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DIELS-ALDER CHEMISTRY AND SYNTHETIC APPLICATIONS OF 4,4-DISUBSTITUTED 2-CYANO-2,5-CYCLOHEXADIENONES

by

JUDY YIP

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1998

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled DIELS-ALDER CHEMISTRY AND SYNTHETIC APPLICATIONS OF 4,4-DISUBSTITUTED 2-CYANO-2,5-CYCLOHEXADIENONES submitted by JUDY YIP in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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For my parents

Abstract

Chapter 1 of this thesis is divided into two parts. The first part describes the Diels-Alder chemistry of 2-cyano-4,4-dimethyl-2,5-cyclohexadienone **62**. Dienone **62** was found to add rapidly to a variety of conjugated dienes under zinc chloride catalysis. Product yields were generally high and ranged from 80-98% with one exception. The regio- and stereochemical outcomes were in general quite predictable with a few exceptions. The regiochemistry follows the *ortho*- and *para*-rules and the stereoselectivity follows the *endo*-to-ketone addition and *cis*-principle.

The second part of Chapter 1 details a facile method for the reductive alkylation of α-cyano ketones using lithium naphthalenide. Adducts prepared from the Diels-Alder reaction of dienone **62** were treated with lithium naphthalenide. The ensuing enolate ions were readily trapped with a variety of alkylating reagents to provide angularly substituted bicyclic compounds. In most cases, the reductive alkylation provided a product in which the stereochemistry of the ring-junction was exclusively *cis*.

The second chapter presents the application of the newly developed reductive alkylation process in the formal syntheses, in racemic form, of two *cis*-clerodanes, 6β-2-oxokolavenool (**10**) and 2-oxo-5α,8α-13,14,15,16-tetranor-clerod-3-en-12-oic acid (**11**). An intermolecular Diels-Alder reaction of cyano activated dienophile **47** with trans-1,3-pentadiene under zinc chloride catalysis gave mainly the desired adduct **48**. A simple one step method for the introduction of the angular methyl group using lithium naphthalenide and methyl iodide afforded compound **52** in high yield. Conjugate addition of

lithium dimethylcuprate to **52** in the presence of bromotrimethylsilane followed by hydrolysis of the resulting silyl enol ethers afforded a mixture of diastereomers **54** and **55**. Conversion of the *tert*-butyldiphenylsilyl protecting group of **54** to a benzyl protecting group gave ketone **25**, a key intermediate in the syntheses of *cis*-clerodane diterpenoids **10** and **11**.

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First, I would like to thank my research director, Dr. H.J. Liu, for his support, wisdom, and encouragement throughout this Ph.D. program. His guidance and help over the years is much appreciated.

I would also like to thank all the members of our research group with whom I've had a chance to work with. They have provided a very sociable and enjoyable working environment.

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List of Abbreviations

Ac	Acetyl
ap	anti-phase
APT	Attached Proton Test
Bn	Benzyl
br	broad
Bu	butyl
calcd.	calculated
cat.	catalytic amount
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEG	Diethylene Glycol
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
equiv.	equivalent
Et	ethyl
FTIR	Fourier Transform Infrared Spectroscopy
GGPP	Geranyl Geranyl Pyrophosphate
hr	hour
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
J	coupling constant

IR	Infrared Spectroscopy
LDA	Lithium Diisopropylamide
m	multiplet
M	Molar
M^+	Molecular ion
m-CPBA	*m*-Chloroperoxybenzoic Acid
Me	Methyl
MHz	Megahertz
min	minute
mmol	millimole
mol	mole
mp	melting point
Ms	Mesyl
m/z	mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
p	para
p	phase
PP	Pyrophosphate
p-TsOH	*p*-Toluenesulfonic Acid
Ph	Phenyl
py	pyridine
q	quartet
R	generalized alkyl group or substituent
r.t.	room temperature
s	singlet

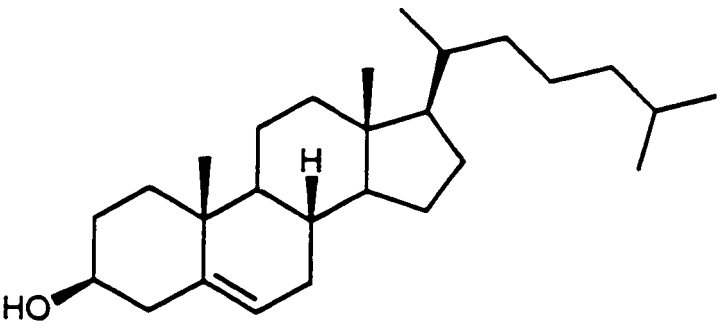
SET	Single Electron Transfer
t	tertiary
t	triplet
tlc	thin-layer chromatography
TBAF	Tetrabutylammonium Fluoride
TBDMS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
TBDPSCl	*t*-Butyldiphenylsilyl chloride
THF	Tetrahydrofuran
TPP	5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine

Chapter One

Diels-Alder Chemistry of 2-Cyano-4,4-dimethyl-2,5-cyclohexadienone and Reductive Alkylation

Introduction

The cycloaddition of dienes with olefins (dienophiles) to give cyclohexenes, better known as the Diels-Alder reaction[1], is a general process for the rapid preparation of polycyclic compounds. The reaction has been used in the syntheses of a variety of natural products. A few examples include the syntheses of steroids such as cholesterol **1**[2], sesquiterpenes such as (-)-khusimone **2**[3], alkaloids such as (+)-luciduline **3**[4] and quassinoids such as (±)-quassin **4**[5-7].



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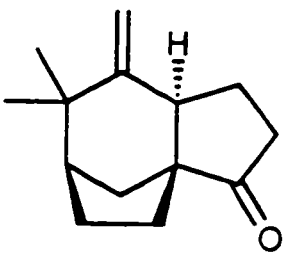

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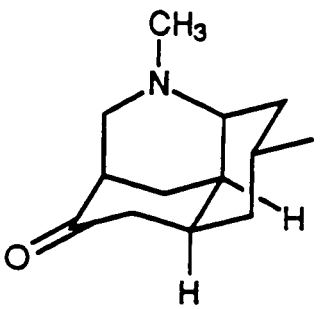

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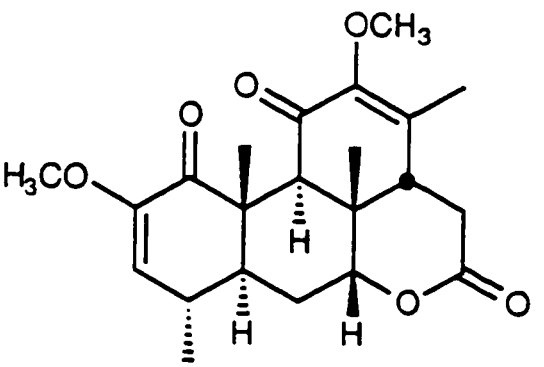
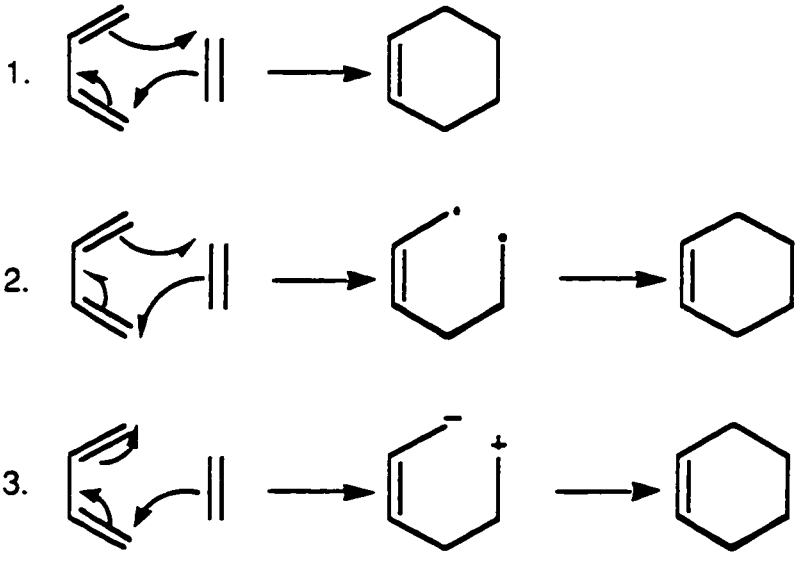


4

The detailed mechanism of the reaction has been investigated extensively[8]. There have been three proposed mechanisms (**Scheme 1-1**). These include a concerted reaction mechanism which occurs in one step with no intermediate.

The second mechanism involves a diradical mechanism in which one end of the diene attaches to one end of the dienophile. The last mechanism is similar to the second mechanism except that bond formation involves the movement of a pair of electrons to form a diion intermediate.

Scheme 1-1

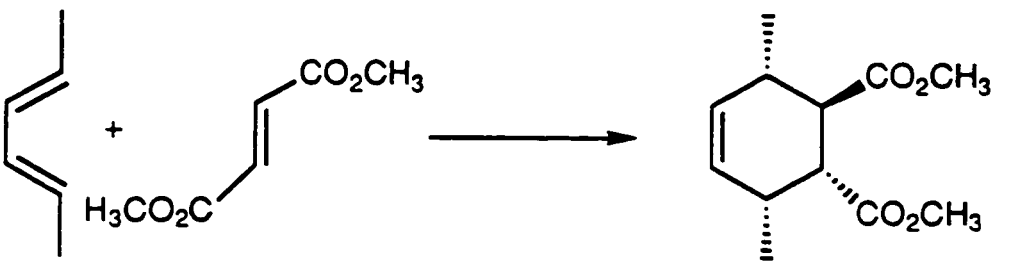


A concerted one-step reaction mechanism is generally the most accepted reaction mechanism for the Diels-Alder reaction[9,10]. This mechanism is supported by the fact that the reaction is highly stereospecific in which the configuration of the reactants is retained in the product. The other two proposed mechanisms, namely the diradical and the diion mechanism, would not be able to retain the configuration of its reactants in the final product.

The reaction may be concerted, but it may not be synchronous, whereby both new sigma bonds are formed to the same extent in the transition state. Woodward and Hoffmann's Orbital Symmetry Conservation theory[11] predicts

that the suprafacial approach [$\pi_{4s} + \pi_{2s}$] of diene and dienophile is symmetry allowed and therefore can be a synchronous reaction. Houk[12] and Gajewski[13] support the argument that in nearly symmetrical dienes and dienophiles, a concerted reaction mechanism with a highly unsymmetrical transition state occurs through a pathway that is nearly synchronous. On the other hand, Dewar[9,10] argues that the reaction occurs via an unsymmetrical transition state and a biradical intermediate in a two-step reaction mechanism in which the two new sigma bonds are formed at two different stages of the reaction, with one being rate-determining.

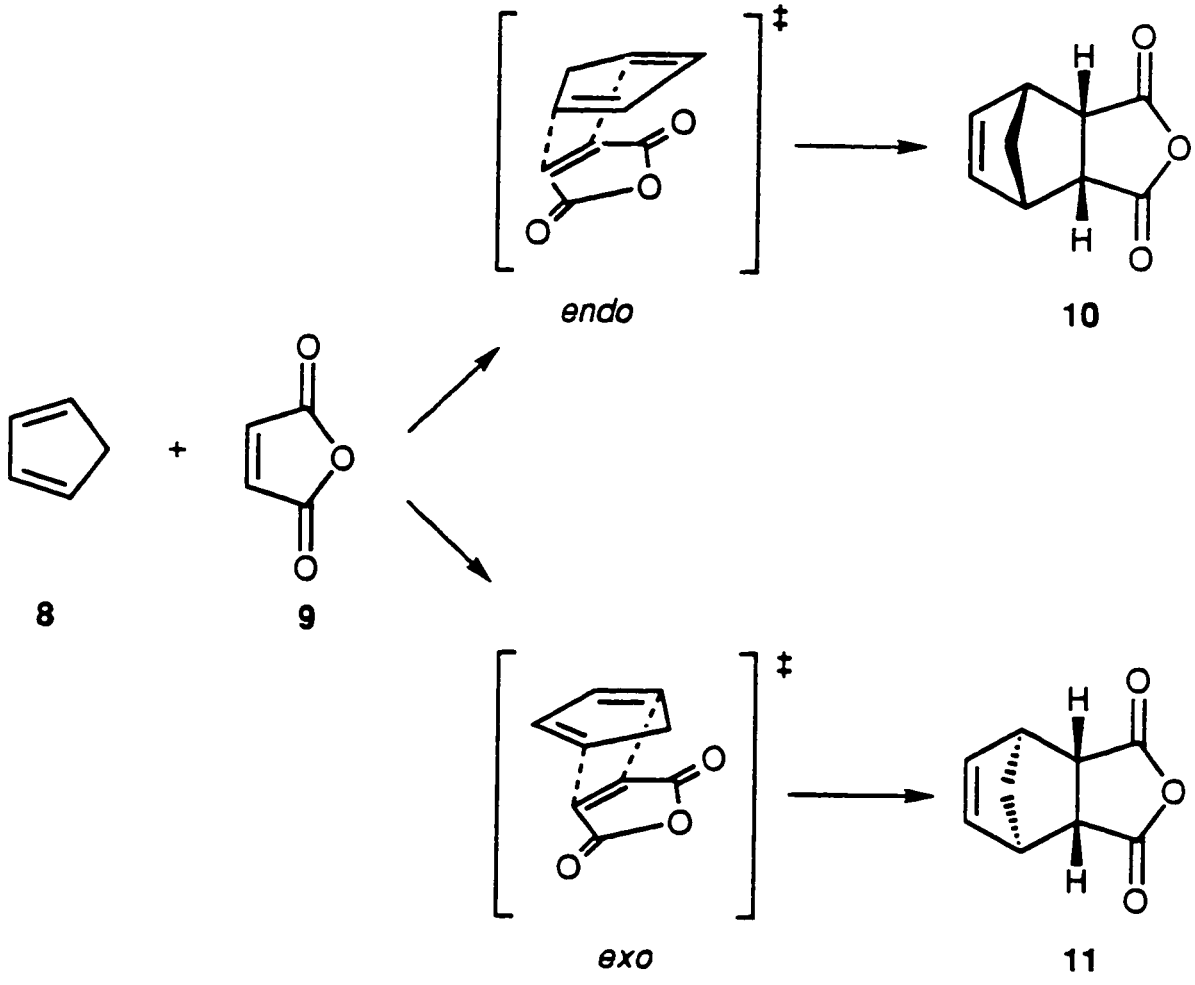
The regiochemical and stereochemical outcome of the Diels-Alder reaction are governed by a set of empirical rules[14]. The stereochemistry of the [4 + 2] cycloaddition is governed by two general rules. These rules include the *cis*-principle which predicts that addition of the diene (in the required cisoid conformation) occurs from the same side of each end of the diene moiety by attack at each end of the dienophilic double bond from the same face. In other words, the addition is stereospecifically *syn* and the configuration of the substituents in the reactants are preserved in the product. Addition of *trans,trans*-2,4-hexadiene **5** with dimethyl fumarate **6** gave adduct **7**, with retention of configuration.



5 **6** **7**

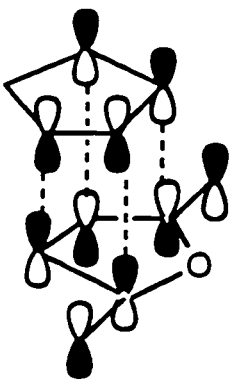
The stereochemical requirement for the diene is that it must be in the cisoid conformation during the Diels-Alder reaction. The conjugated diene may be in the transoid conformation but it must be able to achieve the cisoid conformation during the reaction in order for a reaction to take place.

The *endo* rule or Alder rule was first formulated to describe the stereochemical outcome of the reaction of cyclic dienes with dienophiles. The *endo* rule predicts that of the two transition states, the most favored transition state would involve the "maximum concentration of unsaturation"[15,16]. In the reaction of cyclopentadiene **8** with maleic anhydride **9**, the exclusive product from the reaction was *endo* product **10** with no trace of *exo* adduct **11**.



These results can be explained by the interaction of the HOMO (highest occupied molecular orbital) of the diene and the LUMO (lowest unoccupied molecular orbital) of the dienophile (**Figure 1-1**). This effect can be explained in terms of the secondary orbital overlap[11] that occurs between the π system of the diene and the π system of the conjugated dienophile. The additional overlap (secondary orbital overlap), as indicated by the dotted lines, of the diene π system of cyclopentadiene with the conjugated carbonyl π system of maleic anhydride leads to the exclusive formation of *endo* adduct **10**.

Figure 1-1



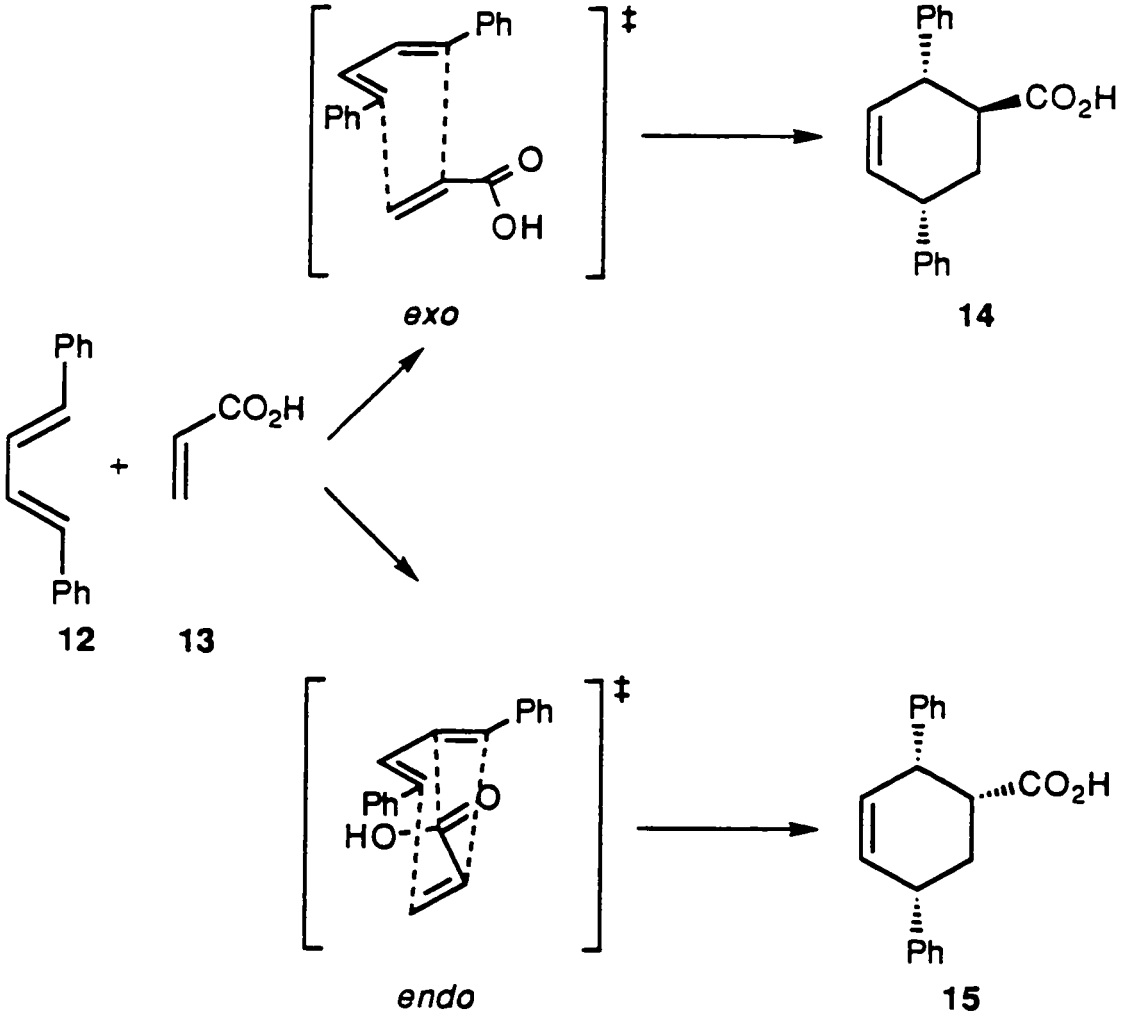
HOMO of cyclopentadiene

LUMO of maleic anhydride

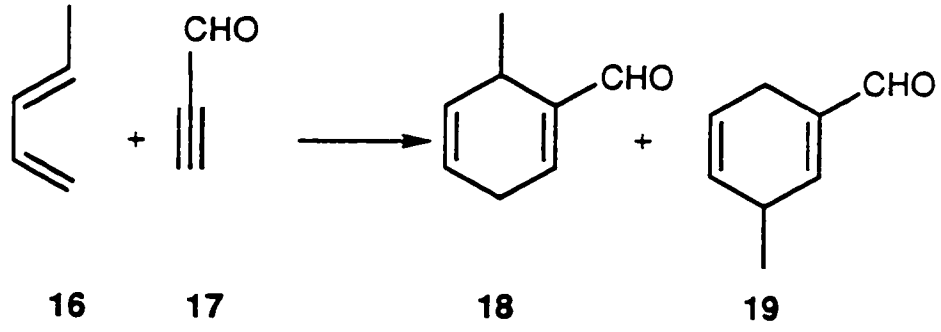
In the case of acyclic systems, *endo* addition occurs when there is secondary orbital overlap, whereas *exo* addition has no secondary orbital overlap. The addition of *trans,trans*-1,4-diphenylbutadiene **12** with acrylic acid **13**[17] gives a mixture of *exo* and *endo* products (**14** and **15**, respectively), with the latter predominating.

The Diels-Alder addition of unsymmetrical dienes and dienophiles display a preference for the formation of specific regio-isomers[18-20]. The orientation of

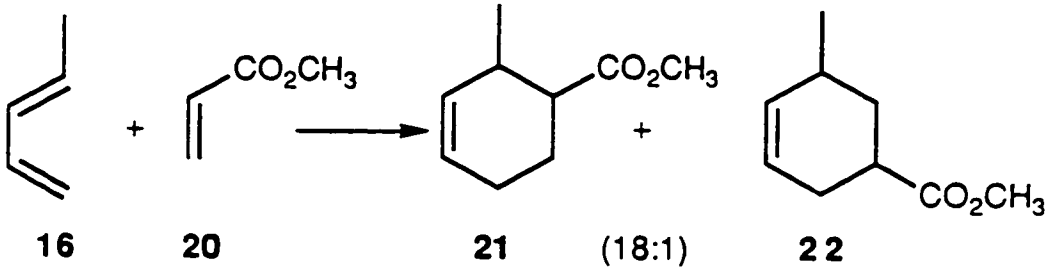
the cycloaddition can be best understood in terms of Frontier Molecular Orbital (FMO) theory[21]. In general, dienophiles possess an electron withdrawing substituent and dienes possess an electron donating substituent. The strongest interaction occurs between the high energy HOMO of the diene and the LUMO of the dienophile. This leads to the preference for formation of *ortho* and *para* oriented products. Therefore, for electron rich dienes and electron deficient dienophiles, C-1 substituted dienes will give preferentially *ortho* isomers, where the C-1 substituent of the diene is adjacent to the substituent from the dienophile.



Addition of propynal **17**[22] and methyl acrylate **20**[19] with *trans*-piperylene (1,3-pentadiene) **16** gave the *ortho* substituted products **18** and **21**, respectively, as the major products from the reactions instead of the *meta* substituted products **19** and **22**, respectively.

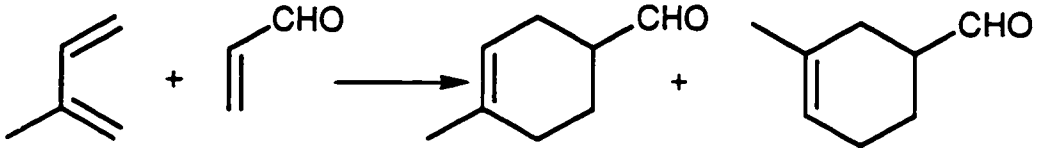


16 **17** **18** **19**

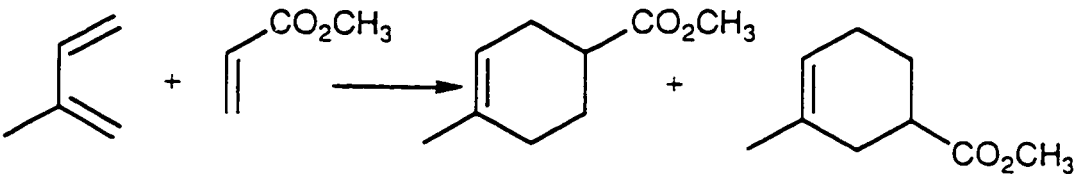


16 **20** **21** (18:1) **22**

In the case of C-2 substituted electron rich dienes, the *para* isomer is formed preferentially. Addition of isoprene (2-methyl-1,3-pentadiene) **23** to acrolein **24**[23] gave predominantly the *para* substituted product **25**, rather than the *meta* substituted product **26**. As an additional example, the addition of isoprene **23** to methyl acrylate **20**[19] provided *para* adduct **27**, predominantly.

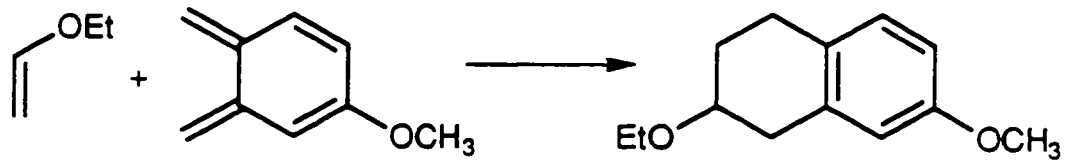


23 **24** **25** **26**



23 **20** **27** (5.4:1) **28**

In cases where an electron rich diene and an electron rich dienophile are involved, the *meta* orientation is favored. The addition of ethyl vinyl ether **29** and diene **30**[24] gave adduct **31** exclusively.



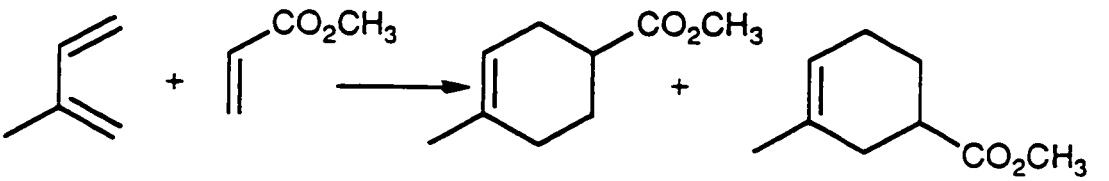
29 **30** **31**

In general, the cycloaddition with simple alkenes occurs more efficiently when the diene possesses an electron donating group. In some instances where an electron poor diene is involved, the strongest interaction in terms of FMO theory is that of the HOMO of an electron rich dienophile and the LUMO of the diene. These reactions are called "inverse electron demand" Diels-Alder reactions[25]. Such a phenomenon is illustrated by the study of the addition of an electron poor diene such as perchlorocyclopentadiene with various dienophiles. Addition of a highly electron deficient dienophile such as tetracyanoethylene is unreactive towards perchlorocyclopentadiene and cycloaddition with maleic anhydride is not efficient. Yet, cycloaddition with cyclopentadiene occurs readily.

The improvement of the Diels-Alder reactivity can be achieved by introduction of an electron withdrawing substituent[26-28] on one of the dienophilic double bond carbons, as discussed previously. It has also been found that Lewis acid

catalysis also enhances reaction rate[29]. The most commonly used Lewis acids include boron trifluoride (BF_3), ferric chloride ($FeCl_3$), zinc chloride ($ZnCl_2$), stannic chloride ($SnCl_4$), and aluminum trichloride ($AlCl_3$).

Catalysis by Lewis acids also influences the regio- and stereochemistry of Diels-Alder reactions by enhancement of the *ortho*[30-32], *para*[33-35], and *endo*[36-39] selectivity of the reaction. For example, addition of methyl acrylate **20** to isoprene **23**[34] in the presence of the Lewis acid aluminum trichloride resulted in an enhancement of the *para* selectivity, as well as an enhanced reaction rate.

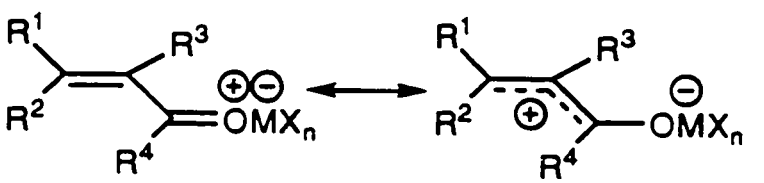


23 **20** **27** **28**

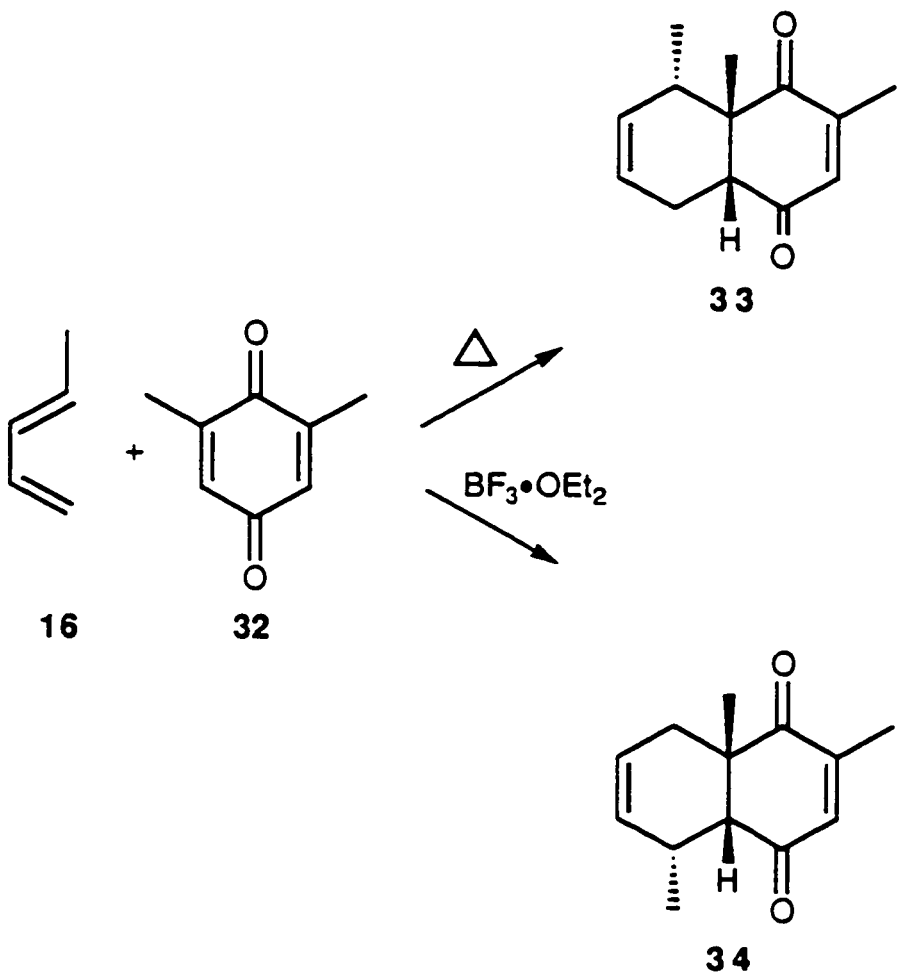
		para	*meta*
uncat.	120 °C, 6 hr	70	30
$AlCl_3$	20 °C, 3 hr	95	5

This catalytic influence is the result of complexation of the Lewis acid with the dienophile. The Lewis acid coordinates with the carbonyl oxygen, which renders the dienophile more reactive due to the polarization of the enone system (**Figure 1-2**).

Figure 1-2

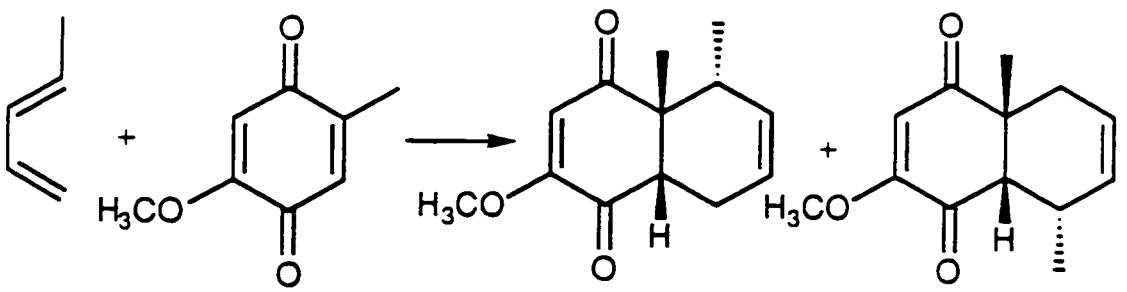


It had been previously assumed that Lewis acid catalyzed Diels-Alder reactions would enhance the formation of the favored regioisomer, yet it appears it may not always be the case. Valenta and co-workers[40] reported a unique "reversal of orientation" in which Lewis acid catalyzed addition of 2,6-dimethyl quinone **32** with *trans*-piperylene **16** gave **34**, whereas the thermal reaction afforded **33**.



It appears that the orientation is also dependent on the particular type of Lewis acid used. Take for example the reaction of 2-methoxy-5-methyl benzoquinone **35** with *trans*-piperylene **16**[41]. Boron trifluoride catalyzed Diels-Alder reaction gave a 4:1 mixture of adducts **36** and **37**, yet when stannic chloride was used

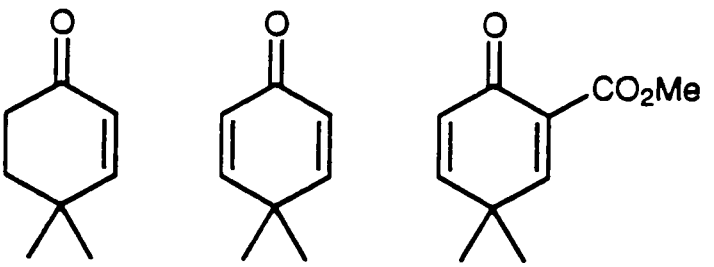
as the Lewis acid, a reversal of the regiochemistry occurred where a 1:20 mixture of adducts **36** and **37** was formed.



16 **35** **36** **37**

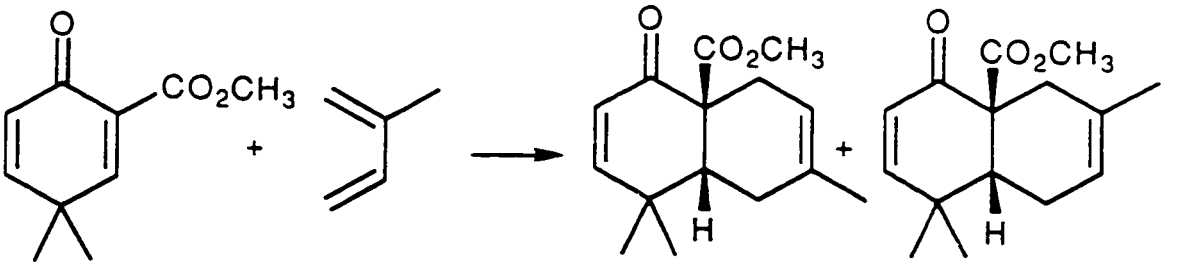
$BF_3 \bullet OEt_2$	4	1
$SnCl_4$	1	20

The addition of substituted cyclohexenones to a substituted 1,3-butadiene is a versatile approach to the decalin system. Lewis acid catalysis of specifically functionalized dienes and dienophiles has been used to produce regio- and stereochemically unique substitution patterns. The Diels-Alder reaction of 4,4-dimethyl-2-cyclohexenones **38-40**[42-45] was affected by the Lewis acid that was used.



38 **39** **40**

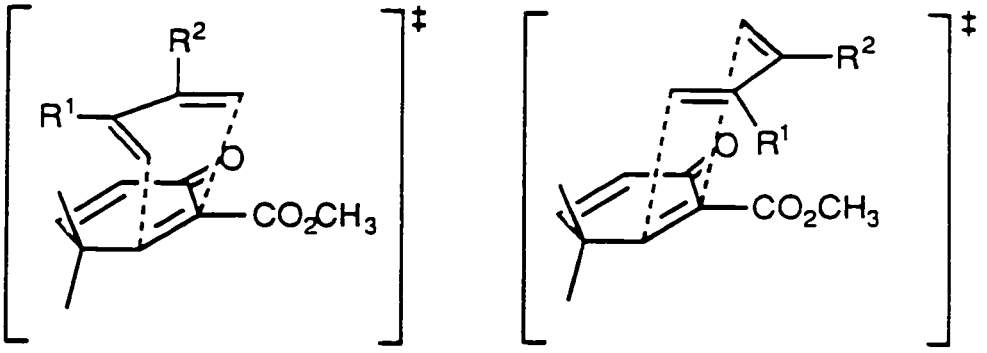
Addition of isoprene **23** with **40** gave a mixture of *para* and anti-*para* adducts **41** and **42** in a 30:70 ratio under boron trifluoride catalysis, but gave an 82:18 ratio of these adducts under stannic chloride catalysis.



40 **23** **41** **42**

	para	*anti-para*
$BF_3 \bullet OEt_2$	30	70
$SnCl_4$	82	18

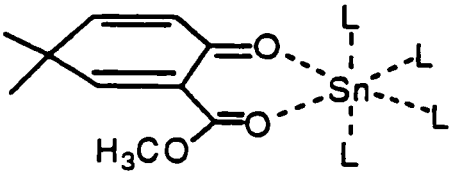
These results were explained on the basis of preferential coordination of the boron trifluoride with the ketone carbonyl. This leads to preferential *endo*-to-ketone addition (**43b**), whereby the electron withdrawing effect promoting *para* addition is insufficient to counteract the steric directing effect which promotes anti-*para* addition (**43a**). For stannic chloride, coordination occurs at both the ketone carbonyl and the ester carbonyl due to its ability to form 1:2 complexes[46] (**Figure 1-3**). The electron withdrawing effect through two carbonyl groups promotes addition via transition state **44**. In this case, *endo*-to-ester addition promotes secondary orbital overlap with the ester group at the expense of secondary orbital overlap with the ketone carbonyl. Also, a soft Lewis acid such as stannic chloride might exhibit a preference towards complexation with the ester carbonyl over the ketone carbonyl. This would account for the increased contribution of transition state **44b** to give an enhancement of the electronically favored *para* addition product. There is little contribution of transition state **44a** to the product distribution due to the steric interaction between the methyl group of the diene and the ester group of the dienophile.



43a R^1=H, R^2=CH_3 **44a** R^1=H, R^2=CH_3

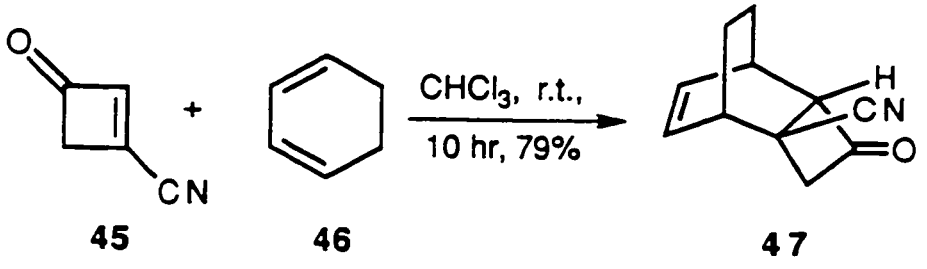
43b R^1=CH_3, R^2=H **44b** R^1=CH_3, R^2=H

Figure 1-3

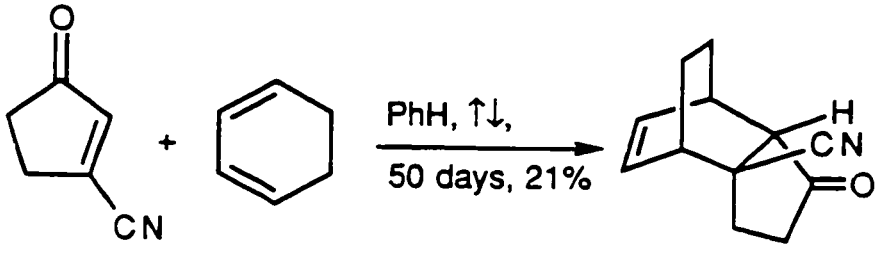


In general, the use of an activating substituent to enhance the dienophilicity of 2-cycloalkenones[26] and to facilitate the preparation of polycyclic compounds has drawn considerable interest in recent years. The use of doubly conjugated cycloalkenones, such as **40**, as dienophiles are preferred due to their enhanced dienophilicity. This enhancement is accounted for by the presence of an electron withdrawing substituent as well as making the dienophile flat to enhance orbital overlap in the transition state during Diels-Alder cycloaddition. A large number of activating substituents have been applied including carbalkoxyl[42,47-49], formyl[50-52], nitro[53], phenylthio[54], phenylselenyl[55], bromo[56,57], etc. Placement of an electron withdrawing substituent at the C-2 or alpha position is more common than that at the C-3 or beta position, although there have been a few examples involving 3-substituted-2-cycloalkenones[47,48,53]. One such example involves the use of a cyano

group[58] to activate the beta position of cyclobutenone **45** and cyclopentenone **48**. Under thermal conditions [4 + 2] cycloaddition of cyclobutenone **45** occurs with 1,3-cyclohexadiene **46** at room temperature. Its five membered analog **48** did not react at room temperature, but in refluxing benzene, the reaction occurred slowly to afford the *endo* adduct **49** exclusively in low yield (21%).



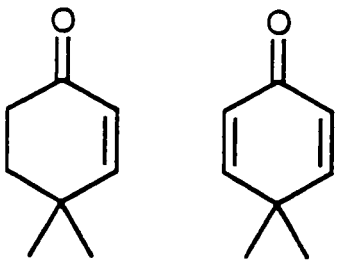
45 **46** **47**



48 **46** **49**

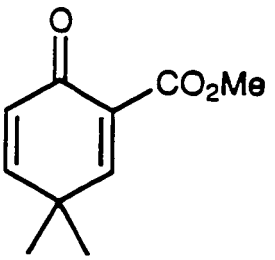
In past years, our research group has investigated the Diels-Alder chemistry of 4,4-dimethyl-2-cyclohexenone **38** and several closely related cross-conjugated cyclic unsaturated carbonyl compounds **39**, **40**, and **50**[43,44,59], the latter two contain a methyl ester as an additional activating substituent. In these cases, the reactions of these cyclic enone systems involved the use of both Lewis acid catalysis and the attachment of an activating substituent on the dienophilic bond to enhance the reactivity of the Diels-Alder reaction. The outcomes of these additions, in terms of the stereochemistry and regiochemistry, influenced by the usual steric and electronic effects, are in general quite predictable. The parent enone **38** is a very unreactive dienophile[60] in the Diels-Alder cycloaddition

reaction, yet an activated system **50**[59] under Lewis acid catalysis proceeds smoothly.

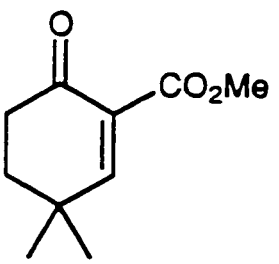


38

39



40

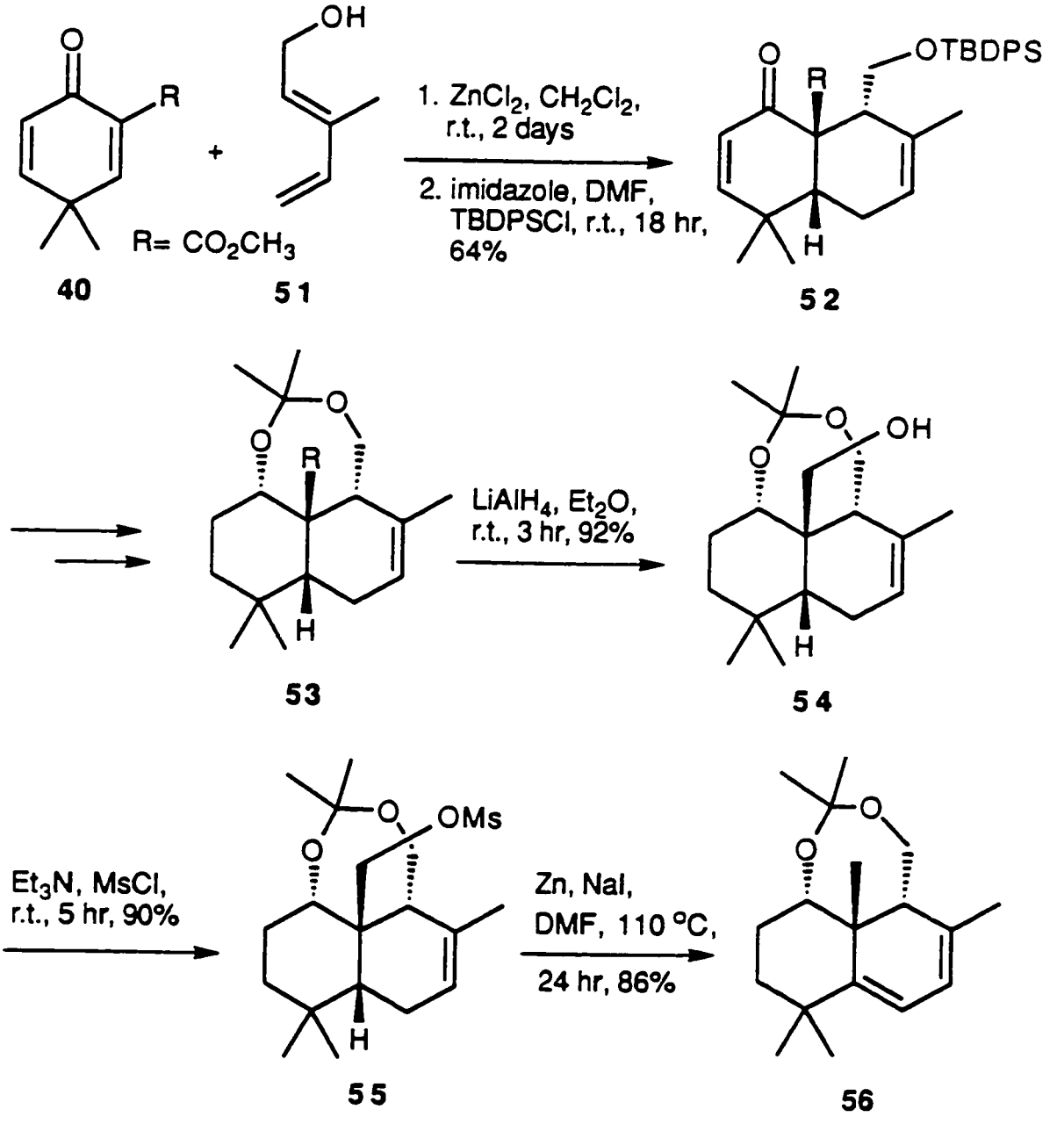


50

A general strategy for the synthesis of natural products involves the use of a Diels-Alder reaction as a key step to construct the decalin system. Placement of an electron withdrawing group on the dienophile serves to activate the dienophile as well as a method of introducing an alkyl group through functional group transformation. An example of such an approach was conducted in our laboratory towards the synthesis of forskolin[61], a labdane diterpene which stimulates adenylate cyclase and could be used as an anti-hypertensive, anti-glaucoma, and anti-asthma agent. The key step in the synthesis of the decalin system (**Scheme1-2**) involved the Diels-Alder reaction of dienophile **40** and diene **51**. Subsequent manipulation of the methyl ester to provide a methyl group proceeded via alcohol intermediate **54**. This was accomplished by reduction of the methyl ester **53** to alcohol **54**, then deoxygenation of **54** via

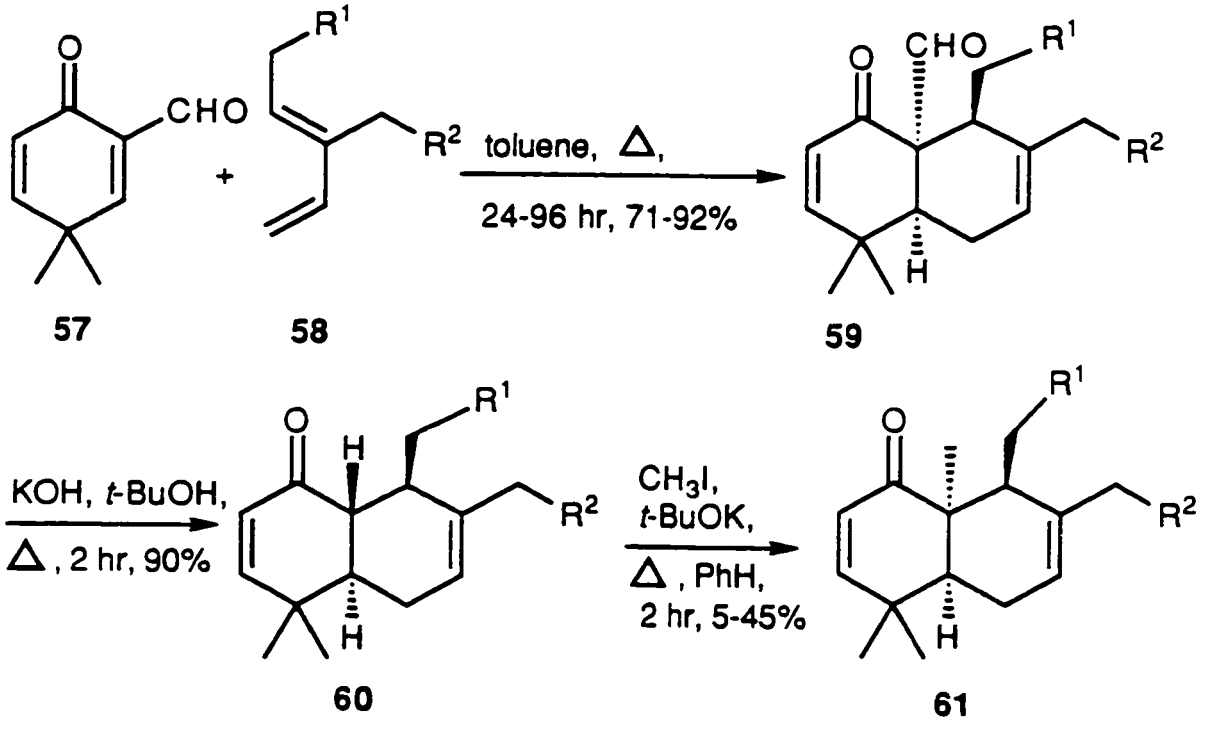
mesylate **55.** The latter compound was reduced with zinc dust in the presence of sodium iodide to afford the desired angular methyl group present in intermediate **56.**

Scheme 1-2



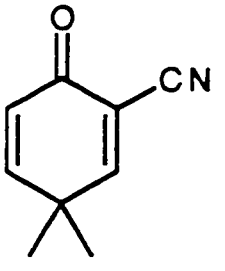
Bhat, and co-workers[62] also took this approach towards the synthesis of biologically active terpenoids, such as forskolin. Diels-Alder reaction of various substituted dienes **58** with dienophile **57** afforded adducts with general structure **59.** Introduction of an angular methyl group was accomplished by deformylation with potassium hydroxide followed by treatment with methyl iodide and potassium *tert*-butoxide to afford **61**. This method gave low yields (5-45%) of the angular methyl adducts **61**. It appears that the removal of the ring-junction proton to form the enolate ion is a difficult process.

Scheme 1-3



The preceding examples are only a few in which an activating group was used to promote the Diels-Alder reaction. In addition to the promotion of the Diels-Alder reaction, the activating group was also useful in providing a "latent" methyl group.

The dienophile, 2-cyano-4,4-dimethyl-2,5-cyclohexadienone **62**, was used in a study to demonstrate the viability of such an approach to polycyclic compounds. The first part of this chapter will describe the Diels-Alder reaction characteristics of dienophile **62** with a variety of dienes. It was envisioned that the placement of a cyano group at the alpha position of such systems as **39** would provide a useful synthetic route towards the decalin system. The cyano group was a group of choice due to its ability to undergo functional transformations. A few examples of the versatility of the cyano group include methods to convert nitriles to ketones involving the use of alkyllithium reagents[63]. The cyano group can also be selectively reduced using various methods such as diisobutylaluminum hydride (DIBAL), reduction to an aldehyde[64,65], lithium aluminum hydride ($LiAlH_4$), reduction to an aminomethyl group[66], or dissolving metal reduction to the decyanated product[67,68].



62

The decyanation reaction provides a very interesting option in the process of performing functional group transformation of a bicyclic compound. It appears that reductive decyanation occurs via an enolate ion intermediate before quenching the reaction with a proton source. Since the decyanation process proceeds via an enolate, it is possible that trapping of the enolate with an alkyl halide could provide us with an angular alkyl group on the bicyclic adduct. The

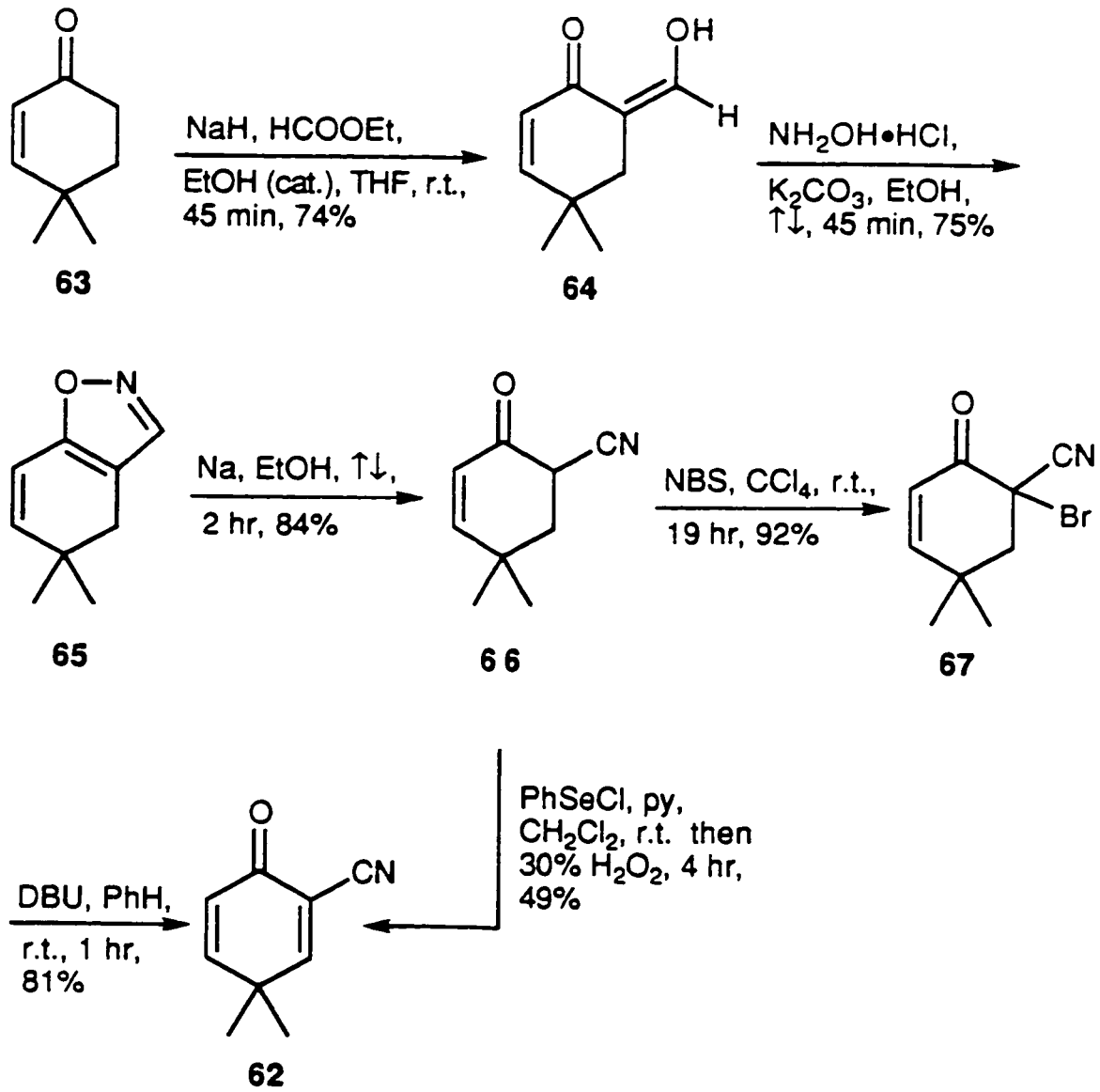
second part of this chapter will focus on an investigation on the decyanation and reductive alkylation of adducts produced from nitrile activated Diels-Alder cycloaddition.

Results and Discussion

I. Preparation of 2-cyano-4,4-dimethyl-2,5-cyclohexadienone (62)

The dienophile, 2-cyano-4,4-dimethyl-2,5-cyclohexadienone **62**, was easily prepared by established procedures (**Scheme 1-4**). 4,4-Dimethyl-2-cyclohexenone **63** was prepared from isobutyraldehyde and methyl vinyl ketone according to literature procedure[69]. Formylation[70-72] of enone **63** using ethyl formate and sodium metal (or sodium hydride) in the presence of a catalytic amount of absolute ethanol afforded hydroxymethylene enone **64** (74%). No traces of the aldehyde form were present. Conversion of the hydroxymethylene enone **64** to the isoxazole derivative **65**[72-74] (75%) was easily achieved by treatment with hydroxylamine hydrochloride and anhydrous potassium carbonate in absolute ethanol at refluxing temperature. Isoxazole **65** was then converted to the cyano enone **66** (84%) by treatment with sodium ethoxide[72]. The cyano enone **66** could be converted to the desired dienophile **62** by one of two methods. Initial attempts to convert the cyano enone **66** to the dienone **62** in one step involved the application of a phenylselenenylation-oxidation reaction[75]. Treatment of the cyano enone **66** with phenylselenenyl chloride and pyridine followed by oxidative work-up with hydrogen peroxide afforded the desired dienone **62**, albeit in low yields (40-50%). The low yield obtained from this reaction prompted the application of a different method, involving less toxic and less expensive reagents, to effect the conversion of **66** to dienophile **62**. Such a method involved bromination[76] at the alpha position using *N*-bromosuccinimide (92%) to give the bromo keto nitrile **67**, followed by dehydrobromination[76] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base to afford the desired dienophile **62** in 81% yield.

Scheme 1-4


O
NaH, HCOOEt,
EtOH (cat.), THF, r.t.,
45 min, 74%
OH
H
NH2OH•HCl,
K2CO3, EtOH,
↑↓, 45 min, 75%
63
64
O—N
Na, EtOH, ↑↓,
2 hr, 84%
CN
NBS, CCl4, r.t.,
19 hr, 92%
Br
65
66
67
PhSeCl, py,
CH2Cl2, r.t. then
30% H2O2, 4 hr,
49%
DBU, PhH,
r.t., 1 hr,
81%
62

II. Diels-Alder reactions of 2-cyano-4,4-dimethyl-2,5-cyclohexadienone (62)

Once we had the dienophile in hand, its Diels-Alder reactivity with various dienes was studied. Initially, the Diels-Alder cycloaddition with 2-methyl-1,3-butadiene under thermal conditions was studied. The reaction at room temperature proceeded very slowly, with little product formation even after a few weeks of reaction time. This led us to examine the reaction at elevated temperatures. The cycloaddition reaction in refluxing toluene also proceeded very slowly.

These poor results prompted us to study a Lewis acid mediated Diels-Alder reaction. In addition to the Lewis acids listed in **Table 1-1**, ferric chloride ($FeCl_3$) and stannic chloride ($SnCl_4$) were also studied using 2-methyl-1,3-butadiene as the diene. Ferric chloride gave little conversion to adducts **74** and **75** after 5 days at room temperature. Stannic chloride was not a useful Lewis acid since it was found to induce rapid decomposition of dienophile **62** within 30 minutes at room temperature. Preliminary reactions using 2-methyl-1,3-butadiene were abandoned in favor of 2,3-dimethyl-1,3-butadiene because the cycloaddition would provide only one reaction product. This would allow for the simple interpretation of the spectral data without the complication of introducing a second reaction product. A variety of Lewis acids and conditions were used in order to establish the reactivity of cyano dienone **62** towards cycloaddition reactions, using 2,3-dimethyl-1,3-butadiene as a model (**Table 1-1**).

The results from this study showed visible trends in the Diels-Alder reactivity of dienophile **62**. Boron trifluoride etherate ($BF_3 \bullet Et_2O$) mediated cycloaddition (entries 1 and 2) gave fair yields (48-57%) of adduct **68**. The employment of

two equivalents of $BF_3 \bullet Et_2O$ increased the yield as well as the reaction rate of the cycloaddition over the use of only one equivalent. Previous publications[77,78] have shown that zinc iodide (ZnI_2) was a good Lewis acid for cycloaddition reactions involving acrylonitrile systems. Zinc iodide mediated cycloaddition (entries 3 and 4) gave good yields (69-85%) of cycloadduct **68**. The use of two equivalents of zinc iodide improved the yield of the reaction significantly over the use of one equivalent, yet the reaction rate was slow (7 days).

We looked at the possibility of using a mixture of Lewis acids. We believed that a hard Lewis acid such as $BF_3 \bullet Et_2O$ would preferentially complex with the carbonyl and a soft Lewis acid such as zinc iodide would complex with the cyano group. A mixed Lewis acid system provided adduct **68** in good yield (entries 5 and 6; 69 and 72%, respectively) but with lower yields than catalysis with two equivalents of zinc iodide.

One equivalent of zinc chloride (entry 7) gave a good yield (74%) of adduct **68**, only after a long period of time (10 days). The most superior conditions employed two equivalents of zinc chloride (entries 8 and 9) which gave high yields (93%) and fair reaction times (40-65 hours). From this investigation, it was clear that at least two equivalents of the Lewis acid were required to effect the cycloaddition at a reasonable rate. The reaction rate of the cycloaddition was greatly affected by the amount of the catalyst that was employed. Employment of two equivalents of Lewis acid enhanced the reaction rate from approximately a 0.3-fold to a 5-fold increase in rate (entry 4 and entry 8, respectively). The study also showed that an improvement in yield accompanied the reaction rate increase. The use of two different solvents,

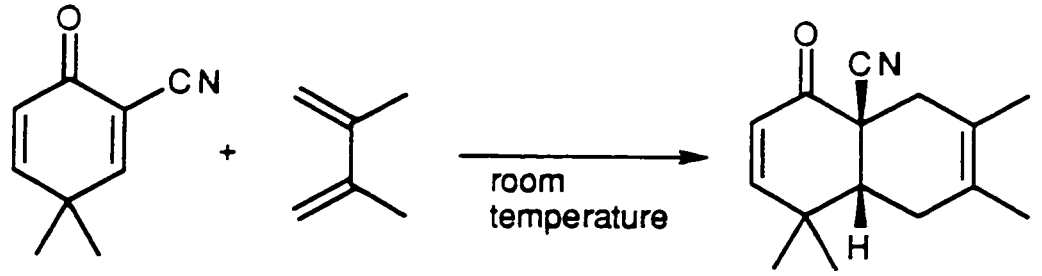
diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) also showed differing reaction rates. In these cases (entries 4, 5, 8, and 9) it may be due to the solubility of the Lewis acid.

Under optimum conditions, the Lewis acid mediated Diels-Alder reaction of 2-cyano-4,4-dimethyl-2,5-cyclohexadienone **62** was investigated using various dienes. The experimental procedure for zinc chloride (2 equivalents) catalyzed reactions involved initially the careful flame-fuse drying of zinc chloride under an inert atmosphere. This was followed by dissolution of the Lewis acid in diethyl ether, then addition of the dienophile dissolved in diethyl ether. The diene was added after allowing the complexation of the dienophile and Lewis acid to occur (approximately 15 to 30 minutes). The results from this study are shown in **Table 1-2.**

The cyano group proved to be a good activating group. In contrast to the low Diels-Alder reactivity observed previously for the parent dienone **39**, enone **62**, under Lewis acid catalysis, showed a high degree of dienophilicity towards all the dienes examined.

In general, the Diels-Alder reactions that were investigated gave very good yields with one exception (entry 7). The regiochemistry of the adducts follows from the *ortho* and *para* rules whereas the stereochemistry results from the *endo*-to-ketone addition with the following exceptions. The addition of **62** to 2-methyl-1,3-butadiene (entry 6) gave the anti-*para* addition product **74** as the major product. With 2-methyl-1,3-pentadiene (entry 5), the *endo*-to-nitrile product **73** was formed in a large amount in addition to the expected *endo*-to-ketone product **72**.

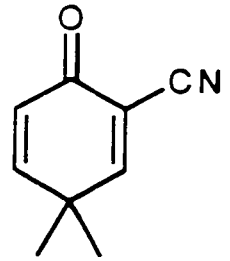
Table 1-1. Effect of catalysts on addition of 2,3-dimethyl-1,3-butadiene to 2-cyano-4,4-dimethyl-2,5-cyclohexadienone **62**.



62 **68**

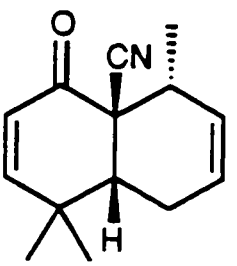
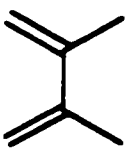
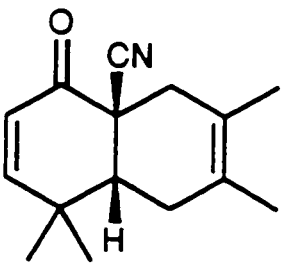
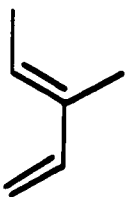
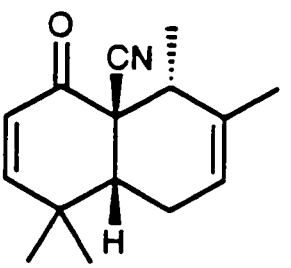
Entry	Catalyst	Solvent	Time	Yield (%)
1	$BF_3 \cdot Et_2O$ (2 equiv.)	CH_2Cl_2	44 hr	57
2	$BF_3 \cdot Et_2O$ (1 equiv.)	CH_2Cl_2	4 days	48
3	ZnI_2 (2 equiv.)	Et_2O	7 days	85
4	ZnI_2 (1 equiv.)	CH_2Cl_2	9 days	69
5	$BF_3 \cdot Et_2O$ (1 equiv.) ZnI_2 (1 equiv.)	CH_2Cl_2	40 hr	69
6	$BF_3 \cdot Et_2O$ (1 equiv.) ZnI_2 (1 equiv.)	Et_2O	5 days	72
7	$ZnCl_2$ (1 equiv.)	CH_2Cl_2	10 days	74
8	$ZnCl_2$ (2 equiv.)	Et_2O	40 hr	93
9	$ZnCl_2$ (2 equiv.)	CH_2Cl_2	65 hr	93

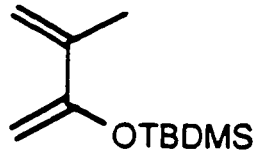
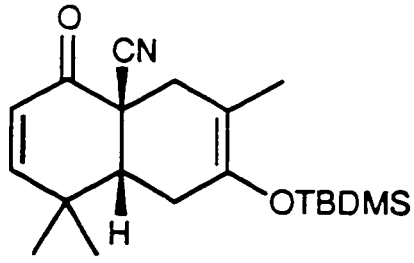
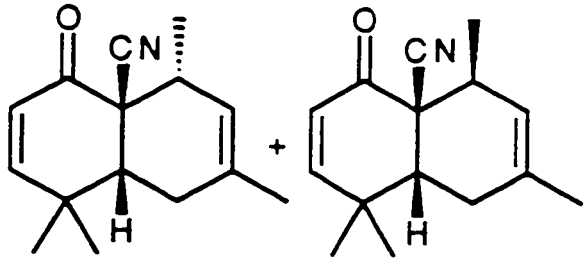
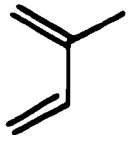
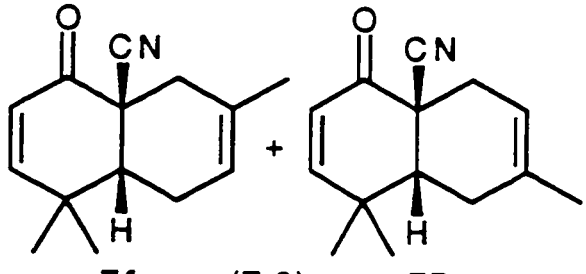
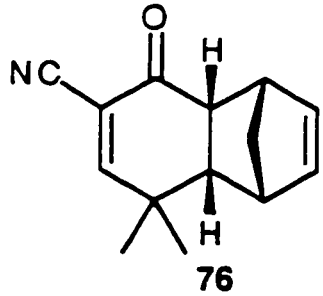
Table 1-2. Diels-Alder reactions of 2-cyano-4,4-dimethyl-2,5-cyclohexadienone **62**.



62

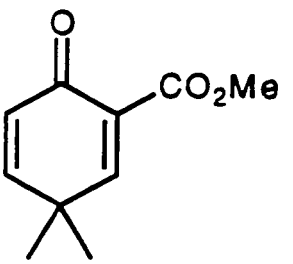
\+ Diene (20 equiv.) $\xrightarrow[Et_2O,\ r.t.]{ZnCl_2\ (2\ equiv.),}$ Adduct(s)

Entry	Diene	Time (hr)	Adduct(s)	Yield (%)
1		5	 **69**	98
2		40	 **68**	93
3		25	 **70**	80

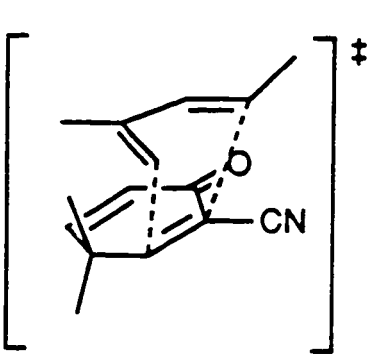
Entry	Diene	Time (hr)	Adduct(s)	Yield (%)
4		22	 **71**	89
5		3.5	 **72** (1:1) **73**	89
6		22.5	 **74** (7:3) **75**	91
7		66.5	 **76**	49[a-c]

[a]The reaction was run at -25 °C. [b]The yield was based on the consumed dienophile. [c]Dienophile was recovered in 27% by flash chromatography (silica gel, 20% ethyl acetate in *n*-hexane).

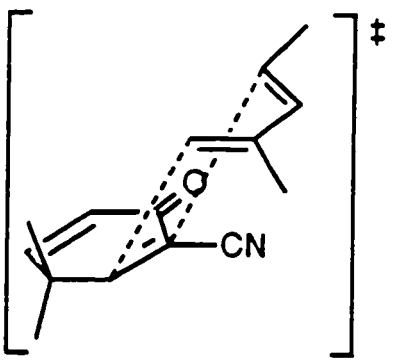
These abnormal results, however, are consistent with those observed previously for the Diels-Alder reactions of an analogous dienophile, 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadienone **40**. This could be accounted for by invoking the unfavorable steric interaction in each case between the C-2 methyl group of the diene and one of the C-4 methyl groups of the dienophile in a *para*-oriented *endo*-to-ketone transition state (e.g. **77**). Transition state **77** is electronically favored by the secondary orbital overlap of the diene with the other π-bond as well as the overlap with the carbonyl carbon. Steric considerations lead to adduct formation via a *para*-oriented *exo*-to-ketone transition state **78**. The case of 2-methyl-1,3-butadiene will be discussed later.



40



77

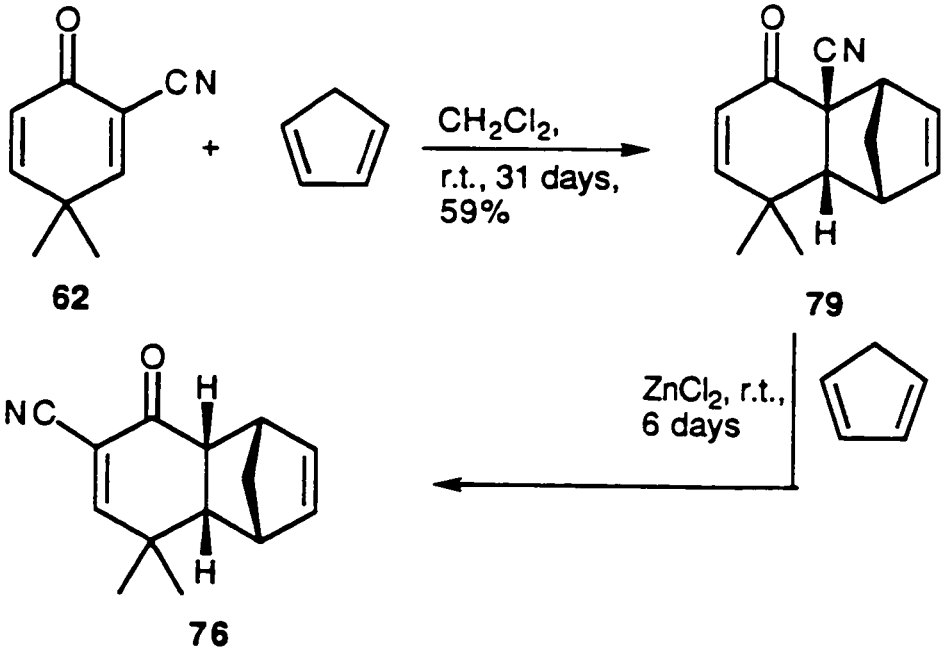


78

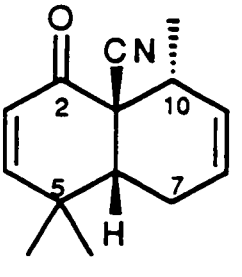
It is also worth noting that the dienophilicity of **62** is restricted to the more substituted double bond, with one exception. The addition of cyclopentadiene

(entry 7) gave adduct **76** as the exclusive product. As indicated by the following experiments (**Scheme 1-5**), this compound was formed via a thermodynamically controlled process. The expected adduct **79** could be obtained in a small amount from the thermal reaction (room temperature) of **62** and cyclopentadiene. When compound **79** was treated with cyclopentadiene in the presence of two equivalents of zinc chloride, the isomeric compound **76** was produced as the sole product, apparently via a retro Diels-Alder process.

Scheme 1-5

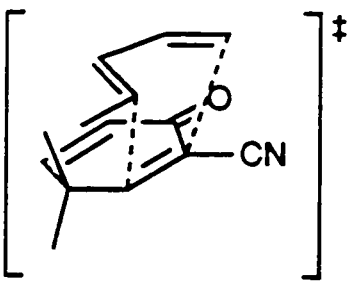


II.A. Addition to *trans*-1,3-pentadiene (Entry 1)



69

The zinc chloride mediated Diels-Alder reaction of *trans*-1,3-pentadiene gave adduct **69** in 5 hours (98% yield). Adduct **69** was the sole product produced from the reaction. The regiochemistry of cycloadduct **69** could be easily predicted. In transition state **80** there is an unfavorable steric interaction of one of the geminal methyl groups of the dienophile with the methyl group of the diene in the anti-*ortho* product. Therefore, the electronically and the sterically favored *ortho*-oriented *endo*-to-ketone cycloadduct **69** was produced as the only product.

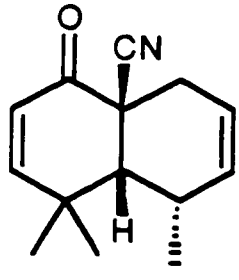


80

The ^{13}C NMR APT spectrum of **69** displayed one set of signals, which included two notable signals at δ 190.84 (α,β-unsaturated carbonyl) and 121.39 (nitrile). The spectrum showed a total of 14 signals, which supports the generation of a single cycloadduct. The infrared spectrum of **69** displayed a carbonyl absorption at 1702 cm^{-1} and a nitrile absorption at 2227 cm^{-1}. In the high resolution mass spectrum, a molecular ion peak at m/*z* 215.1321 was consistent with the molecular formula $C_{14}H_{17}NO$. The ^1H NMR spectrum showed two mutually coupled vinylic protons (J = 10.5 Hz) at δ 6.48 and 5.91 and a multiplet corresponding to two other vinylic protons at δ 5.58. The presence of four vinylic protons in the spectrum confirmed that cycloadduct **69** was formed by the addition of the diene at the more substituted double bond of dienophile **62**.

The ring-fusion stereochemistry of the adduct **69** was formed in accordance with the *cis*-principle[14,21,27] of Diels-Alder chemistry. This was supported by the ^{1}H NMR signal of the C-4 proton at δ 6.48. This signal showed a long range W-type coupling[79] of 1.5 Hz to the proton at δ 2.47 which corresponds to the ring-junction proton at C-6. Molecular modeling showed that the required W-type configuration could be attained in the *cis*-fused ring system only. Since there have been no reported violations to the *cis*-principle, we can conclude that a *cis* ring-fusion operates in our dienone system as well.

Additional information from the ^{1}H NMR spectrum of **69** supports the assigned regiochemistry of the methyl moiety derived from the diene, *trans*-1,3-pentadiene. The C-6 ring-junction proton signal at δ 2.47 also shows two additional coupling constants of 10 Hz and 6 Hz. This indicated that there must be two neighboring protons present, which correspond to the methylene protons on C-7 in structure **69**, the regiochemistry expected for addition according to the *ortho*-rule, and not of structure **81**, the anti-*para* addition product.

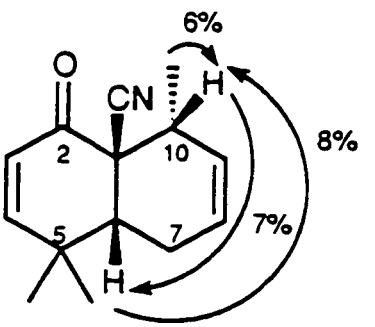


81

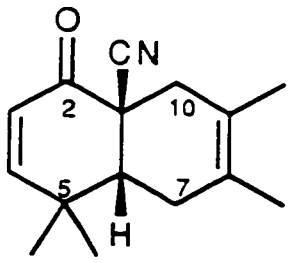
The following results are also consistent with the placement of the methyl substituent at C-10 and not at C-7. Decoupling experiments assisted in the

assignment of all the signals in the ^1H NMR spectrum. A multiplet at δ 2.75 was assigned to the methine proton on C-10. The two allylic methylene protons on C-7 appeared as signals at δ 2.32 and 1.96, each as a set of doublet (J = 18 Hz) of multiplets. A doublet (J = 6 Hz) at δ 1.45 coupled to the allylic methine proton (H_{10}) was attributed to the methyl group on C-10. Geminal methyl groups were shown at δ 1.62 and 1.14 as two singlets. The stereochemistry of the methyl group at C-10 was confirmed by NOE experiments. As depicted in **Figure 1-4**, irradiation of the allylic methine proton (H_{10}) signal at δ 2.75 resulted in a 7% enhancement on the ring-junction proton (H_6) signal at δ 2.47. Conversely, when the ring-junction proton (H_6) signal was irradiated, an enhancement of 8% on H_{10} was observed. Irradiation of the allylic methyl group on C-10 at δ 1.45 gave a 6% enhancement of the allylic methine proton (H_{10}). There was no enhancement of the ring-junction proton (H_6) signal.

Figure 1-4



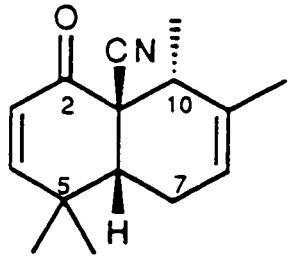
II.B. Addition to 2,3-dimethyl-1,3-butadiene (Entry 2)



68

Dienophile **62** reacted slowly with a less reactive diene, 2,3-dimethyl-1,3-butadiene (40 hours), yet cycloadduct **68** was produced in high yield (93%). The ^{13}C NMR APT spectrum displayed two distinctive signals at δ 192.10 (α,β-unsaturated carbonyl) and 121.07 (nitrile). The infrared spectrum of **68** displayed characteristic absorptions at 1687 (α,β-unsaturated carbonyl) and 2241 cm^{-1} (nitrile). Its molecular formula $C_{15}H_{19}NO$ was supported by the high resolution mass spectrum showing a molecular ion peak at m/*z* 229.1466. Elemental analysis also supported the molecular formula $C_{15}H_{19}NO$. The ^1H NMR spectrum displayed two enone proton signals as doublets (J = 10.5 Hz) at δ 6.60 and 5.93, corresponding to H_4 and H_3, respectively. Allylic methylene protons appeared at δ 2.52, 2.40, 2.31, and 2.02 as broad doublets (J = 18 Hz). The methine ring-junction proton on C-6 appeared as an overlapped signal at δ 2.39 (dd, J_1 = 7, J_2 = 2.5 Hz). Vinylic methyl groups appeared as singlets at δ 1.67 and 1.62. Geminal methyl groups were also represented by singlets at δ 1.24 and 0.96. The stereochemical assignment of cycloadduct **68** was made on the basis of the *cis*-principle.

II.C. Addition to *trans*-3-methyl-1,3-pentadiene (Entry 3)

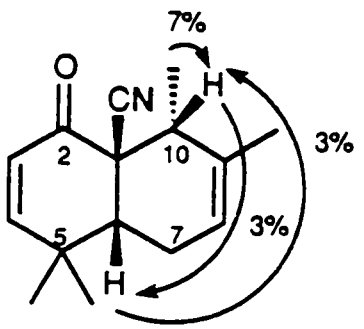


70

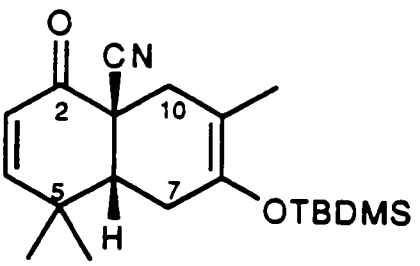
The cycloaddition of dienone **62** with *trans*-3-methyl-1,3-pentadiene over 25 hours gave cycloadduct **70** in a 96% yield. The *ortho*-oriented *endo*-to-ketone adduct **70** was formed as the only product. The results from this cycloaddition are analogous to that found with *trans*-1,3-pentadiene (entry 1). There were a total of 15 signals displayed in the ^{13}C NMR APT spectrum of adduct **70** which confirms the generation of only one adduct. Two notable signals at δ 191.39 and 121.77 were characteristic of an α,β-unsaturated carbonyl and a nitrile, respectively. The *cis* ring-junction was assigned on the basis of a small W-type coupling (J = 1.5 Hz) of the beta proton of the enone system at δ 6.48 with the ring-junction proton at δ 2.42 (ddd, J_1 = 9 Hz, J_2 = 6.5 Hz, J_3 = 1.5 Hz). Two other vinylic proton signals were visible in the spectrum. These appeared as signals at δ 5.93 representing H_3 coupled to H_4 (J = 10.5 Hz) and a multiplet at δ 5.32, attributed to H_8. Three methyl groups at δ 1.73 (C-9 methyl), 1.55, and 1.10 (geminal dimethyl) appeared as singlets. The C-10 methyl group appeared as a doublet at δ 1.39 (J = 6 Hz). Proton decoupling experiments assisted in the assignment of the rest of the signals. A multiplet at δ 2.66 representing one proton was assigned to the allylic methine proton at C-10. The methylene protons appeared at δ 2.31 (dddd, J_1 = 18 Hz, J_2 = 9 Hz, J_3 = 4 Hz, J_4 = 1.5 Hz) and 1.97 (dm, J = 18 Hz).

The regiochemistry and the stereochemistry of cycloadduct **70** were assigned on the basis of NOE experiments, as depicted in **Figure 1-5**. Irradiation of the ring-junction proton (H_6) signal at δ 2.43 gave a 3% enhancement of the methine allylic proton (H_{10}) signal at δ 2.66. Alternatively, there was a 3% enhancement of the proton at C-6 when the methine allylic proton (H_{10}) signal was irradiated. Irradiation of the C-10 methyl group at δ 1.39 did not give any enhancement of the ring-junction proton (H_6) signal but only enhancement (7%) of the C-10 methine proton.

Figure 1-5



II.D. Addition to 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene (Entry 4)

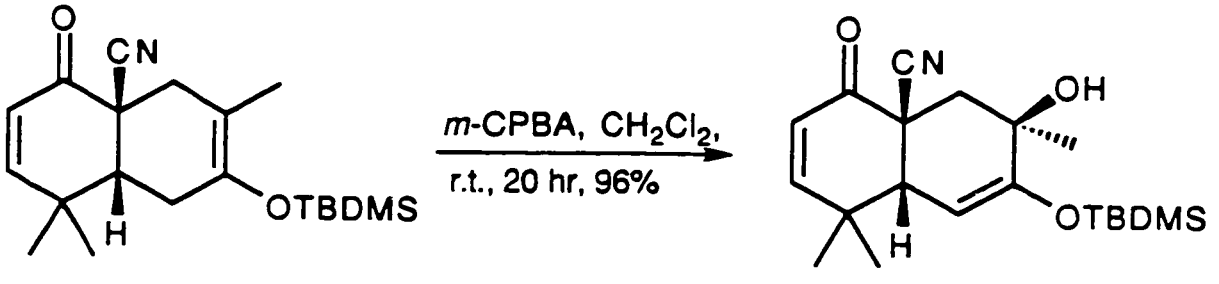


71

The zinc chloride mediated Diels-Alder reaction of 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene[80] with dienone **62** for 22 hours gave adduct **71** in a yield of 80%. The tentative assignment of the regiochemistry of cycloadduct **71** was based on the *para* rule with respect to the more powerful electron donating group.

In order to confirm this assignment, an additional experiment was conducted. Treatment of cycloadduct **71** with *meta*-chloroperoxybenzoic acid afforded compound **82** in a 96% yield (**Scheme 1-6**), likely as a result of the expected epoxidation followed by epoxy ring opening .

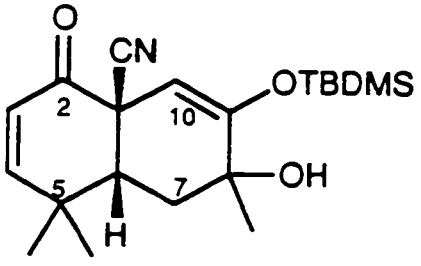
Scheme 1-6



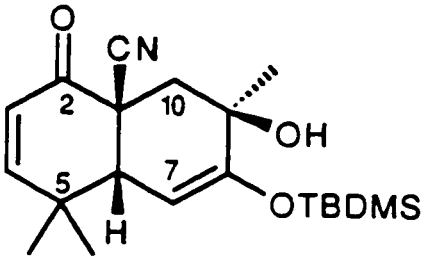
71 **82**

The ^1H NMR spectrum of **82** showed three vinylic proton signals. Two mutually coupled doublets (J = 10.5 Hz) at δ 6.82 and 6.01, representing the H_4 and the H_3 protons, respectively. Another vinylic proton signal at δ 4.96 appeared as a doublet (J = 6 Hz) coupled to the ring-junction proton H_6 at δ 3.0. The results are consistent with structure **82** and not with structure **83**, which would result from the "anti-*para* " addition product in the Diels-Alder cycloaddition.

The structure of cycloadduct **82** was further confirmed by conducting NOE experiments. As shown in **Figure 1-6**, irradiation of the ring-junction proton (H_6) signal at δ 3.00 gave a 14% enhancement of the C-7 vinylic proton signal at δ 4.96, as well as a 16% enhancement of the hydroxyl group signal at δ 2.48. Irradiation of the C-9 methyl group at δ 1.36 gave only enhancement on the C-10 methylene proton signals at δ 2.38 and 2.14 (9% and 2%, respectively).

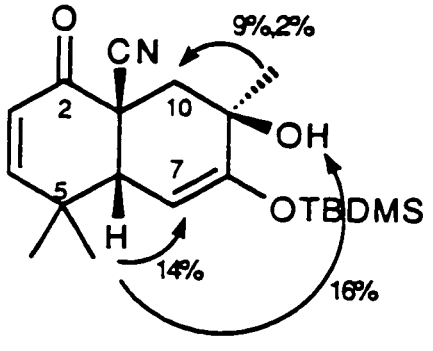


83



82

Figure 1-6



On the basis of the above experiment, it was concluded that the Diels-Alder reaction of dienone **62** with 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene afforded compound **71**. Its ^{13}C NMR APT spectrum displayed distinctive signals at δ 191.81 (α,β-unsaturated carbonyl) and 120.31 (nitrile), and two high field signals at δ -3.71 and -3.87 (dimethylsiloxy). A strong signal at δ 25.82 was representative of the three methyl carbons of the *tert*-butyl group.

The infrared spectrum of **71** displayed characteristic absorption bands at 1693 (α,β-unsaturated carbonyl) and 2241 cm^{-1} (nitrile). In the high resolution mass spectrum, a molecular ion peak at m/*z* 345.2124 was consistent with the molecular formula $C_{20}H_{31}NO_2Si$. The ^1H NMR spectrum showed enone proton signals as doublets (J = 10.5 Hz) at δ 6.62 and 5.94, representing H_4 and H_3, respectively. Five methyl group singlets appeared at δ 1.59 (C-8 methyl), 1.27, 1.06 (geminal methyl groups), 0.95 (*tert*-butyl group), and a high field signal at δ 0.15 (dimethylsiloxy). The *cis* ring-fusion was assigned on the basis of previous examples in this series of cycloadducts, as well as on the strength of the *cis*-principle.

II.E. Addition to *trans*-2-methyl-1,3-pentadiene (Entry 5)

After 3.5 hours, the Diels-Alder cycloaddition of dienone **62** with *trans*-2-methyl-1,3-pentadiene gave a 1:1 mixture (by ^1H NMR integration) of two isomeric cycloadducts in an 89% overall yield. The two cycloadducts were separated by flash column chromatography. Elution with ethyl acetate-Skelly B (5:95) gave one adduct, then subsequent elution gave the more polar adduct, each as a single adduct, as proven by their ^{13}C NMR APT spectra.

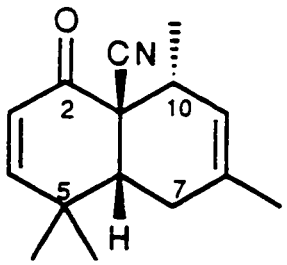
The less polar compound displayed absorption bands at 1686 cm^{-1} for the α,β-unsaturated carbonyl and at 2228 cm^{-1} for the nitrile in its infrared spectrum. A molecular ion peak at m/*z* 229.1466 in the high resolution mass spectrum was consistent with the molecular formula $C_{15}H_{19}NO$. Three vinylic proton signals were displayed in its ^1H NMR spectrum. The protons of the enone system appeared as a doublet of doublets at δ 6.46 (J_1 = 10.5 Hz, J_2 = 1.5 Hz), which included a small W-type coupling and a doublet at δ 5.88 (J = 10.5 Hz)

corresponding to H_4 and H_3, respectively. The other vinylic proton signal appeared as a multiplet at δ 5.26. As stated previously, the required W-type configuration is only possible in the *cis*-isomer. Therefore, the *cis* ring-fusion was assigned on the basis of this long range W-type coupling. The signal for the ring-fusion proton H_6 displayed two other couplings (ddd, J_1 = 10.5 Hz, J_2 = 6.5 Hz, J_3 = 1.5 Hz) thereby indicating that two neighboring protons must be present. As predicted by Alder, the regiochemistry of the cycloadduct follows the *ortho* and *para* rules. Methyl singlets appeared at δ 1.61 (vinylic methyl group), 1.58, and 1.12 (geminal methyl groups). A methyl doublet appeared at δ 1.39 (J = 7.5 Hz).

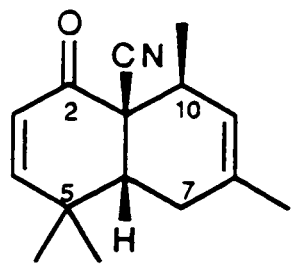
The more polar compound showed absorption bands for the α,β-unsaturated carbonyl at 1684 cm^{-1} and the nitrile at 2239 cm^{-1}. Its high resolution mass spectrum displayed a molecular ion peak at m/*z* 229.1467 which was consistent with the molecular formula $C_{15}H_{19}NO$. The ^{13}C NMR APT spectrum displayed a total of 14 signals including two notable signals at δ 192.50 and 118.28, representing the α,β-unsaturated carbonyl and the nitrile, respectively. In the ^1H NMR spectrum three vinylic proton signals included mutually coupled (J = 10.5 Hz) H_3 and H_4 protons at δ 5.92 and 6.59, respectively, and a multiplet at δ 5.19. The *cis* ring-fusion of the cycloadduct was assigned on the basis of the *cis*-principle. Four methyl groups appeared as a doublet (J = 7.5 Hz) at δ 1.14 and three singlets at δ 1.76 (vinylic methyl group), 1.20, and 1.03 (geminal methyl groups).

The former compound was assigned as the *endo*-to-ketone adduct **72** on the basis of its ^1H NMR spectrum, in comparison with previous examples (entry 1 and entry 3). The latter compound was tentatively assigned as the *endo*-to-

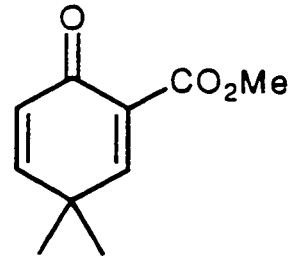
nitrile adduct **73** on the basis of the Diels-Alder reactions of an analogous dienophile, 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadienone **40**[44].



72

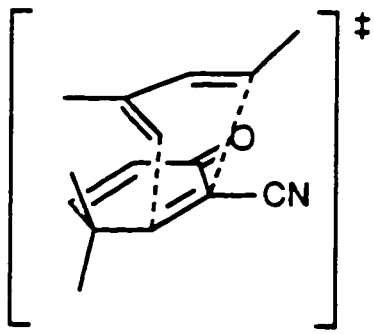


73

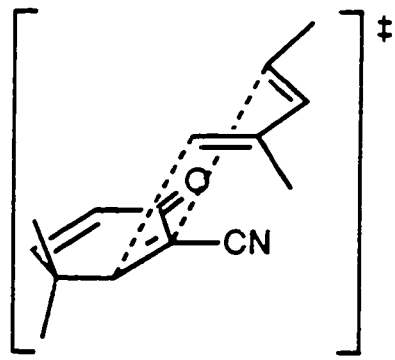


40

Such an assignment of the regiochemistry and the stereochemistry requires the analysis of each transition state. The formation of two epimeric cycloadducts **72** and **73** results from the addition via two different transition states.



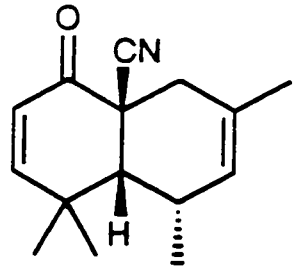
77



78

The *endo*-to-ketone transition state **77** is favored due to its preference for secondary orbital overlap with the ketone carbonyl carbon as well as overlap with the unactivated π-bond. The *endo*-to-nitrile transition state **78** is less favored due to the absence of secondary orbital overlap with the unactivated π-bond. The destabilization of transition state **77** due to steric interaction of the C-2 methyl group of the diene and one of the geminal methyl groups of dienone

62 is overcome by the electronically favored *ortho* and *para* directing effects. Therefore no trace of the anti-*para* adduct **84** was found.

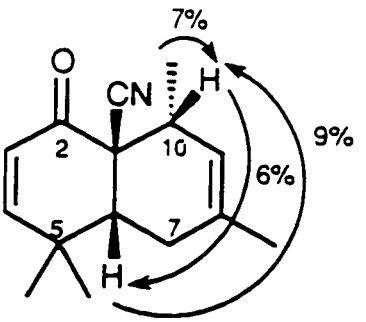


84

The steric destabilization could be overcome by cycloaddition via the *endo*-to-nitrile transition state **78**, in which the steric interaction of the C-2 methyl group of the diene and one of the C-4 methyl groups of the dienophile is alleviated. Competition between the two transition states in the addition of 2-methyl-1,3-pentadiene is comparable, therefore resulting in the formation of equal amounts of each cycloaddition adduct.

NOE experiments as shown in **Figure 1-7** also confirmed the stereochemistry of adduct **72**. Irradiation of the ring-junction proton (H_6) proton signal at δ 2.46 gave a 9% enhancement of the methine proton (H_{10}) signal at δ 2.70. Conversely, irradiation of the methine proton (H_{10}) gave a 6% enhancement of the ring-junction proton (H_6). Irradiation of the C-10 methyl at δ 1.39 gave 7% enhancement of the C-10 methine proton signal, but no enhancement of the ring-junction proton (H_6).

Figure 1-7

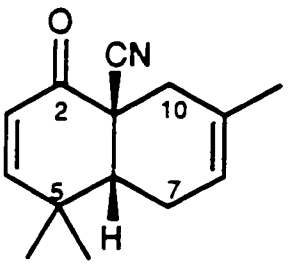


II.F. Addition to 2-methyl-1,3-butadiene (Entry 6)

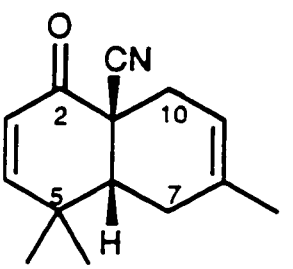
After 22.5 hours, the zinc chloride mediated cycloaddition of dienone **62** with 2-methyl-1,3-butadiene gave a 7:3 mixture (by ^{1}H NMR integration) of isomeric adducts in high yield (91%). A pure sample of the major isomer could be obtained by subjecting the mixture to flash column chromatography (ethyl acetate-Skelly B, 5:95) several times, in which the sample became more enriched with the major isomer each time. The pure sample was deduced as a single compound by the appearance of 14 signals in its ^{13}C NMR APT spectrum. The signals for the ^{13}C NMR APT of the minor cycloadduct was determined from the ^{13}C NMR APT spectrum of the 7:3 mixture.

The mixture of cycloadducts showed absorption bands at 1687 cm^{-1} for the α,β-unsaturated carbonyl and at 2241 cm^{-1} for the nitrile. The high resolution mass spectrum of the mixture gave a molecular ion peak at m/z 215.1305, which was consistent with the molecular formula $C_{14}H_{17}NO$. Each compound gave signals in its ^{13}C NMR APT spectrum for the α,β-unsaturated carbonyl at δ 192.38 and 191.97 (major and minor, respectively) and for the nitrile at δ 120.39 and 120.41 (major and minor, respectively).

The *cis* ring-fusion for both adducts was assigned on the strength of the *cis*-principle. The major adduct showed two mutually coupled (J = 10.5 Hz) vinylic protons at δ 6.63 and 5.95 corresponding to enone protons H_4 and H_3, respectively and another vinylic signal at δ 5.41 which appeared as a multiplet. The minor adduct also showed three vinylic proton signals including two mutually coupled signals (J = 10.5 Hz) at δ 6.63 and 5.96, due to the enone protons and a multiplet at δ 5.53. Based on these spectral data, it is obvious that addition occurred at the more substituted double bond of the dienophile **62**. Therefore, only two structures are possible, **74** and **75**. On the basis of the analogous dienone system, 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-one **40**[44], the major adduct was tentatively assigned to structure **74** and the minor adduct was assigned to structure **75.**



74

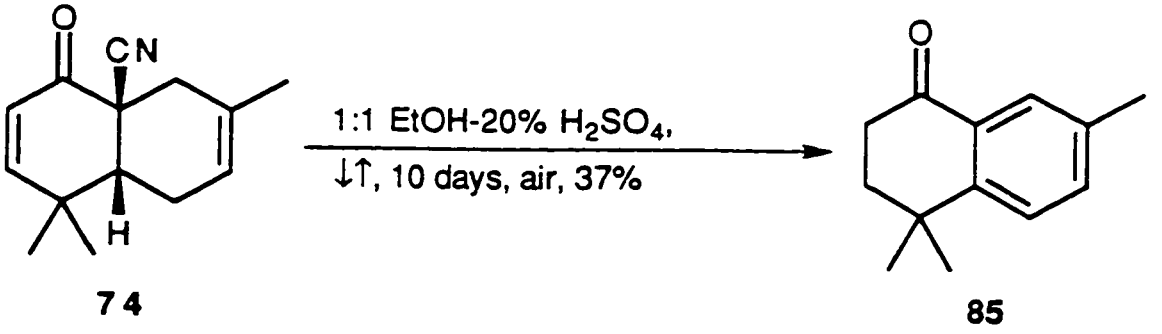


75

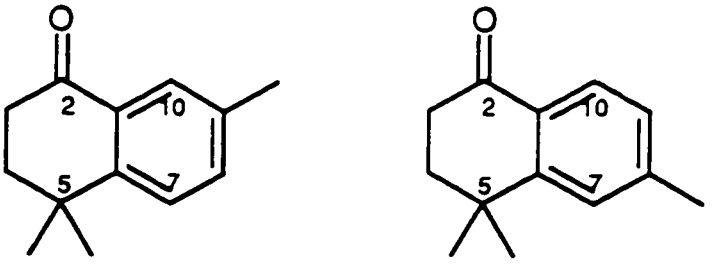
The regiochemistry of the major adduct was determined indirectly by aromatization of the B-ring by refluxing the pure major adduct in a 1:1 mixture of ethanol-20% sulfuric acid (**Scheme 1-7**) to give in 37% yield a product with the following spectral data. The infrared spectrum displayed an absorption band at 1686 cm^{-1} for the aryl ketone. The high resolution mass spectrum displayed a molecular ion peak at m/*z* 188.1202 which is consistent with the molecular formula $C_{13}H_{16}O$. Analysis of the ^1H NMR spectrum showed

aromatic proton signals as a singlet at δ 7.83 (1 proton) and a multiplet at δ 7.34 (2 protons). Two sets of triplets (J = 8 Hz) representing two protons each, appeared at δ 2.72 and 2.00 due to saturation of the enone double bond. Methyl groups appeared as singlets at δ 2.35 (C-9 methyl group) and 1.34 (geminal methyl groups). Elucidation of the structure of the major adduct was based on the signal at δ 7.83 which is consistent with **85** (derived from the anti-*para* addition product) and not with **86** (the *para* addition product).

Scheme 1-7



74 **85**

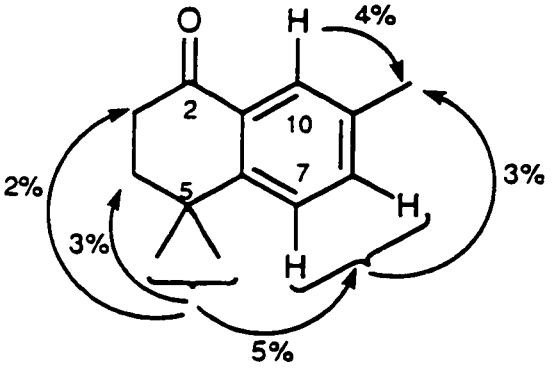


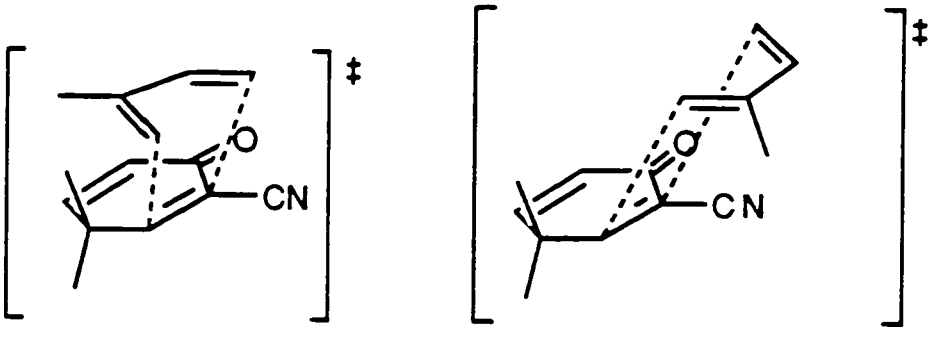
85 **86**

NOE experiments were conducted to confirm the regiochemistry of **85** (**Figure 1-8**). Irradiation of the geminal dimethyl at δ 1.34 gave a 3% and a 2% enhancement of the methylene proton signals (H_4 and H_3, respectively), as well as a 5% enhancement of the aromatic proton signal at δ 7.34 (2 protons). An

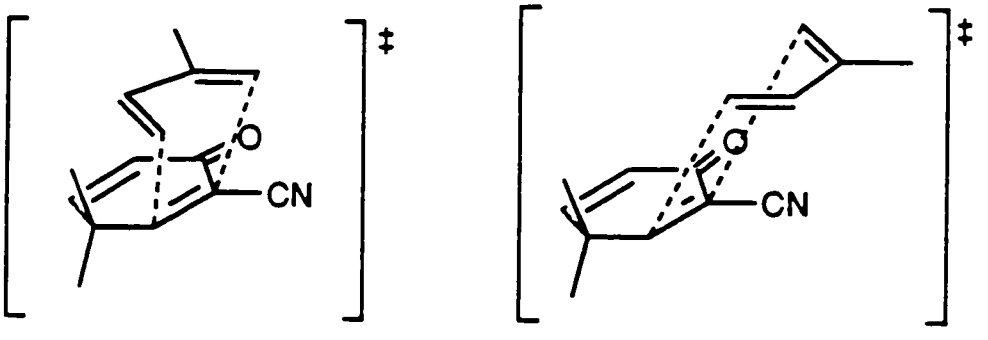
enhancement of the C-9 methyl signal at δ 2.35 was observed when the two aromatic proton signals at δ 7.34 and 7.83 (3% and 4%, respectively) were irradiated. No enhancement of the geminal dimethyl signal was seen when H_{10} was irradiated. Compound **85** must be derived from cycloadduct **74**, as determined from the aromatization reaction above.

Figure 1-8





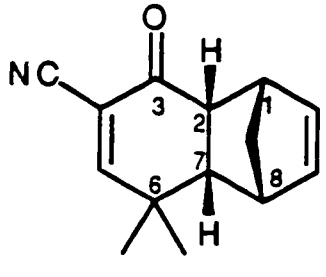
87 **88**



89 **90**

The regiochemical outcome of the cycloadditon of dienone **62** with 2-methyl-1,3-butadiene can be rationalized by observing the four transition states. The anti-*para* *endo*-to-ketone transition state **89** is electronically disfavored but is sterically favored. The C-2 methyl group of the diene is not sterically encumbered by one of the C-4 geminal methyl groups of dienone **62**. The *para* directed *endo*-to-ketone transition state **87** is electronically favored but is sterically disfavored. The *para* oriented *endo*-to-nitrile transition state **88** is favored electronically in contrast to the anti-*para* *endo*-to-nitrile transition state **90** which is disfavored electronically. Both transition states (**88** and **90**) are sterically favored. A large portion of adduct **74** would be formed via transition state **89** in which there is secondary orbital overlap with the unactivated π-bond of the dienophile and the carbonyl carbon as well as a lack of steric influence. Electronically favored *para* oriented transition states **87** and **88** would lead to the formation of adduct **75**. Transition state **87** has additional secondary orbital overlap, but transition state **88** has no steric interference. Therefore, the ratio of products **74** and **75** would be dependent on the relative strength of the electronic and the steric directing effects. The weighing of these two factors would determine the relative ratios of the two cycloadducts produced in the Diels-Alder cycloaddition reaction.

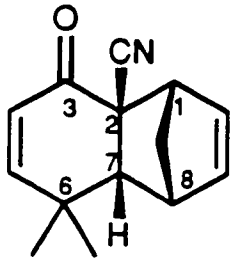
II.G. Addition to cyclopentadiene (Entry 7)



76

The slow reaction rate or fast retro Diels-Alder reaction of the cycloaddition of dienone **62** with cyclopentadiene under zinc chloride catalysis resulted in 27% recovery of dienone **62** and 49% yield of adduct **76** (based on consumed dienone) after 66.5 hours. The reaction temperature was critical. Since rapid dimerization of the diene occurs at elevated temperatures, the reaction was performed at a lower temperature (-25 °C) than the others that were explored in this series.

Contrary to the results obtained from the other cycloaddition reactions previously discussed in this series, the addition of cyclopentadiene to dienone **62** took place at the less substituted double bond of the dienone. Examination of the spectral data of **76** led to this conclusion. The structure of **76** was based on its ^{1}H NMR and ^{13}C NMR APT spectra. The ^{1}H NMR spectrum displayed three vinylic proton signals as a doublet (J = 1.5 Hz) at δ 7.13 and two mutually coupled signals (J_1 = 5.5 Hz, J_2 = 3 Hz) at δ 6.08 and 5.92. The ^{13}C NMR APT spectrum displayed three anti-phase vinylic carbon signals at δ169.27, 135.72 and 134.48, representing sp^2 carbons with one proton attached. The normal addition product **79**, in which addition occurred at the more substituted double bond would give four vinylic proton signals, as well as four anti-phase vinylic carbon signals.

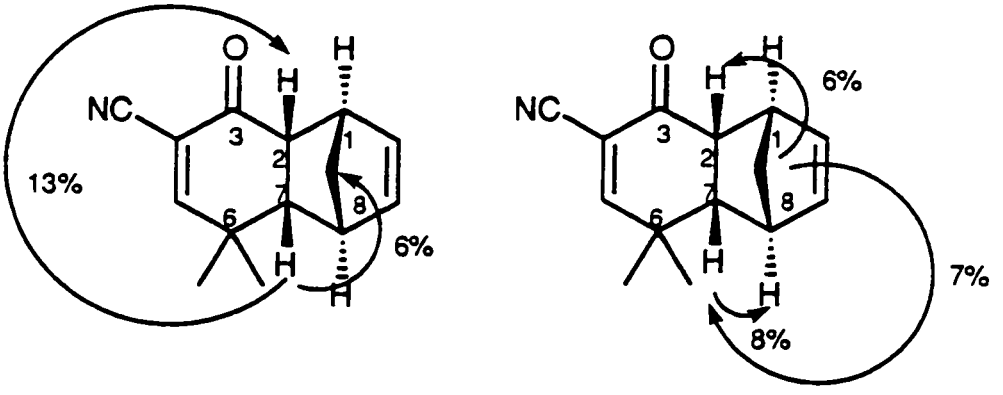


79

The *cis* ring-junction was assigned on the basis of a W-type long range coupling of the beta enone proton at δ 7.13 (J = 1.5 Hz) with the ring junction proton at δ 2.52 (ddd, J_1 = 9 Hz, J_2 = 3.5 Hz, J_3 = 1.5 Hz). Geminal methyl groups appeared as singlets at δ 1.24 and 1.20.

The stereochemistry of the adduct was assigned with the assistance of decoupling and NOE experiments, **Figure 1-9**. Irradiation of the ring-junction proton (H_7) signal at δ 2.52 gave enhancement of the ring-junction proton (H_2) signal at δ 3.19 (13%), the methine proton (H_8) at δ 3.07 (8%), and the methylene protons at δ 1.48 and 1.35 (6%). These results support the *cis* ring-fusion as shown previously from the ^1H NMR spectral data. Irradiation of the methylene protons gave enhancements of 6% and 7% to the ring-junction protons H_2 and H_7, respectively.

Figure 1-9



The molecular ion peak at m/*z* 213.1154 in the high resolution mass spectrum was consistent with the molecular formula $C_{14}H_{15}NO$.

A kinetically controlled process may operate in the formation of the normal cycloaddition product **79**. The normal cycloaddition product **79** could be obtained in a small amount (59%, based on consumed starting material) via a thermal reaction (mixing the diene with the dienone in dichloromethane at room temperature after 31 days). Its infrared spectrum gave absorption bands at 1672 cm^{-1} for the α,β-unsaturated carbonyl and at 2232 cm^{-1} for the nitrile. The ^{13}C NMR APT spectrum gave 14 signals including signals for the α,β-unsaturated carbonyl at δ 190.96 and for the nitrile at δ 122.16. The ^{1}H NMR spectrum gave two sets of coupled vinylic proton signals, one set at δ 6.47 and 5.81 (J = 10.5 Hz; H_5 and H_4, respectively) and the other at δ 6.15 and 5.80 (J_1= 6 Hz, J_2 = 3 Hz). An additional long range coupling of the signal at δ 6.47 to the ring-junction proton H_7 (J = 1.5 Hz) confirmed the ring-junction stereochemistry as *cis*, as observed with the previous examples.

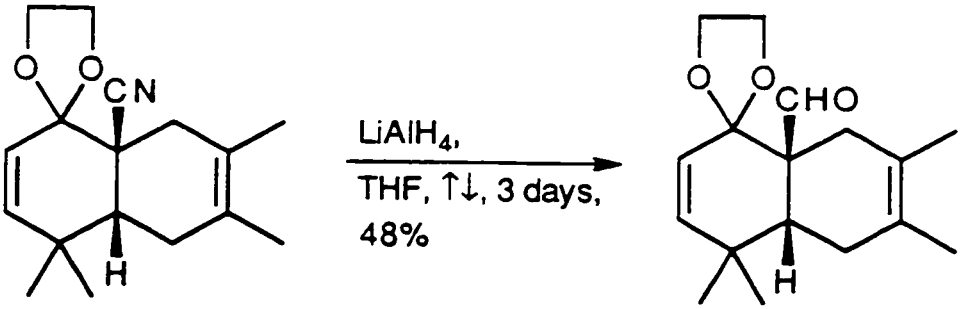
An experiment was conducted in which the normal cycloaddition product **79** was treated with two equivalents of zinc chloride and twenty equivalents of cyclopentadiene in diethyl ether. After six days, the reaction mixture was worked up in the usual manner. After examining the ^{1}H NMR spectrum of the residue, it was found that the abnormal addition product **76** as well as dienone **62** were present with no traces of the starting material **79**. These results can be explained on the basis of a retro-Diels-Alder reaction and subsequent addition of enone **62** with the diene under Lewis acid catalysis to give **76**, **Scheme 1-5**. We concluded that the Lewis acid mediated cycloaddition reaction of dienone **62** with cyclopentadiene to give the unusual cycloaddition adduct **76** may be due to a thermodynamically controlled process.

The zinc chloride mediated Diels-Alder reaction of dienophile **62** with a variety of dienes proved to be very effective. Reaction yields were generally high and ranged from 80-98% with one exception, and the regio- and stereochemical outcomes were in general quite predictable.

III. Reductive cleavage and alkylation of the Diels-Alder adducts

The previous section described the synthetic utility of the cyano group as an activating group in the Diels-Alder approach towards polycyclic systems. From the results obtained, it was found that the cyano group is a good synthetic tool in promoting the [4 + 2] cycloaddition reaction. The cyano group is a versatile functionality which can be transformed to a wide number of functional groups. There are methods to convert nitriles to ketones including the use of alkyllithium reagents[63]. The cyano group can also be reduced using various methods such as diisobutylaluminum hydride (DIBAL), reduction to an aldehyde[64,65], lithium aluminum hydride ($LiAlH_4$), reduction to an amine[66], or dissolving metal, reduction to the decyanated product[67,68]. Initially, we believed that the amine could be easily introduced to the bicyclic system by reduction of the nitrile by several general methods[81-83]. These methods have been used extensively in the literature to convert the nitrile moiety to an amine moiety. In order to investigate the applicability of such methods, we first needed to protect the carbonyl group from the reaction conditions. We converted the carbonyl to a ketal group by treatment with ethylene glycol in the presence of a catalytic amount of *para*-toluenesulfonic acid in benzene. In our system of adducts, the expected amine products were not produced. Instead, protection of the carbonyl as a ketal **91**, followed by reduction with lithium aluminum hydride[84] in refluxing THF afforded aldehyde **92**, **Scheme 1-8**.

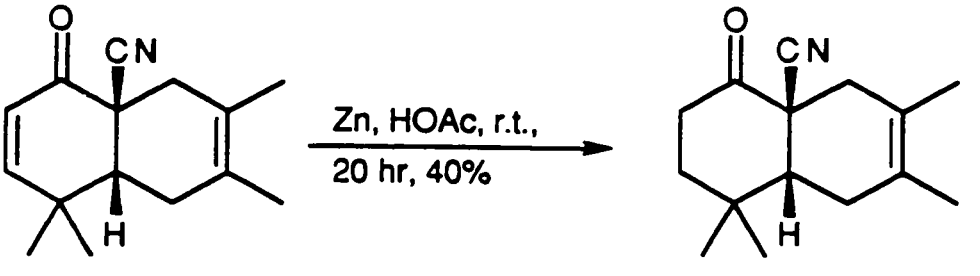
Scheme 1-8



91 **92**

It appeared that the reduction of the nitrile to the amine moiety was difficult to execute, therefore we turned our attention towards the reductive cleavage of the cyano group. Several methods[85] can be applied to the cleavage of the nitrile to give the reduced adduct. The cyano group could be considered a good leaving group. Under this premise, we attempted to reduce the cycloadduct using conditions involved in dehalogenation reactions. The nitrile (R-CN) could possibly be reduced to the decyanated (R-H) adduct by treatment with zinc dust in acetic acid[86]. Interestingly under these conditions, the enone moiety of the α,β-unsaturated ketone **68** was reduced to give the saturated ketone **93**, leaving the cyano group untouched (**Scheme 1-9**).

Scheme 1-9

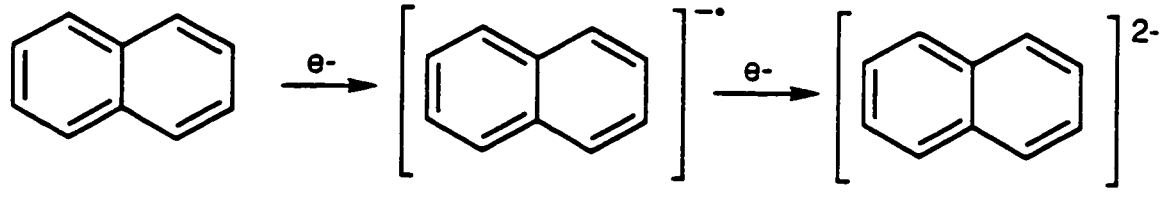


68 **93**

These undesirable results led us to investigate dissolving metal reduction and related methods as a means to generate the desired cleavage reaction. Radical anions of aromatic hydrocarbons and alkali metals[87-90] have found wide applications in organic synthesis, organometallic, inorganic, environmental[91], and analytical chemistry[92]. Sodium and lithium are the most commonly used metals. Various aromatic hydrocarbons that have been employed include biphenyl, naphthalene, anthracene, perylene, phenanthrene, pyrene, tetracene, and their derivatives. The radical anions of biphenyl and naphthalene in an ethereal solvent, usually THF, are powerful reducing agents. 4,4'-Di-*tert*-butylbiphenyl is preferred over its parent compound for its solidity and ease of handling, while α-(*N,N*-dimethylamino)naphthalene is used in place of naphthalene to facilitate the separation of the products when they are as nonpolar as naphthalene[93].

When the metal is dissolved in a solution of naphthalene, with THF being the most commonly used ethereal solvent, a deep green to blue solution of the radical anion is formed, like other "electron solutions". If more than one equivalent of the metal is added, the dianion will be produced (**Scheme 1-10**), although its presence can never be completely excluded even with less than one equivalent of lithium due to the disproportionation of the radical anion.

Scheme 1-10



The chemical reactions of these radical anions can be classified into two general classes, namely, proton abstraction reactions, due to the high basicity of the radical anion and single electron transfer (SET) reactions. These radical anions were effective in abstracting protons form compounds having a pK_a less than 33. Cases of proton abstraction from aldehydes, ketones, carboxylic acids, esters, carboxylates, nitriles, and epoxides are known in the literature, although the reactions might be complicated by the SET mechanism. The majority of the radical anion reactions involved the SET reactions. Therefore, a catalytic amount instead of a stoichiometric equivalent of the aromatic hydrocarbon can be used in conjunction with the metal powder to effect the SET reactions[94-96].

The carbon-carbon σ-bonds in alkanes are, as expected, inert to radical anions. The most commonly seen examples of lithium naphthalenide SET reactions are probably the reductions of alkyl, silyl[97], vinyl[98] or aryl halides[99], dihalides[100-103], and pseudo halides (ArX, RX or R_3SiX, where X = F, Cl, Br, I, CN[104], SePh). A variety of products could be formed due to the different pathways that these reductions could proceed. The R· or R- formed[105] can add to another functional group in the same molecule, abstract a hydrogen atom or a proton from the media to yield the reduced product R-H, couple with the naphthalenide radical anion to form alkylated naphthalenes or alkylated dihydronaphthalenes or dimerize to give R-R. If a leaving group is present at the beta position, β-elimination will occur to give a carbon-carbon double bond[106]. The reductions are usually very fast and proceed at low temperatures. This allows for the trapping of the anions produced with a variety of electrophiles.

This reductive process led us to attempt the reductive cleavage of the cycloadducts using lithium naphthalenide as the reducing agent. Lithium naphthalenide[18,68,107] has been used extensively as an alternative method to dissolving metal reduction. In this case, the choice of lithium naphthalenide as a reducing agent is not complicated by the presence of any functional groups that are sensitive to lithium naphthalenide. The use of this approach in our system to effectively remove the nitrile moiety and subsequent replacement of the nitrile group with an alkyl substituent has a wide range of synthetic applications towards the elaboration of polycyclic systems. Such an application is possible, due to the nature of the adduct. The cyano group is in an alpha relationship to the ketone carbonyl. Initial formation of the enolate in the lithium naphthalenide reduction occurs at only one site which in turn could be readily trapped with an alkylating agent. This process could prove to be a very useful tool, whereby a very simple operation could incorporate a variety of different functional groups, without the complications invoked by lengthy functional group manipulations.

It was observed that the cyano group could easily be removed by reduction using lithium naphthalenide. The temperature of the reductive cleavage was important. It was found in preliminary studies that the reductive cleavage was achieved at a temperature of -25 °C. The reductive cleavage was also studied at temperatures of -78 °C and -40 °C. In these cases, at temperatures below -25 °C, no reduced product was formed and only the starting adduct was recovered from the reaction mixture. The color of the reaction mixture was an indication of the presence of an excess of lithium naphthalenide. In general, the presence of a dark green to blue solution indicates the presence of an excess of reducing agent. The use of an excess amount of lithium naphthalenide did not

alter the yields of the ensuing reductive cleavage process. Although, only two equivalents were required to achieve the reductive cleavage and six equivalents were required by the reaction, for convenience, all reactions performed in this study used a total of twelve equivalents of lithium naphthalenide to ensure that the reaction goes to completion.

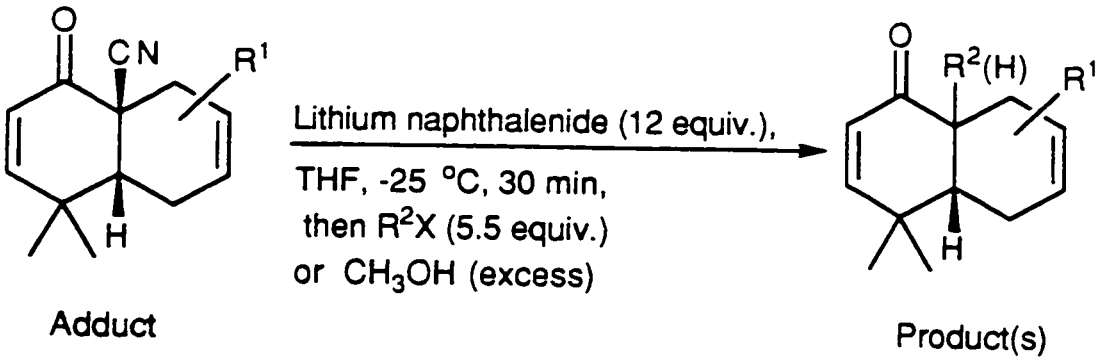
The lithium naphthalenide solution was freshly prepared prior to use. In general, the solution was made as a stock solution and used immediately after preparation. It was found that the solution was stable enough that it could be stored at -4 °C for a month or even longer without any appreciable loss in reactivity[61].

The stock solution used in the reductive cleavage reactions employed an excess of lithium metal to naphthalene (2:1)[107]. The mixture was stirred in THF under an inert atmosphere overnight and used the next day.

The general procedure for reductive cleavage reactions involved the dissolution of the adduct in THF, followed by pre-cooling the solution at -25 °C under an inert atmosphere. Addition of a pre-cooled (-25 °C) stock solution of lithium naphthalenide (12 equivalents) by syringe to the adduct solution followed by quenching of the mixture with methanol after 30 minutes afforded an epimeric mixture of *cis* and *trans* products. The reductive cleavage of several adducts using lithium naphthalenide were investigated (**Table 1-3**).

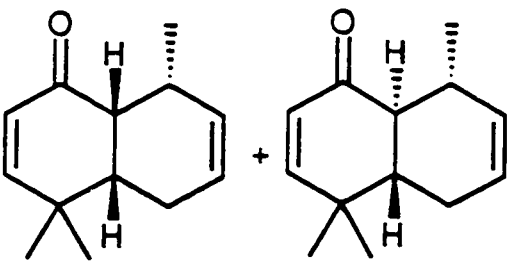
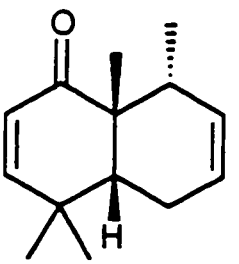
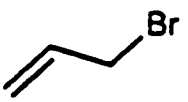
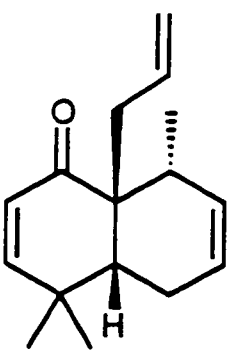
The reductive removal of the cyano group (entries 1, 6, and 9) appears to be a general process. The reaction yields were fair (50-75%). In general, the reaction gave the *trans* ring-junction product as the major product, when the electrophile is a proton.

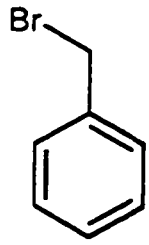
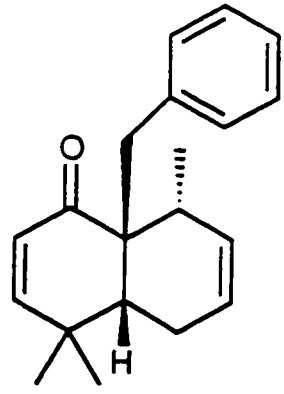
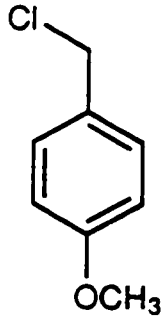
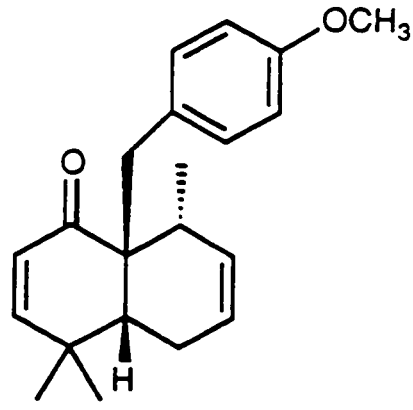
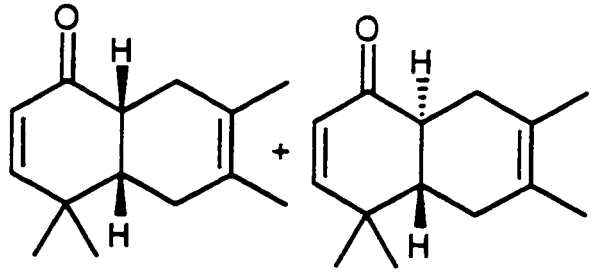
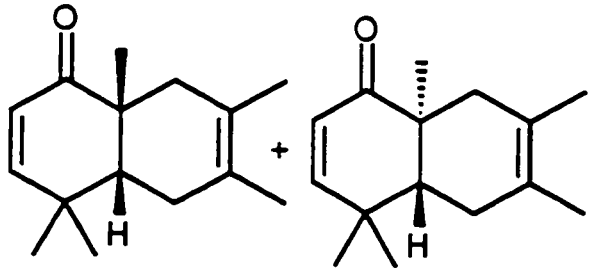
Table 1-3. Reductive decyanation and alkylation of the Diels-Alder adducts.

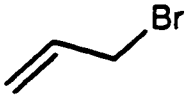
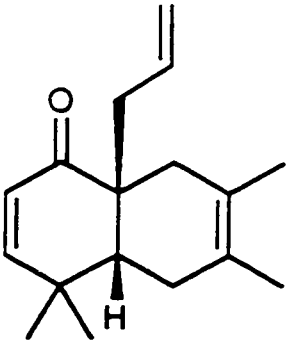
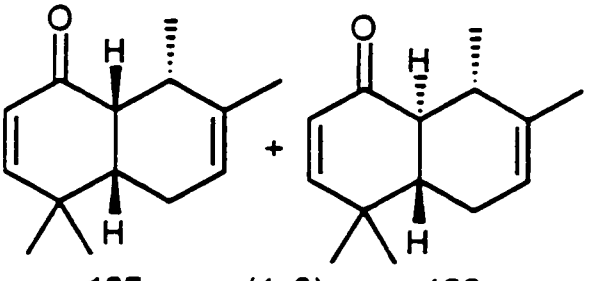
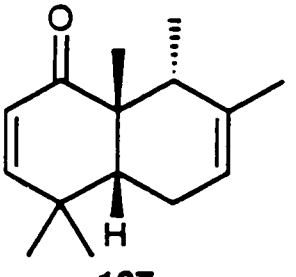
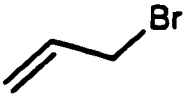
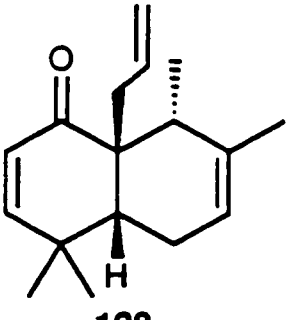


Adduct

Product(s)

Entry	Adduct	R^2X or CH_3OH	Time (hr)	Product(s)	Yield (%)
1	**69**	CH_3OH	0.5	 **94** (1:5) **95**	73
2	**69**	CH_3I	22	 **96**	83
3	**69**		21	 **97**	70[a]

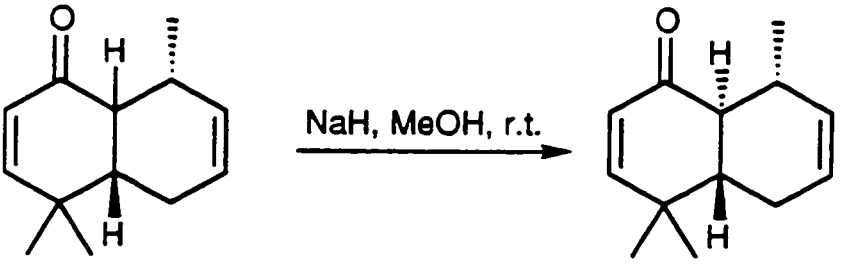
Entry	Adduct	R^2X or CH_3OH	Time (hr)	Product(s)	Yield (%)
4	**69**		18	 **98**	57[b]
5	**69**		18	 **99**	49[b]
6	**68**	CH_3OH	0.5	 **100** (1:2) **101**	50
7	**68**	CH_3I	21	 **102** (1:1) **103**	40

Entry	Adduct	R^2X or CH_3OH	Time (hr)	Product(s)	Yield (%)
8	**68**		18	 **104**	68[a]
9	**70**	CH_3OH	0.5	 **105** (1:2) **106**	75
10	**70**	CH_3I	23	 **107**	78
11	**70**		17	 **108**	94[a]

[a]The reaction was run at room temperature after addition of allyl bromide. [b]The reaction was run in refluxing THF after addition of the alkylating agent.

The product ratio was based on the ^1H NMR integration of the beta proton of the dienone system. The *cis* ring junction was confirmed by observing the vinylic proton signal with a long range W-type coupling. As discussed previously, the W-type configuration is only possible in the *cis* conformation and not in the *trans* conformation. The product ratio appears to be the result of a kinetically controlled process. The epimeric mixtures could easily be isomerized to the thermodynamically controlled products by treatment with sodium methoxide in methanol at room temperature (**Scheme 1-11**). The *trans* ring-junction product was formed either exclusively (entries 1 and 9) or predominantly (entry 6) in which a thermodynamic ratio of 2:1 (*trans*:*cis*) was found.

Scheme 1-11



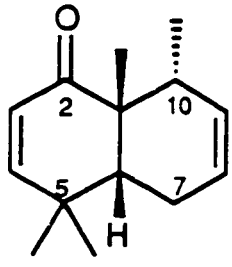
94 and 95 **95**

The facile removal of the cyano group led us to investigate the trapping of the enolate ion with an alkylating agent. Several alkylating agents were chosen for this reductive alkylation process. These included methyl iodide, allyl bromide, and two bulky alkylating reagents, benzyl bromide and *para*-methoxybenzyl chloride (**Table 1-3**).

stereoisomers. A less reactive alkylating agent such as allyl bromide (entry 8) gives a more selective reaction.

III.A. Reductive alkylation of (1R*,6R*,10R*)-1-cyano-5,5,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (69)

Treatment of adduct **69** with the reducing agent, lithium naphthalenide, followed by alkylation with methyl iodide afforded methylated adduct **96** in an 83% yield. The infrared spectrum showed a strong absorption at 1670 cm^{-1} for the α,β-unsaturated carbonyl. The notable absence of an absorption around 2200 cm^{-1} for the cyano group, indicated that the cyano group was in fact removed and possibly replaced by a methyl group. The ^{13}C NMR APT spectrum displayed 14 signals, including a signal at δ 204.58 characteristic for the α,β-unsaturated carbonyl carbon. The noticeable absence of a nitrile carbon signal in the spectrum at approximately 120 ppm also supports the fact that the cyano group was removed from the adduct. The presence of 14 signals indicates that the methyl group was added. The high resolution mass spectrum supports the molecular formula $C_{14}H_{20}NO$, as indicated by the molecular ion peak at m/*z* 204.1491.



96

The ^{1}H NMR spectrum of **96** showed the presence of four methyl groups. Three methyl group signals appeared as singlets at δ 1.32, 1.12, and 1.05. The low field singlet was attributed to the methyl group derived from methyl iodide at

In general, the procedure for the reductive alkylation was similar to that of the reductive cleavage reaction. Instead of quenching the reaction mixture with methanol, the reaction mixture was quenched with an alkylating agent (5.5 equivalents). An attempt to monitor the reaction by thin layer chromatography (tlc) showed that, in most cases, the sample spot for the reductive cleavage product was identical to that of the alkylated product. Therefore, it was difficult to monitor the progress of the reaction. Usually the reaction mixture was stirred overnight to ensure the completion of the alkylation reaction.

The alkylation reactions gave a wide range of yields (40-94%). The reactivity of the enolate derived from adduct **68** (entries 7 and 8) towards alkylating agents was not very high. Even with a highly reactive alkylating agent, such as methyl iodide, the alkylated product was still produced in low yield (40%).

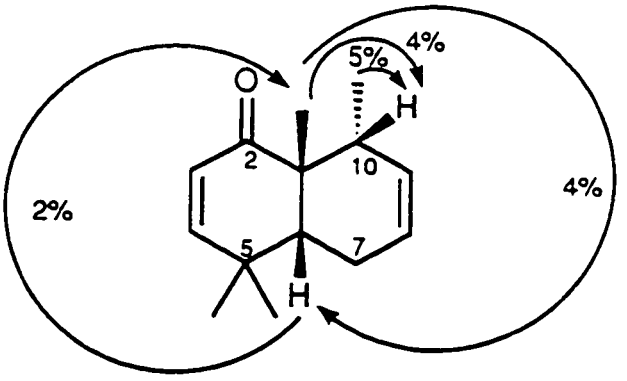
The reactivity of the alkylating agents used in the reductive alkylation reactions was apparent by the temperatures required to induce alkylation. At -25 °C, methyl iodide added to the enolate derived from the adduct afforded the alkylated product. Less reactive alkylating agents required elevated temperatures. Allyl bromide required room temperature, whereas benzyl bromide and *para*-methoxybenzyl chloride required refluxing THF to afford the desired alkylated products.

The reductive alkylation reactions afforded only one product, with one exception (entry 7). In this case, it is possible that the absence of a methyl group at C-10 may not sterically interfere with the formation of the *trans* ring-junction product. In addition, a more reactive alkylating agent such as methyl iodide might have lower selectivity (entry 7) which results in the formation of an equal mixture of

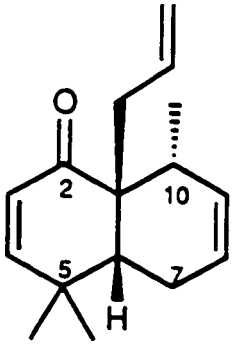
C-1. The other two methyl singlets were assigned as the geminal methyl groups. Another methyl group appeared as a doublet (J = 8 Hz) at δ 0.94 corresponding to the C-10 methyl. The presence of four methyl group signals supports the formation of the alkylated product **96**. It also supports the production of only one product. Mutually coupled proton signals (J = 10.5 Hz), representing the enone protons at δ 6.48 and 5.92 (H_4 and H_3, respectively) were displayed in the ^1H NMR spectrum, as well as two other vinylic proton signals at δ 5.67 (multiplet) and 5.52 (dm, J = 10 Hz). Overlapped signals at δ 2.06-2.14 representing one methylene proton H_7 and the allylic methine proton H_{10} and a doublet (J = 8 Hz) at δ 1.90 for H_6 were identified by proton decoupling experiments.

The stereochemistry of **96** was supported by NOE experiments, **Figure 1-10**. Irradiation of the C-1 methyl at δ 1.32 gave a 4% enhancement of the ring-junction proton at δ 1.90, in addition to a 4% enhancement of the allylic methine proton (H_{10}) signal, indicating the formation of a *cis* ring-junction product. Conversely, there was a 2% enhancement of the C-1 methyl signal upon irradiation of the ring-junction proton (H_6) signal at δ 1.90. Enhancement of the methine proton signal (5%) was found upon irradiation of the C-10 methyl signal at δ 0.94, without any enhancement of either the ring-junction or the C-1 methyl signal.

Figure 1-10



Reductive alkylation of **69** with allyl bromide at room temperature afforded **97** in 70% yield. Its high resolution mass spectrum displayed a molecular ion peak at m/*z* 230.1666 which corresponds to the molecular formula $C_{16}H_{22}O$. Elemental analysis of **97** also confirmed the molecular formula $C_{16}H_{22}O$. The disappearance of the nitrile absorption band in the infrared spectrum at approximately 2200 cm^{-1} confirmed that the cyano group was removed from **69**. The ^{13}C NMR APT spectrum displayed 16 carbon signals, including 6 sp^2 vinylic carbons, as well as a carbonyl carbon signal at δ 204.58.



97

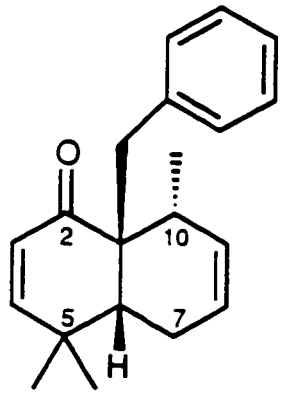
The ^1H NMR spectrum of **97** displayed two mutually coupled doublets (J = 10.5 Hz) at δ 6.50 and 5.96 corresponding to H_4 and H_3 enone protons, respectively.

Two other vinylic proton signals derived from the other endocyclic double bond appeared as two multiplets at δ 5.70 (H_9) and 5.53 (H_8). The vinylic protons derived from allyl bromide displayed the typical coupling constants indicative of a terminal olefin. Signals appeared for the terminal vinylic protons at δ 5.07 (ddd, J_1 = 17 Hz, J_2 = 2 Hz, J_3 = 2 Hz) and 5.00 (ddd, J_1 = 10 Hz, J_2 = 2 Hz, J_3 = 2 Hz). The non-terminal vinylic proton derived from allyl bromide appeared at δ 5.58 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 10 Hz, J_4 = 2 Hz). Geminal methyl groups appeared as singlets at δ 1.11 and 1.07. The methyl group at C-10 appeared as a doublet at δ 0.93 (J = 8 Hz).

The stereochemistry of the ring-junction of **97** was tentatively assigned based on the previous example, compound **96**. The NOE experiments showed that a *cis* ring-junction was present in the alkylation with methyl iodide. The allyl group is not much larger than the methyl group, therefore, we believe that since there was only one product formed from the alkylation reaction with allyl bromide, we can conclude that the same stereochemistry at the ring-junction will also apply. We are tentatively assigning the stereochemistry of the ring-junction of **97** to be in a *cis* relationship.

Reductive alkylation of **69** with benzyl bromide in refluxing THF afforded enone **98** in a yield of 57%. The ^1H NMR spectrum displayed coupled benzylic protons as doublets at δ 3.77 and 2.70 (J = 14 Hz). An aromatic proton signal (5 protons) appeared as a multiplet at approximately δ 7.15. Enone protons appeared as mutually coupled doublets (J = 10 Hz) at δ 6.46 for the beta proton and at δ 5.99 for the alpha proton. Additional vinylic proton signals appeared as multiplets at δ 5.77 and 5.60 for H_9 and H_8, respectively. The allylic methine proton H_{10} appeared as a multiplet at δ 2.21. Three methyl group signals

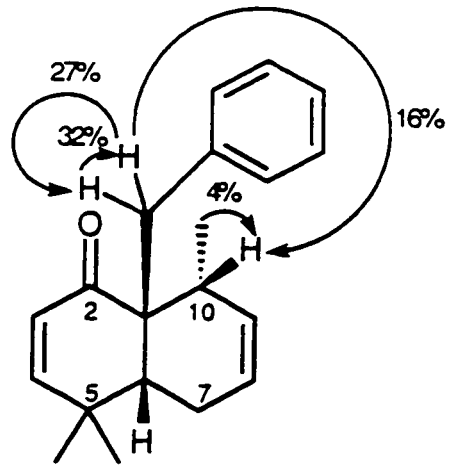
included a doublet (J = 8 Hz) at δ 0.98 corresponding to the C-10 methyl group and two singlets for the geminal methyl groups at δ 1.06 and 0.92. Elemental analysis and high resolution mass spectrometry confirmed the molecular formula $C_{20}H_{24}O$ for **98**.



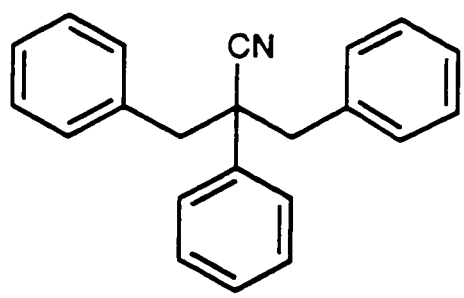
98

The stereochemistry of **98** was assigned on the basis of NOE experiments, as well as NOE experiments conducted on the other compounds in this series. Irradiation of the the benzylic proton at δ 3.77 gave a 27% enhancement of the other benzylic proton at δ 2.70, as well as enhancement (16%) of the allylic methine proton (H_{10}) signal at δ 2.21. The benzylic proton signal at δ 3.77 was enhanced (32%) when the other benzylic proton signal at δ 2.70 was irradiated. Irradiation of the C-10 methyl group at δ 0.98 gave enhancement of the allylic methine proton H_{10} only. No enhancement of the benzylic proton signals was found. On the basis of NOE experiments, as well as the results from previous reductive alkylation reactions, the stereochemistry of **44** was assigned as depicted in **Figure 1-11**.

Figure 1-11



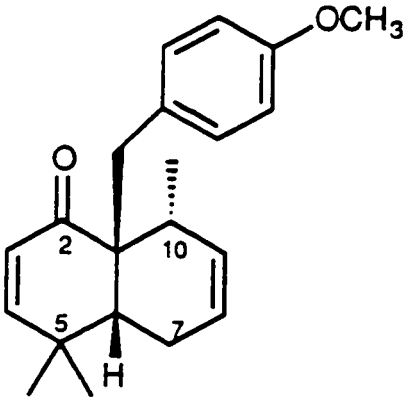
A side-product was formed from the reductive alkylation reaction with benzyl bromide. This compound was identified as nitrile **109** on the basis of the following spectral data. The ^1H NMR spectrum showed aromatic signals at δ 7.32 (5 protons), 7.20 (6 protons), and 7.05 (4 protons) as multiplets. The spectrum also showed a singlet at δ 3.35 due to the four benzylic protons. The infrared spectrum displayed an absorption band for the nitrile group at 2241 cm^{-1} as the only distinctive absorption. The high resolution mass spectrum displayed a molecular ion peak at m/*z* 297.1522 corresponding to the molecular formula $C_{22}H_{19}N$.



109

The formation of this side-product is not unreasonable. In the presence of excess amounts of lithium naphthalenide and benzyl bromide, cleavage of the cyano group occurs and displacement of the bromide of the alkylating agent affords phenylacetonitrile. Subsequent alkylation of this compound resulted in the formation of **109**. Therefore, in this reductive alkylation process an excess of benzyl bromide is required to conduct the reaction in which three equivalents will be used in the formation of the side-product.

Treatment of **69** with lithium naphthalenide followed by addition of *p*-methoxybenzyl chloride and refluxing for 18 hours afforded ketone **99** (49% yield).



99

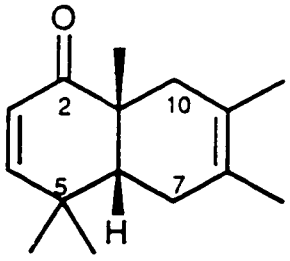
The infrared spectrum of **99** displayed no absorptions for the nitrile group confirming that the cleavage of the cyano group had occurred. The high resolution mass spectrum gave a molecular ion peak at m/*z* 310.1924 which corresponds to the molecular formula $C_{21}H_{26}O_2$. The ^1H NMR spectrum displayed a singlet at δ 3.76 corresponding to the methyl ether and doublets (J = 9 Hz) at δ 7.05 and 6.74 representing the aromatic protons. These results confirmed that the alkylation had taken place. Signals for the enone protons at

δ 6.45 and 5.97 (beta and alpha protons, respectively), as well as multiplets for the H_8 and H_9 protons at δ 5.76 and δ 5.59 also appeared in the ^1H NMR spectrum. Benzylic methylene protons appeared as doublets (J = 14 Hz) at δ 3.67 and 2.59. The allylic methine proton appeared as a multiplet at δ 2.18. Three methyl group signals appeared as two singlets for the geminal methyl groups at δ 1.05 and 0.93 and a doublet (J = 8 Hz) for the C-10 methyl group at δ 0.96.

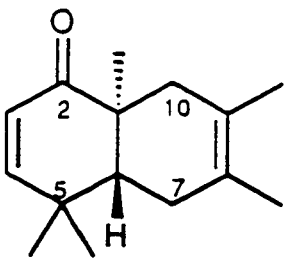
The benzyl group and the *p*-methoxybenzyl group are both bulky groups. According to the alkylation reaction with benzyl bromide, in which the *cis* stereochemistry is confirmed from NOE experiments, we also believed that a *cis*-ring-junction is found in the reductive alkylation with *p*-methoxybenzyl chloride.

III.B. Reductive alkylation of (1R*,6R*)-1-cyano-5,5,8,9-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (68)

Reductive alkylation of **68** with methyl iodide at -25 °C provided **102** and **103** as a 1:1 mixture of stereoisomers in low yield (40%). A mixture was formed in this case (entry 7) probably due to the absence of a methyl group at C-10. In the previous cases with adduct **69** and also with adduct **70**, in which there is a methyl group at C-10, only one product was formed in the reductive alkylation. In these cases the methyl group at C-10 may sterically hinder the formation of the other stereoisomer.

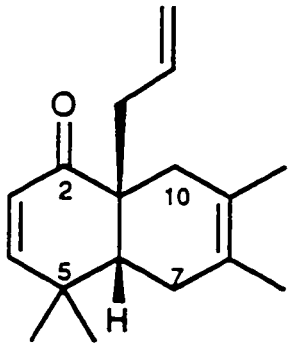


102



103

The high resolution mass spectrum for the mixture of **102** and **103** showed a molecular ion peak at m/*z* 218.1667 corresponding to the molecular formula $C_{15}H_{22}O$. The ^{13}C NMR APT spectrum of the mixture of **102** and **103** displayed a total of 30 signals, corresponding to two sets of signals for two compounds. The infrared spectrum displayed a strong absorption at 1674 cm^{-1} characteristic of the α,β-unsaturated carbonyl. No absorption for the nitrile was found. The ^{1}H NMR spectrum of the mixture displayed seven singlets for the methyl groups at δ 1.66 (6 protons), 1.63 (6 protons), 1.18 (3 protons), 1.11 (6 protons), 1.10 (3 protons), 1.07 (3 protons), and 0.90 (3 protons).



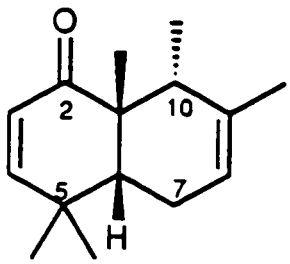
104

Reductive decyanation of **68** and trapping with allyl bromide at room temperature provided enone **104** (68%). Only one product was formed from

the reaction probably due to a less reactive alkylating agent, allyl bromide, which results in a more stereoselective reaction.

There were 17 signals displayed in the ^{13}C APT NMR spectra **104** which confirmed the formation of only one product. The lack of a nitrile absorption and the presence of a carbonyl absorption (1671 cm^{-1}) in the infrared spectrum confirmed that the cyano group was removed from the cycloadduct. The high resolution mass spectra of **104** gave a molecular ion peak at m/*z* 244.1812 corresponding to the molecular formula $C_{17}H_{24}O$. The ^1H NMR spectra of **104** displayed the typical proton signals for the addition of an allyl group, as compared with **97**. Enone proton signals at δ 6.50 and 5.84 appeared as mutually coupled doublets (J = 10.5 Hz) representing the beta and alpha protons, respectively. The terminal olefin derived from allyl bromide was verified by signals at δ 5.03 (dm, J = 17 Hz) and 4.98 (dm, J = 10 Hz) for the terminal vinylic protons and at δ 5.61 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 10 Hz, J_4 = 5 Hz) for the non-terminal vinylic proton . The ring-junction proton H_6 appeared as a broad doublet at δ 1.98 (J = 8 Hz). Four methyl singlets appeared at δ 1.67 (C-8 methyl), 1.57 (C-9 methyl), and at δ 1.10 and 0.90 (geminal methyl groups).

III.C. Reductive alkylation of (1R*,6R*,10R*)-1-cyano-5,5,9,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (70)

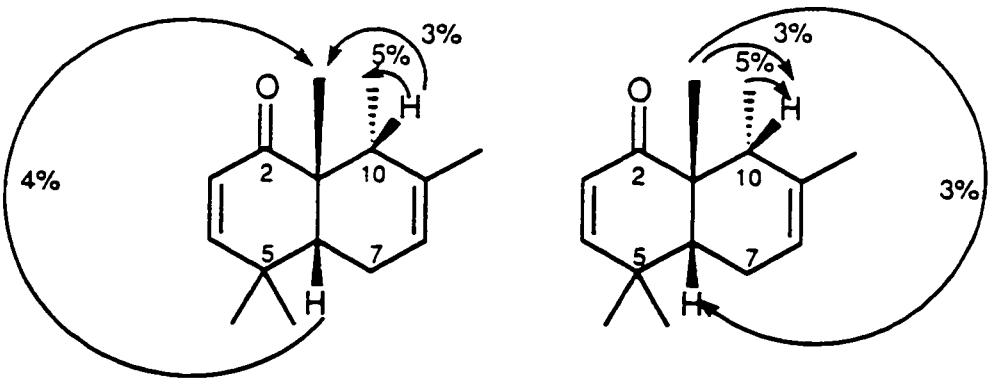


107

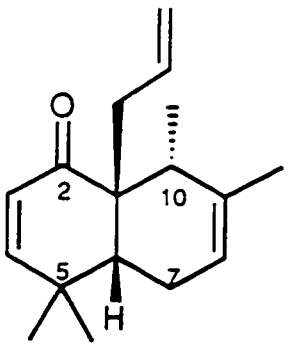
Alkylation of adduct **70** with methyl iodide after reductive cleavage with lithium naphthalenide afforded enone **107** in 78% yield. The high resolution mass spectrum for **107** displayed a molecular ion peak at m/z 218.1665 corresponding to the molecular formula $C_{15}H_{22}O$. The ^{13}C NMR APT spectrum of **107** displayed a total of 15 signals which supports the formation of one compound. The ^1H NMR spectrum displayed vinylic proton signals at δ 6.50 (d, J = 10 Hz, H_4), 5.95 (d, J = 10 Hz, H_3), and 5.42 (m, H_8). The ring-junction proton H_6 appeared as a broad doublet (J = 8 Hz) at δ 1.85. Allylic methine proton H_{10} appeared as a quartet (J = 7.5 Hz) at δ 1.93. The C-10 methyl group appeared as a doublet (J = 7.5 Hz) at δ 0.94. Four methyl groups appeared as singlets at δ 1.68, 1.28, 1.11, and 1.04. The latter two singlets were attributed to the geminal methyl groups. The low field singlet was assigned to the C-9 methyl group and the last singlet at δ 1.28 was attributed to the C-1 methyl group.

The stereochemistry of the ring-junction of **107** was confirmed by NOE experiments, **Figure 1-12**. Irradiation of the ring-junction proton (H_6) signal at δ 1.85 gave enhancement (4%) of the ring-junction methyl group at δ 1.28. Irradiation of the ring-junction methyl group gave a 3% enhancement of the ring-junction proton H_6 as well as a 3% enhancement of the C-10 proton signal at δ 1.93. Irradiation of methine proton H_{10} gave enhancement of the ring-junction methyl group signal at δ 0.94 (3%) in addition to enhancement of the C-10 methyl group (5%). The C-10 methyl group gave only enhancement of the allylic methine proton H_{10} (5%). The *cis* ring-junction of **107** was confirmed from NOE experiments.

Figure 1-12



Reductive alkylation of **70** with allyl bromide afforded enone **108** in 94% yield. The infrared spectrum displayed a characteristic absorption at 1667 cm^{-1} for the α,β-unsaturated carbonyl. The high resolution mass spectrum displayed the molecular ion peak at m/z 244.1818 corresponding to the molecular formula $C_{17}H_{24}O$. Elemental analysis also supports the molecular formula $C_{17}H_{24}O$. The ^1H NMR spectrum displayed 6 vinylic proton signals including the enone proton signals as doublets (J = 10.5 Hz) at δ 6.51 and 5.95 (H_4 and H_3, respectively) and a multiplet at δ 5.46 for the proton from the other endocyclic double bond. The vinylic protons derived from allyl bromide appeared at δ 5.05 (ddd, J_1 = 17 Hz, J_2 = 2 Hz, J_3 = 2 Hz) and 4.99 (ddd, J_1 = 10 Hz, J_2 = 2 Hz, J_3 = 2 Hz) for the terminal olefinic protons and at δ 5.58 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 10 Hz, J_4 = 5 Hz) for the non-terminal olefinic proton. Methylene protons derived from allyl bromide appeared as mutually coupled signals at δ 2.91 (dddd, J_1 = 14 Hz, J_2 = 5 Hz, J_3 = 2 Hz, J_4 = 2 Hz) and 2.15 (dd, J_1 = 14 Hz, J_2 = 10.5 Hz). Two methine proton signals appeared as a doublet at δ 2.06 (J = 8 Hz) for the ring-junction proton and a quartet at δ 1.88 (J = 7.5 Hz) for the proton on C-10 which was coupled to the C-10 methyl group at δ 1.68. Two other methyl groups appeared as singlets at δ 1.06 and 0.95.



108

Overall, this reductive alkylation process proves to be a very useful tool in organic synthesis. Introduction of an angular methyl group to decalin systems prepared by Diels-Alder cycloaddition of a dienone activated by an aldehyde (**Scheme 1-3**) proved to be difficult. The best yield attained by Bhat and co-workers in the methylation of the deformylated adduct was 45% whereas the best yield in our one-step reductive methylation process was 83%. We have developed a very simple method for the introduction of an angular alkyl group via a reductive decyanation and alkylation process. Diels-Alder cycloaddition using a cyano activated dienophile readily afforded an alpha cyano ketone system. The use of different dienes would allow for the introduction of unique functional groups into the polycyclic system, in addition, the presence of a cyano group at the angular position would give facile access to different angularly substituted decalin systems via reductive alkylation. The next chapter will describe the use of reductive alkylation as a key step towards the synthesis of clerodane diterpenoids.

Experimental

General

Melting points were recorded on a Köfler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra were recorded on a Nicolet 7-199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using the following spectrometers: Bruker AM-200 (200 MHz), Bruker AM-300 (300 MHz), Bruker AM-400 (400 MHz), and Varian Unity 500 (500 MHz). Coupling constants are reported to within ±0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Carbon-13 magnetic resonance spectra (^{13}C NMR) were recorded on Bruker AM-300 (75 MHz) and were obtained as solutions in deuteriochloroform as the internal standard setting the central peak at 77.00 ppm. Carbon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test). Methylene groups and quaternary carbons appeared as in-phase (p) with respect to the deuteriochloroform signal, while the signals anti-phase (ap) to that of deuteriochloroform were due to the methyl and methine groups. Nuclear Overhauser Enhancement (NOE) experiments were carried out in the difference mode in which a blank (unirradiated) spectrum was computer-subtracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals being antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon for 10 minutes

prior to use. High resolution electron impact mass spectra (HRMS) were recorded using an A.E.I. model MS-50 mass spectrometer. Spectral data were recorded as m/*z* values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. Concentrations of solvent systems used in column chromatography are given by volumes, e.g. 20% ethyl acetate in Skelly B means 20 parts of ethyl acetate by volume to 80 parts of Skelly B by volume.

Materials

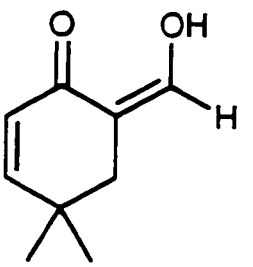
Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. Reactions requiring anhydrous conditions were performed in flame-dried glassware, assembled, and allowed to cool while being purged with a stream of argon. Unless otherwise stated, reactions were carried out under argon and monitored by analytical thin-layer chromatography (tlc) performed on aluminum-backed plates precoated with silica gel 60 F_{254} as supplied by Merck. The visualization of the chromatograms were done by looking under an ultraviolet lamp (λ=254 nm) and/or dipping in an ethanol solution of vanillin (5%, w/v) containing sulfuric acid (3%, v/v), followed by charring on a hot plate.

Skelly B refers to the Skelly Oil Company light petroleum, bp 62-70 °C. Skelly B and ethyl acetate were distilled prior to use. Solvents and liquid reagents used in this and the following chapter were dried and distilled under an argon atmosphere prior to use as follows: tetrahydrofuran (THF) and diethyl ether from a blue or purple solution of sodium benzophenone ketyl; methanol and ethanol from magnesium turnings; benzene, dichloromethane, pyridine, ethyl formate, diisopropylamine, and carbon tetrachloride from calcium hydride.

Solvents were removed under water aspirator pressure using a Büchi rotoevaporator. Argon was passed through a column of 4 Å molecular sieves with a self-indicating silica gel (coarse grained) as an indicator.

Flash chromatography developed by Still[108] was used routinely for purification and separation of product mixtures using silica gel (Merck) of 230-400 mesh.

4,4-Dimethyl-6-hydroxymethylene-2-cyclohexenone (64)

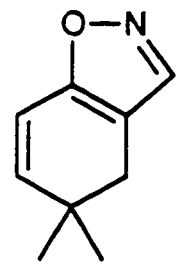


64

Ethyl formate (57 mL, 0.71 mol) was added dropwise to a suspension of sodium hydride (60% purity, 3.049 g, 76.21 mmol) in THF (50 mL) at 0 °C under an argon atmosphere. The mixture was stirred with a mechanical stirrer for an additional 10 minutes, then a mixture of 4,4,-dimethyl-2-cyclohexenone **63** (4.733 g, 38.11 mmol) and absolute ethanol (3 drops) in THF (10 mL) were added dropwise over a period of 30 minutes. Several portions of THF (3 x 30 mL) were added to the viscous pale yellow solution to ensure that the mixture was stirred properly. The ice bath was removed and the mixture was stirred at room temperature for an additional 45 minutes. The reaction mixture was quenched with water (30 mL) and then acidified with aqueous concentrated

HCl. The resulting mixture was extracted with dichloromethane (3 x 50 mL). The organic extracts were washed with saturated sodium chloride solution (3 x 20 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a yellow/brown oil (5.432 g). Kugelrohr distillation at 52-58 °C/4-6 mm of Hg gave a pale yellow liquid **64** (4.315 g, 28.35 mmol, 74%): IR ($CHCl_3$, cast): 3452 (OH), 1646 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 13.71 (br s, 1H, C=CHO**H**), 7.42 (br s, 1H, C=C**H**OH), 6.51 (d, J = 10 Hz, 1H, C**H**=CHC=O), 5.90 (d, J = 10 Hz, 1H, CH=C**H**C=O), 2.29 (s, 2H, CH_2), 1.07 (s, 6H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 188.35 (p), 166.82 (ap), 157.74 (ap), 125.93 (ap), 106.61 (p), 37.09 (p), 33.15 (p), 28.07 (two carbons, ap); HRMS M^+: 152.0832 (calcd. for $C_9H_{12}O_2$: 152.0837).

8-Aza-4,4-dimethyl-9-oxabicyclo[4.3.0]nona-1(6),2,7-triene (65)

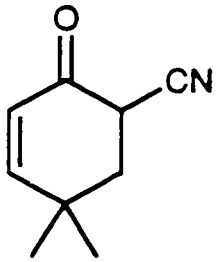


65

Potassium carbonate (2.452 g, 17.74 mmol) and hydroxylamine hydrochloride (1.513 g, 21.72 mmol) were added to a solution of **64** (3.002 g, 19.73 mmol) in absolute ethanol (25 mL) at 0 °C under argon. The solution was refluxed for 2 hours. The resulting dark orange solution with a pale yellow suspension was cooled then slowly quenched with aqueous 2N HCl (30 mL). The resulting solution was extracted with dichloromethane (2 x 30 mL). The organic extracts

were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a red/orange residue. The crude product was subjected to flash chromatography. Elution with ethyl acetate-Skelly B (5:95) followed by Kugelrohr distillation at 51 °C/1 mm of Hg afforded **65** (2.213 g, 14.83 mmol, 75%): IR (film): 1627, 1590 (N=C), 966 cm^{-1} (N-O); ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, CC**H**=N), 6.36 (dd, J_1 = 10 Hz, J_2 = 1 Hz, 1 H, C**H**=CHCO), 5.83 (d, J = 10 Hz, 1H, CH=C**H**CO), 2.52 (s, 2H, CH_2), 1.10 (s, 6H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 164.37 (p), 148.41 (ap), 144.51 (ap), 112.58 (ap), 109.33 (p), 34.03 (p), 32.31 (p), 27.91 (two carbons, ap); HRMS M^+: 149.0841 (calcd. for $C_9H_{11}NO$: 149.0844). Anal. calcd. for $C_9H_{11}NO$: C 72.44%, H 7.44%, N 9.39%; found: C 72.04%, H 7.37%, N 9.37%.

6-Cyano-4,4-dimethyl-2-cyclohexenone (66)

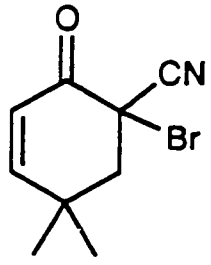


66

Absolute ethanol (30 mL) was added dropwise to a dry round-bottomed flask containing sodium (3.232 g, 1.40 mol) under an argon atmosphere at 0 °C. The grey suspension was stirred for 1 hour then isoxazole **65** (10.484 g, 70.27 mmol) in absolute ethanol (20 mL) was added dropwise to the suspension over 15 minutes. The thick yellow solution was refluxed for 2 hours, cooled to room

temperature, and then quenched with aqueous 2N HCl. The mixture was extracted with dichloromethane (3 x 30 mL), washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was recrystallized from ethyl acetate-Skelly B to afford white crystals of cyano enone **66** (8.761 g, 58.72 mmol, 84%): mp 73-74 °C; IR (CH_2Cl_2, cast): 2251 (CN), 1692 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 6.72 (dd, J_1 = 10 Hz, J_2 = 1 Hz, 1H, C**H**=CHC=O), 5.86 (d, J = 10 Hz, 1H, CH=C**H**C=O), 3.70 (dd, J_1 = 10.5 Hz, J_2 = 8 Hz, 1H, C**H**CN), 2.20, (d, J = 10.5 Hz, 2H, CH_2), 1.18 (s, 6H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 188.28 (p), 160.25 (ap), 124.54 (ap), 116.86 (p), 39.63 (p), 36.91 (ap), 33.16 (p), 29.40 (ap), 24.89 (ap); HRMS M^+: 149.0842 (calcd. for $C_9H_{11}NO$: 149.0841). Anal. calcd. for $C_9H_{11}NO$: C 72.44%, H 7.44%, N 9.39%.; found: C 72.44%, H 7.45%, N 9.35%.

6-Bromo-6-cyano-4,4-dimethyl-2-cyclohexenone (67)

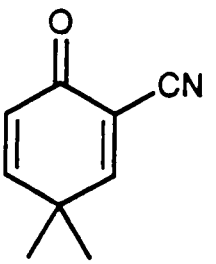


67

Enone nitrile **66** (537 mg, 3.60 mmol) was dissolved in carbon tetrachloride (15 mL). The reaction flask was protected from light and affixed with an anhydrous calcium sulfate drying tube. *N*-Bromosuccinimide (1.299 g, 7.30 mmol) was added to the solution and the suspension was stirred at room temperature for

19 hours. The pale yellow suspension was filtered and washed with carbon tetrachloride (2 x 5 mL). The residue was discarded and the filtrate was concentrated in vacuo to give a pale yellow oil. The oil was distilled using a Kugelrohr apparatus at 123-125 °C/0.9 mm of Hg to yield a pale yellow oil **67** (0.755 g, 3.31 mmol, 92%): IR (film): 2245 (CN), 1692 (C=O), 1617 cm^{-1}(C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 6.78 (d, J = 10 Hz, 1H, C**H**=CHC=O), 6.00 (d, J = 10 Hz, 1H, CH=C**H**C=O), 2.73 (d, J = 15 Hz, 1H, CH_2), 2.62 (dd, J_1 = 15 Hz, J_2 = 1 Hz, 1H, CH_2), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 182.59 (p), 160.34 (ap), 121.67 (ap), 116.43 (p), 47.92 (p), 43.64 (p), 34.35 (p), 29.41 (ap), 28.01 (ap); HRMS M^+: 226.9946 (calcd. for $C_9H_{10}NO^{79}Br$: 226.9946), M^+: 228.9924 (calcd. for $C_9H_{10}NO^{81}Br$: 228.9926). Anal. calcd. for $C_9H_{10}NOBr$: C 47.39%, H 4.42%, N 6.14%.; found: C 47.42%, H 4.53%, N 6.16%.

2-Cyano-4,4-dimethyl-2,5-cyclohexadienone (62)



62

To a solution of cyano enone **67** (604 mg, 2.65 mmol) in benzene (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.64 mL, 4.28 mmol) at room temperature under an argon atmosphere. After 1 hour, the solid which precipitated from the yellow solution was filtered using a sintered glass funnel

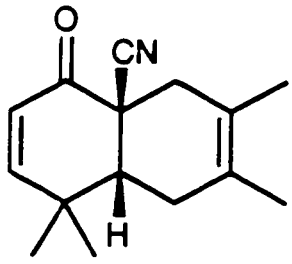
packed with Celite as a filter-aid. The filtrate was extracted with diethyl ether (2 x10 mL). The organic extracts were washed successively with aqueous 10% HCl (2 x 5 mL), water (2 x 5 mL), saturated sodium bicarbonate solution (2 x 5 mL), and saturated sodium chloride solution (2 x 5 mL). The organic solution was dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a pale yellow residue (0.365 g). The crude residue was recrystallized from ethyl acetate-Skelly B to afford white crystals **62** (319 mg, 2.17 mmol, 81%): mp 107-108 °C; IR ($CHCl_3$, cast): 2234 (CN), 1666 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 3 Hz, 1H, C**H**=CCN), 6.91 (dd, J_1 = 10.5 Hz, J_2 = 3 Hz, 1H, C**H**=CHC=O), 6.24 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 1.32 (s, 6H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 178.82 (p), 166.80 (ap), 156.65 (ap), 125.95 (ap), 115.77 (p), 113.99 (p), 39.01 (p), 26.10 (two carbons, ap); HRMS M^+: 147.0679 (calcd. for C_9H_9NO: 147.0684). Anal. calcd. for C_9H_9NO: C 73.45%, H 6.16%, N 9.52%; found: C 73.23%, H 6.00%, N 9.40%.

General procedure for $ZnCl_2$ catalyzed Diels-Alder reactions

Zinc chloride (286 mg, 2.10 mmol, 2 equivalents) was flame-fuse dried in a round-bottomed flask under an argon atmosphere. The flask was cooled to room temperature and diethyl ether (5 mL) was added to the flask. The resulting solution was stirred at room temperature until the zinc chloride was completely dissolved (1 hour). Dienophile **62** (154 mg, 1.05 mmol, 1 equivalent) dissolved in diethyl ether (2 mL) was added and the resulting solution was stirred at 0 °C for 15 minutes. The diene (20.92 mmol, 20 equivalents) was then added and the resulting solution was warmed to room

temperature after 30 minutes. When the reaction was complete, it was neutralized with saturated aqueous sodium bicarbonate solution. The diethyl ether layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed successively with water (2 x 10 mL) and saturated sodium chloride solution (2 x 10 mL), dried with anhydrous magnesium sulfate, filtered, concentrated in vacuo, and purified by either flash chromatography (ethyl acetate-Skelly B; 5:95), Kugelrohr distillation or recrystallization (ethyl acetate-Skelly B) to give the desired adduct(s).

(1R*,6R*)-1-Cyano-5,5,8,9-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (68)

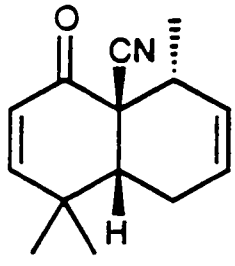


68

Dienophile **62** (154 mg, 1.05 mmol) and 2,3-dimethyl-1,3-butadiene (2.2 mL, 1.597 g, 19.44 mmol) under zinc chloride catalysis for 40 hours afforded after Kugelrohr distillation (70 °C/0.7 mm Hg) adduct **68** as a pale yellow solid (223 mg, 0.97 mmol, 93%): mp 86-87 °C; IR (CH_2Cl_2, cast): 2241 (CN), 1687 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 6.60 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.93 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 2.52 (br d, J = 18 Hz, 1H, CH_2), 2.40 (br d, J = 18 Hz, 1H, CH_2), 2.39 (dd, J_1 = 7 Hz, J_2 = 2.5 Hz, 1H, C**H**CH_2), 2.31 (br d, J = 18 Hz, 1H, CH_2), 2.02 (br d, J = 18 Hz, 1H, CH_2), 1.67 (s, 3H, C=CCH_3),

1.62 (s, 3H, C=CC**H**$_3$), 1.24 (s, 3H, C**H**$_3$), 0.96 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 192.10 (p), 158.69 (ap), 125.31 (p), 122.61 (ap), 121.07 (p), 120.56 (p), 47.58 (p), 42.21 (ap), 36.36 (p), 36.23 (p), 30.39 (ap), 30.22 (p), 23.54 (ap), 18.80 (ap), 18.50 (ap); HRMS M$^+$: 229.1466 (calcd. for $C_{15}H_{19}NO$: 229.1467). Anal. calcd. for $C_{15}H_{19}NO$: C 78.56%, H 8.35%, N 6.11%; found: C 78.34%, H 8.58%, N 6.13%.

(1R*,6R*,10R*)-1-Cyano-5,5,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (69)

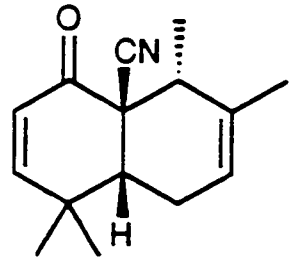


69

Dienophile **62** (143 mg, 0.97 mmol) and *trans*-1,3-pentadiene (2.0 mL, 1.366 g, 20.05 mmol) under zinc chloride catalysis for 5 hours afforded after Kugelrohr distillation (70 °C/0.2 mm Hg) adduct **69** (206 mg, 0.97 mmol, 98%): mp 92-93 °C; IR (CH_2Cl_2, cast): 2227 (CN), 1702 cm^{-1} (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H, C**H**=CHC=O), 5.91 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.58 (m, 2H, C**H**=C**H**), 2.75 (m, 1H, C**H**CH$_3$) 2.47 (ddd, J_1 = 10 Hz, J_2 = 6 Hz, J_3 = 1.5 Hz, 1H, C**H**CH$_2$), 2.32 (dm, J = 18 Hz, 1H, CHC**H**$_2$), 1.96 (dm, J = 18 Hz, 1H, CHC**H**$_2$), 1.62 (s, 3H, C**H**$_3$), 1.45 (d, J = 6 Hz, 3H, CHC**H**$_3$), 1.14 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 190.84 (p), 155.71 (ap), 128.92 (ap), 124.87 (ap), 123.47 (ap), 121.39 (p), 48.61 (p), 46.23 (ap), 37.91 (ap), 37.67 (p), 28.59 (ap), 27.24 (ap), 25.50 (p), 16.87 (ap); HRMS M$^+$:

215.1321 (calcd. for $C_{14}H_{17}NO$: 215.1310). Anal. calcd. for $C_{14}H_{17}NO$: C 78.09%, H 7.96%, N 6.51%; found: C 77.94%, H 8.19%, N 6.23%.

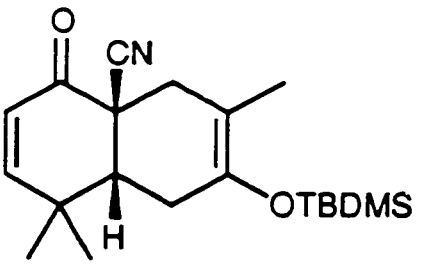
(1R*,6R*,10R*)-1-Cyano-5,5,9,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (70)



70

Dienophile **62** (148 mg, 1.01 mmol) and 3-methyl-1,3-pentadiene (2.2 mL, 1.606 g, 19.55 mmol) under zinc chloride catalysis for 25 hours afforded after Kugelrohr distillation (65 °C/0.2 mm Hg) adduct **70** as a white solid (222 mg, 0.97 mmol, 96%): mp 56-57 °C; IR (CH_2Cl_2, cast): 2228 (CN), 1686 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 6.48 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H, CH=CHC=O), 5.93 (d, J = 10.5 Hz, 1H, CH=CHC=O), 5.32 (m, 1H, $CH{=}CCH_3$), 2.66 (m, 1H, $CHCH_3$), 2.43 (ddd, J_1 = 9 Hz, J_2 = 6.5 Hz, J_3 = 1.5 Hz, 1H, $CHCH_2$), 2.31 (dddd, J_1 = 18 Hz, J_2 = 9 Hz, J_3 = 4 Hz, J_4 = 1.5 Hz, 1H, $CHCH_2$), 1.97 (dm, J = 18 Hz, 1H, $CHCH_2$), 1.73 (m, 3H, $CH{=}CCH_3$), 1.55 (s, 3H, CH_3), 1.39 (d, J = 6 Hz, 3H, $CHCH_3$), 1.10 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 191.39 (p), 156.25 (ap), 133.39 (p), 125.05 (ap), 121.77 (p), 119.35 (ap), 49.69 (p), 45.40 (ap), 40.41 (ap), 37.25 (p), 29.09 (ap), 26.50 (ap), 25.31 (p), 21.48 (ap), 14.57 (ap); HRMS M^+: 229.1468 (calcd. for $C_{15}H_{19}NO$: 229.1467). Anal. calcd. for $C_{15}H_{19}NO$: C 78.56%, H 8.35%, N 6.11%; found: C 78.15%, H 8.66%, N 6.05%.

(1R*,6R*)-8-*tert*-Butyldimethylsiloxy-1-cyano-5,5,9-trimethylbicyclo-[4.4.0]deca-3,8-dien-2-one (71)

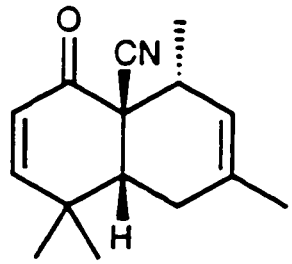


71

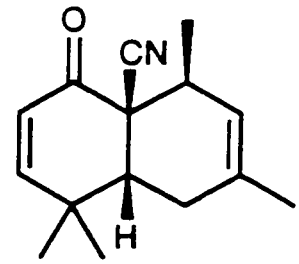
Dienophile **62** (150 mg, 1.02 mmol) and 2-*tert*-butyldimethylsiloxy-3-methyl-1,3-butadiene (2.030 g, 10.2 mmol) under zinc chloride catalysis for 22 hours afforded after flash column chromatography, **71** as a pale yellow solid (280 mg, 0.81 mmol, 80%): mp 94-96 °C; IR (CH_2Cl_2, cast): 2241 (CN), 1693 (C=O), 1622 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 6.62 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.94 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 2.56 (dm, J = 17.5 Hz, 1H, CH_2), 2.46-2.53 (complex, 2H, C**H** and CH_2), 2.38 (d, J = 17 Hz, 1H, CH_2), 2.06 (d, J = 17.5 Hz, 1H, CH_2), 1.59 (s, 3H, C=CCH_3), 1.27 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.95 (s, 9H, *tert*-butyl), 0.15 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 191.81 (p), 158.42 (ap), 142.15 (p), 122.72 (ap), 120.31 (p), 107.31 (p), 47.23 (p), 43.40 (ap), 36.39 (p), 35.77 (p), 30.34 (ap), 29.11 (p), 25.82 (ap), 23.50 (ap), 18.16 (p), 15.75 (ap), -3.71 (ap), -3.87 (ap); HRMS M+: 345.2124 (calcd. for $C_{20}H_{31}NO_2Si$: 345.2124). Anal. calcd. for $C_{20}H_{31}NO_2Si$: C 69.52%, H 9.05%, N 4.06%; found: C 69.69%, H 9.20%, N 4.01%.

(1R*,6R*,10R*)-1-Cyano-5,5,8,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (72) and

(1R*,6R*,10S*)-1-Cyano-5,5,8,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (73)



72

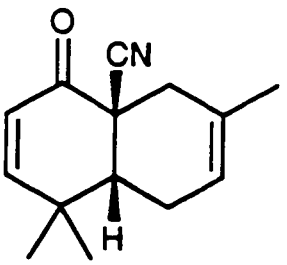


73

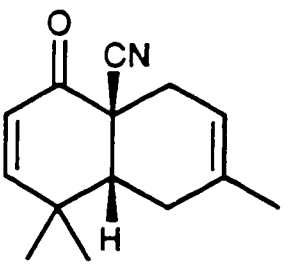
Dienophile **62** (145 mg, 0.99 mmol) and *trans*-2-methyl-1,3-pentadiene (2.20 mL, 19.23 mmol) under zinc chloride catalysis for 3.5 hours gave after purification by flash chromatography the less polar adduct **72** (119 mg, 0.52 mmol) and the more polar adduct **73** (96 mg, 0.42 mmol) in 89% yield. Compound **72**: IR (film): 2228 (CN), 1686 (C=O), 1616 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 6.46 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H, C**H**=CHC=O), 5.88 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.26 (m, 1H, C**H**=CCH_3), 2.70 (m, 1H, C**H**CH_3), 2.46 (ddd, J_1 = 10.5 Hz, J_2 = 6.5 Hz, J_3 = 1.5 Hz, 1H, C**H**CH_2), 2.16 (ddm, J_1 = 18 Hz, J_2 = 6.5 Hz, 1H, C**H**$_2$), 1.86 (ddm, J_1 = 18 Hz, J_2 = 10 Hz, 1H, C**H**$_2$), 1.61 (br s, 3H, C=CCH_3), 1.58 (s, 3H, C**H**$_3$), 1.39 (d, J = 7.5 Hz, 3H, CHC**H**$_3$), 1.12 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 191.05 (p), 155.81 (ap), 130.71 (p), 124.97 (ap), 123.44 (ap), 121.50 (p), 48.35 (p), 46.34 (ap), 38.11 (ap), 37.49 (p), 30.23 (p), 28.69 (ap), 26.88 (ap), 22.99 (ap), 17.10 (ap); HRMS M^+: 229.1466 (calcd. for $C_{15}H_{19}NO$: 229.1467). Anal. calcd. for $C_{15}H_{19}NO$: C 78.56%, H 8.35%, N 6.11%; found: C 78.63 %, H 8.53%, N 6.06%. Compound **73**: mp 102-104 °C; IR (CH_2Cl_2, cast): 2239 (CN), 1684

(C=O), 1626 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 6.59 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.92 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.19 (m, 1H, C**H**=CCH_3), 2.55 (complex, 3H), 2.02 (dm, J = 17 Hz, 1H, CH_2), 1.76 (br s, 3H, C=CCH_3), 1.20 (s, 3H, CH_3), 1.14 (d, J = 7.5 Hz, 3H, $CHCH_3$), 1.03 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 192.50 (p), 158.00 (ap), 133.29 (p), 123.57 (ap), 122.72 (ap), 118.28 (p), 53.67 (p), 43.11 (ap), 36.47 (p), 32.75 (ap), 30.99 (two carbons, ap), 28.49 (p), 23.26 (ap), 17.20 (ap); HRMS M^+: 229.1467 (calcd. for $C_{15}H_{19}NO$: 229.1467). Anal. calcd. for $C_{15}H_{19}NO$: C 78.56%, H 8.35%, N 6.11%; found: C 78.77 %, H 8.48%, N 6.14%.

(1R*,6R*)-1-Cyano-5,5,9-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (74) and (1R*,6R*)-1-Cyano-5,5,8-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (75)



74

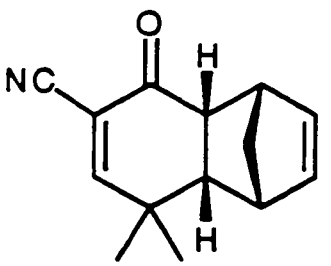


75

Dienophile **62** (147 mg, 1.00 mmol) and 2-methyl-1,3-butadiene (2.0 mL, 1.362 g, 20.00 mmol) under zinc chloride catalysis for 22.5 hours afforded after Kugelrohr distillation (70 °C/0.2 mm Hg) a 7:3 mixture of adducts **74** and **75**, respectively (196 mg, 0.91 mmol, 91%): IR (mixture, CH_2Cl_2, cast): 2241 (CN), 1687 cm^{-1} (C=O). Compound **74**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.63 (d, J =

10.5 Hz, 1H, C**H**=CHC=O), 5.95 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.41 (m, 1H, C**H**=CCH$_3$), 2.40-2.55 (m, 4H), 2.02 (m, 1H), 1.75 (br s, 3H, CH=CC**H**$_3$), 1.26 (s, 3H, C**H**$_3$), 1.03 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 192.38 (p), 158.63 (ap), 133.92 (p), 122.59 (ap), 120.39 (p), 116.24 (ap), 46.72 (p), 42.19 (ap), 36.44 (p), 30.93 (p), 30.46 (ap), 28.56 (p), 23.41 (ap), 23.36 (ap). Compound **75**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.96 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.53, (m, 1H, C**H**=CCH$_3$), 2.57 (dm, J = 18 Hz, 1H, C**H**$_2$), 2.38 (complex, 3H), 2.17 (dm, J = 18 Hz, 1H, C**H**$_2$), 1.70 (br s, 3H, CH=CC**H**$_3$), 1.27 (s, 3H, C**H**$_3$), 1.03 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 191.97 (p), 158.70 (ap), 128.98 (p), 122.71 (ap), 120.51 (ap), 120.41 (p), 47.38 (p), 41.32 (ap), 36.34(p), 34.86 (p), 30.41 (ap), 24.14 (p), 23.82 (ap), 23.05 (ap). HRMS (mixture) M$^+$: 215.1305 (calcd. for $C_{14}H_{17}NO$: 215.1310). Anal. calcd. for $C_{14}H_{17}NO$ (mixture): C 78.10%, H 7.96%, N 6.51%; found: C 78.03%, H 8.23%, N 6.47%.

(1S*,2R*,7S*,8R*)-4-Cyano-6,6-dimethyltricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3-one (76)

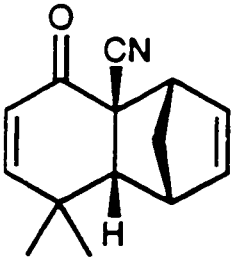


76

Dienophile **62** (147 mg, 1.00 mmol) and cyclopentadiene (1.50 mL, 1.200 g, 18.20 mmol) under zinc chloride catalysis at -25 °C gave adduct **76** (72 mg, 0.34 mmol, 48% yield based on consumed starting material) and unconsumed

dienophile **62** (42 mg, 0.29 mmol) after 66.5 hours: IR (CH_2Cl_2, cast): 2229 (CN), 1680 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 1.5 Hz, 1H, C**H**=CCN), 6.08 (dd, J_1 = 5.5, J_2 = 3 Hz, 1H, C**H**=CHCHCHC=O), 5.92 (dd, J_1 = 5.5 Hz, J_2 = 3 Hz, 1H, CH=C**H**CHCHC=O), 3.40 (m, 1H, C**H**CH_2), 3.19 (dd, J_1 = 9 Hz, J_2 = 5 Hz, 1H, C**H**C=O), 3.07 (m, 1H, C**H**CH_2), 2.52 (ddd, J_1 = 9 Hz, J_2 = 3.5 Hz, J_3 = 1.5 Hz, 1H, C**H**$C(CH_3)_2$), 1.48 (ddd, J_1 = 9 Hz, J_2 =1.5 Hz, J_3 = 1.5 Hz, 1H, C**H**$_2$), 1.35 (dm, J = 9 Hz, 1H, C**H**$_2$), 1.24 (s, 3H, C**H**$_3$), 1.20 (s, 3H, C**H**$_3$): ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 194.68 (p), 169.27 (ap), 135.72 (ap), 134.48 (ap), 117.29 (p), 114.16 (p), 51.22 (ap), 47.93 (ap), 47.54(ap), 46.99 (ap), 49.60 (p), 35.42 (p), 35.08 (ap), 25.93 (ap); HRMS M^+: 213.1154 (calcd. for $C_{14}H_{15}NO$: 213.1154).

(1S*,2R*,7R*,8R*)-2-Cyano-6,6-dimethyltricyclo[6.2.1.$0^{2,7}$]undeca-4,9-dien-3-one (79)

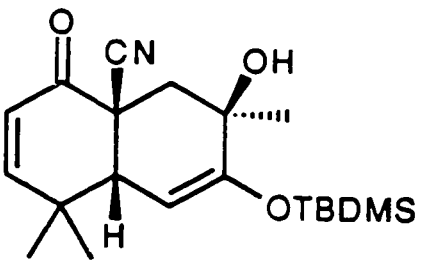


79

Dienophile **62** (67 mg, 0.46 mmol) dissolved in dichloromethane (1 mL) was added dropwise to a solution of cyclopentadiene (0.76 mL, 610 mg, 9.22 mmol) dissolved in dichloromethane (4 mL) at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 31 days. The solution was concentrated in vacuo and purified by flash chromatography (ethyl acetate-Skelly B, 15:85) to give **79** as a pale yellow oil (21 mg, 0.10 mmol, 59% yield

based on consumed starting material) and recovered dienophile **62** (43 mg, 0.29 mmol): IR (CH_2Cl_2, cast): 2232 (CN), 1672 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 6.47 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H, C**H**=CHC=O), 6.15 (dd, J_1 = 6 Hz, J_2 = 3 Hz, 1H, C**H**=CH), 5.81 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.80 (dd, J_1 = 6 Hz, J_2 = 3 Hz, 1H, CH=C**H**), 3.65 (m, 1H, C**H**CH_2), 3.18 (m, 1H, C**H**CH_2), 2.86 (dd, J_1 = 4 Hz, J_2 = 1.5 Hz, 1H, C**H**C$(CH_3)_2$), 1.77 (d, J = 9.5 Hz, 1 H, CH_2), 1.64 (ddd, J_1 = 9.5 Hz, J_2 = 2 Hz, J_3 = 2 Hz, 1H, CH_2), 1.33 (s, 3H, CH_3), 1.20 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 190.96 (p), 158.70 (ap), 136.74 (ap), 134.35 (ap), 127.31 (ap), 122.16 (p), 58.01 (ap), 55.57 (ap), 48.90 (p), 48.76 (p), 48.72 (p), 47.59 (ap), 35.69 (ap), 34.25 (p), 26.22 (ap); HRMS M^+: 213.1133 (calcd. for $C_{14}H_{15}NO$: 213.1154).

(1R*,6R*,9R*)-8-*tert*-Butyldimethylsiloxy-1-cyano-9-hydroxy-5,5,9-trimethylbicyclo[4.4.0]deca-3,7-dien-2-one (82)

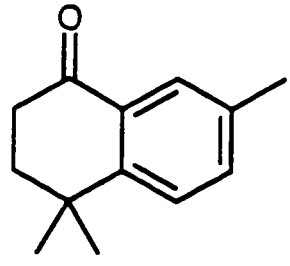


82

Adduct **71** (120 mg, 0.35 mmol) was dissolved in dichloromethane (5 mL) and *meta*-chloroperoxybenzoic acid (75 mg, 0.43 mmol) was added to the solution under an argon atmosphere. The colorless solution was stirred at room temperature for 20 hours. The resulting solution was diluted with dichloromethane (20 mL), washed sequentially with 10% sodium bisulfite solution (5 mL), saturated sodium bicarbonate solution (2 x 5 mL), and

saturated sodium chloride solution. The organic extract was dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a colorless oil. Kugelrohr distillation of the crude product at 70 °C/0.5 mm of Hg afforded **82** as a colorless oil (193 mg, 0.53 mmol, 96%): IR (CH_2Cl_2, cast): 3486 (OH), 2239 (CN), 1684 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.82 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 6.01 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 4.96 (d, J = 6 Hz, 1H, C=C**H**), 3.00 (dd, J_1 = 6 Hz, J_2 = 1.5 Hz, 1H, C**H**CH=C), 2.48 (br s, 1H, O**H**), 2.38 (dd, J_1 = 15 Hz, J_2 = 1.5 Hz, 1H, CH_2), 2.14 (d, J = 15 Hz, 1H, CH_2), 1.36 (s, 3H, CCH_3(OH)), 1.25 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.99 (s, 9H, *tert*-butyl), 0.28 (s, 3H, $SiCH_3$), 0.26 (s, 3H, $SiCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 191.62 (p), 160.52 (ap), 155.68 (p), 123.57 (ap), 121.00 (p), 100.40 (ap), 68.83 (p), 46.70 (ap), 45.29 (p), 42.16 (p), 36.96 (p), 30.33 (ap), 27.33 (ap), 25.75 (ap), 25.68 (ap), 18.25 (p), -4.21 (ap), -4.54 (ap); HRMS M^+: 361.2074 (calcd. for $C_{20}H_{31}NO_3Si$: 361.2073). Anal. calcd. for $C_{20}H_{31}NO_3Si$: C 66.44%, H 8.64%, N 3.87%; found: C 66.73%, H 8.80%, N 3.84%.

5,5,9-Trimethylbicyclo[4.4.0]deca-1(10),6,8-trien-2-one (85)

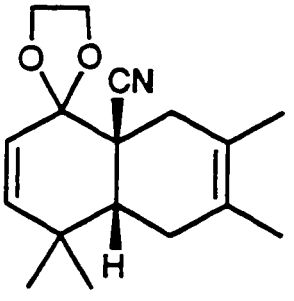


85

Compound **74** (9 mg, 0.042 mmol) was added to a 1:1 solution of aqueous 20% sulfuric acid-ethanol (20 mL). The colorless solution was refluxed for 10 days, cooled, and extracted with Et_2O (2 x 10 mL). The ethereal layer was washed with water (10 mL), dried with anhydrous magnesium sulfate, filtered,

and concentrated in vacuo to give a yellow oil. The residue was subjected to flash column chromatography eluting with ethyl acetate-Skelly B (5:95) to give **85** (3 mg, 0.016 mmol, 37%): IR (CH_2Cl_2, cast): 1686 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (br s, 1H, C**H**CC=O), 7.34 (m, 2H, C**H**=C**H**), 2.72 (t, J = 8 Hz, 2H, CH_2C=O), 2.35 (s, 3H, C=CCH_3), 2.00 (t, J = 8 Hz, 2H, CH_2CH_2C=O), 1.34 (s, 6H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 199.73 (p), 152.29 (p), 149.55 (p), 134.84 (ap), 131.01 (p), 127.48 (ap), 125.85 (ap), 37.26 (p), 35.27 (p),33.67 (p), 29.82 (ap), 20.85 (ap); HRMS M^+: 188.1202 (calcd. for $C_{13}H_{16}O$: 188.1201).

(1R*,6R*)-2,2-Ethylenedioxy-1-cyano-5,5,8,9-tetramethylbicyclo-[4.4.0]deca-3,8-diene (91)

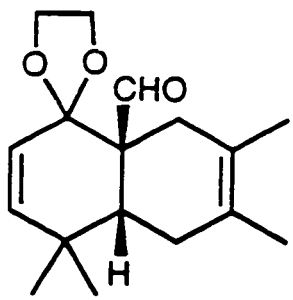


91

Adduct **68** (136 mg, 0.59 mmol) was added to a mixture of *p*-toluenesulfonic acid (36 mg, 0.19 mmol), ethylene glycol (0.5 mL, 557 mg, 8.96 mmol), and benzene (40 mL). The flask was affixed with a Dean-Stark trap charged with 3Å molecular sieves for sequential removal of water and refluxed for 19 hours. Some of the benzene was distilled away (25 mL) and the resulting solution was concentrated in vacuo to give a yellow oil (198 mg). The crude product was subjected to flash chromatography on silica gel. The column was pre-washed

with a dilute solution (5%) of triethylamine in Skelly B. Elution with ethyl acetate-Skelly B (10:90) afforded **91** as a colorless oil (134 mg, 0.54 mmol, 91%): IR (CH_2Cl_2, cast): 2236 (CN), 1173, 1161, 1106 and 1037 cm^{-1} (C-O-C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.05 (d, J = 10 Hz, 1H, CH=C**H**C$(CH_3)_2$), 5.37 (d, J = 10 Hz, 1H, C**H**=CHC$(CH_3)_2$), 4.01-4.33 (complex m, 4H, OC**H**$_2$C**H**$_2$O), 2.58 (dm, J = 18 Hz, 1H, C**H**$_2$CCN), 2.34 (d, J = 18 Hz, 1H, CHC**H**$_2$), 2.30 (t, J = 7 Hz, 1H, C**H**CH$_2$), 2.17 (dm, J = 18 Hz, 1H, CHC**H**$_2$), 1.98 (d, J = 18 Hz, 1H, C**H**$_2$CCN), 1.68 (s, 3H, C=CC**H**$_3$), 1.61 (s, 3H, C=CC**H**$_3$), 1.05 (s, 3H, C**H**$_3$), 0.75 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 140.36 (ap), 125.48 (p), 122.64 (p), 122.25 (p), 121.70 (ap), 106.61 (p), 65.92 (p), 65.62 (p), 46.60 (p), 39.78 (ap), 34.88 (p), 34.29 (p), 31.50 (ap), 30.89 (p), 24.31 (ap), 18.81 (ap), 18.60 (ap); HRMS M^+: 273.1728 (calcd. for $C_{17}H_{23}NO_2$: 273.1729). Anal. calcd. for $C_{17}H_{23}NO_2$: C 74.69%, H 8.48%, N 5.12%; found: C 74.34%, H 8.60%, N 5.09%.

(1R*,6R*)-2,2-Ethylenedioxy-1-formyl-5,5,8,9-tetramethylbicyclo-[4.4.0]deca-3,8-diene (92)

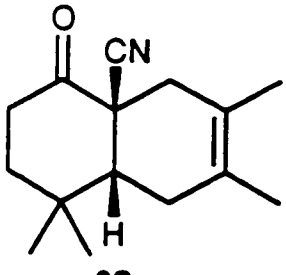


92

Compound **91** (33 mg, 0.12 mmol) dissolved in THF (5 mL) was added to a suspension of lithium aluminum hydride (9 mg, 0.24 mmol) in THF (5 mL) at 0 °C under an argon atmosphere. The grey suspension was refluxed for 3 days.

The mixture was cooled, quenched with water (10 mL), and extracted with diethyl ether-petroleum ether (1:1, 2 x 20 mL). The organic extract was washed with saturated sodium chloride solution (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a colorless oil. The crude product was subjected to flash chromatography. Elution with ethyl acetate-Skelly B (5:95) afforded **92** as a colorless oil (16 mg, 0.06 mmol, 48%): IR (CH_2Cl_2, cast): 2890 (CH of aldehyde), 1730 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H, CHO), 5.52 (d, J = 10 Hz, 1H, CH=CHC$(CH_3)_2$), 5.34 (d, J = 10 Hz, 1H, CH=CHC$(CH_3)_2$), 3.98-4.30 (complex m, 4H, OCH_2CH_2O), 2.46 (dm, J = 18 Hz, 1H, CH_2), 2.32 (dm, J = 18 Hz, 1H, CH_2), 2.26 (dm, J = 7 Hz, 1H, $CHCH_2$), 2.14 (dm, J = 18 Hz, 1H, CH_2), 1.96 (dm, J = 18 Hz, 1H, CH_2), 1.66 (br s, 3H, C=CCH_3), 1.58 (br s, 3H, C=CCH_3), 1.03 (s, 3H, CH_3), 0.75 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.73 (ap), 140.40 (ap), 125.51 (p), 122.28 (p), 121.72 (ap), 106.64 (p), 65.94 (p), 65.65 (p), 46.63 (p), 39.81 (ap), 34.91 (p), 34.32 (p), 31.52 (ap), 30.91 (p), 24.33 (ap), 18.83 (ap), 19.63 (ap); HRMS M^+: 276.1726 (calcd. for $C_{17}H_{24}O_3$: 276.1726).

(1R*,6R*)-1-Cyano-5,5,8,9-tetramethylbicyclo[4.4.0]deca-8-en-2-one (93)



93

To an ice cold solution of acetic acid (10.0 mL) and adduct **68** (51 mg, 0.22 mmol) was added zinc dust (500 mg, 7.65 mmol) in portions over a one hour

period. The cloudy grey suspension was stirred at room temperature for 20 hours. Then the solution was poured into water (100 mL) and extracted with diethyl ether (5 x 20 mL). The combined organic extracts were washed successively with water (2 x 25 mL) and dilute sodium carbonate solution (4% w/v, 2 x 40 mL). The ethereal solution was dried over sodium sulfate, filtered, and concentrated in vacuo. The yellow oil was subjected to flash chromatography eluting with ethyl acetate-Skelly B (5:95) to afford **93** as a pale yellow oil (20 mg, 0.086 mmol, 30%): IR (CH_2Cl_2, cast): 1720 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.69 (ddd, J_1 = 15 Hz, J_2 = 11.5 Hz, J_3 = 5.5 Hz, 1H), 2.56 (complex, 1H), 2.54 (br d, J = 18 Hz, 1H), 2.40 (dm, J = 18 Hz, 1H), 2.26 (br d, J = 18 Hz, 1H), 2.19 (dd, J_1 = 7.5 Hz, J_2 = 3.5 Hz, 1H, C**H**CH_2), 1.98 (br d, J = 18 Hz, 1H), 1.72-1.88 (complex, 2 H), 1.67 (br s, 3H, C=CC**H**$_3$), 1.65 (br s, 3H, C=CC**H**$_3$), 1.20 (s, 3H, C**H**$_3$), 0.98 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.63 (p), 125.00 (p), 121.02 (p), 120.48 (p), 50.44 (p), 47.08 (ap), 38.89 (p), 36.41 (p), 34.44 (p), 33.07 (p), 31.10 (ap), 30.17 (p), 22.98 (ap), 19.02 (ap), 18.43 (ap); HRMS M^+: 231.1626 (calcd. for $C_{15}H_{21}NO$: 231.1623).

Preparation of lithium naphthalenide stock solution

Lithium metal (180 mg, 25.93 mmol) was added to a solution of naphthalene (1.660 g, 12.94 mmol) dissolved in THF under an argon atmosphere. The resulting solution began to change color from yellow to green to dark green, and sometimes to a dark purple color. The mixture was stirred overnight and used the next day.

General procedure for reductive decyanation

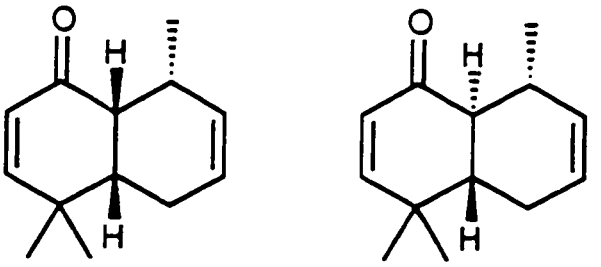
The adduct (0.22 mmol, 1 equivalent) was dissolved in THF (2 mL) and cooled to -25 °C under an argon atmosphere. A stock solution of lithium naphthalenide (1.39 M) was pre-cooled at -25 °C for 10 minutes. Lithium naphthalenide (2.0 mL, 2.78 mmol, 12 equivalents) was added to the adduct solution and the resulting dark green/purple solution was stirred for 30 minutes at -25 °C. The mixture was quenched with methanol (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed successively with water (2 x 10 mL) and saturated sodium chloride solution (2 x 10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography by elution with Skelly B to remove naphthalene and then elution with ethyl acetate-Skelly B (5:95) to give the desired decyanated product(s).

General procedure for reductive alkylation

The adduct (0.22 mmol, 1 equivalent) was dissolved in THF (2 mL) and then cooled to -25 °C under an argon atmosphere. A stock solution of lithium naphthalenide (1.39 M) was pre-cooled to -25 °C for 10 minutes and then lithium naphthalenide (2.0 mL, 2.78 mmol, 12 equivalents) was added to the adduct solution. The resulting dark green/purple solution was stirred for 30 minutes at -25 °C then quenched with an alkylating reagent (5.5 equivalents) and stirred overnight at the appropriate temperature. The reaction was worked up in the same manner as described previously for the reductive cleavage reactions.

(1R*,6R*,10R*)-5,5,10-Trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (94) and

(1S*,6R*,10R*)-5,5,10-Trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (95)

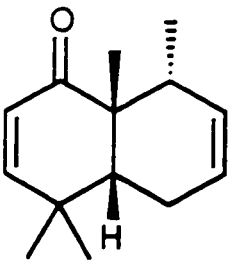


94 **95**

Adduct **69** (50 mg, 0.23 mmol) gave an inseparable 1:5 mixture of **94**:**95** as a colorless oil (32 mg, 0.17 mmol, 73%): IR (CH_2Cl_2, cast): 1675 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 6.59 (d, 0.83H, J = 10 Hz, C**H**=CHC=O, **95**), 6.25 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 0.17H, C**H**=CHC=O, **94**), 5.82 (d, J = 10 Hz, 1H, CH=C**H**C=O), 5.40-5.70 (complex, 2H, **H**C=C**H**CH_2), 2.98 (m, 0.17H, **94**), 2.50 (m, 0.83H, C**H**CH_3, **95**), 1.89-2.15 (complex, 4H), 1.42 (d, J = 6.5 Hz, 0.5H, CHC**H**$_3$, **94**), 1.31 (s, 0.5H, C**H**$_3$, **94**), 1.22 (d, J = 7 Hz, 2.5H, CHC**H**$_3$, **95**), 1.12 (s, 2.5H, C**H**$_3$, **95**), 1.08 (s, 0.5H, C**H**$_3$, **94**), 1.04 (s, 2.5H, C**H**$_3$, **95**); HRMS (mixture) M^+: 190.1362 (calcd. for $C_{13}H_{18}O$: 190.1358).

The spectral data are in agreement with those found in our laboratory[44].

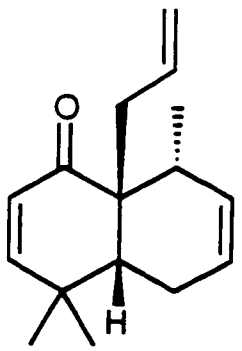
(1R*,6R*,10R*)-1,5,5,10-Tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (96)



96

Methyl iodide was added to a mixture of adduct **69** (50 mg, 0.23 mmol) and lithium naphthalenide in THF to afford in 22 hours compound **96**. Kugelrohr distillation at 56 °C/0.1 mm of Hg gave **96** as a colorless oil (38 mg, 0.19 mmol, 83%): IR (CH_2Cl_2, cast): 1670 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.92 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.67 (m, 1H, CH=C**H**), 5.52 (dm, J = 10 Hz, 1H, CH=C**H**), 2.28 (dm, J = 18 Hz, 1H, C**H**$_2$), 2.06-2.14 (complex, 2H), 1.90 (d, J = 8 Hz, 1H, CH_2C**H**), 1.32 (s, 3H, C(C**H**$_3$)C=O), 1.12 (s, 3H, C**H**$_3$), 1.05 (s, 3H, C**H**$_3$), 0.94 (d, J = 8 Hz, 3H, CHC**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.58 (p), 157.58 (ap), 130.65 (ap), 127.01 (ap), 123.66 (ap), 45.77 (p), 44.39 (ap), 36.86 (ap), 35.84 (p), 32.25 (ap), 26.78 (ap), 23.66 (ap), 22.78 (p), 17.65 (ap); HRMS M^+: 204.1491 (calcd. for $C_{14}H_{20}O$: 204.1514). Anal. calcd. for $C_{14}H_{20}O$: C 82.30%, H 9.87%; found: C 82.02%, H 9.53%.

(1R*,6R*,10R*)-1-Allyl-5,5,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (97)

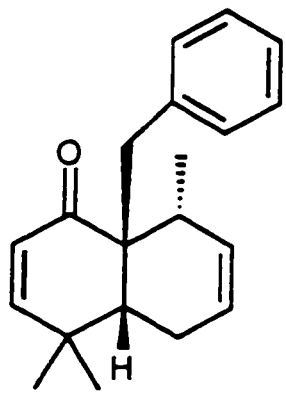


97

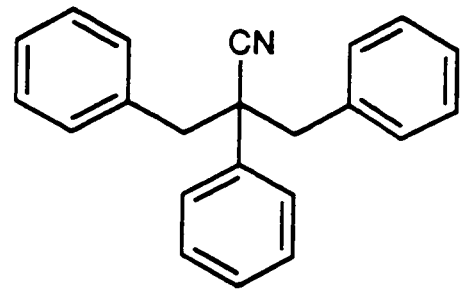
Allyl bromide was added to a mixture of adduct **69** (100 mg, 0.47 mmol) and lithium naphthalenide in THF. The mixture was stirred at room temperature for 21 hours to afford after Kugelrohr distillation at 56-58 °C/0.1 mm of Hg, compound **97** as a colorless oil (75 mg, 0.33 mmol, 70%): IR (CH_2Cl_2, cast): 1667 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.50 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.96 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.70 (m, 1H, CH=C**H**), 5.58 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 10 Hz, J_4 = 2 Hz, 1H, C**H**=CH_2), 5.53 (m, 1H, CH=C**H**), 5.07 (ddd, J_1 = 17 Hz, J_2 = 2 Hz, J_3 = 2 Hz, 1H, CH=CH_2), 5.00 (ddd, J_1 = 10 Hz, J_2 = 2 Hz, J_3 = 2 Hz, 1H, CH=CH_2), 2.95 (dddd, J_1 = 14 Hz, J_2 = 4 Hz, J_3 = 2 Hz, J_4 = 2 Hz, 1H, CH_2CH=CH_2), 2.20 (dd, J_1 = 14 Hz, J_2 = 10 Hz, 1H, CH_2CH=CH_2), 2.16 (m, 1H), 2.11 (d, J = 8 Hz, 1H), 2.03 (q, J = 5.5 Hz, 1H), 2.00 (dd, J_1 = 15 Hz, J_2 = 5.5 Hz, 1H), 1.11 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.93 (d, J = 8 Hz, 3H, CHCH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.48 (p), 158.20 (ap), 135.54 (ap), 130.57 (ap), 127.64 (ap), 124.06 (ap), 117.38 (p), 49.20 (p), 42.88 (p), 38.58 (ap), 37.18 (ap), 35.58 (p), 32.23 (ap), 23.66 (ap), 21.52 (p), 17.46 (ap); HRMS M^+: 230.1666 (calcd. for $C_{16}H_{22}O$:

230.1671). Anal. calcd. for $C_{16}H_{22}O$: C 83.43%, H 9.63%; found: C 83.58%, H 9.67%.

(1R*,6R*,10R*)-1-Benzyl-5,5,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (98) and α,α-Dibenzylphenylacetonitrile (109)



98

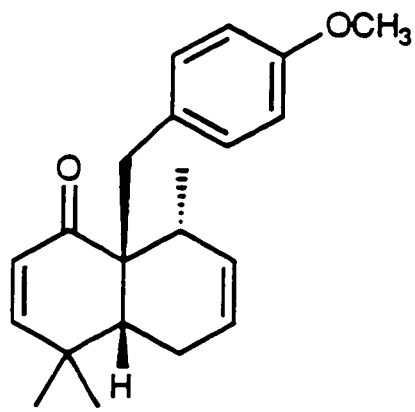


109

Benzyl bromide was added to a mixture of adduct **69** (50 mg, 0.23 mmol) and lithium naphthalenide in THF. The solution was refluxed for 18 hours. Flash column chromatography eluting with ethyl acetate-Skelly B (5:95) afforded compound **98** as a white solid (37 mg, 0.13 mmol, 57%). Further elution gave compound **109**. Compound **98**: IR (CH_2Cl_2, cast): 1665 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.10-7.23 (m, 5H, phenyl), 6.46 (d, J = 10 Hz, 1H, C**H**=CHC=O), 5.99 (d, J = 10 Hz, 1H, CH=C**H**C=O), 5.77 (m, 1H, C**H**=CH), 5.60 (dm, J = 10 Hz, 1H, CH=C**H**), 3.77 (d, J = 14 Hz, 1H, CH_2Ph), 2.70 (d, J = 14 Hz, 1H, CH_2Ph), 2.34 (dm, J = 19 Hz, 1H, CH_2), 2.21 (m, 1H, C**H**CH_3), 2.00 (ddd, J_1 = 19 Hz, J_2 = 5.5 Hz, J_3 = 1 Hz, 1H, CH_2), 1.92 (d, J = 8 Hz, 1H, C**H**CH_2), 1.06 (s, 3H, CH_3), 0.98 (d, J = 8 Hz, 3H, CHCH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.86 (p), 158.47 (ap), 138.98 (p), 130.51 (ap), 130.26 (ap), 128.10 (ap), 127.84 (ap), 126.21 (ap), 123.88 (ap), 51.13 (p), 44.16

(p), 37.74 (ap), 37.71 (ap), 35.54 (p), 32.16 (ap), 23.51 (ap), 22.04 (p), 17.42 (ap); HRMS M+: 280.1821 (calcd. for $C_{20}H_{24}O$: 280.1827). Anal. calcd. for $C_{20}H_{24}O$: C 85.67%, H 8.63%; found: C 85.99%, H 8.63%. Compound **109**: IR (CH_2Cl_2, cast): 2241 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 7.28-7.38 (m, 5H, aryl), 7.15-7.24 (m, 6H, aryl), 7.00-7.10 (m, 4H, aryl), 3.35 (s, 4H, CH_2); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 137.27 (p), 135.01 (p), 130.44 (ap), 128.62 (ap), 128.12 (ap), 127.92 (p), 127.30 (ap), 126.90 (ap), 121.23 (p), 51.14 (p), 46.52 (p); HRMS M+: 297.1522 (calcd. for $C_{22}H_{19}N$: 297.1518).

(1R*,6R*,10R*)-1-(4-Methoxybenzyl)-,5,5,10-trimethylbicyclo[4.4.0]-deca-3,8-dien-2-one (99)

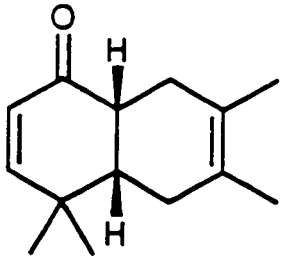


99

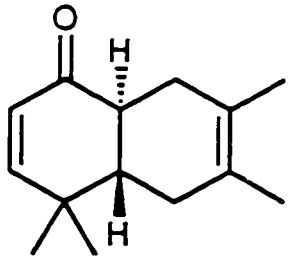
para-Methoxybenzyl chloride was added to a mixture of adduct **69** (50 mg, 0.23 mmol) and lithium naphthalenide in THF. The mixture was refluxed for 18 hours to afford after Kugelrohr distillation at 97 °C/0.3 mm of Hg, compound **99** as a colorless oil (35 mg, 0.11 mmol, 49%): IR (CH_2Cl_2, cast): 1664 (C=O), 1198 cm^{-1} (C-O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 9 Hz, 2H, phenyl), 6.74 (d, J = 9 Hz, 2H, phenyl), 6.45 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.97 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.76 (m, 1H, C**H**=CH), 5.59 (dm, J = 10 Hz, 1H, CH=C**H**),

3.76 (s, 3H, OCH_3), 3.67 (d, J = 14 Hz, 1H, CH_2Ar), 2.59 (d, J = 14 Hz, 1H, CH_2Ar), 2.33 (dm, J = 19 Hz, 1H, CH_2), 2.18 (m, 1H, $CHCH_3$), 2.00 (ddd, J_1 = 19 Hz, J_2 = 5.5 Hz, J_3 = 1 Hz, 1H, CH_2), 1.96 (d, J = 8 Hz, 1H, $CHCH_2$), 1.05 (s, 3H, CH_3), 0.96 (d, J = 8 Hz, 3H, $CHCH_3$), 0.93 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.01 (p), 158.47 (ap), 157.98 (p), 131.25 (ap), 131.03 (p), 129.40 (ap), 127.85 (ap), 123.84 (ap), 113.82 (ap), 113.47 (ap), 55.17 (ap), 51.18 (p), 43.28 (p), 37.63 (ap), 35.54 (p), 32.18 (ap), 23.54 (ap), 22.05 (p), 17.45 (ap); HRMS M^+: 310.1924 (calcd. for $C_{21}H_{26}O_2$: 310.1933). Anal. calcd. for $C_{21}H_{26}O_2$: C 81.25%, H 8.44%; found: C 80.98%, H 8.57%.

(1R*,6R*)-5,5,8,9-Tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (100) and (1S*,6R*)-5,5,8,9-Tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (101)



100

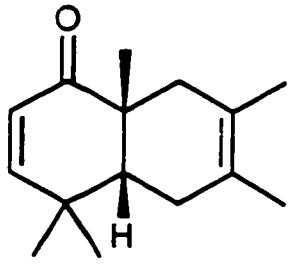


101

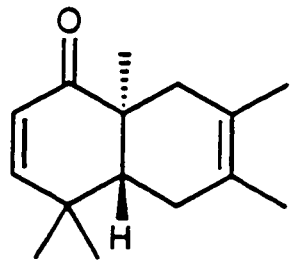
Adduct **68** (50 mg, 0.22 mmol) gave a 1:2 inseparable mixture of **100**:**101** as a colorless oil (22 mg, 0.11 mmol, 50%): IR (CH_2Cl_2, cast): 1674 cm^{-1} (C=O); ^1H NMR (mixture, 400 MHz, $CDCl_3$): δ 6.68 (d, J = 10.5 Hz, 0.67H, CH=CHC=O, **101**), 6.38 (dd, J_1 = 10.5 Hz, J_2 = 2 Hz, 0.33H, CH=CHC=O, **100**), 5.85 (d, J = 10 Hz, 0.67H, CH=CHC=O, **101**), 5.79 (d, J = 10 Hz, 0.33H, CH=CHC=O, **100**), 2.93 (m, 0.33H, **100**), 2.68 (br d, J = 17 Hz, 0.33H, **100**), 2.44 (br dd, J_1 = 17

Hz, J_2 = 5 Hz, 0.67H, CH_2, **101**), 2.31 (ddd, J_1 = 14 Hz, J_2 = 10 Hz, J_3 = 6 Hz, 0.67H, $CHC(CH_3)_2$, **101**), 2.08-1.82 (complex, 4H), 1.62 (br s, 6H, $C=CCH_3$, **100** and **101**), 1.27 (s, 1H, CH_3, **100**), 1.11 (s, 2H, CH_3, **101**),1.09 (s, 1H, CH_3, **100**), 1.02 (s, 2H, CH_3, **101**); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 201.46 (p), 199.99 (p), 160.98 (ap), 155.84 (ap), 126.34 (ap), 126.16 (ap), 124.28 (p), 124.15 (p), 123.99 (p), 123.69 (p), 43.96 (ap), 43.75 (ap), 42.51 (ap), 42.49 (ap), 36.35 (p), 35.17 (p), 32.56 (p), 32.50 (p), 30.74 (p), 30.34 (p), 27.78 (ap), 26.90 (ap), 26.22 (ap), 20.93 (ap), 19.22 (ap), 18.92 (ap), 18.71 (ap); HRMS (mixture) M^+: 204.1505 (calcd. for $C_{14}H_{20}O$: 204.1514). Anal. calcd. for $C_{14}H_{20}O$ (mixture): C 82.30%, H 9.87%; found: C 82.11%, H 10.04%.

(1R*,6R*)-1,5,5,8,9-Pentamethylbicyclo[4.4.0]deca-3,8-dien-2-one (102) and
(1S*,6R*)-1,5,5,8,9-Pentamethylbicyclo[4.4.0]deca-3,8-dien-2-one (103)



102

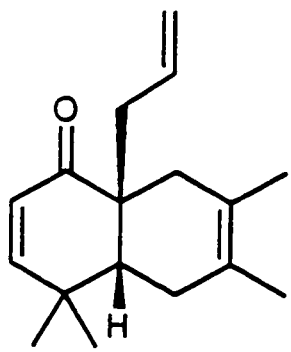


103

Methyl iodide was added to the mixture of adduct **68** (57 mg, 0.25 mmol) and lithium naphthalenide in THF to afford in 21 hours an inseparable 1:1 mixture of **102**:**103** as a colorless oil (22 mg, 0.10 mmol, 40%): IR (CH_2Cl_2, cast): 1674 cm^{-1} (C=O); ^1H NMR (mixture, 400 MHz, $CDCl_3$): δ 6.57 (d, J = 10 Hz, 0.5H, CH=CHC=O, **103**), 6.49 (d, J = 10 Hz, 0.5H, CH=CHC=O, **102**), 5.83 (d, J = 10

Hz, 0.5H, CH=CHC=O, **103**), 5.82 (d, J = 10 Hz, 0.5H, CH=CHC=O, **102**), 1.92-2.30 (complex, 3.5H), 2.33 (br d, J = 15 Hz, 0.5H, **102**), 1.89 (br d, J = 18 Hz, 0.5H, CH_2), 1.79 (br d, J = 7 Hz, 0.5H), 1.66 (br s, 3H, $CH_3C=CCH_3$), 1.63 (br s, 3H, $CH_3C=CCH_3$), 1.18 (s, 1.5H, CH_3, **102**), 1.11 (s, 3H, $C(CH_3)C=O$), 1.10 (s, 1.5H, CH_3, **103**), 1.07 (s, 1.5H, CH_3, **103**), 0.90 (s, 1.5H, CH_3, **102**); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 205.69 (p), 204.42 (p), 159.01 (ap), 157.58 (ap), 124.41 (ap), 124.09 (ap), 123.78 (p), 123.62 (p), 123.39 (p), 122.65 (p), 45.06 (ap), 44.92 (ap), 43.92 (p), 43.35 (p), 42.53 (p), 38.98 (p), 36.20 (p), 35.07 (p), 31.12 (ap), 30.84 (ap), 30.05 (p), 29.99 (p), 22.74 (ap), 22.57 (ap), 22.37 (ap), 19.30 (ap), 19.12 (ap), 19.03 (ap), 18.73 (ap), 18.69 (ap); HRMS (mixture) M^+: 218.1667 (calcd. for $C_{15}H_{22}O$: 218.1667).

(1R*,6R*)-1-Allyl-5,5,8,9-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (104)

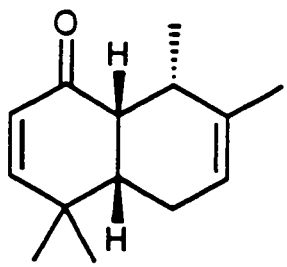


104

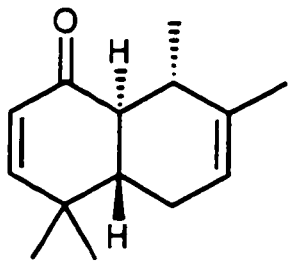
A mixture of adduct **68** (50 mg, 0.22 mmol) and lithium naphthalenide in THF was stirred at room temperature after addition of allyl bromide for 18 hours to afford after Kugelrohr distillation (68 °C/0.3 mm Hg), compound **104** as a colorless oil (36 mg, 0.15 mmol, 68%): IR (CH_2Cl_2, cast): 1671 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.50 (d, J = 10 Hz, 1H, CH=CHC=O), 5.84 (d, J = 10

Hz, 1H, CH=CHC=O), 5.61 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 10 Hz, J_4 = 5 Hz, 1 H, CH=CH_2), 5.03 (dm, J = 17 Hz, 1H, CH=CH_2), 4.98 (dm, J = 10 Hz, 1H, CH=CH_2), 2.77 (dddd, J_1 = 14 Hz, J_2 = 5 Hz, J_3 = 2 Hz, J_4 = 2 Hz, 1H, CH_2CH=CH_2), 2.16 (complex, 3 H), 1.98 (d, J = 7 Hz, 1H, $CHCH_2$), 1.82 (br d, J = 19 Hz, 1H), 1.67 (br s, 3H, C=CCH_3), 1.62 (m, 1H), 1.57 (br s, 3H, C=CCH_3), 1.10 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.32 (p), 158.05 (ap), 135.34 (ap), 124.68 (ap), 124.30 (p), 122.43 (p), 117.26 (p), 47.23 (p), 39.73 (ap), 39.29 (p), 39.14 (p), 36.03 (p), 31.06 (ap), 28.92 (p), 23.08 (ap), 18.98 (ap), 18.71 (ap); HRMS M^+: 244.1812 (calcd. for $C_{17}H_{24}O$: 244.1827).

(1R*,6R*,10R*)-5,5,9,10-Tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (105) and (1S*,6R*,10R*)-5,5,9,10-Tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (106)



105

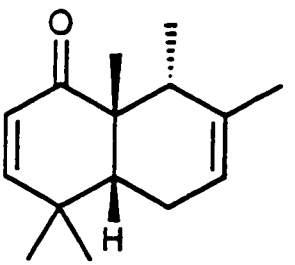


106

Adduct **70** (54 mg, 0.24 mmol) gave an inseparable 1:2 mixture of **105**: **106** as a colorless oil (36 mg, 0.18 mmol, 75%): IR (mixture, CH_2Cl_2, cast): 1684 cm^{-1} (C=O). Epimerization of the mixture with sodium hydride in methanol at room temperature gave pure compound **106**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (d, J = 10 Hz, 1H, CH=CHC=O), 5.85 (d, J = 10 Hz, 1H, CH=CHC=O), 5.44 (m, 1H, CH=$C(CH_3)$), 2.49 (m, 1H), 2.12 (dd, J_1 = 13.5 Hz, J_2 = 8.5 Hz, 1H), 2.07 (m, 1H,

CH_2), 1.93 (m, 1H, CH_2), 1.81 (ddd, J_1 = 13.5 Hz, J_2 = 11.5 Hz, J_3 = 4.5 Hz, 1H, $CHC(CH_3)_2$), 1.68 (br s, 3H, $CH=CCH_3$), 1.21 (d, J = 7 Hz, 3H, $CHCH_3$), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.66 (p), 159.48 (ap), 137.73 (p), 126.36 (ap), 119.43 (ap), 50.18 (ap), 44.21 (ap), 35.80 (p), 34.15 (ap), 28.15 (ap), 25.37 (p), 21.53 (ap), 21.33 (ap), 20.50 (ap); HRMS M^+: 204.1508 (calcd. for $C_{14}H_{20}O$: 204.1514). Anal. calcd. for $C_{14}H_{20}O$: C 82.30%, H 9.87%; found: C 82.21%, H 9.86%. Compound **105**: ^1H NMR (200 MHz, $CDCl_3$): δ 6.25 (dd, J_1 = 10.5 Hz, J_2 = 2 Hz, 1H, $CH=CH=O$), 5.70 (d, J = 10.5 Hz, 1H, $CH=CHC=O$), 5.18-5.29 (m, 1H, $CH=CCH_3$), 2.95-3.03 (m, 1H), 1.80-2.20 (m, 4H), 1.72 (br s, 3H, $CH=CCH_3$), 1.40 (d, J = 7.5 Hz, 3H, $CHCH_3$), 1.32 (s, 3H, CH_3), 1.07 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.06 (p), 153.45 (ap), 136.56 (p), 126.98 (ap), 119.21 (ap), 49.12 (ap), 46.95 (ap), 46.47 (p), 36.92 (ap), 26.72 (ap), 25.91 (ap), 25.63 (p), 20.85 (ap) 17.03 (ap).

(1R*,6R*,10R*)-1,5,5,9,10-Pentamethylbicyclo[4.4.0]deca-3,8-dien-2-one (107)

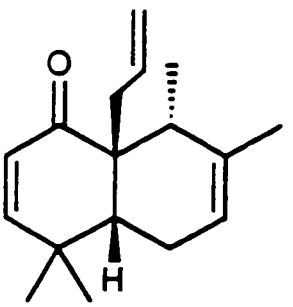


107

Methyl iodide was added to a mixture of adduct **70** (50 mg, 0.22 mmol) and lithium naphthalenide in THF to afford in 23 hours after Kugelrohr distillation (60 °C/0.15 mm Hg), compound **107** as a colorless oil (35 mg, 0.17 mmol, 78%): IR (CH_2Cl_2, cast): 1668 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 6.50 (d, J = 10

Hz, 1H, C**H**=CHC=O), 5.95 (d, J = 10 Hz, 1H, CH=C**H**C=O), 5.42 (m, 1H, C**H**=CCH$_3$), 2.28 (dm, J = 19 Hz, 1H, C**H**$_2$), 2.05 (ddm, J_1 = 19 Hz, J_2 = 2 Hz, 1H, C**H**$_2$), 1.93 (br q, J = 7.5 Hz, 1H, C**H**CH$_3$), 1.85 (d, J = 8 Hz, 1H, C**H**CH$_2$), 1.68 (br s, 3H, C=CC**H**$_3$), 1.28 (s, 3H, C(C**H**$_3$)C=O), 1.11 (s, 3H, C**H**$_3$), 1.04 (s, 3H, C**H**$_3$), 0.94 (d, J = 7.5 Hz, 3H, CHC**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.95 (p), 157.77 (ap), 134.43 (p), 127.32 (ap), 119.62 (ap), 46.46 (p), 44.20 (ap), 40.70 (ap), 35.67 (p), 32.48 (ap), 26.75 (ap), 23.22 (p), 23.07 (ap), 22.72 (ap), 15.50 (ap); HRMS M$^+$: 218.1665 (calcd. for $C_{15}H_{22}O$: 218.1671).

(1R*,6R*,10R*)-1-Allyl-5,5,9,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (108)



108

Allyl bromide was added to a mixture of adduct **70** (83 mg, 0.36 mmol) and lithium naphthalenide in THF. The reaction mixture was stirred at room temperature for 17 hours to afford after Kugelrohr distillation at 55 °C/0.1 mm of Hg, **108** as a colorless oil (83 mg, 0.34 mmol, 94%): IR (CH_2Cl_2, cast): 1667 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.95 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.58 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 10 Hz, J_4 = 5 Hz, 1H, C**H**=CH$_2$), 5.46 (m, 1H, C**H**=CCH$_3$), 5.05

(ddd, J_1 = 17 Hz, J_2 = 2 Hz, J_3 = 2 Hz, 1H, CH=C**H**$_2$), 4.99 (ddd, J_1 = 10 Hz, J_2 = 2 Hz, J_3 =2 Hz, 1H, CH=C**H**$_2$), 2.91 (dddd, J_1 = 14 Hz, J_2 = 5 Hz, J_3 = 2 Hz, J_4 = 2 Hz, 1H, C**H**$_2$CH=CH$_2$), 2.16 (dm, J = 18 Hz, 1H, C**H**$_2$), 2.15 (dd, J_1 = 14 Hz, J_2 = 10.5 Hz, 1H, C**H**$_2$CH=CH$_2$), 2.06 (d, J = 8 Hz, 1H, C**H**CH$_2$), 2.00 (ddm, J_1 = 18 Hz, J_2 = 5 Hz, 1H, C**H**$_2$), 1.88 (q, J = 7 Hz, 1H, C**H**CH$_3$), 1.68 (d, J = 1.5 Hz, 3H, C=CC**H**$_3$), 1.10 (s, 3H, C**H**$_3$), 1.06 (s, 3H, C**H**$_3$), 0.95 (d, J = 7.5 Hz, 3H, CHC**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.76 (p), 158.15 (ap), 135.59 (ap), 134.33 (p), 127.86 (ap), 120.04 (ap), 117.25 (p), 49.96 (p), 42.83 (p), 41.13 (ap), 38.51 (ap), 35.44 (p), 32.37 (ap), 23.21 (ap), 22.67 (ap), 22.14 (p), 15.22 (ap); HRMS M^+: 244.1818 (calcd. for $C_{17}H_{24}O$: 244.1827). Anal. calcd. for $C_{17}H_{24}O$: C 83.55%, H 9.90%; found: C 83.76%, H 9.93%.

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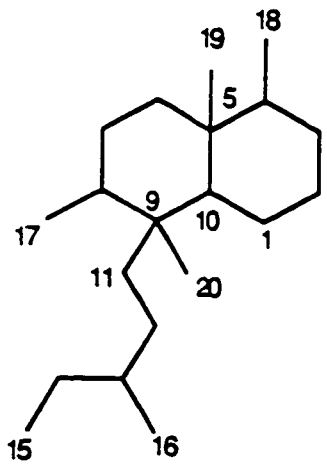
Chapter 2

Formal Syntheses of (±)-6β-2-Oxokolavenool and (±)-2-Oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic Acid via Reductive Alkylation of the α-Cyano Ketone System

Introduction

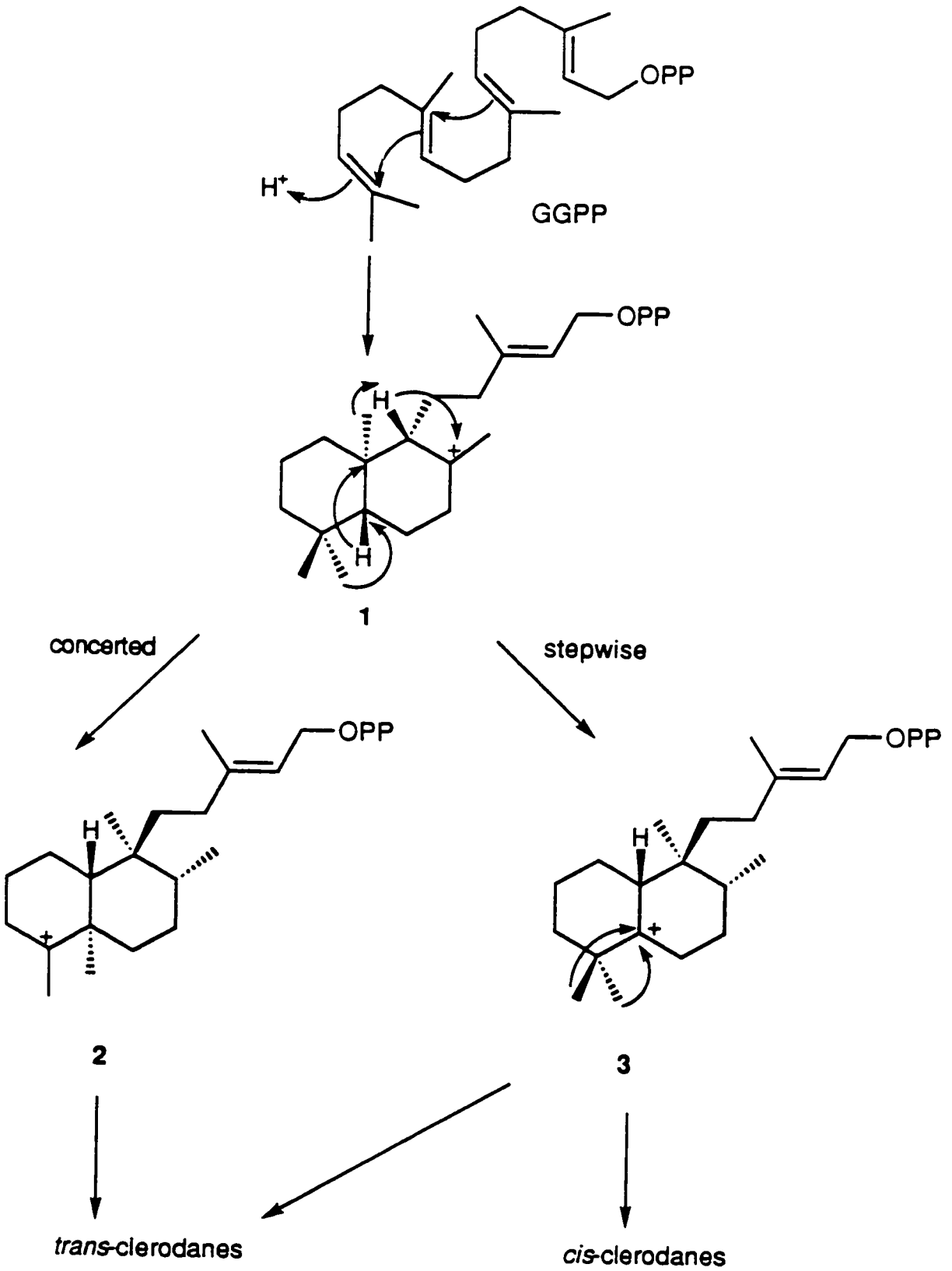
The clerodane carbon skeleton (**Figure 2-1**) constitutes one of the largest growing families of diterpenoids. Over the past thirty years approximately eight hundred compounds have been isolated from various natural sources[1].

Figure 2-1



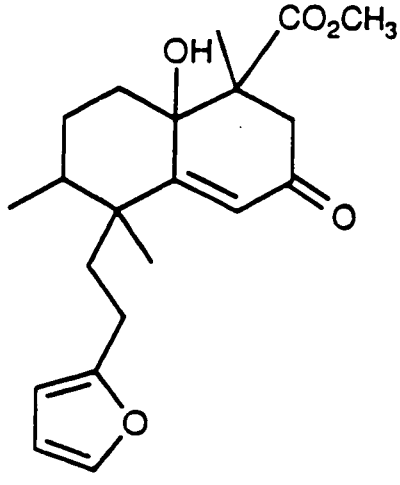
The clerodane family of compounds are sub-divided into two series. These include the *cis* series and the *trans* series of compounds, depending on the stereochemistry of the ring junction in the decalin system. The clerodanes appear to follow the same biosynthetic pathway as that of the labdane diterpenoids. The clerodanes are derived from geranyl geranyl pyrophosphate (GGPP) as shown in **Scheme 2-1**[2]. The two families of compounds are related via a series of methyl and hydride shifts.

Scheme 2-1

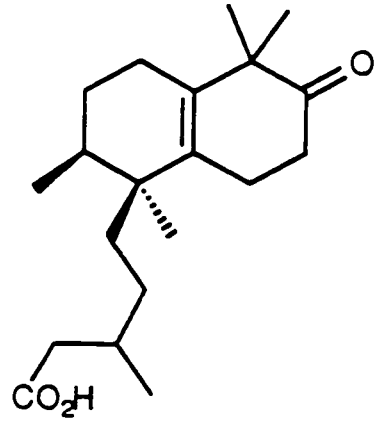

OPP
H+
GGPP
OPP
H
H
1
concerted
stepwise
OPP
H
2
OPP
H
3
trans-clerodanes
cis-clerodanes

Cyclization of geranyl geranyl pyrophosphate (GGPP) leads to a *trans* decalin intermediate **1**. A concerted migration mechanistic pathway affords the *trans* clerodanes via intermediate **2**, while a stepwise mechanistic pathway with a "pause" at intermediate **3** can lead to the *cis* clerodanes. Intermediate **3** can lead to either *cis* or *trans* compounds, depending on which of the C-4 methyl groups migrates.

This proposed biosynthetic pathway is supported by the isolation of the partially rearranged labdane compounds chettaphanin **4**[3] and salmantic acid **5**[4].



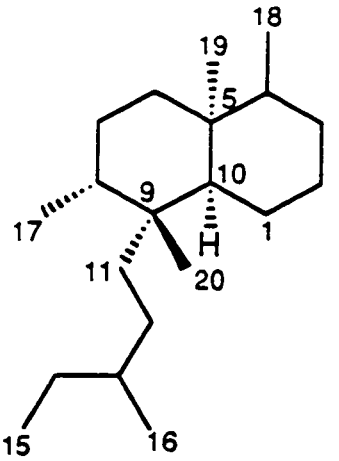
4



5

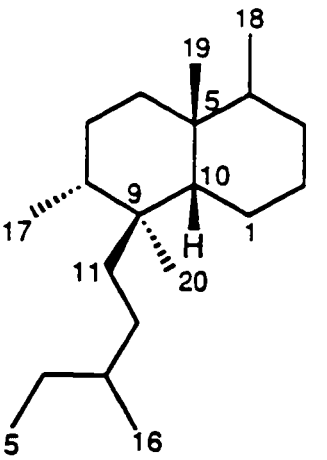
There has been considerable interest towards the total synthesis of these clerodane compounds due to their structural complexity and biological activity. Some were found to be potentially useful as antiviral, antitumor, antifungal, antibiotic, anti-peptic ulcer, and psychotropic agents[1,2]. *cis*-Clerodanes can be further classified into two subgroups in a diastereomeric relationship according to the absolute stereochemistry of the A-B ring junction. These subgroups include the *cis*-normal-clerodane (5α,10α-*cis*-clerodane, **Figure 2-2**) and the *cis*-ent-clerodane (5β,10β-*cis*-clerodane, **Figure 2-3**).

Figure 2-2



cis-normal-clerodanes

Figure 2-3

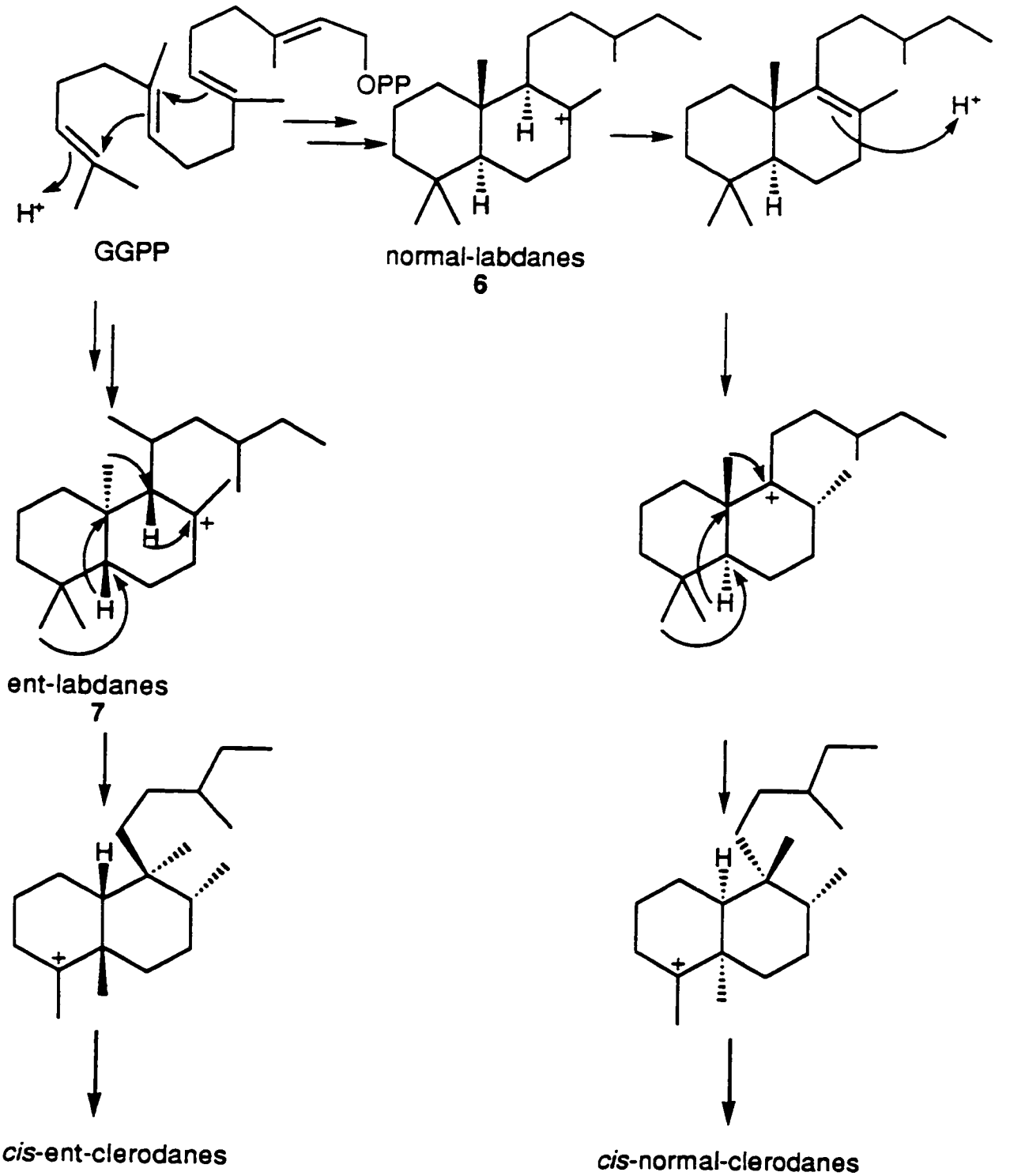


cis-ent-clerodanes

The proposed biosynthetic route for *cis*-normal and *cis*-ent clerodanes is depicted in **Scheme 2-2.** Enzyme catalyzed cyclization generates normal-labdane **6** and ent-labdane skeletons **7** from geranyl geranyl pyrophosphate (GGPP). Subsequent rearrangement of **6** and **7** via methyl and hydride shifts results in the formation of *cis*-normal- and *cis*-ent-clerodane, respectively.

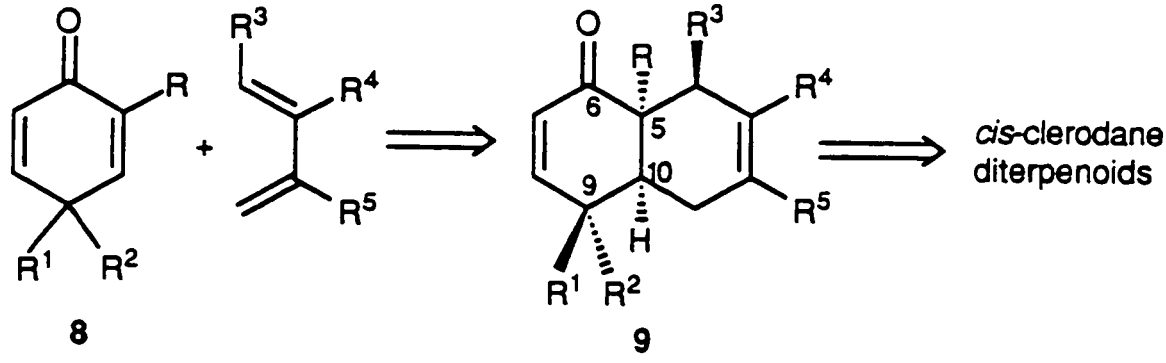
There have been less than thirty total syntheses reported of clerodane natural products[5-29], in which only five have produced compounds derived from the *cis*-clerodanes[21-29]. This is probably due to the limited approaches available to the *cis*-decalin nucleus as compared to the *trans*-decalin nucleus. In most cases, a linear approach towards the target molecule has been developed in the total synthesis of clerodane compounds. Since naturally occurring clerodanes differ slightly in their structures in terms of stereochemistry, oxidation level, and oxygen contents of various centers, it is desirable to develop a general non-linear synthetic approach which makes it possible to synthesize a large number of target molecules by a common strategy with some slight structural changes.

Scheme 2-2


OPP
H+
GGPP
normal-labdanes
6
H+
ent-labdanes
7
cis-ent-clerodanes
cis-normal-clerodanes

This general non-linear approach developed by Liu and co-workers[27,28] involved a face-selective Diels-Alder reaction as the key step. The Diels-Alder approach implements three contiguous chiral centers C-5, C-9, and C-10 (clerodane numbering) of **9**. The relative stereochemistry of these centers is arranged in the same manner as those found in the natural *cis*-clerodanes. The introduction of stereogenic centers into the decalin system was easily accomplished by one simple step. In the presence of two groups at C-9 (clerodane numbering) where R^2 is bulkier than R^1, the addition of the diene to dienophile **8** occurs preferentially from the sterically less hindered R^1 face (**Scheme 2-3**). This approach led to the first total synthesis of 6β-acetoxy-2-oxokolavenool **10**[29] and 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11**[27-29] in racemic form.

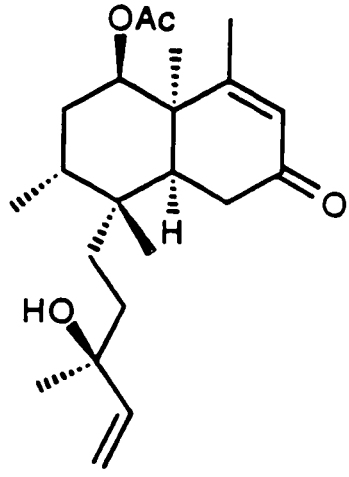
Scheme 2-3



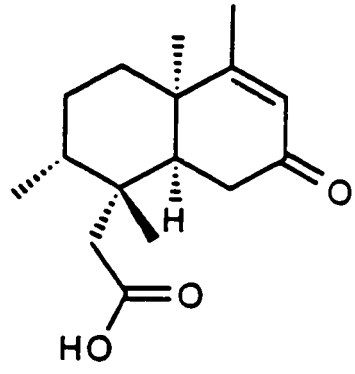
8 **9**

6β-Acetoxy-2-oxokolavenool **10** was isolated by Bohlmann and Zdero[30] from the aerial parts of three Mexican Stevia species and its structure was deduced using spectroscopic methods (IR, mass spectrometry, ^1H NMR, and ^{13}C NMR). 2-Oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11** was isolated from the ethyl acetate extracts of the roots, stem, and leaf sheaths of *Vellozia bicolor*

L.B. Smith by Garcez *et al.*[31] in 1994. The structure was deduced based on spectroscopic methods (IR, mass spectrometry, ^{1}H NMR, and ^{13}C NMR). The clerodanes (both *cis*- and *trans*-clerodanes) are known for their insect antifeedant properties and related insecticidal properties[32,33]. There have been considerable current interests in searching for natural pesticides like clerodanes and their analogues.

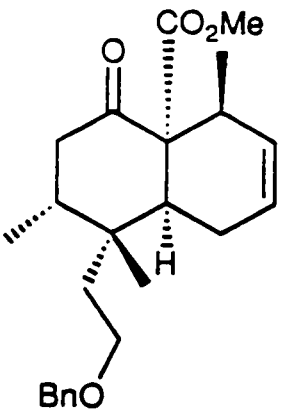


10



11

The key step of the synthesis of (±)-6β-acetoxy-2-oxokolavenool **10** and (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11** involved an intermolecular Diels-Alder reaction with dienophile **18** and *trans*-piperylene (*trans*-1,3-pentadiene). Subsequent structural modification of the resulting adduct led to **12** as a common intermediate in the synthesis of **10** and **11**. The Diels-Alder process facilitated the rapid construction of a decalin system having four contiguous stereogenic centers.

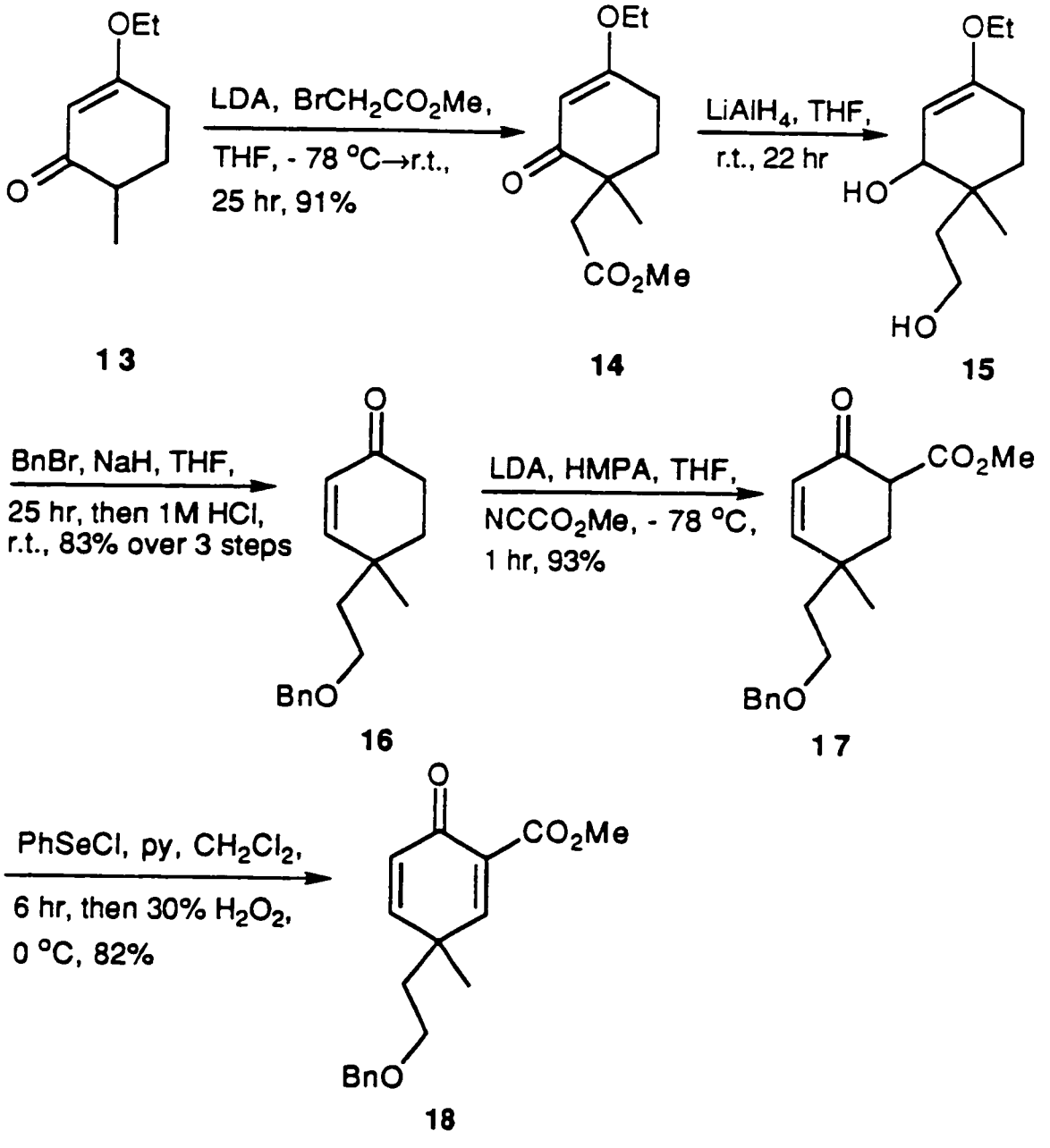


12

Dienophile **18** was readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone **13**[34] according to the synthetic sequence shown in **Scheme 2-4**. Stork-Danheiser alkylation[35] of ethoxy enone **13** with methyl bromoacetate in THF followed by bulb-to-bulb distillation gave enone ester **14** in 91% yield. Reduction of enone ester **14** with lithium aluminum hydride[36] gave a diastereomeric mixture of two unstable diols **15** in nearly equal amounts. Selective benzylation of the crude diol mixture **15** with a slight excess of sodium hydride and benzyl bromide followed by treatment of the crude product with dilute hydrochloric acid gave cyclohexenone **16** in 83% yield over three steps.

Enone **16** was subjected to carbomethoxylation using lithium diisopropylamide (LDA) and methyl cyanoformate[37] to give keto ester **17** as a mixture of three isomers (a pair of epimers and an enol ester) in a ratio of 2:1.4:1 as indicated by ^{1}H NMR integration. Keto ester **17** was treated with phenylselenyl chloride in the presence of pyridine[38] followed by oxidative elimination of the resulting selenide with hydrogen peroxide to give dienone ester **18** in 82% yield.

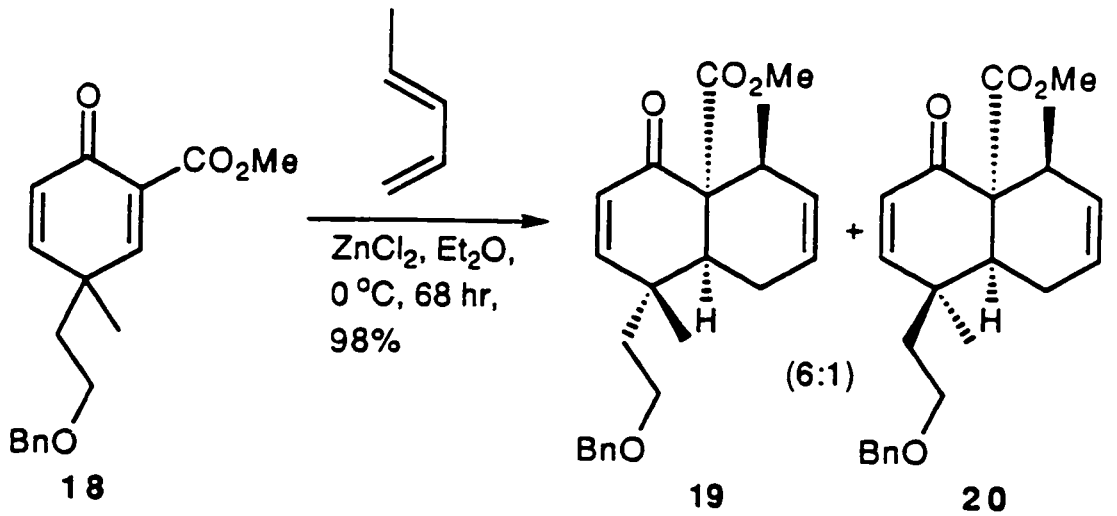
Scheme 2-4



The facial selective Diels-Alder cycloaddition of dienophile **18** with *trans*-piperylene (*trans*-1,3-pentadiene) under zinc chloride catalysis[39] gave adducts **19** and **20** in a ratio of 3.5:1 to 6:1 (**Scheme 2-5**). Cycloaddition occurred with complete regioselectivity (*ortho*-addition), stereoselectivity (addition of

diene occurred in an *endo*-to-ketone fashion), and a high degree of facial selectivity (addition of the diene occurred from the sterically less hindered methyl face of the dienophile).

Scheme 2-5



Introduction of a methyl group to give the last stereogenic center at C-4 was achieved by a 1,4-addition process by treatment of **19** with 3 equivalents of lithium dimethylcuprate in ether at 0 °C for 1 hour, followed immediately by treatment with an excess (3 to 5 equivalents) of lithium aluminum hydride at 0 °C (**Scheme 2-6**). The enolate formed from the 1,4-addition reaction served as an effective protection for the more reactive ketone carbonyl to afford alcohol **21**.

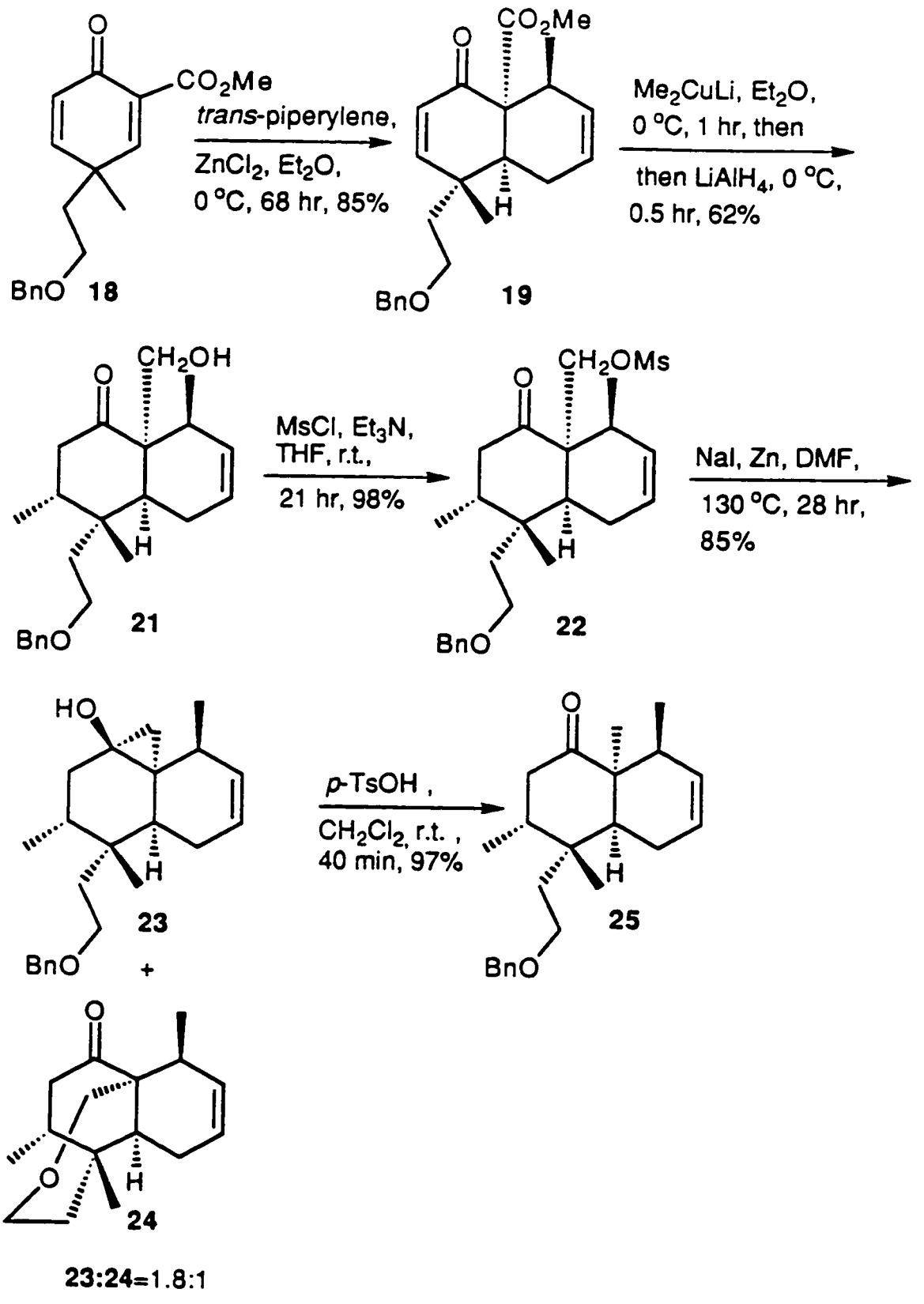
The hydroxyl group of alcohol **21** was removed via the corresponding mesylate. Treatment of alcohol **21** with methanesulfonyl chloride and triethylamine afforded, in virtually quantitative yield, mesylate **22**.

Reduction of mesylate **22** with sodium iodide and zinc dust in *N,N*-dimethylformamide (DMF)[40] at 130 °C gave rise to a 55% yield of cyclopropanol **23** and a 30% yield of tricyclic ketone **24**. The cyclopropane ring of compound **23** underwent rapid cleavage upon exposure to a trace amount of *p*-toluenesulfonic acid in methylene chloride at room temperature to give the desired ketone **25** in near quantitative yield.

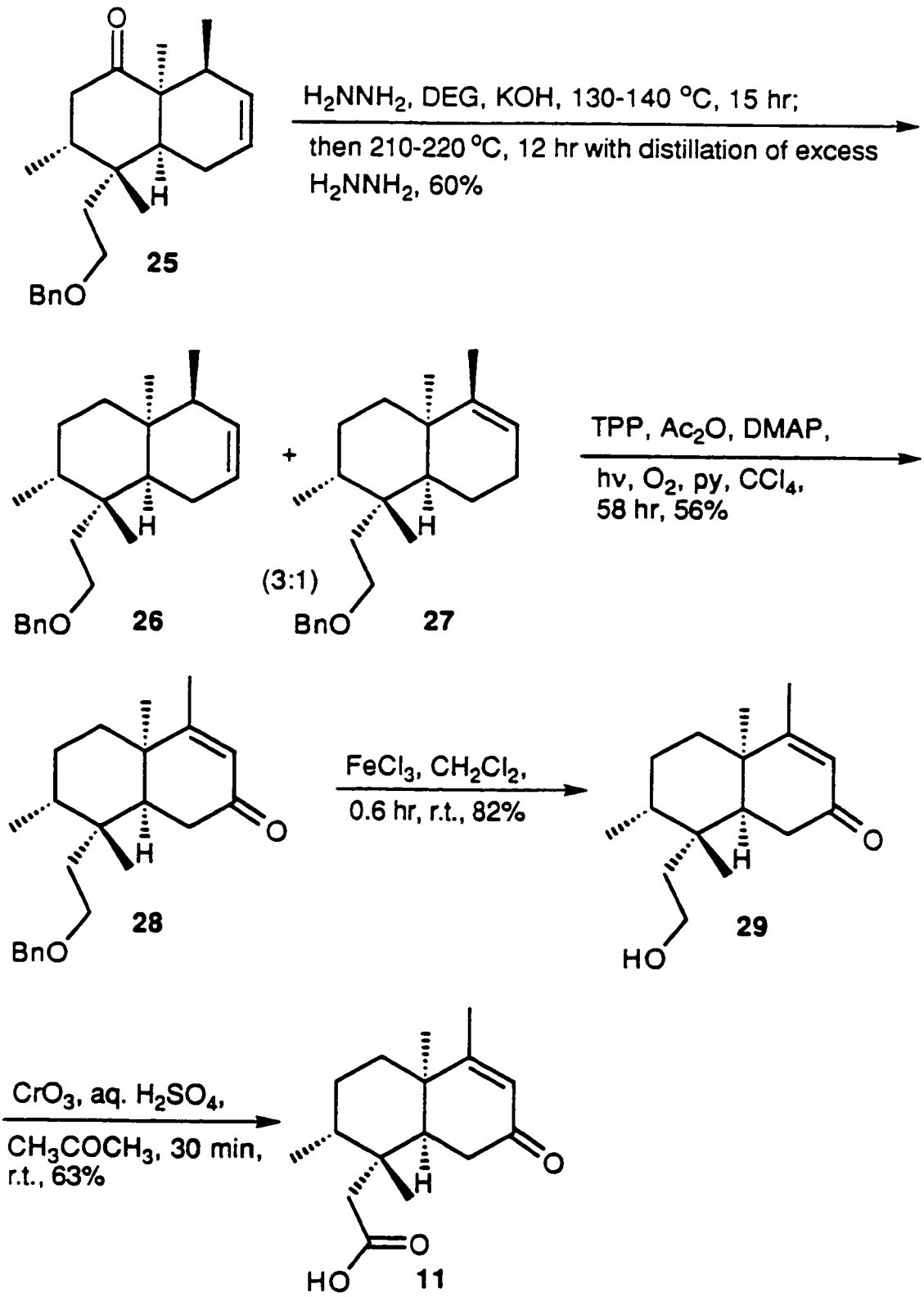
Wolff-Kishner reduction[41] of intermediate **25** afforded a 3:1 mixture by NMR analysis of two isomeric olefins **26** and **27** in 60% yield (**Scheme 2-7**). Subsequent photooxygenation[42] (tungsten lamps) of this mixture with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine in carbon tetrachloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine gave a 56% yield of enone **28**.

Deprotection of **28** with ferric chloride[43] (3 equivalents) in dichloromethane at room temperature afforded enone alcohol **29** in 82% yield. Finally, Jones oxidation[44] of the terminal hydroxy group to a carboxylic acid afforded (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11** in 63% yield.

Scheme 2-6


CO2Me
trans-piperylene,
ZnCl2, Et2O,
0 °C, 68 hr, 85%
Me2CuLi, Et2O,
0 °C, 1 hr, then
then LiAlH4, 0 °C,
0.5 hr, 62%
BnO
18
19
CH2OH
MsCl, Et3N,
THF, r.t.,
21 hr, 98%
CH2OMs
NaI, Zn, DMF,
130 °C, 28 hr,
85%
21
22
HO
p-TsOH ,
CH2Cl2, r.t. ,
40 min, 97%
23
+
25
24
23:24=1.8:1

Scheme 2-7


H2NNH2, DEG, KOH, 130-140 °C, 15 hr;
then 210-220 °C, 12 hr with distillation of excess H2NNH2, 60%
25
BnO
26
27
(3:1)
TPP, Ac2O, DMAP,
hv, O2, py, CCl4,
58 hr, 56%
28
29
FeCl3, CH2Cl2,
0.6 hr, r.t., 82%
CrO3, aq. H2SO4,
CH3COCH3, 30 min,
r.t., 63%
11
HO

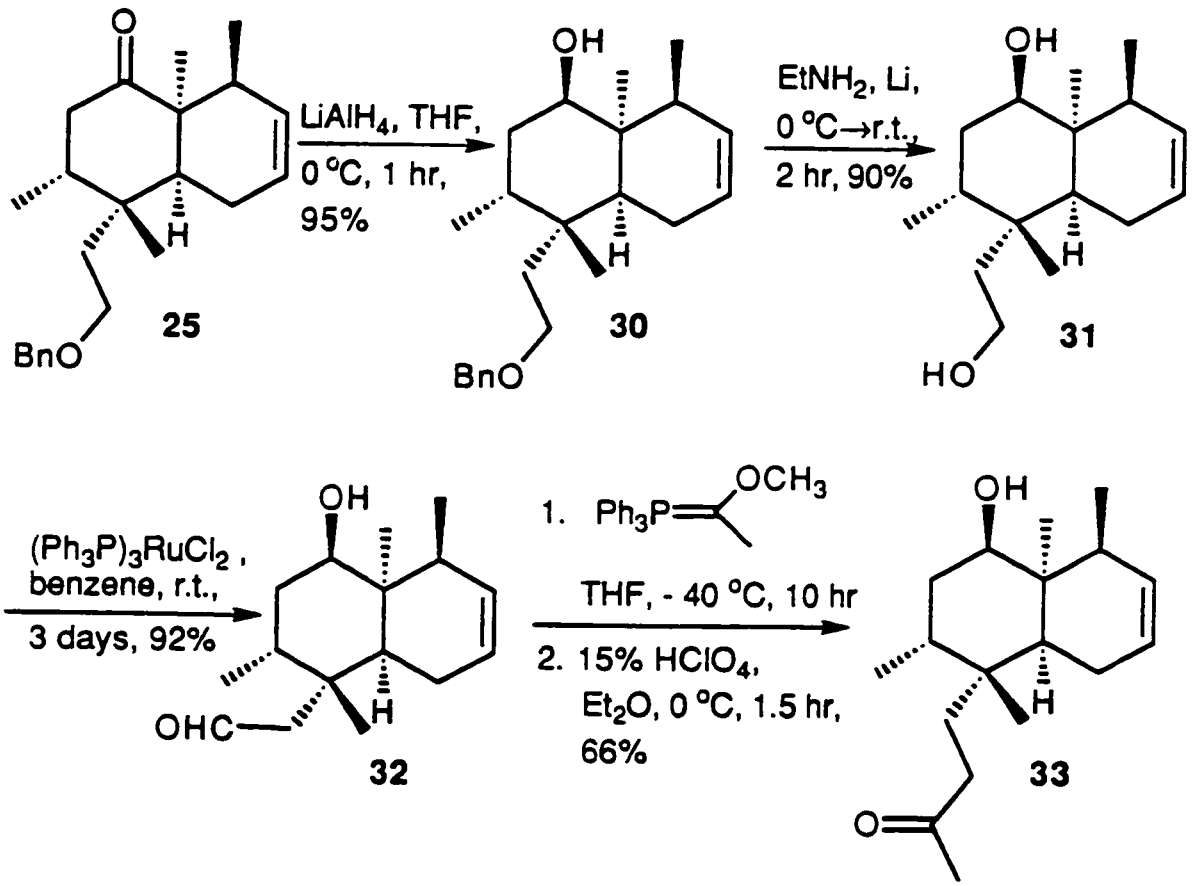
The synthesis of (±)-6β-2-oxokolavenool **10**[29], which contains an oxygen functionality at C-6 (clerodane numbering) involved reduction of ketone **25** with lithium aluminum hydride in THF at 0 °C to afford alcohol **30** in 95% yield as a single stereoisomer (**Scheme 2-8**).

Debenzylation[45] of alcohol **30** with lithium metal and ethylamine in 1 hour furnished diol **31** in 90% yield. In a later publication[46] the yield of the reductive cleavage of the benzyl ether protecting group was improved to 94% by treatment of **30** with lithium naphthalenide. Selective oxidation of the primary hydroxyl of diol **31** in the presence of a secondary alcohol to an aldehyde using dichlorotris-(triphenylphosphine)ruthenium[47] (0.8 equivalent) in dry benzene at room temperature provided hydroxy aldehyde **32** in 92% yield based on the consumed starting material.

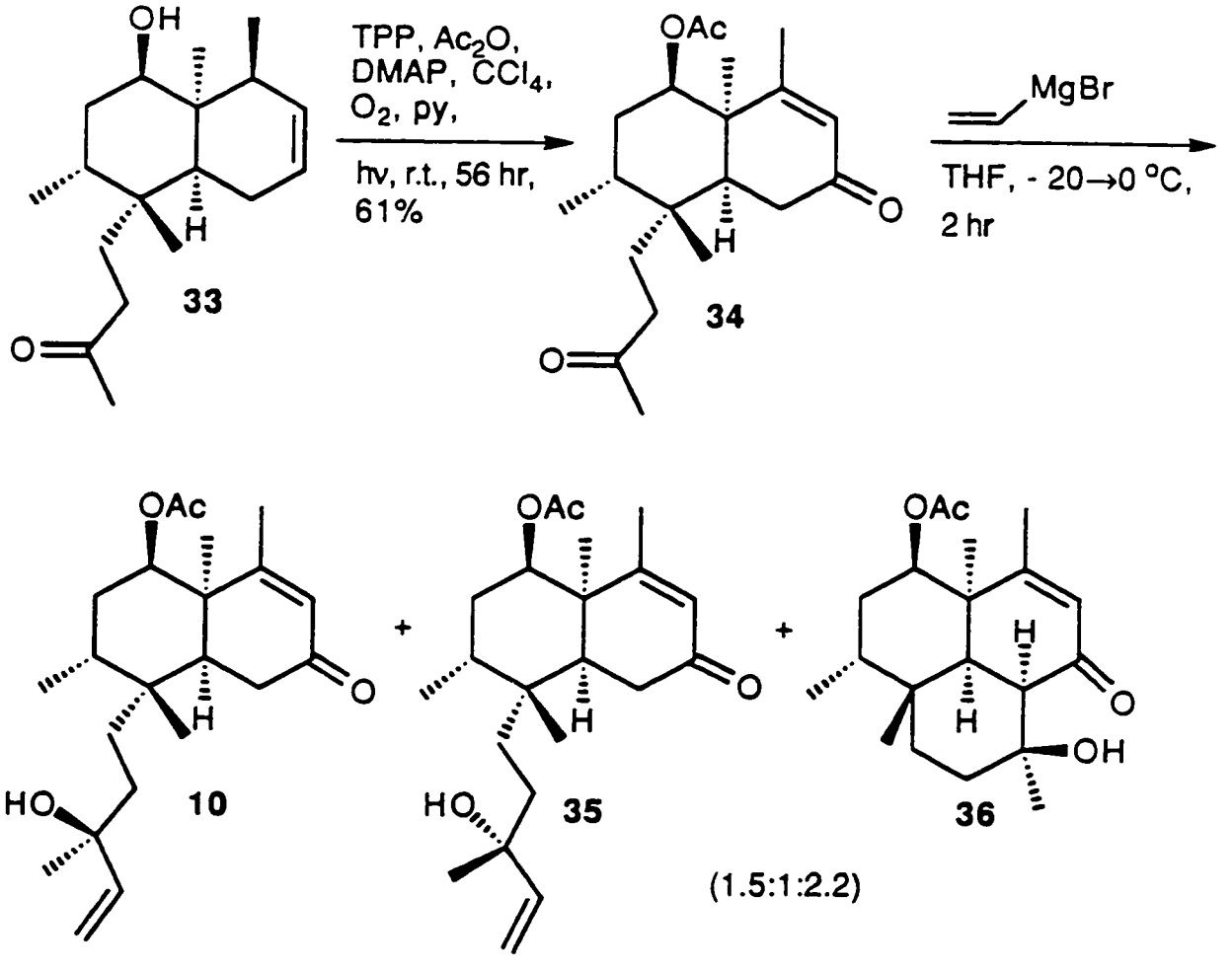
The "butenol" unit was introduced via a Wittig reaction[47]. The Wittig reagent was formed by treatment of α-methoxyethyltriphenylphosphonium chloride with *n*-butyllithium in THF at - 78 °C to form the corresponding ylid. Treatment of **32** with the Wittig reagent at - 40 °C for 10 hours afforded an unstable enol ether which was hydrolyzed in a mixture of aqueous 15% perchloric acid and distilled ether (1:1 ratio) at 0 °C in 1.5 hours to give keto alcohol **33** in 66% yield. Photooxygenation of **33** with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine in carbon tetrachloride in the presence of acetic anhydride, pyridine, and 4-dimethylaminopyridine gave enone **34** in 61% yield.

Finally, introduction of the vinyl group to the saturated ketone carbonyl involved treatment of **34** with vinylmagnesium bromide (2 equivalents) in THF at - 20 °C. Warming the mixture to 0 °C afforded a mixture of two diastereomers **10** and **35** (1.5:1 by ^{1}H NMR analysis) in 40% yield along with a less polar product **36** (35%). The total synthesis of (±)-6β-2-oxokolavenool **10** from ketone **25** was accomplished in six steps.

Scheme 2-8



Scheme 2-8 (continued)



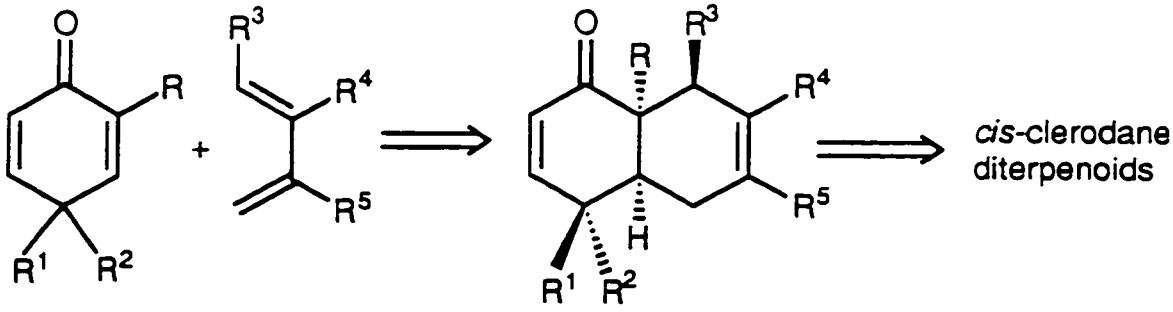
The focus of this second chapter involves the implementation of a simpler method for the introduction of the methyl group at C-5 (clerodane numbering). As discussed previously, the introduction of the methyl group at this position involved the conversion of the carbomethoxy group to a methyl group (**Scheme 2-6**). Conversion of compound **12**, formed via the Diels-Alder approach to the desired intermediate **25** involved several functional group manipulations including reduction of the ester to an alcohol **21**, removal of the alcohol as a mesylate **22** via reduction to cyclopropanol **23**, and finally

cyclopropyl ring opening to form the methyl group. A total of four steps were involved in the synthesis of intermediate **24**.

In the previous chapter we described a very simple method for the conversion of a cyano group to a methyl group. Conversion of the cyano group of the α-cyano ketone system to a methyl group could easily be accomplished via reductive alkylation using lithium naphthalenide[49] with methyl iodide as the trapping agent. We believe such an approach could be applied towards the synthesis of key intermediates in the synthesis of clerodane diterpenoids. Reductive methylation could be utilized in a synthetic scheme in which a cyano group would act as a "latent" methyl group replacing the methyl ester as the activating group in the Diels-Alder cycloaddition.

The following section will involve the synthetic work towards the formal synthesis of (±)-6β-acetoxy-2-oxokolavenool **10** and (±)-2-oxo-5α,8α-13,14,15,15-tetranorclerod-3-en-12-oic acid **11**. This will include the use of a dienophile such as **37**, which introduces a cyano group into the clerodane structure at C-5 (clerodane numbering) after the Diels-Alder cycloaddition (**37**→**38**, **Scheme 2-9**). Incorporation of the nitrile will facilitate the introduction of a methyl group via reductive alkylation (**38**→**39**).

Scheme 2-9



37 R = CN

38

reductive
alkylation

39 R = CH_3

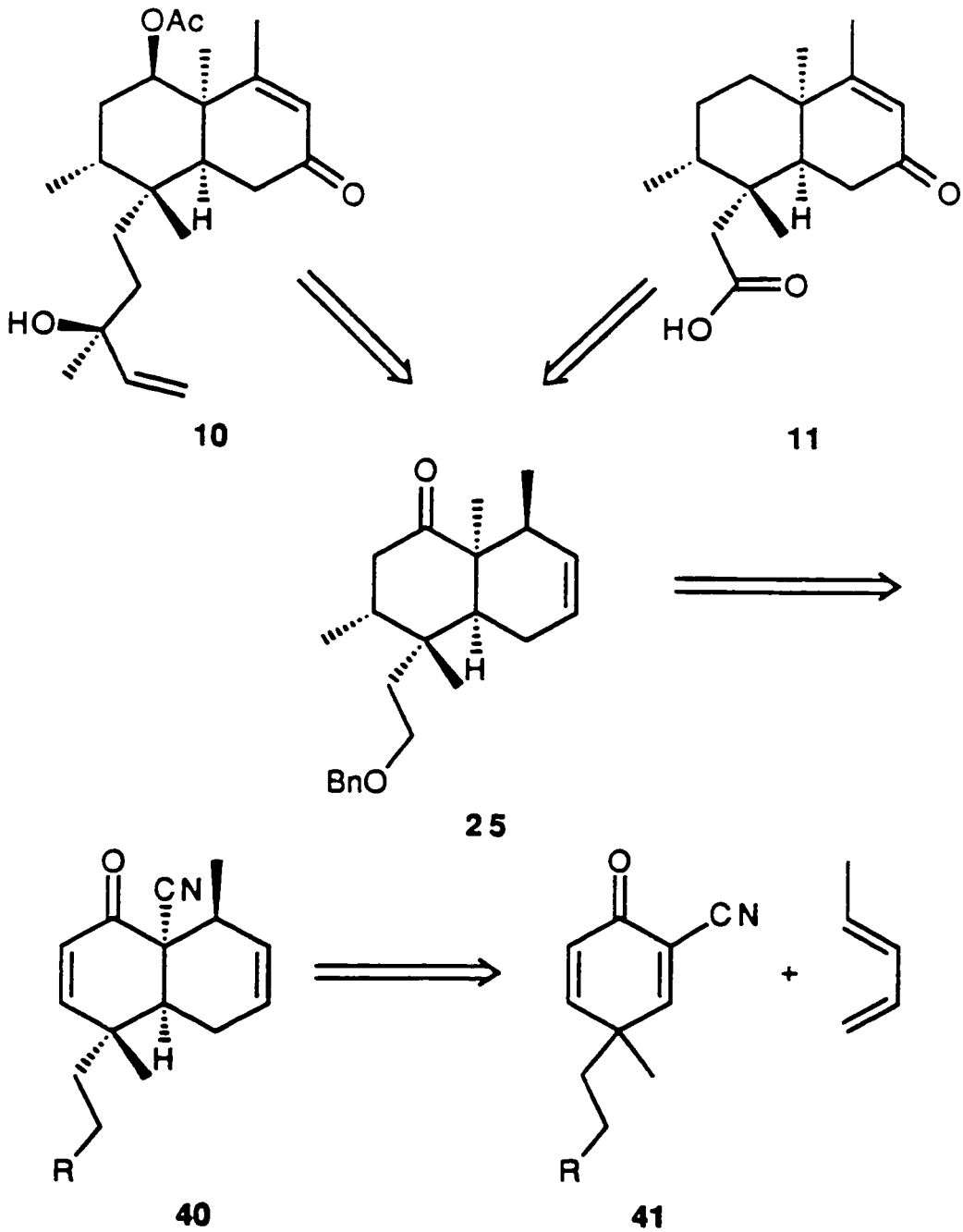
Results and Discussion

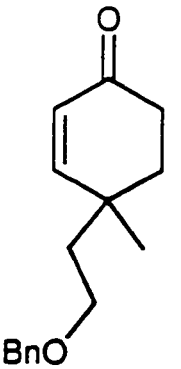
A retrosynthetic analysis in our approach towards the formal synthesis of (±)-6β-acetoxy-2-oxokolavenool **10** and (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11** is outlined in **Scheme 2-10**. Compound **25** is a common intermediate in the synthetic pathway of *cis*-clerodanes **10** and **11**.

The choice of a suitable dienone to begin the synthesis was important in terms of its compatibility with the conditions employed for incorporation of the cyano group, as well as its stability in the presence of the lithium naphthalenide[49] reagent during reductive alkylation.

We need to take a closer look at enone **16** and the possibility of constructing a dienophile modeled after **16**. First of all, the choice of enone **16** could lead to a problem in our synthetic sequence during the reductive alkylation process. As described in chapter one, lithium naphthalenide behaves in a similar manner as dissolving metal reduction. It is well known that benzyl groups are readily cleaved by dissolving metal reduction[51,52]. Due to the presence of a benzyl group, the possibility of cleavage of the protecting group could occur. A model study using benzylated cholesterol[46] as the model compound showed that the cleavage of the benzyl group occurred quickly under the same reducing conditions employed for the reductive cleavage of the cyano group. This result was not surprising to us and was quite predictable. A current publication[46] describes the effectiveness of debenzylation using lithium naphthalenide as the reagent.

Scheme 2-10



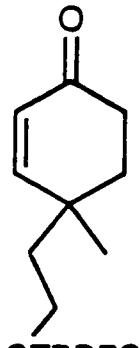


16

The benzyl group in enone **16** had to be replaced by a suitable protecting group which was stable to both acidic and basic conditions employed in the introduction of the cyano group, as well as to the reducing conditions of lithium naphthalenide. The choice of a silyl protecting group[50-52] proved to be favored due to its stability in a wide range of solution pHs. The *tert*-butyldiphenylsilyl protecting group was chosen as a suitable protecting group. Treatment of the model compound, *tert*-butyldiphenylsilyl (TBDPS) protected cholesterol, with lithium naphthalenide overnight gave no reaction and the starting material was recovered in quantitative yield. The *tert*-butyldiphenylsilyl protecting group proved to be unaffected under lithium naphthalenide conditions and it appeared to be quite stable under these conditions.

From this preliminary test we proceeded to use *tert*-butyldiphenylsilyl protected enone **42** as the starting dienone in the synthesis. Not only was the TBDPS group highly stable under these reductive cleavage conditions but it also provides one large advantage. The advantage of using such a large protecting group is its influence in the Diels-Alder cycloaddition in terms of facial selectivity. The large TBDPS group could possibly direct the cycloaddition of the diene from the less sterically hindered methyl side and favor addition from

this face of the dienophile. In this case, assuming that there is a high degree of facial selectivity in the Diels-Alder cycloaddition, the correct stereochemical arrangement would be produced in which the cycloadduct would have four contiguous stereochemical centers (C-4, C-5, C-9, and C-10; clerodane numbering) that are representative of the clerodane skeleton.

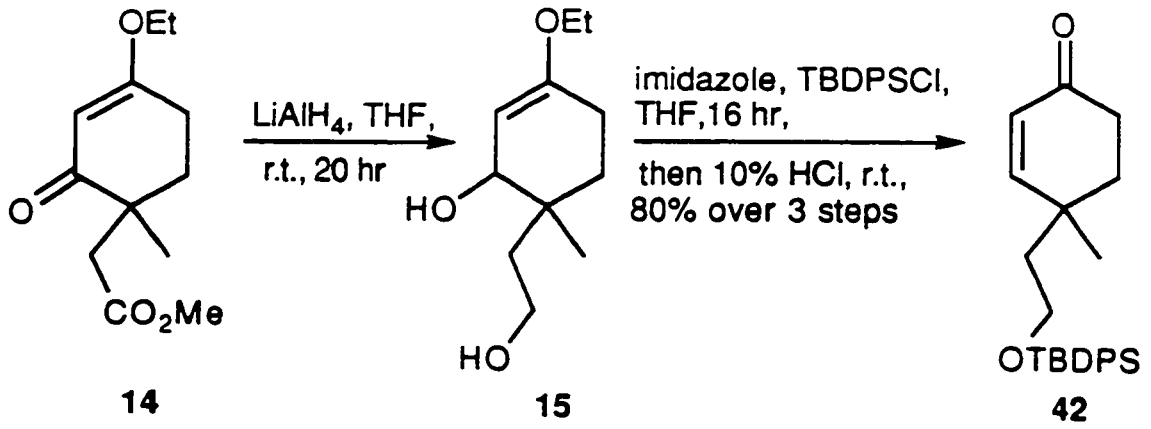


42

Synthesis of the enone **42** involved a similar route as described previously for enone **16** (**Scheme 2-11**). Reduction of enone ester **14** with lithium aluminum hydride in THF to diol **15** was followed immediately by treatment of the crude diol **15** with imidazole and *tert*-butylchlorodiphenylsilane[50]. Acidification of the crude product with dilute hydrochloric acid afforded enone **42** in 80% yield from **14**.

Enone **42** displayed an absorption at 1693 cm^{-1} for the α,β-unsaturated ketone carbonyl, as well as strong Si-O and Si-C absorptions at 1113 cm^{-1} and 701 cm^{-1}, respectively. Its molecular formula ($C_{25}H_{32}O_2Si$) was confirmed from elemental analysis and from the high resolution mass spectrum displaying a signal at m/*z* 335.1477 ($C_{21}H_{23}O_2Si$) representing the loss of the *tert*-butyl group from the molecular ion peak.

Scheme 2-11



14 **15** **42**

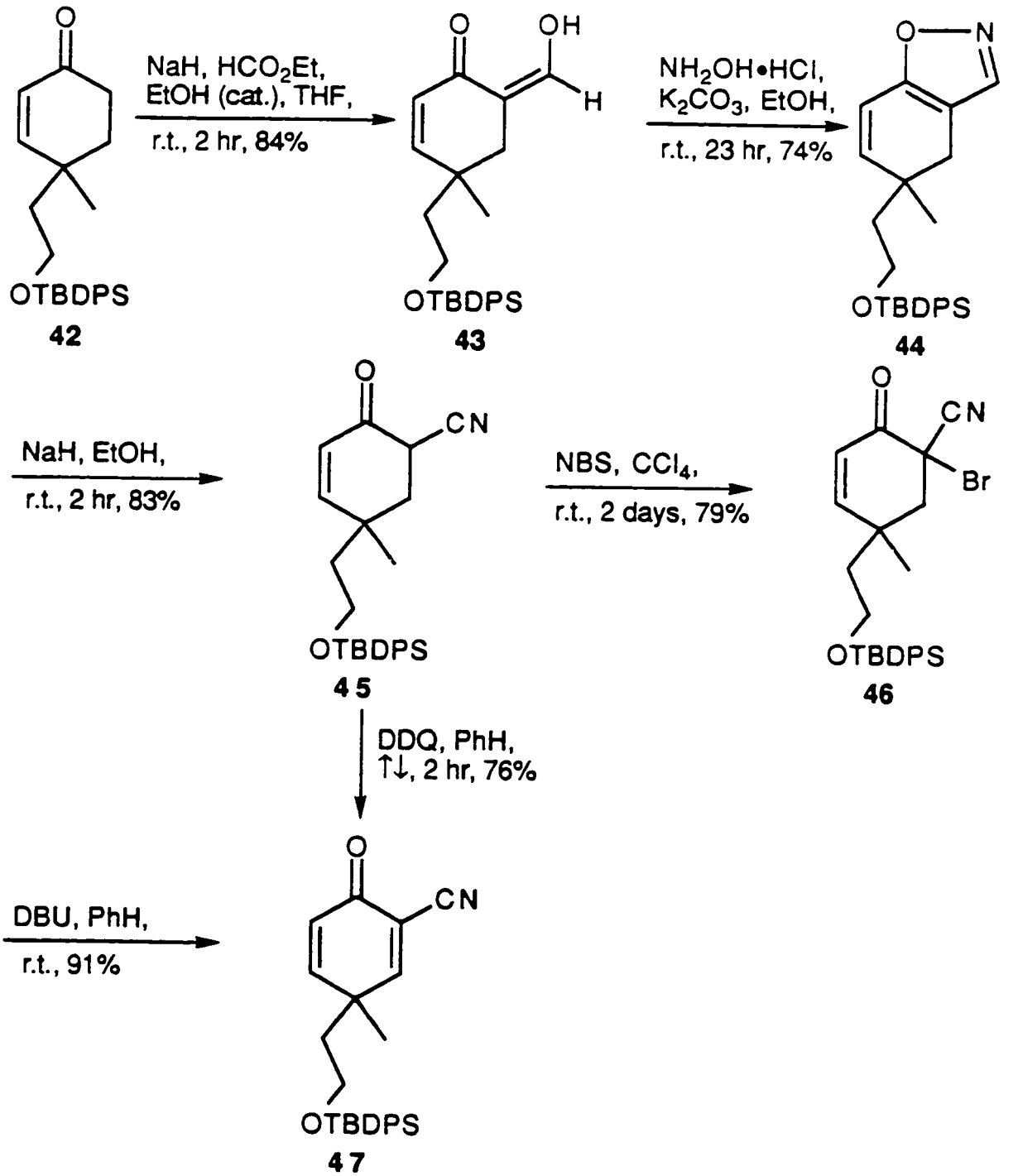
Once we had the starting enone in hand, introduction of the cyano group was done according to the same method as described in chapter one (**Scheme 2-12**). Formylation[53-55] of enone **42** with ethyl formate in the presence of sodium hydride and a catalytic amount of absolute ethanol afforded hydroxymethylene enone **43** in 84% yield. The high resolution mass spectrum of **43** displayed a peak at m/*z* 363.1417 for the formula $C_{22}H_{23}O_3Si$, which represents loss of a *tert*-butyl group from the molecular ion ($C_{26}H_{32}O_3Si$). Its infrared spectrum displayed a strong absorption for the hydroxyl group at 3432 cm^{-1}, as well as one for the α,β-unsaturated ketone carbonyl at 1685 cm^{-1}.

Treatment of **43** with hydroxylamine hydrochloride and potassium carbonate gave isoxazole **44**[55-57] in 74% yield. Nitrile **45** was obtained in 83% yield as an inseparable 1:1 mixture of diastereomers (by ^1H NMR integration) by treatment of isoxazole **44** with sodium ethoxide[55]. The infrared spectrum showed an absorption at 2251 cm^{-1} for the cyano group. The high resolution mass spectrum of **45** confirmed its molecular formula of $C_{26}H_{31}NO_2Si$ by the

presence of a peak representing the molecular ion peak with the loss of the *tert*-butyl group at m/*z* 360.1419 ($C_{22}H_{22}NO_2Si$).

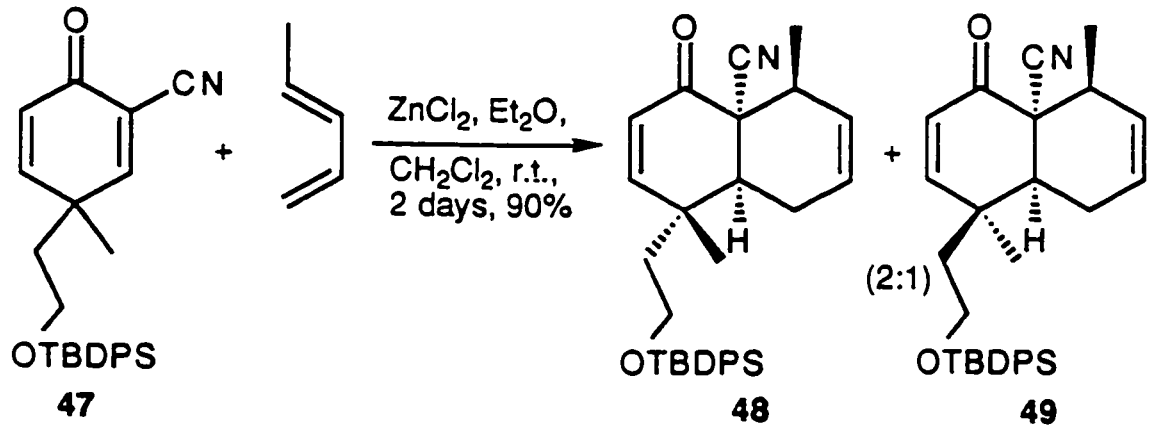
Finally, the formation of dienophile **47** was accomplished by two different methods. Treatment of nitrile **45** with *N*-bromosuccinimide[58] gave bromo nitrile **46** in 79% based on consumed starting material. It appears that there is an equilibrium occurring between the nitrile **45** and the brominated enone **46**. This was followed by dehydrobromination[58] of **46** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford dienophile **47** in 91% yield. Due to the slow bromination reaction to form **46**, the method of choice for formation of dienophile **47** involved treatment of cyano enone **45** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[59] in refluxing benzene to afford dienophile **47** in 76% yield. The molecular formula of $C_{26}H_{29}NO_2Si$ was confirmed from elemental analysis as well as from high resolution mass spectrometry. The ^1H NMR spectrum displayed enone protons at δ 6.83 (dd, J_1 = 10.5 Hz, J_2 = 2 Hz) and 6.31 (d, J = 10.5 Hz) for the beta and alpha protons, respectively on the unsubstituted enone system, as well as an overlapped enone signal (with phenyl signals) at δ 7.54-7.62 (multiplet, 5 protons) for the beta proton of the substituted enone system. Another aromatic multiplet appeared at δ 7.36-7.47 (6 protons). The ethylene moiety appeared as two multiplets at δ 3.45-3.61 and 1.90-2.10, representing two protons each. Two singlets attributed to the methyl group and the *tert*-butyl group were observed at δ 1.32 and 1.03, respectively.

Scheme 2-12

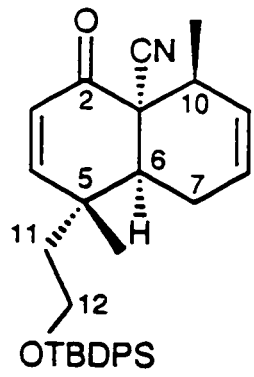

NaH, HCO2Et,
EtOH (cat.), THF,
r.t., 2 hr, 84%
NH2OH•HCl,
K2CO3, EtOH,
r.t., 23 hr, 74%
NaH, EtOH,
r.t., 2 hr, 83%
NBS, CCl4,
r.t., 2 days, 79%
DDQ, PhH,
↑↓, 2 hr, 76%
DBU, PhH,
r.t., 91%
OTBDPS
42
OTBDPS
43
OTBDPS
44
OTBDPS
45
OTBDPS
46
OTBDPS
47

The facial selective Diels-Alder cycloaddition of dienone **47** with *trans*-piperylene (*trans*-1,3-pentadiene) was conducted under the same conditions employed in the cycloaddition of 2-cyano-4,4-dimethyl-2,5-cyclohexadienone in chapter one. Under zinc chloride catalysis, after two days at room temperature, two cycloadducts were formed in 2:1 ratio (90% yield). The facial selectivity was not as good as first predicted. At this point we speculated that the major isomer **48** would be a result of addition of the diene from the less hindered face (methyl side) in an *endo*-to-ketone fashion. The minor adduct **49** was assumed at this point to be a result of addition from the more hindered face in an *endo*-to-ketone fashion as well (**Scheme 2-13**). This tentative assignment was based on the observed preferential addition of *trans*-piperylene to dienophile **18** with *ortho* orientation and in an *endo*-to-ketone fashion.

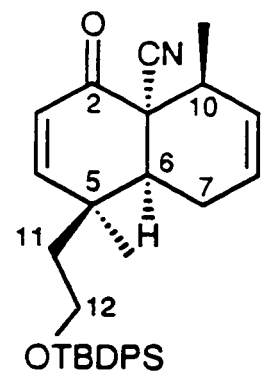
Scheme 2-13



The two Diels-Alder adducts **48** and **49** were separated by flash chromatography by elution of the less polar compound **49**, followed by elution of the more polar major adduct **48**.



48



49

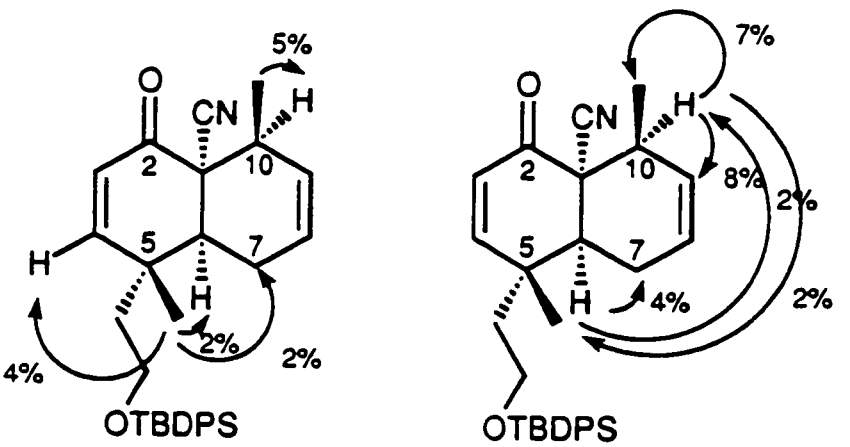
The minor cycloadduct **49** displayed a strong absorption at 1702 cm^{-1} (α,β-unsaturated carbonyl) as well as an absorption at 2229 cm^{-1} for the nitrile in the infrared spectrum. The ^{13}C NMR APT spectrum displayed a total of 21 signals. Seven signals appeared in the region between δ 123.61 and 135.65. It appears that overlap of some benzene ring carbon signals occurred due to the intensity of some of the signals. An intense signal at δ 26.87 was attributed to the three methyl group carbons on the *tert*-butyl group. A carbonyl carbon signal appeared at δ 190.64. The molecular formula of $C_{31}H_{37}NO_2Si$ was confirmed from the high resolution mass spectrum which displayed a peak at m/*z* 426.1898 ($C_{27}H_{28}NO_2Si$) representing loss of the *tert*-butyl group from the molecular ion peak. In the ^1H NMR spectrum, two aromatic signals appeared as multiplets at δ 7.64-7.70 (4 protons) and 7.36-7.48 (6 protons), representing the phenyl groups of the TBDPS protecting group. Enone protons appeared at δ 6.53 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz) and 5.86 (d, J = 10.5 Hz) for the H_4 and H_3 protons, respectively. The signal at δ 6.53 had one additional long range coupling with the ring-junction proton H_6 of 1.5 Hz. The long range W-type coupling also confirmed the formation of a *cis* ring-junction, since long range W-type coupling is only possible in the *cis* conformation[60]. Two additional vinylic proton signals appeared as multiplets at δ 5.53 and 5.43 for the isolated double

bond protons H_8 and H_9. The ring-junction proton H_6 at δ 2.45 displayed two additional couplings (ddd, J_1 = 10, J_2 = 6, J_3 = 1.5 Hz) indicating that the cycloadduct formed from the Diels-Alder reaction was indeed an *ortho* product. A low field multiplet at δ 3.72-3.82 was attributed to the C-12 protons. The C-5 methyl singlet appeared at δ 1.59. An additional singlet at δ 1.05 was attributed to the *tert*-butyl group. A doublet (J = 7 Hz) representing the C-10 methyl group appeared at δ 1.47.

The major adduct **48** showed a carbonyl absorption at 1704 cm^{-1} for the α,β-unsaturated ketone carbonyl and a nitrile absorption at 2229 cm^{-1} in the infrared spectrum. In the ^{13}C NMR APT spectrum 21 signals were observed including a signal at δ 191.11 for the carbonyl carbon, a strong signal at δ 26.90 for the three *tert*-butyl methyl groups, and several overlapped aromatic carbon signals. The high resolution mass spectrum showed a peak at m/*z* 426.1888 corresponding to the formula $C_{27}H_{28}NO_2Si$, which represents the loss of the *tert*-butyl group from the molecular ion peak ($C_{31}H_{37}NO_2Si$). The ^1H NMR spectrum displayed a unique splitting pattern for the ring-junction proton H_6 at δ 2.78 (ddd, J_1 = 10 Hz, J_2 = 6 Hz, J_3 = 1.5 Hz). This suggests that this isomer is also an *ortho* product. Signals at δ 6.53 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz) and 5.92 (d, J = 10.5 Hz) were attributed to H_4 and H_3 protons, respectively. An additional long range coupling (1.5 Hz) of the beta proton at δ 6.53 also confirms a *cis* conformation for the ring-junction of the adduct. An additional vinylic proton signal appeared as a broad singlet at δ 5.57, representing two protons for the isolated double bond protons H_8 and H_9. The methyl groups of the *tert*-butyl group appeared as a singlet at δ 1.06. The other two methyl groups appeared as a singlet at δ 1.12 for the C-5 methyl group and a doublet at δ 1.41 (J = 7.5 Hz) for the C-10 methyl group.

NOE experiments were conducted to determine the stereochemistry of cycloadduct **48** (see **Figure 2-4**). Irradiation of the C-5 methyl group signal at δ 1.12 gave enhancement of the C-4 vinylic proton signal at δ 6.53 (4%) as well as enhancements of the ring-junction proton (H_6) signal at δ 2.78 (2%) and the C-7 methylene signals at δ 2.25 and 1.94 (2% each). Irradiation of the ring junction proton H_6 gave a 4% enhancement of the adjacent methylene protons and the C-10 methine proton at δ 2.70 (2%) Irradiation of the C-10 methyl signal at δ 1.41 gave a 5% enhancement of the H_{10} signal. Irradiation of the methine proton signal H_{10} gave enhancements of the adjacent vinylic proton signal (8%) and the C-10 methyl signal (7%), as well as enhancement of the ring-junction proton (H_6) signal (2%).

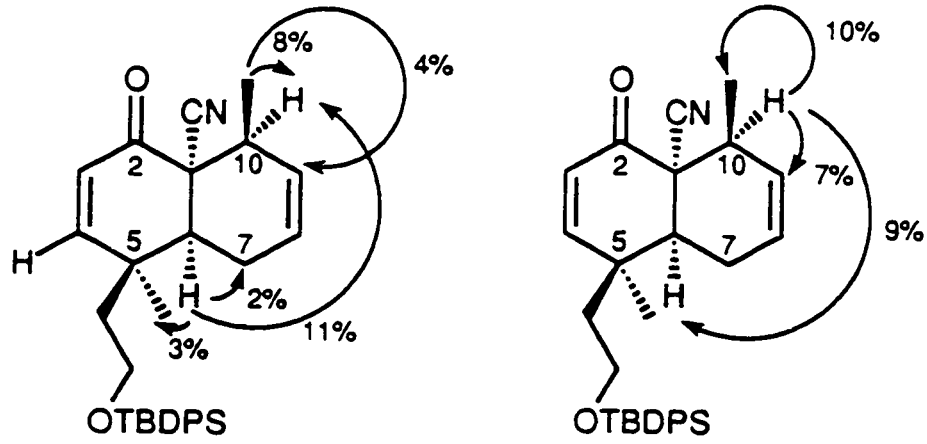
Figure 2-4



NOE experiments were also conducted on minor cycloadduct **49** (**Figure 2-5**). Irradiation of the C-10 methine proton at δ 2.65 gave enhancements of the C-10 methyl signal at δ 1.47 (10%), the vinylic proton (H_9) signal at δ 5.53 (7%) and enhancement of the ring-junction proton H_6 at δ 2.45 (9%). Conversely, irradiation of the C-10 methyl signal gave enhancements of the C-10 methine

signal (8%) and the vinylic proton signal (4%). Irradiation of the C-6 ring junction proton gave enhancement of the C-10 methine proton (11%), the C-7 methylene protons at δ 2.25 and 1.94, as well as an enhancement of the C-5 methyl signal at δ 1.59 (3%).

Figure 2-5

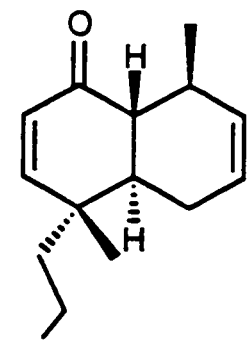


The cycloaddition of dienophile **47** with *trans*-piperylene appears to occur via an *endo*-to-ketone transition state based on the NOE experiments, in which enhancements of the ring-junction proton signal occurred when the methine proton signal on C-10 was irradiated and vice versa. It is believed that the two cycloadducts (**48** and **49**) formed from the face selective Diels-Alder reaction are actually in a diastereomeric relationship at C-5.

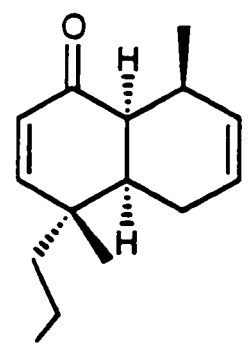
We proceeded in the synthesis using the major cycloadduct **48** obtained from the Diels-Alder cycloaddition based on the assumption that the structure as depicted is correct. At this point the structure possesses the required stereochemistry for the synthesis of *cis*-clerodanes.

The target molecule in the formal synthesis of (±)-6β-acetoxy-2-oxokolavenool **10** and (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11** is compound **25**. Having formed the cycloadduct, the next stages of the synthesis involved the introduction of a methyl group each to C-1 and C-4, as well as the conversion of the *tert*-butyldiphenylsilyl protecting group to the benzyl protecting group.

The introduction of the methyl group at C-1, found in many clerodane diterpenoids, could be easily carried out via our reductive decyanation approach, as discussed in chapter 1. Treatment of cycloadduct **48** with lithium naphthalenide (15 equivalents) at -25 °C for 30 minutes followed by addition of methyl iodide (5.5 equivalents) for 18 hours at -25 °C afforded an inseparable 5:2 mixture of reduced products **50** and **51**, respectively, in 49% yield. In this case, the desired trapping product was not formed from the reaction. The infrared spectrum of the mixture displayed an absorption for the α,β-unsaturated carbonyl at 1676 cm^{-1} and the absence of an absorption band at approximately 2200 cm^{-1} for the cyano group. The molecular formula $C_{30}H_{38}O_2Si$ was confirmed from the high resolution mass spectrum of the mixture which showed a peak at m/*z* 401.1939 ($C_{26}H_{29}O_2Si$) for the loss of a *tert*-butyl group from the molecular ion peak.

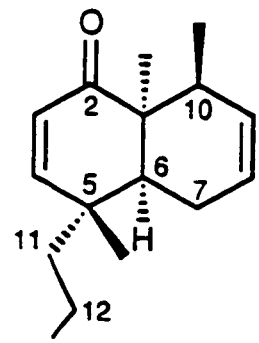


50



51

In previous cases where only the reduced product was formed, the temperature of the reaction was elevated to assist in the alkylation process. We then decided to change the reaction temperature and perform the reaction under the same conditions, with one exception. Upon addition of methyl iodide, the reaction was warmed up to room temperature and worked up after 24 hours. Under these conditions the alkylation product **52** was produced as the sole product in 86% yield (see **Scheme 2-14**). The stereochemistry of the quaternary center at C-1 was assumed at this point to be a *cis*-decalin system, based on the stereochemistry of similar decalin systems discussed in Chapter 1. Subsequent conversion to the required intermediate **25** will further confirm the stereochemistry of the reductive alkylation process.



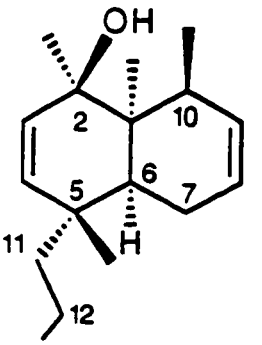
52

The infrared spectrum for **52** showed a strong absorption for the α,β-unsaturated carbonyl at 1670 cm^{-1}, but no absorption for the nitrile at 2200 cm^{-1}. This indicates that the nitrile was successfully removed from **48**. The ^{13}C NMR APT spectrum showed a total of 21 signals including a signal at δ 204.33 for the carbonyl carbon, as well as a strong signal at δ 26.87 for the *tert*-butyl methyl groups. The absence of an in-phase signal at approximately δ 120 confirmed the removal of the cyano group from **48**. The high resolution mass

spectrum showed a peak at m/z 415.2091 ($C_{27}H_{31}O_2Si$) for the loss of a *tert*-butyl group from the molecular ion peak. The molecular formula $C_{30}H_{40}O_2Si$ was also confirmed from elemental analysis. The ^1H NMR spectrum of **52** showed that the *tert*-butyldiphenylsilyl group remained intact by the presence of signals for the phenyl groups at δ 7.64 (4 protons) and 7.41 (6 protons) as multiplets, as well as a singlet for the *tert*-butyl group at δ 1.04. The enone protons appeared as coupled doublets (J = 10.5 Hz) at δ 6.48, and 5.93, corresponding to the beta and alpha protons, respectively. The vinylic protons of the isolated double bond (H_8 and H_9) appeared as multiplets at δ 5.68 and 5.52. The introduction of the angular methyl group at C-10 was confirmed by the presence of two singlets at δ 1.28 and 1.03, the latter singlet was attributed to the C-5 methyl group. One other methyl group appeared as a doublet at δ 0.92 (J = 7.5 Hz) which corresponds to the C-10 methyl group. The angular methyl group was easily implemented into the bicyclic system via a one step reductive alkylation process.

The next step in the synthesis towards intermediate **25** involves the introduction of a methyl group to C-4 with the correct stereochemistry. The most conventional method would be via a 1,4-addition process. Lithium dimethylcuprate[61] addition to enone **52** proceeded smoothly to give the 1,2-addition compound **53** as the sole product in 92% yield, instead of the expected 1,4-addition products **54** and **55**. The infrared spectrum of **53** showed an intense absorption at 3478 cm^{-1} for the hydroxyl group. An absorption expected for a carbonyl group (at approximately 1700 cm^{-1}) was not present in the infrared spectrum. This proved that the carbonyl in **52** was converted to an alcohol. The ^1H NMR spectrum showed signals for three methyl groups including a doublet (J = 7.5 Hz) for the C-10 methyl group at δ

1.07 and two singlets at δ 1.03 and 0.90. The presence of four vinylic protons appearing as a multiplet at δ 5.54 (three protons) and a doublet at δ 5.08 (J = 10.5 Hz) is also consistent with the formation of a 1,2-addition product **53**. The stereochemistry at C-2 was not ascertained at this point, but we believe that the addition would occur form the sterically less hindered side to give **53** as the sole product.

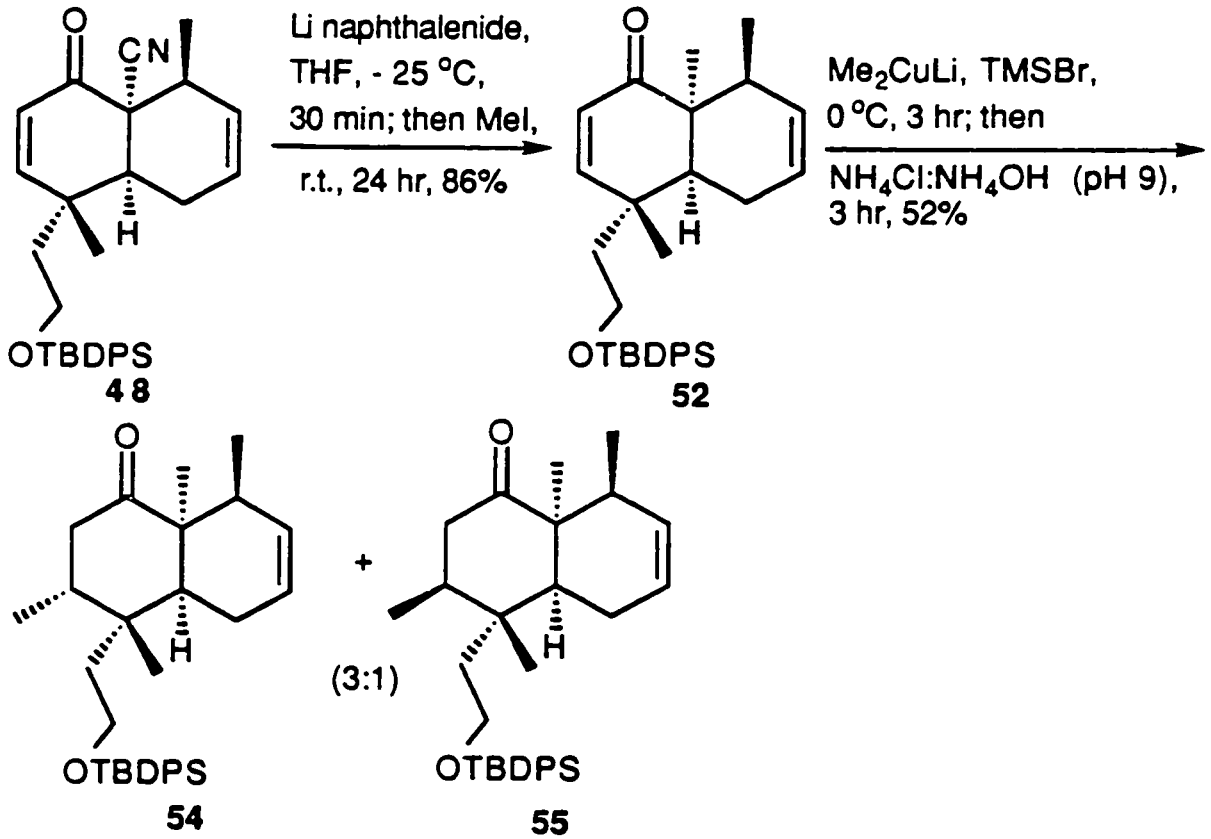


53

Although the more general 1,4-addition process did not provide the desired product, we sought out different methods and variations of conjugate addition. These included manganese-copper catalyzed Grignard reagents (RMgCl, $MnCl_2$, $CuCl_2$)[62], cuprous iodide mediated Grignard reagents (MeMgBr, CuI)[63,64], Lewis acid catalyzed organocuprate reagents (Me_2CuLi, $BF_3 \bullet OEt_2$)[65], and high order cuprates ($Li_2(Me_2CuCN)$, $BF_3 \bullet OEt_2$)[66-69]. These methods proved to be ineffective, giving starting enone **52** or 1,2-addition product **53**. Nickel catalyzed conjugate addition in the presence of trimethylaluminum[70] provided the 1,4-addition product **54** and its C-4 epimer **55** as a 1:1 mixture of stereoisomers in poor yield (30 to 40%). We then turned to treating enone **52** with a cuprate in the presence of bromotrimethyl-silane[71-73]. The addition of lithium dimethylcuprate (6 equivalents) to **52** in the

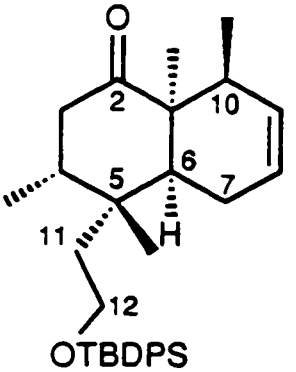
presence of bromotrimethylsilane (6 equivalents), followed by cleavage of the silyl enol ether after 3 hours afforded the desired products **54** and **55**. Interestingly, cuprate addition in the absence of bromotrimethylsilane gave the 1,2-addition product **53** exclusively. The yield from the bromotrimethylsilane cuprate addition was improved (52%) and the selectivity was enhanced to give a 3:1 mixture of **54**:**55**, in favor of the required stereochemistry for the synthesis of *cis*-clerodanes.

Scheme 2-14



The major stereoisomer **54** could be separated from the mixture by subjecting the mixture to flash column chromatography several times. The infrared spectrum showed a strong absorption for the carbonyl at 1700 cm^{-1}. The ^{13}C

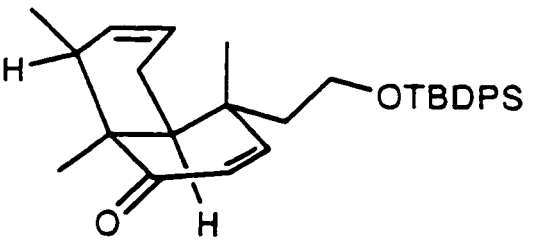
NMR APT spectrum displayed a distinctive signal at δ 217.29 for the carbonyl carbon. In the high resolution mass spectrum of **54** the molecular formula $C_{32}H_{44}O_2Si$ was confirmed by the appearance of a peak at m/*z* 431.2397 ($C_{28}H_{35}O_2Si$) for the loss of a *tert*-butyl group from the molecular ion peak. The ^1H NMR spectrum displayed signals for the vinylic protons at δ 5.81 and 5.70 as multiplets. Four methyl signals appeared in the spectrum. These included two singlets at δ 1.20 and 0.85 corresponding to the angular methyl group at C-1 and the C-5 methyl group, respectively. Two other methyl groups appeared as doublets at δ 0.97 (J = 7.5 Hz) and 0.81 (J = 7 Hz). The latter signal represents the newly introduced methyl group at C-4 and the former signal represents the C-10 methyl group.



54

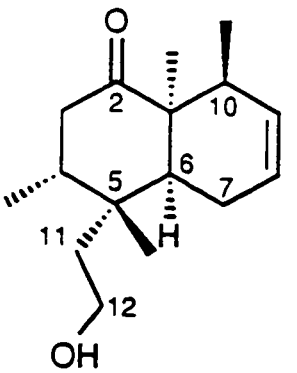
At this point the stereochemistry of the major isomer **54** isolated from the conjugate addition could not be ascertained. It was presumed that the 1,4-addition was a result of axial addition of lithium dimethylcuprate to the conformer depicted in **Figure 2-6**. The stereochemistry of **54** will be confirmed by its conversion to intermediate **25**. This type of addition was found previously in the conjugate addition to cycloadduct **12** and confirmed later by x-ray crystal analysis[29].

FIGURE 2-6



After introducing two methyl groups at C-1 and C-4 by reductive alkylation and cuprate addition, respectively and assuming that we have **54** in hand, we proceeded with the synthesis towards intermediate **25**. The next steps will involve the removal of the *tert*-butyldiphenylsilyl protecting group followed by introduction of a benzyl protecting group.

Deprotection using tetrabutylammonium fluoride[50,74] at room temperature in 2 hours afforded keto alcohol **56** in 59% yield (**Scheme 2-15**). The ^{1}H NMR spectrum showed the disappearance of aromatic proton signals as well as the disappearance of the sharp singlet attributed to the *tert*-butyl group at approximately δ 1.00. Two vinylic proton signals appeared as multiplets at δ 5.87 and 5.73. Methyl signals appeared at δ 1.27 (singlet, C-1 methyl), 0.98 (d, J = 8 Hz, C-10 methyl), 0.97 (singlet, C-5 methyl), and 0.90 (d, J = 7 Hz, C-4 methyl). The infrared spectrum showed strong absorptions at 3347 and 1705 cm^{-1} for the hydroxyl and carbonyl, respectively. The ^{13}C NMR APT spectrum displayed a total of 16 carbon signals including a signal at δ 217.33 for the carbonyl carbon. The high resolution spectrum of **56** confirmed the molecular formula $C_{16}H_{26}O_2$ by the presence of a molecular ion peak at m/*z* 250.1928.

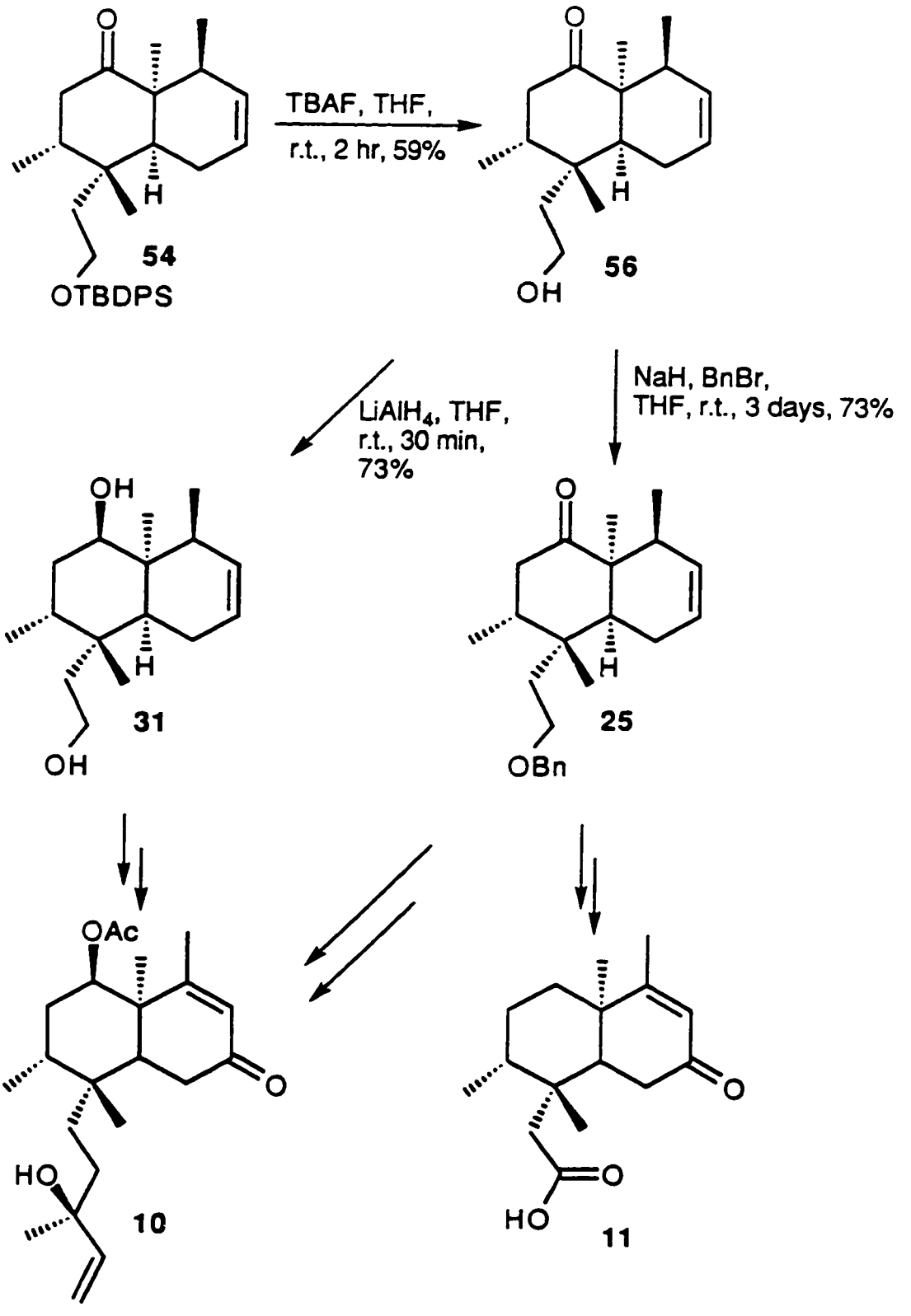


56

Finally treatment of **56** with sodium hydride and benzyl bromide for 3 days afforded the desired intermediate **25** in 73% yield. The spectral data were consistent with those found for the intermediate leading to the synthesis of (±)-6β-acetoxy-2-oxokolavenool **10**[29] and (±)-2-oxo-5α,8α-13,14,15,16-tetranor-clerod-3-en-12-oic acid **11**[27,28,29].

An alternative route towards the synthesis of (±)-6β-acetoxy-2-oxokolavenool **10** involved reduction of the ketone carbonyl of **56**. Lithium aluminum hydride reduction of **56** afforded, after 30 minutes, diol **31** as the sole product in 73% yield. This was the product expected by delivery of the hydride to the carbonyl from the less hindered face. The spectral data of **31** were consistent with those found for the synthetic intermediate leading to (±)-6β-acetoxy-2-oxokolavenool **10**[29].

Scheme 2-15


TBAF, THF,
r.t., 2 hr, 59%
54
OTBDPS
56
OH
NaH, BnBr,
THF, r.t., 3 days, 73%
LiAlH4, THF,
r.t., 30 min,
73%
31
OH
25
OBn
OAc
HO
10
HO
11

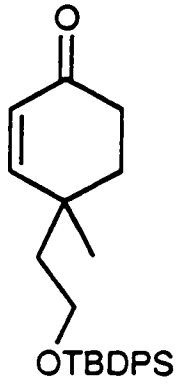
In conclusion, the formal syntheses of (±)-6β-acetoxy-2-oxokolavenool **10**[29] and (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid **11**[27-29] were successfully completed by the formation of key intermediate **25**. In the process a much simpler method was introduced to install the C-1 angular methyl group via a reductive alkylation process. Previously the conversion of a methyl ester to a methyl group was accomplished in four steps (**Scheme 2-6**), whereas reductive alkylation provides a "latent" methyl group in one step. The methodology developed in Chapter 1 was successfully applied towards the synthesis of *cis*-clerodane diterpenoids and provides a powerful synthetic tool for the construction of polycylic compounds.

Experimental

General

For general remarks see Chapter 1 of this thesis.

4-(2-*tert*-Butyldiphenylsiloxyethyl)-4-methyl-2-cyclohexenone (42)

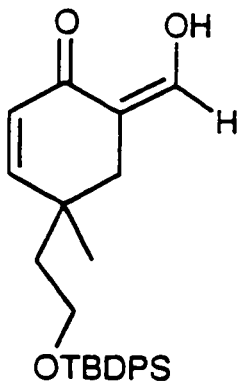


42

THF (20 mL) was added to a cooled flask (0 °C) charged with lithium aluminum hydride (420 mg, 11.07 mmol) under an argon atmosphere. Then 6-(carbomethoxymethyl)-3-ethoxy-6-methyl-2-cyclohexenone[34] (1.000 g, 4.42 mmol) in THF (2 mL) was added dropwise to the lithium aluminum hydride suspension. The reaction mixture was stirred at room temperature for 20 hours then quenched by sequential addition of water (4 drops) and aqueous 3N sodium hydroxide solution (4 drops) until a white precipitate remained. The mixture was extracted with diethyl ether (3 x 20 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 821 mg of the crude diol which was used for the subsequent step without further purification. The diol (821 mg, 4.10 mmol) was dissolved in

THF (5 mL). This solution was added to a solution of imidazole (601 mg, 8.83 mmol) in THF (10 mL) then *tert*-butylchlorodiphenylsilane (4.0 mL, 4.228 g, 15.38 mmol) was added to the solution forming a cloudy white suspension. The reaction mixture was stirred at room temperature for 16 hours and then acidified with aqueous 10% HCl. The acidified solution was stirred for an additional 1.5 hours and then extracted with diethyl ether (3 x 20 mL). The organic extracts were washed with saturated sodium chloride solution (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a colorless oil. The crude material was purified by flash column chromatography by elution with ethyl acetate-Skelly B (5:95) to give **42** as a colorless oil (1.388 g, 3.54 mmol, 80%): IR (CH_2Cl_2, cast): 1693 (C=O), 1113 (SiO), 701 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.78 (m, 4H, phenyl), 7.34-7.50 (m, 6H, phenyl), 6.72 (d, J = 10 Hz, 1H, C**H**=CHC=O), 5.85 (d, J = 10 Hz, 1H, CH=C**H**C=O), 3.97 (m, 2H, CH_2OSi), 2.41-2.46 (m, 2H), 2.00 (ddd, J_1 = 13 Hz, J_2 = 8 Hz, J_3 = 5.5 Hz, 1H, CH_2C=O), 1.70-1.80 (m, 2H), 1.13 (s, 3H, CH_3), 1.08 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 199.40 (p), 159.11 (ap), 135.53 (ap), 133.47 (p), 129.72 (ap), 127.70 (ap), 126.99 (ap), 60.33 (p), 42.77 (p), 34.94 (p), 34.10 (p), 34.01 (p), 26.82 (ap), 25.36 (ap), 19.05 (p); HRMS: 335.1477 (M^+ - *tert*-butyl, calcd. for $C_{21}H_{23}O_2Si$: 335.1467). Anal. calcd. for $C_{25}H_{32}O_2Si$: C 76.48%, H 8.22%; found: C 76.21%, H 8.61%.

4-(2-*tert*-Butyldiphenylsiloxyethyl)-6-hydroxymethylene-4-methyl-2-cyclohexenone (43)

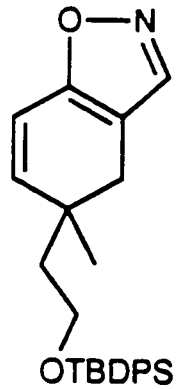


43

Ethyl formate (10.0 mL, 9.170 g, 123.79 mmol) was added dropwise to a suspension of sodium hydride (95% purity, 263 mg, 1.04 mmol) in THF (10 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 10 minutes and then a mixture of **42** (200 mg, 0.51 mmol) and absolute ethanol (3 drops) in THF (5 mL) was added dropwise over a period of 30 minutes. The reaction mixture was stirred at room temperature under argon for an additional 20 hours. The resulting mixture was quenched with aqueous 10% HCl (5 mL) and extracted with dichloromethane (2 x 10 mL). The organic extracts were washed with water (5 mL) and saturated sodium chloride solution (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a yellow oil. The crude product was subjected to flash chromatography. Elution with ethyl acetate-Skelly B (5:95) afforded **43** as a pale yellow liquid (180 mg, 0.43 mmol, 84%): IR (CH_2Cl_2, cast): 3432 (OH), 1685 (C=O), 1111 (SiO), 702 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 13.85 (br s, 1H, OH), 7.64-7.68 (m, 4H, phenyl), 7.37-7.46 (m, 7H, phenyl and C=C**H**(OH)), 6.60 (d, J = 10 Hz, 1H, C**H**=CHC=O), 5.93 (d, J = 10 Hz, 1H, CH=C**H**C=O), 3.75 (ddd, J_1 = 7 Hz, J_2 = 7

Hz, J_3 = 2.5 Hz, 2H, C**H**$_2$OSi), 2.41 (d, J = 15 Hz, 1H, C**H**$_2$C=CH(OH)), 2.19 (d, J = 15 Hz, 1H, C**H**$_2$C=CH(OH)), 1.72 (complex m, 2H, C**H**$_2$CH$_2$OSi), 1.08 (s, 3H, C**H**$_3$), 1.05 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 188.66 (p), 167.02 (ap), 157.26 (ap), 135.60 (ap), 133.56 (p), 129.78 (ap), 127.75 (ap), 126.25 (ap), 106.61 (p), 60.53 (p), 42.63 (p), 35.78 (p), 35.60 (p), 26.88 (ap), 25.51 (ap), 19.14 (p); HRMS: 363.1417 (M^+ - *tert*-butyl, calcd. for $C_{22}H_{23}O_3Si$: 363.1417).

8-Aza-4-(2-*tert*-butyldiphenylsiloxyethyl)-4-methyl-9-oxabicyclo-[4.3.0]nona-1(6),2,7-triene (44)

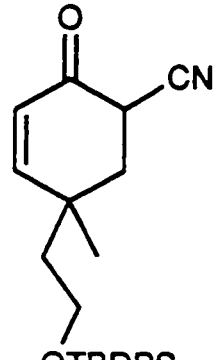


44

Anhydrous potassium carbonate (92 mg, 0.67 mmol) and hydroxylamine hydrochloride (60 mg, 0.86 mmol) were added to a solution of **43** (180 mg, 0.43 mmol) in absolute ethanol (15 mL) under argon at 0 °C. The yellow suspension was stirred at room temperature for 23 hours and then quenched with aqueous 10% HCl (5 mL). The solution was extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with water (5 mL) and saturated sodium chloride solution (5 mL) then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a pale yellow oil. The crude product was

subjected to flash column chromatography eluting with ethyl acetate-Skelly B (5:95) to give **44** as a pale yellow oil (132 mg, 0.32 mmol, 74%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H, C**H**=N), 7.64-7.73 (m, 4H, phenyl), 7.37-7.42 (m, 6H, phenyl), 6.63 (d, J = 10 Hz, 1H, C**H**=CHCO), 5.77 (d, J = 10 Hz, 1H, CH=C**H**CO), 3.72-3.80 (m, 2H, C**H**$_2$OSi), 2.71 (d, J = 16 Hz, 1H, C**H**$_2$C=C), 2.43 (d, J = 16 Hz, 1H, C**H**$_2$C=C), 1.68-1.80 (m, 2H, C**H**$_2$CH$_2$OSi), 1.09 (s, 3H, C**H**$_3$), 1.07 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 164.65 (p), 148.68 (ap), 143.54 (ap), 135.53 (ap), 133.59 (p), 133.41 (p), 129.71 (ap), 127.72 (ap), 113.19 (ap), 109.43 (p), 60.67 (p), 43.27 (p), 33.58 (p), 30.55 (p), 26.92 (ap), 26.87 (ap), 19.14 (p).

4-(2-*tert*-Butyldiphenylsiloxyethyl)-6-cyano-4-methyl-2-cyclohexenone (45)

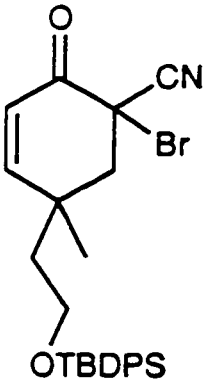


45

Absolute ethanol (5 mL) was slowly added dropwise to a dry round-bottomed flask containing sodium hydride (95% purity, 6 mg, 0.25 mmol) under an argon atmosphere at 0 °C. The grey suspension was stirred for 1 hour and then a solution of **44** (50 mg, 0.12 mmol) in absolute ethanol (1 mL) was added dropwise to the suspension over 5 minutes. The resulting solution was stirred

at room temperature for 2 hours and then quenched with aqueous 10% HCl (5 mL). The mixture was extracted with diethyl ether (2 x 20 mL) and the organic extracts were washed with saturated sodium chloride solution (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a pale yellow oil. The crude product was subjected to column chromatography eluting with ethyl acetate-Skelly B (10-15:85-90) to afford **45** (an inseparable 1:1 mixture of diastereoisomers) as a pale yellow oil (40 mg, 0.10 mmol, 83%): IR (CH_2Cl_2, cast): 2251 (CN), 1694 (C=O), 1112 (SiO), 703 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (m, 4H, phenyl), 7.38-7.50 (m, 6H, phenyl), 6.82 (dd, J_1 = 10.5 Hz, J_2 = 2 Hz, 0.5H, C**H**=CHC=O), 6.73 (dd, J_1 = 10.5 Hz, J_2 = 2 Hz, 0.5H, C**H**=CHC=O), 5.94 (d, J = 10.5 Hz, 0.5H, CH=C**H**C=O), 5.91 (d, J = 10.5 Hz, 0.5H, CH=C**H**C=O), 3.71-3.80 (m, 2H, C**H**$_2$OSi), 3.69 (dd, J_1 = 14 Hz, J_2 = 5 Hz, 0.5H, C**H**CN), 3.62 (dd, J_1 = 14 Hz, J_2 = 5 Hz, 0.5H, C**H**CN), 2.34-2.48 (m, 1H, C**H**$_2$CHCN), 2.07-2.16 (m, 1H, C**H**$_2$CHCN), 1.60-1.70 (m, 2H, C**H**$_2$CH$_2$OSi), 1.21 (s, 1.5H, C**H**$_3$), 1.17 (s, 1.5H, C**H**$_3$)1.05 (s, 4.5H, *tert*-butyl), 1.07 (s, 4.5H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 188.45 (p), 188.16 (p), 159.76 (ap), 159.70 (ap), 135.60 (ap), 135.57 (ap), 133.15 (p), 133.07 (p), 130.08 (ap), 130.04 (ap), 129.98 (ap), 129.96 (ap), 127.94 (ap), 127.88 (ap), 125.14 (ap), 124.99 (ap), 116.92 (p), 116.82 (p), 60.08 (p), 59.86 (p), 44.34 (p), 40.30 (p), 38.27 (p), 37.75 (p), 37.07 (ap), 36.88 (ap), 35.80 (p), 35.49 (p), 27.04 (ap), 26.91 (ap), 26.88 (ap), 23.91 (ap), 19.12 (p), 19.07 (p); HRMS: 360.1419 (M^+ - *tert*-butyl, calcd. for $C_{22}H_{22}NO_2Si$: 360.1420).

6-Bromo-4-(2-*tert*-butyldiphenylsiloxyethyl)-6-cyano-4-methyl-2-cyclohexenone (46)

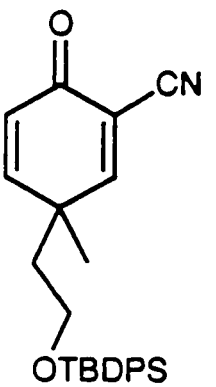


46

Compound **45** (212 mg, 0.51 mmol) was dissolved in carbon tetrachloride (15 mL). The reaction flask was protected from light and affixed with an anhydrous calcium sulfate drying tube. *N*- Bromosuccinimide (500 mg, 2.81 mmol) was added to the solution and the suspension was stirred at room temperature for 2 days. The pale yellow suspension was filtered and washed with carbon tetrachloride (2 x 5 mL). The residue was discarded and the filtrate was concentrated in vacuo to give a pale yellow oil. The crude product was subjected to column chromatography eluting with ethyl acetate-Skelly B (10:90) to afford **46** (an inseparable 1:1 mixture of diastereoisomers) as a pale yellow oil (42 mg, 0.08 mmol, 79% yield based on consumed starting material). Further elution with ethyl acetate-Skelly B (15:85) afforded **45** (167 mg, 0.40 mmol): IR (CH_2Cl_2, cast): 2230 (CN), 1699 (C=O), 1112 (SiO), 703 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.63-7.68 (m, 4H, phenyl), 7.38-7.48 (m, 6H, phenyl), 6.90 (d, J = 10.5 Hz, 0.5H, C**H**=CHC=O), 6.82 (d, J = 10.5 Hz, 0.5H, C**H**=CHC=O), 6.06 (d, J = 10.5 Hz, 0.5H, CH=C**H**C=O), 6.04 (d, J = 10.5 Hz, 0.5H, CH=C**H**C=O), 3.73-3.82 (m, 2H, CH_2OSi), 3.07 (d, J = 15.5 Hz, 0.5H,

$CH_2CBr(CN)$), 2.96 (d, J = 15 Hz, 0.5H), 2.69 (dd, J_1 = 15 Hz, J_2 = 1 Hz, 0.5H, $CH_2CBr(CN)$), 2.58 (dd, J_1 = 15.5 Hz, J_2 = 1 Hz, 0.5H), 1.86-1.92 (m, 1H, CH_2CH_2OSi), 1.79-1.86 (m, 1H, CH_2CH_2OSi), 1.41 (s, 1.5H, CH_3), 1.39 (s, 1.5H, CH_3), 1.07 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 182.88 (p), 182.61 (p), 160.11 (ap), 159.35 (ap), 135.56 (ap), 133.04 (p), 132.96 (p), 129.96 (ap), 127.88 (ap), 122.31 (ap), 122.13 (ap), 116.89 (p), 116.39 (p), 59.87 (p), 47.19 (p), 45.89 (p), 44.77 (p), 44.49 (p), 43.19 (p), 43.12 (p), 37.57 (p), 36.63 (p), 26.87 (ap), 26.04 (ap), 25.61 (ap), 19.07 (p); HRMS: 438.0523 (M^+ - *tert*-butyl, calcd. for $C_{22}H_{21}NO_2Si^{79}Br$: 438.0525) and 440.0506 (M^+ - *tert*-butyl, calcd. for $C_{22}H_{21}NO_2Si^{81}Br$: 440.0505).

4-(2-*tert*-Butyldiphenylsiloxyethyl)-6-cyano-4-methyl-2,5-cyclohexadienone (47)



47

Method A:

To a solution of **46** (40 mg, 0.081 mmol) dissolved in benzene (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.030 mL, 0.20 mmol) under

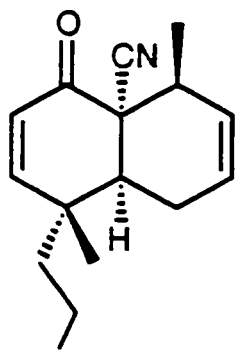
an argon atmosphere at 0 °C. After 1 hour, the reaction mixture was filtered and the resulting filtrate was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed successively with 10% aqueous HCl (5 mL), saturated sodium bicarbonate solution (5 mL), and saturated sodium chloride solution (5 mL). The extract was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford **47** as a pale yellow solid (30 mg, 0.072 mmol, 90%).

Method B:

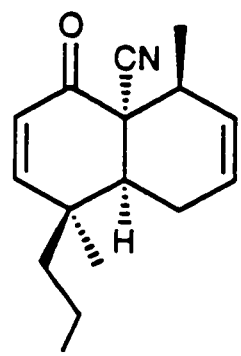
In a round-bottomed flask were added **45** (50 mg, 0.12 mmol) and benzene (5 mL) under an argon atmosphere, then 2,3-dichloro-5.6-dicyano-1,4-benzo-quinone (DDQ) (41 mg, 0.18 mmol) was added. The orange solution was refluxed for 2 hours during which a precipitate of the hydroquinone formed. The resulting orange/brown suspension was cooled to room temperature and the precipitate was filtered through a small pore sintered glass funnel. The resulting filtrate was concentrated in vacuo. The residue was chromatographed twice eluting with ethyl acetate-Skelly B (10.:90) to remove traces of unreacted DDQ. The resulting crude product was subjected to column chromatography eluting with ethyl acetate-Skelly B (15:85) to afford **47** as a white solid. The product was recrystallized from ethyl acetate-Skelly B to afford white crystals (38 mg, 0.009 mmol, 76%): mp 133-135 °C; IR (CH_2Cl_2, cast): 2235 (CN), 1668 (C=O), 1111 (SiO), 703 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.54-7.62 (m, 5H, phenyl and C**H**=CCN), 7.36-7.47 (m, 6H, phenyl), 6.83 (dd, J_1 = 10.5 Hz, J_2 = 2 Hz, 1H, C**H**=CHC=O), 6.31 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 3.45-3.61 (m, 2H, CH_2OSi), 1.90-2.10 (m, 2H, CH_2CH_2OSi), 1.32 (s, 3H, CH_3), 1.03 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 179.18 (p), 169.61 (ap),

166.36 (ap), 135.48 (ap), 132.89 (p) and 132.82 (p), 129.98 (ap), 127.88 (ap), 116.16 (p), 114.04 (p), 60.39 (p), 43.51 (p), 42.03 (p), 26.83 (ap), 25.94 (ap), 19.01 (p); HRMS: 358.1261 (M^+ - *tert*-butyl, calcd. for $C_{26}H_{29}NO_2Si$: 358.1263). Anal. calcd. for $C_{26}H_{29}NO_2Si$: C 75.15%, H 7.04%, N 3.37%; found: C 74.91%, H 6.91%, N 3.31%.

(1S*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-1-cyano 5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (48) and (1S*,5S*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-1-cyano 5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (49)



48



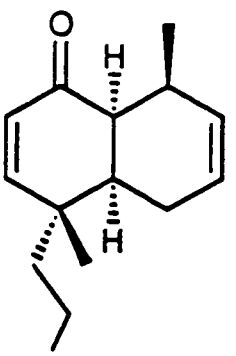
49

Zinc chloride (36 mg, 0.26 mmol) was flame-fuse dried in a round-bottomed flask under an argon atmosphere. The flask was cooled to room temperature and diethyl ether (2 mL) was added to the flask. The resulting solution was stirred at room temperature until the zinc chloride was completely dissolved (1 hour). Dienophile **47** (50 mg, 0.12 mmol) dissolved in dichloromethane (1 mL) was added and the resulting solution was cooled to 0 °C for 5 minutes, then *trans*-1,3-pentadiene (0.20 mL, 2.0 mmol) was added and the solution was

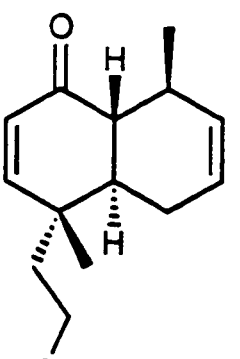
stirred at room temperature for 2 days. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution. The diethyl ether layer was separated and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed successively with water (2 x 10 mL) and saturated sodium chloride solution (2 x 10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography eluting with ethyl acetate-Skelly B (3-5:95-97) to give a 2:1 mixture of **48**:**49** (52 mg, 0.11 mmol, 90%). Separation of the two compounds by flash column chromatography by elution with ethyl acetate-Skelly B (2:98) gave **49** then compound **48**. Compound **48**: IR (CH_2Cl_2, cast): 2229 (CN), 1704 (C=O), 1112 (SiO), 703 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.66-7.71 (m, 4H, phenyl), 7.38-7.46 (m, 6H, phenyl), 6.53 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H, C**H**=CHC=O), 5.92 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.57 (br s, 2H, C**H**=C**H**CH_2), 3.85 (t, J = 6 Hz, 2H, CH_2OSi), 2.78 (ddd, J_1 = 10 Hz, J_2 = 6 Hz, J_3 = 1.5 Hz, 1H, CH_2C**H**), 2.70 (m, 1H, C**H**CH_3), 2.40 (ddd, J_1 = 15 Hz, J_2 = 6 Hz, J_3 = 6 Hz, 1H, C**H**$_2$$CH_2$OSi), 2.25 (dm, J = 20 Hz, 1H, C**H**$_2$C=C), 2.13 (ddd, J_1 = 15 Hz, J_2 = 6 Hz, J_3 = 6 Hz, 1H, C**H**$_2$$CH_2$OSi), 1.94 (dm, J = 20 Hz, 1H, C**H**$_2$C=C), 1.41 (d, J = 7.5 Hz, 3H, CHC**H**$_3$), 1.12 (s, 3H, C**H**$_3$), 1.06 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 191.11 (p), 155.44 (ap), 135.65 (ap), 133.29 (p), 129.83 (ap), 128.87 (ap), 127.82 (ap), 125.11 (ap), 123.68 (ap), 121.19 (p), 60.61 (p), 48.61 (p), 42.86 (ap), 41.57 (p), 39.76 (p), 37.61 (ap), 26.90 (ap), 24.87 (p), 24.25 (ap), 19.13 (p), 16.86 (ap); HRMS: 426.1888 (M^+ - *tert*-butyl, calcd. for $C_{27}H_{28}NO_2Si$: 426.1889). Compound **49**: IR (CH_2Cl_2, cast): 2229 (CN), 1702 (C=O), 702 (SiO), 1112 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.70 (m, 4H, phenyl), 7.36-7.48 (m, 6H, phenyl), 6.53 (dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz, 1H, C**H**=CHC=O), 5.86 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.50-5.56 (m, 1H, C**H**=CH), 5.40-5.47

(m, 1H, CH=C**H**), 3.72-3.82 (m, 2H, C**H**$_2$OSi), 2.62-2.72 (m, 1H, C**H**CH$_3$), 2.45 (ddd, J_1 = 10 Hz, J_2 = 6 Hz, J_3 = 1.5 Hz, 1H, C**H**CH$_2$), 2.20 (dm, J = 20 Hz, 1H, C**H**$_2$), 1.60-1.93 (complex, 3H), 1.59 (s, 3H, C**H**$_3$), 1.47 (d, J = 7 Hz, 3H, CHC**H**$_3$), 1.05 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 190.64 (p), 155.33 (ap), 135.65 (ap), 135.60 (ap), 133.29 (p), 133.26 (p), 129.95 (ap), 129.92 (ap), 128.76 (ap), 127.85 (ap), 124.70 (ap), 123.61 (ap), 121.28 (p), 59.54 (p), 48.43 (p), 46.36 (ap), 40.99 (p), 39.91 (p), 38.42 (ap), 26.87 (ap), 25.33 (p), 24.68 (ap), 19.10 (p), 16.96 (ap); HRMS: 426.1898 (M^+ - *tert*-butyl, calcd. for $C_{27}H_{28}NO_2Si$: 426.1889).

(1S*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (50) and (1R*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (51)



50

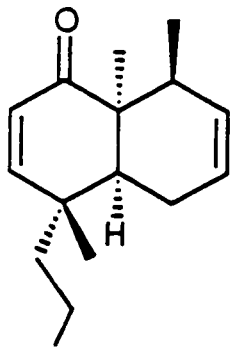


51

Compound **48** (50 mg, 0.10 mmol) was dissolved in THF (2 mL) and then cooled to -25 °C under an argon atmosphere. A solution of lithium naphthalenide in THF (0.35 M, 4.5 mL, 1.58 mmol) at -25 °C was added. The

resulting dark green/purple solution was left to stir for 30 minutes at -25 °C then methyl iodide (0.032 mL, 73 mg, 0.51 mmol) was added to the solution. The resulting yellow solution was stirred at -25 °C for 18 hours then quenched with methanol (3 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed successively with water (2 x 10 mL) and saturated sodium chloride solution (2 x 10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography by elution with Skelly B to remove naphthalene and then elution with ethyl acetate-Skelly B (5:95) to give a 1:1 mixture of **50** and **51** as a pale yellow oil (24 mg, 0.05 mmol, 49%): IR (CH_2Cl_2, cast): 1676 (C=O), 1112 (SiO), 702 cm^{-1} (SiC); ^1H NMR (200 MHz, $CDCl_3$): δ 7.60-7.75 (m, 4H, phenyl), 7.30-7.48 (m, 6H, phenyl), 6.63 (d, J = 10.5 Hz, 0.5H, C**H**=CHC=O), 6.58 (d, J = 10.5 Hz, 0.5H, C**H**=CHC=O), 5.80 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.50-5.65 (m, 1H, C**H**=CH), 5.40-5.50 (m, 1H, CH=C**H**), 3.55-3.90 (m, 2H, C**H**$_2$OSi), 2.38-2.56 (m, 1H, C**H**CH$_3$), 1.53-2.15 (m, 6H), 1.24 (d, J = 7 Hz, 1.5H, CHC**H**$_3$), 1.23 (d, J = 7 Hz, 1.5H, CHC**H**$_3$),1.06 (s, 1.5H, C**H**$_3$), 1.03 (s, 1.5H, C**H**$_3$),1.04 (s, 9H, *tert*-butyl); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.34 (p), 158.58 (ap), 158.22 (ap), 135.62 (ap), 133.57 (p), 133.49 (p), 132.89 (ap), 132.82 (ap), 129.74 (ap), 127.73 (ap), 127.25 (ap), 127.16 (ap), 123.26 (ap), 123.09 (ap), 60.81 (p), 60.50 (p), 48.76 (ap), 42.01 (p), 39.69 (ap), 38.32 (p), 38.18 (ap), 31.70 (ap), 31.13 (ap), 26.86 (ap), 26.28 (ap), 24.82 (p), 24.64 (p), 23.15 (ap), 20.75 (ap), 19.07 (p); HRMS: 401.1939 (M^+ - *tert*-butyl, calcd. for $C_{26}H_{29}O_2Si$: 401.1937).

(1S*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-1,5,10-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (52)

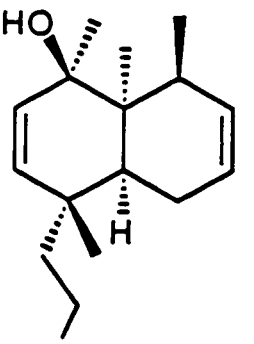


52

Compound **48** (38 mg, 0.08 mmol) was dissolved in THF (2 mL) and then cooled to -25 °C under an argon atmosphere. A solution of lithium naphthalenide in THF (0.62 M, 1.4 mL, 0.87 mmol) at -25 °C was added. The resulting dark green/purple solution was stirred for 30 minutes at -25 °C, then methyl iodide (0.024 mL, 56 mg, 0.39 mmol) was added to the solution. The resulting yellow solution was stirred at room temperature for 24 hours then quenched with methanol (1 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed successively with water (2 x 5 mL) and saturated sodium chloride solution (2 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography by elution with Skelly B to remove naphthalene and then elution with ethyl acetate-Skelly B (5:95) to give **52** as a pale yellow oil (32 mg, 0.068 mmol, 86%): IR (CH_2Cl_2, cast): 1670 (C=O), 1112 (SiO), 702 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61-7.67 (m, 4H, phenyl), 7.36-7.46 (m, 6H, phenyl), 6.48 (d, J = 10.5 Hz, 1H, C**H**=CHC=O), 5.93 (d, J = 10.5 Hz, 1H, CH=C**H**C=O), 5.64-5.71 (m, 1H, C**H**=CH), 5.48-5.56 (m, 1H,

CH=C**H**), 3.60-3.68 (m, 2H, C**H**$_2$OSi), 2.17 (dm, J = 18 Hz, 1H, CHC**H**$_2$), 2.08 (m, 1H, C**H**CH$_3$), 2.05 (d, J = 8 Hz, 1H, C**H**CH$_2$), 2.01 (ddd, J_1 = 18 Hz, J_2 = 5.5 Hz, J_3 = 1 Hz, 1H, CHC**H**$_2$), 1.80 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 7 Hz, 1H, C**H**$_2$CH$_2$OSi), 1.62 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 7 Hz, 1H, C**H**$_2$CH$_2$OSi), 1.28 (s, 3H, C(C**H**$_3$)C=O), 1.04 (s, 9H, *tert*-butyl), 1.03 (s, 3H, C**H**$_3$), 0.92 (d, J = 7.5 Hz, 3H, CHC**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.33 (p), 156.33 (ap), 135.62 (ap), 135.59 (ap), 133.56 (p), 130.57 (ap), 129.77 (ap), 127.95 (ap), 127.77 (ap), 123.91 (ap), 60.55 (p), 45.78 (p), 45.13 (p), 40.52 (ap), 38.43 (p), 36.83 (ap), 26.87 (ap), 23.08 (ap), 22.51 (p), 19.11 (p), 17.66 (ap); HRMS: 415.2091 (M^+ - *tert*-butyl, calcd. for $C_{27}H_{31}O_2Si$: 415.2093). Anal. calcd. for $C_{31}H_{40}O_2Si$: C 78.76%, H 8.53%; found: C 79.16%, H 8.91%.

(1S*,2R*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-1,2,5,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-ol (53)

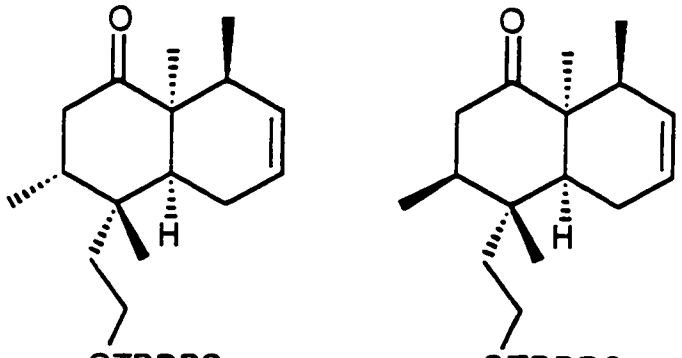


53

Cuprous iodide (44 mg, 0.23 mmol) was placed in a flame-dried round-bottomed flask under an argon atmosphere. Diethyl ether (2 mL) was added to the flask and then cooled to 0 °C. Methyllithium (1.4 M, 0.33 mL, 0.56 mmol)

was added dropwise to the pale grey suspension. Initially, a bright yellow suspension was formed, which turned to a pale yellow solution and eventually, upon addition of enough methyllithium to form the cuprate complex, the solution became clear and colorless. The resulting cuprate solution was cooled at 0 °C for an additional hour and then **52** (36 mg, 0.076 mmol) in diethyl ether (1 mL) was added to the solution, forming a bright yellow suspension. The mixture was stirred at 0 °C for 30 minutes and then quenched with saturated ammonium chloride solution (3 mL). The resulting mixture was extracted with Et_2O (2 x 10 mL). The organic extracts were washed with water (5 mL) and saturated sodium chloride solution (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography eluting with ethyl acetate-Skelly B (5:95) to give **43** as a colorless oil (34 mg, 0.070 mmol, 92%): IR (CH_2Cl_2, cast): 3478 (OH), 1112 (SiO), 702 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.68 (m, 4H, phenyl), 7.36-7.46 (m, 6H, phenyl), 5.47-5.62 (m, 3H, C**H**=C**H** and C**H**=CHCOH), 5.08 (d, J = 10.5 Hz, 1 H, CH=C**H**COH), 3.64-3.69 (m, 2H, CH_2OSi), 2.13 (dm, J = 20 Hz, 1H, CHCH_2), 2.01 (m, 1H), 1.94 (dd, J_1 = 18 Hz, J_2 = 5 Hz, 1H), 1.70 (d, J = 7.5 Hz, 1H, C**H**CH_2), 1.54-1.64 (m, 1H), 1.42-1.52 (m, 2H), 1.12 (s, 3H, CH_3(C)COH), 1.07 (d, J = 7.5 Hz, 3H, CHCH_3), 1.05 (s, 9H, *tert*-butyl), 1.03 (s, 3H, CH_3), 0.90 (s, 3H, CH_3); HRMS: 431.2424 (M^+ - *tert*-butyl, calcd. for $C_{28}H_{35}O_2Si$: 431.2406).

(1S*,4R*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (54) and (1S*,4S*,5R*,6S*,10S*)-5-(2-*tert*-Butyldiphenylsiloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]deca-3,8-dien-2-one (55)

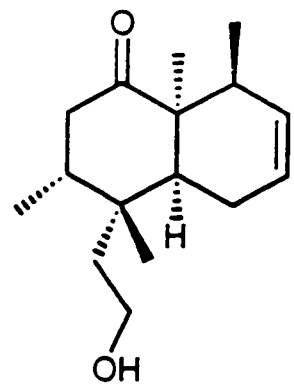


54 **55**

Cuprous iodide (147 mg, 0.77 mmol) was placed in a flame-dried round-bottomed flask under an argon atmosphere. Diethyl ether (2 mL) was added to the flask and then cooled to 0 °C. Methyllithium (1.4 M, 1.67 mL, 2.32 mmol) was added dropwise to the pale grey suspension. Initially, a bright yellow suspension was formed, which turned to a pale yellow solution and eventually, upon addition of enough methyllithium to form the cuprate complex, the solution became clear and colorless. The resulting cuprate solution was cooled at 0 °C for an additional hour and then bromotrimethylsilane (0.102 mL, 0.77 mmol) was added to the cuprate complex. Compound **52** (61 mg, 0.13 mmol) in diethyl ether (1 mL) was added to the solution, forming a bright yellow suspension. The mixture was stirred at 0 °C for 3 hours and then the resulting silyl enol ether was cleaved by quenching the mixture with an ammonium chloride-ammonium hydroxide solution (pH=9, 3 mL) for an additional 3 hours. The resulting mixture was extracted with Et_2O (2 x 15 mL). The organic extracts

were washed with water (5 mL) and saturated sodium chloride solution (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography eluting with ethyl acetate-Skelly B (5:95) to give a 3:1 mixture of **54** and **55** as a colorless oil (32 mg, 0.068 mmol, 52%). Flash column chromatography eluting with ethyl acetate-Skelly B (3:98) of the mixture several times allowed for the separation of pure compound **54**. Compound **54**: IR (CH_2Cl_2, cast): 1700 (C=O), 1112 (SiO), 702 cm^{-1} (SiC); ^1H NMR (400 MHz, $CDCl_3$): δ 7.63-7.72 (m, 4H, phenyl), 7.36-7.46 (m, 6H, phenyl), 5.78-5.84 (m, 1H, C**H**=CH), 5.66-5.74 (m, 1H, CH=C**H**), 3.75 (t, J = 7.5 Hz, 2H, C**H**$_2$OSi), 2.14-2.20 (complex m, 2H), 1.94-2.14 (complex m, 4H), 1.88 (t, J = 6.5 Hz, 1H), 1.56 (t, J = 7.5 Hz, 2H), 1.20 (s, 3H, C(C**H**$_3$)C=O), 1.06 (s, 9H, *tert*-butyl), 0.97 (d, J = 7.5 Hz, 3H, CH=CHCH(C**H**$_3$)), 0.85 (s, 3H, C**H**$_3$), 0.81 (d, J = 7 Hz, 3H, CH$_2$CH(C**H**$_3$)); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 217.29 (p), 135.60 (ap), 133.81 (p), 132.45 (ap), 129.64 (ap), 127.67 (ap), 126.56 (ap), 60.75 (p), 50.88 (p), 47.27 (ap), 44.96 (ap), 39.24 (ap), 38.05 (p), 37.60 (p), 36.32 (ap), 29.54 (ap), 26.89 (ap), 23.56 (p), 22.88 (ap), 19.09 (p), 17.08 (ap), 15.95 (ap); HRMS: 431.2397 (M^+ - *tert*-butyl, calcd. for $C_{28}H_{35}O_2Si$: 431.2406). Compound **55**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.63-7.72 (m, 4H, phenyl), 7.36-7.46 (m, 6H, phenyl), 5.75 (m, 1H, C**H**=CH), 5.52 (m, 1H, CH=C**H**), 3.65 (m, 2H, C**H**$_2$OSi), 1.94-2.14 (complex, 5H), 1.65 (m, 2H), 1.21 (s, 3H, C(C**H**$_3$)C=O), 1.04 (s, 9H, *tert*-butyl), 0.93 (d, J = 7.5 Hz, 3H, CH=CHCH(C**H**$_3$)), 0.83 (s, 3H, C**H**$_3$), 0.82 (d, J = 7 Hz, 3H, CH$_2$CH(C**H**$_3$)).

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Hydroxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]deca-8-en-2-one (56)

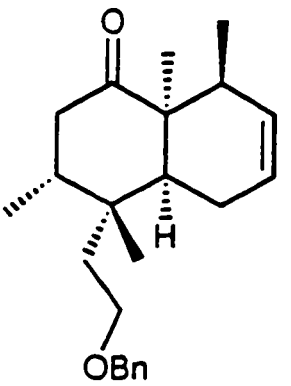


56

Compound **54** (62 mg, 0.13 mmol) was dissolved in THF (2 mL) then tetrabutylammonium fluoride (1.0 M in THF, 0.25 mL, 0.25 mmol) was added to the solution under argon. The resulting pale yellow solution was stirred at room temperature for 2 hours, then quenched with water (3 mL) and extracted with Et_2O (3 x 5 mL). The organic extracts were washed with saturated sodium chloride solution (2 x 5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a colorless oil. The crude product was subjected to flash chromatography eluting with ethyl acetate-Skelly B (30:70) to give **56** (32 mg, 0.13 mmol, 59%): IR (CH_2Cl_2, cast): 3347 (OH), 1705 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.82-5.92 (m, 1H, C**H**=CH), 5.70-5.76 (m, 1H, CH=C**H**), 3.74 (ddd, J_1 = 9.5 Hz, J_2 = 6 Hz, J_3= 6 Hz, 2 H, CH_2OH), 2.12-2.28 (complex, 2H), 2.02-2.16 (complex, 4H), 1.95 (t, J = 6.5 Hz, 1H), 1.46-1.72 (complex, 3H), 1.27 (s, 3H, CH_3CC=O), 0.98 (d, J = 8 Hz, 3H, C=CHCHCH_3), 0.97 (s, 3H, CH_3), 0.90 (d, J = 7 Hz, 3H, CH_2CHCH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 217.33 (p), 132.98 (ap), 126.79 (ap), 59.51 (p), 51.10 (p), 47.74 (ap), 45.05 (p), 39.39 (ap), 38.36 (p), 37.77 (p), 35.75 (ap), 29.51 (ap), 23.68 (p),

23.12 (ap), 17.01 (ap), 16.03 (ap); HRMS M^+: 250.1928 (calcd. for $C_{16}H_{26}O_2$: 250.1933).

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]deca-8-en-2-one (25)



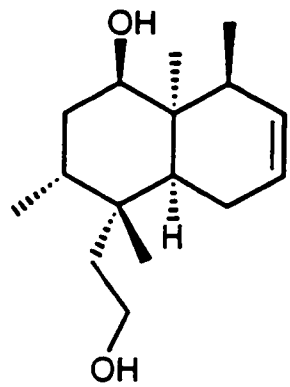
25

THF (1 mL) was added dropwise to a flask charged with sodium hydride (95% purity, 4 mg, 0.16 mmol) at 0 °C under an argon atmosphere. Ketone **56** (19 mg, 0.076 mmol) in THF (1 mL) was added dropwise followed by benzyl bromide (0.020 mL, 0.17 mmol). The resulting mixture was warmed to ambient temperature and stirred for three days. The mixture was then quenched with water and extracted with diethyl ether. The organic extract was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was subjected to flash column chromatography eluting with ethyl acetate-Skelly B (10:90) to afford **25** (19 mg, 0.056 mmol, 73%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5 H, phenyl), 5.86 (m, 1H, CH=C**H**), 5.74 (m, 1H, C**H**=CH), 4.50 (m, 2H, OCH_2Ph), 3.56 (m, 2H, CH_2OBn), 2.20 (complex, 2H), 2.00-2.17 (complex, 3H), 1.95 (t, J = 7 Hz, 1H), 1.55-1.72 (complex, 3H), 1.25 (s, 3H, $C(CH_3)C=O$),

0.99 (d, J = 7 Hz, 3H, C=CHCH(CH_3)), 0.96 (s, 3H, CH_3), 0.90 (d, J = 6 Hz, 3H, CH_2CHCH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 217.10 (p), 138.44 (p), 132.68 (ap), 129.73 (ap), 128.44 (ap), 127.63 (ap), 126.71 (p), 73.20 (p), 67.14 (p), 51.05 (p), 47.53 (ap), 45.08 (p), 39.44 (ap), 37.70 (p), 35.86 (ap), 35.18 (p), 29.51 (ap), 23.71 (p), 23.15 (ap), 17.08 (ap), 16.06 (ap); HRMS M^+: 340.2387 (calcd. for $C_{23}H_{32}O_2$: 340.2402).

The spectral data are in agreement with those found in our laboratory[27-29].

(1S*, 2R*, 4R*, 5R*, 6S*, 10S*)-5-(2-Hydroxyethyl)-1,4,5,10-tetramethylbicyclo[4.4.0]deca-8-en-2-ol (31)



31

THF (1 mL) was added dropwise to a cooled (0 °C) reaction vessel charged with lithium aluminum hydride (7 mg, 0.2 mmol). Ketone **56** (22 mg, 0.088 mmol) dissolved in THF (1 mL) was added to the grey suspension. After 30 minutes the mixture was quenched with water and then aqueous 1N HCl. The reaction mixture was extracted with diethyl ether (3 x 5 mL). The organic extract was washed successively with water (5 mL) and saturated sodium chloride solution (5 mL), dried over anhydrous magnesium sulfate, filtered, and

concentrated in vacuo. The residue was purified by flash column chromatography eluting with ethyl acetate-Skelly B (20:80) to afford diol **31** (16 mg, 0.063 mmol, 72%): IR (CH_2Cl_2 cast): 3382 cm^{-1} (OH); ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (m, 1H, C**H**=CH), 5.58 (dm, J = 10 Hz, 1H, CH=C**H**), 3.88 (ddd, J_1 = 11 Hz, J_2 = 11 Hz, J_3 = 5.5 Hz, 1H, C**H**$_2$OH), 3.76 (ddd, J_1 = 11 Hz, J_2 = 11 Hz, J_3 = 5.5 Hz, 1H, C**H**$_2$OH), 3.74 (m, 1H), 2.38 (m, 1H), 2.00-2.20 (complex, 4H), 1.45-1.80 (complex, 6H), 1.18 (s, 3H, C(C**H**$_3$)C=O), 1.16 (d, J = 7.5 Hz, 3H, C=CHCH(C**H**$_3$)), 1.03 (s, 3H, C**H**$_3$), 0.88 (d, J = 7 Hz, 3H, CH_2CHCH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 132.31 (ap), 128.68 (ap), 73.28 (ap), 60.14 (p), 41.97 (ap), 40.67 (ap), 39.68 (p), 39.18 (p), 38.84 (p), 35.22 (p), 30.45 (ap), 28.41 (p), 27.58 (ap), 26.40 (ap), 15.57 (ap), 15.10 (ap).

The spectral data are in agreement with those found in our laboratory[29].

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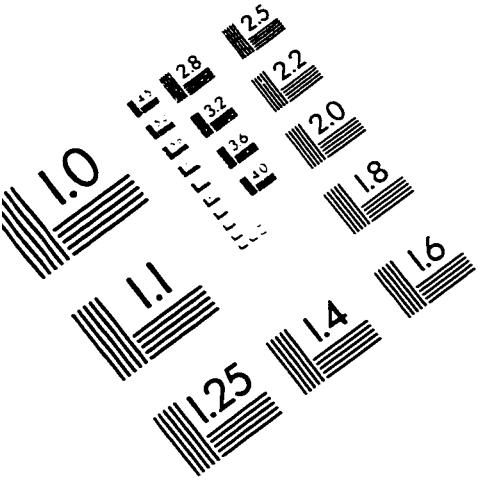
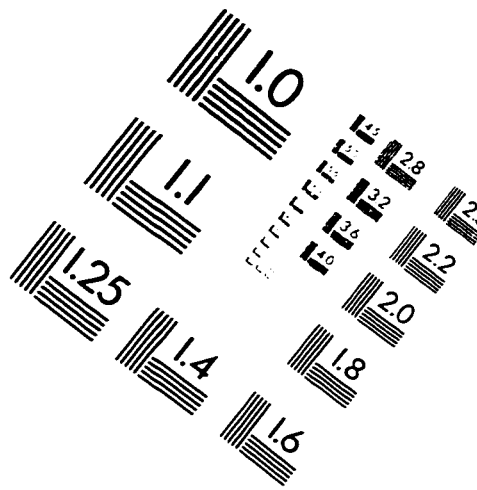
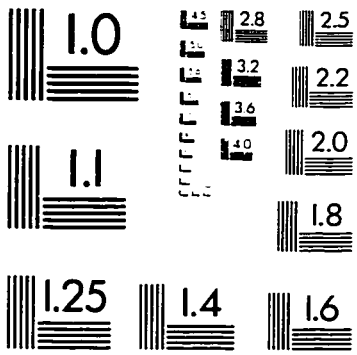
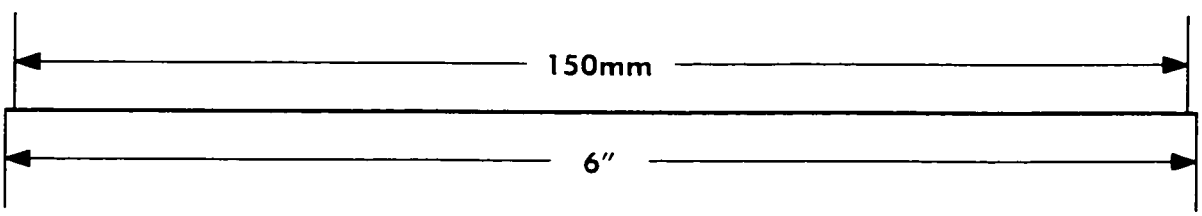
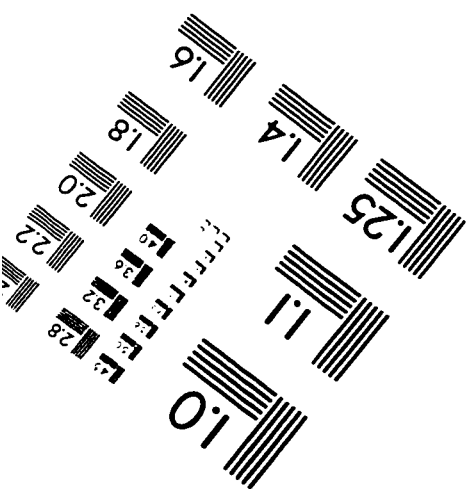
IMAGE EVALUATION TEST TARGET (QA-3)

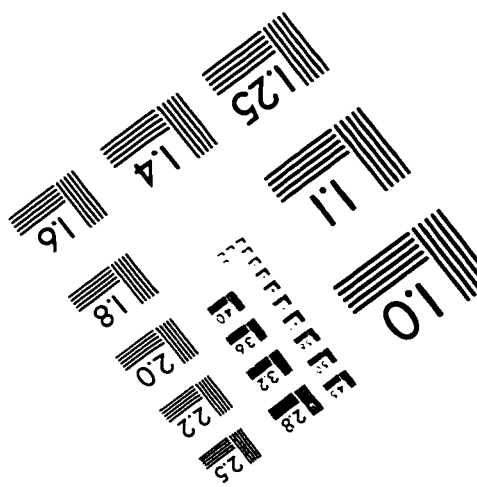












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