach was to attach the dienophile

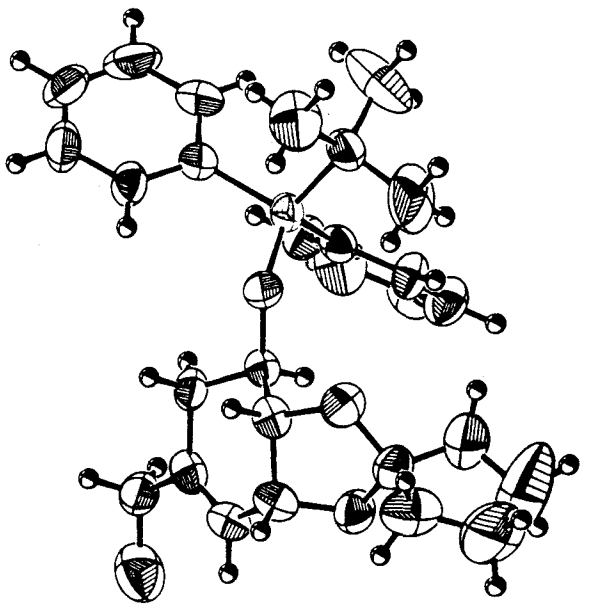
to **44** and thereby take advantage of the benefits of an intramolecular version of a cycloaddition.

Intramolecular Diels-Alder reactions have the advantage over their intermolecular counterparts of both increased rate due to the proximity of reacting pi systems and greater control of face selectivity in the orientation of diene and dienophile. The hydroxyl substituents of a shikimic acid would afford a locus for attachment of the dienophile via acylation or alkylation. With this in mind, our synthetic course was altered toward an intramolecular version of a Diels-Alder reaction of **44**.

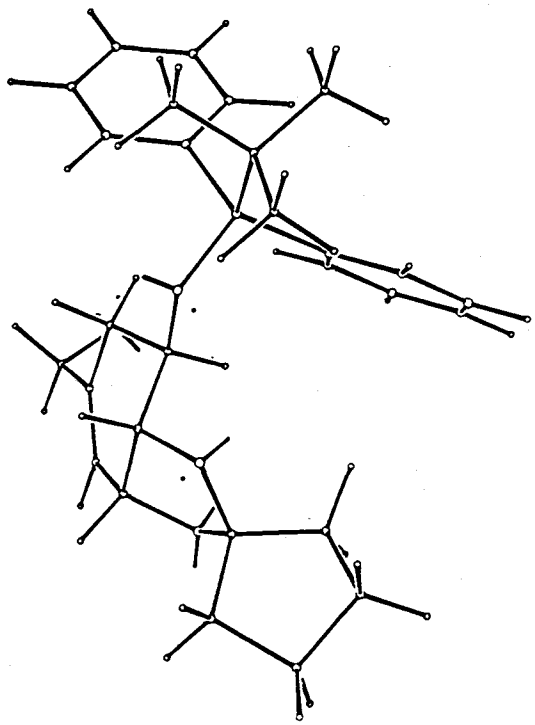
This sequence required deprotection of the 3- and 4-hydroxyl groups and attachment of a suitable dienophile at one of these sites. It was at this point that it became clear that the tert-butyldimethylsilyl ether was not the best choice for protection of the C-5 alcohol, since selective hydrolysis of the cyclopentylidene ketal with aqueous acetic acid caused a substantial amount of silyl ether cleavage. This outcome necessitated the use of a more resistant protecting group, and a logical choice appeared to be the tert-butyldiphenylsilyl ether. Accordingly, **34** was treated with one equivalent of tert-butyldiphenylsilyl chloride and an excess of imidazole in dimethyl formamide to produce the silyl ether **45** in quantitative yield.

The next operation was reduction of the ester to an aldehyde and, since this passed through the primary alcohol, protection of the C-3,4 diol moiety was retained in order to avoid unwanted oxidation of these centers. Ester **45** was reduced with two equivalents of diisobutylaluminum hydride in toluene at -78°C, yielding the primary alcohol **46** in 83% yield as a crystalline solid. As this compound was the first crystalline intermediate that we had encountered beyond methyl shikimate (and, as it turned out, the only crystalline shikimate derivative obtained in this entire study), an x-ray crystal structure of **46** was obtained. The ORTEP plot of **46**, as revealed by single crystal analysis, as well as a packing diagram is shown in figure 6. The packing diagram shows that the allylic hydroxyl group is directed outward from the center of the unit cell. Hence, intermolecular hydrogen bonding is not an important factor in the solid state. Alongside the ORTEP plot is a drawing obtained from an MMX calculation for the same compound. The MMX data was obtained using the molecular modeling programs MODEL (version KS 2.9) and MMX (version 87) which compute the theoretical lowest energy conformation of a molecule in the gas phase. A comparison of this calculated conformation with that obtained in the x-ray experiment reveals the striking similarity of the two. Therefore, the

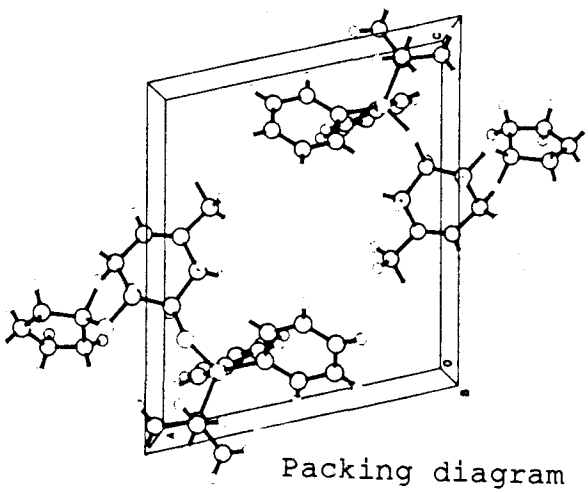
solution state conformation can be predicted to resemble that which is illustrated in figure 6.



X-ray ORTEP



MMX conformation

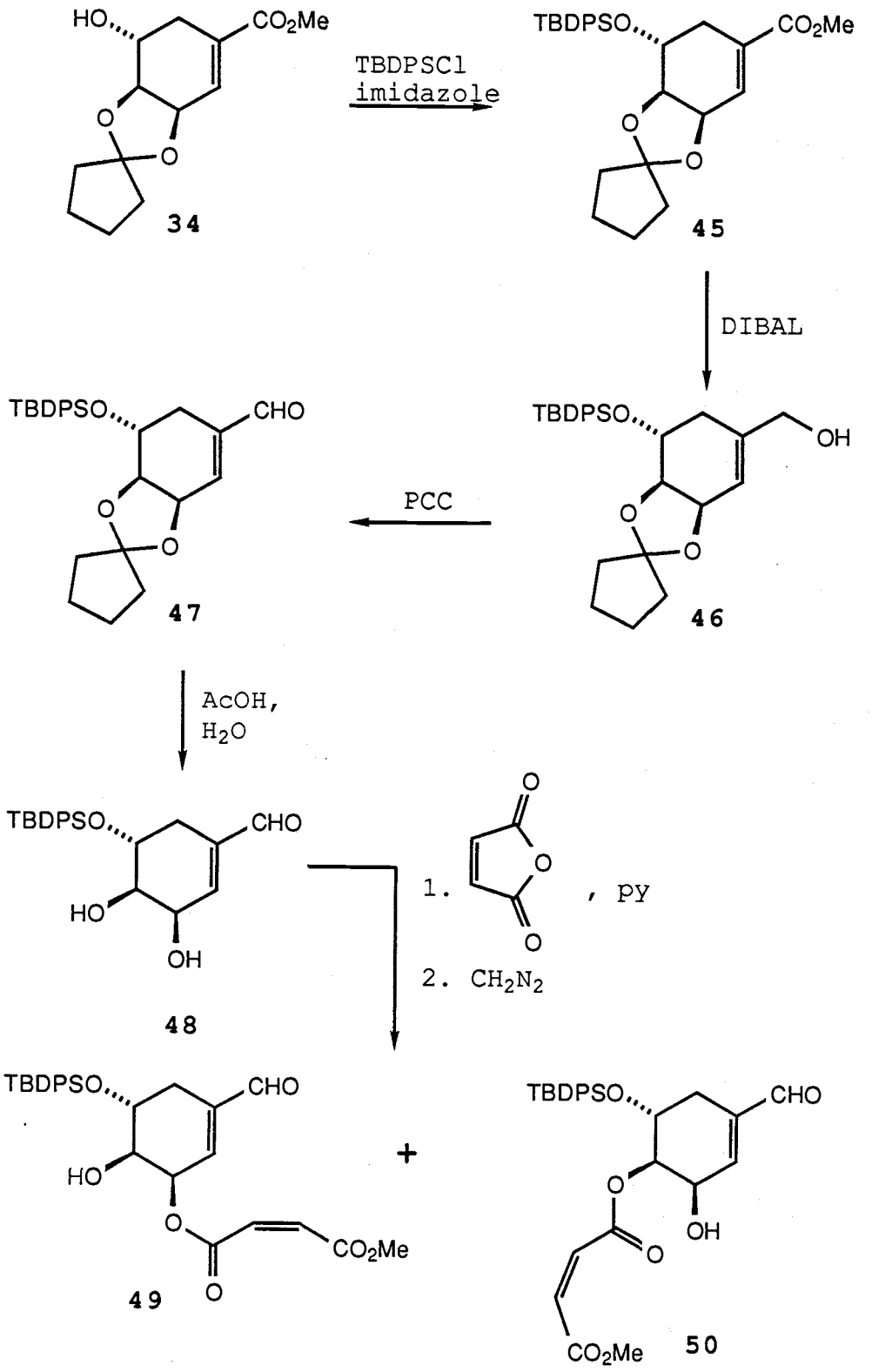


Packing diagram (x-ray)

Figure 6. ORTEP plot and MMX conformation of **46**.

Aldehyde **47** was obtained in 98% yield by oxidation of the primary alcohol **46** with a slight excess of pyridinium chlorochromate in dichloromethane. Hydrolysis of **47** with 80% acetic acid in water resulted in an 82% conversion to the free diol **48**. With this diol in hand, attachment of the dienophile to one of the free hydroxyl groups via an acylation process could be readily envisioned. Although acylation could conceivably take place at either of the hydroxyl groups, it was expected that the 3-acylated product would be preferred due to the fact that it is further removed from the large silyl protecting group and is significantly less hindered. Since both products would be useful in the context of an intramolecular Diels-Alder reaction, there was little concern for which product predominated as long as some preference for one of them was realized.

The dienophile selected for the intramolecular Diels-Alder reaction was a maleate derivative, and diol **48** was therefore treated with one equivalent of maleic anhydride and pyridine in dichloromethane. Subsequent methylation of the carboxylic acid with diazomethane produced a 2:1 mixture of esters **49** and **50** respectively. This modest selectivity for the allylic ester was less than had been anticipated, and the situation was complicated by the inseparability of the two products. In order to ascertain whether the same poor selectivity would result from the use


HO
CO2Me
TBDPSCl
imidazole
TBDPSO
CO2Me
34
45
DIBAL
TBDPSO
CHO
PCC
TBDPSO
OH
47
46
AcOH,
H2O
TBDPSO
CHO
HO
OH
48
1.
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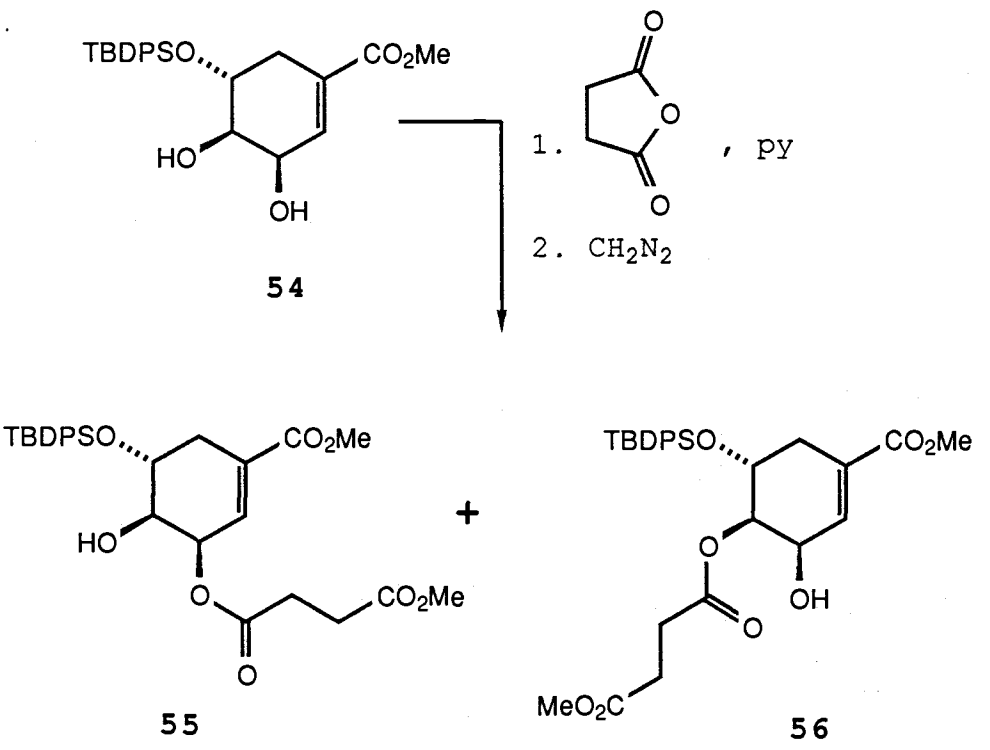
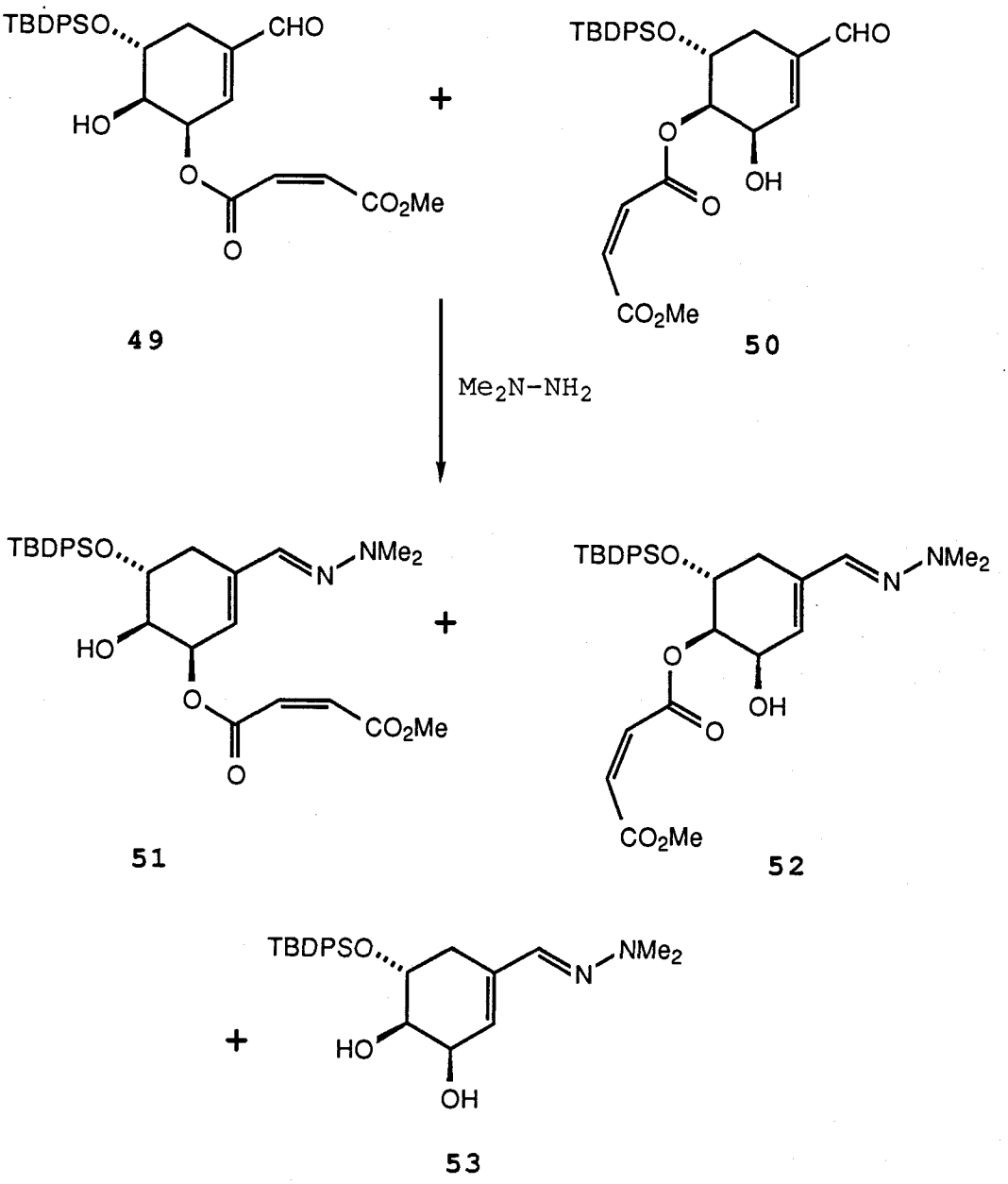


of a different acylating agent, diol **54**, available from hydrolysis of **45**, was treated with succinic anhydride and pyridine in dichloromethane. Again, a similar 5:3 mixture of esters **55** an **56** was obtained. It was concluded from these observations that selectivity for the C-3/C-4 hydroxyl groups in acylation was not likely to be improved, and therefore, the mixture of **49** and 50 was carried forward to the next step.

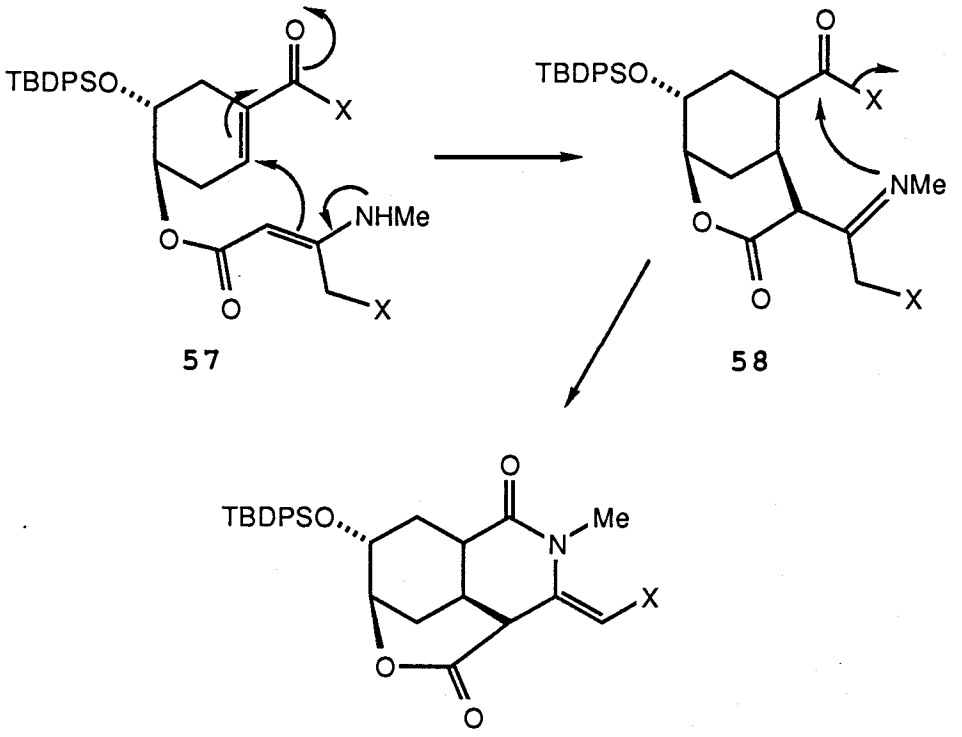
Condensation of **49** and **50** with 1,1-dimethylhydrazine in methanol gave a mixture of the hydrazones **51** and **52** in poor yield along with **53** arising from hydrazinolysis of the maleate ester. The acylated hydrazones **51** and **52** were easily separated from the diol **53** although the esters



again could not be separated from each other. Nevertheless, a pair of substrates was now in hand with which the feasibility of an intramolecular Diels-Alder reaction could be tested.

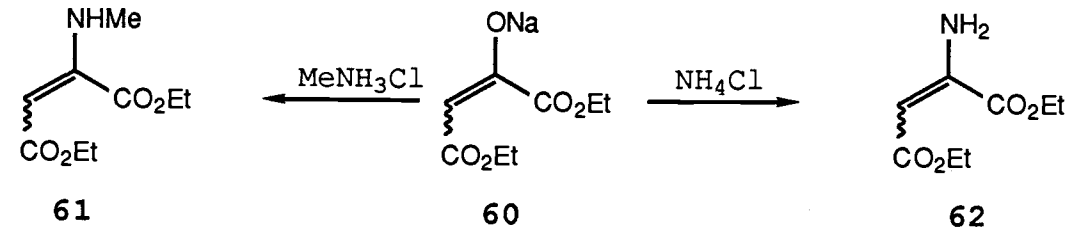
The unfortunate reality which unfolded was that this plan, like that of the intermolecular Diels-Alder reaction, was abortive. At temperatures up to 110°C, neither hydrazone **51** or **52** was changed. Increasing the temperature to 150°C in dimethylformamide as solvent caused decomposition and loss of starting materials. The absence of any indication of a [4+2] cycloaddition with the 1-azadiene prepared for this purpose prompted us to abandon this strategy in favor of an alternate approach to annulation of the shikimate structure. While it would be premature to discount an approach based on the cycloaddition concept elaborated above, it is clear that any plan for construction of **30** must deal with an azadiene component that is significantly less reactive than the simple acyclic examples examined by Ghosez.

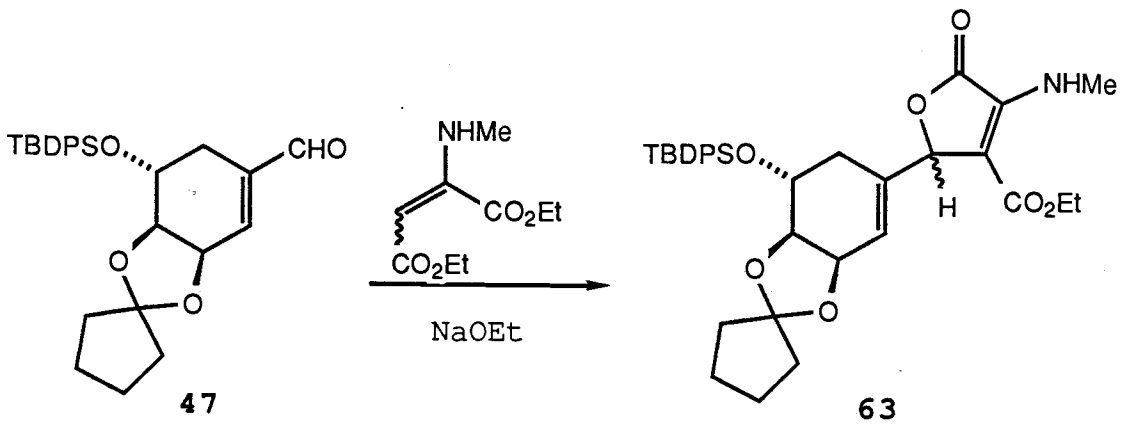
An alternate synthetic approach to the koumine precursor **30** could fabricate the tricyclic structure of this intermediate from a shikimate derivative such as **57**. This route would exploit the α,β-unsaturated carbonyl system of shikimic acid as a Michael acceptor in a tandem process involving conjugate addition followed by an intramolecular amine condensation. Success in this double annulation would hinge on initial attack by the enamine at C-2 of **57** to give **58** thus allowing the lactam **59** to be generated in a geometrically favorable cyclization.



In a model study of the Michael component of this annulation process, **45** and **47** were exposed to enamines **61** and **62**. The latter were derived from the commercially available sodium salt of diethyl oxalacetate (**60**) by treatment with one equivalent of either methylamine hydrochloride or ammonium hydrochloride in ethanol. This resulted in good yields of **61** and **62** respectively.

The ester **45** was treated in dimethylformamide with both **61** and **62** at a variety of temperatures up to 150°C. In no case did a reaction occur; starting materials were recovered unchanged. In the hope of increasing the nucleophilicty of **61** and **62**, enamines were deprotonated



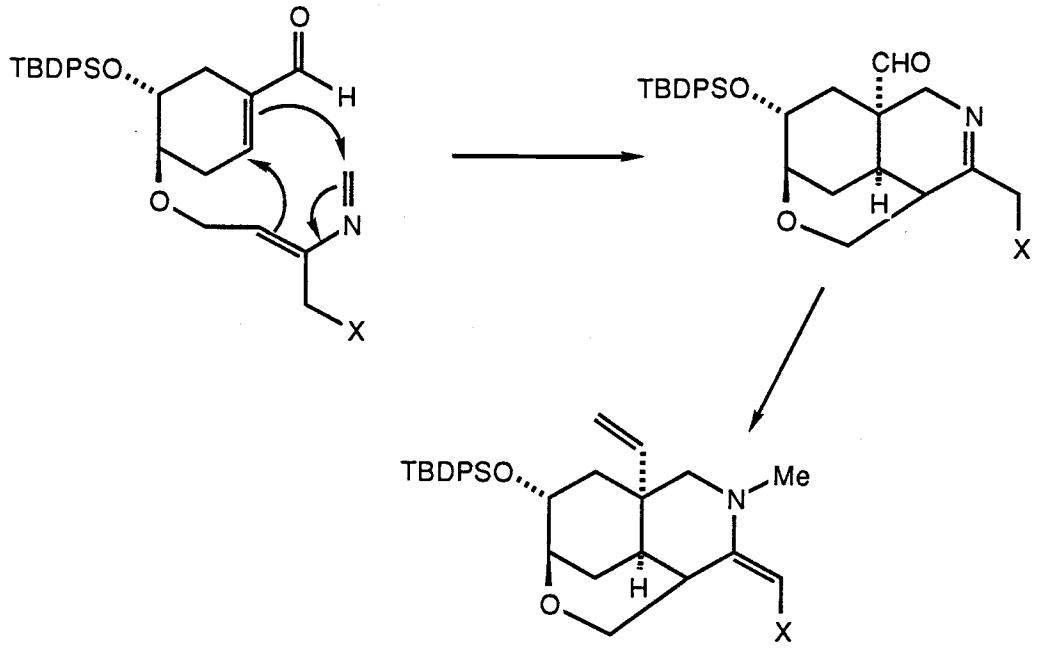


with a base before contact with **45**, but neither a catalytic quantity of sodium ethoxide nor quantitative deprotonation with a full equivalent of sodium hydride produced a reaction below 150°C. At 150°C in dimethylformamide, treatment of **45** with the sodio derivative of **61** resulted in decomposition and loss of starting materials.

An attempt to effect this tandem annulation on **47** was also made. When **47** was mixed with **61** or **62** without added base, no reaction occurred. However, treatment of **47** with enamine **61** and a catalytic amount of sodium ethoxide in ethanol resulted in a 40% conversion to γ-lactone **63**. The formation of **63** apparently indicates a preference for attack by the enamine at the aldehyde carbonyl carbon

rather than Michael addition. Subsequent intramolecular attack of the intermediate alkoxide on the fumarate ester leads to **63**. This discouraging result, although not surprising, provided convincing evidence that a Michael addition of an enamine to a shikimate derivative such as **45** or **47** had little prospect of success. The double bond of the α,β-unsaturated carbonyl system of these shikimate derivatives was either too hindered for attack of a nucleophile at the β-carbon or the double bond was not sufficiently electrophilic. Consideration of the structure of alcohol **46** (figure 6), as derived from x-ray analysis and as deduced from MMX calculations, would lend credence to a rationale based on the inaccessibility of this double bond to an external nucleophile. Therefore, removal of the cyclopentylidene group seemed to be an appropriate prelude to any further annulation attempts.

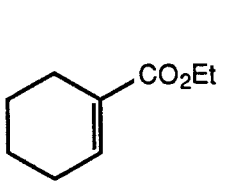
A previous approach to **30** focused on a hetero Diels-Alder reaction in which a shikimate system served as the diene. In principle, the same goal can be reached by reversal of the role of shikimate to that of dienophile. In this case, the α,β-unsaturated double bond of the shikimate moiety would serve as the dienophile. In this scheme, C-7 of shikimic acid would not be incorporated into the newly formed ring, but would become an angular substituent on a cis fused bicyclic structure (scheme 1). An attractive feature of this approach is that it would



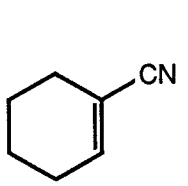
Scheme 1. Proposed intramolecular 2-azadiene Diels-Alder reaction.

install, with correct absolute configuration, the angular functionality needed to construct the vinyl group of **30**.

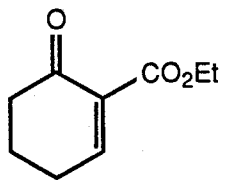
With the dienophiles **48** and **54** already in hand, the initial task was to prepare a suitable diene with which to test an intermolecular equivalent of the reaction proposed in scheme 1. Such a diene must be capable of surmounting the predictably sluggish reactivity of these 1-carboxyl-cyclohexene systems in Diels-Alder reactions. In fact, cyclohexenecarboxylates are notoriously poor dienophiles, and their application in the synthesis of fused decalins has been disappointing when paired with conventional dienes.[34] Attempts to form a cycloadduct of 1,3-butadiene



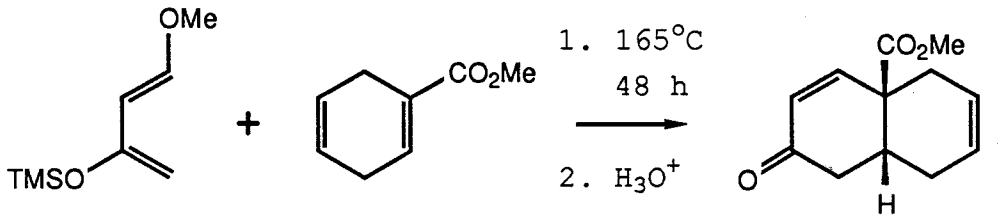
64



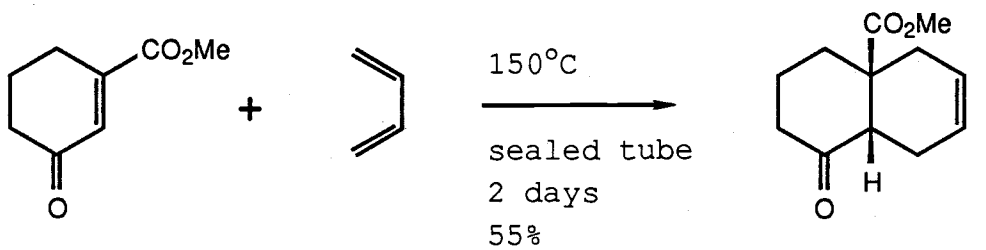
65



66



68 67 69



79 80

with ethyl 1-cyclohexenecarboxylate (**64**), 1-cyanocyclohexene (**66**), and 1-carboethoxylcyclohexene-6-one (**66**) have met with failure under a broad range conditions.[35] The little success that has been obtained in Diels-Alder reactions of these systems has resulted from temperatures usually exceeding 180°C. However, Danishefsky has obtained a modest 50% yield of **69** by reacting the dienophile **67** with the electron rich diene **68** in refluxing mesitylene

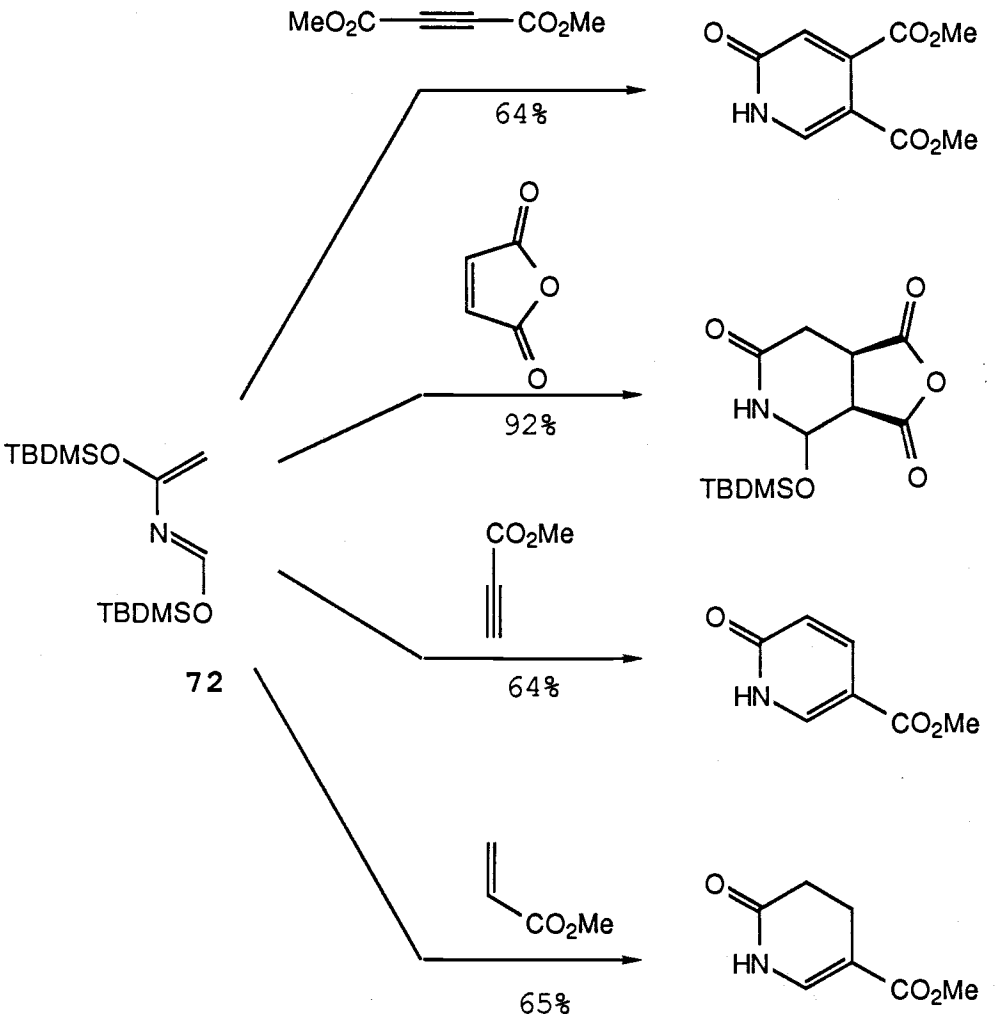
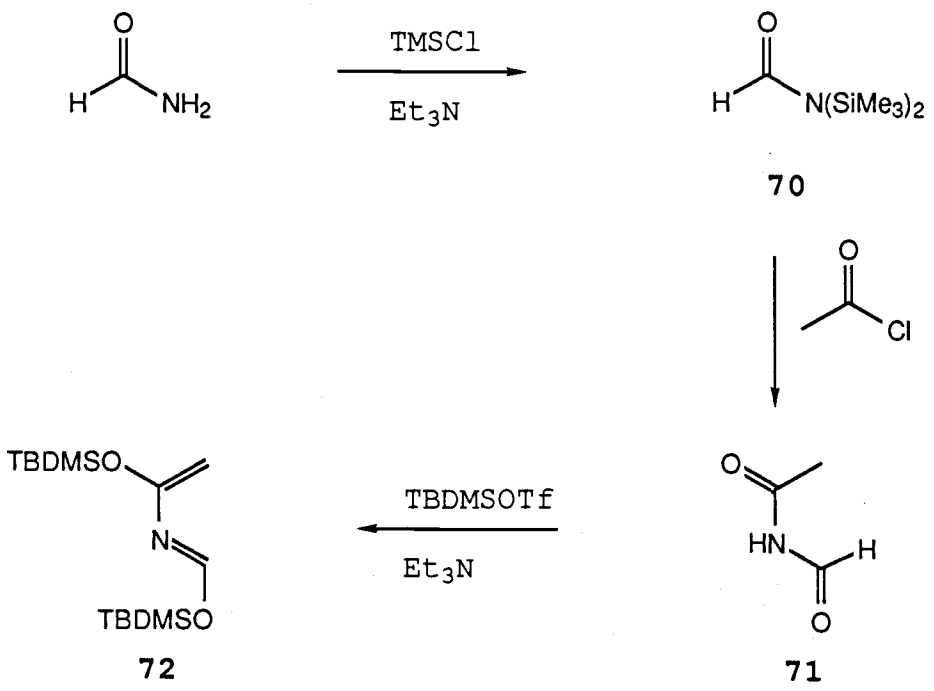


Figure 7. Diels-Alder reactions of **72**.

for 48 hours.[36] Thus, a diene to be used with either **48** or **54** should be highly reactive.

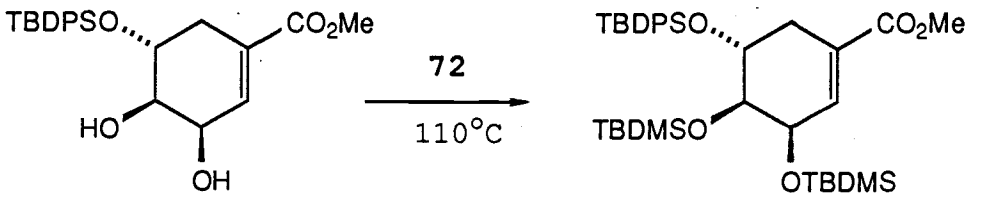
For this plan, the synthesis of a 2-azadiene was required. Ghosez has successfully prepared Diels-Alder cycloadducts of the bis(tert-butyldimethylsiloxy)-2-azabutadiene **72** with a number of dienophiles as shown in figure 7.[24] This same diene **72** appeared to be an ideal model for the purposes of our investigation. Accordingly, formamide



70 **71** **72**

was converted to the bis N-silylated amide **70** by reaction with two equivalents of trimethylsilyl chloride and an excess of triethylamine,[37] and imide **71** was then obtained by treatment of **70** with acetyl chloride.[38] Treatment of **71** with tert-butyldimethylsilyl chloride and triethylamine produced the labile azadiene **72**, which was used immediately in subsequent reactions.

Efforts to form a cycloadduct of **72** with either the ester **54** or the aldehyde **48** in refluxing chloroform produced no success. Starting materials were recovered unchanged in each case. When **54** was heated to 110°C with diene **72** in toluene, a 20% conversion to the tris-silylated ester **73** was obtained after an 80% recovery of starting materials. Although there was no evidence that

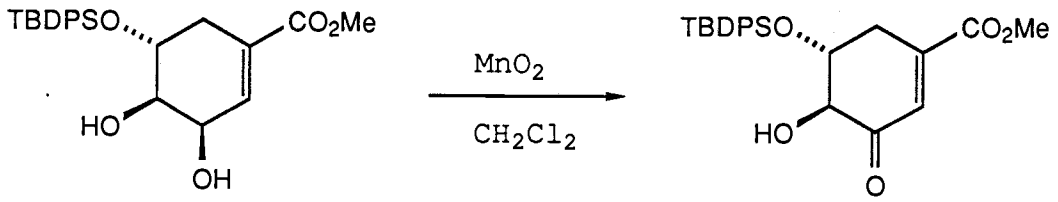


54 **73**

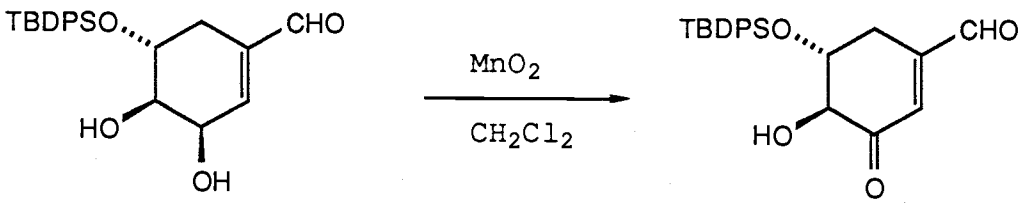
any cycloaddition had occurred, the observed silylation of **54** is not without precedence. Compounds similar to **72** have been employed as silylating agents in the past.[37]

The failure of **72** to undergo cycloaddition with **48** and **54** was tentatively rationalized on the basis of the low reactivity of these types of dienophiles as discussed above. Therefore, a modification to the shikimate system that would enhance its reactivity as a dienophile would clearly be advantageous.

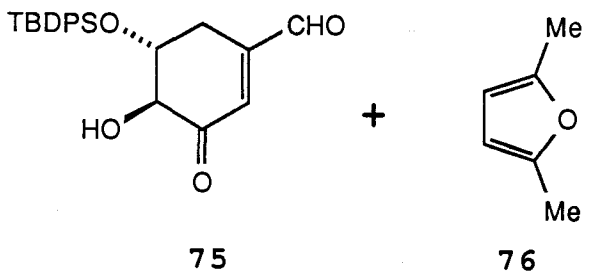
Tori has had success with Diels-Alder reactions of 3-carbomethoxyl-2-cyclohexenone (**79**). By heating **79** with 1,3-butadiene to 150°C in a sealed tube for two days, he obtained a 55% yield of **80**. Therefore, the dienophilic reactivity of the olefin of either **48** or **54** would undoubtedly be amplified if the C-3 alcohol were transformed to the corresponding ketone. Since the hydroxyl group at this position is allylic, it can be oxidized selectively, and treatment of **54** with an excess of manganese dioxide resulted in a 70% yield of ketoester **74**. The ketoaldehyde **75** was prepared in the same manner.



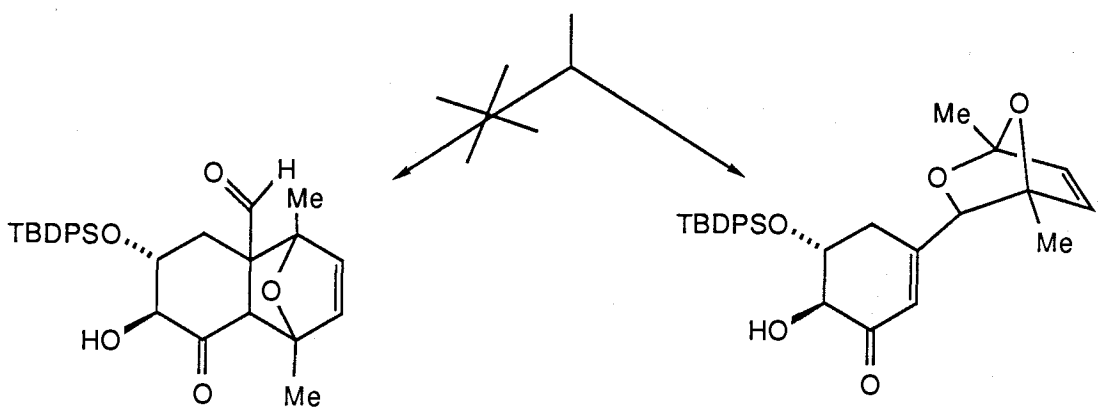
54 74



48 75



75 76



78 77

Unfortunately, the increased electrophilicity of these dienophiles did not change the outcome with **72**. No reaction between either **74** or **75** and **72** was observed in refluxing chloroform or refluxing toluene. In an attempt to determine whether these shikimate derivatives possessed any dienophilic properties at all, **75** was treated with 2,5-dimethylfuran (**76**). At temperatures up to 150°C in acetonitrile (sealed tube) no reaction took place between **75** and **76**. However, catalysis of the reaction with the Lewis acid boron trifluoride etherate produced adduct **77** in 54% yield after three hours at room temperature.

The unexpected occurrence of a Diels-Alder reaction at the aldehyde carbonyl was a sobering reminder of the extremely inert nature of the carbon-carbon double bond of these shikimate derivatives. A reasonable explanation for the formation of **77** rather than **78** is difficult to find. By any estimation the ketoaldehyde **75** should be an excellent dienophile when paired with an electron rich diene.

It is conceivable that the size of the tert-butyldiphenylsilyl protecting group in **75** hinders the approach of the diene to such an extent that pi overlap cannot be attained in the transition state. Figure 8 shows a conformation of **75** obtained by an MMX calculation which provides convincing evidence in support of this postulate. It can be seen that the approach trajectory of the diene

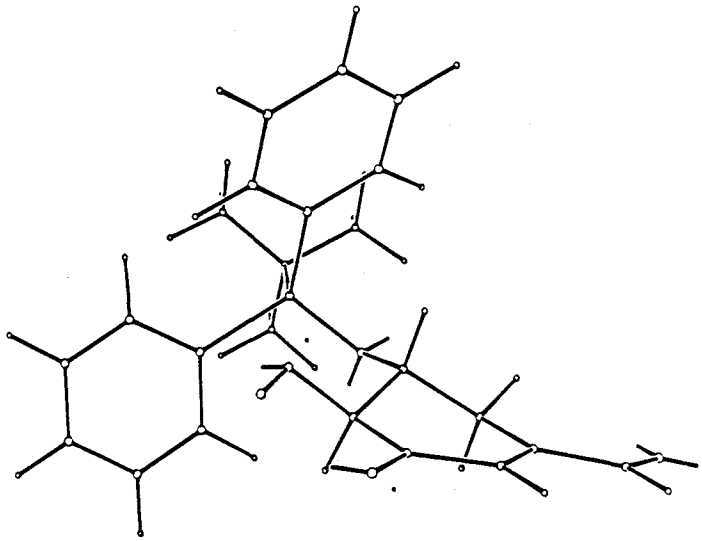


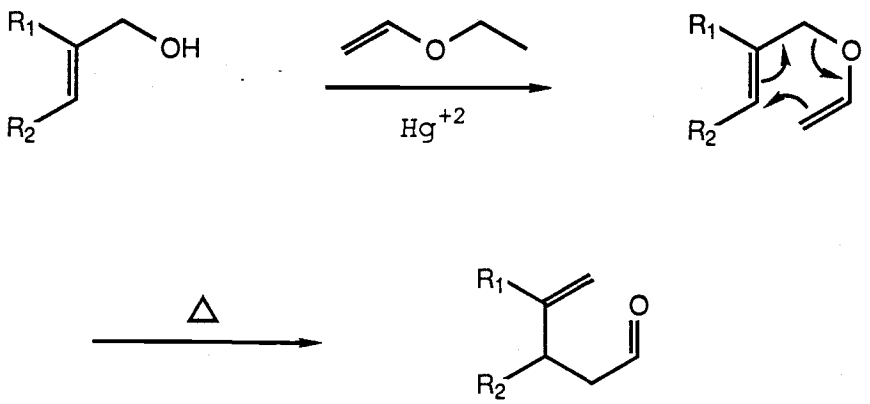
Figure 8. Diagram of **75** from MMX calculation.

for good orbital overlap in this cycloaddition would necessitate compression of the diene between the cyclohexenone ring and the other three substituents around silicon. The longer oxygen-silicon bond tends to exacerbate the crowding problem by allowing the two phenyl rings and the tert-butyl group to interfere with both faces of the cyclohexenone ring.

It had become painfully obvious from the foregoing results that a Diels-Alder strategy based on shikimate as either diene or dienophile was destined to failure. Consequently, a fundamentally different approach to synthesis of the koumine precursor **30** was considered. Since there appeared to be little hope of a single-step construction of the pyridine nucleus of **30**, a stepwise approach to this annulation seemed likely to be more

productive, and the synthetic plan was revised by taking a hard turn toward a sequence that elaborated the shikimate nucleus through attachment of a substituent at C-2.

In order to put the plan outlined above into practice, a protocol which would allow extension of the shikimate framework by attaching functionality at the C-2 carbon was required. This maneuver must be one which can overcome the steric hindrance associated with attack at this center and, at the same time, should provide some degree of stereoselectivity in the carbon-carbon bond forming step. Both of these factors suggested an intramolecular process, and a Claisen rearrangement[39] appeared to be an ideal method for accomplishing this objective.

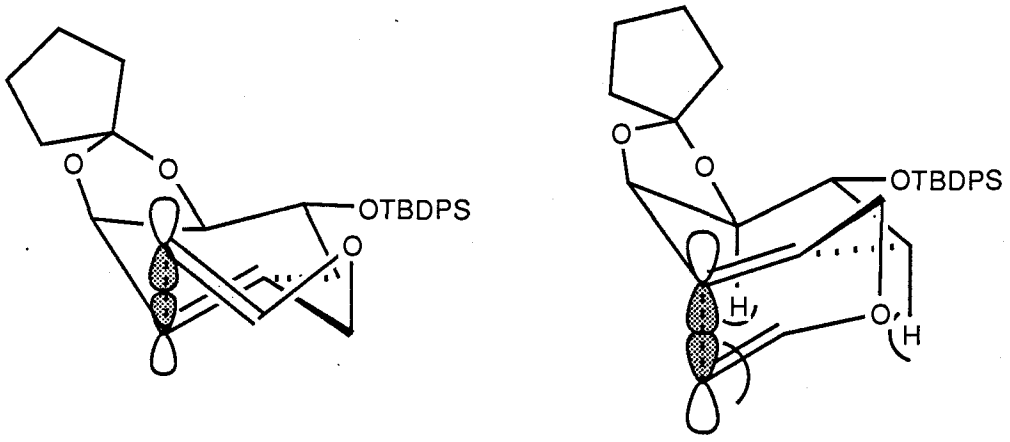


Scheme 2. Claisen rearrangement.

Scheme 2 presents a general view of this process using a vinyl ether derived from an allylic alcohol. The Claisen rearrangement of such a system results in an exocyclic methylene group and an aldehyde, each of which provides a

locus for further structural development. Our goal, therefore, was to exploit this rearrangement in the context of a suitable shikimate derivative such as **46**.

Transetherification of allylic alcohol **46** with ethyl vinyl ether was accomplished by refluxing the mixture in the presence of a catalytic amount of mercuric trifluoroacetate. This procedure gave the vinyl ether **81** as a colorless oil in 92% yield. When a neat sample of **81** was heated to 210°C for twenty minutes a quantitative conversion to a 3:1 mixture of the diastereomeric aldehydes **82** and **83** took place. The stereo selectivity observed in this reaction is a result of a bias toward one of two transition states, and figure 9 depicts two conformations of the vinyl ether which could intervene in the pericyclic rearrangement. The hexenyl ring of **81** is shown in a rigid twist chair conformation, in accord with both the predicted mode from the MMX calculation and the experimental findings of the x-ray crystal structure of **46**. Experiments modeled after those conducted on the Cope rearrangement by Doering and Roth have shown that the chair transition state is preferred in Claisen rearrangements.[41] Thus, if it is assumed that a chair-like conformation of the cyclic transition state is preferred to a boat conformation for the rearrangement of **81**, there are only two transition states, **81a** and **81b**, to consider. In **81b** two significant 1,3 steric interactions, one between the vinyl group and



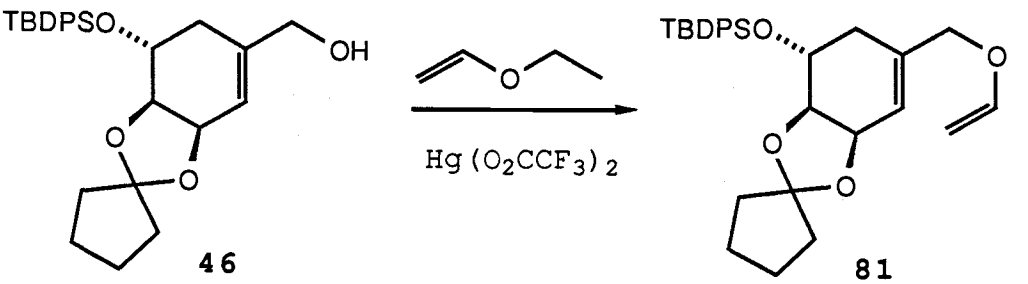
81a **81b**

Figure 9. Claisen rearrangement transition state.

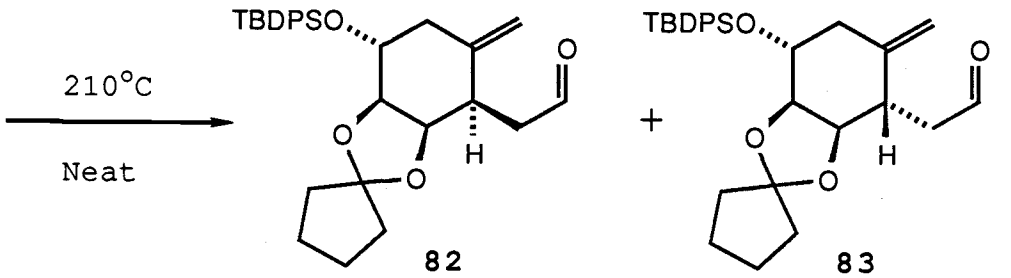
the C-4 hydrogen and the other between the oxygen and C-6 positions of the hexenyl ring, raise the energy of this pathway relative to **81a** where there are no such interactions. Transition state **81a** is that which leads to the major product **82**.

Our next objective was to append an α-methylene group adjacent to the aldehyde of **82**, so that release of the C-4 hydroxyl function from the cyclopentylidene ketal **84** would be followed by conjugate addition. This would set in place the tetrahydopyran ring of **30**, and hence of koumine, leaving construction of the piperidine nucleus until last.

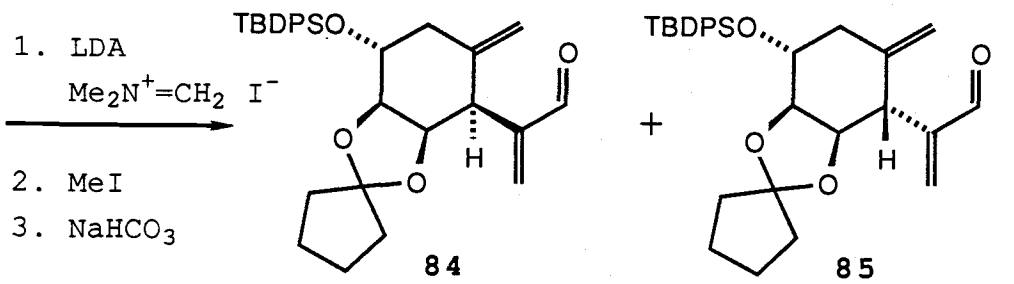
The inseparable mixture of **82** and **83** was subjected to methylenation using Eschenmoser's method.[40] Enolates of the pair of aldehydes were treated with N,N-dimethyl-



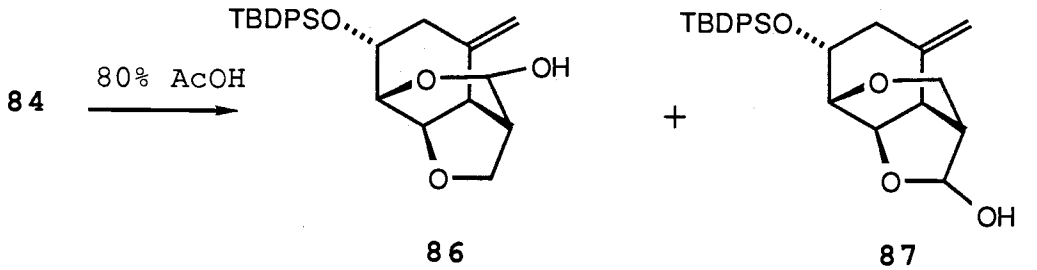
46 81



82 83



84 85



86 87

methyleneammonium iodide and the resulting tertiary amines were quaternized with methyl iodide. Elimination of the quaternary methiodides was accomplished with sodium bicarbonate and yielded **84** and **85** which were separated by flash chromatography.

Aldehyde **84** possesses the absolute configuration of the bisallyic, angular hydrogen required for koumine, and this stereoisomer was therefore exposed to conditions which were expected to remove the cyclopentylidene ketal. As expected, when **84** was hydrolyzed with 80% aqueous acetic acid the intermediate diol was not isolated, but instead a 2:1 mixture of products, which were assigned the structures **86** and **87**, was obtained.

The tentative assignment of structures **86** and **87** to the products of this reaction are based on ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and infrared spectra. A key feature of all three sets of spectral data is the absence of an aldehyde signal. This, combined with the presence of a ^{13}C peak at δ 103 and an infrared band at 1469 cm^{-1} supports the presence of an acetal. Although the ^{1}H NMR spectra of **86** and **87** show two signals at δ 4.72 and δ 4.94 and at δ 4.69 and δ 4.72 respectively, corresponding to the two protons on the exomethylene group at C-1 of the shikimate ring, there are no other olefinic proton signals in the spectra of either **86** or **87**. Taken with the fact that the ^{13}C spectra of these isomers show only two peaks

in the chemical shift region of a carbon-carbon double bond, these data are firm evidence that there is only one double bond in each compound. Therefore, it is reasonable to assume that conjugate addition of the C-3 and C-4 hydroxyl groups to the α,β-unsaturated aldehyde did, in fact, take place, and that this was followed by intramolecular acetal formation between the aldehyde and the remaining hydroxyl substituent.

The formation of both acetals was neither particularly surprising nor disappointing. Although **87**, containing the tetrahydropyran ring, is the more direct progenitor of **30**, schemes can be envisioned for utilizing **86** as well. Both acetals embody suitable functionality for building the piperidine ring, and both can therefore be considered useful intermediates for advancing the synthesis of koumine.

III. EXPERIMENTAL

General

(-)-Shikimic acid was obtained from Aldrich Chemical Company. Other starting materials and reagents were obtained from various commercial suppliers and used without further purification except as described in specific procedures. Solvents were dried by distillation from an appropriate drying agent prior to use. Toluene, tetrahydrofuran, and ether were distilled from potassium and benzophenone under an argon atmosphere. Pyridine, diisopropylamine, triethylamine, and dichloromethane were distilled from calcium hydride under argon. Methanol and solvents used for routine flash chromatography were glass distilled.

A rotary evaporator was used to remove solvents from reaction materials at water aspirator pressures which were typically between 12 and 20 torr. Residual solvent was removed by vacuum pump at pressures usually less than 0.5 torr. Glassware and other reaction apparatus were either oven dried at 160°C or flame dried under a stream of argon.

E. Merck neutral silica gel (230-400 mesh ASTM) was used for flash chromatography. All analytical thin layer chromatography (TLC) was conducted on either 1.75 x 7 or 2.5 x 7 cm precoated E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254).

Melting points were measured on a Buchi melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer model 243 polarimeter using a 1 decimeter cell with a 1 mL capacity at ambient temperature. Infrared (IR) spectra were measured with a Nicolet 5DXB FT-IR spectrometer. Ultraviolet spectra (UV) were obtained on a Cary-Varian 210 UV/Visible Spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were obtained with either an IBM NR-80F or a Bruker AM-400 spectrometer. Carbon (^{13}C) NMR spectra were obtained with a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR data are tabulated in order of: chemical shift, number of protons, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad), and coupling constant (J) in Hertz. Mass spectra (MS) were obtained from either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

Molecular mechanics calculations were performed on a VAX 11-750 computer using MODEL version KS 2.9 and MMX version 87 programs obtained from Serena Software, c/o Kosta Steliou, University of Montreal. X-ray crystallography was performed on a Rigaku AFC 6R single crystal x-ray diffractometer, and analysis of x-ray data was done with a

Micro-VAX minicomputer using TEXSAN Version 2.0 software available from Molecular Structure Corporation, College Station, Texas.

(-)-Methyl Shikimate (**33**)

(-)-Shikimic acid (1.003 g, 5.76 mmol) was added to 30 mL of methanol in a clean, scratch-free flask and was dissolved with heating. The colorless solution was cooled to 0°C and an ethereal solution of diazomethane (ca. 0.3 M) was slowly added until the reaction solution remained yellow (ca. 25 mL). The reaction mixture was allowed to stand at room temperature for 1 h, after which the solvent was evaporated under vacuum to yield 1.084 g (100%) of a colorless solid which required no further purification. Rf (ethyl acetate) 0.15; mp 113-114°C; $[\alpha]_D^{20}$ -138° (c 0.037, CH_3OH); IR (KBr) 3333, 1718, 1243 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.22 (dd, 1H, J=17, 6), 2.84 (dd, 1H, J=17, 5), 3.62 (dd, 1H, J=8, 4), 3.77 (s, 3H), 3.97 (bs, 4H), 4.39 (m, 1H), 4.39 (m, 1H), 6.85 (m, 1H); ^{13}C NMR (CD_3OD) δ 31.4, 52.2, 66.0, 66.7, 72.4, 130.2, 137.1, 167.6.

Methyl (3R,4S,5R)-3,4-O-Cyclopentylideneshikimate (**34**)

A solution of (-)-methyl shikimate (**33**, 1.008 g, 5.36 mmol), cyclopentanone (7.8 g, 92.7 mmol), and p-toluenesulfonic acid (10 mg, 0.006 mmol) in benzene (30 mL) was heated to reflux temperature for 3 h with water removal

via a Dean-Stark trap. After cooling to room temperature, 5 mL of saturated sodium bicarbonate was added and the mixture was stirred for an additional 15 min. The reaction mixture was added to 50 mL water in a separatory funnel and the organic layer was separated. The aqueous layer was extracted thrice with ether (3 x 30 mL), and all organic extracts were combined and washed with water (1 x 50 mL). The combined organic extract was dried over magnesium sulfate and boiled with decolorizing charcoal. After filtration through a bed of Celite, the solvent was evaporated and the residual oil was taken up in methylene chloride and boiled again with decolorizing charcoal. Filtration and solvent evaporation yielded an amber oil which was purified by flash chromatography (silica gel, 50% EtOAc in hexanes) yielding 1.287 g (94%) of **34** as a colorless oil: Rf (50% EtOAc in hexanes) 0.45; $[\alpha]_D^{20}$ -110° (c 0.021, CH_3OH); IR (neat, NaCl) 3473, 2957, 1721, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18-1.38 (8H, m), 2.25 (1H, m), 2.54 (1H, bs), 2.82 (1H, dd, J=12.9, 4.6), 3.78 (3H, s), 3.87 (1H, m, 4.04 (1H, dd, J=7.2, 6.8), 4.64 (1H, dd, J=6, 5), 6.95 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 23.7, 29.5, 36.9, 37.3, 52.1, 68.7, 72.3, 101.2, 119.5, 131.1, 133.7, 166.5. MS m/z 254(M^+), 226, 225, 193, 153, 139, 121, 109, 95, 85, 67, 59, 55, 53. Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.41%; H, 7.14%. Found: C, 61.30%; H, 7.15%.

Methyl (3R,4R,5R)-3,4-O-Cyclopentylidene-5-O-(t-butyldimethylsilyl)shikimate (**35**)

A solution of methyl (3R,4S,5R)-3,4-O-cyclopentylidene shikimate (**29**, 1.21 g, 4.76 mmol), t-butyldimethylsilyl chloride (760 mg, 5.04 mmol), and imidazole (1.40 g, 20 mmol) in dimethylformamide (6 mL) was stirred at 50°C for 3 h under nitrogen. The reaction mixture was then added to 30 mL water in a separatory funnel and extracted with ether (4 x 20 mL). The combined extracts were washed with water (3 x 20 mL) and dried over magnesium sulfate. Filtration through a bed of Celite/charcoal and solvent evaporation left an amber oil which was purified via flash chromatography (silica gel, 30% EtOAc in hexanes) to yield 1.694 g (97%) of **35** as a lightly yellow colored oil: Rf (30% ethyl acetate in hexanes) 0.7; $[\alpha]_D^{20}$ -71° (c 0.092, CH_3OH); IR (neat, NaCl) 2960, 1721, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.62 (m, 8H), 2.37 (m, 2H), 3.70 (s, 3H), 4.12 (m, 2H), 4.69 (m, 1H), 6.82 (m, 1H), 7.2-7.8 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.83, -4.70, 18.05, 23.20, 23.49, 25.76, 29.75, 36.97, 37.38, 52.02, 68.69, 72.26, 76.91, 119.25, 129.83, 134.29, 166.99. MS m/z 368 (M^+), 291, 199, 181, 153, 125, 93, 77. Anal. Calcd. for $C_{19}H_{32}O_5Si$: C, 61.92%; H, 8.75%. Found: C, 62.02%; H, 8.81%.

Propargyl Aldehyde

A three necked, 1 L flask was fitted with an addition funnel, a capillary tube for introduction of nitrogen near the bottom of the flask, and an exit tube connected to an aspirator through a series of three cold traps and a manometer. Into the flask were placed propargyl alcohol (38 g, 0.68 mol), 80 mL of water, and a cooled (0°C) solution consisting of 45 mL of conc. sulfuric acid in 65 mL of water. The reaction vessel was cooled to -8°C in an ice/salt bath and stirred magnetically. While the solution was cooling, the first cold trap was cooled to -20°C with dry ice in 30% isopropanol/water and the second and third traps were cooled to -78°C with Dry Ice and acetone. The system pressure was reduced to 45 torr by water aspiration controlled by a needle valve, and nitrogen was bubbled through the solution. A precooled (0°C) solution of 70 g of chromium trioxide in 130 mL water and 45 mL of conc. sulfuric acid was then added dropwise over 2 h while maintaining reaction temperature at about 0°C. Following complete addition of chromium trioxide, the reaction mixture was allowed to warm to room temperature and the pressure was reduced to 20 torr. After an additional 30 min, the condensates from the three cold traps were combined and distilled at atmospheric pressure to give 11.51 g (32%) of propargyl aldehyde as a colorless liquid: bp 53-54°C (lit.[32] 54-57°C); IR (neat) 2100, 1671 cm^{-1}; ^{1}H NMR (400

MHz, $CDCl_3$) δ 3.62 (1H, s), 9.21 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.6, 83.1, 176.8.

1-Formyl-1,4-cyclohexadiene (**37**)

Under an argon atmosphere, a solution of boron trifluoride etherate (1.4 mL, 8.5 mmol) in 5 mL of ether was added dropwise over 15 min to a solution of propargyl alcohol (**31**, 1.96 g, 36.3 mmol) in 25 mL of ether with stirring. The resulting solution was stirred at room temperature for an additional 20 min, after which a saturated solution of 1,3-butadiene in benzene (25 mL, ca 100 mmol) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for 3 h, then cooled to 0°C and saturated sodium bicarbonate (25 mL) was added. The mixture was placed in a separatory funnel and the organic layer was separated. The organic layer was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with water (2 x 20 mL) and dried over magnesium sulfate. The resulting yellow oil was purified by flash chromatography (1:2 ethyl acetate-hexanes) yielding 1.61 g (41%) of **37** as a colorless oil: Rf (1:2 ethyl acetate-hexanes) 0.61; IR (neat) 1685, 1634 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 2.91 (4H, m), 5.73 (2H, m), 6.80 (1H, m), 9.48 (1H, s).

1-(N,N-Dimethylhydrazonylmethyl)-1,4-cyclohexadiene (**38**)

To a solution of **37** (0.68 g, 6.3 mmol) in 25 mL of methanol was added 1,1-dimethylhydrazine (0.7 g, 11 mmol). The resulting solution was stirred under nitrogen for 1 h. Solvent removal at reduced pressure left an amber residue. Purification by flash chromatography (1:2 ethyl acetate-hexanes) afforded 0.74 g (78%) of **33** as a light yellow oil: Rf (1:2 ethyl acetate-hexanes) 0.70; IR (neat) 3027, 2955, 2820, 1687, 1025 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.81 (6H, s), 2.90 (4H, m), 5.77 (3H, m), 7.02 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.85, 46.23, 47.10, 122.78, 128.87, 130.82, 135.55, 142.09; MS m/z 151(M+1), 150(M^+), 149, 148, 106, 91, 79, 78, 77, 59. Anal. Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65; Found: C, 71.86; H, 9.30; N, 18.93.

2,3-Dicarbomethoxy-1-(N,N-dimethylhydrazonylmethyl)-5-bicyclo[2.2.2]octene (**40**)

A solution of **38** (103 mg, 0.68 mmol) and maleic anhydride (70 mg, 0.71 mmol) in 20 mL of toluene was heated to reflux for 17 h. Solvent was removed under reduced pressure and replaced with methanol. This solution was refluxed for 12 h, after which it was cooled to room temperature and treated with an ethereal solution of diazomethane (25 mL) until the color of the solution remained yellow. Solvent evaporation and flash chromatography (1:2 ethyl acetate-hexanes) gave 30 mg (11%) of **40** as a yellow oil. Rf (1:2

ethyl acetate-hexanes): 0.40; UV (MeOH) λ_{max} 243 nm (4210); IR (neat) 1739, 1725, 1569, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (2h, m), 1.68 (2H, m), 2.71 6H, s), 2.97, (1H, dddd, J= 5.1, 4.5, 2.8, 2.1), 3.10 (1H, dd, J= 2.0, 10.0), 3.26 (1H, d, J= 10.0), 3.53 (3H, s), 3.57 (3H, s), 6.44 (1H, dd, J= 4.5, 1.4), 6.69 (1H, d, J= 1.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 30.8, 32.7, 42.8, 43.0, 48.8, 51.0, 51.5, 52.3, 131.7, 133.0, 138.9, 172.3, 173.0; Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21%; H, 7.53%; N, 9.52%. Found: C, 61.42%; H, 7.43%; N, 9.41%.

(3R,4R,5R)-1-Hydroxymethyl-3,4-O-Cyclopentylidene-5-O-(t-butyldimethylsilyl)cyclohexene (**42**)

To a stirred solution of methyl (3R,4R,5R)-3,4-O-cyclopentylidene-5-O-(t-butyldimethylsilyl)shikimate (**35**, 100 mg, 0.27 mmol) in toluene (20 mL), cooled to -78°C under an argon atmosphere, was added 3.5 mL of diisobutylaluminum hydride (0.55 mL, 1M in hexane, 0.55 mmol) . The reaction mixture was stirred at -78°C for 3 h after which time 0.5 mL of saturated sodium chloride and 0.5 mL of methanol was added and the mixture was allowed to warm to room temperature. To this was added 2 g of magnesium sulfate, and the resulting slurry was stirred for 1 h. Filtration of the solution through a bed of Celite and solvent evaporation yielded 82 mg (89%) of **42** as a colorless oil which required no further purification. Rf (30% ethyl acetate in hexanes)

0.55; $[\alpha]_D^{20}$ -39° (c 0.049, CH_3OH); IR (neat, NaCl) 3350, 2956, 1249, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (3H, s), 0.11 (3H, s), 0.89 (9H, s), 1.58 (1H, bt, J= 6.9), 1.60-1.73 (8H, m), 2.18 (2H, ddd, J= 13.2, 5.4, 2.1), 3.88 (2H, dd, J= 8.9, 6.9), 3.98 (1H, ddd, 5.4, 2.9, 2.1), 4.54 (1H, dd, J= 2.9, 1.6), 5.79 (1H, d, J= 1.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.58, -4.60, 19.58, 23.29, 23.58, 26.78, 31.65, 36.11, 36.56, 64.76, 71.21, 72.99, 78.01, 119.53, 133.29, 139.01.

(3R,4R,5R)-3,4-O-Cyclopentylidene-5-O-(t-butyldimethylsilyl)shikimaldehyde **43**

A mixture of (3R,4R,5R)-1-hydroxymethyl-3,4-O-cyclopentylidene-5-O-(t-butyldimethylsilyl)cyclohexene (**42**, 650 mg, 1.91 mmol), pyridinium chlorochromate (575 mg, 2.67 mmol), and dichloromethane (30 mL) was stirred at room temperature for 3 h. The resulting dark brown heterogeneous solution was added to 50 mL water in a separatory funnel, shaken, and separated. The aqueous layer was extracted with ether (3 x 30 mL) and all organic extracts were combined, dried over magnesium sulfate, and boiled with decolorizing charcoal. Filtration through a bed of Celite and solvent evaporation produced an amber oil which was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to yield 628 mg (97%) of **43** as a colorless oil: Rf (30% EtOAc in hexanes) 0.67; $[\alpha]_D^{20}$ -42° (c 0.083, CH_3OH); IR (neat, NaCl) 2956, 1694, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05

(3H, s), 0.09 (3H, s), 0.85 (9H, s), 1.64-1.80 (8H, m), 2.29 (1H, ddd, J = 12.4, 4.0, 1.2), 2.45 (1H, ddd, J = 12.4, 4.2, 1.3), 4.08 (1H, dd, J = 5.4, 3.9), 4.11 (1H, dd, J = 5.4, 3.4), 4.76 (1H, ddd, J = 5.3, 3.4, 1.7), 6.65 (1H, dd, J = 1.8, 1.7), 9.54 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.91, -4.86, 17.93, 23.14, 23.45, 25.64, 26.21, 36.93, 37.34, 67.94, 71.90, 77.13, 119.53, 139.07, 144.02, 193.63; MS m/z 339(M^+), 311, 267, 228, 227, 195, 167, 141, 89, 75, 73.

(3R,4R,5R)-3,4-O-Cyclopentylidene-5-O-(t-butyldimethylsilyl)-1-(N,N-dimethylhydrazonylmethyl)cyclohexene **44**

To a solution of (3R,4R,5R)-3,4-O-cyclopentylidene-5-O-(t-butyldimethylsilyl)shikimaldehyde (**43**, 105 mg, 0.31 mmol) in 10 mL of methanol was added 1,1-dimethylhydrazine (20 mg, 0.33 mmol). The reaction mixture was stirred for 3 h after which TLC indicated complete consumption of **43**. Solvent evaporation yielded an amber oil which was purified by flash chromatography (silica gel, 30% EtOAc in hexanes). This produced 101 mg (86%) of hydrazone **44** as a light yellow gummy solid: Rf (30% ethyl acetate in hexanes) 0.75; $[\alpha]_D^{20}$ -42° (c 0.053, CH_3OH); IR (neat, NaCl) 2955, 1623, 1580, 1100, 830 cm^{-1}; ^1H NMR (400 Mhz, $CDCl_3$) δ 0.09 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.65-1.88 (8H, m), 2.18 (1H, dd, J = 17.1, 8.6), 2.75 (1H, dd, J = 17.1, 4.5), 2.87 (6H, s), 3.87 (1H, ddd, J = 7.6, 4.5, 2.1), 3.97 (1H, dd, J = 7.6, 5.0), 4.64 (1H, dd, J = 5.0, 2.7), 5.76 (1H, d, J = 2.7), 6.93

(1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.5, 18.2, 23.1, 23.5, 25.9, 30.2, 36.9, 37.4, 42.7, 69.9, 73.4, 78.6, 118.6, 122.3, 134.4, 138.2; MS m/z 381(M+1), 380(M^+), 336, 278, 240, 239, 194, 167, 137, 129, 111, 75, 73, 59, 55. Anal. Calcd. for $C_{20}H_{36}N_2O_3Si$: C, 63.12; H, 9.53; N, 7.36. Found: C, 63.42; H, 9.59, N, 7.58.

Methyl (3R,4R,5R)-3,4-O-Cyclopentylidene-5-O-(t-butyldiphenylsilyl)shikimate **45**

A solution of methyl (3R,4S,5R)-3,4-O-cyclopentylidene shikimate (**34**, 1.186 g, 4.66 mmol), t-butyldiphenylsilyl chloride (1.4 g, 5.1 mmol), and imidazole (1.5 g, 22 mmol) in dimethylformamide (10 mL) was stirred at 50°C for 2 h. The reaction mixture was then added to 50 mL water in a separatory funnel and extracted with ether (4 x 30 mL). The combined extracts were washed with water (3 x 20 mL) and dried over magnesium sulfate. Filtration through a bed of Celite/charcoal and solvent evaporation left an amber oil which was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to yield 2.29 g (100%) of **40** as a lightly yellow colored oil. Rf (30% ethyl acetate in hexanes) 0.7; $[\alpha]_D^{20}$ -17° (c 0.068, CH_3OH); IR (neat, NaCl) 2960, 1721, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.59-1.74 (8H, m), 2.37 (2H, m), 3.70 (3H, s), 4.12 (1H, dd, J = 5.6, 5.5), 4.18 (1H, dd, J = 5.5, 4.2), 4.74 (1H, m), 6.87 (1H, d, J = 3.0), 7.35-7.74 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ

19.0, 19.2, 23.2, 23.4, 26.6, 26.9, 28.9, 37.0, 37.3, 51.9, 69.1, 72.0, 76.1, 119.3, 127.6, 127.7, 129.2, 129.6, 129.8, 133.4, 133.8, 134.6, 134.8, 135.3, 135.7, 135.9, 167.0. MS m/z 436, 435, 352, 351, 273, 245, 213, 199, 181, 135. Anal. Calcd. for $C_{29}H_{36}O_5Si$: C, 70.70%; H, 7.37%. Found: C, 71.00%; H, 7.35%.

(3R,4R,5R)-1-Hydroxymethyl-3,4-O-cyclopentylidene-5-O-(t-butyldiphenylsilyl)cyclohexene **46**

To a stirred solution of methyl (3R,4R,5R)-3,4-O-cyclopentylidene-5-O-(t-butyldiphenylsilyl)shikimate (**45**, 850 mg, 1.7 mmol) in toluene (25 mL), cooled to -78°C under an argon atmosphere, was added a 1M solution of diisobutylaluminum hydride (3.5 mL, 3.5 mmol) in hexane. The reaction mixture was stirred at -78°C for 3 h, after which 1 mL of saturated sodium chloride and 1 mL of methanol was added and the mixture was allowed to warm to room temperature. To this mixture was added 4 g of magnesium sulfate, and the resulting slurry was stirred for 1 h. Filtration of the solution through a bed of Celite, and solvent evaporation yielded 607 mg (76%) of **46** as a colorless oil which required no further purification: Rf (30% ethyl acetate in hexanes) 0.50; $[\alpha]_D^{20}$ -29° (c 0.039, CH_3OH); IR (neat, NaCl) 3387, 2934, 1468, 1108, 703 cm^{-1}; ^1H NMR (400 Mhz, $CDCl_3$) δ 1.07 (9H, s), 1.28 (1H, bt, J = 7.1), 1.58-1.75 (8H, m), 1.97 (2H, d, J = 6.0), 3.87 (2H, dd, J =

14.1, 7.1), 3.94 (1H, dd, J = 6.6, 6.4), 4.10 (1H, dd, J = 6.7, 6.6), 4.57 (1H, dd, J = 6.7, 3.3), 5.74 (1H, dd, J = 3.3, 1.8), 7.33-7.43 (6H, m), 7.64 (2H, dd, J = 6.4, 1.1), 7.73 (2H, dd, J = 6.4, 1.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 23.1, 23.4, 26.6, 27.0, 31.6, 36.9, 37.1, 65.8, 70.2, 72.8, 77.8, 118.3, 118.7, 127.5, 127.6, 127.7, 129.6, 129.7, 133.6, 134.4, 134.8, 135.8, 136.1, 139.8. Anal. Calcd. for $C_{28}H_{36}O_4Si$: C, 72.37%; H, 7,80%. Found: C, 72.40%; H, 7.80%.

(3R,4R,5R)-3,4-O-Cyclopentylidene-5-O-(t-butyldiphenylsilyl)shikimaldehyde (**47**)

A mixture of (3R,4R,5R)-1-hydroxymethyl-3,4-O-cyclopentylidene-5-O-(t-butyldiphenylsilyl)cyclohexene (**46**, 530 mg, 1.14 mmol), pyridinium chlorochromate (300 mg, 1.39 mmol), and dichloromethane (20 mL) was stirred at room temperature for 3 h. The resulting dark brown heterogeneous solution was added to 50 mL of water in a separatory funnel and the organic layer was separated. The aqueous layer was extracted with ether (3 x 30 mL) and all organic extracts were combined, dried over magnesium sulfate, and boiled with decolorizing charcoal. Filtration through a bed of Celite and solvent evaporation produced an amber oil which was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to yield 515 mg (98%) of **47** as a colorless oil: Rf (30% EtOAc in hexanes) 0.70; $[\alpha]_D^{20}$ -38° (c 0.075, CH_3OH);

IR (neat, NaCl) 2958, 1691, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 1.58-1.72 (8H, m), 2.26 (1H, dd, J = 12.9, 2.0,), 2.34 (1H, dd, J = 12.9, 4.2,), 4.15 (1H, dd, J = 5.3, 5.2), 4.20 (1H, dd, J = 5.2, 4.5), 4.81 (1H, dd, J = 4.8, 1.0), 6.65 (1H, bd, J = 1.0), 7.33-7.44 (6H, m), 7.56-7.73 (4H, m), 9.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.20, 23.15, 23.43, 25.54, 26.89, 36.99, 37.32, 50.69, 68.53, 71.82, 76.75, 119.63, 129.58, 129.93, 133.36, 133.43, 134.84, 135.42, 135.80, 135.86, 138.81, 144.27, 193.74. Anal. Calcd. for $C_{28}H_{34}O_4Si$: C, 72.69%; H, 7.41%. Found: C, 72.61%; H, 7.40%.

(3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)shikimaldehyde (**48**)

A solution of (3R,4R,5R)-3,4-O-cyclopentylidene-5-O-(t-butyldiphenylsilyl)shikimaldehyde (**47**, 225 mg, 0.49 mmol) in 10 mL of 80% acetic acid was stirred at 56°C for 12 h. Removal of solvent as an azeotrope with cyclohexane yielded 160 mg (82%) of **48** as a colorless oil which required no further purification: Rf (50% EtOAc in hexanes) 0.20; $[\alpha]_D^{20}$ -98° (c 0.032, CH_3OH); IR (neat, NaCl) 3421, 3398, 2954, 2859, 1685, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s), 2.23 (1H, dd, J = 18.2, 4.6), 2.39 (1H, ddd, J = 18.2, 4.5, 2.1), 2.42 (1H, bs), 2.62 (1H, bs), 3.85 (1H, dd, J = 4.6, 4.5), 4.17 (1H, ddd, J = 6.3, 4.6, 4.5), 4.71 (1H, bs), 6.63 (1H, bd, J = 1.7), 7.35-7.46 (6H, m), 7.60 (2H, d, J = 6.5), 7.64 (2H, dd, J = 6.2, 1.1), 9.48 (s, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 19.16, 26.92, 27.19, 66.38, 69.20, 71.57, 127.82, 127.92, 130.06, 133.14, 133.31, 135.64, 135.70, 139.44, 146.34, 193.52. MS m/z 396(M^+), 368, 355, 309, 277, 217, 199, 125, 77, 28. Anal. Calcd. for $C_{23}H_{28}O_4Si$: C, 69.66%; H, 7.12%. Found: C, 69.71%; H, 7.10%.

(3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-3-O-(methylmaleoyl)-shikimaldehyde (**49**) and (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-4-O-(methylmaleoyl)shikimaldehyde (**50**)

A mixture of (3R,4R,5R)-5-O-(t-butyldiphenylsilyl)-shikimaldehyde (**48**, 140 mg, 0.35 mmol), maleic anhydride (35 mg, 0.36 mmol), and pyridine (40 mg, 0.5 mmol) in 10 mL of dichloromethane was stirred at room temperature for 24 h. The solvent was removed at reduced pressure, and the residual oil was dissolved in a mixture of 5 mL of ether and 5 mL of methanol. To the resulting homogeneous solution was added 5 mL of an ethereal solution of diazomethane (ca 0.2M, 1 mmol) and the reaction mixture was allowed to stand at room temperature for 1 h. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (silica gel, 50% EtOAc in hexanes) to yield 128 mg (72%) of an inseparable 2:1 mixture of **49** and **50** as a colorless oil: Rf (50% EtOAc in hexanes) 0.40 and 0.44; IR (neat, NaCl) 3496, 3415, 1719, 1713, 1694, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):

49: δ 1.05 (9H, s), 2.36 (2H, m), 3.42 (1H, bs), 3.74 (3H, s), 4.26 (1H, ddd, J = 4.9, 4.5, 2.6), 4.43 (1H, m), 6.05 (1H, bd, J = 3.1), 6.23 (1H, d, J = 12.2), 6.45 (1H, d, J = 12.2), 6.61 (1H, bd, J = 1.5), 7.35-7.45 (6H, m), 7.58-7.70 (4H, m), 9.54 (1H, s).

50: δ 1.04 (9H, s), 2.28 (1H, dd, J = 14.3, 4.6), 2.41 (1H, bs), 2.44 (1H, dd, J = 14.3, 4.3), 3.70 (3H, s), 4.29 (1H, ddd, 6.1, 4.6, 4.3), 4.97 (1H, m), 5.18 (1H, dd, J = 6.1, 3.9), 5.88 (1H, d, J = 11.9), 6.06 (1H, d, J = 11.9), 6.68 (1H, bd, J = 1.7), 7.35-7.45 (6H, m), 7.58-7.70 (4H, m), 9.51 (1H, s).

(3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-4-hydroxyl-3-O-(methylmaleoyl)-1-(N,N-dimethylhydrazonylmethyl)cyclohexene (**51**), (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-3-hydroxyl-4-O-(methylmaleoyl)-1-(N,N-dimethylhydrazonylmethyl)cyclohexene (**52**), and (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-3,4-hydroxyl)-1-(N,N-dimethylhydrazonylmethyl)cyclohexene (**53**)

A 2:1 mixture of aldehydes **49** and **50** (50 mg, 0.098 mmol) was dissolved in 5 mL of methanol under an argon atmosphere. To this solution was added 1,1-dimethylhydrazine (10 mg, 0.16 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum and the residual oil was purified by flash chromatography (silica gel, 50% EtOAc in hexanes). This method produced 20 mg

(37%) of a 2:1 mixture of hydrazones **46** and **47** and 20 mg (46%) of hydrazone **48** (83% overall).

48: Rf (50% EtOAc in hexanes) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 2.19 (1H, dd, J = 15.3, 5.6), 2.42 (1H, bs), 2.55 (1H, bs), 2.65 (1H, J = 15.3, 4.7), 2.83 (6H, s), 3.74 (1H, m), 4.27 (1H, ddd, 7.2, 5.6, 4.6), 4.49 (1H, m, J = 2.1, 1.7), 5.70 (1H, bd, J = 2.1), 6.83 (1H, s), 7.33-7.44 (6H, m), 7.69 (4H, m).

46 and **47**: Rf (50% EtOAc in hexanes) 0.65 and 0.75. IR (neat, NaCl) 3411, 3387, 1712, 1705, 1576, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.78 (1H, bs), 2.33 (1H, dd, J = 15.1, 4.8), 2.75 (1H, dd, J = 15.1, 5.5), 2.83 (6H, s), 3.84 (3H, s), 4.51 (1H, m), 4.62, (1H, dd, J = 5.5, 3.2), 5.59 (1H, bd, J = 2.1), 5.91 (1H, d, J = 11.9), 6.51 (1H, d, J = 11.9), 6.88 (1H, s), 7.32-7.43 (6H, m), 7.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.55, 27.09, 39.86, 43.74, 51.13, 51.99, 62.61, 73.39, 111.92, 123.00, 126.19, 127.10, 127.68, 127.93, 129.74, 129.84, 132.63, 135.11, 135.76, 136.10, 169,20, 170.58.

Methyl (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)shikimate (**54**)

A solution of methyl (3R,4R,5R)-3,4-O-cyclopentylidene-5-O-(t-butyldiphenylsilyl)shikimate (**45**, 315 mg, 0.64 mmol) in 20 mL of 80% acetic acid/water was stirred at 60°C for 24 h. Solvent removal under vacuum produced a light yellow oil. Purification by column chromatography (silica gel, 30%

EtOAc in hexanes) yielded 250 mg (92%) of **49** as a colorless, viscous oil: Rf (50% EtOAc in hexanes) 0.48; $[\alpha]_D^{20}$ -25°; IR (neat, NaCl, cm^{-1}) 758, 1106, 1256, 1715, 2955, 3429. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 2.25 (1H, dd, J = 18.2, 4.3), 2.45 (1H, ddd, J = 18.2, 4.0, 1.8), 3.68 (3H, s), 3.77 (1H, dd, J = 6.1, 4.3), 4.16 (1H, dd, J = 4.5, 1.8), 4.56 (1H, m), 6.77 (1H, bd, J = 1.7), 7.33-7.43 (6H, m), 7.61 (2H, dd, J = 7.9, 1.4) 7.65 (2H, dd, J = 7.9, 1.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.27, 27.00, 30.30, 51.95, 66.29, 69.48, 71.26, 127.82, 127.96, 129.67, 130.02, 130.08, 133.46, 133.56, 135.77, 135.84, 136.72, 167.02; MS m/z 426(M^+), 389, 387, 200, 199, 181, 153, 135, 125, 93, 77, 57. Anal. Calcd. for $C_{24}H_{30}O_5Si$: C, 67.57%; H, 7.09%. Found: C, 67.03%; H, 7.37%.

Methyl (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-3-O-(O-methylsuccinoyl)shikimate (**55**) and Methyl (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-4-O-(O-methylsuccinoyl)shikimate (**56**)

A solution of methyl (3R,4R,5R)-5-O-(t-butyldiphenylsilyl) shikimate (**54**, 50 mg, 0.12 mmol), succinic anhydride (12 mg, 0.12 mmol), and triethylamine (12 mg, 0.12 mmol) in dichloromethane was stirred at room temperature for 24 h. Solvent evaporation left a viscous amber oil which was purified by flash chromatography (silica gel, 30% EtOAc in hexanes). This method yielded 62 mg (98%) of an inseparable 5:3 mixture of **55** and **56** as a colorless,

viscous oil: Rf (50% EtOAc in hexanes) 0.70; IR (neat, NaCl, cm^{-1}) 1108, 1249, 1725, 1740, 3483, 3508.

50: ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 2.27- 2.68 (7H, m), 3.77 (3H, s), 3.84 (3H, s), 4.04 (1H, m), 4.18 (1H, ddd, J = 8.1, 4.6, 2.1), 5.80 (1H, bs), 6.74 (1H, bs), 7.33-7.45 (6H, m), 7.57-7.68 (4H, m).

51: ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (9H, s), 2.27- 2.68 (7H, m), 3.62 (3H, s), 3.86 (3H, s), 4.28 (1H, m), 4.73 (1H, m), 5.11 (1H, dd, J = 7.3, 6.3), 6.84 (1H, bs), 7.33-7.45 (6H, m), 7.57-7.68 (4H, m).

Diethyl 2-(N-Methylamino)fumarate (**61a**) and Diethyl 2-(N-Methylamino)maleate (**61b**)

Sodium diethyl oxaloacetate (6.4 g, 0.03 mol) was dissolved by heating in ethanol (100 mL). In a separate flask, charged with ethanol (50 mL), was dissolved methylamine hydrochloride (2 g, 0.031 mol). The two solutions were mixed (with magnetic stirring) and heated to 70°C until a white precipitate formed, at which point the resulting slurry was allowed to stand at room temperature for 1 h. Solvent evaporation produced a light yellow solid which was redissolved in 100 mL water, placed in a separatory funnel, and extracted with ether (5 x 50 mL). The organic extracts were dried over magnesium sulfate and filtered through a bed of Celite. Solvent evaporation yielded 4.24 g (70%) of an inseparable 1.3 : 1 mixture of

61a and **61b** respectively as a yellow oil: Rf (30% ethyl acetate in hexanes) 0.35 and 0.40; IR (neat, NaCl) 3350, 3318, 2983, 1736, 1695, 1661, 1607, 1271.

61a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2), 1.34 (3H, t, J = 7.2), 3.02 (3H, d, J = 5.3), 4.12 (2H, q, J = 7.2), 4.29 (2H, q, J = 7.2), 5.07 (1H, s), 8.01 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.04, 14.44, 30.23, 59.28, 61.88, 86.59, 152.58, 163.69, 170.33.

61b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.2), 1.34 (3H, t, J = 7.2), 3.02 (3H, d, J = 5.3), 4.12 (2H, q, J = 7.2), 4.29 (2H, q, J = 7.2), 4.67 (1H, s), 4.92 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.85, 14.04, 31.63, 59.41, 62.25, 84.59, 153.02, 166.46, 167.41.

Diethyl 2-Aminofumarate (**62a**) and Diethyl 2-Aminomaleate (**62b**)

In 75 mL of ethanol were dissolved 4.0 g (0.02 mol) of sodium diethyl oxaloacetate. In a separate flask, charged with 25 mL ethanol, was dissolved ammonium chloride (1.1 g, 0.021 mol) and the two solutions were mixed (with magnetic stirring) and heated to 70°C until a white precipitate formed. The slurry was stirred at room temperature for 1 h. Solvent evaporation produced a light yellow solid which was redissolved in 50 mL water, placed in a separatory funnel, and extracted with ether (5 x 30 mL). The combined organic extracts were dried over magnesium sulfate and filtered

through a bed of Celite. Solvent evaporation yielded 2.62 g (76%) of a 2.5:1 mixture of Z and E enamines **62a** and **62b** respectively as a yellow oil: Rf (30% ethyl acetate in hexanes) 0.25 and 0.35; IR (neat, NaCl) 3469, 3349, 2984, 1728, 1678, 1620, 1293.

62a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.2), 1.34 (3H, t, J = 7.2), 4.17 (2H, q, J = 7.2), 4.31 (2H, q, J = 7.2), 5.51 (1H, s), 7.00-7.89 (2H, vbs).

62b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (3H, t, J = 7.2), 1.34 (3H, t, J = 7.2), 3.96 (1H, s), 4.17 (2H, q, J = 7.2), 4.31 (2H, q, J = 7.2), 7.00-7.89 (2H, vbs).

(3R,4R,5R)-3,4-O-Cyclopentylidene-1-[4-carboethoxyl-3-(N-methylamino)-2-[5H]-furanonyl]-5-(t-butyldiphenylsiloxyl)-cyclohexene (**63**)

A solution of (3R,4R,5R)-3,4-O-cyclopentylidene-5-O-(t-butyldimethylsilyl)shikimaldehyde (**43**, 90 mg, 0.266 mmol) and a 1.3 : 1 mixture of diethyl 2-(N-methyl)aminolfumarate and diethyl 2-(N-methyl)aminomaleate (**60a** and **60b**, 55 mg, 0.273 mmol) in 15 mL of ethanol was stirred at room temperature for 1 h. Two drops of a saturated solution of sodium ethoxide in ethanol were then added and the solution immediately darkened. After standing at room temperature for 3 h, the solution was added to 50 mL of water in a separatory funnel. The pH was adjusted to 7 with 0.1 N HCl and the solution was extracted with ether (3 x 30 mL). The

organic extracts were combined and dried over magnesium sulfate. Solvent evaporation resulted in a dark oil which was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to yield 52 mg (40%) of an inseparable 1 : 1 diastereomeric mixture of **63** as a colorless oil. Rf (30% ethyl acetate in hexanes) 0.55; IR (neat, NaCl) 3357, 2955, 1771, 1684, 1645, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (3H, s), 0.05 (3H, s), 0.07 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 0.91 (9H, s), 1.25 (3H, t, J = 7.2), 1.63-1.86 (9H, m), 1.98-2.09 (1H, m), 3.29 (3H, d, J = 5.3), 3.79 (1H, m), 3.95 (1H, m), 3.98 (2H, q, J = 7.2), 4.18 (2H, q, J = 7.2), 4.20 (1H, m), 4.53 (1H, m), 4.59 (1H, m), 5.39 (1H, s), 5.42 (1H, s), 5.91 (1H, bd, J = 1.1), 5.93 (1H, bd, J = 1.1), 6.50 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.82, -4.65, 14.22, 18.02, 23.10, 23.40, 25.76, 28.94, 36.99, 37.40, 60.06, 69.18, 72.69, 77.62, 81.65, 105.53, 118.99, 125.72, 134.37, 164.23, 167.34. MS m/z 449, 436, 392, 352, 308, 262, 235, 184, 129, 110, 75, 77. Anal. Calcd. for $C_{25}H_{39}NO_7Si$: C, 60.82%; H, 7.96%; N, 2.84%. Found: C, 61.10%; H, 8.19%; N, 2.42%.

Bis-(trimethylsilyl)formamide (**70**)

To a solution of formamide (2.1 g, 48 mmol) and triethylamine (11 g, 108 mmol) in toluene (18 mL), was added chlorotrimethylsilane (10.4 g, 96 mmol) dropwise over 30 min. A white precipitate formed immediately. The stirred

mixture was heated to 90°C for 1 h. After cooling to room temperature, the precipitate was filtered off under an argon atmosphere. Solvent was removed from the filtrate by rotary evaporator and the residual oil was distilled at reduced pressure to give 7.1 g (78%) of **70** as a colorless liquid: bp (25 torr) 69-70°C (lit. bp (13 torr) 54-55°C)[37]; IR (neat, NaCl) 3297, 2958, 2898, 1660, 1255, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (18H, s), 8.46 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.18, 171.71; MS m/z 189(M^+), 117, 103, 102, 76, 75, 73.

N-Formylacetamide (**71**)

Acetyl chloride (0.82 g, 10.4 mmol) was cooled to -8°C in an ice-salt bath. Stirring was commenced and bis-(trimethylsilyl)-formamide (**70**, 1.97 g, 10.4 mmol) was added dropwise at a rate of ca. one drop every two seconds. An exothermic reaction took place and a yellow solid was formed. The reaction mixture was warmed to room temperature and stirred for an additional h. The remaining clear liquid was removed directly from the reaction vessel by attaching the flask to a water aspirator and stirring until only a yellow solid remained. The solid was recrystallized from n-heptane to give 0.72 g (79%) of **71** as colorless needles: mp 84-85°C (lit. mp 85-86°C)[38]; IR (neat, NaCl) 3278, 3205, 2955, 1746, 1693, 1488, 1374, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s), 9.09 (1H, d, J = 5.2), 9.32 (1H, bs);

^{13}C NMR (100 MHz, $CDCl_3$) δ 23.71, 163.32, 170.67; MS m/z 87 (M^+), 57, 43, 29.

1,3-Di-(t-butyldimethylsilyloxyl)-2-aza-1,3-butadiene (**72**)

To a solution of **71** (25 mg, 0.29 mmol) and triethylamine (60 mg, 0.59 mmol) in ether and under argon was added t-butyldimethylsilyl triflate (152 mg, 0.58 mmol). The homogeneous solution was stirred at room temperature for 1 h. Solvent removal left an amber oil which was subjected to distillation at reduced pressure to give 72 mg (79%) of **72** as a colorless liquid: bp (0.1 torr) 80°C (lit. b.p. (0.06 torr) 76°C)[24]; IR (neat, NaCl) 2955, 1693, 1650, 1469, 1255, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.35 (6H, s), 0.87 (9H, s), 0.91 (9H, s), 2.18 (3H, s), 3.82 (1H, s), 4.05 (1H, s), 7.91 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.91, -4.35, 8.64, 26.09, 26.69, 46.79, 121.35, 158.83, 167.08, 184.55.

Methyl (3R,4R,5R)-5-O-(t-Butyldiphenylsilyl)-3,4-O-(di-t-butyldimethylsilyl)shikimate (**73**)

A solution of **54** (20 mg, 0.047 mmol) and **72** (15 mg, 0.048 mmol) in toluene was refluxed for 20 h. Little change in starting material was detected by TLC with the exception of a new, less polar spot. The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography led to recovery of 16 mg (80%) of **54** and 5 mg

(17%) of **73**: Rf ((1:2 ethyl acetate-hexanes) 0.75; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.12 (6H, s), 0.82 (9H, s), 0.91 (9H, s), 0.93 (9H, s), 2.31 (1H, dd, J = 15.6, 3.2), 2.45 (1H, dd, J = 15.6, 4.3), 3.68 (1H, m), 3.73 (3H, s), 4.26 (1H, m), 4.67 (1H, m), 6.67 (1H, bs), 7.31-7.43 (6H, m), 7.52, (2H, d, J = 8.9), 7.61 (2H, d, J = 8.9).

(4S,5R)-1-Carbomethoxyl-4-hydroxyl-2-oxo-5-(t-butyldiphenylsiloxyl)cyclohexene (**74**)

To a solution of **54** (30 mg, 0.070 mmol) in dichloromethane (5 mL) was added manganese dioxide (60 mg, 0.69 mmol). The black slurry was stirred for 2 h at room temperature, after which it was filtered through silica gel (4 g) in a sintered glass funnel. The solvent was removed from the filtrate and the residual amber oil was purified by flash chromatography (1:2 ethyl acetate-hexanes) to give 21 mg (70%) of **74** as a colorless oil: Rf (1:2 ethyl acetate-hexanes) 0.59; $[\alpha]_D^{20}$ -20° (c 0.078, CH_3OH); IR (neat, NaCl) 3500, 3070, 2956, 1727, 1691, 1432, 1246, 1114 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, s), 2.59 (1H, ddd, J = 18.0, 8.4, 2.1), 2.82 (1H, dd, J = 18.0, 4.8), 3.40 (1H, d, J = 3.4), 3.77 (3H, s), 3.94 (1H, ddd, J = 8.4, 4.8, 3.4), 4.26 (1H, dd, 8.4, 3.1), 6.76 (1H, d, J = 3.0), 7.35-7.45 (6H, m), 7.71 (2H, dd, J = 8.0, 1.8) 7.76 (2H, dd, J = 8.0, 1.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.68, 19.40, 26.95, 34.17, 46.81, 52.87, 73.62, 79.56, 127.64, 127.79, 129.89, 129.96,

130.75, 136.02, 136.19, 146.78, 165.66, 199.32; Anal. Calcd. for $C_{24}H_{28}O_5Si$: C, 67.90%; H, 6.65%. Found: C, 67.88%; H, 6.71%.

(4S,5R)-1-Formyl-4-hydroxyl-2-oxo-5-(t-butyldiphenyl-siloxyl)cyclohexene (**75**)

A mixture of **48** (140 mg, 0.35 mmol) and manganese dioxide (500 mg, 5.75 mmol) in dichloromethane (10 mL) was stirred for 2 h at room temperature. The suspension was then filtered through silica gel (6 g) and charcoal (2 g) in a sintered glass funnel. The solvent was removed from the filtrate and the residual oil was purified by flash chromatography (1:2 ethyl acetate-hexanes) to give 105 mg (76%) of **75** as a colorless oil: Rf (1:2 ethyl acetate-hexanes) 0.55; $[\alpha]_D^{20}$ -24° (c 0.082, CH_3OH); IR (neat, NaCl) 3489, 3065, 2957, 1694, 1468, 1427, 1247, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (9H, s), 2.44 (1H, ddd, J = 18.4, 9.5, 3.0), 2.79 (1H, dd, J = 18.0, 5.2), 3.36 (1H, bs), 3.94 (1H, ddd, J = 10.1, 5.2, 4.8), 4.33 (1H, d, 10.1), 6.60 (1H, d, J = 3.0), 7.35-7.47 (6H, m), 7.70 (2H, dd, J = 8.0, 1.8), 7.75 (2H, dd, J = 8.0, 1.8), 9.69 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.37, 26.92, 30.74, 73.48, 80.17, 127.62, 127.79, 129.88, 130.00, 132.90, 133.49, 135.92, 136.10, 136.26, 151.69, 192.16, 199.39; Anal. Calcd. for $C_{23}H_{26}O_4Si$: C, 70.02%; H, 6.64%. Found: C, 70.12%; H, 6.60%.

Reaction of **75** with 2,5-dimethylfuran. Preparation of **77**.

To a solution of ketoaldehyde **75** (10 mg, 0.025 mmol) in benzene (2 mL) was added boron trifluoride etherate (7 mg, 0.05 mmol) and the resulting solution was stirred at room temperature for 15 min. An excess of 2,5-dimethylfuran (100 mg, 1.04 mmol) was then added and the darkened solution was stirred for 3 h. The reaction mixture was then added to water (10 mL), saturated sodium bicarbonate (3 mL), and ether (13 mL) in a separatory funnel and shaken. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The organic extracts were combined, washed with water (2 x 10 mL), and dried over anhydrous magnesium sulfate. Filtration and solvent evaporation gave a dark residue which was purified by flash chromatography (1:4 ethyl acetate-hexanes) to furnish 7 mg (56%) of **77** as a colorless oil: Rf (1:2 ethyl acetate-hexanes) 0.71; $[\alpha]_D^{20}$ -18° (c 0.075, CH_3OH); IR (neat, NaCl) 3473, 2955, 1674, 1627, 1110; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (9H, s), 2.01 (3H, s), 2.04 (3H, s), 2.19 (1H, dd, J = 18.1, 5.5), 2.33 (1H, dd, J = 18.1, 6.3), 3.61 (1H, bs), 3.94 (1H, ddd, J = 9.1, 6.3, 5.5), 4.02 (1H, s), 4.19 (1H, d, 9.1), 5.53 (1H, s), 5.57 (1H, s), 5.88 (1H, s), 7.29-7.43 (6H, m), 7.63 (2H, dd, J = 8.0, 2.1) 7.71 (2H, dd, J = 8.0, 2.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.51, 13.50, 19.26, 26.88, 38.11, 39.96, 74.04, 78.99, 106.25, 119.13, 123.41, 127.49, 127.52,

127.71, 129.65, 129.70, 134.79, 135.78, 136.14, 165.56, 198.92.

(3R,4R,5R)-1-(Ethylenoxymethyl)-3,4-O-(cyclopentylidene)-5-(t-butyldiphenylsilyloxyl)cyclohexene (**81**)

To a stirred solution of allylic alcohol **46** (45 mg, 0.097 mmol) in ethyl vinyl ether (20 mL, freshly distilled from calcium hydride) at 0°C was added mercuric trifluoroacetate (20 mg, 0.046 mmol) in one portion. The mixture was allowed to warm to room temperature and was then heated to reflux. After refluxing for 24 h, TLC indicated complete consumption of **46**. The solvent was removed at reduced pressure, and the resulting yellow residue was redissolved in 15% ethyl acetate in hexanes (5 mL). The cloudy solution was then filtered through silica gel (2 g) in a 20 mL sintered glass funnel. Solvent evaporation produced a lightly colored oil which was chromatographed (silica gel, 15% ethyl acetate in hexanes) to yield 44 mg (92%) of **81** as a colorless oil: Rf (15% ethyl acetate in hexanes) 0.61; $[\alpha]_D^{20}$ -37° (c 0.098, CH_3OH); IR (neat, NaCl) 2959, 1638, 1614, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.59-1.74 (8H, m), 2.00 (2H, m), 3.97-4.10 (4H, m, J = 6.6, 5.7), 4.13 (1H, dd, J = 5.7, 5.6), 4.17 (1H, dd, J = 14.1, 2.0), 4.59 (1H, m), 5.77 (1H, m), 6.36 (1H, dd, J = 14.1, 6.6), 7.33-7.43 (6H, m), 7.64 (2H, dd, J = 8.0, 1.4), 7.64 (2H, dd, J = 8.0, 1.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ

19.28, 23.14, 23.40, 26.96, 31.48, 37.05, 37.25, 69.91, 71.06, 72.69, 77.41, 87.38, 118.78, 120.97, 127.51, 127.58, 129.67, 133.59, 134.37, 135.42, 135.83, 136.03, 151.33. Anal. Calcd. for $C_{30}H_{38}O_4Si$: C, 73.43; H, 7.81. Found: C, 73.62; H, 7.85.

1-[(1R,2R,3R,4R)-2,3-O-(Cyclopentylidene)-4-(t-butyldiphenylsilyloxyl)-6-methylenylcyclohexane]acetaldehyde (**82**) and
1-[(1S,2R,3R,4R)-2,3-O-(Cyclopentylidene)-4-(t-butyldiphenylsilyloxyl)-6-methylenylcyclohexane]acetaldehyde (**83**)

(3R,4R,5R)-1-(Ethylenoxymethyl)-3,4-O-(cyclopentylidene)-5-(t-butyldiphenylsilyloxyl)cyclohexene (**81**, 30 mg, 0.061 mmol) was transferred into a 10 mL round bottom flask. After complete removal of residual solvents, the air was purged with argon and the flask was mounted on a bulb-to-bulb distillation apparatus. The vessel containing neat **81** was then heated to 210°C for 20 min. After cooling, a small portion of the oil was dissolved in chloroform. TLC indicated complete transformation of starting material to a more polar substance (one spot). Chromatography (1:6 ethyl acetate-hexanes) yielded 29 mg (97%) of a colorless oil which consisted of an inseparable 3 : 1 mixture of diastereomers **82** and **83** respectively: Rf (15% ethyl acetate in hexanes) 0.37; IR (neat, NaCl) 2959, 1725, 1429,

1108 cm^{-1}; MS m/z 469, 445, 362, 361, 283, 253, 199, 197, 135, 91.

82: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.54-1.81 (8H, m), 2.16 (1H, dd, J = 14.0, 5.2), 2.33 (1H, dd, J = 14.0, 3.6), 2.66 (2H, ddd, J = 10.3, 7.0, 2.2), 2.79 (1H, dt, J = 7.0, 1.0), 3.84 (1H, ddd, J = 7.4, 5.2, 3.6), 3.87 (1H, m), 4.19 (1H, dd, J = 8.4, 3.6), 4.72 (1H, s), 4.82 (1H, s), 7.36-7.45 (6H, m), 7.63-7.70 (4H, m), 9.74 (1H, t, J = 2.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.25, 23.33, 23.47, 26.95, 37.38, 37.50, 38.14, 40.10, 44.45, 70.15, 77.95, 78.72, 111.78, 118.67, 127.62, 127.71, 129.78, 129.81, 133.70, 133.80, 135.83, 142.45, 201.71.

83: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.54-1.81 (8H, m), 2.13 (1H, dd, J = 14.2, 5.8), 2.33 (1H, dd, J = 14.2, 3.3), 2.79 (2H, m), 3.30 (1H, m), 3.81 (1H, dd, J = 4.2, 3.3), 4.12 (1H, dd, J = 6.2, 4.2), 4.25 (1H, dd, J = 6.3, 3.3), 4.67 (1H, s), 4.70 (1H, s), 7.36-7.45 (6H, m), 7.63-7.70 (4H, m), 9.86 (1H, t, J = 1.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.19, 23.03, 23.79, 26.56, 35.13, 36.23, 36.47, 36.99, 43.69, 71.24, 76.68, 78.07, 111.01, 118.60, 127.58, 127.62, 129.65, 129.78, 133.70, 133.86, 134.79, 142.84, 201.71.

2-[1-[(1R,2R,3R,4R)-2,3-O-(Cyclopentylidene)-4-(t-butyldiphenylsilyloxyl)-6-methylenylcyclohexane]acraldehyde (**84**)

n-Butyllithium (1.30M, 0.095 mL, 0.12 mmol) was added to a stirred solution of diisopropylamine (12 mg, 0.12 mmol) in tetrahydrofuran (2 mL) at -78°C under argon. The mixture was warmed to 0°C for 10 min and then recooled to -78°C. After this solution had stirred for 45 min, a 3 : 1 mixture of aldehydes **82** and **83** (55 mg, 0.11 mmol) in tetrahydrofuran (2 mL) was added dropwise over 2 min. After 45 min, this solution was cannulated into a slurry of N,N-dimethylmethylenammonium iodide (50 mg, 0.27 mmol) in tetrahydrofuran (2 mL) which had been washed with solvent (3 x 5 mL THF). The resulting mixture was stirred at -78°C for 1 h then warmed to room temperature and stirred for an additional 17 h. The solvent was evaporated and replaced with methanol (3 mL), and iodomethane (1 g, 7.0 mmol) was added. The amber mixture was stirred at room temperature for 20 h, after which the solvents were removed and replaced with dichloromethane (2 mL) and saturated sodium bicarbonate (2 mL). The heterogeneous mixture was stirred at room temperature for 22 h, then placed in a separatory funnel with water (15 mL) and extracted with ether (3 x 15 mL). The organic extracts were combined, washed with water (1 x 15 mL), and dried over magnesium sulfate. Solvent evaporation left an amber oil which was purified by flash

chromatography (15% ethyl acetate in hexanes) to yield 27 mg (49%) of **84** and 4 mg (7%) of **85** as colorless oils.

84: Rf (15% ethyl acetate in hexanes) 0.35; $[\alpha]_D^{20}$ -12° (c 0.067, CH_3OH); IR (neat, NaCl) 2959, 1697, 1468, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.56-1.79 (8H, m), 2.20 (1H, dd, J = 13.4, 3.8), 2.37 (1H, dd, J = 13.4, 2.1), 3.51 (1H, d, J = 8.5), 3.97 (1H, dd, J = 5.0, 4.5), 4.23 (1H, ddd, J = 4.5, 3.8, 2.1), 4.27 (1H, dd, J = 8.5, 5.0), 4.57 (1H, s), 4.73 (1H, s), 6.35 (1H, s), 6.42 (1H, s), 7.35-7.45 (6H, m), 7.65-7.71 (4H, m), 9.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.28, 23.46, 23.57, 26.96, 37.57, 37.64, 38.08, 43.41, 70.29, 77.31, 78.63, 112.43, 118.67, 127.61, 129.76, 133.76, 133.88, 134.79, 135.84, 136.16, 141.58, 148.29, 193.62.

Deprotection of **84**. Preparation of Exomethylene tricyclic acetals (**86**) and (**87**)

A solution of **84** (20 mg, 0.040 mmol) in 80% acetic acid (2 mL) was stirred at 55°C for 24 h. Solvents were removed under vacuum and the residual oil was chromatographed (1:2 ethyl acetate-hexanes) to yield 10 mg (57%) of **72** and 4 mg (23%) of **73** as colorless oils.

86: Rf (30% ethyl acetate in hexanes) 0.15; IR (neat NaCl) 3390, 2956, 1469, 1428, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.88 (1H, ddd, J = 8.4, 7.2, 1.8), 2.23 (1H, dd, J = 14.5, 6.2), 2.29 (2H, m), 2.46 (1H, d, J = 2.1),

2.69 (1H, dd, J = 8.5, 4.1), 3.04 (1H, d, J = 3.6), 3.81 (1H, m), 3.94 (2H, m), 4.27 (1H, ddd, J = 7.3, 2.1, 1.8), 4.72 (1H, s), 4.94 (1H, s), 7.35-7.46 (6H, m), 7.65-7.72 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.31, 27.05, 32.39, 38.42, 44.29, 72.69, 73.80, 81.58, 103.98, 113.45, 127.61, 127.76, 129.81, 129.97, 133.64, 133.76, 135.71, 135.85, 144.44; MS m/z 389,349, 253, 199, 181, 163, 139, 105, 91.

87: Rf (30% ethyl acetate in hexanes) 0.20; IR (neat NaCl) 3395, 2955, 1467, 1422, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.85 (1H, ddd, J = 8.1, 3.2, 2.5), 2.10 (1H, dd, J = 15.3, 6.2), 2.32 (1H, dd, J = 8.1, 4.1), 2.35 (1H, dd, J = 15.3, 5.4), 2.50 (1H, d, J = 1.9), 2.84 (1H, d, J = 5.4), 3.68 (1H, ddd, J = 12.4, 4.5, 1.5), 3.86 (1H, ddd, J = 12.4, 6.2, 2.5), 4.09 (2H, m), 4.22 (1H, ddd, J = 7.5, 4.3, 1.9), 4.69 (1H, s), 4.72 (1H, s), 7.33-7.45 (6H, m), 7.59-7.73 (4H, m).

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