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UNIVERSITY OF ALBERTA

REDUCTIVE ALKYLATION OF α-CYANO KETONES

by

Jia Liang Zhu

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

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

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Dedicated to my parents

Abstract

Chapter one of this thesis describes a facile method for the consecutive introduction of two alkyl groups to the α-carbon of a ketone carbonyl. The procedure involves an alkylation-reduction-alkylation process of α-cyano ketones which are readily accessible via the base induced rearrangement of isoxazoles or Thorpe-Ziegler reaction. The introduction of various alkyl groups to the α-carbon of α-cyano ketones was effected by treatment with appropriate alkylating agents under basic conditions. By the use of proper bases and solvents, the competing *O*-alkylation could be suppressed to a large extent. The mono-alkylated cyano ketones were found to be easily reduced under mild conditions using lithium naphthalenide as a reducing agent. The ensuing enolate ions were readily trapped with a variety of alkylating reagents to provide α,α-dialkylated ketones in good yields.

The second chapter is divided into two parts. The first part described the Diels-Alder chemistry of five-, six-, seven- and eight-membered 2-cyano-2-cycloalkenones. Under zinc chloride catalysis, they were found to add rapidly to a variety of dienes to give various fused bicyclic carbon ring skeletons possessing a cyano group at the angular position. The regiochemistry follows the *ortho*- and *para*-rules and the stereoselectivity follows the *endo*-to-ketone addition and *cis*-principle. Reductive alkylation of the Diels-Alder adducts induced by lithium naphthalenide allows efficient replacement, in each case, of the angular cyano group with an alkyl group. Thus, 2-cyano-2-cycloalkenones can be considered as a synthetic equivalent of 2-alkyl-2-cycloalkenones, which are notorious for their poor dienophilicity, to facilitate the preparation of polycyclic compounds angularly substituted with an alkyl group using Diels-

Alder chemistry. Based on this newly developed process, a preliminary investigation on the total synthesis of the naturally occurring sesquiterpenoids neolemnane and neolemnanyl acetate (structures **56** and **57**, respectively, in Chapter 2) has been carried out. The key steps in the projected synthesis are the construction of the fused bicyclo[6.4.0]dodecane carbon skeleton via the Diels-Alder reaction of 2-cyano-8-methyl-2-cyclooctenone, and the installation of the required angular methyl group through a reductive alkylation process. This investigation resulted in the preparation of an advanced intermediate (**80** in Chapter 2) which contains the complete carbon framework of the target molecules as well as suitable functional groups for further elaboration.

In the third chapter of this thesis, samarium(II) iodide is introduced as an alternative reducing agent for the reductive alkylation process. This reagent proved to be also effective as shown by the formation of a variety of α,α-dialkylated ketones from α-cyano ketones.

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First, I would like to express my sincerest gratitute to Professor H.J. Liu for his ever willing support, guidance and encouragement throughout this work. His invaluable assistance over the years is much appreciated.

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Table of Contents

List of Tables

List of Figures

List of Schemes

List of abbreviations

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

IR	Infrared Spectroscopy
LDA	Lithium Diisopropylamide
m	multiplet
M	Molar
M^+	Molecular ion
Me	Methyl
MHz	Megahertz
min	minute
mmol	millimole
mol	mole
mp	melting point
m/z	mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
p	para
p	phase
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
THF	Tetrahydrofuran

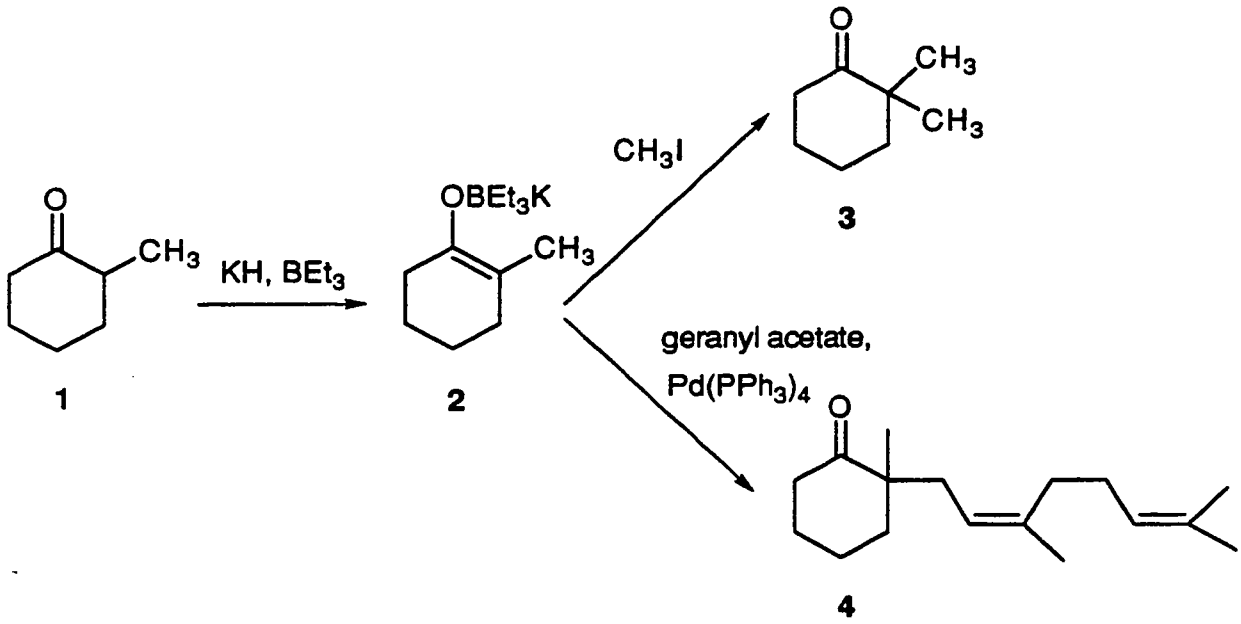
Introduction

The consecutive introduction of two alkyl groups to the α-carbon of a ketone carbonyl is among the most commonly used processes in organic chemistry. For this important synthetic operation, the most challenging problem that has received considerable attention is the control of regioselectivity. In the past years, several procedures have been developed in order to improve yield and regioselectivity for the desired α,α-dialkylation of ketones and to eliminate or suppress the certain side reactions such as polyalkylation and isomer formation. A brief summary of these procedures is given in the first part of this chapter.

The early study of regiocontrol of α,α-dialkylation of ketones was mainly focused on the selective generation of regiospecific enolate anions from unsymmetrical ketones by deprotonation.[1] Upon treatment with a base, an unsymmetrical ketone can potentially form two different, isomeric enolate anions. Experimental conditions can often be chosen to provide a substantial preference for the more-substituted thermodynamic enolate. The enolate thus generated is able to either react with an alkylating agent to give an α,α-dialkylated ketone[2] or be trapped with an electrophile to afford an enol derivative. The enolate can subsequently be regenerated from the enol derivative and react with an alkylating agent to afford a dialkylated product. Since the early 1960's, this process has been extensively used in regioselective alkylation of ketone compounds. For example, in 1982, Negishi *et al.* reported a method of preparing 2,2-dimethylcyclohexanone (**3**) and 2-methyl-2-nerylcyclohexanone (**4**) from 2-methylcyclohexanone (**1**).[3,4] They described that the thermodynamic enolate of ketone **1** could be obtained by

treating **1** with potassium hydride in tetrahydrofuran (THF). Further reaction of the enolate with triethylborane afforded a potassium enoxyborate **2** in 90% yield. Treating the enol derivative **2** with methyl iodide and with geranyl acetate in the presence of a catalytic amount of a palladium-phosphine complex $Pd(PPh_3)_4$ produced **3** (79%) and **4** (77%), respectively (**Scheme 1-1**).

Scheme 1-1

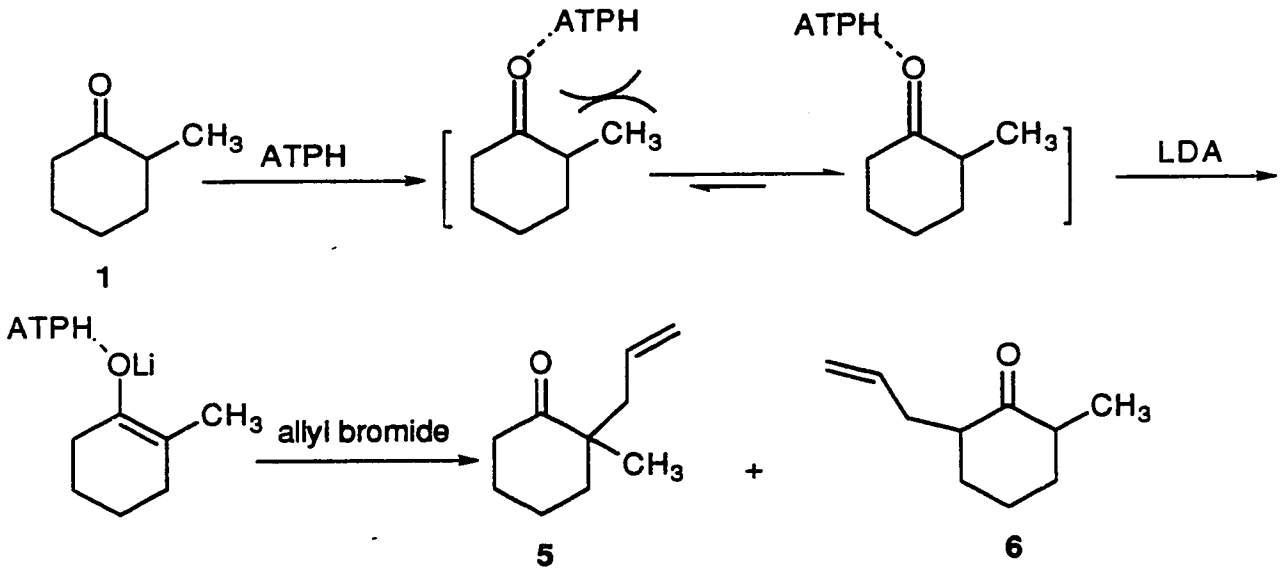


In addition to potassium enoxyborates, other thermodynamically generated enol derivatives which have been applied to the preparation of α,α-dialkylated ketones include enol acetates,[5] trimethylsilyl enol ethers[6] and tin enol ethers.[7]

An interesting procedure for the generation of the more-substituted enolates under the kinetically controlled condition has recently been developed by

Yamamoto *et al.*[8] They found that, precomplexing unsymmetrical ketones with aluminum tris(2,6-diphenylphenoxide) (ATPH) followed by treating ketone complexes with lithium diisopropylamide (LDA) could preferentially give the formation of the more-substituted enolates. For example, treatment of ketone **1** with ATPH and LDA in toluene at -78°C, followed by addition of allyl bromide led to the formation of ketone **5** in 52% yield. In this case, only about 1% of regioisomer **6** was formed. The regioselective deprotonation could be interpreted in terms of the influence of ATPH on the inherent coordination preferences of unsymmetrical ketones (**Scheme 1-2**).

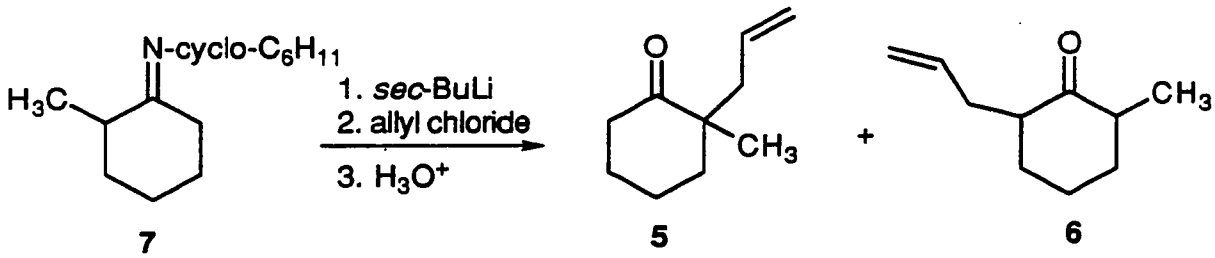
Scheme 1-2



The application of regioselective deprotonation of unsymmetrical imines to regiocontrol of α,α-dialkylation of ketones was first explored by Hosomi *et al.* in 1982.[9] As they reported, when treated with *n*-, *sec*- or *tert*-butyllithium, the

deprotonation of *N*-cyclohexylimine **7** occurred preferentially at the methyl-substituted α position. Subsequent treatment of imine anion with alkyl halides followed by hydrolyzing the reaction mixtures with 2N HCl afforded a mixture of two regioisomers in which the α,α-dialkylated ketones proved to be the major products. For example, sequential treatment of imine **7** with *sec*-butyllithium and allyl chloride, followed by acidic hydrolysis furnished ketone **5** and its regioisomer **6** in 76% and 8% yields, respectively (**Eq. 1-1**). Furthermore, it was found that under the same condition, deprotonation of acyclic *N*-cyclohexylimines occurred similarly at the more-substituted α position to a considerable extent. However, the regioselectivity apparently decreased presumably due to the decrease of the steric hindrance of the acyclic imine compounds.

Equation 1-1

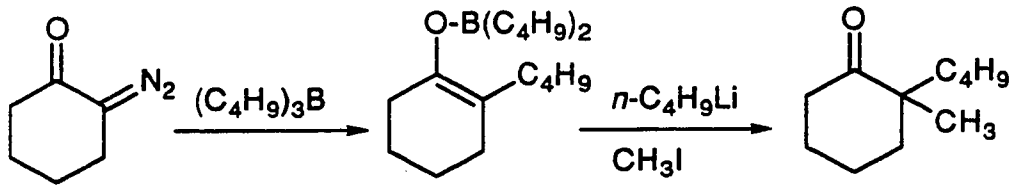


7 **5** **6**

As illustratred in the aboved-mentioned procedures, under the specified conditions, the regiocontrol of α,α-dialkylation of ketones can be achieved to a certain extent by the base induced deprotonation. However, it may not be possible to direct deprotonation so as to form one enolate to the exclusion of the other. In order to attain the complete regiocontrol of formation of enol derivatives, two other methods have been proposed. Pasto *et al.* have

described a procedure of using diazo ketones as a starting material to prepare dialkylated ketones.[10] They reported that the reaction of diazo ketones with trialkylboranes could give vinyloxyboranes as a single regioisomer. Treatment of vinyloxyboranes with *n*-butyllithium afforded the corresponding lithium enolates which could undergo facile alkylation to give the regioisomerically pure ketones. The preparation of ketone **10** from diazo ketone **8** *via* the intermediary enol derivative **9** provides an example of this procedure (**Scheme 1-3**). The other method for the genaration of the regiospecific enol derivatives has been proposed by Kuo *et al.*[11] They described that, upon heating in THF, trimethylsilyl β-keto esters underwent a pyrolytic decarboxylation reaction to give the formation of trimethylsilyl enol ethers. The subsequent treatment of enol ethers with methyllithium and alkylating agents afforded dialkylated ketones possessing the complete regiospecificity.

Scheme 1-3

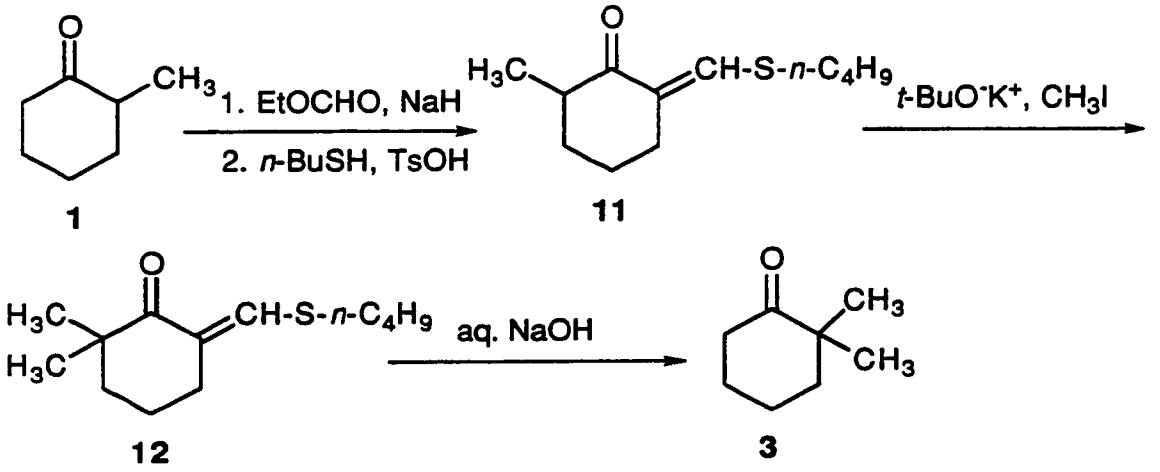


8 **9** **10**

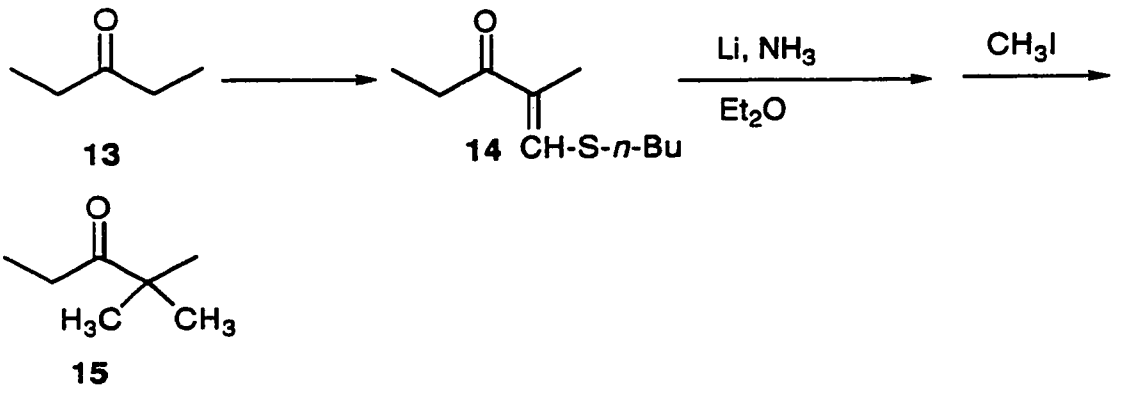
As reported in some cases, the regiocontrol of α,α-dialkylation of ketones can also be achieved by the use of blocking groups. Blocking groups effectively applied to the regiocontrol of alkylation of ketones include *N*-methylanilinomethylene,[12] benzylidene,[13] isopropoxymethylene,[14] dithioketal,[15] double bond conjugated with a ketone carbonyl group,[16] hydroxymethylene[17]

and *n*-butylthiomethylene.[18] All of these blocking groups have the ability to render the methylene group on one side of a ketone carbonyl inert, therefore prevent the formation of regioisomers during the alkylation on the other side. Take an example for *n*-butylthiomethylene group which was first utilized as a blocking group in α,α-dialkylation of ketones by Ireland *et al.* in 1962.[18] As they described in the preparation of ketone **3** from ketone **1**, *n*-butylthiomethylene group could be easily introduced to the α position of ketone **1** by treating **1** with ethyl formate and sodium hydride followed by *n*-butyl mercaptan and *p*-toluenesulfonic acid. With the presence of the blocking group, the methylation of **11** occurred regiospecifically to give the alkylated compound **12**. After the alkylation, *n*-butylthiomethylene group could be readily removed by treating **12** with aqueous sodium hydroxide to yield ketone **3** in 70% yield (**Scheme 1-4**). It was also observed that 2-*n*-butylthiomethylene ketones could undergo a "double reduction" with a lithium-ammonia solution to afford a methyl-substituted enolate anion at the original methylene position which could be alkylated *in situ*.[19] This operation permits the direct introduction of a methyl group and a variable alkyl substituent to an α position of ketones. The preparation of ketone **15** from ketone **13** *via* the intermediate **14** gives an example of this method (**Scheme 1-5**).[19]

Scheme 1-4



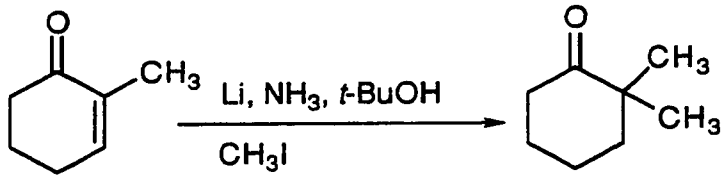
Scheme 1-5



The ease of directing alkylation to relatively inaccessible α positions by reductive alkylation of α,β-unsaturated ketones provides a possibility of using this operation to regiocontrol of α,α-dialkylation of ketones. In general term, the procedure involves the generation of regiospecific lithium enolates of

unsymmetrical ketones by reducing the corresponding α,β-unsaturated ketones with lithium and liquid ammonia followed by the reaction of enolates with alkylating agents. As a typical example, the unsaturated ketone **16** could be converted to ketone **3** in 80% yield through the sequential treatment with lithium-ammonia solution and methyl iodide in the presence of *t*-butyl alcohol (**Eq. 1-2**).[20]

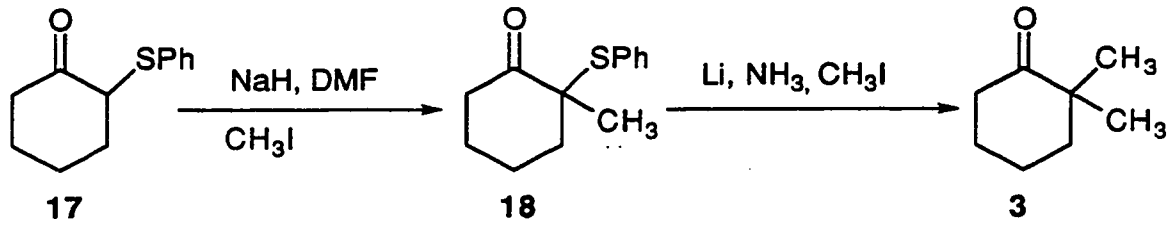
Equation 1-2



16 **3**

Other than dissolving metal reduction of α,β-unsaturated ketones, reductive cleavage of α-heterosubstituted ketones provides another approach for the generation of regiospecific enolates. The ease of removal of α-alkylthio groups by dissolving metal reduction makes α-alkylthio ketones as an useful precursor in α,α-dialkylation of ketones.[21,22] For example, in the preparation of ketone **3** from 2-phenylthiocyclohexanone (**17**) reported by Coates *et al.*,[22] the α-phenylthio group could direct the methylation to occur regiospecifically at the C-2 position to give **18**. When subjected to lithium and liquid ammonia treatment, the intermediate **18** underwent a reductive desulfurization reaction resulting in the formation of a regiospecific lithium enolate which was then trapped by methyl iodide to give **3** in 80% yield (**Scheme 1-6**).

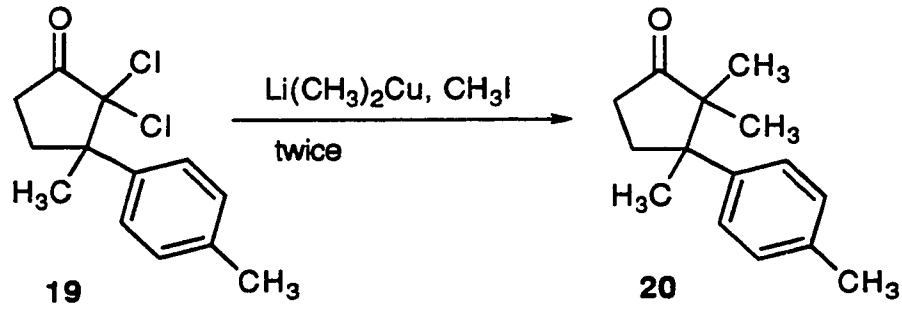
Scheme 1-6



17 **18** **3**

The application of reductive cleavage of α,α-dihaloketones to α,α-dialkylation of ketones, although may not be commonly used, has also been realized experimentally. For example, Greene *et al.* have reported that, on treatment with lithium dimethylcopper followed by methyl iodide, α,α-dichloroketones could undergo a clean reductive methylation to give dimethylated compounds.[23] By using this procedure, they prepared α-cuparenone (**20**) from the dichloride **19** in 52% yield (**Equation 1-3**).[24]

Equation 1-3



19 **20**

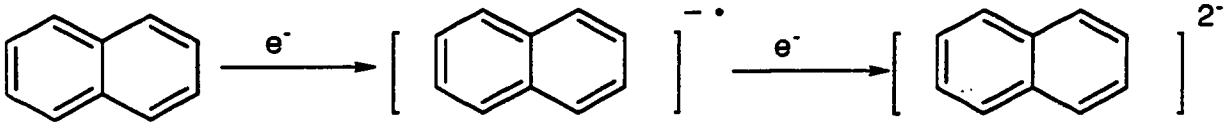
Generally speaking, the methods described above have proved to be applicable to a certain extent to regiocontrol of α,α-dialkylation of ketones.

However, some deficiencies associated with these procedures such as the difficulty of handling highly volatile reagents, the difficulty of separating regioisomers, the unsatisfied yields and the poor accessibility of starting materials provide a stimulus for us to search for the more effective methods for this important synthetic operation. Accordingly, an efficient general procedure has been developed in our group, making use of the aromatic radical anion induced reductive alkylation of an α-cyano ketone system as a key operation.

Radical anions of aromatic hydrocarbons have found wide applications in organic synthesis.[25-27] This type of reagents can simply be prepared by dissolving alkali metals into aromatic hydrocarbon ethereal solutions, with THF being the most commonly used solvent. Sodium and lithium are the most commomly used metals. Various aromatic hydrocarbons that have been employed include biphenyl, naphthalene, anthracene, perylene, phenanthrene, pyrene, tetracene and their derivatives. As reducing agents, the radical anions of biphenyl and naphthalene in THF are almost as powerful as the corresponding metals. This made lithium naphthalenide (LN) as the choice in our reductive alkylation process.

When metallic lithium is dissolved in a naphthalene THF solution, a deep green to blue solution of the radical anion is formed, like other "electron solution". If more than one equivalent of metal is added, the dianion will be produced (**Scheme 1-7**), although its presence can never be excluded even with less than one equivalent of lithium due to the disproportionation of the radical anion.

Scheme 1-7



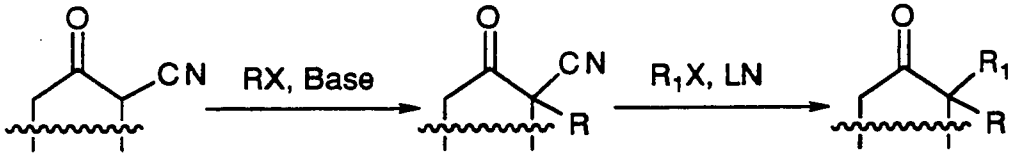
Radical anions are known to undergo two general types of reactions, namely, proton abstraction reactions and single electron transfer (SET) reactions. As a strong base, it was estimated that radical anions were effective in abstracting protons from compounds having PK_a less than 33. Cases of applying proton abstraction to condensation reactions are known in the literature.[28]

The more typical reactions of radical anions are SET reactions. This type of reactions are believed to occur through a process in which an electron is transferred from aromatic nucleus to a receptor which then may undergo a variety of transformations depending on its nature. The most commonly seen examples are probably the reductive cleavage of alkyl, silyl,[29] vinyl[30] or aryl halides,[31] dihalides[32-35] and perseudo halides (ArX, RX or R_3SiX where X = F, Cl, Br, I, CN[36] or SePh). In these reactions, the initially formed R· or R^- can add to another functional group in the same molecule, abstract a hydrogen atom or a proton from the media to yield R-H, couple with the arene radical anions to form alkylated arenes or dimerize to give R-R. All of these different possible pathways make aromatic radical anions seem to be not quite useful for single chemical transformations. However, it has been noted that the reductive cleavage induced by aromatic radical anions are usually very fast and can proceed at low temperatures. This allows for the trapping of R· or R^- with a

variety of electrophiles as soon as they are generated. In some reactions, a catalytic instead of a stoichiometric amount of aromatic hydrocarbons was used in order to prevent the formation of by-products resulting from the reaction between arene radical anions and electrophiles.[27]

It was due to this reducing ability of aromatic radical anions that a research project was initiated in our group to study the utility of lithium naphthalenide in the reductive alkylation of α-cyano ketones. The synthetic facility of this new procedure lies in the ease of α-alkylation of α-cyano ketones directed by the cyano group and that of the subsequent reductive alkylation to replace the cyano group by an alkyl group. (**Scheme 1-8**).

Scheme 1-8



Compared with lithium-ammonia solution which has been employed as a reducing agent in a similar process,[37] lithium naphthalenide THF solution is apparently a better choice to us since it can be easily prepared and stored as a stork solution.[38] Furthermore, it is much easier to be handled during reactions.

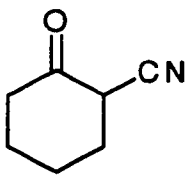
A series of cyclic and one acyclic α,α-dialkylated ketones were prepared by this process. In each case, the transformation was shown to be completely regioselective and easy to be carried out experimentally. The yields of products

were ranged from 60% to 90%. The findings of this study are discussed in the following part.

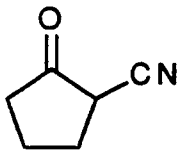
Results and Discussion

I. Preparation of α-cyano ketones

Six selected α-cyano ketones used for the present study were prepared by two established procedures. 2-Cyanocyclohexanone (**21**) and 2-cyanocyclopentanone (**22**) were easily prepared by the modified Thorpe-Ziegler reaction.[39] Treatment of pimelonitrile with sodium hydride and *N*-methylaniline in THF at refluxing temperature for two hours followed by acidic work-up with concentrated hydrochloride acid gave the desired product **21** in 90% yield. Compound **22** was similarly prepared from adiponitrile in 85% yield.



21



22

Compound **21** showed, in the infrared spectrum, absorption bands at 1722 (ketone carbonyl) and 2250 cm^{-1} (nitrile). The ^1H NMR spectrum displayed a signal at δ 3.52 as a doublet of doublets (J_1 = 13 Hz, J_2 = 7 Hz) which was readily attributed to the α methine proton. In the ^{13}C NMR APT spectrum, a signal at δ 200.5 was assigned to the carbonyl carbon. The cyano signal was displayed at δ 116.6. In the high resolution mass spectrum, compound **21** showed a molecular ion peak at m/z 123.0682 in accordance with the molecular formula C_7H_9ON. The infrared, ^1H NMR and ^{13}C NMR APT spectra of compound **22** displayed the similar characteristic signals and absorption bands as those of compound **21**. The high resolution mass spectrum showed a

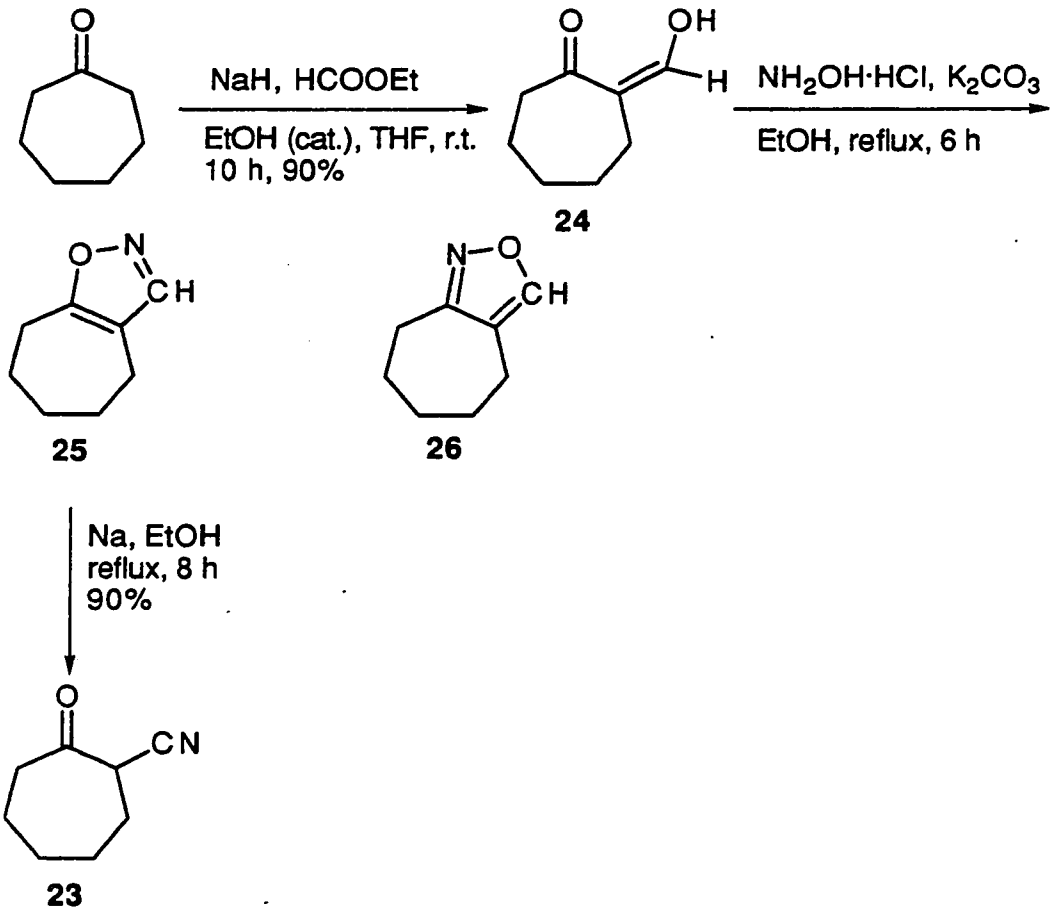
molecular ion peak at m/z 109.0514 which was consistent with the molecular formula C_6H_7ON.

The attempt to prepare compound **23** from suberonitrile under the same reaction condition was not successful. Even with the prolonged reaction time (8 h), the starting material was recovered intact. This unsuccessful result led us to use a different method to prepare **23**. This method, which was previously used successfully in our group,[40] involves formylation of cyclic ketones, isoxazole formation and the base induced rearrangement of isoxazoles.

Formylation of cycloheptanone using ethyl formate and sodium hydride in the presence of a catalytic amount of 95% ethanol gave the hydroxymethylene ketone **24** in 90% yield **(Scheme 1-9)**. Treatment of **24** with hydroxylamine hydrochloride and anhydrous potassium carbonate in absolute ethanol at refluxing temperature afforded isoxazole derivative **25** and the side-product **26** in 70% and 20% yields, respectively. Isoxazole **25** was then converted to the α-cyano ketone **23** in 90% yield by treatment with sodium ethoxide. When this compound was subjected to purification by column chromatography on silica gel, a substantial deterioration was observed. The pure material, however, could be obtained by vacuum distillation of the crude product. In the infrared spectrum of **23**, the carbonyl absorption was displayed at 1719 cm^{-1} and the cyano absorption was shown at 2248 cm^{-1}. In the ^1H NMR spectrum, the α methine proton was shown at δ 2.80 as a doublet of doublets (J_1 = 12 Hz, J_2 = 5 Hz). In the high resolution mass spectrum, compound **23** displayed a molecular ion peak at m/z 137.0842 in agreement with the molecular formula $C_8H_{11}ON$. Like compounds **21** and **22**, compound **23** existed exclusively in the keto form. This was confirmed by its ^1H NMR spectrum which did not show any signal for

the enol hydroxyl proton and by its ^{13}C NMR APT spectrum which displayed only one set of carbon signals including a carbonyl signal at δ 202.1 and a cyano signal at δ 117.6.

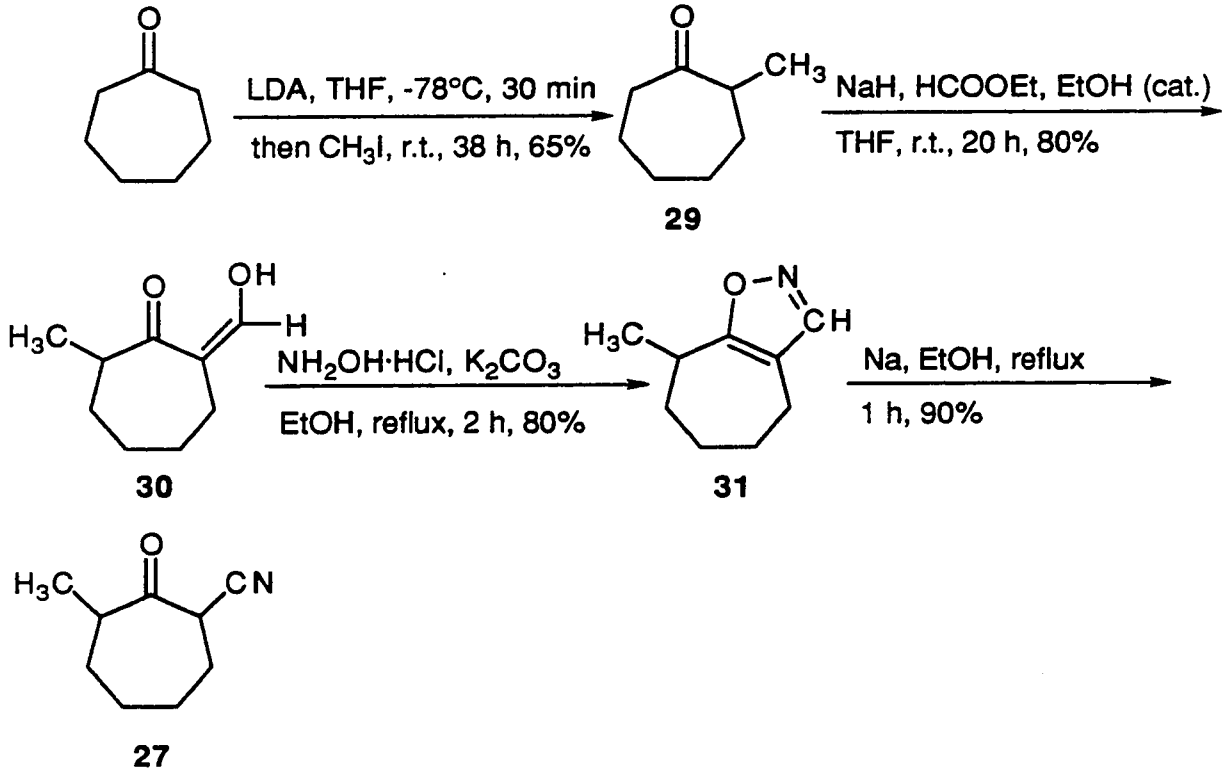
Scheme 1-9



In order to attest the possibility of applying the reductive alkylation process to preparing α,α,α'-trialkylated ketones, 2-cyano-7-methylcycloheptanone (**27**) and 2-cyano-5-methylcyclopentanone (**28**) were similarly prepared.

The preparation of compound **27** is outlined in **Scheme 1-10**. The methylation of 2-methylcycloheptanone with LDA and methyl iodide gave compound **29** in 65% yield.[41] Formylation of **29** followed by treatment of the resulting compound **30** with hydroxylamine hydrochloride gave isoxazole **31** as the only product isolated. Subsequent treatment of **31** with sodium ethoxide gave the cyano ketone **27** as a mixture of two inseparable diastereomers (1 : 1) in 90% yield. With an additional methyl group on the α' position, compound **27** appeared to be more stable than compound **23** and could be purified by column chromatography on silica gel without decomposition.

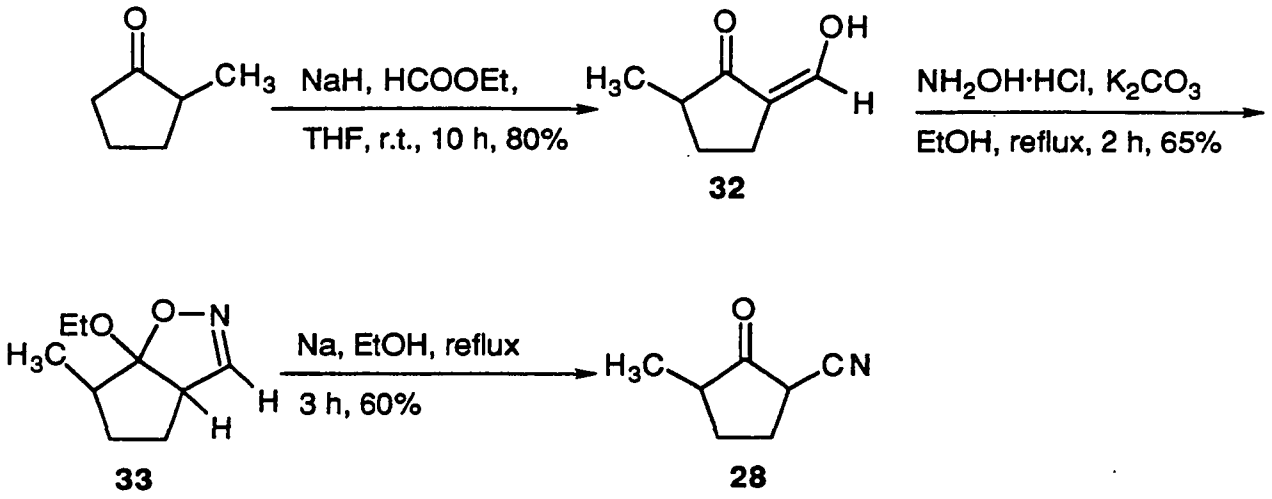
Scheme 1-10



The ratio of two diastereomers of **27** was obtained from the integration of the related peaks in the ^1H NMR spectrum. The signals of the methyl group of two isomers appeared as two doublets at δ 1.10 (J = 7 Hz) and 1.05 (J = 6.5 Hz). For one diastereoisomer, the proton adjacent to the cyano group appeared as a triplet (J = 5 Hz) at δ 3.74. For the other one, this proton was displayed as a doublet of doublets (J_1 = 11 Hz, J_2 = 5 Hz) at δ 3.64. The existence of two stereoisomers was further confirmed by the ^{13}C NMR APT spectrum which displayed two sets of signals including two carbonyl signals at δ 205.6 and 205.2 and two nitrile signals at δ 117.8 and 117.7. A pair of signals at δ 17.8 and 17.1 were assigned to the methyl group. In the infrared spectrum, two diagnostic bands were shown at 1715 (carbonyl) and 2247 cm^{-1} (nitrile). The high resolution mass spectrum exhibited the required molecular ion peak at m/z 151.0998.

The preparation of the cyano ketone **28** was started from the commercially available 2-methylcyclopentanone (**Scheme 1-11**). After the formylation, the reaction of the formylated product **32** with hydroxylamine hydrochloride and potassium carbonate in absolute ethanol at refluxing temperature gave the unexpected ethoxide addition product **33** as a mixture of two diastereomers (1 : 1), instead of the normal isoxazole derivative. On treatment with sodium ethoxide, however, this addition product could be converted to the desired compound **28**, again as a mixture of two diastereomers in a ratio of 1.3 : 1.

Scheme 1-11



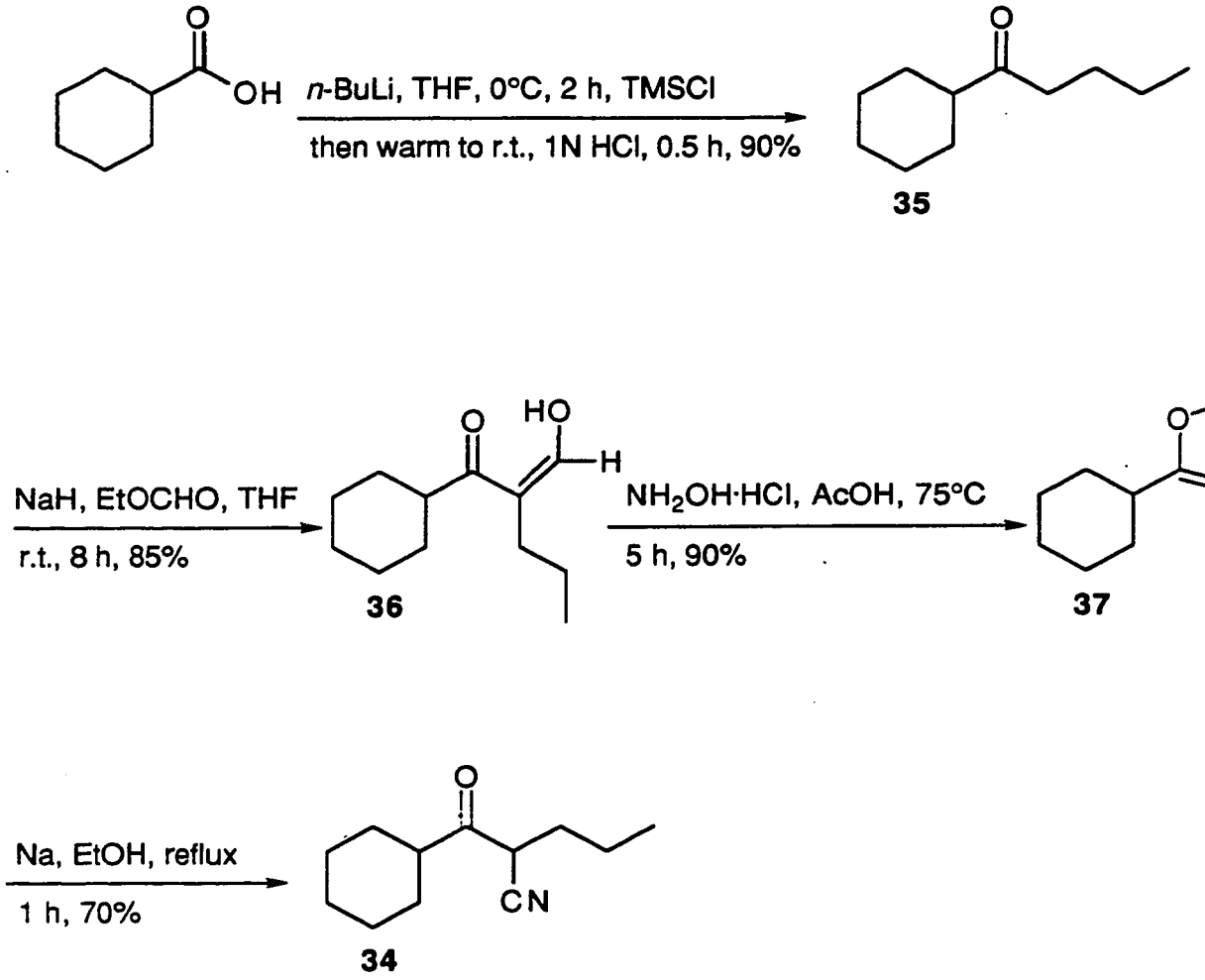
32 **33** **28**

The ratio of two isomers of compound **28** was obtained from the integration of the related peaks in the ^1H NMR spectrum. The methyl protons of the major isomer was shown at δ 1.18 as a doublet (J = 7 Hz), while the methine proton adjacent to the cyano group was displayed at δ 3.13 as a doublet of doublets (J_1 = 10 Hz, J_2 = 5 Hz). For the minor isomer, the signal of the methyl group was shown as a doublet (J = 7.5 Hz) at δ 1.22. A weak signal at δ 3.30 (t, J = 8 Hz) was assigned to the α proton adjacent to the cyano group. In the ^{13}C NMR APT spectrum, the carbonyl signals of two isomers were shown at δ 208.7 and 206.4, and the cyano signals were displayed at δ 116.7 and 116.4. The infrared spectrum displayed an absorption at 1711 cm^{-1} for the carbonyl group as well as a band at 2247 cm^{-1} for the cyano group. The high resolution mass spectrum showed a molecular ion peak at m/z 123.0686 in accordance with the molecular formula C_7H_9ON.

The preparation of acyclic cyano ketone **34** is outlined in **Scheme 1-12**. The unsymmetric ketone **35** was prepared by the sequential treatment of cyclohexanecarboxylic acid with *n*-butyllithium and trimethylsilyl chloride in THF, followed by hydrolyzing the reaction mixture with 1N HCl aqueous solution. In this case, trimethylsilyl chloride was supposed to consume the excess of *n*-butyllithium, thereby, leaving no butyllithium to react with ketone **35** in the subsquent aqueous work-up.[42] After the formylation step, the reaction of the formylated product **36** with hydroxylamine hydrochloride and potassium carbonate in absolute ethanol provided the isoxazole derivative **37** only in 20% yield. The yield of **37** was greatly improved by treating **36** with hydroxylamine hydrochloride using glacial acetic acid as a solvent.[43] Compound **37** was then converted to **34** in 70% yield by treating with sodium ethoxide.

In the ^{1}H NMR spectrum of compound **34**, the α proton adjacent to the cyano group was displayed at δ 3.65 as a triplet (J = 7 Hz), while the methine proton on the cyclohexyl ring was shown at δ 2.82 as a multiplet. A triplet (J = 8 Hz) at δ 0.97 was observed for the terminal methyl group. The infrared spectrum displayed a carbonyl absorption at 1721 cm^{-1} and a nitrile absorption at 2240 cm^{-1}. The high resolution mass spectrum showed a molecular ion peak at m/z 193.1466 which was consistent with the molecular formula $C_{12}H_{19}NO$.

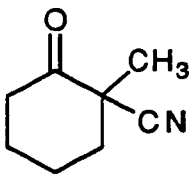
Scheme 1-12


OH
n-BuLi, THF, 0°C, 2 h, TMSCl
then warm to r.t., 1N HCl, 0.5 h, 90%
35
NaH, EtOCHO, THF
r.t., 8 h, 85%
HO
H
36
NH2OH·HCl, AcOH, 75°C
5 h, 90%
N
CH
37
Na, EtOH, reflux
1 h, 70%
CN
34

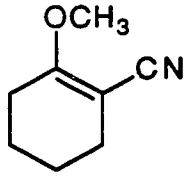
II. Alkylation of α-cyano ketones

Once α-cyano ketones were in hand, the alkylation of these cyano ketones with various alkylating agents was studied. The methylation of cyano ketone **21** with methyl iodide was the first reaction to be investigated.

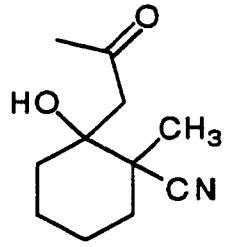
Due to the ambient nucleophilic character of the enolate anion, we expected that the methylation of compound **21** might occur either at carbon atom or at oxygen atom. This expectation was experimentally proven to be correct. By using sodium hydride as a base and THF as a solvent, compound **21** was found to undergo *O*-alkylation more readily than *C*-alkylation. The reaction provided only 10% of *C*-alkylation product **38** and 50% of *O*-alkylation product **39**. In the reaction in which potassium carbonate was employed as a base and acetone as a solvent, compound **39** was also obtained as the major product (30%). During the reaction, compound **38** continued to react with the enolate of acetone to afford the addition product **40** in 17% yield. For these two reactions, the high ratio of **39** might be attributed to the weak coordination between the metal cations and the enolate oxygen atom, which could result in the large exposure of the enolate oxygen atom to the alkylating agent.



38



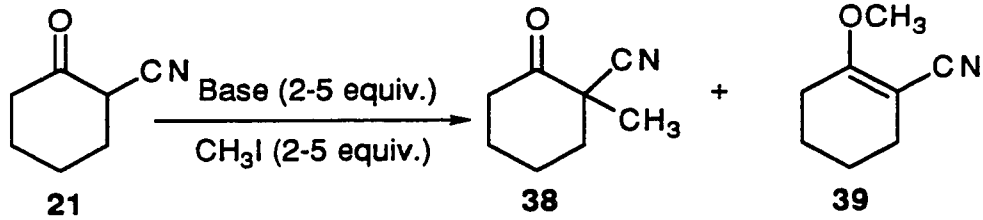
39



40

Considering that the tighter coordination between lithium cation and the enolate oxygen atom might suppress the undesired *O*-alkylation, we decided to look at the possibility of using lithium bases in the methylation of **21**. Three different lithium bases including LDA, LiOH and LiH and several solvents were examined in order to find the favorable condition for the formation of compound **38**. The experimental results are compiled in **Table 1-1**.

Table 1-1. Lithium bases induced methylation of 2-cyanocyclohexanone **21**



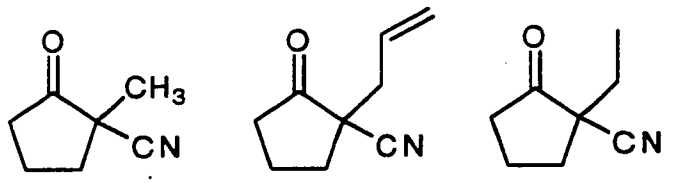
21 **38** **39**

Base (solvent)	Ratio (**38** : **39**)	Yield (%, combined)
LDA (THF)	6 : 1	38
LiOH (H_2O)	9 : 1	30
LiOH (acetonitrile)	1 : 4	40
LiOH (acetone)	2 : 1	75
LiH (THF)	3 : 1	80

Of these conditions, lithium hydride combined with THF was shown to be most effective, giving the highest yield of **38**. In this reaction, compound **21** was treated with LiH (3 eq.) and CH_3I (4 eq.) using THF as the solvent. After stirring at room temperature for 24 hours, the reaction mixture was quenched with water and extracted with dichloromethane. The usual work-up of the organic

solution followed by column chromatography of the crude products on silica gel gave **38** in 60% yield and **39** in 20% yield. The infrared spectrum of **38** indicated the presence of the carbonyl group (1729 cm^{-1}) and the cyano group (2232 cm^{-1}). In the ^1H NMR spectrum, the methyl group was displayed as a singlet at δ 1.43. The high resolution mass spectrum exhibited the required molecular ion peak at m/z 137.0844.

Under the similar conditions, alkylation of the five-membered cyclic α-cyano ketones **22** proceeded even better than the methylation of **21**. By using LiH as a base and THF as a solvent, the reactions of **22** with methyl iodide, allyl bromide and ethyl iodide provided three alkylated products **41** (85%), **42** (80%) and **43** (70%) without the formation of the *O*-alkylated by-products.



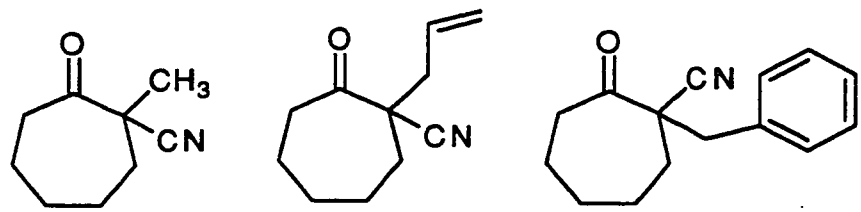
41 **42** **43**

For compound **41**, its high resolution mass spectrum displayed a molecular ion peak at m/z 123.0683 which corresponded to the molecular formula C_7H_9ON. The ^{13}C NMR APT spectrum gave 7 carbon signals including a carbonyl carbon signal at δ 209.5 and a nitrile carbon signal at δ 119.8. In the ^1H NMR spectrum, the methyl group was shown as a strong singlet at δ 1.43. The infrared spectrum displayed a carbonyl absorption band at 1753 cm^{-1} and a nitrile absorption band at 2241 cm^{-1}.

For compound **42**, the high resolution mass spectrum gave a molecular ion peak at m/z 149.0838 corresponding to the molecular formula $C_9H_{11}ON$. The ^{13}C NMR APT spectrum displayed 9 carbon signals including two sp^2 vinylic carbon signals at δ 130.7 and 120.9, as well as a carbonyl carbon signal at δ 208.8 and a nitrile carbon signal at δ 118.7. The ^1H NMR spectrum of **42** displayed the signals of the terminal vinylic protons at δ 5.23 (dm, J = 20 Hz) and 5.27 (dm, J = 7 Hz). The signal of the non-terminal vinylic proton appeared at δ 5.82 (dm, J = 20 Hz). One of the allylic methylene protons was displayed at δ 2.62 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 1.5 Hz). The infrared spectrum exhibited an intense absorption band at 1752 cm^{-1} for the carbonyl group and a band at 2237 cm^{-1} for the nitrile group. An absorption band at 1653 cm^{-1} was observed for the carbon-carbon double bond.

For compound **43**, the high resolution mass spectrum showed a molecular ion peak at m/z 137.0856 in agreement with the molecular formula $C_8H_{11}ON$. The ^{13}C NMR APT spectrum displayed a total of eight signals including a carbonyl signal at δ 209.4, a nitrile signal at δ 118.9 and a methyl signal at δ 9.4. The ^1H NMR spectrum gave a triplet at δ 1.07 (J = 8 Hz) for the methyl group. In the infrared spectrum, the carbonyl band was displayed at 1752 cm^{-1}, while the nitrile band was displayed at 2237 cm^{-1}.

The alkylation of the seven-membered cyclic α-cyano ketone **23** with methyl iodide, allyl bromide and benzyl bromide proceeded equally well to give the alkylated products **44** (80%), **45** (85%) and **46** (90%), respectively.



44 **45** **46**

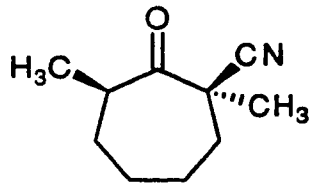
In the infrared spectra of compounds **44**, **45** and **46**, the absorption bands at 1716, 1714 and 1713 cm^{-1} were respectively observed for the carbonyl group. The bands at 2239, 2240 and 2238 cm^{-1} indicated the presence of the cyano group. The high resolution mass spectra of these three compounds gave the molecular ion peaks at m/z 151.1003, 177.1159 and 227.1304 which corresponded to the molecular formulas $C_9H_{13}ON$, $C_{11}H_{15}ON$ and $C_{15}H_{17}ON$.

The ^1H NMR spectrum of **44** displayed a strong singlet at δ 1.52 representing the protons of the methyl group. The ^{13}C NMR APT spectrum displayed a carbonyl carbon signal at δ 205.4, a cyano carbon signal at δ 121.1 and a methyl carbon signal at δ 23.5.

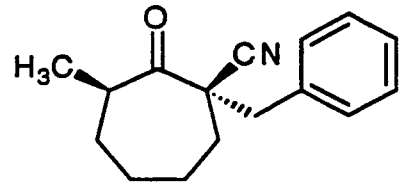
The ^1H NMR spectrum of **45** displayed two mutually coupled signals at δ 2.37 (ddd, J_1 = 13 Hz, J_2 = 7 Hz, J_3 = 1 Hz) and 2.15 (dd, J_1 = 13 Hz, J_2= 8 Hz), corresponding to the allylic methylene protons. Signals for the terminal vinylic protons were displayed at δ 5.30 (dm, J = 17 Hz) and 5.23 (dm, J = 10 Hz). The non-terminal vinylic proton appeared at δ 5.78 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 8 Hz, J_4 = 3 Hz). In the ^{13}C NMR APT spectrum, the signals of the vinylic carbons were shown at δ 130.9 and 120.8.

The ^1H NMR spectrum of compound **46** displayed two coupled doublets (J = 13 Hz) for the benzylic protons at δ 3.20 and 2.97. The aromatic protons appeared as a multiplet at approximately δ 7.32. The ^{13}C NMR APT spectrum exhibited a total of 13 carbon signals including four aromatic carbon signals at δ 134.1, 130.3, 128.5 and 127.7, as well as a carbonyl signal at δ 205.4 and a nitrile signal at δ 120.1.

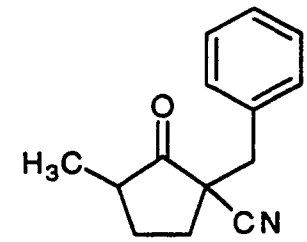
It was found that the alkylation of cyano ketone **27**, which contained an equal amount of two diastereomers, with methyl iodide and benzyl bromide resulted in the formation of two single diastereomers **47** (85%) and **48** (90%), respectively. For both **47** and **48**, the newly introduced alkyl groups proved to be in a *trans* relationship with the methyl group on the C-7 carbon. This stereoselectivity, however, was not observed in the benzylation of compound **28** which, on the similar treatment with lithium hydride and benzyl bromide, afforded compound **49** as a mixture of two inseparable stereoisomers (1 : 1) in 60% yield.



47



48



49

The high resolution mass spectrum of **47** supported the molecular formula $C_{10}H_{15}ON$, as indicated by the molecular ion peak at m/z 165.1154. The infrared spectrum showed a strong absorption at 1714 cm^{-1} for the ketone carbonyl. An absorption band at 2240 cm^{-1} indicated the presence of the cyano

group. In the ^{1}H NMR spectrum, two methyl groups were displayed at δ 1.47 as a singlet (C-2 methyl) and δ 1.15 as a doublet (J = 7 Hz, C-7 methyl). The ^{13}C NMR APT spectrum showed 10 carbon signals including a carbonyl signal at δ 208.2, a nitrile signal at δ 121.1 and two methyl signals at δ 18.0 and 24.5. The stereochemistry of **47** was supported by NOE experiments (**Figure 1-1**). Irradiation of the C-2 methyl protons at δ 1.47 gave a 4% enhancement of the C-7 methine proton at δ 2.82. No enhancement was observed for the C-7 methyl group. Conversely, there was a 2.06% enhancement of the C-2 methyl signal upon irradiation of the C-7 methine proton at δ 2.82.

In the high resolution mass spectrum of compound **48**, a molecular ion peak was found at m/z 241.1465 which was consistent with the molecular formula $C_{16}H_{19}ON$. The infrared spectrum displayed a carbonyl absorption band at 1790 cm^{-1} as well as a nitrile absorption band at 2239 cm^{-1}. In the ^{1}H NMR spectrum, two mutually coupled doublets (J = 13 Hz) at δ 3.11 and 3.05 were readily assigned to the benzylic protons. The methyl group was displayed at δ 1.10 as a doublet (J = 8 Hz). The α methine proton appeared at δ 2.64 as a multiplet. In ^{13}C NMR APT spectrum, the aromatic carbon signals were found at δ 133.6, 130.2, 128.6 and 127.9. The depicted stereochemistry of **48**, as suggested by NOE experiments (**Figure 1-2**), was verified by an X-ray crystallographic analysis (**Figure 1-3**).

Figure 1-1 The NOE results of compound **47**

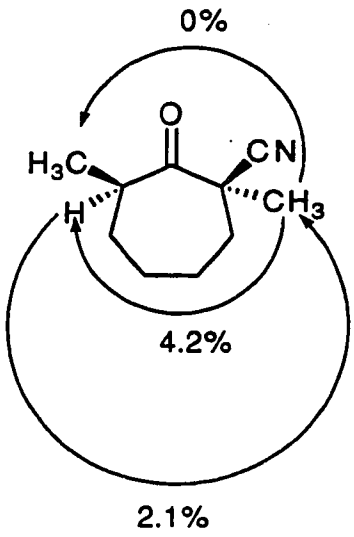


Figure 1-2 The NOE results of compound **48**

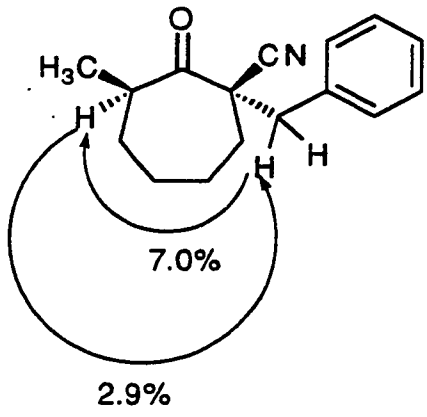
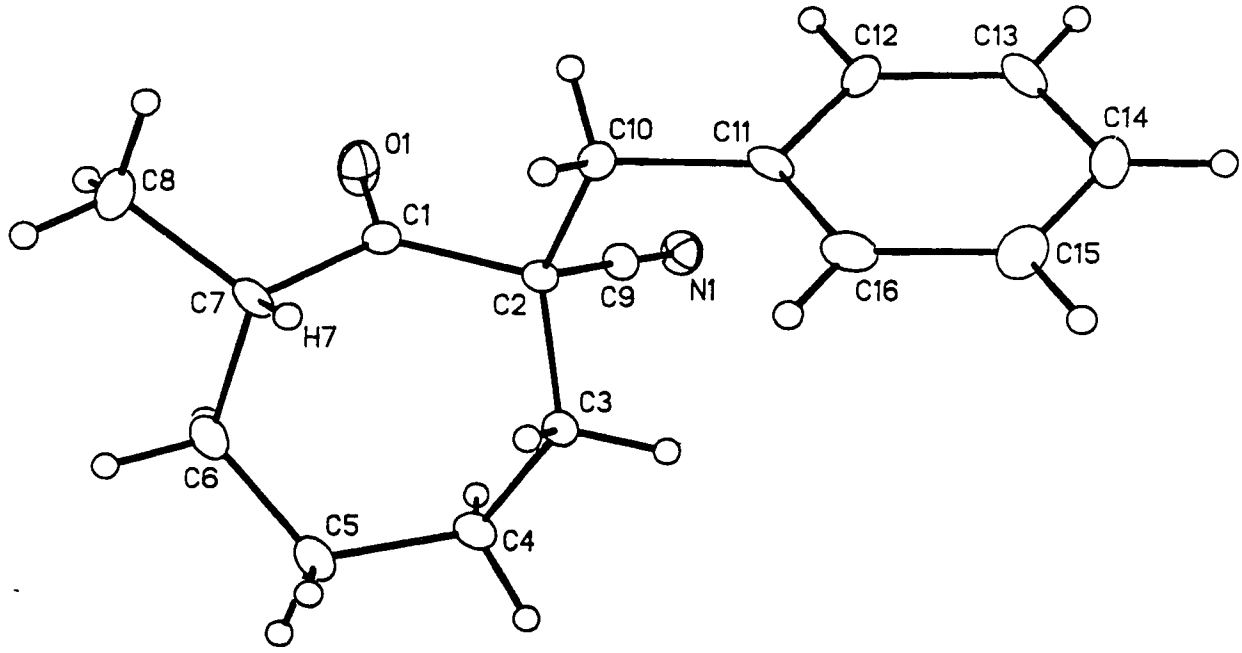
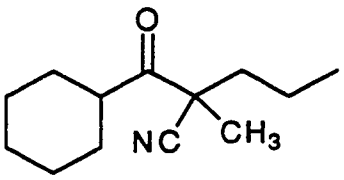


Figure 1-3 The three dimensional X-ray crystallographic structure of compound **48**



The ratio of two diastereomers of compound **49** was deduced from the integration of the related peaks in the ^{1}H NMR spectrum. The benzylic protons of two isomers were displayed as four doublets (J = 13 Hz) at δ 2.98, 3.23, 3.10 and 2.87. For one isomer, the methyl protons were shown at δ 1.10 as a doublet (J = 7 Hz). For the other isomer, the signal of the methyl protons was found at δ 1.23 (d, J = 6.5 Hz). There were two sets of carbon signals displayed in the ^{13}C NMR APT spectrum including two carbonyl signals at δ 210.3 and 210.2, two nitrile signals at δ 119.8 and 118.9 and two methyl signals at δ 14.9 and 14.1. In the infrared spectrum, the carbonyl band was displayed at 1751 cm^{-1}, while the nitrile band was shown at 2232 cm^{-1}. The high resolution mass spectrum showed a molecular ion peak at m/z 213.1154 in agreement with the molecular formular $C_{14}H_{15}ON$.

The methylation of the acyclic cyano ketone **34** with methyl iodide by using LiH as a base and THF as a solvent gave the alkylated product **50** only in 20% yield. In order to improve the yield of this compound, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a base which has been proven to be effective to facilitate the monoalkylation of several active methylene compounds,[44] was employed. By using DBU as a base and dichloromethane as a solvent, the methylation of **34** afforded compound **50** with a greatly improved yield (70%). For the alkylation of cyclic α-cyano ketones, DBU, however, did not show to be more efficient to improve the yields of the desired products compared with LiH.



50

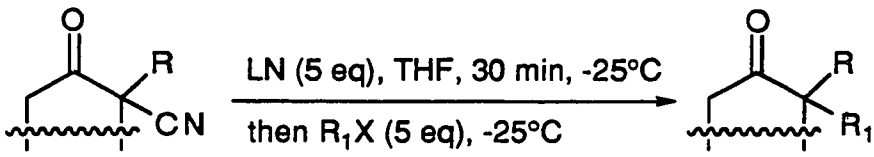
The infrared spectrum of **50** displayed two diagnostic bands at 1751 and 2236 cm^{-1} for the carbonyl group and the cyano group. The high resolution mass spectrum showed a molecular ion peak at 207.1624 which was consistent with the molecular formula $C_{13}H_{21}ON$. The ^1H NMR spectrum displayed two methyl signals. The terminal methyl protons was shown at δ 0.92 as a triplet (J = 7 Hz). The other methyl group appeared at δ 1.45 as a strong singlet. The ^{13}C NMR APT spectrum displayed a total of 13 carbon signals which were consistent with the assigned molecular structure.

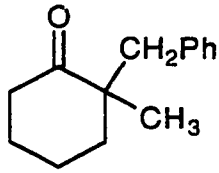
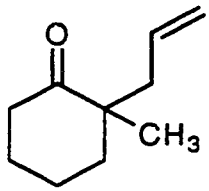
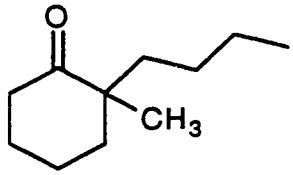
III. Reductive alkylation of α-cyano ketones

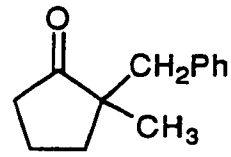
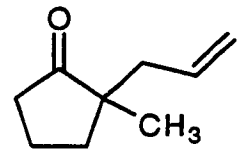
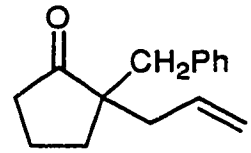
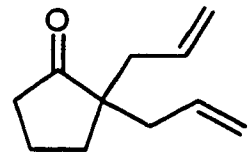
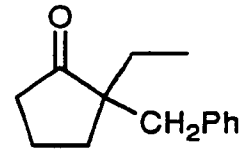
With the completion of preparing monoalkylated α-cyano ketones, the reductive alkylation of these compounds with lithium naphthalenide and various alkylating agents was investigated. The lithium naphthalenide solution was freshly prepared prior to use. The preparation of lithium naphthalenide solution is as follows. Chunks of lithium metal were cut into small pieces, which were washed with dry Skelly B and added to a solution of naphthalene in THF. It took about 3-4 hours at room temperature for the lithium metal to dissolve, yielding a dark blue solution. An excess of naphthalene to lithium was used to prepare the lithium naphthalenide solution (1.5 : 1). The previous study in our group showed that lithium naphthalenide solution was stable enough to be stored at -4°C for a month or even longer without any appreciable loss in reactivity.[38]

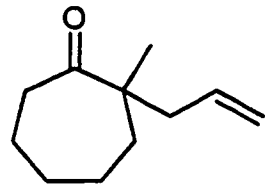
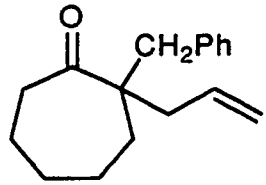
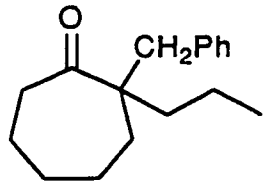
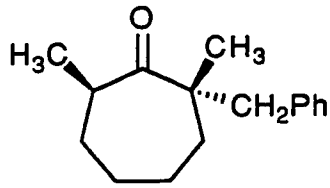
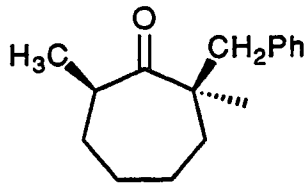
The general procedure for reductive alkylation of α-cyano ketones involved pre-cooling the lithium naphthalenide solution at -25°C under an inert atmosphere, followed by addition of this solution to an α-cyano ketone by syringe. The resulting solution was stirred at -25°C for 30 minutes before an alkylating agent was added. Further reaction gave rise to an α,α-dialkylated product. In theory, the reductive decyanation process requires only two equivalents of lithium naphthalenide. In practice, however, the use of less than five equivalents of the reagent often resulted in incompletion of the reaction. To ensure that the reaction goes to completion, all reactions performed in this study used a total of five equivalents of lithium naphthalenide. The amount of the alkylating agents was accordingly adjusted to five equivalents in order to cover the expected side reactions with cyanide and with the excess lithium naphthalenide such as reductive dehalogenation. The results obtained from reductive alkylation of α-cyano ketones are compiled in **Table 1-2**. Most of the reactions listed in **Table 1-2** were essentially performed at -25°C except two cases (Entries 3 and 11), in which the elevated temperatures were required to complete the reactions due to the reduced reactivity of the alkylating agents.

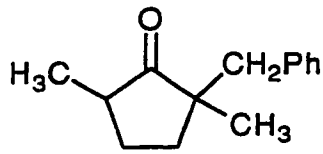
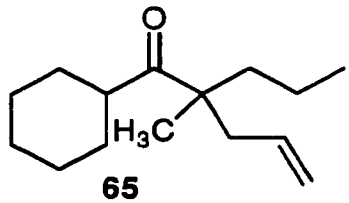
Table 1-2 Reductive alkylation of α-cyano ketones with lithium naphthalenide (LN)



Entry	α-Cyano ketone	Alkylating agent	Time (min)	Product	% Yield
1	**38**	benzyl bromide	45	 **51**	72
2	**38**	allyl bromide	40	 **5**	70
3	**38**	1-bromobutane	a	 **10**	65

Entry	α-Cyano ketone	Alkylating agent	Time (min)	Product	% Yield
4	**41**	benzyl bromide	30	 **54**	80
5	**41**	allyl bromide	30	 **55**	70
6	**42**	benzyl bromide	30	 **56**	70
7	**42**	allyl bromide	30	 **57**	80
8	**43**	benzyl bromide	30	 **58**	60

Entry	α-Cyano ketone	Alkylating agent	Time (min)	Product	% Yield
9	**44**	allyl bromide	30	 **59**	90
10	**45**	benzyl bromide	30	 **60**	80
11	**46**	1-bromopropane	b	 **61**	65
12	**47**	benzyl bromide	60	 **62**	70
13	**48**	methyl iodide	30	 **63**	80

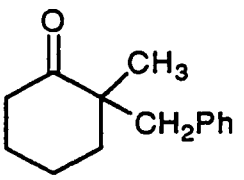
Entry	α-Cyano ketone	Alkylating agent	Time (min)	Product	% Yield
14	**49**	methyl iodide	60	 **64**[c]	70
15	**50**	allyl bromide	120	 **65**	90

[a]This reaction was carried out in refluxing THF for 10 hours.

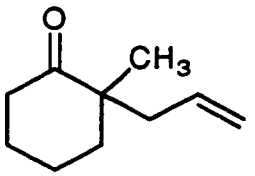
[b]This reaction was carried out at room temperature for 24 hours.

[c]Two diastereoisomers were formed in a ratio of 1 : 0.7.

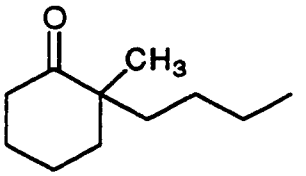
Treatment of cyano ketone **38** with the reducing agent, lithium naphthalenide, followed by alkylation with benzyl bromide, allyl bromide and 1-bromobutane afforded products **51** (72%), **5** (70%)[8] and **10** (65%),[10] respectively (Entries 1-3).



51



5

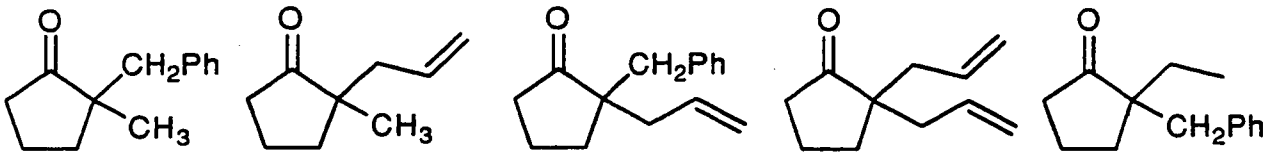


10

The infrared spectra of these three products displayed respectively the strong carbonyl absorption bands at 1704, 1706 and 1707 cm^{-1}. The notable absence of the nitrile absorption bands around 2200 cm^{-1} indicated that the cyano groups were removed and possibly replaced by the alkyl groups. In the high resolution mass spectra of **51**, **5** and **10**, the molecular ion peaks were observed at m/z 202.1352, 152.1198 and 168.1514, supporting the molecular formulas $C_{14}H_{18}O$, $C_{10}H_{16}O$ and $C_{11}H_{20}O$. The ^1H NMR and ^{13}C NMR APT spectra of these three products were also in support of the assigned structures. In the ^1H NMR spectrum of compound **51**, the signals of the benzylic protons overlapped as a triplet (J = 13 Hz) and appeared at δ 2.93. The aromatic protons appeared as two multiplets at δ 7.20 and 7.35. The methyl group was displayed as a singlet at δ 1.05. The ^{13}C NMR APT spectrum of **51** showed 12 carbon signals including four aromatic carbon signals as well as one carbonyl signal. For compound **5**, its ^1H NMR spectrum showed a singlet at δ 1.14 corresponding to the methyl group. The terminal vinylic protons appeared as two multiplets at δ 5.04 and 5.12. The non-terminal vinylic proton was displayed at δ 5.73 (dm, J = 20 Hz). Two signals at δ 2.35 (dd, J_1 = 13 Hz, J_2 = 7.5 Hz) and

2.25 (dd, J_1 = 13 Hz, J_2 = 7 Hz) were assigned to the allylic methylene protons. The ^{13}C NMR spectrum of **5** displayed two vinylic carbon signals at δ 133.8 and 117.9. In the ^1H NMR spectrum of compound **10**, the terminal methyl group of the *n*-butyl substituent appeared as a triplet (J = 7 Hz) at δ 0.92, while the other methyl group at the C-2 position appeared as a singlet at δ 1.03. The ^{13}C NMR APT spectrum of **10** displayed eleven signals including two methyl signals at δ 14.0 and 22.6 as well as a carbonyl signal at δ 216.2.

Reductive alkylation of five-membered cyano ketones **41** with benzyl bromide and allyl bromide, **42** with benzyl bromide and allyl bromide and **43** with benzyl bromide afforded the dialkylated ketones **54** (80%), **55** (70%), **56** (70%), **57** (80%) and **58** (60%), respectively (Entries 4-8).

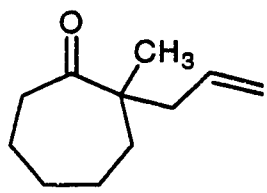


54 **55** **56** **57** **58**

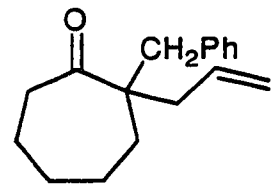
The infrared spectra of these products displayed the carbonyl absorption bands at 1735, 1736, 1734, 1735 and 1733 cm^{-1}, respectively. The disappearance of the nitrile absorption bands confirmed that the cleavage of the cyano group had occurred. The high resolution mass spectra showed the molecular ion peaks at m/z 188.1208, 138.1050, 214.1346, 164.1199 and 202.1364 supporting the required molecular formulas. The ^1H NMR spectrum of compound **54** displayed two mutually coupled doublets (J = 13 Hz) at δ 2.92 and 2.63 due to the benzylic protons and a singlet at δ 1.05 due to the methyl group. The aromatic

protons appeared as two multiplets at δ 7.40 and 7.25. The ^{1}H NMR spectrum of compound **55** displayed a singlet for the methyl group at δ 0.95. The terminal vinylic protons appeared at δ 5.10 (dm, J = 18 Hz) and 5.05 (dm, J = 8 Hz). The signal of the non-terminal vinylic proton was observed at δ 5.68 (dm, J = 18 Hz). The ^{1}H NMR spectrum of compound **56** displayed, in addition to two doublets (J = 13 Hz) at δ 2.93 and 2.66 for the benzylic protons, two signals at δ 5.09 (dm, J = 20 Hz) and 5.12 (dm, J = 8 Hz) for the terminal vinylic protons and one signal at δ 5.73 (dddd, J_1 = 20 Hz, J_2 = 10 Hz, J_3 = 8 Hz, J_4 = 1 Hz) for the non-terminal vinylic proton. In the ^{1}H NMR spectrum of compound **57**, four terminal vinylic protons were displayed at δ 5.05 (dm, J = 18 Hz) and 5.08 (dm, J = 8 Hz), while the non-terminal vinylic protons were shown at δ 5.69 (ddd, J_1 = 18 Hz, J_2 = 10 Hz, J_3 = 8 Hz). In the ^{1}H NMR spectrum of compound **58**, a triplet at δ 0.94 (J = 7 Hz) and a quartet at δ 1.48 (J = 7 Hz) indicated the presence of the ethyl group. The benzylic protons were found at δ 2.94 and 2.63 as two doublets (J = 13 Hz). The aromatic protons were displayed as a multiplet at approximately δ 7.30.

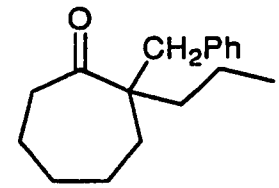
From cyano ketones **44**, **45** and **46**, seven-membered α,α-dialkylated cyclic ketones **59**, **60** and **61** were similarly prepared by this reductive alkylation method using allyl bromide, benzyl bromide and 1-bromopropane as the alkylating agents (Entries 9-11).



59



60

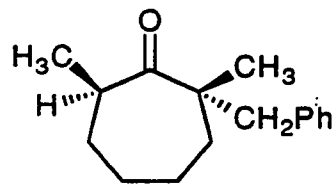


61

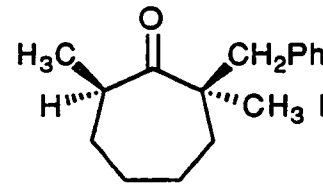
The spectral data of these three products are as follows. For compound **59**, the infrared spectrum displayed a carbonyl absorption band at 1701 cm^{-1} as well as a carbon-carbon double bond absorption band at 1684 cm^{-1}. The high resolution mass spectrum gave a molecular ion peak at m/z 166.1362 corresponding to the molecular formula $C_{11}H_{18}O$. The ^{13}C NMR ATP spectrum displayed 13 carbon signals including two vinylic carbon signals and one carbonyl carbon signal. The ^1H NMR spectrum showed two signals for the allylic methylene protons at δ 2.57 (ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 2 Hz) and 2.42 (dd, J_1 = 12 Hz, J_2 = 8 Hz). The terminal vinylic protons were displayed at δ 5.05 (dm, J = 20 Hz) and 5.10 (dm, J = 9 Hz). The non-terminal vinylic proton appeared at δ 5.72 (dddd, J_1 = 20 Hz, J_2 = 9 Hz, J_3 = 8 Hz, J_4 = 2 Hz). The methyl protons were displayed as a singlet at δ 1.02. For compound **60**, its infrared spectrum showed a carbonyl absorption at 1696 cm^{-1}. The molecular ion peak at m/z 242.1667 was displayed in the high resolution mass spectrum, in agreement with the molecular formula $C_{17}H_{22}O$. A total of 15 carbon signals were shown in the ^{13}C NMR APT spectrum, including one carbonyl carbon signal, four aromatic carbon signals and two vinylic carbon signals. In the ^1H NMR spectrum, the signals of the benzylic protons overlapped and appeared as a triplet (J = 13 Hz) at δ 2.80. The aromatic protons were shown as two multiplets at δ 7.10 and 7.32. Two terminal vinylic protons were displayed at δ 5.08 (dm, J = 17 Hz) and 5.12 (dm, J = 10 Hz), while the non-terminal proton was displayed at δ 5.83 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 7 Hz, J_4 = 2 Hz). For compound **61**, the infrared spectrum gave a notable carbonyl absorption band at 1697 cm^{-1}. The molecular ion peak at m/z 244.1821 in the high resolution mass spectrum supported the required molecular formula $C_{17}H_{24}O$. The ^{13}C NMR APT spectrum displayed a carbonyl signal at δ 217.8 and a methyl signal at δ 14.6. In the ^1H NMR spectrum, two mutually coupled doublets at δ 2.90 and

2.78 (J = 14 Hz) were assigned to the benzylic protons. The methyl group of the propyl substituent appeared as a triplet (J = 7 Hz) at δ 0.88. The aromatic protons were found as a multiplet at approximately δ 7.30.

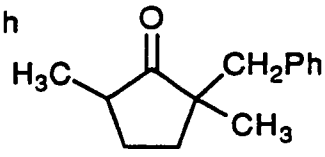
Interestingly, it was observed that the reductive alkylation of the single diastereomeric cyano ketones **47** and **48** with benzyl bromide and methyl iodide resulted in the formation of products **62** and **63**, again as two single stereoisomers. In both reactions, the alkyl groups were added to the enolates from the side opposite to the methyl group on the C-7 carbon, giving two epimeric α,α,α'-trisubstituted ketones (Entries 12 and 13). It was also found that, under the similar treatment with lithium naphthalenide and methyl iodide, the reductive alkylation of compound **49** which existed as a mixture of two diastereoisomers (1 : 1) afforded product **64,** again as a mixture of two diastereoisomers in a ratio of 1 : 0.7 (Entry 14).



62



63



64

The high resolution mass spectra of the epimeric ketones **62** and **63** displayed the required molecular ion peaks at m/z 230.1673 and 230.1670 which were consistent with the molecular formula $C_{16}H_{22}O$. The infrared spectra of these two products showed respectively absorption bands at 1716 and 1720 cm^{-1} indicating the presence of the carbonyl group. The ^1H NMR spectrum of **62** displayed two doublets (J = 13 Hz) at δ 2.72 and 2.52 for the benzylic protons. The methine proton at the C-7 position was observed as a multiplet at δ 2.45.

There were two methyl signals displayed in the spectrum, a doublet (J = 7 Hz) at δ 1.15 corresponding to the methyl at the C-7 position, and singlet at δ 1.18 due to the C-2 methyl group. The ^{1}H NMR spectrum of **63** displayed the similar characteristic signals as those of **62**, which included two doublets (J = 12 Hz) at δ 3.18 and 2.93 for the benzylic protons, one multiplet at δ 2.62 for the C-7 methine proton, one doublet (J = 7 Hz) at δ 1.18 for the C-7 methyl group and one singlet at δ 0.82 for the C-2 methyl group. There were a total of 14 carbon signals displayed in the ^{13}C NMR APT spectrum for each compound confirming the formation of the single stereoisomers. The stereochemistry of **62** and **63** was deduced from the results of NOE experiments shown in **Figure 1-4** and **Figure 1-5**.

Figure 1-4 The NOE results of compound **62**

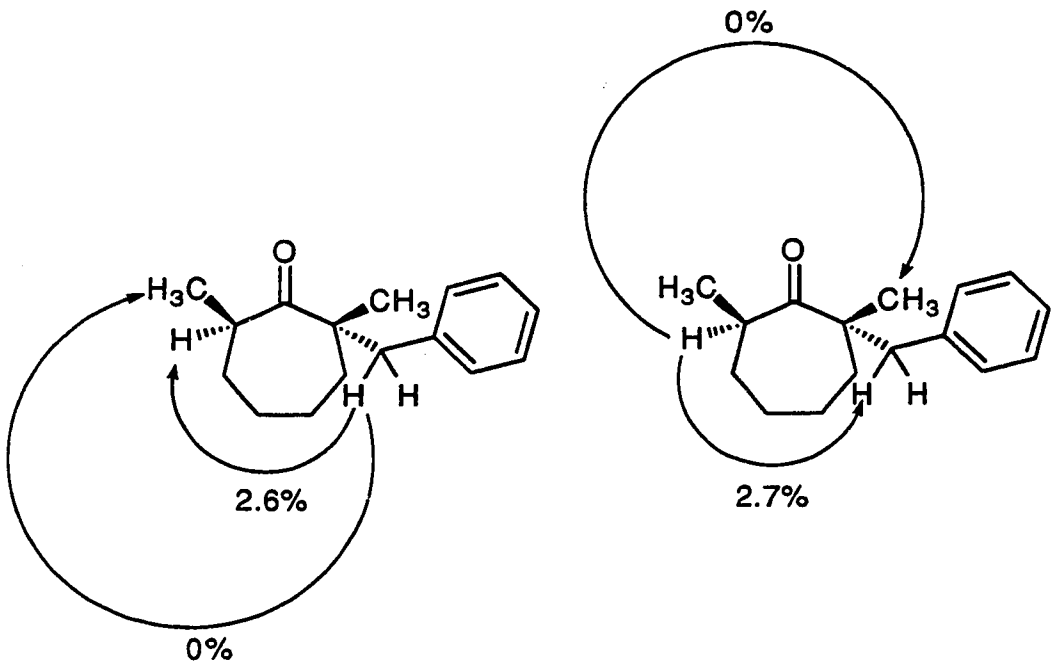
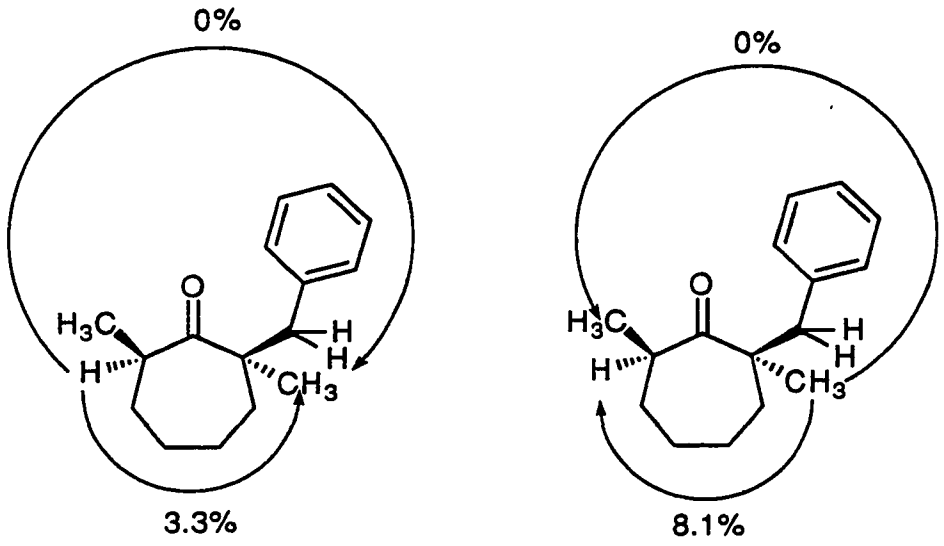
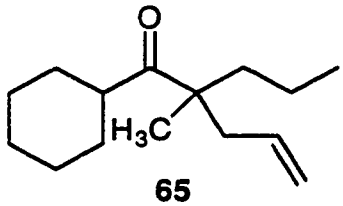


Figure 1-5 The NOE results of compound **63**



For compound **64**, the high resolution mass spectrum displayed a molecular ion peak at m/z 202.1351 in agreement with the molecular formula $C_{14}H_{18}O$. The infrared spectrum showed a strong absorption at 1717 cm^{-1}, diagnostic of the carbonyl group. No nitrile absorption band was found. The ^{13}C NMR APT spectrum displayed two sets of signals for two stereoisomers. Once again, the ratio of two isomers was obtained from the integration of the related peaks in the ^{1}H NMR spectrum. In the spectrum, there were four doublets displayed at δ 2.95 (J = 13 Hz), 2.83 (J = 14 Hz), 2.63 (J = 13 Hz) and 2.53 (J = 14 Hz) corresponding to the benzylic protons of two stereoisomers. Two singlets at δ 1.01 and 1.09 were assigned to the C-2 methyl group. The C-5 methyl group appeared as two doublets at δ 0.93 and 1.12 with the same coupling constant (J = 7 Hz). The stereochemistry of the diastereomers remains to be determined.

The reductive alkylation of cyano ketone **50** with lithium naphthalenide and allyl bromide proceeded equally well to give product **65** in 90% yield (Entry 15).



65

The high resolution mass spectrum of **65** showed a molecular ion peak at m/z 222.0154 corresponding to the molecular formula $C_{15}H_{26}O$. The infrared spectrum displayed a carbonyl absorption band at 1699 cm^{-1}. A carbon-carbon double bond absorption at 1639 cm^{-1} along with the lack of the nitrile absorption around 2200 cm^{-1} indicated replacement of the cyano group by the allyl group. There were 15 carbon signals displayed in the ^{13}C NMR APT spectrum, including one carbonyl signal at δ 218.2 and two vinylic carbon signals at δ 134.5 and 117.6. In the ^{1}H NMR spectrum, the allylic protons were displayed at δ 2.43 (dd, J_1 = 13 Hz, J_2 = 7 Hz) and 2.21 (dd, J_1 = 13 Hz, J_2 = 7.5 Hz). Two terminal vinylic protons appeared as two multiplets at δ 5.06 and 5.00. The singnal of the non-terminal vinylic proton was displayed at δ 5.65 (dm, J = 18 Hz). The α methyl group appeared as a singlet at δ 1.10, while the terminal methyl group was shown as a triplet at δ 0.85 (J = 7 Hz).

IV. Conclusion

As illustrated by the experimental results described above, lithium naphthalenide induced reductive alkylation of α-cyano ketones can be applied as an efficient method for regiocontrol in ketone α,α-dialkylation. The cyano

group of the α-cyano ketone system has been proven to be an effective directing group for the consecutive incorporation of two α substituents with complete regiocontrol. This salient feature, coupled with the operational simplicity and the high accessibility of starting substrates makes this method an attractive alternative for a frequently encountered synthetic process.

The usefulness of the reductive alkylation process is further demonstrated in the next chapter in which a convenient synthetic approach leading to polycyclic systems is described. In this approach, the cyano group serves effectively as an activating group to facilitate the Diels-Alder cycloaddition, as well as a latent alkyl group for the introduction of an angular substituent.

Experimental

General

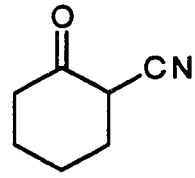
Elemental analyses were carried out using a Perkin 240-B for C and H detection. Fourier transform infrared spectra (IR) were recorded on a Nicolet 7-199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnatic resonance (^{1}H NMR) spectra were recorded using the following spectrometers: Bruker 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 a Bruker AM-300 (75 MHz) NMR spectrometer 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 signal 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 10-15 minutes prior to use. High resolution electron impact (EI) mass spectra (HRMS) were determined using a AEI Kratos MS-50 mass

spectrometer. Spectral data were recorded as m/z values. X-ray analyses were performed by the structure determination laboratory of this department. Concentrations of solvents 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. Products were purified by flash chromatography, developed by Still,[45] using silica gel 60 (Merck, 230-400 mesh) or by distillation using a Kugelrohr apparatus. Reactions were monitored by thin layer chromatography performed on Merck aluminum-backed plates precoated with silica gel 60 GF_{254}, 0.2 mm thickness. 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. Solvents and reagents were purified prior to use as follows. Absolute ethanol was obtained from 98% or higher purity commercially available reagent by distillation from magnesium turnings. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium-benzophenone. Toluene was freshly distilled from sodium. Dichloromethane, benzene, pyridine and diisopropylamine were distilled from calcium hydride. Purified argon (99.8%) was passed through 4 Å molecular sieves. Skelly B and ethyl acetate used for chromatography were distilled at atmospheric pressure prior to their use.

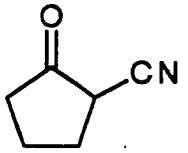
2-Cyanocyclohexanone (21)



21

Under an argon atmosphere, a solution of pimelonitrile (0.5 g, 0.53 mL, 4.1 mmol) in THF (10 mL) was added dropwise over a 30 minutes period to a suspension of sodium hydride (95% purity, 0.31 g, 12.3 mmol) and *N*-methylaniline (1.32 mL, 12.3 mmol) in THF (30 mL). The mixture was refluxed for 2 hours. The resulting dark yellow suspension was cooled and then acidified with aqueous concentrated HCl and diluted with water (15 mL). The resulting solution was extracted with ether (2 x 50 mL). The organic extracts were washed with water (2 x15 mL) and aqueous saturated sodium chloride solution (1 x 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product (0.64 g), a dark orange oil, was subjected to flash chromatography on silica gel, eluting with ethyl acetate-Skelly B (1 : 3), to afford **21** as a colorless oil (0.453 g, 3.66 mmol, 90%): IR (CH_2Cl_2, cast): 1722 (C=O), 2250 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 3.52 (dd, J_1 = 13 Hz, J_2 = 7 Hz, 1H, **CH**CN), 2.65 (m, 1H, HC**H**C=O), 2.52-2.28 (m, 2H), 2.15-1.93 (m, 3H), 1.90-1.58 (m, 2H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 200.5 (p), 116.6 (p), 43.3 (ap), 40.6 (p), 32.1 (p), 26.8 (p), 23.6 (p); HRMS M^+: 123.0682 (calcd. for C_7H_9ON: 123.0685).

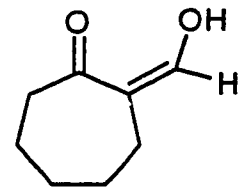
2-Cyanocyclopentanone (22)



22

A solution of adiponitrile (0.2 g, 0.21 mL, 1.85 mmol) in THF (5 mL) was added dropwise over a 20 minutes period to a suspension of sodium hydride (95% purity, 0.14 g, 5.55 mmol) and *N*-methylaniline (0.6 mL, 5.55 mmol) in THF (15 mL) under argon. The mixture was refluxed for 2 hours. The resulting dark yellow suspension was cooled and then acidified with aqueous concentrated HCl and diluted with water (10 mL). The mixture was extracted with ether (2 x 25 mL). The organic extracts were washed with water (2 x 15 mL) and saturated aqueous sodium chloride solution (1 x 15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give a dark brown oil (0.23 g). The crude residue was subjected to flash chromatography, eluting with ethyl acetate-Skelly B (1 : 5), to afford **22** (0.171g, 1.57 mmol, 85%): IR (CH_2Cl_2, cast): 1757 (C=O), 2245 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 3.17 (dd, J_1 = 18 Hz, J_2 = 8 Hz, 1H, **CH**CN), 2.50 (m, 1H, **H**CHC=O), 2.39 (m, 1H, HC**H**C=O), 2.30-2.09 (m, 2H), 2.03-1.91 (m, 2H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 207.0 (p), 116.6 (p), 39.2 (ap), 36.4 (p), 28.4 (p), 21.1 (p); HRMS M^+: 109.0514 (calcd. for C_6H_7ON: 109.0517). Anal. calcd. for C_6H_7ON: C 66.06%, H 6.39%; found: C 66.17%, H 6.28%.

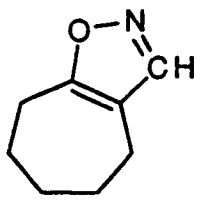
2-Hydroxymethylenecycloheptanone (24)



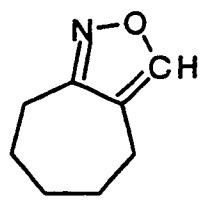
24

Ethyl formate (7.2 mL, 89.15 mmol) was added to a suspension of sodium hydride (95% purity, 0.45 g, 17.38 mmol) in THF (50 mL) at 0°C under an argon atmosphere. To this mixture, a solution of cycloheptanone (1 g, 8.92 mmol) and ethanol (95%, 4 drops) in THF (10 mL) was added dropwise over a period of 10 minutes. The ice bath was removed and the mixture was stirred at room temperature for an additional 8 hours then quenched with water (20 mL) and acidified with aqueous 2N HCl (30 mL). The resulting mixture was extracted with ether (2 x 90 mL). The organic extracts were combined and washed with saturated sodium chloride solution (2 x 20 mL), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a red oil (2.5 g). The crude product was purified by flash chromatography on silica gel. Elution with ethyl acetate-Skelly B (1 : 20) afforded **24** as a pale red oil (1.124 g, 8.02 mmol, 90%): IR (CH_2Cl_2, cast): 3252 (OH), 1639 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 14.65 (d, J = 8 Hz, 1H, C=CHO**H**), 7.58 (d, J = 8 Hz, 1H, C=C**H**OH), 2.50 (m, 1H, **H**CHC=O), 2.20 (m, 1H, HC**H**C=O), 1.76-1.50 (m, 8H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.3 (p), 171.0 (ap), 114.7 (p), 42.0 (p), 31.7 (p), 29.8 (p), 29.0 (p), 24.6 (p); HRMS M^+: 140.0836 (calcd. for $C_8H_{12}O_2$: 140.0839).

9-Aza-10-oxabicyclo[5.3.0]deca-1(7),8-diene (25) and 8-aza-9-oxabicyclo[5.3.0]deca-1(10),7-diene (26)



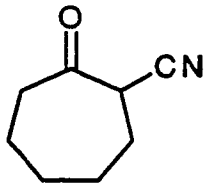
25



26

Potassium carbonate (0.987 g, 7.14 mmol) and hydroxylamine hydrochloride (0.745 g, 10.71 mmol) were added to a solution of **24** (1 g, 7.14 mmol) in absolute ethanol (20 mL) at 0°C under argon. The thick pale yellow solution was refluxed for 6 hours, cooled to room temperature and slowly quenched with aqueous 2N HCl (15 mL). The resulting solution was extracted with dichloromethane (2 x 40 mL). The organic extracts were washed with saturated sodium chloride solution (2 x 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product (1.64 g) was purified by Kugelrohr distillation at 54°C/5 mm of Hg to afford **25** as a colorless oil (0.69 g, 5.0 mmol, 70%). Further distillation at 70°C gave **26** as a pale yellow oil (0.19 g, 1.4 mmol, 20%). For compound **25**: IR (CH_2Cl_2, cast): 1633 (N=C), 960 cm^{-1} (N-O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (s, br, 1H, CC**H**=N), 2.69 (m, 2H), 2.32 (m, 2H), 1.50 (m, 6H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 169.6 (p), 151.0 (ap), 115.2 (p), 29.9 (p), 27.8 (p), 27.0 (p), 25.3 (p), 22.7 (p); HRMS M^+: 137.0846 (calcd. for $C_8H_{11}NO$: 137.0849). For compound **26**: IR (CH_2Cl_2, cast): 1613 (N=C), 936 cm^{-1} (N-O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H, C=C**H**O), 2.62 (m, 2H), 2.39 (m, 2H), 1.68 (m, 6H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 164.1 (p), 153.2 (ap), 119.7 (p), 31.4 (p), 28.6 (p), 26.8 (p), 26.5 (p), 22.3 (p); HRMS M^+: 137.0851 (calcd. for $C_8H_{11}NO$: 137.0849).

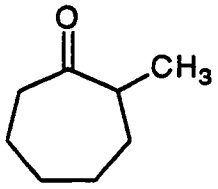
2-Cyanocycloheptanone (23)



23

Absolute ethanol (15 mL) was added dropwise to a dry round-bottomed flask containing sodium (0.11 g, 4.82 mmol) under an argon atmosphere at 0°C. The suspension was stirred for 30 minutes to generate sodium ethoxide. Isoxazole **25** (0.33 g, 2.41 mmol) in absolute ethanol (5 mL) was added dropwise to the ethoxide solution. The resulting mixture was refluxed for 1 hour, cooled to room temperature and acidified with aqueous 2N HCl. The solution was then extracted with dichloromethane (2 x 40 mL). The organic extracts were washed with saturated sodium chloride solution (1 x 30 mL), dried over magnesium sulfate and concentrated to give a pale yellow oil (0.57 g). The residue was subjected to Kugelrohr distillation (67°C/5 mm of Hg) to yield **23** as a colorless oil (0.297 g, 2.16 mmol, 90%): IR (CH_2Cl_2, cast): 1719 (C=O), 2248 cm^{-1} (CN); ^1H NMR (300 MHz, C_6D_6): δ 2.80 (dd, J_1 = 12 Hz, J_2 = 5 Hz, 1H, **CH**CN), 2.09 (m, 1H, **H**CHC=O), 1.99 (m, 1H, HC**H**C=O), 1.35-1.19 (m, 4H), 1.05-0.90 (m, 4H); ^{13}C NMR APT (75 MHz, C_6D_6): δ 202.1 (p), 117.6 (p), 44.4 (ap), 41.9 (p), 28.9 (p), 28.6 (p), 27.5 (p), 23.2 (p); HRMS M^+: 137.0842 (calcd. for $C_8H_{11}ON$: 137.0849).

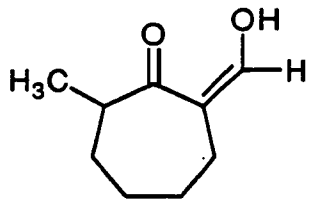
2-Methylcycloheptanone (29)



29

Diisopropylamine (4.997 mL, 0.036 mol) was dissolved in THF (23 mL) and cooled to 0°C with an ice-water bath with stirring under an argon atmosphere. *n*-Butyllithium (2.5 M in THF, 14.3 mL, 0.036 mol) was added dropwise over a 20 minute period followed by cooling to -78°C. A solution of cycloheptanone (2 g, 0.018 mol) in THF (10 mL) was added dropwise over 30 minutes. The resulting solution was stirred for another 30 minutes followed by rapid addition of methyl iodide (2.2 mL, 0.036 mol). After 5 minutes, the mixture was allowed to warm to room temperature. After 48 hours, the reaction mixture was quenched with water (20 mL) and extracted with ether (2 x 60 mL). The organic layers were washed with water (2 x 25 mL) and saturated sodium chloride solution (1 x 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was subjected to flash chromatography on silica gel, eluting with ethyl acetate-Skelly B (1 : 20) to give **29** (1.46 g, 0.012 mol, 65%) along with a 20% recovery of starting material. For compound **29**: IR (CH_3Cl, cast): 1705 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.65 (m, 1H, $CHCH_3$), 2.45 (m, 2H, $CH_2C=O$), 1.90-1.52 (m, 5H), 1.50-1.23 (m, 3H), 1.05 (d, J = 7 Hz, 3H, CH_3); HRMS M^+: 126.1201 (calcd. for $C_8H_{14}O$: 126.1198).

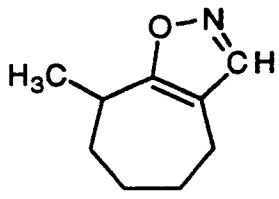
2-Hydroxymethylene-7-methylcycloheptanone (30)



30

Compound **30** was prepared from ketone **29** by using the same formylation process described previously for the preparation of **24**. Treatment of **29** (1.419 g, 11.26 mmol) with ethyl formate (9.1 mL, 112.6 mmol), sodium hydride (95% purity, 0.57 g, 22.52 mmol) and ethanol (95%, 3 drops) in THF (60 mL) for 10 hours at room temperature afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **30** as a reddish oil (1.387 g, 9 mmol, 80%): IR (CH_2Cl_2, cast): 3250 (OH), 1700 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 14.54 (d, J = 9 Hz, 1H, C=CHOH), 7.37 (d, J = 9 Hz, 1H, C=CHOH), 2.69 (m, 1H, $CHCH_3$), 2.32-2.14 (m, 2H), 1.93-1.80 (m, 2H), 1.73-1.15 (m, 4H), 1.08 (d, J = 7 Hz, 3 Hz, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 207.9 (p), 167.0 (ap), 114.6 (p), 44.5 (ap), 33.6 (p), 30.8 (p), 29.9 (p), 28.5 (p), 16.3 (ap); HRMS M^+: 154.0992 (calcd. for $C_9H_{14}O_2$: 154.0989).

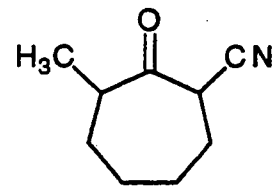
9-Aza-2-methyl-10-oxabicyclo[5.3.0]deca-1(7),8-diene (31)



31

The procedure described previously for the preparation of isoxazole **25** was applied. Treatment of compound **30** (1.287 g, 8.35mmol) with potassium carbonate (1.15 g, 8.35 mmol) and hydroxylamine hydrochloride (0.87 g, 12.5 mmol) in absolute ethanol (20 mL) at refluxing temperature for 2 hours, followed by acidic work-up, extraction and concentration afforded a dark brown oil. Flash chromatography of the crude product on silica gel, eluting with ethyl acetate-Skelly B (1 : 25), gave isoxazole **31** (1.01 g, 6.69 mmol, 80%): IR (CH_2Cl_2, cast): 1621 (N=C), 990 cm^{-1} (N-O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H, CC**H**=N), 3.05 (m, 1H, CH_3C**H**), 2.46 (m, 2H), 2.05-1.79 (m, 2H), 1.75-1.47 (m, 4H), 1.32 (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 173.0 (p), 151.8 (ap), 114.4 (p), 34.2 (p), 33.4 (ap), 28.0 (p), 27.6 (p), 23.2 (p), 17.9 (ap); HRMS M^+: 151.0997 (calcd. for $C_9H_{13}ON$: 151.1001).

2-Cyano-7-methylcycloheptanone (27)

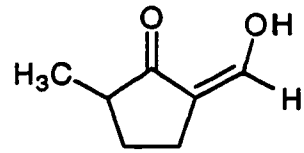


27

The procedure used for the preparation of cyano ketone **23** was applied. Compound **31** (1 g, 6.62 mmol) was added to a solution of sodium ethoxide (2 equivalents) in ethanol (40 mL) and refluxed for 1 hour. After acidic work-up, extraction and concentration, a yellow residue was obtained (1.6 g). This crude product was subjected to flash chromatography. Elution with ethyl acetate-Skelly B (1 : 8) afforded **27** as an inseparable 1 : 1 mixture of two

diastereomers (0.91 g, 5.96 mmol, 90%): IR (mixture, CH_2Cl_2, cast): 1715 (C=O), 2247 cm^{-1} (CN); ^1H NMR (mixture, 400 HMz, $CDCl_3$): δ 3.74 (t, J = 5 Hz, 0.5H CHCN), 3.64 (dd, J_1 = 11 Hz, J_2 = 5 Hz, 0.5H, CHCN), 2.75 (m, 1H, $CHCH_3$), 2.19-2.00 (m, 1H), 1.98-1.62 (m, 5.5H), 1.54-1.34 (m, 1.5H), 1.10 (d, J = 7 Hz, 1.5H, CH_3), 1.05 (d, J = 6.5 Hz, 1.5H, CH_3); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 205.6 (p), 205.2 (p), 117.8 (p), 117.7 (p), 46.0 (ap), 45.8 (ap), 44.2 (ap), 42.9 (ap), 32.6 (p), 32.0 (p), 30.0 (p), 28.7 (p), 28.1 (p), 27.1 (p), 27.0 (p), 26.3 (p), 17.8 (ap), 17.1 (ap); HRMS (mixture) M^+: 151.0998 (calcd. for $C_9H_{13}ON$: 151.1001).

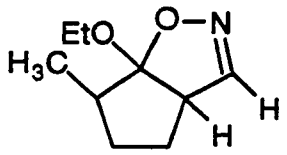
2-Hydroxymethylene-5-methylcyclopentanone (32)



32

Treatment of 2-methylcyclopentanone (2 g, 0.0204 mol) with ethyl formate (16 mL, 0.204 mol), sodium hydride (95% purity, 1.02 g, 0.0408 mol) and ethanol (95%, 4 drops) in THF (60 mL) at room temperature for 10 hours afforded, after flash chromatography, compound **32** as a dark yellow oil (2.05 g, 0.0163 mol, 80%): IR (CH_2Cl_2, cast): 3200 (OH), 1721 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 14.67 (d, J = 8 Hz, 1H, C=CHOH), 7.46 (d, J = 8 Hz, 1H, C=CHOH), 2.40 (m, 1H $CHCH_3$), 2.24 (m, 1H), 2.03-1.42 (m, 3H), 1.06 (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): 204.7 (p), 173.6 (ap), 119.7 (p), 45.2 (ap), 37,6 (p), 31.5 (p), 17.5 (ap); HRMS M^+ 126.0832 (calcd. for $C_7H_{10}O_2$: 126.0829).

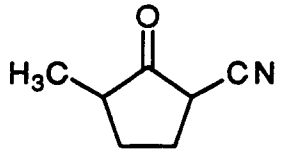
7-Aza-1-ethoxy-2-methyl-8-oxabicyclo[3.3.0]oct-6-ene (33)



33

Potassium carbonate (3.29 g, 23.8 mmol) and hydroxylamine hydrochloride (2.48 g, 35.7 mmol) were added to a solution of **32** (3 g, 23.8 mmol) in absolute ethanol (50 mL) at 0°C under an argon atmosphere. The solution was refluxed for 6 hours then cooled to room temperature and slowly quenched with aqueous 2N HCl (40 mL). The resulting mixture was extracted with dichloromethane (3 x 50 mL). The organic extracts were washed with saturated sodium chloride (2 x 20 mL), dried with anhydrous magnesium sulfate, filtered and concentrated to give a dark yellow residue. The crude product was subjected to flash chromatography, eluting with ethyl acetate-Skelly B (1 : 10), to yield **33** (2.6 g, 15.5 mmol, 65%) as a mixture of two inseparable stereoisomers (1 : 1): IR (mixture, CH_2Cl_2, cast): 1731 (N=C), 1157 cm^{-1} (C-O-C); ^1H NMR (mixture, 300 MHz, $CDCl_3$): δ 7.14 (m, 1H, CC**H**=N), 3.52 (q, J = 7.5 Hz, 1H, CH_3CH_2O), 3.35 (q, J = 6.5 Hz, 1H, CH_3CH_2O), 2.45 (m, 1H), 2.25 (m, 1H), 2.20-2.01 (m, 2H), 1.79-1.65 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H, CH_3CH_2O), 1.10 (d, J = 6.5 Hz, 1.5H, CH_3CH), 1.00 (d, J = 7 Hz, 1.5H, CH_3CH); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 150.4 (ap), 150.3 (ap), 121.2 (p), 119.3 (p), 59.5 (p), 59.5 (p), 52.5 (ap), 51.3 (ap), 44.1 (ap), 40.3 (ap), 31.0 (p), 30.9 (p), 27.5 (p), 26.4 (p), 15.4 (ap), 15.3 (ap), 14.9 (ap), 12.5 (ap); HRMS (mixture) M^+: 169.1101 (calcd for $C_9H_{15}O_2N$: 169.1105).

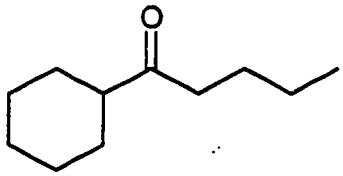
2-Cyano-5-methylcyclopentanone (28)



28

Absolute ethanol (8 mL) was dropwise added to a dry round-bottomed flask containing sodium (27.22 mg, 1.183 mmol) under argon at 0°C. The suspension was stirred for 20 minutes to form sodium ethoxide and then a solution of **33** (100 mg, 0.592 mmol) in absolute ethanol (4 mL) was dropwise added. The mixture was refluxed for 3 hours, cooled to room temperature and quenched with aqueous 2N HCl (10 mL). The solution was extracted with dichloromethane (2 x 20 mL). The extracts were washed with saturated sodium chloride solution (1 x 15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography, eluting with ethyl acetate-Skelly B (1 : 4), to give **28** (43.67 mg, 0.355 mmol, 60%) as a 1.3 : 1 mixture of two inseparable diastereomers: IR (mixture, CH_2Cl_2, cast): 1711 (C=O), 2247 cm^{-1} (CN); ^1H NMR (mixture, 200 MHz, $CDCl_3$): for the major stereoisomer: δ 3.13 (dd, J_1 = 10 Hz, J_2 = 5 Hz, 0.57H, CHCN), 1.18 (d, J = 7 Hz, 1.7H, CH_3); for the minor stereoisomer: δ 3.30 (t, J = 8 Hz, 0.43H, CHCN), 1.22 (d, J = 7.5, 1.3H, CH_3); for the mixture: δ 2.57-2.05 (m, 2.7H), 1.62-1.35 (m, 1.3H); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 208.7 (p), 206.4 (p), 116.7 (p), 116.4 (p), 43.5 (ap), 42.3 (ap), 38.6 (ap), 38.2 (ap), 29.8 (p), 29.4 (p), 26.6 (p), 25.9 (p), 15.0 (ap), 14.4 (ap); HRMS (mixture) M^+: 123.0686 (calcd. for C_7H_9ON: 123.0685).

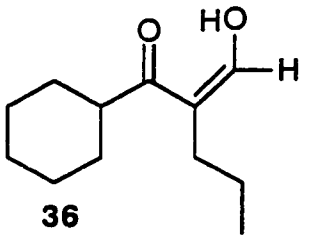
Butyl cyclohexyl ketone (35)



35

To a stirring solution of cyclohexanecarboxylic acid (2.5 g, 19.5 mmol) in THF (120 mL) at 0°C under an argon atmosphere, *n*-butyllithium (1.6 M in THF, 48 mL, 78.02 mmol) was added. The resulting solution was stirred at 0°C for 2 hours, followed by rapid addition of trimethylsilyl chloride (45.5 mL, 380 mmol). The reaction mixture was allowed to warm to room temperature and then quenched with aqueous 1N HCl (100 mL). The solution was stirred at room temperature for 30 minutes and extracted with ether (2 x 100 mL). The organic extracts were combined, washed with water (3 x 50 mL) and saturated sodium chloride solution (50 mL), dried over anhydrous magnesium sulfate, and concentrated to give a yellow oil (4 g). Flash chromatography of the crude product, eluting with ethyl acetate-Skelly B (1 : 20), afforded **35** as a colorless oil (2.95, 17.56 mmol, 90%): IR (CH_2Cl_2, cast): 1780 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (t, J = 7 Hz, 2H, CH_2C=O), 2.29 (m, 1H, CHC=O), 1.65 (m, 4H), 1.52 (m, 1H), 1.40 (m, 3H), 1.26-0.95 (m, 6H), 0.85 (t, J = 8 Hz, 3H, CH_2CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 214.3 (p), 50.8 (ap), 40.3 (p), 28.5 (p), 25.9 (p), 25.9 (p), 25.7 (p), 22.4 (p), 13.9 (ap); HRMS M^+: 168.1513 (calcd. for $C_{11}H_{20}O$: 168.1512).

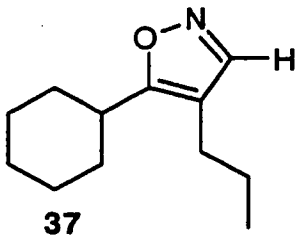
Cyclohexyl (1-hydroxymethylene)butyl ketone (36)



36

Under an argon atmosphere, treatment of ketone **35** (1.337 g, 7.96 mmol) with ethyl formate (5.43 mL, 63.7 mmol), sodium hydride (95% purity, 0.402 g, 15.9 mmol) and ethanol (95%, 3 drops) in THF (60 mL) at room temperature for 8 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 20), compound **36** as a red oil (1.32 g, 6.76 mmol, 85%): IR (CH_3Cl, cast): 3400 (OH), 1697 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 13.63 (s, br, 1H, C=CHO**H**), 7.40 (s, br, 1H, C=C**H**OH), 2.48 (m, 1H, C**H**C=O), 2.30 (t, J = 7.5 Hz, 2H, CH_2C=CHOH), 1.98-1.54 (m, 8H), 1.46-0.92 (m, 4H), 0.83 (t, J = 7 Hz, 3H, CH_3); HRMS M^+: 196.1458 (calcd. for $C_{12}H_{20}O_2$: 196.1461).

4-Butyl-5-cyclohexylisoxazole (37)

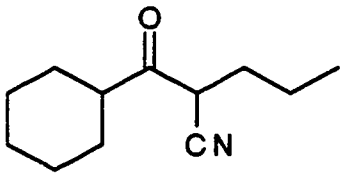


37

Hydroxylamine hydrochloride (0.76 g, 10.96 mmol) was added to a solution of **36** (1.074 g, 5.48 mmol) in glacial acetic acid (40 mL). The resulting solution

was refluxed for 5 hours, then cooled to room temperature and diluted with water (50 mL). The mixture was extracted with ether (2 x 70 mL). The organic extracts were washed with water (2 x 20 mL) and saturated sodium chloride solution (1 x 30 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with ethyl acetate-Skelly B (1 : 30) gave **37** as a pale yellow oil (0.95 g, 4.93 mmol, 90%): IR (CH_2Cl_2, cast): 1705, 1622 (N=C), 938 cm^{-1} (N-O); ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, CC**H**=N), 2.75 (m, 1H, C**H**C-O), 2.33 (t, J = 7.5 Hz, 2H, CH_2C=C), 1.94-1.65 (m, 6H), 1.50-1.47 (m, 3H), 1.44-1.23 (m, 3H), 0.95 (t, J = 7 Hz, 3H, CH_3CH_2); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 171.4 (p), 163.2 (ap), 114.4 (p), 35.9 (ap), 31.1 (p), 26.3 (p), 25.8 (p), 25.5 (p), 24.3 (p), 13.7 (ap); HRMS M^+: 193.1465 (calcd. for $C_{12}H_{19}ON$: 193.1468).

(1-Cyano)butyl cyclohexyl ketone (34)

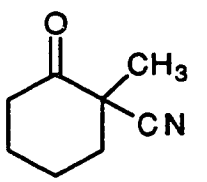


34

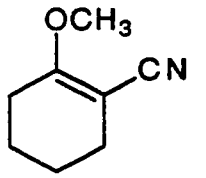
Absolute ethanol (30 mL) was dropwise added to a flask containing sodium (0.24 g, 10.36 mmol) at 0°C under argon. The suspension was stirred for 30 minutes until sodium was completely consumed. A solution of **37** (1 g, 5.18 mmol) in absolute ethanol (6 mL) was added to the ethoxide solution. The reaction mixture was refluxed for 1 hour, cooled to room temperature and acidified with aqueous 2N HCl (30 mL). The mixture was extracted with dichloromethane (2 x 50 ml), washed with saturated sodium chloride solution (2

x 20 ml), dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product (1.54 g) was subjected to flash chromatography, eluting with ethyl acetate-Skelly B (1 : 10), to afford **34** as a colorless oil (0.70 g, 3.63 mmol, 70%): IR (CH_2Cl_2, cast): 1721 (C=O), 2240 cm^{-1} (CN); ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, J = 7 Hz, 1H, CHCN), 2.82 (m, 1H, CHC=O), 1.92-1.86 (m, 2H), 1.85-1.76 (m, 4H), 1.72 (m, 1H), 1.59-1.42 (m, 3H), 1.39-1.17 (m, 4H), 0.97 (t, J = 8 Hz, 3H, CH_3CH_2); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.9 (p), 117.7 (p), 49.2 (ap), 42.2 (ap), 30.9 (p), 28.7 (p), 28.4 (p), 25.6 (p), 20.4 (p), 13.4 (ap); HRMS M^+: 193.1466 (calcd. for $C_{12}H_{19}ON$: 193.1468). Anal. calcd. for $C_{12}H_{19}ON$: C 74.61%, H 9.84%; found: C 74.77%, H 10.02%.

2-Cyano-2-methylcyclohexanone (38) and (2-methoxy)cyclohexenecarbonitrile (39)



38



39

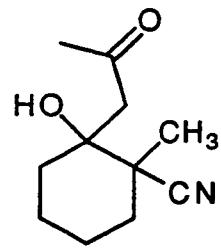
To a dry flask containing lithium hydride (63.6 mg, 8 mmol), a solution of cyano ketone **21** (0.246 g, 2 mmol) in THF (10 mL) was added at room temperature under an argon atmosphere. The suspension was stirred for 15 minutes and then methyl iodide (0.5 mL, 8 mmol) was added. The mixture was stirred at room temperature for 24 hours. The resulting pale yellow suspension was cooled to 0°C and slowly quenched with water (10 mL). The resulting solution was extracted with ether (2 x 20 mL). The organic extracts were combined, washed with saturated sodium chloride solution (15 mL), dried with anhydrous

magnesium sulfate, filtered and concentrated in vacuo to afford a yellow residue (0.28 g). The crude products were subjected to flash chromatography on silica gel, eluting with ethyl acetate-Skelly B (1 : 6), to give **38** (164.4 mg, 1.2 mmol, 60%) as a colorless oil and **39** (82.2 mg, 0.6 mmol, 30%) as a pale yellow oil. This procedure was also used for the preparation of other cyclic monoalkylated α-cyano ketones described in this chapter.

For compound **38**: IR (CH_2Cl_2, cast): 1792 (C=O), 2232 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 2.85 (m, 1H, CH_2C=O), 2.52 (m, 1H, CH_2C=O), 2.32 (m, 1H), 2.20-1.95 (m, 2H), 1.87-1.62 (m, 3H), 1.43 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.0 (p), 120.7 (p), 46.4 (p), 40.4 (p), 38.9 (p), 27.8 (p), 22.3 (p), 20.4 (ap); HRMS M^+: 137.0844 (calcd. for $C_8H_{11}ON$: 137.0849).

For compound **39**: IR (CH_2Cl_2, cast): 2202 (CN), 1239 (C-O-C), 1635 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, CH_3), 2.35-2.20 (m, 4H), 1.87-1.53 (m, 4H); HRMS M^+: 137.0838 (calcd. for $C_8H_{11}ON$: 137.0849).

1-(1-Hydroxy-2-cyano-2-methyl)cyclohexylpropan-2-one (40)



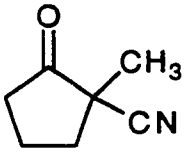
40

To a flask containing potassium carbonate (0.62 g, 4.47 mmol), was added a solution of **21** (0.11 g, 0.89 mmol) in acetone (10 mL). The suspension was stirred for 15 minutes at room temperature and then methyl iodide was added

(0.28 mL, 4.47 mmol). The resulting mixture was stirred at room temperature for 11 hours and slowly quenched with aqueous 2N HCl (10 mL). The solution was extracted with ether (2 x 20 mL). The organic extracts were washed with saturated sodium chloride solution (1 x 15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated. The crude residue was subjected to flash chromatography. Elution with ethyl acetate-Skelly B (1 : 10) afforded **40** (29.64 mg, 0.152 mmol, 17%) as a single diastereomer along with **39** (36.76 mg, 0.268 mmol, 30%) as the major product . No attempt was made to assign the stereochemistry of **40**.

For compound **40**: IR (CH_2Cl_2, cast): 3743 (OH), 2232 (CN), 1701 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 2.95 (d, J = 17 Hz, 1H, CH_2C=O), 2.80 (d, J = 17 Hz, 1H, CH_2C=O), 2.25 (s, 3H, CH_3C=O), 1.97-1.72 (m, 2H), 1.70-1.45 (m, 6H), 1.32 (s, 3H, CH_3CCN); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 211.6 (p), 116.4 (p), 72.5 (p), 47.9 (p), 34.5 (p), 33.0 (p), 32.4 (p), 32.4 (ap), 22.9 (p), 21.1 (ap), 20.3 (p); HRMS M^+: 195.1258 (calcd. for $C_{11}H_{17}NO_2$: 195.1253).

2-Cyano-2-methylcyclopentanone (41)

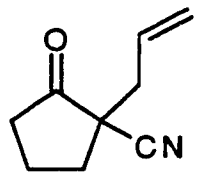


41

A suspension of cyano ketone **22** (0.13 g, 1.19 mmol), lithium hydride (37.9 mg, 4.77 mmol) and methyl iodide (0.29 mL, 4.77 mmol) in THF (7 mL) was stirred at room temperature for 20 hours to afford, after flash chromatography (ethyl

acetate-Skelly B 1 : 20), compound **41** as a colorless oil (0.125 g, 1.01 mmol, 85%): IR (CH_2Cl_2, cast): 1753 (C=O), 2241 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 2.55-2.40 (m, 2H, CH_2C=O), 2.39-2.30 (m, 1H), 2.22-1.89 (m, 3H), 1.43 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 209.5 (p), 119.8 (p), 43.7 (p), 36.4 (p), 36.0 (p), 20.4 (p), 19.1 (ap); HRMS M^+: 123.0683 (calcd. for C_7H_9ON: 123.0685). Anal. calcd. for C_7H_9ON: C 68.29%, H 7.32%; found: C 68.46%, H 7.63%.

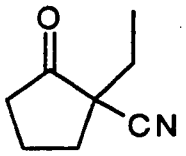
2-Allyl-2-cyanocyclopentanone (42)



42

Allyl bromide (0.15 mL, 1.69 mmol) was added to a mixture of **22** (46 mg, 0.42 mmol) and lithium hydride (13.42 mg, 1.69 mmol) in THF (5 mL). The suspension was stirred at room temperature for 30 hours to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 15), compound **42** as a pale yellow oil (50.3 mg, 0.34 mmol, 80%): IR (CH_2Cl_2, cast): 2237 (CN), 1752 (C=O), 1653 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (dm, J = 20 Hz, 1H, CH=CH_2), 5.27 (dm, J = 7 Hz, 1H, CH=CH_2), 5.23 (dm, J = 20 Hz, 1H, CH=CH_2), 2.62 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 1.5 Hz, 1H, CH_2CH=CH_2), 2.57-2.24 (m, 4H), 2.22-1.95 (m, 3H); ^{13}C NMR APT (75 MHz, $CDCl_3$); δ 208.8 (p), 130.7 (ap), 120.9 (p), 118.7 (p), 48.3 (p), 37.9 (p), 36.6 (p), 33.5 (p), 19.2 (p); HRMS M^+: 149.0838 (calcd. for $C_9H_{11}ON$: 149.0841).

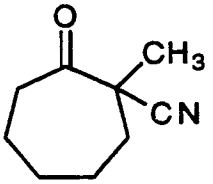
2-Cyano-2-ethylcyclopentanone (43)



43

Ethyl iodide (0.45 mL, 5.61 mmol) was added to a mixture of **22** (0.153 g, 1.4 mmol) and lithium hydride (44.63 mg, 5.61 mmol) in THF (10 mL). The suspension was refluxed for 12 hours. Flash chromatography on silica gel, eluting with ethyl acetate-Skelly B (1 : 5), afforded **43** as a colorless oil (0.135 g, 0.98 mmol, 70%): IR (CH_2Cl_2, cast): 1752 (C=O), 2237 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (m, 2H, CH_2C=O), 2.36 (m, 1H), 2.19-1.97 (m, 3H), 1.92 (dm, J = 13 Hz, 1H, CH_2CH_3), 1.61 (dm, J = 13 Hz, 1H, CH_2CH_3), 1.07 (t, J = 8 Hz, 3H, CH_2CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 209.4 (p), 118.9 (p), 49.4 (p), 36.5 (p), 33 9 (p), 27.2 (p), 19.2 (p), 9.4 (ap); HRMS M^+: 137.0856 (calcd. for $C_8H_{11}ON$: 137.0849).

2-Cyano-2-methylcycloheptanone (44)

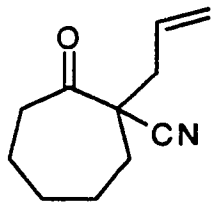


44

Methyl iodide (0.48 mL, 7.77 mmol) was added to a mixture of **23** (0.266 g, 1.94 mmol) and lithium hydride (61.74 mg, 7.77 mmol) in THF (10 mL). The mixture

was stirred for 20 hours at room temperature to give, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **44** as a colorless oil (0.235, 1.55 mmol, 80%): IR (CH_2Cl_2, cast): 1716 (C=O), 2239 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 2.75 (m, 1H, CH_2C=O), 2.62 (m, 1H, CH_2C=O), 2.15 (m, 1H), 2.01-1.72 (m, 4H), 1.70-1.65 (m, 2H), 1.52 (s, 3H, CH_3), 1.45 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 205.4 (p), 121.1 (p), 49.3 (p), 40.5 (p), 37.5 (p), 28.7 (p), 26.0 (p), 24.3 (p), 23.5 (ap); HRMS M^+: 151.1003 (calcd. for $C_9H_{13}ON$: 151.1001).

2-Allyl-2-cyanocycloheptanone (45)

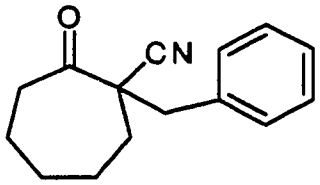


45

Allyl bromide (0.67 mL, 7.77 mmol) was added to a suspension of **23** (0.266 g, 1.94 mmol) and lithium hydride (61.74 mg, 7.77 mmol) in THF (10 mL). The mixture was stirred for 20 hours to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 20), compound **45** as a pale yellow oil (0.292 g, 1.65 mmol, 85%): IR (CH_2Cl_2, cast): 2240 (CN), 1714 (C=O), 1642 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 8 Hz, J_4 = 3 Hz, 1H, CH=CH_2), 5.30 (dm, J = 17 Hz, 1H, CH=CH_2), 5.23 (dm, J = 10 Hz, 1H, CH=CH_2), 2.80-2.55 (m, 2H, CH_2C=O), 2.37 (ddd, J_1 = 13 Hz, J_2 = 7 Hz, J_3 = 1 Hz, 1H, CH_2CH=CH_2), 2.15 (dd, J_1 = 13 Hz, J_2 = 8 Hz, 1H, CH_2CH=CH_2), 2.00-1.84 (m, 3H), 1.82-1.55 (m, 4H), 1.32 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ

204.9 (p), 130.9 (ap), 120.8 (p), 119.9 (p), 54.6 (p), 40.9 (p), 40.8 (p), 35.2 (p), 28.2 (p), 25.8 (p), 24.3 (p); HRMS M^+: 117.1159 (calcd. for $C_{11}H_{15}ON$: 117.1154).

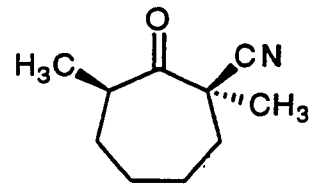
2-Benzyl-2-cyanocycloheptanone (46)



46

Benzyl bromide (1.01 mL, 8.49 mmol) was added to a mixture of **23** (0.291 g, 2.12 mmol) and lithium hydride (67.54 mg, 8.49 mmol) in THF (10 mL). The resulting pale yellow suspension was stirred at room temperature for 20 hours to afford, after flash chromatography, compound **46** as a white solid (0.433 g, 1.91 mmol, 90%): mp 173.5°C (hexane); IR (CH_2Cl_2, cast): 3450, 3087 (aromatic C-H), 2238 (CN), 1713 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H, phenyl), 3.20 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.97 (d, J = 13 Hz, 1H C**H**$_2$Ph), 2.70 (m, 1H, C**H**$_2$C=O), 2.52 (m, 1H, C**H**$_2$C=O), 2.01 (m, 1H), 2.00-1.85 (m, 3H), 1.82-1.49 (m, 3H), 1.03 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 205.4 (p), 134.1 (p), 130.3 (ap), 128.5 (ap), 127.7 (ap), 120.1 (p), 55.9 (p), 42.3 (p), 41.2 (p), 34.9 (p), 28.6 (p), 25.8 (p), 24.4 (p); HRMS M^+: 227.1304 (calcd. for $C_{15}H_{17}ON$: 227.1307). Anal. calcd. for $C_{15}H_{17}ON$: C 80.30%, H 7.70%, N 6.16%; found: C 80.35%, H 7.73%, N 6.16%.

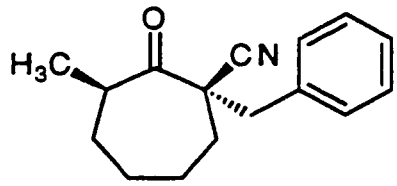
(2R*,6R*)-2,7-Dimethyl-2-cyanocycloheptanone (47)



47

Methyl iodide was added to a mixture of cyano ketone **27** (0.357 g, 2.36 mmol) and lithium hydride (75.2 mg, 9.46 mmol) in THF (12 mL). The reaction mixture was stirred at room temperature for 23 hours. The crude product was purified by flash chromatography, eluting with ethyl acetate-Skelly B (1 : 10) to give compound **47** as a white solid (0.332 g, 2.01 mmol, 85%): mp 164.3°C (hexane); IR (CH_2Cl_2, cast): 2240 (CN), 1714 cm^{-1} (C=O); ^1H NMR (360 MHz, $CDCl_3$): δ 2.82 (m, 1H, CH_3CH), 2.25 (dd, J_1 = 12 Hz, J_2 = 6.5 Hz, 1H), 2.03-1.89 (m, 2H), 1.84-1.65 (m, 2H), 1.55-1.37 (m, 3H), 1.47 (s, 3H, CH_3CCN), 1.15 (d, J = 7 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 208.2 (p), 121.1 (p), 50.6 (p), 43.3 (ap), 36.8 (p), 34.5 (p), 29.1 (p), 25.8 (p), 24.5 (ap), 18.0 (ap); HRMS M^+: 165.1154 (calcd. for $C_{10}H_{15}ON$: 165.1158).

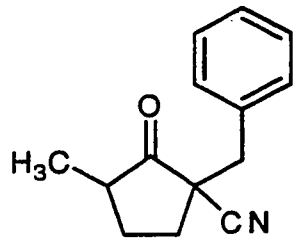
(2S*,7R*)-2-Benzyl-2-cyano-7-methylcycloheptanone (48)



48

Treatment of **27** (0.203 g, 1.34 mmol) with lithium hydride (42.75 mg, 5.38 mmol) and benzyl bromide (0.64 mL, 5.38 mmol) in THF (10 mL) for 24 hours at room temperature afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 15), compound **48** as white crystals (0.292 g, 1.21 mmol, 90%): mp 204.6°C (hexane); IR (CH_2Cl_2, cast): 3033 (aromatic C-H), 2239 (CN), 1709 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 5H, phenyl), 3.11 (d, J = 13 Hz, 1H, CH_2Ph), 3.05 (d, J = 13 Hz, 1H, CH_2Ph), 2.64 (m, 1H, CH_3CH), 2.15 (m, 1H), 2.04-1.70 (m, 5H), 1.53-1.34 (m, 2H), 1.10 (d, J = 8 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 207.9 (p), 133.6 (p), 130.2 (ap), 128.6 (ap), 127.9 (ap), 120.4 (p), 56.8 (p), 44.2 (ap), 43.8 (p), 34.7 (p), 34.1 (p), 29.2 (p), 25.3 (p), 17.5 (ap); HRMS M^+: 241.1465 (calcd. for $C_{16}H_{19}ON$: 241.1470). Anal. calcd. for $C_{16}H_{19}ON$: C 79.66%, H 7.89%; found C 79.31%, H 7.92%.

2-Benzyl-2-cyano-5-methylcyclopentanone (49)

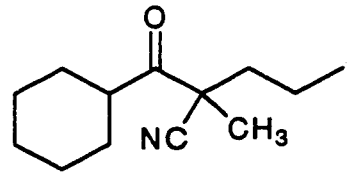


49

A mixture of cyano ketone **28** (0.1 g, 0.81 mmol), lithium hydride (25.85 mg, 3.25 mmol) and benzyl bromide (0.39 mL, 3.25 mmol) in THF (7 mL) was stirred at room temperature for 12 hours to give, after flash chromatography (ethyl acetate-Skelly B 1 : 15), compound **49** as a 1 : 1 mixture of two inseparable stereoisomers (0.104 g, 0.488 mmol, 60%): IR (mixture, CH_2Cl_2, cast): 3031

(aromatic C-H), 2232 (CN), 1751 cm^{-1} (C=O); ^1H NMR (mixture, 300 MHz, $CDCl_3$): δ 7.25 (m, 5H, phenyl), 3.23 (d, J = 13 Hz, 0.5H, CH_2Ph), 3.10 (d, J = 13 Hz, 0.5H, CH_2Ph), 2.98 (d, J = 13 Hz, 0.5H, CH_2Ph), 2.87 (d, J = 13 Hz, 0.5H, CH_2Ph), 2.45 (m, 1H, CH_3CH), 2.35-2.10 (m, 2.5H), 1.90 (m, 0.5H), 1.77 (m, 0.5H), 1.45 (m, 0.5H), 1.23 (d, J = 6 Hz, 1.5H, CH_3CH), 1.10 (d, J = 7 Hz, 1.5H, CH_3CH); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 210.3 (p), 210.2 (p), 135.2 (p), 134.8 (p), 130.4 (ap), 130.3 (ap), 128.8 (ap), 128.7 (ap), 128.3 (ap), 127.9 (ap), 119.8 (p), 118.9 (p), 50.0 (p), 48.9 (p), 43.5 (ap), 42.8 (ap), 40.0 (p), 39.2 (p), 31.5 (p), 30.3 (p), 28.1 (p), 27.2 (p), 14.9 (ap), 14.1 (ap); HRMS (mixture) M^+: 213.1154 (calcd. for $C_{14}H_{15}ON$: 213.1157).

(1-Cyano-1-methyl)butyl cyclohexyl ketone (50)



50

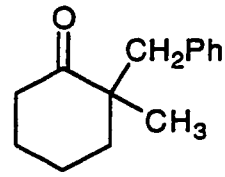
Cyano ketone **34** (0.4 g, 2.07 mmol) was dissolved in dichloromethane (12 mL). The solution was stirred at room temperature under argon while 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) (0.68 mL, 4,56 mmol) and methyl iodide (0.26 mL, 4.15 mmol) were successively added. The resulting solution was stirred for 2 hours then quenched with water (10 mL) and extracted with dichloromethane (2 x 30 mL). The combined extracts were washed with water (2 x 15 mL) and saturated sodium chloride solution (1 x 15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product (0.78 g) was purified by flash chromatography, eluting with ethyl acetate-Skelly

B (1 : 7), to give compound **50** as a colorless oil (0.3 g, 1.45 mmol, 70%): IR (CH_2Cl_2, cast): 2236 (CN), 1715 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.98 (m, 1H, **CH**C=O), 2.07-1.79 (m, 6H), 1.72 (m, 1H), 1.64-1.50 (m, 3H), 1.45-1.16 (m, 4H), 1.45 (s, 3H, CH_3CCN), 0.92 (t, J = 7 Hz, 3H, CH_3CH_2); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 207.9 (p), 121.8 (p), 48.7 (p), 48.5 (ap), 39.6 (p), 29.5 (p), 28.8 (p), 25.6 (p), 25.4 (p), 25.3 (p), 23.1 (ap), 18.9 (p), 16.6 (ap); HRMS M^+: 207.1624 (calcd. for $C_{13}H_{21}ON$: 207.1629). Anal. calcd. for $C_{13}H_{21}ON$: C 75.31%, H 10.14%; found C 75.69%, H 10.16%.

General procedure for reductive alkylation

Lithium metal (12.7 mg, 1.82 mmol, 5 equivalents) was added to a solution of naphthalene (0.351 g, 2.74 mmol, 7.5 equivalents) dissolved in THF (10 mL) under an argon atmosphere. The resulting solution was stirred at room temperature for 3-4 hours until lithium was completely consumed to yield a dark green solution. The solution was cooled to -25°C and added to a pre-cooled flask containing a cyano ketone (0.365 mmol, 1 equivalent) by syringe under argon. The resulting solution was stirred at -25°C for 30 minutes and then an alkylating agent (1.82 mmol, 5 equivalent) was added. After stirring over a period of time at the appropriate temperature, the reaction mixture was quenched with ethanol (8 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (2 x 10 mL) and saturated sodium chloride solution (1 x 10 mL), dried with anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography, first eluting with Skelly B to remove naphthalene and then with ethyl acetate-Skelly B to give the desired product.

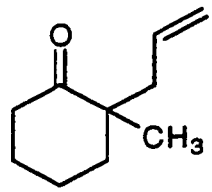
2-Benzyl-2-methylcyclohexanone (51)



51

Benzyl bromide (0.43 mL, 3.65 mmol) was added to a mixture of cyano ketone **38** (100 mg, 0.73 mmol) and lithium naphthalenide in THF. The resulting solution was stirred at -25°C for 45 minutes. The usual work-up followed by flash column chromatography, eluting with ethyl acetate- Skelly B (1 : 40), gave compound **51** as a pale yellow oil (0.11 g, 0.53 mmol, 72%): IR (CH_2Cl_2, cast): 3027 (aromatic C-H), 1704 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H, phenyl), 2.93 (t, J = 13 Hz, 2H CH_2Ph), 2.50 (m, 2H, CH_2C=O), 1.94-1.65 (m, 4H), 1.63-1.55 (m, 2H), 1.05 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 215.5 (p), 137.7 (p), 130.6 (ap), 128.1 (ap), 127.5 (ap), 49.3 (p), 43.2 (p), 38.9 (p), 38.2 (p), 27.3 (p), 22.9 (ap), 21.2 (p); HRMS M^+: 202.1352 (calcd. for $C_{14}H_{18}O$: 202.1358). Anal. calcd. for $C_{14}H_{18}O$: C 83.17%, H 8.91%; found: C 83.46%, H 9.03%.

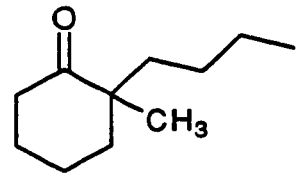
2-Allyl-2-methylcyclohexanone (5)



5

Allyl bromide (1.04 mL, 12.04 mmol) was added to a mixture of **38** (0.33 g, 2.41 mmol) and lithium naphthalenide in THF. The mixture was stirred at -25°C for 40 minutes to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 30), product **5** as a pale yellow oil (0.256 g, 1.69 mmol, 70%): IR (CH_2Cl_2, cast): 1706 (C=O), 1639 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (dm, J = 20 Hz, 1H, C**H**=CH_2), 5.12 (m, 1H, CH=C**H**$_2$), 5.04 (m, 1H, CH=C**H**$_2$), 2.40 (m, 2H, C**H**$_2$C=O), 2.35 (dd, J_1 = 13 Hz, J_2 = 7.5 Hz, 1H, C**H**$_2$CH=CH_2), 2.25 (dd, J_1 = 13 Hz, J_2 = 7 Hz, 1H, C**H**$_2$CH=CH_2), 1.92-1.64 (m, 5H), 1.57 (m, 1H), 1.14 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 215.4 (p), 133.8 (ap), 117.9 (p), 48.5 (p), 42.0 (p), 38.8 (p), 38.6 (p), 27.4 (p), 22.7 (ap), 21.1 (p); HRMS M^+: 152.1198 (calcd. for $C_{10}H_{16}O$: 152.1203).

2-Butyl-2-methylcyclohexanone (10)

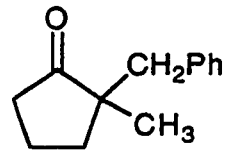


10

1-Bromobutane (0.2 mL, 1.82 mmol) was added to a mixture of **38** (50 mg, 0.36 mmol) and lithium naphthalenide in THF. The solution was refluxed for 10 hours. After work-up, the crude product was purified by flash chromatography. Elution with ethyl acetate-Skelly B (1 : 60) gave **10** as a colorless oil (39.9 mg, 0.24 mmol, 65%): IR (CH_2Cl_2, cast) 1707 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (m, 2H, C**H**$_2$C=O), 1.95-1.47 (m, 7H), 1.40-1.13 (m, 3H), 1.06-0.82 (m, 2H), 1.03 (s, 3H, C**H**$_3$), 0.92 (t, J = 7 Hz, 3H, CH_2C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 216.2 (p), 48.7 (p), 39.5 (p), 38.9 (p), 37.3 (p), 27.6 (p), 25.9 (p), 23.4 (p), 22.6 (ap), 21.1 (p), 14.0 (ap); HRMS M^+: 168.15514 (calcd. for

$C_{11}H_{20}O$: 168.1514). Anal. calcd. for $C_{11}H_{20}O$: C 78.57%, H 11.90%; found: C 78.72%, H 11.66%.

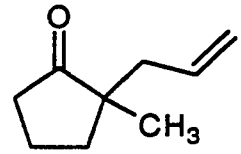
2-Benzyl-2-methyl-cyclopentanone (54)



54

A solution of cyano ketone **41** (0.1 g, 0.81 mmol), lithium naphthalenide and benzyl bromide (0.48 mL, 4.07 mmol) in THF was stirred at -25°C for 30 minutes to give, after flash chromatography (ethyl acetate-Skelly B 1 : 35), compound **54** as a pale yellow oil (0.12 g, 0.65 mmol, 80%); IR (CH_2Cl_2, cast): 3061 (aromatic C-H), 1735 (C=O), 1495, 1453 cm^{-1} (aromatic C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.25 (m, 5H, phenyl), 2.92 (d, J = 13 Hz, 1H, CH_2Ph), 2.63 (d, J = 13 Hz, 1H CH_2Ph), 2.35 (m, 1H, $CH_2C=O$), 2.15 (m, 1H, $CH_2C=O$), 2.06 (m, 1H), 1.84-1.62 (m, 2H), 1.57 (m, 1H), 1.05 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 223.3 (p), 138.0 (p), 130.3 (ap), 128.2 (ap), 126.4 (ap), 49.8 (p), 42.7 (p), 38.0 (p), 34.7 (p), 22.7 (ap), 18.7 (p); HRMS M^+: 188.1208 (calcd. for $C_{13}H_{16}O$: 188.1204). Anal. calcd. for $C_{13}H_{16}O$: C 82.98%, H 8.51%; found: C 82.72%, H 8.60%.

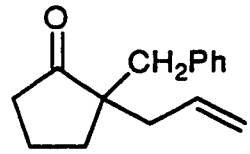
2-Allyl-2-methylcyclopentanone (55)



55

Reductive alkylation of cyano ketone **41** (0.12 g, 0.98 mmol) with lithium naphthalenide and allyl bromide (0.42 mL, 4.88 mmol) in THF at -25°C for 30 minutes afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **55** as a colorless oil (94 mg, 0.68 mmol, 70%); IR (CH_2Cl_2, cast): 1736 (C=O), 1684 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.68 (dm, J = 18 Hz, 1H, $CH=CH_2$), 5.10 (dm, J = 18 Hz, 1H, $CH=CH_2$), 5.05 (dm, J = 8 Hz, 1H, $CH=CH_2$), 2.39-2.05 (m, 4H), 2.00-1.77 (m, 3H), 1.65 (m, 1H), 0.95 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 223.0 (p), 133.9 (ap), 118.2 (p), 48.2 (p), 41.0 (p), 37.7 (p), 35.2 (p), 33.8 (p), 21.9 (ap); HRMS M^+: 138.1050 (calcd. for $C_9H_{14}O$: 138.1046).

2-Allyl-2-benzylcyclopentanone (56)

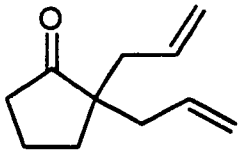


56

Treatment of cyano ketone **42** (95 mg, 0.64 mmol) with lithium naphthalenide and benzyl bromide (0.38 mL, 3.19 mmol) for 30 minutes at -25°C gave, after

chromatographic purification (ethyl acetate-Skelly B 1 : 30), product **56** as a yellow oil (95 mg, 0.45 mmol, 70%): IR (CH_2Cl_2, cast): 3075 (aromatic C-H), 1734 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30-7.12 (m, 5H, phenyl), 5.73 (dddd, J_1 = 20 Hz, J_2 = 10 Hz, J_3 = 8 Hz, J_4 = 1 Hz, 1H, C**H**=CH_2), 5.09 (dm, J = 20 Hz, 1H, CH=C**H**$_2$), 5.12 (dm, J = 8 Hz, 1H, CH=C**H**$_2$), 2.93 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.66 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.27 (dd, J_1 = 14 Hz, J_2 = 8 Hz, 1H, C**H**$_2$CH=CH_2), 2.20 (m, 1H, C**H**$_2$C=O), 2.13 (dd, J_1 = 14 Hz, J_2 = 7 Hz, 1H, C**H**$_2$CH=CH_2), 2.02 (m, 1H, C**H**$_2$C=O), 1.95-1.83 (m, 2H), 1.72 (m, 1H), 1.50 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$); δ 222.9 (p), 137.8 (p), 133.7 (ap), 130.3 (ap), 128.4 (ap), 126.5 (ap), 118.7 (p), 53.3 (p), 41.8 (p), 41.0 (p), 38.9 (p), 31.1 (p), 18.7 (p); HRMS M^+: 214.1346 (calcd. for $C_{15}H_{18}O$: 214.1351).

2,2-Diallylcyclopentanone (57)

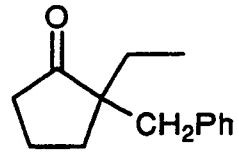


57

Allyl bromide (0.26 mL, 3.02 mmol) was added to a mixture of **42** (90 mg, 0.604 mmol) and lithium naphthalenide in THF. The resulting solution was stirred at -25°C for 30 minutes to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **57** as a pale yellow oil (79 mg, 0.48 mmol, 80%): IR (CH_2Cl_2, cast): 1735 (C=O), 1639 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.69 (ddd, J_1 = 18 Hz, J_2 = 10 Hz, J_3 = 8 Hz, 2H, C**H**=CH_2), 5.08 (dm, J = 8 Hz, 2H, CH=C**H**$_2$), 5.05 (dm, J = 18 Hz, 2H, CH=C**H**$_2$), 2.25-2.07 (m, 6H), 1.93-1.77 (m, 4H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 222.3 (p), 133.7 (ap), 118.4 (p), 51.7

(p), 39.9 (p), 38.5 (p), 32.0 (p), 18.8 (p); HRMS M^+: 164.1199 (calcd. for $C_{11}H_{16}O$: 164.1152). Anal. calcd. for $C_{11}H_{16}O$: C 81.49%, H 9.76%; found: C 81.82%, H 9.94%.

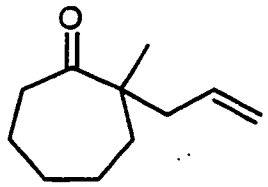
2-Benzyl-2-ethylcyclopentanone (58)



58

A solution of cyano ketone **43** (0.313 g, 2.28 mmol), lithium naphthalenide and benzyl bromide (1.35 mL, 11.42 mmol) in THF was stirred for 30 minutes at -25°C to give, after flash chromatography (ethyl acetate-Skelly B 1 : 50), compound **58** as a pale yellow oil (0.28 g, 1.37 mmol, 60%): IR (CH_2Cl_2, cast): 3084 (aromatic C-H), 1733 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5H, phenyl), 2.94 (d, J = 13 Hz, 1H, CH_2Ph), 2.63 (d, J = 13 Hz, 1H, CH_2Ph), 2.43-2.10 (m, 2H), 1.95-1.07 (m, 3H), 1.62 (m, 1H), 1.48 (q, J = 7 Hz, 2H, CH_2CH_3), 0.94 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 223.4 (p), 138.1 (p), 130.6 (ap), 128.7 (ap), 127.9 (ap), 53.5 (p), 41.2 (p), 38.9 (p), 31.2 (p), 29.0 (p), 18.7 (p), 8.6 (ap); HRMS M^+: 202.1364 (calcd. for $C_{14}H_{18}O$: 202.1358).

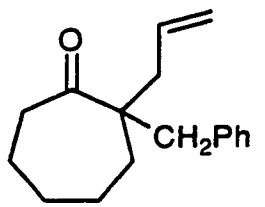
2-Allyl-2-methylcycloheptanone (59)



59

Allyl bromide (0.44 mL, 5.06 mmol) was added to a mixture of cyano ketone **44** (0.153 g, 1.01 mmol) and lithium naphthalenide in THF. The solution was stirred at -25°C for 30 minutes to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **59** as a colorless oil (0.151 g, 0.91 mmol, 90%): IR (CH_2Cl_2, cast): 1701 (C=O), 1684 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.72 (dddd, J_1 = 20 Hz, J_2 = 9 Hz, J_3 = 8 Hz, J_4 = 2 Hz, 1H, C**H**=CH_2), 5.10 (dm, J = 9 Hz, 1H CH=C**H**$_2$), 5.05 (dm, J = 20 Hz, 1H, CH=C**H**$_2$), 2.57 (ddd, J_1 = 12 Hz, J_2 = 9 Hz, J_3 = 2 Hz, 1H, C**H**$_2$CH=CH_2), 2.42 (dd, J_1 = 12 Hz, J_2 = 8 Hz, 1H, C**H**$_2$CH=CH_2), 2.15 (m, 2H, C**H**$_2$C=O), 1.75-1.63 (m, 3H), 1.62-1.42 (m, 4H), 1.03 (m, 1H), 1.02 (s, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 217.4 (p), 133.9 (ap), 118.0 (p), 50.9 (p), 43.7 (p), 40.7 (p), 36.6 (p), 30.7 (p), 26.5 (p), 24.4 (p), 22.3 (ap); HRMS M^+: 166.1362 calcd. for $C_{11}H_{18}O$: 166.1360).

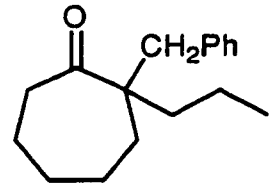
2-Allyl-2-benzylcycloheptanone (60)



60

Reductive alkylation of cyano ketone **45** (0.186 g, 1.05 mmol) with lithium naphthalenide and benzyl bromide (0.62 mL, 5.25 mmol) at -25°C in THF for 30 minutes afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **60** as a yellow oil (0.204 g, 0.84 mmol, 80%): IR (CH_2Cl_2, cast): 3048 (aromatic C-H), 1696 (C=O), 1676 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.10 (m, 5H, phenyl), 5.83 (dddd, J_1 = 17 Hz, J_2 = 10 Hz, J_3 = 7 Hz, J_4 = 2 Hz, 1H, C**H**=CH_2), 5.12 (dm, J = 10 Hz, 1H, CH =**CH**$_2$), 5.08 (dm, J = 17 Hz, 1H, CH=**CH**$_2$), 2.82 (t, J = 13 Hz, 2H, **CH**$_2$Ph), 2.50 (m, 1H), 2.32-2.20 (m, 3H), 1.72 (m,1H), 1.49 (m, 4H), 1.40 (m, 3H) ; ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 217.2 (p), 137.7 (p), 134.1 (ap), 130.5 (ap), 128.0 (ap), 127.6 (ap), 118.3 (p), 55.0 (p), 42.4 (p), 42.2 (p), 40.7 (p), 32.4 (p), 30.6 (p), 26.2 (p), 24.3 (p); HRMS M^+: 242.1167 (calcd. for $C_{17}H_{22}O$: 242.1669). Anal. calcd. for $C_{17}H_{22}O$: C 84.30%, H 9.09%; found C 84.77%, H 9.43%.

2-Benzyl-2-propylcycloheptanone (61)

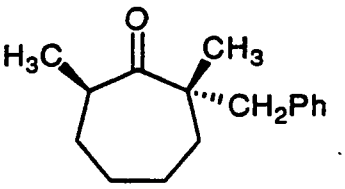


61

1-Bromopropane (0.13 mL, 1.37 mmol) was added to a mixture of cyano ketone **46** (62 mg, 0.27 mmol) and lithium naphthalenide in THF. The solution was stirred at room temperature for 10 hours. The usual work-up followed by flash chromatography, eluting with ethyl acetate-Skelly B (1 : 60), gave compound **61** as a colorless oil (43 mg, 0.178 mmol, 65%): IR (CH_2Cl_2, cast): 3083 (aromatic C-H), 1697 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H,

phenyl), 2.90 (d, J = 14 Hz, 1H CH_2Ph), 2.78 (d, J = 14 Hz, 1H, CH_2Ph), 2.62 (m, 1H, $CH_2C{=}O$), 2.30 (m, 1H, $CH_2C{=}O$), 2.19 (m, 1H), 1.82-1.60 (m, 4H), 1.57-1.30 (m, 6H), 1.22 (m, 1H), 0.88 (t, J = 7 Hz, CH_2CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 217.8 (p), 138.4 (p), 130.6 (ap), 128.0 (ap), 126.2 (ap), 55.1 (p), 41.8 (p), 40.2 (p), 39.2 (p), 33.2 (p), 30.9 (p), 30.8 (p), 26.5 (p), 24.3 (p), 14.6 (ap); HRMS M^+: 244.1821 (calcd. for $C_{17}H_{24}O$: 244.1827).

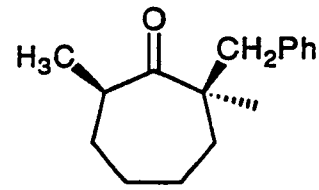
(2S*,7R*)-2-Benzyl-2,7-dimethylcycloheptanone (62)



62

To a mixture of cyano ketone **47** (100 mg, 0.61 mmol) and lithium naphthalenide in THF, benzyl bromide (0.36 mL, 3.05 mmol) was added. The resulting solution was stirred at -25°C for 1 hour to give, after flash chromatography (ethyl acetate-Skelly B 1 : 50), **62** as a single diastereomer (97 mg, 0.42 mmol, 70%): IR (CH_2Cl_2, cast): 3084 (aromatic C-H), 1716 cm^{-1} (C=O); ^1H NMR (200 MHz, C_6D_6): δ 7.37 (m, 5H, phenyl), 2.72 (d, J = 13 Hz, 1H, CH_2Ph), 2.52 (d, J = 13 Hz, 1H, CH_2Ph), 2.45 (m, 1H, CH_3CH), 1.85 (m, 1H), 1.79 (m, 2H), 1.63-1.60 (m, 2H), 1.41 (m, 1H), 1.24-1.20 (m, 2H), 1.18 (s, 3H, CH_3), 1.15 (d, J = 7 Hz, 3H, $CHCH_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 219.2 (p), 137.1 (p), 130.3 (ap), 128.0 (ap), 126.5 (ap), 52.1 (p), 48.0 (p), 43.4 (ap), 36.5 (p), 35.6 (p), 30.2 (p), 24.1 (p), 22.3 (ap), 17.8 (ap); HRMS M^+: 230.1673 (calcd. for $C_{16}H_{22}O$: 230.1668).

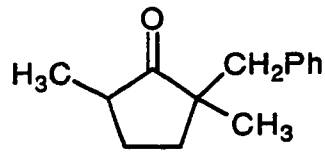
(2R*,7R*)-Benzyl-2,7-dimethylcycloheptanone (63)



63

Methyl iodide (0.13 mL, 2.07 mmol) was added to a mixture of cyano ketone **48** (0.1 g, 0.41 mmol) and lithium naphthalenide in THF. The mixture was stirred at -25°C for 30 minutes to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 50), compound **63** as a colorless oil (76 mg, 0.33 mmol, 80%): IR (CH_2Cl_2, cast): 3082 (aromatic C-H), 1720 cm^{-1} (C=O); ^1H NMR (200 MHz, C_6D_6): δ 7.25-7.15 (m, 5H, phenyl), 3.18 (d, J = 10 Hz, 1H, CH_2Ph), 2.93 (d, J = 10 Hz, 1H, CH_2Ph), 2.62 (m, 1H, CH_3CH), 1.82-1.64 (m, 4H), 1.43 (m, 1H),1.27-1.04 (m, 3H), 1.18 (d, J = 7 Hz, 3H, $CHCH_3$), 0.82 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 219.2 (p), 138.9 (p), 131.1 (ap), 127.9 (ap), 126.1 (ap), 51.4 (p), 42.0 (ap), 39.6 (p), 35.7 (p), 33.3 (p), 30.3 (p), 25.1 (ap), 24.4 (p), 18.1 (ap); HRMS M^+: 230.1670 (calcd. for $C_{16}H_{22}O$: 230.1668).

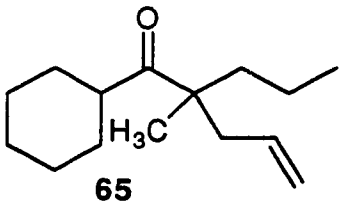
2-Benzyl-2,5-Dimethylcyclopentanone (64)



64

Reductive alkylation of cyano ketone **49** (0.27 g, 1.27 mmol) with lithium naphthalenide and methyl iodide (0.39 mL, 6.34 mmol) in THF at -25°C for 1 hour gave, after flash chromatography (ethyl acetate-Skelly B 1 : 30), an oily product **64** as an inseparable 1 : 0.7 mixture of two diastereomers (0.154 g, 0.76 mmol, 60%): IR (mixture,CH_2Cl_2, cast): 3851 (aromatic C-H), 1717 cm^{-1} (C=O); ^1H NMR (mixture, 400 MHz, $CDCl_3$): for the major isomer: δ 2.95 (d, J = 13 Hz, 0.59H, CH_2Ph), 2.63 (d, J = 13 Hz, 0.59H, CH_2Ph), 2.03 (m, 0.59H, CH_3CH), 1.09 (s, 1.77H, CH_3), 0.93 (d, J = 7 Hz, 1.77H, $CHCH_3$); for the minor isomer: δ 2.83 (d, J = 14 Hz, 0.41H, CH_2Ph), 2.53 (d, J = 14 Hz, 0.41H, CH_2Ph), 2.17 (m, 0.41H, CH_3CH), 1.01 (s, 1.23H, C-2 CH_3), 1.12 (d, J = 7 Hz, 1.23H, $CHCH_3$); for the mixture: δ 7.20-7.40 (m, 5H, phenyl), 1.83-1.52 (m, 2.5H), 1.39-1.17 (m, 1.5H); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 213.1 (p), 212.2 (p), 137.2 (p), 136.9 (p), 136.4 (ap), 136.2 (ap), 136.0 (ap), 134.9 (ap), 132.7 (ap), 51.3 (p) 50.7 (p), 43.2 (ap), 40.2 (ap), 37.1 (p), 34.5 (p), 33.7 (p), 30.2 (p), 27.2 (p), 25.1 (p), 24.8 (ap), 21.3 (ap), 15.7 (ap), 14.1 (ap); HRMS M^+: 202.1351 (calcd. for $C_{14}H_{18}O$: 202.1358).

(1-Allyl-1-methyl)butyl cyclohexyl ketone (65)



65

Allyl bromide (0.22 mL, 2.58 mmol) was added to a mixture of cyano ketone **50** (0.107 g, 0.52 mmol) and lithium naphthalenide in THF. The solution was stirred at -25°C for 2 hours. The usual work-up followed by flash column

chromatography, eluting with ethyl acetate-Skelly B (1 : 50), gave compound **65** as a colorless oil (0.103 g, 0.47 mmol, 90%): IR (CH_2Cl_2, cast): 1699 (C=O), 1639 cm^{-1} (C=C); ^1H (300 MHz, $CDCl_3$): δ 5.65 (dm, J = 18 Hz, 1H, C**H**=CH_2), 5.06 (m, 1H, CH=C**H**$_2$), 5.00 (m, 1H, CH=C**H**$_2$), 2.43 (dd, J_1 = 13 Hz, J_2 = 7 Hz, 1H, C**H**$_2$CH=CH_2), 2.21 (dd, J_1 = 13 Hz, J_2 = 7.5 Hz, 1H, C**H**$_2$CH=CH_2), 2.79 (m, 1H, C**H**C=O), 1.82-1.57 (m, 5H), 1.52-1.38 (m, 5H), 1.23-1.06 (m, 4H), 1.10 (s, 3H, CH_3), 0.85 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 218.2 (p), 134.5 (ap), 117.6 (p), 51.5 (p), 45.3 (ap), 41.6 (p), 39.9 (p), 29.9 (p), 29.7 (p), 25.9 (p), 25.8 (p), 25.8 (p), 20.9 (ap), 17.9 (p), 14.7 (ap); HRMS M^+: 222.1979 (calcd. for $C_{15}H_{26}O$: 222.1976). Anal. calcd. for $C_{15}H_{26}O$: C 81.08%, H 11.71%; found: C 80.82%, H 11.94%.

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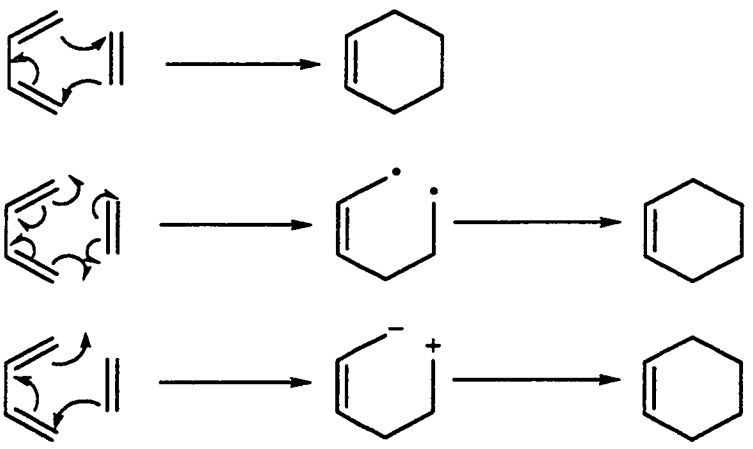
Introduction

The cycloaddition of alkenes (dienophiles) and dienes is a very useful method for forming substituted cyclohexenes. This reaction is known as the Diels-Alder reaction. It was first observed by Diels and Alder in 1928,[1] since then, the Diels-Alder reaction has been widely used as a powerful tool in organic synthesis, especially in the total syntheses of many polycyclic natural products, for instance, in the classical synthesis of aphidicolin,[2] cholesterol[3] and cantharidin.[4] In recent years, several interesting natural products, such as (+)-qinghaosu,[5] and (±)-2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid[6] were also successfully synthesized in our research group making use of the intermolecular Diels-Alder reaction as a key operation.

There have been many mechanistic investigations of the Diels-Alder reaction.[7] So far, three mechanisms have been proposed including a concerted reaction mechanism which occurs in one step with no intermediate, a diradical mechanism in which one end of the diene attaches to one end of the dienophile and a diion mechanism which involves the movement of pair of electrons to form a diion intermediate (**Scheme 2-1**). Of these, the concerted one-step mechanism is generally the most accepted one.[8,9] This mechanism is supported by the fact the reaction is highly stereospecific in which the configuration of the reactants is retained in the product. Besides, it has been observed that the rate of the Diels-Alder reactions is usually independent on the nature of the solvents, which may further indicate that the reactions occur in one step with no diion intermediate.

Over the years, with the in-depth investigation on the Diels-Alder chemistry and with the establishment of Frontier Molecular Orbital theory[10] as well as Woodward-Hoffmann's Orbital Symmetry Conservation theory,[11] a series of empirical rules have been well developed to predict the structural outcome of the Diels-Alder reaction. The development of these rules has resulted in a dramatic increase in the application of Diels-Alder reaction. Furthermore, the observations that Lewis acid catalysis can greatly enhance the rate,[12] as well as improve the stereo-[13] and regioselectivity[14,15] of the reaction have also widened the scope and potential applications tremendously.

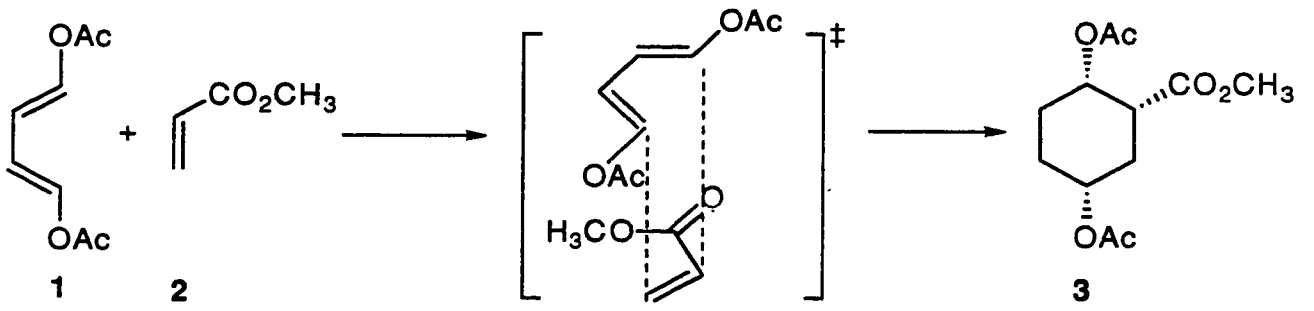
Scheme 2-1 The mechanism of Diels-Alder reaction



The stereochemistry of the Diels-Alder reaction is generally governed by two rules. In the terminology of orbital symmetry classification, the Diels-Alder reaction is a [$\pi 4_s + \pi 2_s$] cycloaddition, an allowed process. The transition state for a concerted reaction requires that the diene adopts the *s-cis* conformation. During the transition state, the diene and dienophile approach each other in approximately parallel planes. In other words, the addition is stereospecifically

syn and the configuration of the substituents in the reactants are preserved in the product. This behavior was sufficiently general that the name *cis*-principle was given to the statement describing this mode of addition. This rule can be illustrated by the reaction of *trans, trans*-1,4-diacetoxy-1,3-butadiene **1** with methyl acrylate **2** to afford adduct **3**, with the retention of configuration (**Scheme 2-2**).[16]

Scheme 2-2

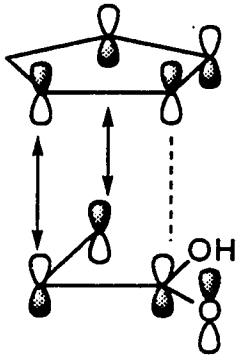


The second rule to predict the stereochemistry of the Diels-Alder adducts is named as *endo* rule or *Alder* rule.[17] For an unsymmetrical dienophile, there are two possible stereochemical orientations, *endo* and *exo*. In the *endo* transition state, the reference substituent on the dienophile is oriented toward the π orbitals of the diene. In the *exo* transition state, the substituent is oriented away from the π system. Except for the symmetrically substituted dienes and dienophiles, these two transition states will lead to two different stereoisomeric products. Generally speaking, the *endo* mode of addition is usually preferred when an unsaturated substituent, such as a carbonyl group, is present in the dienophile. For example, in the reaction of cyclopentadiene **4** with acrylic acid

5, the exclusive product from the reaction was *endo* product **6** instead of *exo* product **7 (Scheme 2-3)**.[18]

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. As illustrated in **Figure 2-1**, in the *endo* transition state, in addition to the primary interactions which are indicated by solid arrows, there is also a stabilizing second interaction (dotted line) between the π system of the diene and the π system of the conjugated dienophile. In the *exo* orientation, the primary interactions are the same but the secondary interaction is absent. Hence the *endo* orientation is more favored due to this secondary orbital overlap effect.[11] The *endo* rule is also applicable to the open-chain diene systems, as shown in **Scheme 2-2**.

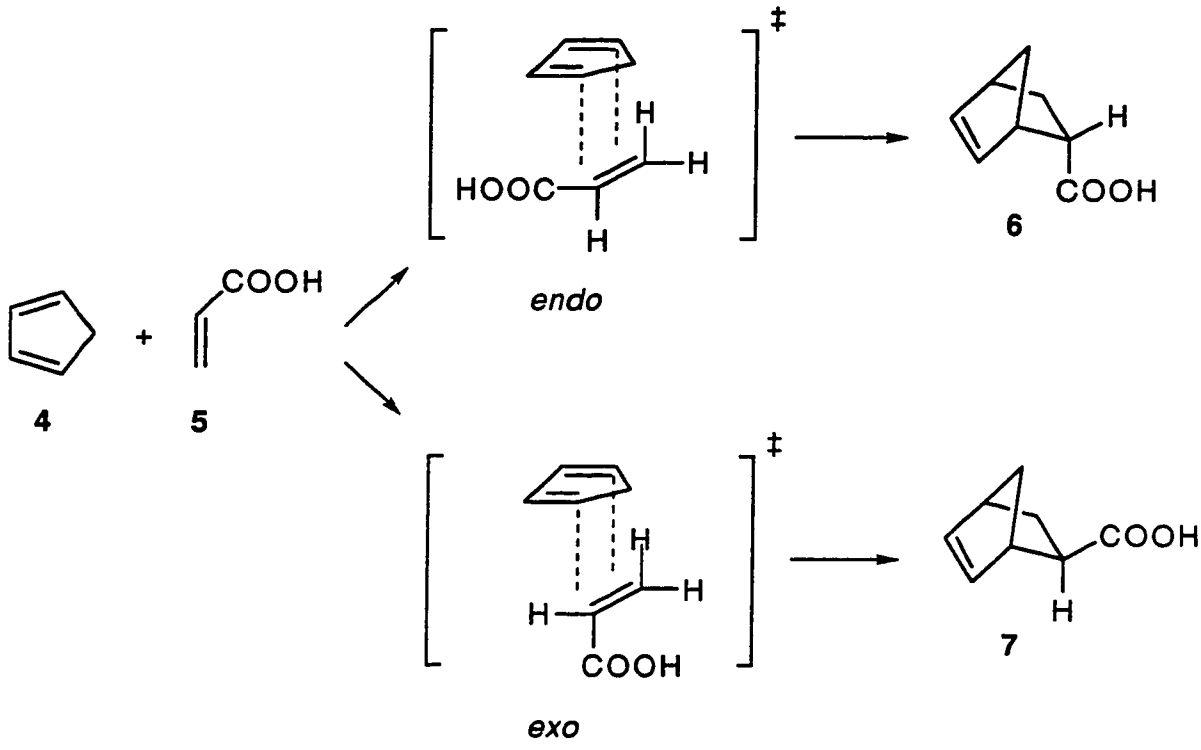
Figure 2-1



HOMO of cyclopentadiene

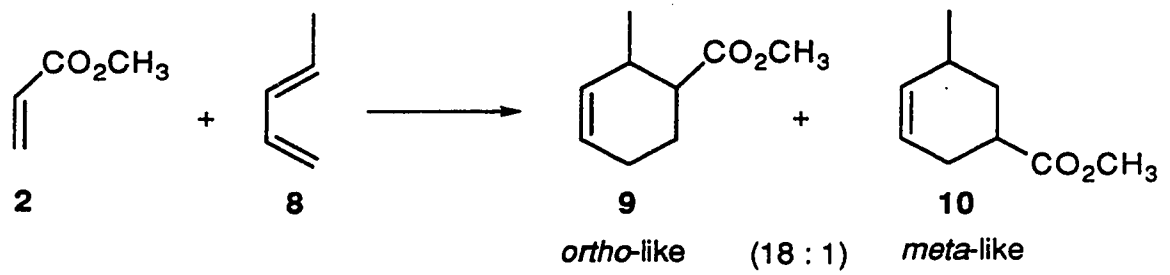
LUMO of acrylic acid

Scheme 2-3



A question of regioselectivity arises when both diene and dienophile are unsymmetrically substituted. In the most common cases, when the dienophile bears an electron-withdrawing substituent and the diene an electron-releasing one, the Diels-Alder addition will give an "*ortho*" or "*para*" product depending on the position of the substituent on the diene (*ortho* and *para* rules). Generally speaking, C-1 substituted dienes will preferentially give the *ortho*-like products. For example, the addition of *trans*-piperylene **8** to dienophile **2** gave the products **9** and **10**, in which the *ortho*-substituted compound **9** was the major product (**Equation 2-1**).[19]

Equation 2-1

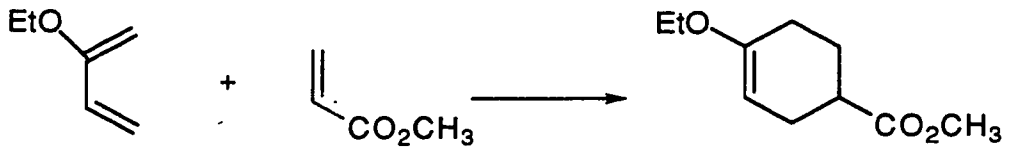


2 **8** **9** **10**

ortho-like (18 : 1) *meta*-like

In the case of the C-2 substituted electron-rich dienes, the *para* isomer is formed preferentially. Take as an example the addition of 2-ethoxy-1,3-butadiene **11** to the dienophile **2**, the exclusive product from the reaction was the *para*-like adduct **12** (**Equation 2-2**).[20]

Equation 2-2



11 **2** **12**

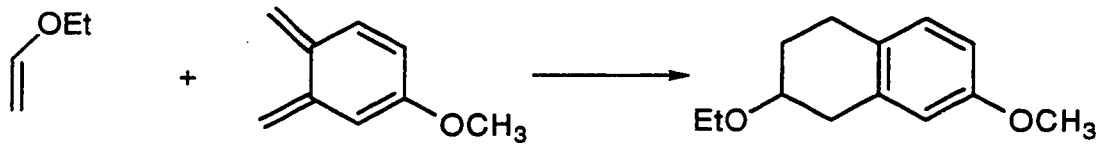
para-like

The regioselectivity in these two cases can be understood in terms of Frontier Molecular Orbital theory.[10] For the reactions between dienophiles possessing an electron-withdrawing substituent and dienes possessing an electron-donating group, the strongest orbital interaction occurs between the LUMO of dienophiles and the HOMO of dienes. Because of this interaction, the reactants will be oriented so that the carbons having the highest coefficients in the frontier orbitals will begin the bonding process which leads to the observed regioselectivity.

Frontier Molecular Orbital theory can also explain the electronic substituent effect in the Diels-Alder reaction. For electron rich dienes, the most reactive dienophiles are those bearing an electron-withdrawing substituent. As described above, the strongest interation in terms of Frontier Molecular Orbital theory is that of the HOMO of dienes and the LUMO of dienophiles. Conversely, if dienes bearing an electron-withdrawing group are used, the most suitable dienophiles should be those in which an electron-donating group(s) is presented. In this case, the strongest orbital interaction occurs between the HOMO of dienophiles and the LUMO of dienes. Such reactions are called inverse electron demand Diels-Alder reactions.[21]

For those reactions which involve electron rich dienes and electron rich dienophiles, the *meta* orientation is mostly favored (*meta* rule). Thus, the product of the addition of ethyl vinyl ether **13** to diene **14** was adduct **15** (**Equation 2-3**).[22]

Equation 2-3



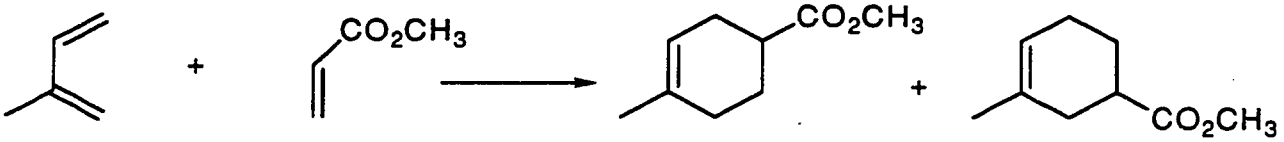
13 **14** **15**

meta-like

In addition to the use of appropriately substituted dienes and dienophiles, the improvement of the Diels-Alder reactivity can also be achieved by Lewis acid catalysis. The most commonly used Lewis acids include boron trifluoride (BF_3), zinc chloride ($ZnCl_2$), aluminum trichloride ($AlCl_3$), stannic chloride ($SnCl_4$) and ferric chloride ($FeCl_3$). For some reactions, the Lewis acid catalysis can not only

enhance the rate but also improve the regio- and stereoselectivity. For example, the addition of dienophile **2** to isoprene **16** in the presence of aluminum trichloride resulted in the enhanced *para*-selectivity and reaction rate (**Equation 2-4**).[23] The catalytic effect is supposed to result from the coordination of the Lewis acid with the dienophile. The complexed dienophile is then more electrophilic and more reactive toward the electron rich diene (**Figure 2-1**).

Equation 2-4



16	**2**	**17** *para*-like	**18** *meta*-like
uncat.	120°C, 6 h	70	30
$AlCl_3$	20°C, 3 h	95	5

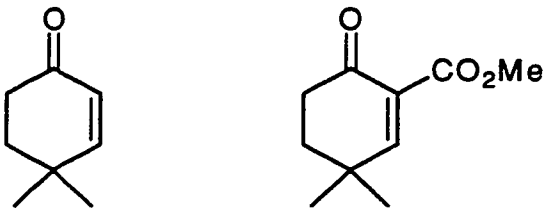
Figure 2-2

The Diels-Alder reaction has long played an important role in synthetic organic chemistry. One of the most important features of its application is to build fused polycyclic skeletons, a process requiring only a straightforward addition of a cyclic dienophile to an appropriately substituted 1,3-butadiene. For example,

the addition of substituted cyclohexenones to substituted 1,3-butadienes can serve as a versatile approach to the decalin systems, a skeleton which has been found in many natural products. However, the early investigations have demonstrated that under thermal conditions, the cycloaddition of dienes to cyclic dienophiles, such as 2-cyclohexenone was a poor process and often resulted in low yields of the products.[24] In order to improve the Diels-Alder reactivity of cycloalkenones, extensive investigations have been done and many methods were reported over the last thirty years.[25] Of these, two major methods stand out for the enhancement of dienophilicity of cycloalkenones. The first method involves the application of Lewis acid catalysis. It has been observed that Lewis acid catalysis can greatly enhance the reaction rate and has made available many polycyclic compounds which were previously obtained with difficulty under thermal conditions. For example, aluminum chloride has been reported to effectively catalyze the addition of a series of cycloalkenones and 2-methylcycloalkenones to several dienes, in which the rate of the reaction was increased tremendously.[26,27] It has also been observed that Lewis acid catalysis has a profound effect on the regio-[14,15] and stereoselectivity[13] of the Diels-Alder addition so that the *ortho*- and *para*-selectivity as well as the *endo*-selectivity are markedly increased.

The second method to increase the reactivity of cycloalkenones is placement of an additional electron-withdrawing group on either the α- or β-carbon of the dienophile. The enhanced reactivity was reflected in the shorter reaction time and the lower reaction temperature required as well as in the high yields obtained for the adducts. The outcome of the additions, in terms of stereo- and regiochemistry is generally quite predictable. For example, the investigation of our research group has demonstrated that, compared with 4,4-dimethyl-2-

cyclohexenone **19** which turned out to be a very unreactive dienophile,[28] the reactivity of the methyl ester-activated compound **20** was greatly improved and the Diels-Alder reactions of this compound could proceed much more smoothly.[29]

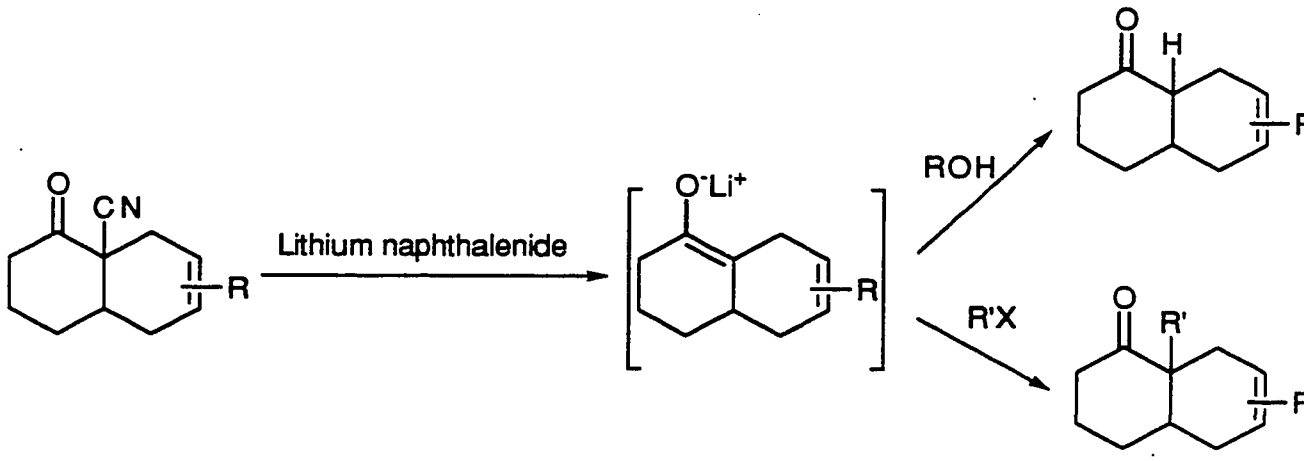


19 **20**

In addition to carbalkoxyl, other activating substituents which have been used to enhance the dienophilicity of cycloalkenones include formyl group[30], nitro group[31], phenylthio group[32], phenylselenenyl group,[33] bromo[34] and nitrile group on the β-carbon.[35]

In the previous chapter, we described a procedure of reductive alkylation of acyclic and monocyclic α-cyano ketones. The results obtained from this investigation led us to study the possibility of applying this process to the bicyclic adducts produced from nitrile-activated Diels-Alder reaction. The addition of the α cyano-substituted 2-cycloalkenones to a variety of dienes could give rise to the bicyclic Diels-Alder adducts with a cyano group at the ring junction position. The reductive cleavage of the cyano group using lithium naphthalenide as the reducing agent could lead to the formation of regiospecific enolates which in turn could be trapped with a proton source or an alkylating agent (**Scheme 2-4**).

Scheme 2-4



This procedure provides an interesting option for introducing an alkyl group to the angular position of polycyclic compounds, an important synthetic process which may not be easy to achieve by other methods.[36,37] During the Diels-Alder reaction, the cyano moiety served as an activating group to facilitate the cycloaddition. In the reductive decyanation step, the cyano group could be easily replaced by an alkyl group or a hydrogen atom. Thus, 2-cyano-2-cycloalkenones can be considered as an useful synthetic equivalent of 2-cycloalkenones and 2-alkyl-2-cycloalkenones, the compounds which do not undergo the Diels-Alder reaction effectively.

In the present study, four 2-cyano-2-cycloalkenones with different ring sizes were prepared as dienophiles. The study of Lewis acid catalyzed Diels-Alder reaction of these dienophiles with several dienes, as well as the reductive decyanation and alkylation of the Diels-Alder adducts will be described in the first part of this chapter. To demonstrate the synthetic utility of this process, we embarked on a project directed towards the total synthesis of two natural

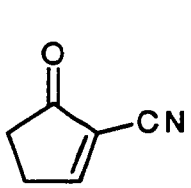
products based on 1-methylbicyclo[6.4.0]dodecane skeleton. The second part of this chapter will focus on this investigation

Results and Discussion

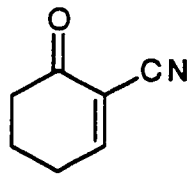
I. Diels-Alder reactions of 2-cyano-2-cycloalkenones and reductive cleavage and alkylation of the Diels-Alder adducts

IA. The preparation of the dienophiles

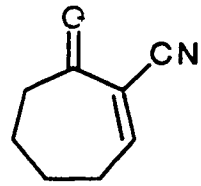
Four 2-cyano-2-cycloalkenones **21**, **22**, **23** and **24** were prepared from the corresponding α-cyano cycloalkanones as the dienophiles. The phenylselenenylation-oxidative elimination process[38] was chosen for the construction of the conjugated enone double bond.



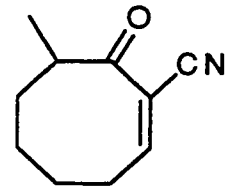
21



22



23



24

2-Cyano-2-cyclopentenone (**21**) was prepared from 2-cyanocyclopentanone, a compound which was synthesized by the procedure described in the previous chapter. For the introduction of the carbon-carbon double bond, 2-cyanocyclopentanone was first treated with phenylselenenyl chloride and pyridine in dichloromethane at 0°C for 40 minutes. The crude product without purification was immediately subjected to oxidation with hydrogen peroxide at 0°C in dichloromethane for 15 minutes to give compound **21** in 80% yield. In the infrared spectrum of **21**, the carbonyl absorption band was displayed at 1759 cm^{-1}. The nitrile absorption band was shown at 2237 cm^{-1}. The absorption

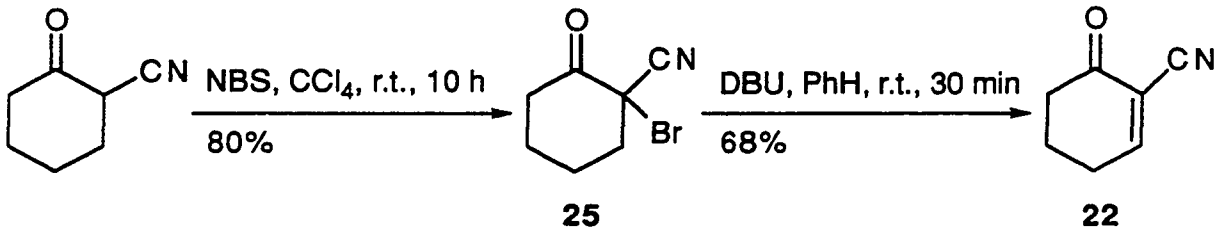
of the conjugated double bond was found at 1606 cm^{-1}. In the ^1H NMR spectrum, the olefinic proton was shown as a triplet (J = 5 Hz) at δ 8.35 , while two α-methylene protons of the ketone carbonyl were displayed as a multiplet at δ 2.97. The ^{13}C NMR APT spectrum of **21** displayed a total of 6 signals, including a carbonyl carbon signal at δ 201.2, a nitrile signal at δ 121.7 and two olefinic carbon signals at δ 174.2 and 118.7. Its high resolution mass spectrum showed a molecular ion peak at m/z 107.0371 which was consistent with the molecular formula C_6H_5NO.

Compound **22** was similarly prepared from 2-cyanocyclohexanone in 75% yield. The infrared spectrum of this compound displayed an absorption band at 1726 cm^{-1} for the carbonyl group and an absorption at 2233 cm^{-1} for the nitrile group. The absorption of the olefinic double bond was shown at 1612 cm^{-1}. The ^1H NMR spectrum of **22** displayed a triplet (J = 4.5 Hz) at δ 6.62 for the olefinic proton, as well as a multiplet at δ 2.43 for the α–methylene protons of the ketone carbonyl. Another multiplet at δ 1.55 was attributed to the allylic methylene protons of the double bond. Seven carbon signals were shown in the ^{13}C NMR APT spectrum including a carbonyl signal at δ 191.5, a nitrile signal at δ 117.6 and two double bond signals at δ 162.4 and 114.7. Its molecular formula C_7H_7NO was supported by the high resolution mass spectrum showing a molecular ion peak at m/z 121.0526.

To prepare compound **22**, an attempt was also made to effect the formation of the double bond using the bromination-dehydrobromination process. This process which involves less toxic reagents has been used successfully in our laboratory on several occasions with the similar compounds.[39] As shown in **Scheme 2-5**, treatment of 2-cyanocyclohexanone with *N*-bromosuccinimide

(NBS) in carbon tetrachloride gave the bromo keto nitrile **25** in 80% yield. Dehydrobromination of **25** using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) as the base afforded compound **22** in 68% yield.

Scheme 2-5



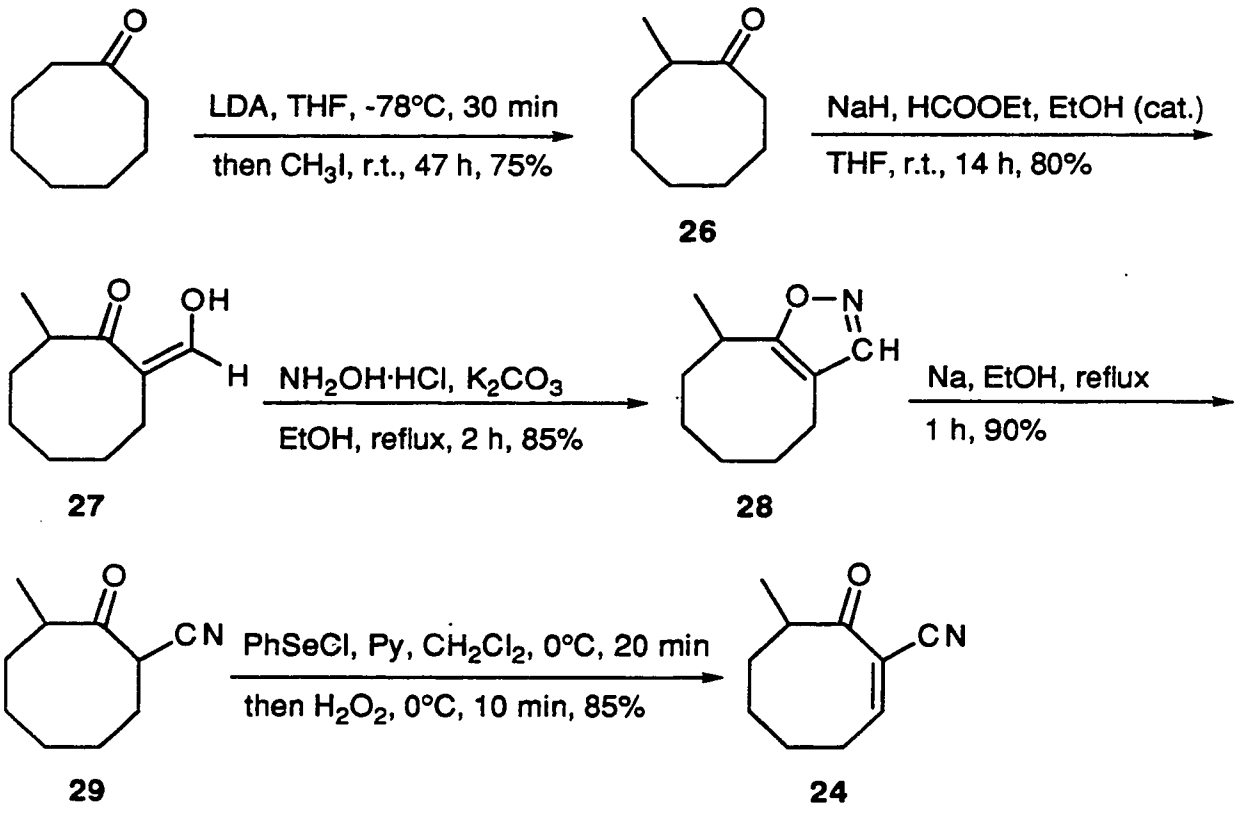
25 **22**

Treatment of 2-cyanocycloheptanone with phenylselenenyl chloride and pyridine followed by oxidative work-up with hydrogen peroxide gave the desired enone nitrile **23** in 78% yield. This compound showed, in the infrared spectrum, a carbonyl absorption band at 1716 cm^{-1}, a nitrile absorption at 2228 cm^{-1} and a conjugated double bond absorption at 1633 cm^{-1}. In the ^1H NMR spectrum, the signal of the vinylic proton was displayed as a triplet (J = 6 Hz) at δ 7.50. The α-methylene protons of the carbonyl moiety were shown as a multiplet at δ 2.64. The ^{13}C NMR APT spectrum displayed a carbonyl signal at δ 196.4, a nitrile signal at δ 120.8 and two vinylic carbon signals at δ 168.8 and 116.6. The high resolution mass spectrum of **23** gave a molecular ion peak at m/z 135.0678 in accordance with the molecular formula C_8H_9NO.

The interest in building the fused bicyclic[6,4,0]dodecane skeleton, a structure which has been found in many biologically active natural products,[40,41] and applying the reductive alkylation process to this system led us to prepare 2-

cyano-8-methyl-2-cyclooctenone (**24**) as the dienophile. The preparation of this compound is schematically illustrated in **Scheme2-6**

Scheme 2-6



Methylation of cyclooctanone, followed by formylation, isoxazole formation and base induced rearrangement of the isoxazole gave the formation of 2-cyano-8-methylcyclooctanone (**29**). The ^{1}H NMR spectrum of this compound indicated that it existed as a mixture of two diastereomers (2 : 1). A phenylselenenylation-oxidative elimination reaction sequence was then applied to cyano ketone **29** for the installation of the conjugated carbon-carbon double bond. Under the

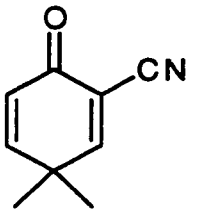
condition virtually identical to that described aboved, the enone nitrile **24** was obtained in 90% yield from **29**. The infrared spectrum of this compound displayed a carbonyl absorption band at 1715 cm^{-1} as well as a nitrile band at 2228 cm^{-1}. In the ^1H NMR spectrum, the methyl protons were shown as a doublet (J = 7 Hz) at δ 1.19. The olefinic proton was displayed as a triplet (J = 6.5 Hz) at δ 7.15. The α-methine proton adjacent to the methyl group was found at δ 2.84 as a multiplet. In the high resolution mass spectrum, a molecular ion peak was observed at m/z 163.1002 in agreement with the molecular formula of $C_{10}H_{13}NO$.

IB. Diels-Alder reactions of 2-cyano-2-cycloalkenones

Once the preparation of dienophiles was completed, the Diels-Alder reactivity of these dienophiles with several dienes was examined. The first question arisen in this study was the selection of an effective Lewis acid to catalyze the reactions.

Recently, an investigation has been conducted in our research group to study the Diels-Alder reactivity of 2-cyano-4,4-dimethyl-2,5-hexadienone (**30**).[42] It was observed that without Lewis acid catalysis, the cycloaddition of **30** to dienes proceeded very slowly. For example, at room temperature or even at elevated temperature, the reaction of **30** with 2-methyl-1,3-butadiene gave little product formation even after a few weeks of reaction time. However, under Lewis acid catalysis, an enhanced reactivity of **30** was observed and the extent of enhancement was dependent on the particular type of Lewis acid, the kind of solvent and the amount of catalyst used. Among a large number of experimental conditions explored, the use of zinc chloride (2 equivalents) as a catalyst and

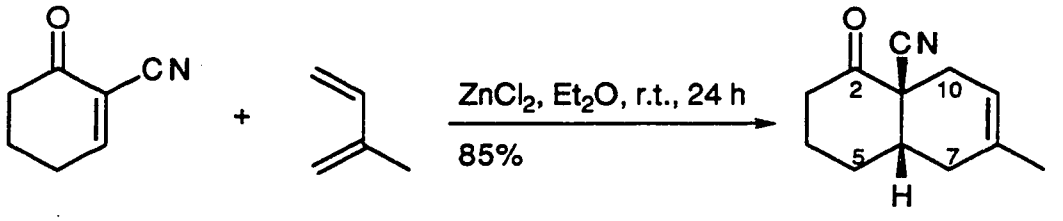
ether as a solvent was found to be superior to other conditions to improve the Diels-Alder reactivity of **30**.



30

It was due to this finding that we first decided to look at the possibility of using zinc chloride as the catalyst in the Diels-Alder reactions of **21-24** which contain a cross conjugated α-cyano enone system similar to that found in compound **30**. The first reaction to be carried out was the addition of dienophile **22** to isoprene (**16**). In the reaction, zinc chloride (2 equivalents) was first flame-fuse dried under an argon atmosphere and dissolved in dry ether. An ethereal solution of dienophile **22** was then added. After stirring at room temperature under argon for 20 minutes, diene **16** (10 equivalents) was introduced. The resulting solution was stirred at room temperature for 24 hours to give exclusively the *para* addition product **31** in good yield (85%) (**Equation 2-6**).

Equation 2-6



22 **16** **31**

The infrared spectrum of **31** displayed a carbonyl absorption band at 1716 cm^{-1} as well as a nitrile absorption band at 2242 cm^{-1}. Its high resolution mass spectrum gave a molecular ion peak at m/z 189.1156, corresponding to the molecular formula $C_{12}H_{15}NO$. The ^{13}C NMR APT spectrum displayed one set of signals including a carbonyl signal at δ 202.9, a nitrile signal at δ 120.1 and two vinylic carbon signals at δ 132.1 and 114.8, indicating the generation of a single stereoisomer. In the ^{1}H NMR spectrum of **31**, the vinylic proton appeared as a multiplet at δ 5.27. The methyl group was displayed as a broad singlet at δ 1.63. The α-methylene protons of the ketone moiety were shown as two multiplets at δ 2.66 and 2.62. The structure of compound **31** was unambiguously confirmed by a X-ray crystallographic analysis as shown in **Figure 2-3**.

Under the similar conditions, a few other Diels-Alder adducts were prepared from 2-cyano-2-cycloalkenones **21-24** using isoprene (**16**), *trans*-piperylene (**8**) and 2,3-dimethyl-1,3-butadiene (**32**) as the dienes. In general, all of these reactions gave reasonably good yields of the products (75-90%). The regiochemistry of the adducts follows from the *ortho* and *para* rules, whereas the stereochemistry results from the *endo*-to-ketone addition. The results from this study are compiled in **Table 2-1**.

Figure 2-3 The three dimensional X-ray crystallographic structure of compound **31**

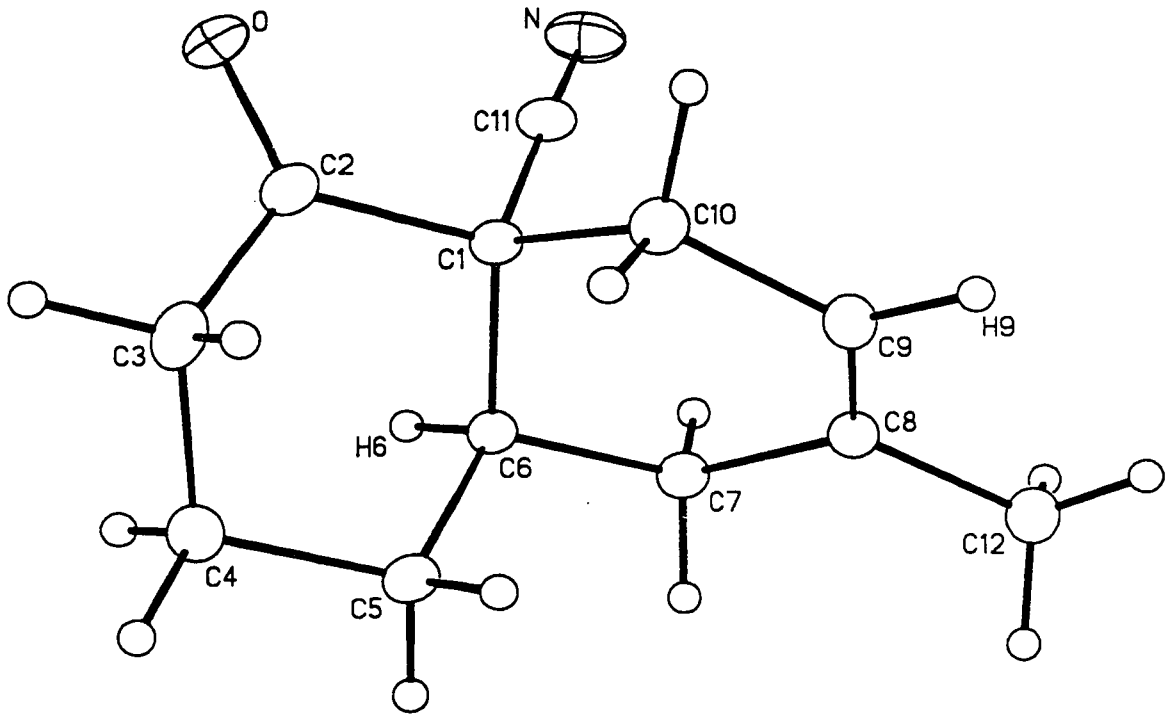
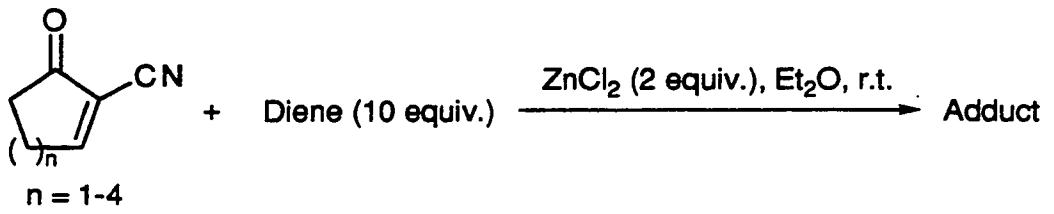
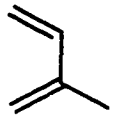
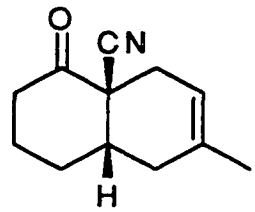
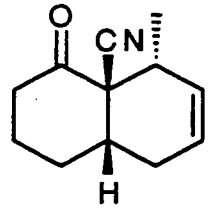
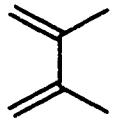
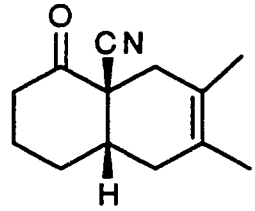
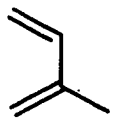
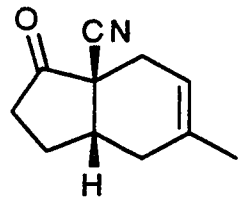
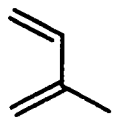
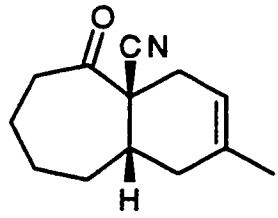
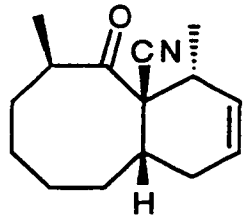


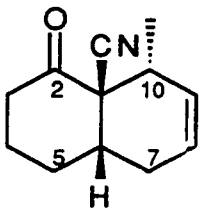
Table 2-1 Diels-Alder reactions of 2-cyano-2-cycloalkenones



Entry	Dienophile	Diene	Time (h)	Adduct	Yield (%)
1	**22**		24	 **31**	85
2	**22**		24	 **33**	75
3	**22**		18	 **34**	90
4	**21**		28	 **35**	80

Entry	Dienophile	Diene	Time (h)	Adduct	Yield (%)
5	**23**		40	 **36**	75
6	**24**		26	 **37**	78

The zinc chloride mediated Diels-Alder reaction of 2-cyano-2-cyclohexenone (**22**) with *trans*-piperylene gave adduct **33** in 75% yield (Entry 2). The infrared spectrum of **33** displayed a carbonyl absorption at 1735 cm^{-1} and a nitrile absorption at 2231 cm^{-1}. In its high resolution mass spectrum, a molecular ion peak at m/z 189.1155 was consistent with the molecular formula $C_{12}H_{15}NO$. The ^{13}C NMR APT spectrum of **33** displayed one set of 12 carbon signals, including a carbonyl signal at δ 201.3, a nitrile signal at δ 121.1 and two vinylic carbon signals at δ 128.7 and 122.9, supporting the generation of a single stereoisomer.

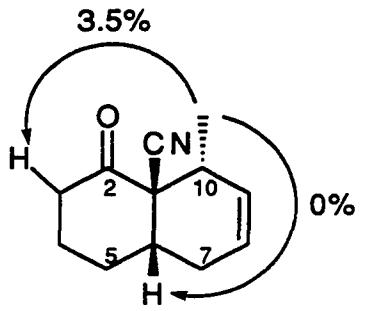


33

The assignment of the ^1H NMR spectrum of **33** was assisted by proton spin decoupling experiments. In the spectrum, two vinylic protons appeared as an overlapped multiplet at δ 5.52. The α-methylene protons of the ketone moiety were displayed at δ 3.05 (ddd, J_1 = 18 Hz, J_2 = 7.5 Hz, J_3 = 7 Hz) and 2.33 (dm, J = 18 Hz). The C-10 methyl group appeared as a doublet (J = 7 Hz) at δ 1.35, while the adjacent methine proton was displayed as a multiplet at δ 2.65. The C-7 allylic methylene protons were shown at δ 1.90 and 2.03 as two multiplets. A multiplet at δ 2.69 was assigned to the C-6 ring junction proton. The regiochemistry of cycloadduct **33** was assigned on the basis of the NOE experiments as illustrated in **Figure 2-4**. Irradiation of the C-10 methyl signal at δ 1.35 gave a 3.5% enhancement of one of the C-3 protons at δ 3.05. No

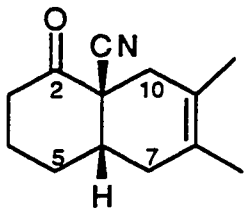
enhancement was observed for the C-6 methine proton, confirming the formation of the *ortho*-like product.

Figure 2-4 The NOE results of compound **33**



The NOE experiments, however, could not help us to confirm the *cis* relationship between the C-6 ring junction proton and the C-10 methine proton. Since the chemical shifts of these two protons were quite close to each other, it was impossible to irradiate them selectively. The stereochemistry of **33**, however, could be indirectly deduced from the structure of the reductive alkylation products which will be detailed in the next section. From the structure of **33**, it could be seen that the transition state of the Diels-Alder reaction between **22** and *trans*-piperylene was *endo*-to-ketone. The secondary orbital overlap between the carbonyl group and the π system of the diene might be responsible for this transition state.

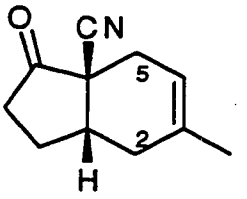
Dienophile **22** reacted with 2,3-dimethyl-1,3-butadiene for 18 hours to afford cycloadduct **34** in 90% yield (Entry 3). The stereochemistry of this compound was assigned on the basis of the *cis*-principle.



34

The ^{13}C NMR APT spectrum of **34** displayed 13 carbon signals, including a carbonyl signal at δ 202.8 and a nitrile signal at δ 120.3. The infrared spectrum showed characteristic absorptions at 1715 cm^{-1} (carbonyl) and 2242 cm^{-1} (nitrile). Its molecular formula $C_{13}H_{17}ON$ was supported by the high resolution mass spectrum by displaying a molecular ion peak at m/z 203.1306. The ^{1}H NMR spectrum displayed two singlets at δ 1.65 and 1.63 for two methyl groups. The α-methylene protons of the carbonyl group appeared as two multiplets at δ 2.64 and 2.52. A multiplet at δ 2.15 was observed for the C-6 methine proton.

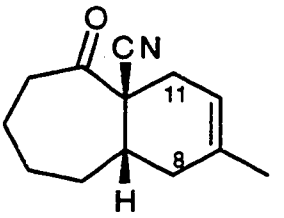
Under the catalysis of zinc chloride, the cycloaddition of five-membered dienophile **21** to 2-methyl-1,3-butadiene gave the *para*-like adduct **35** as white crystals in 80% yield (Entry 4). Its infrared spectrum displayed an absorption at 1732 cm^{-1} for the carbonyl group and another absorption at 2247 cm^{-1} for the nitrile group. In the high resolution mass spectrum, a molecular ion peak was observed at m/z 175.0995 which was consistent with the molecular formula $C_{11}H_{13}NO$. There were a total of eleven signals displayed in the ^{13}C NMR APT spectrum, including a carbonyl signal at δ 207.9, a nitrile signal at δ 119.6 and two vinylic carbon signals at δ 132.7 and 114.6.



35

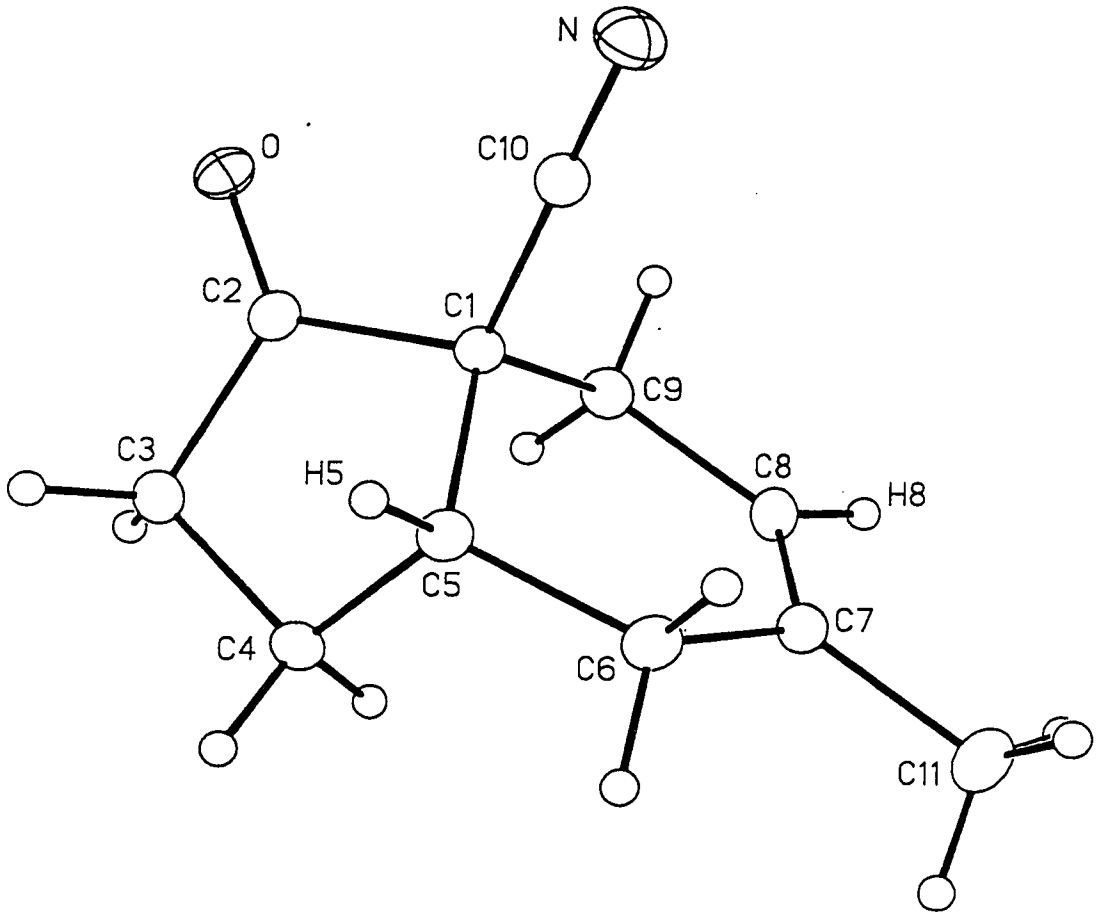
In the ^1H NMR spectrum of **35**, the olefinic proton was shown as a broad singlet at δ 5.36. The methyl group was found at δ 1.72 as a broad singlet. The α-methylene protons of the ketone carbonyl were displayed at δ 2.72 and 2.46 as two multiplets. The structure of compound **35** was verified by a X-ray crystallographic analysis as shown in **Figure 2-5.**

The Diels-Alder addition of dienophile **23** to 2-methyl-1,3-butadiene for 40 hours at room temperature afforded adduct **36** in 75% yield (Entry 5). In the infrared spectrum of **36**, two notable absorption bands were observed at 1731 cm^{-1} (ketone carbonyl) and 2250 cm^{-1} (nitrile). The high resolution mass spectrum gave a molecular ion peak at m/z 203.1301 in agreement with the molecular formula $C_{13}H_{17}ON$. The ^{13}C NMR APT spectrum displayed one set of 13 carbon signals, confirming the formation of a single isomer.



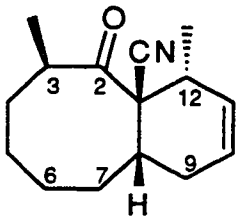
36

Figure 2-5 The three dimensional X-ray crystallographical structure of compound **35**



In the ^1H NMR spectrum of compound **36**, the vinylic proton appeared as a multiplet at δ 5.34. The methyl group was displayed as a broad singlet at δ 1.66. The α-methylene protons of the ketone carbonyl moiety were shown as two multiplets at δ 2.92 and 2.58. The signals of the C-11 allylic methylene protons were found at δ 2.36 (d, J = 16 Hz) and 1.85 (dd, J_1 = 16 Hz, J_2 = 6 Hz). The regiochemistry of **36** was not confirmed until the reductive methylation reaction was carried out. The indirect deduction of the regiochemistry of **36** from the structure of the reductive methylation product will be discussed in the following section.

Finally, the Diels-Alder reaction of dienophile **24** with *trans*-piperylene gave the adduct **37** in a yield of 78%. The infrared spectrum of this product showed similar absorption bands for the carbonyl group and the nitrile group. The ^{13}C NMR APT spectrum displayed one set of 15 carbon signals, indicating the formation of a single stereoisomer. The molecular formula $C_{15}H_{21}NO$ was confirmed by its high resolution mass spectrum which gave a molecular ion peak at m/z 231.1624.

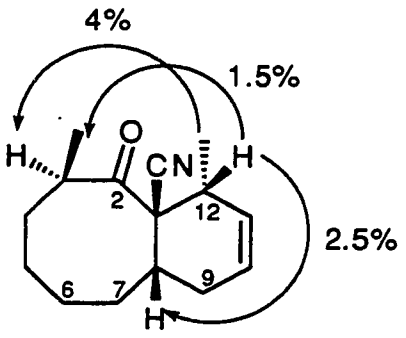


37

The assignment of the ^1H NMR spectrum of compound **37** was assisted by proton decoupling and COSY experiments. The C-10 vinylic proton appeared at δ 5.45 (dm, J = 10 Hz), while the C-11 vinylic proton was displayed at δ 5.72 as

a multiplet. A doublet (J = 7 Hz) at δ 1.10 was assigned to the C-12 methyl group. Another doublet (J = 7.5 Hz) at δ 1.22 was attributed to the C-3 methyl group. The C-12 methine proton was displayed at δ 1.90 as a multiplet. The C-3 methine proton was shown as a multiplet at δ 2.82. The ring junction proton appeared as a multiplet at δ 2.05. The structure of **37** was confirmed on the basis of the NOE experiments as shown in **Figure 2-6**. In this case, the presence of the methyl group at the α position of the ketone moiety of the dienophile introduces a new aspect of stereoselectivity, *i.e.*, the facial selectivity. The diene might add to the enone from either the same face as the methyl group (the methyl face) or the face opposite to the methyl group (the proton face) which is assumed to be the sterically less hindered face.

Figure 2-6 The NOE results of compound **37**



From the structure of **37**, it can be concluded that the transition state of the Diels-Alder reaction is *ortho*-oriented and *endo*-to-ketone, and furthermore, during the transition state, the diene approaches the dienophile from the proton face.

Overall, the zinc chloride mediated Diels-Alder reaction of 2-cyano-2-alkenones proved to be effective for the rapid construction of polycyclic ring systems. The yields of the reactions were reasonably high and the regio- and stereochemical outcomes were generally quite predictable.

IC. 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 is clear that the cyano group is a good synthetic tool in promoting [4 + 2] cycloaddition reaction. The synthetic significance of this addition further lies in the fact that the cyano group is a versatile functionality which can be transformed into a wide variety of other functional groups. For example, upon treatment with various reducing agents, the cyano group can be converted into an aldehyde[43] or an amine.[44] The versatility of the cyano group makes it possible for us to elaborate the Diels-Alder adducts produced from the 2-cyano-2-cycloalkenones.

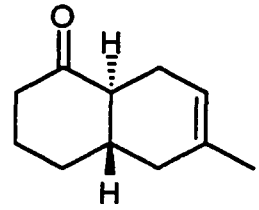
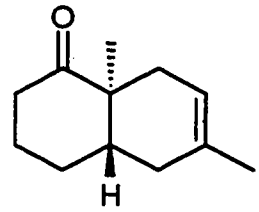
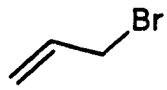
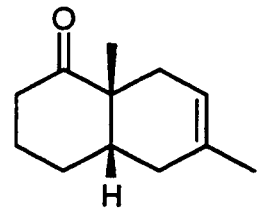
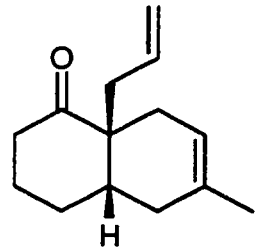
In the first chapter of this thesis, we described a reductive alkylation procedure using monocyclic and acyclic α-cyano ketones. It was observed that the cyano group can be easily removed by reduction using lithium naphthalenide as a reducing agent. The results obtained from this investigation led us to apply the reductive alkylation process to the Diels-Alder adducts. Such an application is possible due to the nature of the cycloaddition products, in which the angular cyano group is attached to the α carbon the ketone carbonyl. Upon treatment with lithium naphthalenide, an enolate is expected to form at a specific site,

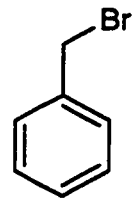
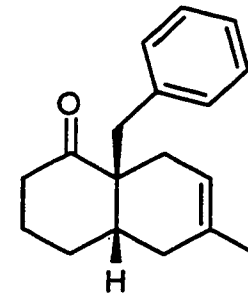
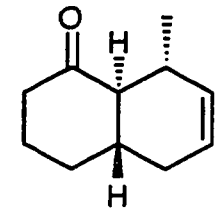
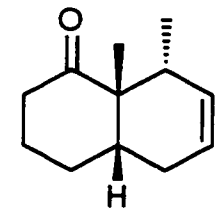
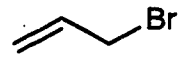
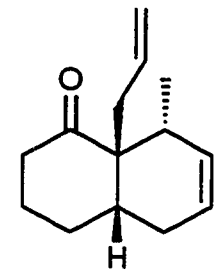
which in turn could be readily trapped with a proton source or an alkylating agent. This procedure could prove to be a very useful tool towards further elaboration of the polycyclic systems generated by the Diels-Alder reactions, whereby a very simple operation could allow incorporation of a variety of functional groups directly, without the complications often associated with lengthy functional group manipulations.

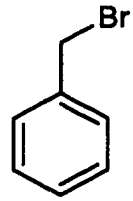
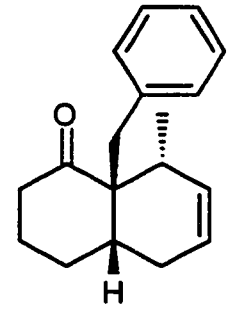
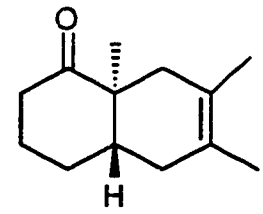
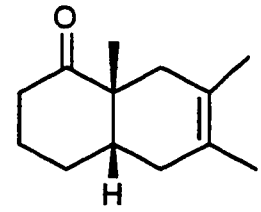
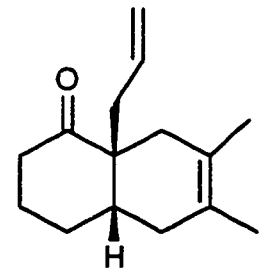
The general procedure used for reductive cleavage of the α-cyano moiety present in each of the Diels-Alder adducts was the same as described in the first chapter. Lithium naphthalenide solution was freshly prepared at room temperature and then cooled to -25°C. The pre-cooled solution was added to the adduct. The reductive decyanation process was usually complete in 30 minutes at -25°C. The reaction mixture was then quenched with methanol to give a product with the cyano group replaced by a hydrogen atom, or with an alkylating agent to afford an alkylated product. All of the six Diels-Alder adducts which were described in the previous section were examined. In each case, six equivalents of lithium naphthalenide were used to ensure the completion of the reaction. The results of this investigation are compiled in **Table 2-2.**

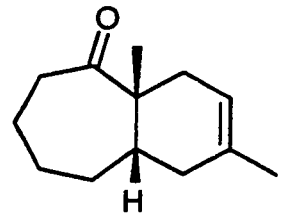
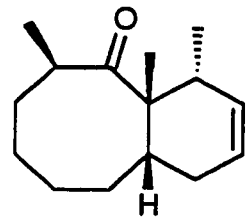
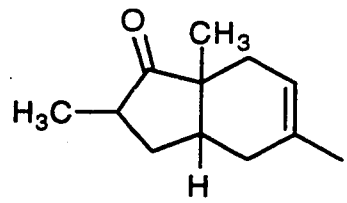
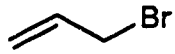
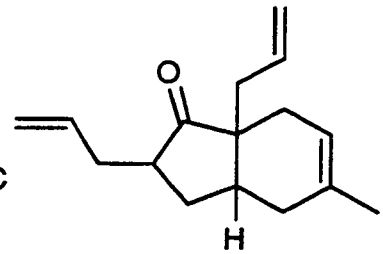
Table 2-2 Reductive decyanation and alkylation of the Diels-Alder adducts

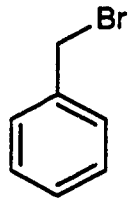
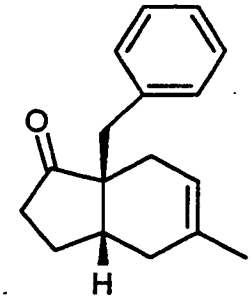
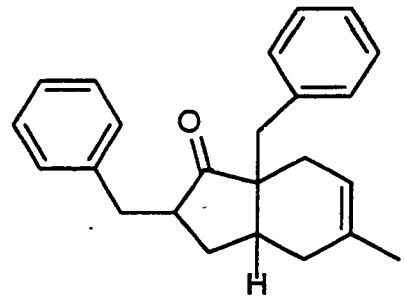
Diels-Alder adduct —(Lithium naphthalenide (6 equiv.); THF, -25°C, 30 min., then RX (10 equiv.) or CH_3OH (excess))→ Reductive decyanation and alkylation product(s)

Entry	Adduct	RX or CH_3OH	Time & Temp.	Product(s)	Yield (%)
1	**31**	CH_3OH	0.5 h, -25°C	 **38**	80
2	**31**	CH_3I	12 h, -25°C	 **39**	75[a]
3	**31**		20 h, -25°C	 **40**  **41**	75

Entry	Adduct	RX or CH_3OH	Time & Temp.	Product(s)	Yield (%)
4	**31**		40 h, r.t.	 **42**	65
5	**33**	CH_3OH	0.5 h, -25°C	 **43**	80
6	**33**	CH_3I	12 h, -25°C	 **44**	70
7	**33**		12 h, -25°C	 **45**	80

Entry	Adduct	RX or CH_3OH	Time & Temp.	Product(s)	Yield (%)
8	**33**		24 h, r.t.	 **46**	74
9	**34**	CH_3I	12 h, -25°C	 **47**	85[b]
				 **48**	
10	**34**		12 h, -25°C	 **49**	70

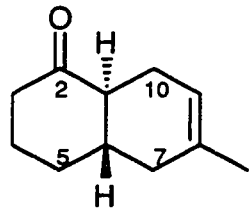
Entry	Adduct	RX or CH_3OH	Time & Temp.	Product(s)	Yield (%)
11	**36**	CH_3I	13 h, -25°C	 **50**	80
12	**37**	CH_3I	14 h, -25°C	 **51**	70
13	**35**	CH_3I	13 h, -25°C	 **52**	80[c]
14	**35**		24 h, -25°C	 **53**	60[d]

Entry	Adduct	RX or CH_3OH	Time & Temp.	Product(s)	Yield (%)
15	**35**		12 h, -10°C	 **54**	60
				 **55**	20[d]

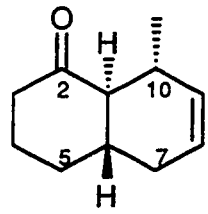
[a]The ratio between **39** and **40** is 4 : 1. [b]The ratio between **47** and **48** is 2 : 1. [c]Two diastereoisomers were formed in a ratio of 2 : 1. Their stereochemistry remains to be determined. [d]Only one diastereoisomer was formed. Its stereochemistry remains to be determined.

Two reductive cleavage reactions were performed in the present study (Entries 1 and 5). Treatment of adducts **31** and **33** with lithium naphthalenide at -25°C for 30 minutes followed by quenching the reaction mixtures with methanol gave products **38** and **43**, respectively. The exclusive formation of the *trans* ring junction products appears to be the result of thermodynamic control.

In the infrared spectra of **38** and **43**, the carbonyl absorption bands were observed at 1708 and 1709 cm^{-1}, respectively. The noticeable absence of the nitrile absorption at approximately 2200 cm^{-1} confirmed the removal of the cyano group. The molecular formulas of these two products ($C_{11}H_{16}O$) were supported by their high resolution mass spectra by showing the molecular ion peaks at m/z 164.1204 for **38** and m/z 164.1195 for **43**. The ^{13}C NMR APT spectrum of **38** displayed 11 signals, including a carbonyl signal at δ 209.3 and two vinylic carbon signals at δ 131.9 and 120.7. For compound **43**, the ^{13}C NMR APT spectrum also gave 11 carbon signals which included a carbonyl signal at δ 209.5 and two vinylic carbon signals at δ 133.4 and 123.6.



38



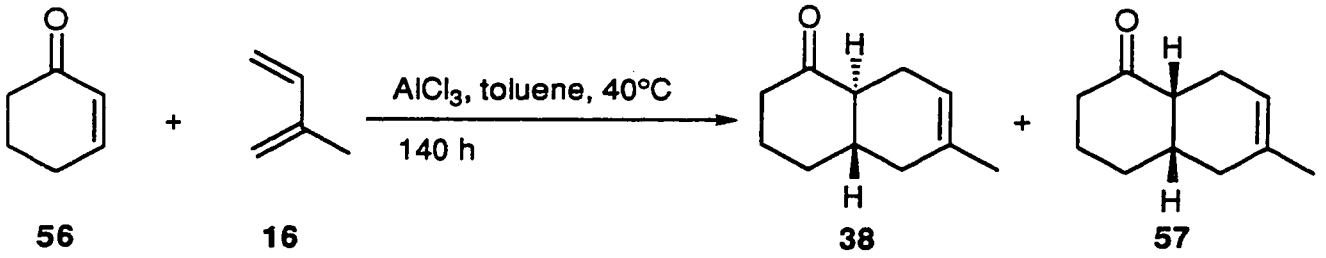
43

In the ^1H NMR spectrum of **38**, the methyl group appeared as a broad singlet at δ 1.62. The olefinic proton was displayed as a multiplet at δ 5.30. The α-methylene protons of the ketone carbonyl were shown at δ 2.45 (multiplet) and 1.85 (ddd, J_1 = 18 Hz, J_2 = 7 Hz, J_3 = 1 Hz). Two multiplets at δ 2.25 and 2.31

were assigned to the C-7 allylic protons. For compound **43**, the ^1H NMR spectrum displayed a doublet at δ 1.03 (J = 7.5 Hz) for the methyl group. Two olefinic protons were shown as an overlapped singlet at δ 5.42. The C-3 α-methylene protons were observed as two multiplets at δ 2.80 and 2.25. The C-10 methine proton appeared at δ 1.75 also as a multiplet.

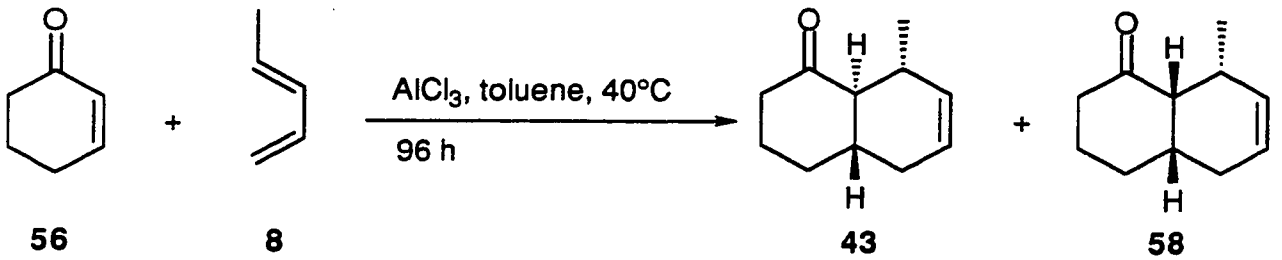
Both **38** and **43** are known compounds. It has been reported that the aluminum chloride catalyzed Diels-Alder reaction of 2-cyclohexenone (**56**) with isoprene (**16**) afforded a 18 : 1 mixture of **38** and **57** (**Equation 2-7**). Under similar conditions, the reaction of **56** with *trans*-piperylene (**8**) gave **43** and **58** in a ratio of 1 : 2 (**Equation 2-8**).[45] Accordingly, the stereochemistry of **38** and **43** could be easily assigned by comparing the spectral data with those reported.

Equation 2-7



56 **16** **38** **57**

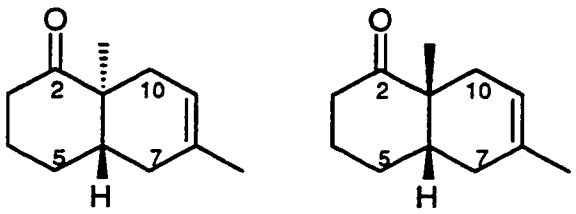
Equation 2-8



56 **8** **43** **58**

The facile removal of the cyano group led us to investigate the trapping of the enolate ion with an alkylating agent. Several alkylating agents including methyl iodide, allyl bromide and benzyl bromide (**Table 2-2**) were chosen for this reductive alkylation process.

The first reaction to be investigated was the reductive methylation of adduct **31** (Entry 2). Treatment of **31** with the reducing agent, lithium naphthalenide, followed by addition of methyl iodide afforded the methylated adducts **39** and **40** as a mixture in a ratio of 4 : 1. The high resolution mass spectrum of the mixture displayed a molecular ion peak at m/z 178.1354 in agreement with the molecular formulas ($C_{12}H_{18}O$). The ^{13}C NMR APT spectrum showed a total of 24 carbon signals corresponding to two stereoisomers. The infrared spectrum of the mixture gave a strong absorption at 1705 cm^{-1} characteristic of the carbonyl group. No absorption for the nitrile group was found.

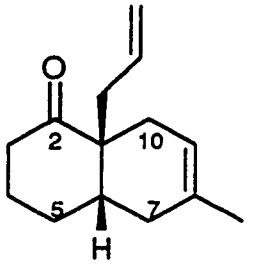


39 **40**

The synthesis of the *cis* compound **40** using a Diels-Alder approach has been reported on several occasions.[45,26] The reported spectral data were fully identical with the spectral data of the reductive alkylation product **40**. After the stereochemistry of **40** was confirmed, the *trans* configuration was assigned to compound **39** since it was the only possibility. The ratio of the products was based on the ^{1}H NMR integration of the related signals. In the ^{1}H NMR spectrum

of the mixture, the *trans* product **39** gave a doublet (J = 1 Hz) at δ 1.02 for the C-1 methyl group. The split of the signal was presumably due to the long range W-type coupling with the C-6 ring-junction proton. The vinylic proton appeared as a multiplet at δ 5.20. The C-8 methyl group was displayed as a singlet at δ 1.63. For the *cis* product **40**, the signal of the C-1 methyl group was observed as a singlet at δ 1.13. The other singlet at δ 1.67 was assigned to the C-8 methyl group. The olefinic proton appeared as a singlet at δ 5.32.

Reductive decyanation of **31** *with lithium naphthalenide at -25°C for 30* minutes, followed by addition of allyl bromide gave the *cis* ring-junction product **41** in a yield of 75% (Entry 3). Interestingly, while the reductive methylation of **31** gave mainly the *trans* ring-junction compound **39**, the reductive allylation resulted in the exclusive formation of the *cis* ring-junction product. The reason for this dichotomy is not clear. Intuitively, the results might be attributed to the different transition states associated with the different reactivities of the alkylating agents.

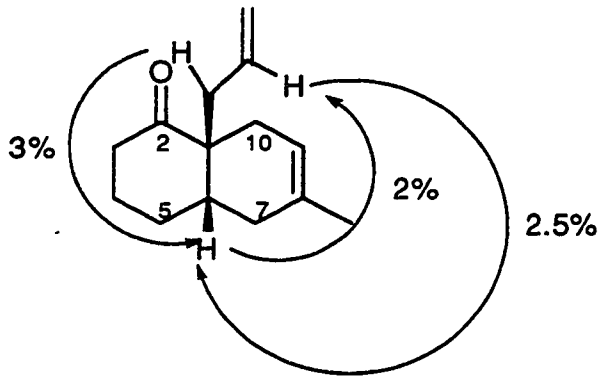


41

In the infrared spectrum of **41**, a strong absorption band was observed at 1708 cm^{-1} for the ketone carbonyl group. The lack of a nitrile absorption confirmed that the cyano group was removed from the adduct. The high resolution mass

spectrum of **41** gave a molecular ion peak at m/z 204.1508 corresponding to the molecular formula $C_{14}H_{20}O$. The ^{13}C NMR APT spectrum diplayed 14 carbon signals including a carbonyl signal at δ 214.4 and 4 vinylic carbon signals at δ 135.1, 131.4, 117.2 and 116.8. The assignment of the ^{1}H NMR spectrum was assisted by extensive proton spin decoupling, ^{1}H COSY and hmqc experiments. The terminal vinylic protons of the allyl group were verified by the signals at δ 5.04 (dm, J = 18 Hz) and 4.98 (dm, J = 10 Hz). The non-terminal vinylic proton of the allyl moiety was displayed at δ 5.75 (dm, J = 18 Hz). The remaining olefinic proton appeared as a multiplet at δ 5.30. The signals of the allylic protons of the allyl group were found at δ 2.52 (dm, J = 18 Hz) and 2.22 (dd, J_1 = 18 Hz, J_2 = 10 Hz). A multiplet at δ 2.02 was assigned to the C-6 ring-junction proton. The methyl group was displayed as a broad singlet at δ 1.66. The stereochemistry of **41** was confirmed by NOE experiments as shown in **Figure 2-7**.

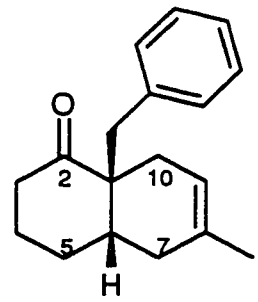
Figure 2-7 The NOE results of compound **41**



Irradiation of the non-terminal vinylic proton at δ 5.75 gave an enhancement (2.5%) of the ring-junction proton signal at δ 2.02. An enhancement (3%) of this

proton was also observed upon irradiation of one of the allylic methylene protons at δ 2.22. Irradiation of the C-6 ring-junction proton at δ 2.02 gave a 2% enhancement of the non-terminal vinylic proton at δ 5.75. The *cis* configuration was thus confirmed.

Reductive alkylation of **31** with benzyl bromide at room temperature for 40 hours gave product **42** in 65% yield (Entry 4). The infrared spectrum of **42** displayed an absorption band at 1702 cm^{-1} for the carbonyl group. The noticeable absence of the nitrile absorption indicated that the cyano group was removed and might be replaced by the alkyl group. The molecular formula $C_{18}H_{22}O$ was supported by the high resolution mass spectrum by showing a molecular ion peak at m/z 254.1669. The ^{13}C NMR APT spectrum of **42** displayed one set of 16 carbon signals, confirming the formation of a single product.

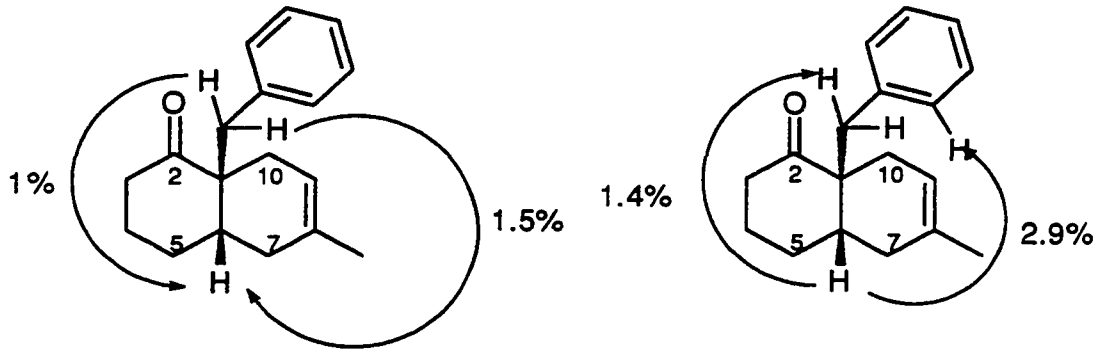


42

In the ^{1}H NMR spectrum, the aromatic protons were displayed as a multiplet at approximately δ 7.15. The benzylic protons were shown as two mutually coupled doublets (J = 13 Hz) at δ 3.35 and 2.80. The signal of the C-9 vinylic proton appeared as a broad singlet at δ 5.34. The C-8 methyl group was shown as a singlet at δ 1.75. With assistance of proton spin decoupling and hmqc

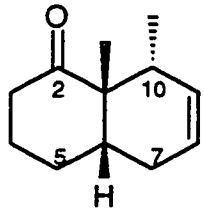
experiments, the signal of the C-6 ring-junction proton was found at δ 1.84 as a multiplet. The stereochemistry of **42** was assigned on the basis of NOE experiments as illustrated in **Figure 2-8**.

Figure 2-8 The NOE results of compound **42**



Irradiation of the benzylic protons at δ 3.35 and 2.80 gave respectively 1% and 1.5% enhancements of the C-6 ring-junction proton signal at δ 1.84. Furthermore, irradiation of the C-6 ring-junction proton resulted in a 1.4% enhancement of one of the benzylic protons at δ 3.35 as well as a 2.9% enhancement of the aromatic protons at δ 7.15.

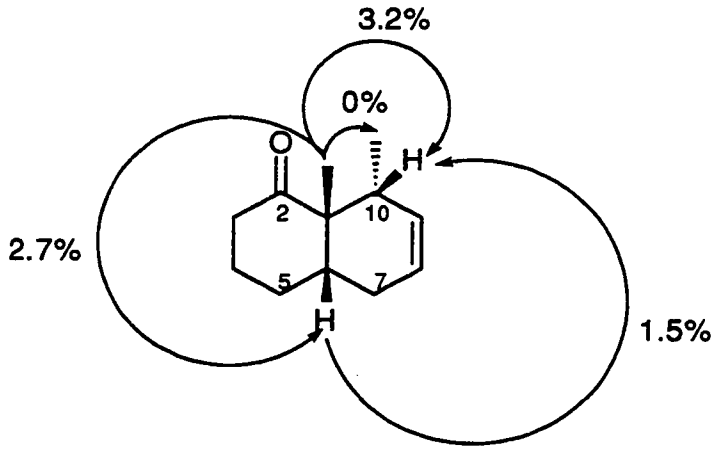
Reductive alkylation of adduct **33** with methyl iodide gave product **44** in 70% yield (Entry 6). In this case, the formation of a single methylated product is probably due to the presence of the methyl group at the C-10 position, which may provide a steric hindrance to prevent the formation of the *trans* ring-junction product.



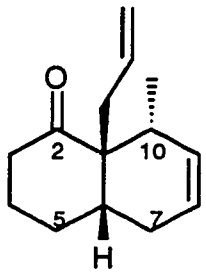
44

The infrared spectrum of **44** indicated the presence of the carbonyl group by showing an absorption band at 1706 cm^{-1}. No absorption of the nitrile group was found. The high resolution mass spectrum displayed a molecular ion peak at m/z 178.1357, supporting the molecular formula $C_{12}H_{18}O$. The ^{13}C NMR APT spectrum showed one set of 12 carbon signals, including a carbonyl signal at δ 212.0 and two vinylic carbon signals at δ 131.6 and 122.8. In the ^{1}H NMR spectrum of **44**, the C-10 methyl group appeared as a doublet at δ 1.17 (J = 7 Hz), while the other methyl group at the angular position was diaplayed as a singlet at δ 1.35. The signals of two vinylic protons overlapped and appeared as a singlet at δ 5.55. With the assistance of proton decoupling experiments, two multiplets at δ 2.10 and 1.90 were respectively assigned to the C-10 methine proton and the C-6 ring-junction proton. The stereochemistry of **44** was verified by NOE experiments as shown in **Figure 2-9**. Based on the structure of **44** and the *cis* principle of Diels-Alder reaction, the stereochemistry of adduct **33** could also be confirmed.

Figure 2-9 The NOE result of compound **44**



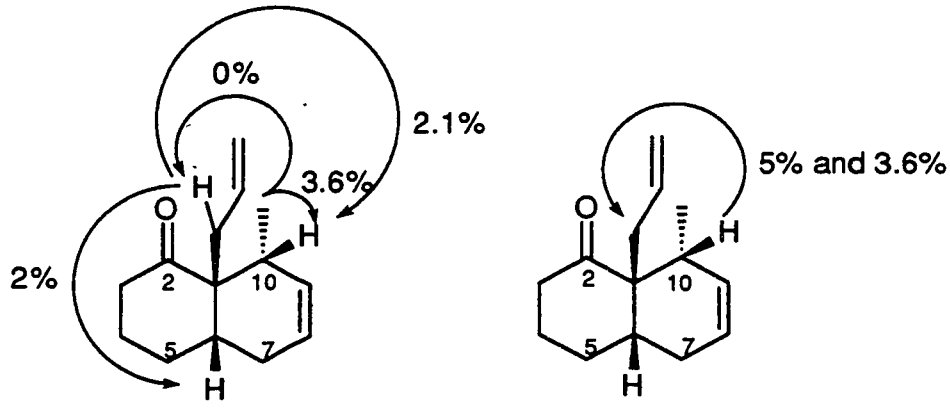
Reductive alkylation of **33** with allyl bromide at -25°C for 12 hours provided product **45** in a yield of 80% (Entry 7). The high resolution mass spectrum of this compound displayed a molecular ion peak at m/z 204.1505 in agreement with the molecular formula $C_{14}H_{20}O$. The disappearance of a nitrile absorption in the infrared spectrum at approximately 2200 cm^{-1} confirmed that the cyano group was removed from the adduct. The ^{13}C NMR APT spectrum displayed 14 carbon signals, including 4 vinylic carbon signals as well as a carbonyl carbon signal at δ 215.0, confirming the formation of a single stereoisomer.



45

Based on the results of proton spin decoupling and ^1H COSY experiments, the assignment of the ^1H NMR spectrum of **45** is as follows. The non-terminal vinylic proton derived from allyl bromide was displayed as a multiplet at δ 5.70, while the terminal vinylic protons were shown at δ 5.10 (dm, J = 17 Hz) and 4.95 (dm, J = 10 Hz). The allylic protons of the allyl group were found at δ 2.80 (ddd, J_1 = 12 Hz, J_2 = 6 Hz, J_3 = 1 Hz) and 2.31 (dd, J_1 = 12 Hz, J_2 = 7 Hz). Two other vinylic protons appeared as a multiplet at δ 5.59. A doublet at δ 1.12 (J = 7 Hz) was assigned to the methyl protons. The adjacent methine proton was displayed as a multiplet at δ 2.06. The C-6 ring-junction proton was found at δ 1.78 as a multiplet. The stereochemistry of **45** was confirmed by NOE experiments as illustrated in **Figure 2-10.**

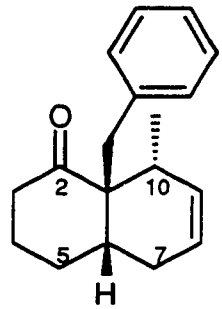
Figure 2-10 The NOE results of compound **45**



Irradiation of the C-10 methyl signal at δ 1.12 gave a 3.6% enhancement of the C-10 methine proton signal at δ 2.06. No enhancement was observed for the allylic methylene protons derived from allyl bromide. Irradiation of the C-10 methine proton at δ 2.06 gave a 3.6% enhancement of one of the allylic methylene protons at δ 2.31, as well as a 5% enhancement of the other allylic

proton at δ 2.80. These results confirmed the *trans* relationship between the C-10 methyl group and the C-1 allyl group. The *cis* ring-junction configuration was verified by irradiation of one of the allylic protons at δ 2.80, which resulted in a 2% enhancement of the C-6 ring-junction proton at δ 1.78.

Reductive alkylation of **33** with benzyl bromide at room temperature for 24 hours afforded compound **46** in 74% yield (Entry 8). In the infrared spectrum of **46**, a carbonyl absorption was observed at 1702 cm^{-1}. The high resolution mass spectrum showed a molecular ion peak at m/z 254.1676, supporting the molecular formula $C_{18}H_{22}O$. There were 16 carbon signals displayed in the ^{13}C NMR APT spectrum, including a carbonyl signal, 2 vinylic carbon signals and 4 aromatic carbon signals.

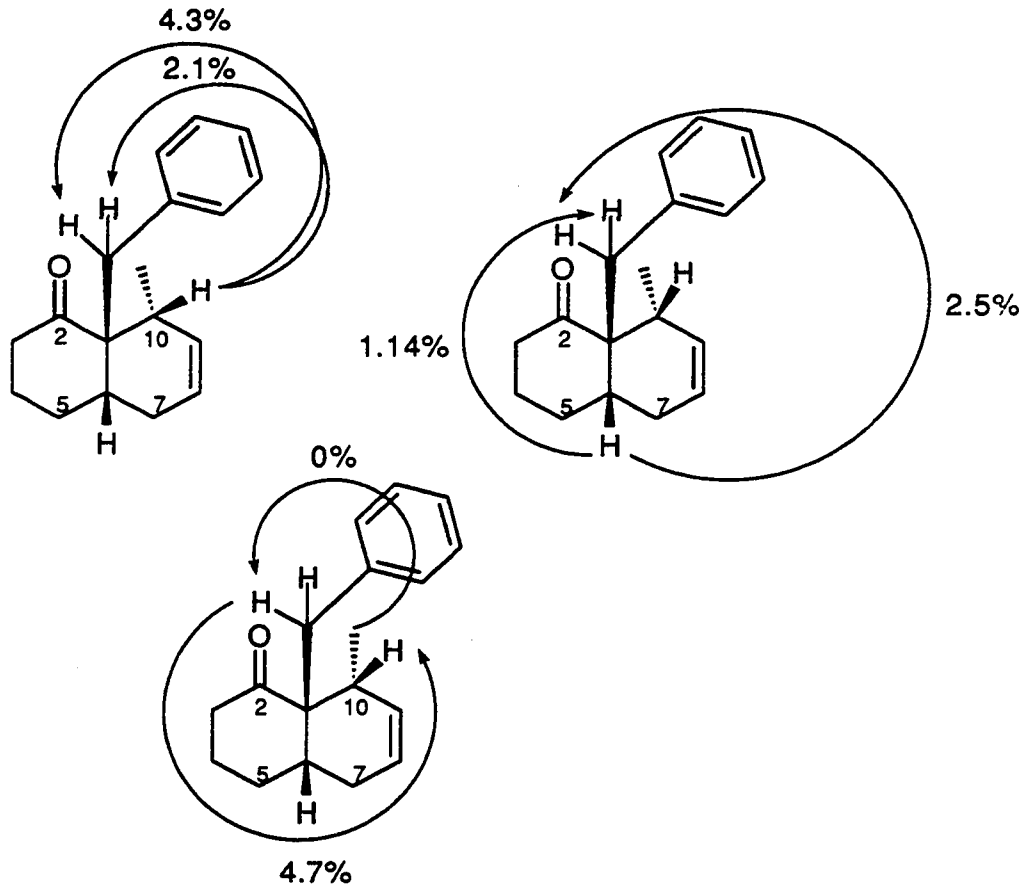


46

In the ^{1}H NMR spectrum of **46**, two multiplets were observed at δ 7.20 and 7.15 for the aromatic protons. The benzylic protons were displayed as two mutually coupled doublets (J = 13 Hz) at δ 3.45 and 2.72. Two vinylic protons appeared as a singlet at δ 5.65. A doublet at δ 1.10 was assigned to the methyl group. Based on the results of proton decoupling experiments, the C-10 methine proton and the C-6 ring-junction proton were found at δ 2.16 and 2.02 as two

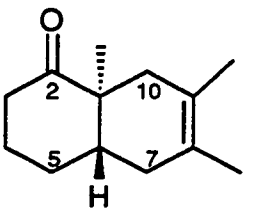
multiplets. The stereochemistry of **46** was confirmed by NOE experiments as shown in **Figure 2-11**.

Figure 2-11 The NOE results of compound **46**

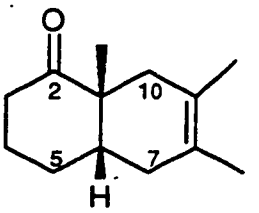


Like the reductive methylation of **31**, reductive alkylation of adduct **34** with methyl iodide also resulted in the formation of two stereoisomers. Compounds **47** and **48** were obtained as an inseparable mixture in a ratio of 2 : 1 (Entry 9). The molecular formulas of these two products ($C_{13}H_{20}O$) were supported by the high resolution mass spectrum by displaying a molecular ion peak at m/z

192.1512. The lack of a nitrile absorption band around 2200 cm^{-1} in the infrared spectrum confirmed that the cyano group was removed. The ^{13}C NMR APT spectrum of the mixture displayed two sets of 26 carbon signals.



47

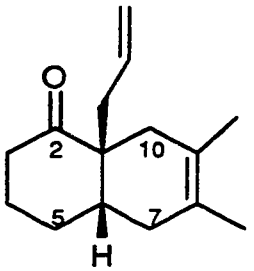


48

The ratio of **47** and **48** was obtained by the integration of the related peaks in the ^{1}H NMR spectrum of the mixture. For the major isomer, the C-1 ring-junction methyl group was displayed as a doublet at δ 1.20 (J = 1 Hz). The signals of the C-8 and C-9 methyl groups overlapped and appeared as a broad singlet at δ 1.62. For the minor isomer, a singlet at δ 1.07 was assigned to the C-1 methyl group. The protons of the C-8 and C-9 methyl groups were displayed as a singlet at δ 1.58. The stereochemistry of **48** was confirmed by comparing its spectral data with the reported ones, since this product is a known compound.[45] By inference, the *trans* configuration was assigned to compound **47**.

Reductive decyanation of **34** with lithium naphthalenide and trapping with allyl bromide at -25°C provided product **49** in 70% yield (Entry 10). There was one set of 15 carbon signals shown in the ^{13}C NMR APT spectrum of **49**, indicating the formation of a single stereoisomer. The absence of the nitrile absorption and the presence of a carbonyl absorption (1073 cm^{-1}) in the infrared spectrum indicated that the cyano group was removed from the cycloadduct. The high

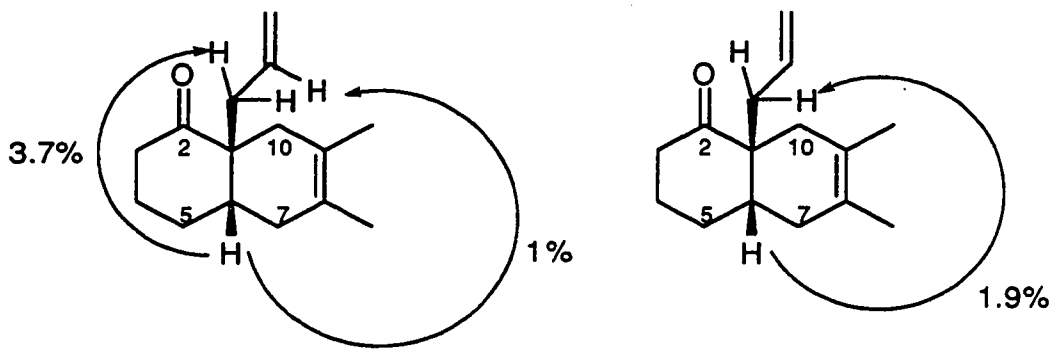
resolution mass spectrum of **49** gave a molecular ion peak at m/z 218.1617 in agreement with the molecular formula $C_{15}H_{22}O$.



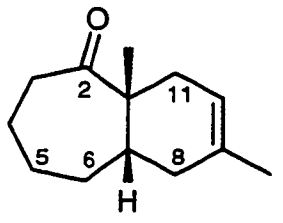
49

In the ^1H NMR spectrum of **49**, the non-terminal vinylic proton derived from allyl bromide was displayed at δ 5.75 as a multiplet. The terminal vinylic protons were shown at δ 5.05 (dm, J = 17 Hz) and 5.00 (dm, J = 9 Hz). The signals of two methyl groups were observed at δ 1.64 and 1.61 as two singlets. With the assistance of proton decoupling experiments, the signals of the allylic protons of the allyl group were found at δ 3.06 (dd, J_1 = 14 Hz, J_2 = 6 Hz) and 2.65 (dd, J_1 = 14 Hz, J_2 = 6.5 Hz). Based on the results of hmqc experiments, a multiplet at δ 2.06 was assigned to the C-6 proton at the ring-junction position. The stereochemistry of **49** was supported by NOE experiments as illustrated in **Figure 2-12**.

Figure 2-12 The NOE results of compound **49**



Reductive alkylation of adduct **36** with methyl iodide at -25°C for 13 hours afforded product **50** in a yield of 80% (Entry 11). The ^{13}C NMR APT spectrum of **50** displayed a total of 13 carbon signals including a carbonyl signal and two vinylic carbon signals, confirming the formation of a single stereoisomer. The molecular formula $C_{13}H_{20}O$ was supported by the high resolution mass spectrum by showing a molecular ion peak at m/z 192.1517. The lack of the nitrile absorption in the infrared spectrum confirmed that the cyano group was removed from the adduct.

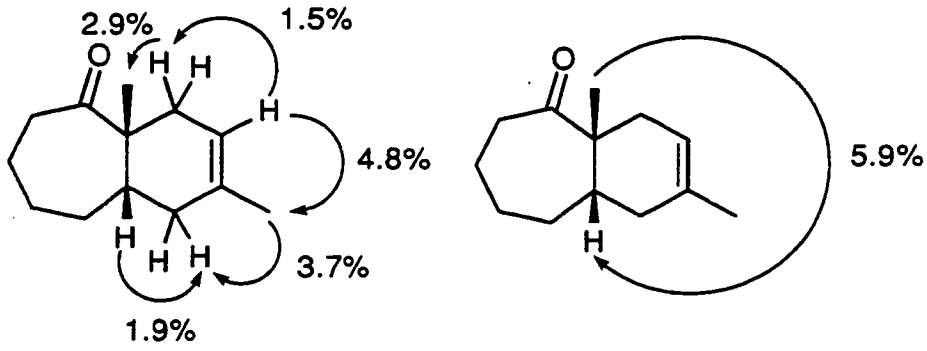


50

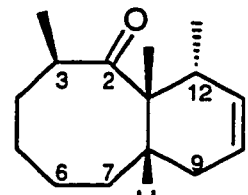
The ^1H NMR spectrum of **50** showed a singlet at δ 5.06 for the vinylic proton. The assignment of other proton signals was assisted by proton spin decoupling and ^1H COSY experiments. A singlet at δ 1.02 was attributed to the C-1 methyl

group, while the other singlet at δ 1.62 was assigned to the C-9 methyl group. The C-11 methylene protons were displayed at δ 2.22 (d, J = 15 Hz) and 2.06 (dm, J = 15 Hz). The C-8 methylene protons were shown at δ 2.36 (dm, J = 12 Hz) and 1.74 (dm, J = 12 Hz). The C-7 ring-junction proton was found as a multiplet at δ 1.98. The NOE experiments of **50**, as shown in **Figure 2-13**, allowed us to depict the stereochemistry and regiochemistry of this product, as well as the regiochemistry of the starting substrate **36**.

Figure 2-13 The NOE results of compound **50**



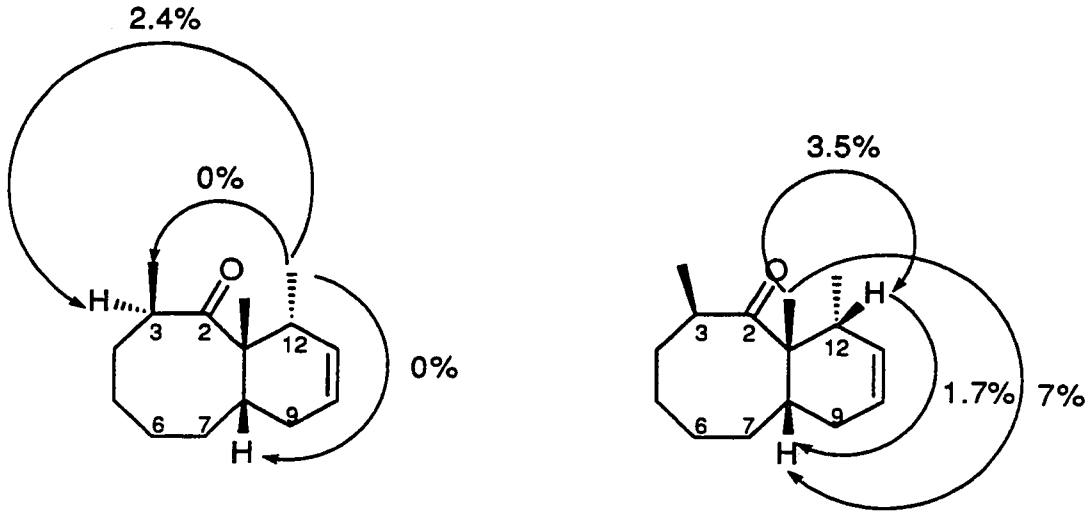
Reductive alkylation of **37** with methyl iodide provided product **51** in 70% yield (Entry 12). The infrared spectrum of this product gave a strong absorption band at 1699 cm^{-1} for the carbonyl group. No absorption for the nitrile group was observed. The high resolution mass spectrum displayed a molecular ion peak at m/z 220.1828, confirming the molecular formula $C_{15}H_{24}O$. The ^{13}C NMR APT spectrum of **51** showed one set of 15 carbon signals, suggesting the formation of only one product.



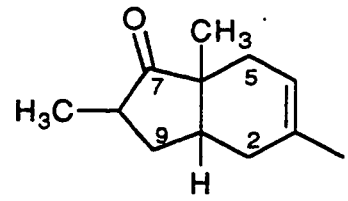
51

In the ^1H NMR spectrum, a multiplet at δ 5.88 was assigned to the C-10 vinylic proton. The C-11 vinylic proton was displayed at δ 5.70 (dm, J = 10 Hz). The C-3 methyl group was shown as a doublet (J = 7 Hz) at δ 1.25, while the C-12 methyl group was found as a doublet (J = 7.5 Hz) at δ 0.52. The C-1 methyl group appeared as a singlet at δ 1.18. The C-3, C-8 and C-12 methine protons were displayed at δ 2.68, 1.82 and 1.96, respectively, each as a multiplet. The stereochemistry of **51** was confirmed by NOE experiments (**Figure 2-14**).

Figure 2-14 The NOE results of compound **51**



Treatment of adduct **35** with lithium naphthalenide followed by addition of methyl iodide gave the dialkylated product **52** instead of the monoalkylated product (Entry 13). Although it has been shown that the radical anions are effective in abstracting protons from compounds having a pK_a less than 33,[46] thus lithium naphthalenide might abstract an α-methylene proton of the ketone moiety to give the dialkylated product, it is not clear why the reductive methylation of **35** gave the dialkylated product, while similar treatment of all the other Diels-Alder adducts provided the monoalkylated products exclusively. To suppress the formation of the dimethylated product, we tried to reduce the amount of lithium naphthalenide. However, it resulted only in the incompletion of the reaction but not in the formation of the desired monoalkylated compound.

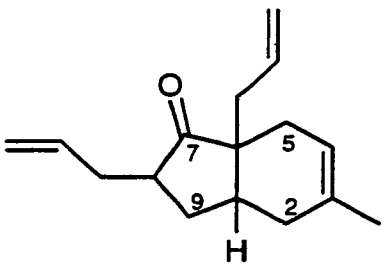


52

Compound **52** existed as a mixture of two diastereoisomers in a ratio of 2 : 1. This was confirmed by its ^{13}C NMR APT spectrum which displayed 2 sets of signals including 2 carbonyl signals at δ 229.8 and 221.2 and 4 vinylic carbon signals at δ 131.5, 130.4, 117.3 and 116.5. The high resolution mass spectrum of the mixture showed a molecular ion peak at m/z 178.1355 in agreement with the molecular formula $C_{12}H_{18}O$. The infrared spectrum of **52** exhibited an absorption band at 1739 cm^{-1} for the carbonyl group. No absorption was observed for the nitrile group. The ratio of two diastereoisomers was obtained from the integration of the related signals in the ^1H NMR spectrum. The major isomer displayed a singlet at δ 1.04 for the C-6 methyl group. The C-8 methyl group appeared as a doublet (J = 7 Hz) at δ 1.14. The signal of the C-3 methyl

group was found at δ 1.68 as a broad singlet. For the minor isomer, the C-6 methyl group was displayed as a singlet at δ 0.88. A doublet (J = 7 Hz) at δ 1.12 was assigned to the C-8 methyl group. The signal of the C-3 methyl protons was observed at δ 1.56 as a singlet. The vinylic protons of two isomers were displayed as a singlet at δ 5.35. The stereochemistry of these two diastereoisomers remains to be confirmed.

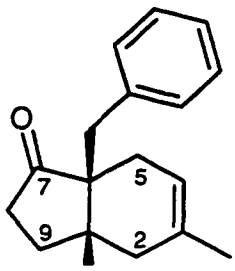
Reductive alkylation of adduct **35** with allyl bromide also resulted in dialkylation to give the dialkylated product **53** in a yield of 60% (Entry 14). The ^{13}C NMR APT spectrum of **53** displayed one set of 16 carbon signals including a carbonyl signal and 6 vinylic carbon signals, verifying the formation of a single stereoisomer. Its high resolution mass spectrum gave a molecular ion peak at m/z 230.1666 corresponding to the molecular formula $C_{16}H_{22}O$.



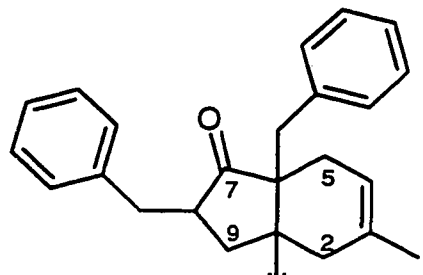
53

In the ^1H NMR spectrum of **53**, two multiplets at δ 5.80 and 5.63 were assigned to the non-terminal vinylic protons of the allyl groups at C-6 and C-8. A broad singlet at δ 5.25 was attributed to the C-4 vinylic proton. The terminal vinylic protons of both allyl groups were displayed as a multiplet at δ 4.91. The signal of the C-3 methyl group was observed at δ 1.20 as a singlet. The stereochemistry of **53** remains to be confirmed.

The reductive benzylation of **35** with benzyl bromide afforded products **54** (60%) and **55** (20%) (Entry 15). The preferential formation of the monoalkylated product in this case is probably due to the larger size of the alkylating agent, which might deter the formation of the dialkylated product.



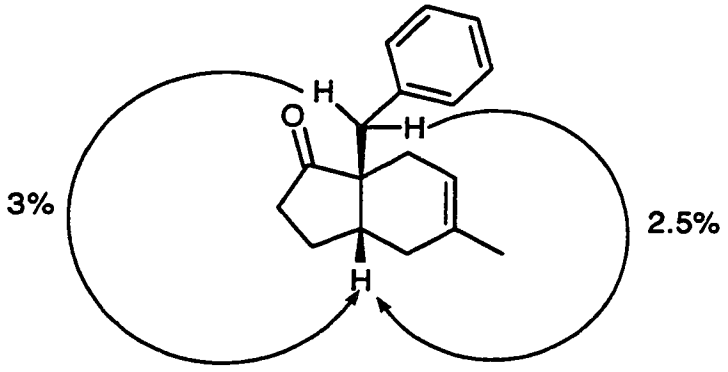
54



55

For compound **54**, the high resolution mass spectrum gave a molecular ion peak at m/z 240.1140 corresponding to the molecular formula $C_{17}H_{20}O$. The infrared spectrum displayed a carbonyl absorption band at 1736 cm^{-1}. The ^{13}C NMR APT spectrum showed 15 carbon signals. In the ^{1}H NMR spectrum, the aromatic protons were displayed as two multiplets at δ 7.05 and 7.30. Two mutually coupled doublets (J = 12 Hz) at δ 3.42 and 2.50 were assigned to the benzylic protons. The C-4 vinylic proton was shown as a singlet at δ 5.10 The signal of the C-3 methyl protons was found as a singlet at δ 1.54. From the results of hmqc experiments, the signal of the C-1 ring-junction proton was determined at δ 1.82 as a multiplet. The *cis* configuration of **54** was supported by NOE experiments as shown in **Figure 2-15.**

Figure 2-15 The NOE results of compound **54**



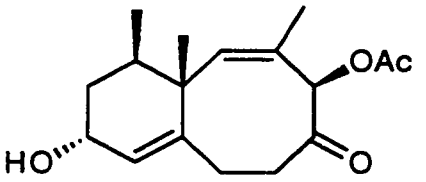
For compound **55**, the molecular formula $C_{24}H_{26}O$ was supported by the high resolution mass spectrum by showing a molecular ion peak at m/z 330.1965. Its ^{13}C NMR APT spectrum displayed one set of 20 carbon signals, indicating the formation of a single stereoisomer. In the ^{1}H NMR spectrum, the aromatic protons were displayed at δ 7.23, 7.04 and 6.90 as three multiplets. The vinylic proton was shown as a singlet at δ 5.22. The benzylic protons of the C-6 substitutent appeared as two mutually coupled doublets at δ 3.35 and 2.50 (J = 13 Hz). The signals of the benzylic protons of the C-8 benzyl group were shown at δ 3.05 (dd, J_1 = 14 Hz, J_2 = 5 Hz) and 2.05 (dd, J_1 = 14 Hz, J_2 = 10 Hz). The C-8 methine proton was displayed as a multiplet at δ 2.47. The C-1 ring-junction proton was observed at δ 1.85 also as a multiplet. The stereochemistry of this product remains to be confirmed.

In general, the reductive decyanation and alkylation process proves to be effective for introducing an alkyl group to the angular position of the bicyclic compounds. Except for a few cases (Entries 13 and 14), all reactions that were investigated gave the expected products in synthetically useful yields (60-85%). Diels-Alder cycloaddition using the cyano-activated dienophiles readily

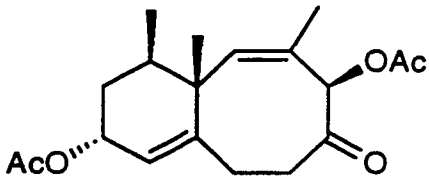
afforded the adducts with a cyano group at the ring junction position. In addition, the presence of a cyano group at the angular position would give facile access to different angularly substituted polycyclic compounds via reductive alkylation. The second part of this chapter will describe the use of this methodology as a key operation in the synthetic studies of two natural products.

II. Synthetic studies on neolemnane (56) and neolemnanyl acetate (57)

In order to demonstrate the synthetic utility of the newly developed process for rapid construction of the polycyclic compounds with an angular alkyl substituent, we embarked on a research project towards the total synthesis of two natural products, neolemnane (**56**) and its acetate **57**.



56



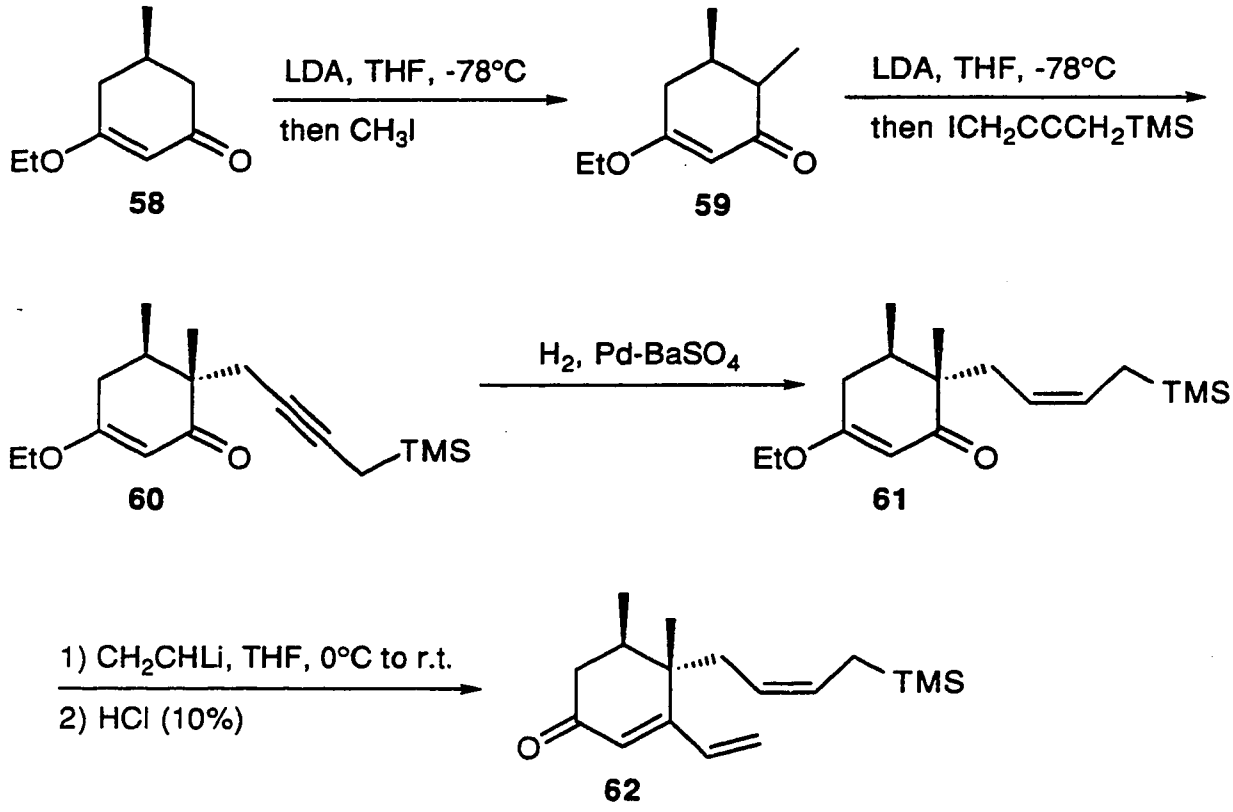
57

These two compounds were first isolated from *L. africana* collected in Palau, Western Caroline Islands by Fenical *et al.* in 1981.[47] Because of their unusual terpenoid skeleton, they suggested the semisystematic name of neolemnane. The biological activity of these two natural products remains unclear and further investigation into this area is required.

Neolemnane (**56**), a crystalline compound with mp 111-112°C, was obtained as the major terpenoidal compound (3% of the crude extract). The structure of **56** was deduced by spectroscopic methods and X-ray crystallographic analysis. Neolemnanyl acetate (**57**), an oil which showed highly analogous ^{1}H NMR features when compared with **56**, was isolated as a minor component (0.15% of the extract). Acetylation of **56** produced a diacetate which was identical with the naturally occurring **57**.

Since their isolation, two total syntheses of **56** and **57** have been accomplished. One of them was reported along with the introduction of a new ring closure methodology in a full paper by Majetich *et al.*[48] The other constituted a part of the Ph.D. dissertation by Ham of Ohio State University.[49] In Majetich's synthesis, the construction of the fused bicyclo[6.4.0]dodecane skeleton was facilitated by the intramolecular Michael reaction of trienone **62** induced by the allylic carbanion generated *in situ* from the corresponding allylsilane using fluoride ion. The preparation of trienone **62** from **58** is illustrated in **Scheme 2-7**.

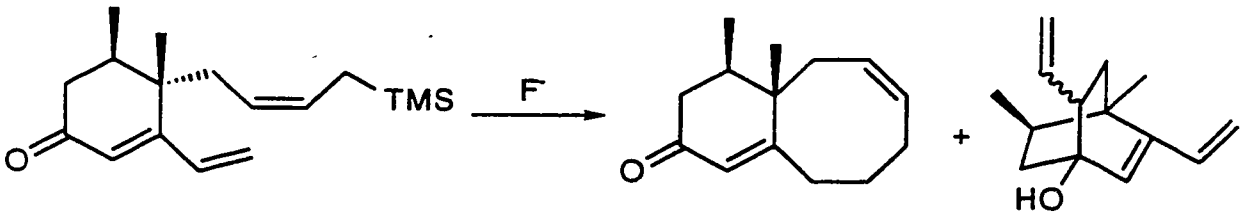
Scheme 2-7



The *cis* relationship of two methyl groups at C-1 and C-12 positions of neolemnane found in trienone **62** was achieved by successive alkylation, first with methyl iodide (**58** → **59**) then with 1-iodo-4-trimethylsilyl-2-butyne (**59** → **60**). Selective hydrogenation of compound **60** was achieved by the use of Lindlar catalyst. Dienone **61** thus obtained was converted to trienone **62** by sequential treatment with vinyllithium and aqueous hydrochloric acid.

After trienone **62** was prepared, the [8.6] fused bicyclic ring was constructed by treating **62** with fluoride ion. From the reaction, the bicyclic enone **63** was obtained in 60% yield along with a small amount of tricyclic alcohol **64** (**Scheme 2-8**).

Scheme 2-8



62 **63** (60%) **64** (10%)

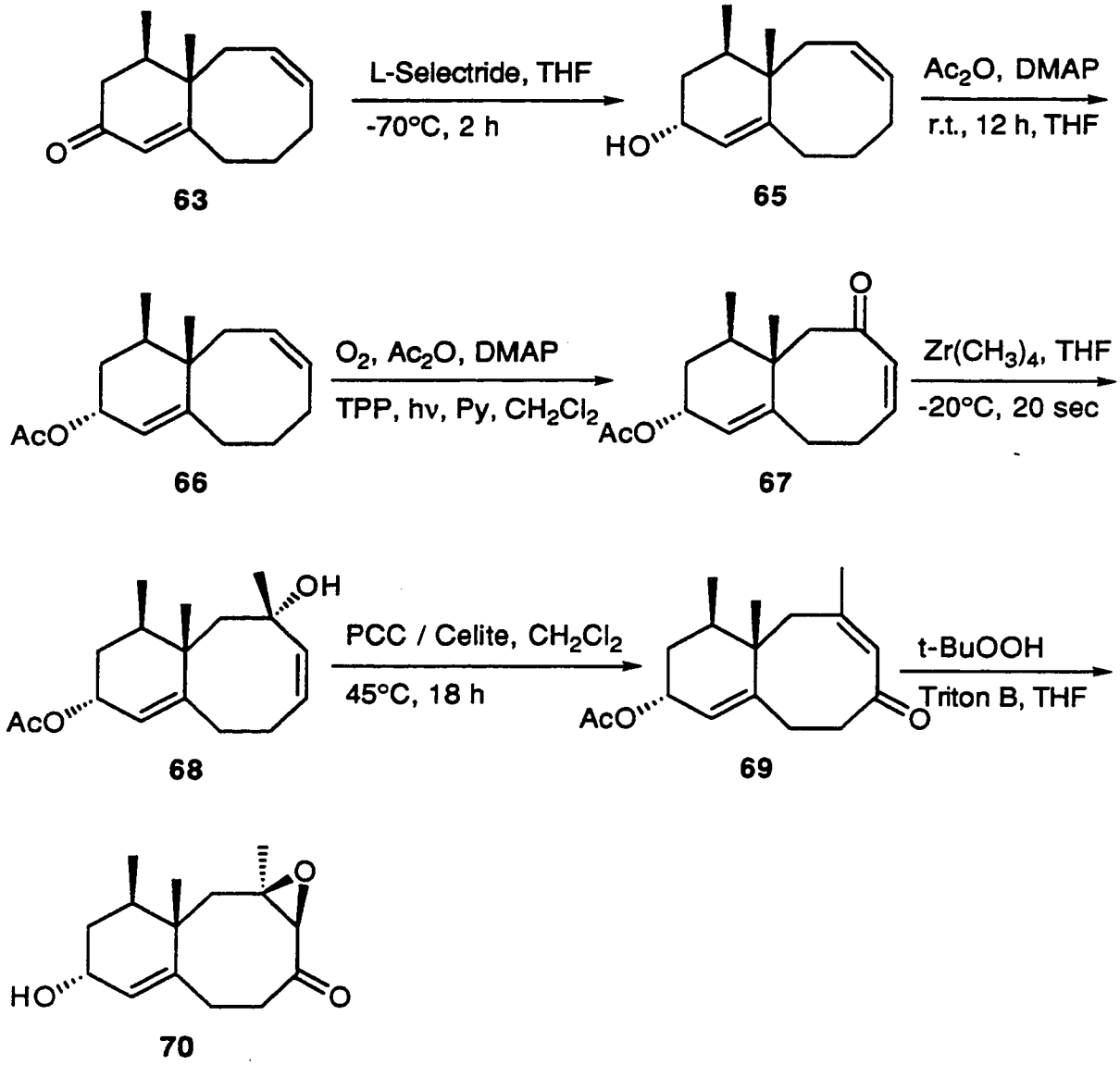
From enone **63**, several transformations were made to prepare compound **70** (**Scheme 2-9**), an intermediate which was used in the preparation of both **56** and **57**. The generation of the required axial allylic alcohol at C-10 from the cyclohexenone system was achieved by using L-selectride as a reducing reagent. The use of this bulky hydride reagent afforded a 1 : 4 mixture of alcohols (95% combined yield) favoring the desired epimer **65**. The

modification of the cyclooctene ring of **66** began with the conversion of its olefinic double bond to an enone system using a photooxygenation reaction. The stereoselective addition of a methyl group to enone **67** at C-3 was effected using tetramethylzirconium to give the desired alcohol **68** in 86% yield. The enone **69** was prepared by oxidative rearrangement of alcohol **68** induced by pyridinium chlorochromate (PCC) on celite. Epoxidation of enone **69** gave intermediate **70**.

The preparation of neolemnane (**56**) from **70** is outlined in **Scheme 2-10**. Upon treatment with acetic formic anhydride, the hydroxyl group of **70** was protected in the form of formate **71**. The epoxide ring of **71** was then opened by treatment with titanium(IV) chloride to give chlorohydrin **72**. The acetylation product **73** was subsequently treated with silver trifluoroacetate to give compounds **74** and **75** in a ratio of 2 : 1. The formyl protecting group of **74** was selectively removed by treatment with $KHCO_3$ in aqueous methanol to give **56**.

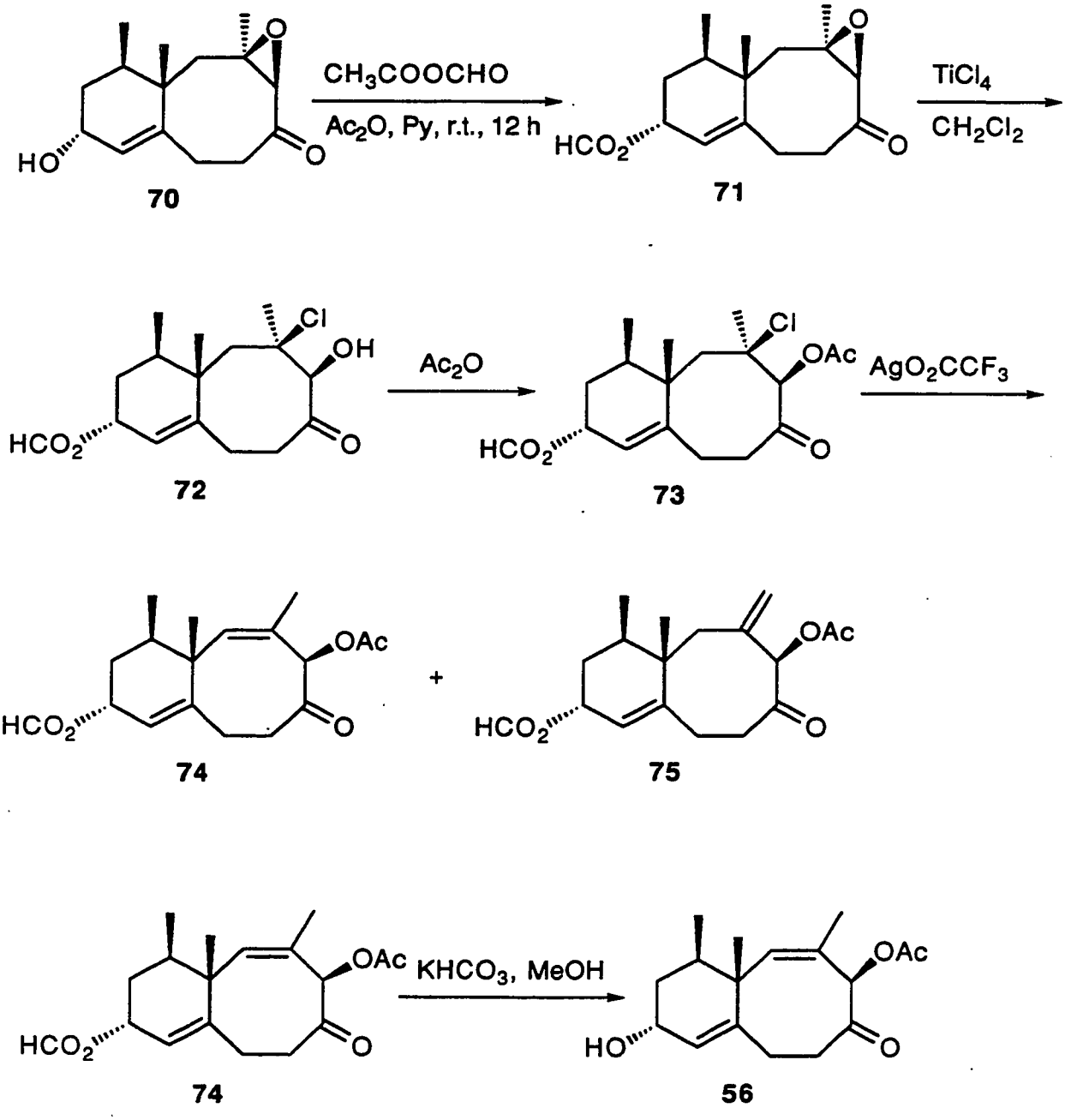
In the preparation of neolemnanyl acetate (**57**), compound **70** was first treated with acetic anhydride. The epoxide ring of the acetylation product **76** was then opened by titanium(IV) chloride to give chloride **77**. The final target molecule **57** was obtained by sequential treatment of **77** with acetic anhydride and silver trifluoroacetate (**Scheme 2-11**).

Scheme 2-9

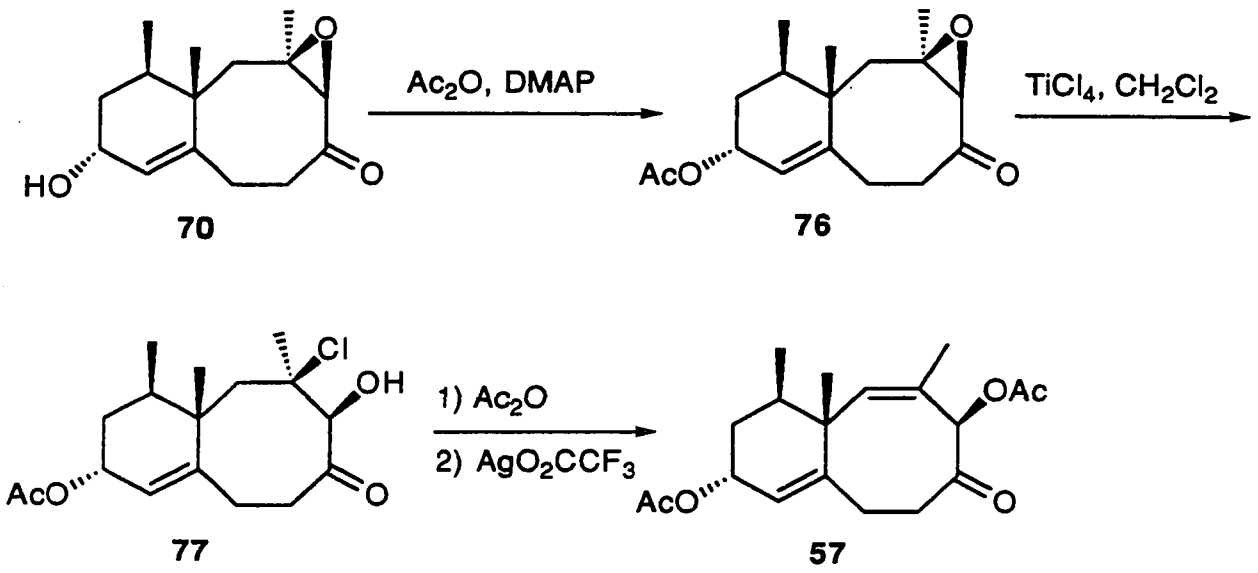


63 **65** **66** **67** **68** **69** **70**

Scheme 2-10


CH3COOCHO
Ac2O, Py, r.t., 12 h
TiCl4
CH2Cl2
Ac2O
AgO2CCF3
KHCO3, MeOH
HO
HCO2
Cl
OH
OAc
O
70
71
72
73
74
75
74
56

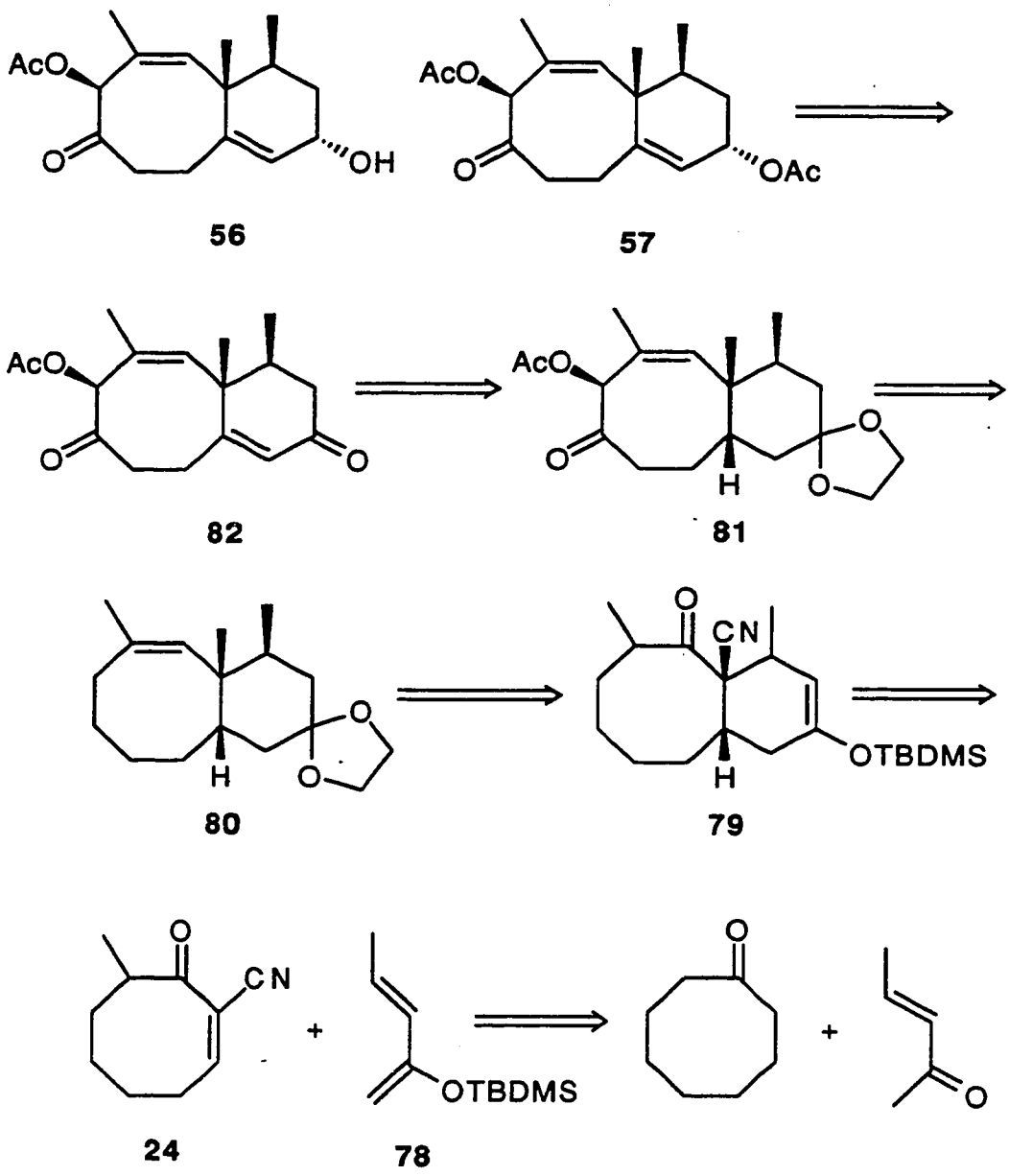
Scheme 2-11



In our previous study, the Lewis acid catalyzed Diels-Alder reaction of 2-cyano-8-methyl-2-cyclooctenone (**24**) displayed a synthetic promise for the rapid construction of the fused bicyclo[6.4.0]dodecane ring system. Furthermore, the angular cyano group of the cycloadduct could be readily replaced by a methyl group through the lithium naphthalenide induced reductive alkylation. Based on these results, we designed a retro-synthetic strategy towards the total syntheses of **56** and **57** as shown in **Scheme 2-12**.

In this strategy, the key operations involve the construction of the fused [8.6] bicyclic ring system by Diels-Alder reaction and the replacement of the cyano group with a methyl group via the reductive alkylation method. Although we have not reached the target compounds **56** and **57** yet, a potential synthetic precursor **80** has been prepared as a result of the current investigation.

Scheme 2-12


AcO
OH
56
AcO
OAc
57
AcO
82
AcO
H
81
H
80
CN
OTBDMS
H
79
CN
24
OTBDMS
78

In order to build the required bicyclo[6.4.0]dodecane skeleton, the Diels-Alder cycloaddition of dienophile **24** to *trans*-2-*tert*-butyldimethylsilyloxy-1,3-pentadiene (**78**) was conducted. Diene **78** was prepared from 3-penten-2-one using lithium diisopropylamide (LDA) and *tert*-butyldimethylsilyl chloride.[50] The Diels-Alder reaction was performed under zinc chloride catalysis. The addition of diene **78** (4.5 equivalents) to an ethereal solution of preformed complex of **24** and zinc chloride at 0°C gave, after stirring at 0°C for 16 hours, compound **79** as a single stereoisomer in a yield of 70%.

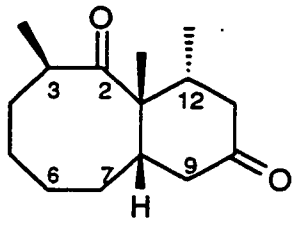
The high resolution mass spectrum of **79** gave a molecular ion peak at m/z 361.2429, supporting the required molecular formula of the addition product ($C_{21}H_{35}O_2SiN$). Its ^{13}C NMR APT spectrum displayed one set of 19 carbon signals, including a carbonyl signal at δ 206.9, a nitrile signal at δ 123.2 and two vinylic carbon signals at δ 148.9 and 108.9, indicating the formation of a single product. The infrared spectrum of **79** showed an absorption at 1705 cm^{-1} for the carbonyl group and another at 2234 cm^{-1} for the nitrile group. In the ^1H NMR spectrum, a singlet at δ 4.60 was observed for the vinylic proton. The protons of two methyl groups on the bicyclic skeleton were displayed as two doublets at δ 1.25 (J = 7.5 Hz) and 1.05 (J = 7 Hz). Two strong singlets at δ 0.92 and 0.20 were attributed to the protons of the *tert*-butyldimethylsilyloxy group. At this point, we could not confirm the stereochemistry of compound **79** due to the overlapped signals in the ^1H NMR spectrum. Hoping that its stereochemistry could be deduced from the reductive methylation product, compound **79** was subjected to reductive methylation.

Treatment of **79** with lithium naphthalenide (6 equivalents) at -25°C for 50 minutes followed by addition of methyl iodide (10 equivalents) afforded, after 16

hours at -25°C, product **83** as a single stereoisomer in 73% yield. The high resolution mass spectrum of **83** supported the required molecular formula of $C_{21}H_{38}O_2Si$ by showing a molecular ion peak at m/z 350.2634. The disappearance of the nitrile absorption around 2200 cm^{-1} in the infrared spectrum as well as the appearance of a singlet in the ^1H NMR spectrum at δ 1.20 indicated that the cyano group was removed and replaced by the methyl group. The ^{13}C NMR APT spectrum of this compound displayed one set of 19 carbon signals, corresponding to a single product. In order to determine the stereochemistry of this compound, an additional reaction was performed to remove the silyl group. Tetrabutylammonium fluoride (TBAF) was selected as a reagent for this purpose.[51]

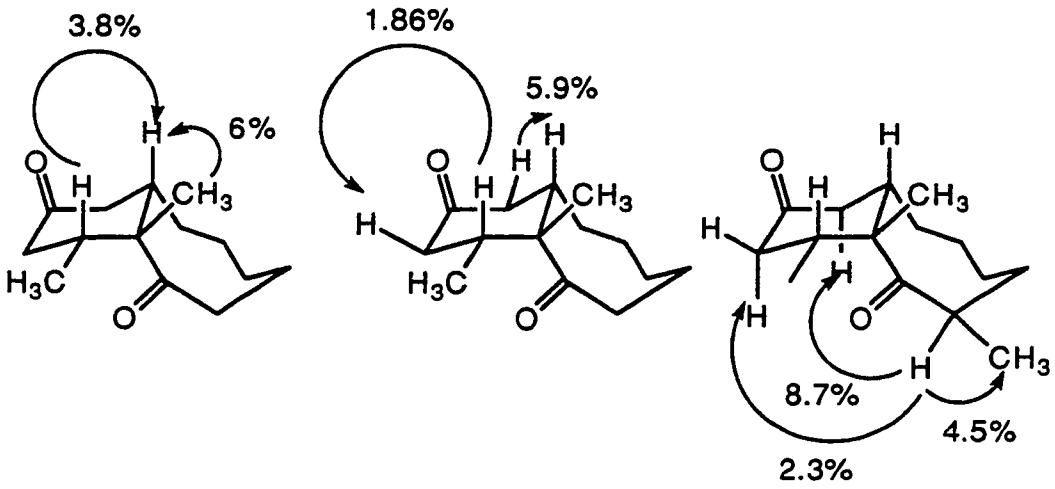
Treatment of **83** with TBAF in THF at -25°C for 50 minutes provided diketone **84** in a yield of 90%. The high resolution mass spectrum of this compound gave a molecular ion peak at m/z 236.1776 in agreement with the molecular formula $C_{15}H_{24}O_2$. In the infrared spectrum, two carbonyl absorptions were observed at 1707 and 1704 cm^{-1}. The ^{13}C NMR APT spectrum of **84** displayed 15 carbon signals for the single stereoisomer. In order to assign the proton signals in the ^1H NMR spectrum, extensive proton spin decoupling and ^1H COSY experiments were conducted. As a result, a singlet at δ 1.05 was assigned to the C-1 methyl group. A doublet (J = 7 Hz) at δ 0.88 was attributed to the C-3 methyl group. The C-12 methyl group was displayed as a doublet (J = 7 Hz) at δ 0.72. The signal for the C-3 methine proton was observed at δ 2.48 as a multiplet. The C-8 ring-junction proton was displayed as a multiplet at δ 1.52. Two C-9 methylene protons were shown at δ 2.70 (dd, J_1 = 14 Hz, J_2 = 13 Hz) and 2.12 (ddd, J_1 = 14 Hz, J_2 = 6 Hz, J_3 = 2 Hz). Of the C-11 methylene protons, one was shown at δ 2.32 (dd, J_1 = 15 Hz, J_2 = 14 Hz) and the other one was displayed at δ 2.22 (ddd,

J_1 = 15 Hz, J_2 = 4.5 Hz, J_3 = 2 Hz). The methine proton adjacent to the C-12 methyl group was found at δ 1.22 as a multiplet. With the assignment of the proton signals of **84**, the stereochemistry of this compound was deduced from the results of NOE experiments as shown in **Figure 2-16**. Based on the complete structural assignment of **84** and the *cis* principle of the Diels-Alder reaction, the stereochemistry of **79** and **83** can also be confirmed. The structure of compound **79** thus established suggested that the transition state of the Diels-Alder reaction between **24** and **78** was *ortho*-oriented and *endo*-to-ketone carbonyl, and that the diene added to the dienophile from the face opposite to the methyl group. The conversion of **79** to **84** is schematically illustrated in **Scheme 2-13**.

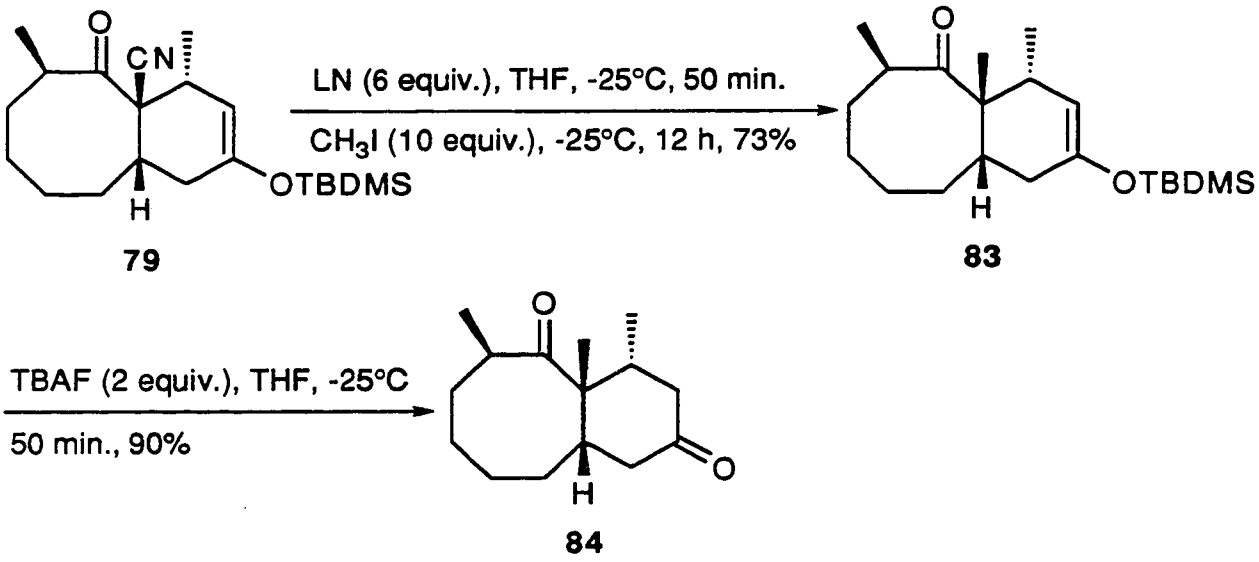


84

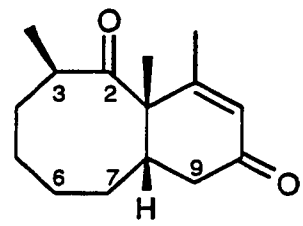
Figure 2-16 The NOE results of compound **84**



Scheme 2-13



Towards the total synthesis of **56** and **57**, the next major synthetic operation was to invert the stereochemistry of C-12. Towards this end, it was decided to transfer the silyl enol ether moiety of **83** into an α,β-unsaturated ketone and then to reduce the conjugated double bond by dissolving metal reduction. To prepare the α,β-unsaturated ketone, compound **83** was subjected to oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of hexamethyldisilazane (HMDS).[52] The reaction was carried out in benzene at 15°C for 30 minutes and compound **85** was formed in a yield of 90%.

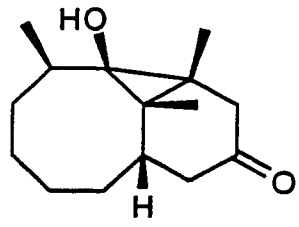


85

The infrared spectrum of **85** displayed an absorption at 1686 cm^{-1} for the α,β-unsaturated carbonyl as well as an absorption at 1704 cm^{-1} for the saturated carbonyl group. The high resolution mass spectrum gave a molecular ion peak at m/z 234.1649 which corresponded to the molecular formula $C_{15}H_{22}O_2$. In the ^1H NMR spectrum, The C-12 methyl group was displayed as a singlet at δ 1.29. A doublet (J = 7 Hz) at δ 0.80 was assigned to the C-3 methyl group. The signal of the C-1 methyl group was found at δ 1.15 as a singlet. The vinylic proton of the conjugated double bond appeared as a sharp singlet at δ 5.92.

In the dissolving metal reduction of compound **85**,[53] lithium metal (6 equivalents) was first dissolved in liquid ammonia at -78°C to yield a dark blue solution. Then *tert*-butyl alcohol (6 equivalents) and a solution of **85** in THF were sequentially added. The resulting solution was stirred at -60°C for 2 hours

to give a single product in 80% yield. This compound, however, was shown by the following spectral data to be alcohol **86**, presumably resulting from an intramolecular addition of the initially formed carbon anion to the C-2 carbonyl group.

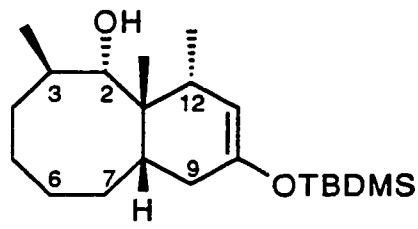


86

In the infrared spectrum of **86**, a strong absorption band was observed at 3422 cm^{-1} due to the hydroxyl group. The carbonyl absorption was found at 1702 cm^{-1}. In the ^1H NMR spectrum, the absence of the vinylic proton signal indicated that the conjugated double bond was reduced. Two singlets at δ 1.10 and 0.92 were displayed for the methyl groups attached to the cyclopropyl ring. The remaining methyl group was shown as a doublet (J = 7.5 Hz) at δ 0.82. Two mutually coupled doublets (J = 14 Hz) at δ 2.35 and 2.15 were assigned to the C-11 methylene protons. The high resolution mass spectrum displayed a molecular ion peak at m/z 236.1775 in agreement with the molecular formula $C_{15}H_{24}O_2$.

As shown by the preceding discussion, the C-2 carbonyl group was clearly incompatible to the dissolving metal reduction required to reduce the conjugated double bond, due to the close proximity of the two functional groups. Hence, we decided to convert the C-2 carbonyl group in compound **83** into a hydroxyl group prior to the oxidation and reduction. Compound **83** was thus

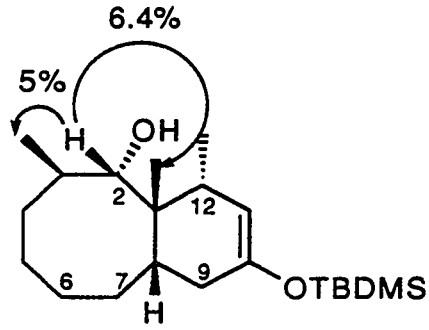
subjected to reduction with lithium aluminum hydride in THF at 0°C for 1 hour to afford alcohol **87** in 75% yield.



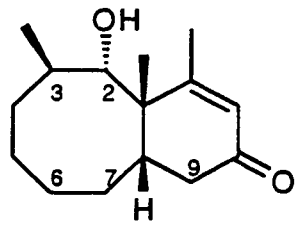
87

For compound **87**, the infrared spectrum displayed a strong absorption at 3478 cm^{-1} characteristic of the hydroxyl group. Its high resolution mass spectrum gave a molecular ion peak at m/z 352.2798 which corresponded to the molecular formula $C_{21}H_{40}O_2Si$. The ^{13}C NMR APT spectrum of **87** showed one set of 19 carbon signals confirming the formation of a single product. In the ^1H NMR spectrum, the C-2 methine proton adjacent to the hydroxyl group was displayed as a broad singlet at δ 3.60. The vinylic proton was observed at δ 4.95 also as a singlet. The C-3 methyl group was shown as a doublet (J = 7 Hz) at δ 1.15, while the other doublet (J = 7 Hz) at δ 0.80 was assigned to the C-12 methyl group. The C-1 ring-junction methyl group was displayed as a singlet at δ 1.10. Two other intense singlets at δ 0.90 and 0.23 were assigned to the protons of the *tert*-butyldimethylsilyloxy substituent. The stereochemistry of **87** was supported by NOE experiments (**Figure 2-17**).

Figure 2-17 The NOE results of compound **87**



With the completion of the reduction, compound **87** was subsequently subjected to oxidation with DDQ and HMDS to give the desired product **88** in 80% yield.

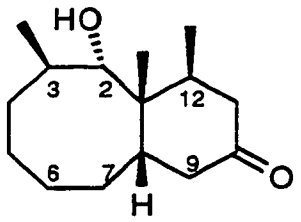


88

The infrared spectrum of this compound displayed an absorption band at 1660 cm^{-1} for the α,β-unsaturated carbonyl group as well as an absorption at 3426 cm^{-1} for the hydroxyl group. Its molecular formula $C_{15}H_{24}O_2$ was supported by the high resolution mass spectrum by giving a molecular ion peak at m/z 236.1786. The ^{13}C NMR APT spectrum displayed a total of 15 carbon signals, including a carbony signal at δ 196.8 and two vinylic carbon signals at δ 164.8 and 128.7. In the ^{1}H NMR spectrum, Two singlets at δ 1.95 and 1.62 were displayed for the C-12 and C-1 methyl groups, respectively. A doublet (J = 7 Hz)

at δ 0.84 was assigned to the C-3 methyl protons. The C-2 methine proton adjacent to the hydroxyl group was shown as a singlet at δ 3.28, while the vinylic proton was displayed at δ 5.82 as a singlet.

Dissolving metal reduction of **88** with lithium and liquid ammonia in the presence of *tert*-butyl alcohol proceeded extremely well to provide product **89** in 90% yield with the desired stereochemistry.

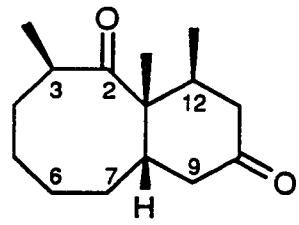


89

The high resolution mass spectrum of **89** showed a molecular ion peak at m/z 238.1928 in agreement with the molecular formula $C_{15}H_{26}O_2$. The infrared spectrum displayed an absorption at 3749 cm^{-1} for the hydroxyl group and an absorption at 1700 cm^{-1} for the carbonyl group. In the ^1H NMR spectrum, two doublets at δ 1.05 (J = 7 Hz) and 0.92 (J = 7 Hz) were readily attributed to the C-3 and C-12 methyl groups. The C-1 angular methyl group was displayed as a singlet at δ 1.20. The C-2 methine proton appeared as a singlet at δ 3.75.

In order to confirm the stereochemistry of **89**, it was decided to oxidize it into a diketone. By comparing the spectral data of the oxidized product with those of compound **84**, the stereochemistry of **89** could, in principle, be deduced. For this purpose, compound **89** was subjected to the treatment with sodium

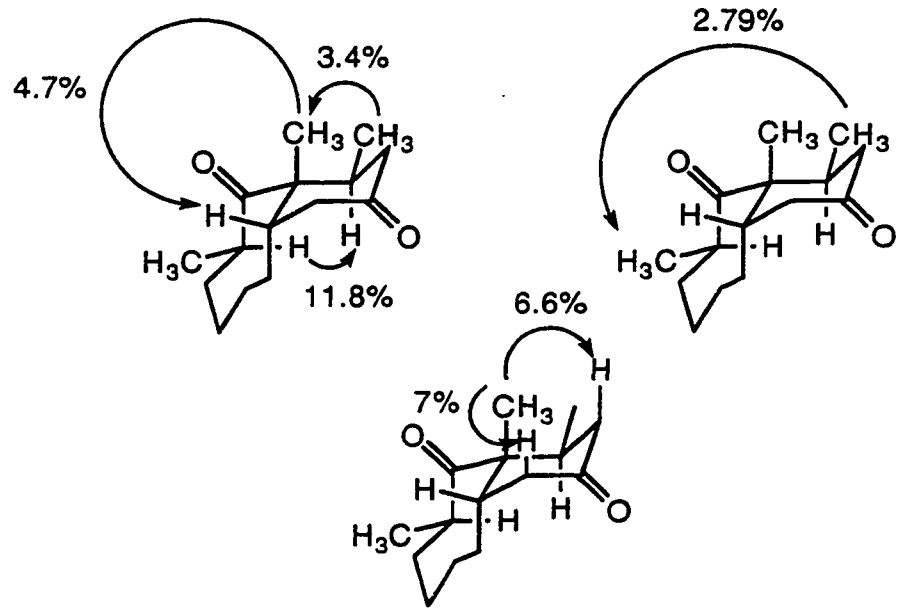
dichromate dihyhydrate and sulfuric acid[54] to give diketone **90** in a yield of 95%.



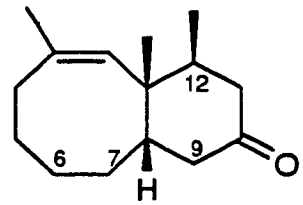
90

Compound **90** proved to have the same molecular formula $C_{15}H_{24}O_2$ as compound **84** as shown by its high resolution mass spectrum. The ^{13}C NMR APT and ^1H NMR spectra of **90**, however, were quite different from those of **84**, suggesting that the stereorelationship of the C-1 and C-12 methyl groups had changed from *trans* to *cis*. To futher confirm this, a large number of proton spin decoupling and ^1H COSY experiments were conducted to assign the signals of the ^1H NMR spectrum of **90** for NOE experiments. The assignment is as follows. A multiplet at δ 2.75 was assigned to the C-3 methine proton, while a doublet at δ 0.95 (J = 7 Hz) was attributed to the adjacent methyl group. The C-1 angular methyl group was displayed at δ 1.05 as a singlet. The C-12 methyl group was observed at δ 0.50 as a doublet (J = 7 Hz). The C-8 ring-junction proton appeared as a multiplet at δ 1.50. The C-12 methine proton was shown as a multiplet at δ 2.20. Of the C-9 methylene protons, one was displayed at δ 2.25 (dd, J_1 = 14 Hz, J_2 = 5 Hz), the other one was shown at δ 1.85 (dm, J = 14 Hz). The C-11 methylene protons were found at δ 2.05 (ddd, J_1 = 16 Hz, J_2 = 6 Hz, J_3 = 2 Hz) and 1.65 (dd, J_1 = 16 Hz, J_2 = 14 Hz). The NOE experiments were then performed. The results compiled in **Figure 2-18**, lent support to the assigned stereochemistry of **90**.

Figure 2-18 The NOE results of compound **90**



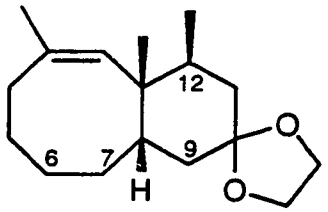
With the stereochemistry of C-12 corrected, the next synthetic operation was to dehydrate compound **89** to install the C-2–C-3 double bond found in **56** and **57**. Treatment of **89** with phosphorus oxychloride in pyridine[55] at room temperature for 14 hours gave the desired product **91** in 70% yield.



91

The high resolution mass spectrum of **91** displayed a molecular ion peak at m/z 220.1827 corresponding to the molecular formula $C_{15}H_{24}O$. The infrared spectrum showed an absorption at 1716 cm^{-1} for the carbonyl group. There were a total of 15 carbon signals displayed in the ^{13}C NMR APT spectrum including a carbonyl signal at δ 208.6 and two vinylic carbon signals at δ 131.2 and 127.7. In the ^{1}H NMR spectrum, the vinylic proton was shown as a singlet at δ 5.42. The C-3 methyl group was displayed as a doublet at δ 1.70 (J = 1 Hz) and C-1 angular methyl group appeared as a singlet at δ 1.20. The signal of the C-12 methyl group was observed at δ 0.95 as a doublet (J = 7 Hz).

The last reaction of the current synthetic investigation was to protect the cyclohexanone carbonyl of **91** in the form of a cyclic ketal. The reaction was carried out with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene for 6 hours to afford 1,3-dioxolane **80** in 75% yield.[56]



80

In the high resolution mass spectrum of **80**, a molecular ion peak was observed at m/z 264.2101 in agreement with the molecular formula $C_{17}H_{28}O_2$. No carbonyl absorption was observed in the infrared spectrum confirming the the formation of the ketal. In the ^{1}H NMR spectrum, the vinylic proton was shown as a singlet at δ 5.35. The C-3 methyl group was displayed at δ 1.07 as a doublet (J = 1 Hz). Two multiplets at δ 3.95 and 3.85 were assigned to the methylene

protons of the 1,3-dioxolane ring. The C-1 methyl group was found at δ 1.05 as a singlet. A doublet (J = 7 Hz) at δ 0.92 was attributed to the C-12 methyl group.

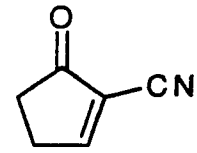
In conclusion, the Diels-Alder approach and the reductive alkylation process developed in our laboratory have been successfully applied to facilitate the preparation of an advanced intermediate in a projected total synthesis of neolemnane (**56**) and its acetate **57**. This intermediate **80** possesses the complete carbon framework of the natural products. Its further elaboration, currently being carried out in our laboratory, requires an array of functional group modifications using the established functionalities which were installed at the strategic positions.

Experimental

General

For general remarks see Chapter 1 of this thesis.

2-Cyano-2-cyclopentenone (21)

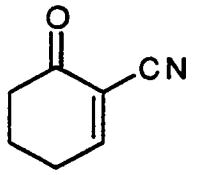


21

Phenylselenenyl chloride (0.838 g, 4.38 mmol) was suspended in 10 mL of dry dichloromethane with stirring under an argon atmosphere and cooled to 0°C. Pyridine (0.4 mL, 5.05 mmol) was then added to the suspension. Stirring and cooling were continued for 20 minutes. Then a solution of 2-cyanocyclopentanone (0.367 g, 3.37 mmol) in dichloromethane (10 mL) was added. The reaction mixture was stirred at 0°C for another 20 minutes, then poured into 10% aqueous hydrochloric acid (8 mL). The organic layer was collected and stirred at 0°C while aqueous H_2O_2 (30%, 5 mL) was added dropwise to the solution. When the oxidation was complete, as indicated by the discharge of the yellow color of the solution, the mixture was quenched with water (15 mL) and extracted with dichloromethane (2 x 15 mL). The organic extracts were washed with water (2 x 10 mL) and aqueous saturated sodium chloride solution (15 mL), dried over anhydrous magnesium sulfate, filter and concentrated in vacuo to give a yellow oil. The crude product was subjected to

flash chromatography. Elution with ethyl acetate-Skelly B (1 : 1) afforded **21** (0.288 g, 2.69 mmol, 80%): IR (CH_2Cl_2, cast): 2237 (CN), 1759 (C=O), 1606 cm^{-1} (C=C); ^1H NMR (200 MHz, $CDCl_3$): δ 8.35 (t, J = 5 Hz, 1H, C**H**=CCN), 2.97 (m, 2H, CH_2C=O), 2.60 (m, 2H, CH_2CH=); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.2 (p), 174.2 (ap), 121.7 (p), 118.7 (p), 33.6 (p), 28.7 (p); HRMS M^+: 107.0371 (calcd. for C_6H_5NO: 107.0376).

2-Cyano-2-cyclohexenone (22)



22

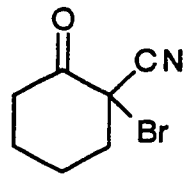
1. From 2-cyanocyclohexanone

This compound was prepared from 2-cyanocyclohexanone (240 mg, 1.95 mmol) using the phenylselenenylation-oxidative elimination process detailed aboved. After work-up, extraction and concentration, the crude product was obtained as a reddish oil, which was then subjected to Kugelrohr distillation at 60°C/1 mm of Hg to afford **22** as a pale yellow oil (180 mg, 1.46 mmol, 75%): IR (CH_2Cl_2, cast): 2233 (CN), 1726 (C=O), 1612 cm^{-1} (C=C); ^1H NMR (300 MHz, C_6D_6): δ 6.62 (t, J = 4.5 Hz, 1H, C**H**=CCN), 2.43 (m, 2H, CH_2C=O), 1.55 (m, 2H, CH_2CH=C), 1.10 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR APT (75 MHz, C_6D_6): δ 191.5 (p), 162.4 (ap), 117.6 (p), 114.7 (p), 36.9 (p), 25.9 (p), 21.1 (p); HRMS M^+: 121.0526 (calcd. for C_7H_7NO: 121.0531).

. 2. From compound **25**

To a solution of **25** (100 mg, 0.49 mmol) in benzene (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.15 mL, 9.9 mmol) at room temperature under argon. After 30 minutures, the mixture was quenched with water (10 mL), and extracted with dichloromethane (2 x 15 mL). The organic extracts were combined and washed with water (10 mL) and saturated sodium chloride solution (10 mL), dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by Kugelrohr distillation at 60°C/1 mm of Hg to yield **22** (40.7 mg, 0.34 mmol, 68%).

2-Bromo-2-cyanocyclohexanone (25)

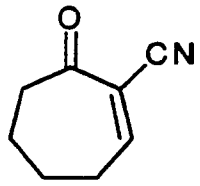


25

2-Cyanocyclohexanone (100 mg, 0.81 mmol) was dissolved in carbon tetrachloride (5 mL). The reaction flask was protected from light and affixed with an anhydrous calcium sulfate drying tube. *N*-Bromosuccinimide (289 mg, 1.63 mmol) was added to the solution and the suspension was stirred at room temperature for 10 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 yellow oil. The oil was distilled using a Kugelrohr apparatus at 85°C/0.5 mm of Hg to give **25** as a yellow oil (131 mg, 1.34 mmol, 80%): IR (CH_2Cl_2, cast): 2241 (CN), 1709 cm^{-1} (C=O); ^1H NMR (300

MHz, $CDCl_3$): δ 2.24 (m, 2H, $CH_2C{=}O$), 1.83 (m, 2H), 1.64 (m, 2H), 1.23 (m, 2H); HRMS M^+: 203.9956 (calcd. for $C_7H_8NO^{81}Br$: 203.9958), 201.9842 (calcd. for $C_7H_8NO^{79}Br$: 201.9844).

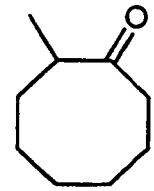
2-Cyano-2-cycloheptenone (23)



23

Compound **23** was prepared from 2-cyanocycloheptanone (1.0 g, 7.3 mmol) using the phenylselenenylation-oxidative elimination method described above. After work-up, extraction and concentration, the crude product was purified by Kugelrohr distillation at 75°C/1 mm of Hg to give **23** as a pale yellow oil (0.77 g, 5.69 mmol, 78%): IR (CH_2Cl_2, cast): 2228 (CN), 1716 (C=O), 1633 cm^{-1} (C=C); ^1H NMR (300 MHz, C_6D_6): δ 7.50 (t, J = 6 Hz, 1H, **CH**=CCN), 2.64 (m, 2H, $CH_2C{=}O$), 1.75 (m, 3H), 1.83 (m, 1H), 1.24 (m, 2H); ^{13}C NMR APT (75 MHz, C_6D_6): δ 196.4 (p), 159.8 (ap), 120.8 (p), 116.6 (p), 34.4 (p), 28.1 (p), 27.3 (p), 26.4 (p); HRMS M^+: 135.0678 (calcd. for C_8H_9NO: 135.0684).

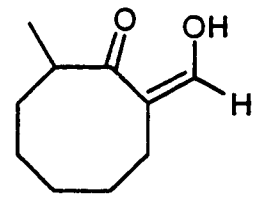
2-Methylcyclooctanone (26)



26

Methylation of cyclooctanone (2 g, 15.8 mmol) with LDA and methyl iodide using the procedure described in Chapter 1 for the preparation of 2-methylcycloheptanone provided, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **26** (1.67 g, 11.9 mmol, 75%): IR ($CHCl_3$, cast): 1701 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 2.55 (m, 1H, $CHCH_3$), 2.35 (m, 2H, $CH_2C{=}O$), 1.00 (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 220.3 (p), 45.3 (ap), 40.4 (p), 33.2 (p), 26.4 (p), 26.0 (p), 25.2 (p), 24.1 (p), 6.9 (ap); HRMS M^+: 140.1198 (calcd. for $C_9H_{16}O$: 140.1201).

2-Hydroxymethylene-8-methylcyclooctanone (27)

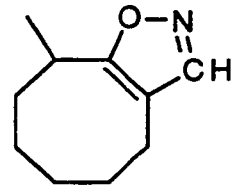


27

Using the formylation process detailed in Chapter 1, the reaction of **26** (1.547 g, 11.05 mmol) with ethyl formate (9 mL, 110.5 mmol) and sodium hydride (95% purity, 0.56 g, 22.1 mmol) in the presence of a catalytic amount of ethanol (3

drops) in THF (40 mL) for 12 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **27** as a pale yellow oil (1.49 g, 8.84 mmol, 80%): IR (CH_2Cl_2, cast): 3200 (OH), 1699 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 15.3 (d, J = 9.5 Hz, 1H, C=CHO**H**), 7.98 (d, J = 9.5 Hz, 1H, C=C**H**OH), 2.95 (m, 1H, C**H**CH_3), 2.52-2.19 (m, 3H), 1.95-1.47 (m, 5H), 1.45-1.20 (m, 2H), 1.02 (d, J = 7 Hz, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.6 (p), 176.7 (ap), 113.7 (p), 37.9 (p), 37.5 (ap), 33.3 (p), 27.1 (p), 26.8 (p), 25.6 (p), 15.8 (ap); HRMS M^+: 168.1146 (calcd. for $C_{10}H_{16}O_2$: 168.1151).

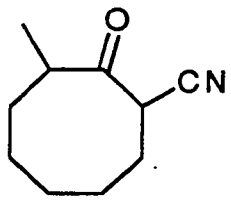
10-Aza-2-methyl-11-oxabicyclo[6.3.0]undec-1(8),9-diene (28)



28

Treatment of **27** (1.384 g, 8.24 mmol) with potassium carbonate (1.14 g, 8.24 mmol) and hydroxylamine hydrochloride (0.86 g, 12.4 mmol) in refluxing absolute ethanol (25 mL) for 2 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **28** as a colorless oil (1.16 g, 7.0 mmol, 85%): IR (CH_2Cl_2, cast): 1698, 1624 (N=C), 974 cm^{-1} (N-O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (s, 1H, C**H**=N), 3.15 (m, 1H, C**H**CH_3), 2.55 (m, 2H), 2.00-1.49 (m, 8H), 1.42 (d, J = 7 Hz, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 171.4 (p), 151.4 (ap), 112.5 (p), 35.1 (p), 31.1 (ap), 28.9 (p), 25.4 (p), 24.9 (p), 21.8 (p), 18.3 (ap); HRMS M^+: 165.1147 (calcd. for $C_{10}H_{15}NO$: 165.1150).

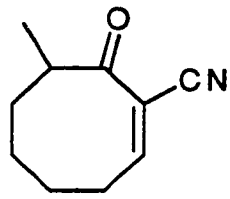
2-Cyano-8-methylcyclooc tanone (29)



29

Compound **29** was prepared using the procedure detailed in Chapter 1. Treatment of **28** (775 mg, 4.69 mmol) with sodium ethoxide in refluxing ethanol for 3 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 5), compound **29** as an inseparable 2 : 1 mixture of two diastereoisomers (659 mg, 3.99 mmol, 85%): IR (mixture, CH_2Cl_2, cast): 1715 (C=O), 2247 cm^{-1} (CN); ^1H NMR (mixture, 360 MHz, $CDCl_3$): δ 3.72 (dd, J_1 = 10 Hz, J_2 = 3 Hz, 0.67H, C**H**CN), 3.60 (dd, J_1 = 13 Hz, J_2 = 4 Hz, 0.33H, C**H**CN), 2.95 (m, 0.33H, CH_3C**H**), 2.79 (m, 0.67H, CH_3C**H**), 2.20-1.80 (m, 3.5H), 1.79-1.44 (m, 4H), 1.20 (m, 1.5H), 1.04 (m, 1H), 1.16 (d, J = 8 Hz, 0.99H, C**H**$_3$), 1.13 (d, J = 8.5 Hz, 2.01H, C**H**$_3$); HRMS (mixture) M^+: 165.1159 (calcd.for $C_{10}H_{15}ON$: 165.1150).

2-Cyano-8-methyl-2-cyclooctenone (24)



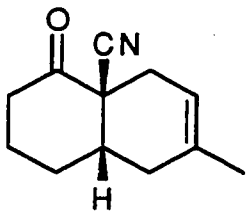
24

Compound **24** was prepared from **29** (603 mg, 3.65 mmol) using the phenylselenenylation-oxidative elimination process detailed above. The crude product was purified by flash chromatography, eluting with ethyl acetate-Skelly B (1 : 1) to afford compound **24** as a reddish oil (506 mg, 3.11 mmol, 85%): IR (CH_2Cl_2, cast): 1715 (C=O), 2228 cm^{-1} (CN); ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (t, J = 6.5 Hz, 1H, C**H**=CCN), 2.84 (m, 1H, CH_3C**H**), 2.45 (m, 2H), 1.82 (m, 1H), 1.80-1.39 (m, 3H), 1.22-1.15 (m, 2H), 1.19 (d, J = 7 Hz, 3H, CH_3); HRMS M^+: 163.1002 (calcd. for $C_{10}H_{13}NO$: 163.1007).

General procedure for $ZnCl_2$ catalyzed Diels-Alder reactions

Zinc chloride (540 mg, 3.97 mmol, 2 equivalents) was flame-fuse dried in a round-bottomed flask under argon. The flask was cooled to room temperature and diethyl ether (10 mL) was added. The resulting mixture was stirred at room temperature until the zinc chloride was completely dissolved (35-40 minutes). The dienophile (1.98 mmol, 1 equivalent) dissolved in ether (5 mL) was added and the solution was stirred at 0°C for 20 minutes. The diene (19.8 mmol, 10 equivalents) was then added and the resulting solution was warmed to room temperature after 10 minutes. When the reaction was complete, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (10 mL). The ether layer was separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic extracts were washed with water (2 x 10 mL) and saturated sodium chloride solution (15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford the crude product, which was then subjected to flash chromatography eluting with ethyl acetate and Skelly B to give the purified product.

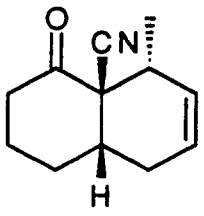
(1R*,6S*)-1-Cyano-8-methylbicyclo[4.4.0]dec-8-en-2-one (31)



31

The reaction of dienophile **22** (240 mg, 1.98 mmol) with 2-methyl-1,3-butadiene (1.98 mL, 1.35 g, 19.8 mmol) under zinc chloride catalysis for 24 hours afford, after flash chromatography (ethyl acetate-Skelly B 1 : 10), adduct **31** as white crystals (319 mg, 1.69 mmol, 85%): mp 76-78°C (hexane); IR ($CHCl_3$, cast): 2242 (CN), 1716 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.27 (m, 1H, =C**H**), 2.66-2.62 (m, 2H, CH_2C=O), 2.50-2.39 (m, 3H), 2.25 (m, 1H), 2.03 (m, 1H), 1.85 (m, 1H), 1.82-1.78 (m, 2H), 1.57 (m, 1H), 1.63 (s, br, 3H, CH_3C=); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 202.9 (p), 132.1 (p), 120.1 (p), 114.8 (ap), 50.2 (p), 39.8 (ap), 36.8 (p), 31.9 (p), 28.8 (p), 26.3 (p), 24.1 (p), 23.6 (ap); HRMS M^+: 189.1156 (calcd. for $C_{12}H_{15}NO$: 189.1161). Anal. calcd. for $C_{12}H_{15}NO$: C 76.19%, H 7.93%; found: C 76.34%, H 8.08%.

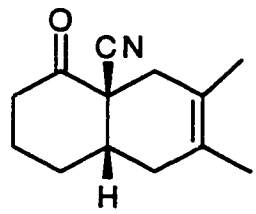
(1S*,10R*)-1-Cyano-10-methylbicyclo[4.4.0]dec-8-en-2-one (33)



33

The reaction of dienophile **22** (820 mg, 6.78 mmol) with *trans*-piperylene (6.8 mL, 4.6 g, 67.8 mmol) under zinc chloride catalysis for 24 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 10), adduct **33** (961 mg, 5.08 mmol, 75%): IR (CH_2Cl_2, cast): 1735 (C=O), 2231 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 5.52 (m, 2H, **CH=CH**), 3.05 (ddd, J_1 = 18 Hz, J_2 = 7.5 Hz, J_3 = 7 Hz, 1H, $CH_2C=O$), 2.33 (dm, J = 18 Hz, 1H, $CH_2C=O$), 2.69 (m, 1H, CH_2CHCH_2), 2.65 (m, 1H, $CHCH_3$), 2.50 (m, 1H), 2.03 (m, 1H, $CH_2CH=CH$), 1.90 (m, 1H, $CH_2CH=CH$), 2.10-2.05 (m, 2H), 1.72 (m, 1H), 1.35 (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 201.3 (p), 128.7 (ap), 122.9 (ap), 121.1 (p), 53.9 (p), 43.2 (ap), 40.0 (p), 36.9 (ap), 27.0 (p), 25.5 (p), 24.2 (p), 16.2 (ap); HRMS M^+: 189.1155 (calcd. for $C_{12}H_{15}NO$: 189.1161).

(1R*,6S*)-1-Cyano-8,9-dimethylbicyclo[4.4.0]dec-8-en-2-one (34)

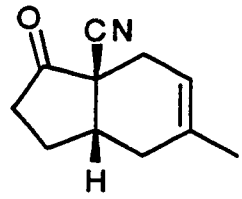


34

Under zinc chloride catalysis, reaction of dienophile **22** (300 mg, 2.48 mmol) with 2,3-dimethyl-1,3-butadiene (2.8 mL, 2.04 g, 24.8 mmol) for 18 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 10), adduct **34** as a white solid (453 mg, 2.23 mmol, 90%): mp 74-75°C (hexane); IR ($CHCl_3$, cast): 1715 (C=O), 2242 cm^{-1} (CN); ^1H NMR (300 MHZ, $CDCl_3$): δ 2.64-2.52 (m, 2H, $CH_2C=O$), 2.20 (d, J = 12 Hz, 1H, $CH_2C=$, C-10), 1.85 (dm, J = 12 Hz, 1H, $CH_2C=$, C-10), 2.15 (m, 1H, CH_2CHCH_2), 2.10-1.79 (m, 5H), 1.70 (m, 1H), 1.65

(s, br, 3H, =CC**H**$_3$), 1.63 (s, br, 3H, =CC**H**$_3$); ^{13}C NMR APT (75 MHZ, $CDCl_3$): δ 202.8 (p), 123.9 (p), 120.3 (p), 119.9 (p), 51.2 (p), 39.9 (ap), 36.9 (p), 34.2 (p), 33.5 (p), 26.2 (p), 24.0 (p), 19.1 (ap), 18.5 (ap); HRMS M$^+$: 203.1306 (calcd. for $C_{13}H_{17}NO$: 203.1307). Anal. calcd. for $C_{13}H_{17}NO$: C 76.85%, H 8.37%, N 6.89%; found: C 76.77%, H 8.40%, N 6.84%.

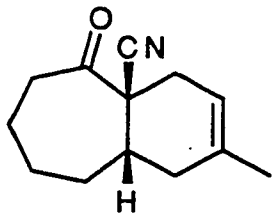
(1S*,6R*)-6-Cyano-3-methylbicyclo[4.3.0]non-3-en-7-one (35)



35

Under zinc chloride catalysis, cycloaddition of dienophile **21** (110 mg, 1.03 mmol) to 2-methyl-1,3-butadiene (1.03 mL, 0.7 g, 10.3 mmol) for 28 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 15), adduct **35** as white crystals (144 mg, 0.82 mmol, 80%): mp 84-85°C (ethyl acetate); IR (CH_2Cl_2, cast): 1732 (C=O), 2247 cm^{-1} (CN); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (s, 1H, **H**C=), 2.72 (m, 1H, C**H**$_2$C=O), 2.46 (m, 1H, C**H**$_2$C=O), 2.43 (dm, J = 13 Hz, 1H, C**H**$_2$CH=), 2.22 (d, J = 13 Hz, 1H, C**H**$_2$CH=), 2.38 (m, 1H), 2.09 (m, 2H), 1.82 (m, 1H), 1.77 (m, 1H), 1.72 (s, br, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 207.9 (p), 132.7 (p), 119.6 (p), 114.6 (ap), 53.5 (p), 41.5 (ap), 35.3 (p), 29.9 (p), 26.5 (p), 25.7 (p), 23.7 (ap); HRMS M$^+$: 175.0995 (calcd. for $C_{11}H_{13}NO$: 175.0997).

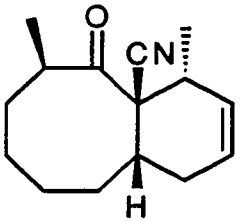
(1R*,7S*)-1-Cyano-9-methylbicyclo[5.4.0]undec-9-en-2-one (36)



36

The reaction of dienophile **23** (0.5 g, 3.7 mmol) with 2-methyl-1,3-butadiene (3.7 mL, 2.5 g, 37 mmol) under zinc chloride catalysis for 40 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 25), adduct **36** (0.564g, 2.78 mmol, 75%): IR ($CHCl_3$, cast): 1731 (C=O), 2250 cm^{-1} (CN); ^1H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H, **H**C=), 2.92 (m, 1H, CH_2C=O), 2.58 (m, 1H, CH_2C=O), 2.36 (d, J = 14 Hz, 1H, CH_2CH=), 1.85 (dd, J_1 = 14 Hz, J_2 = 6 Hz, 1H, CH_2CH=), 2.40 (m, 1H, CH_2C**H**CH_2), 2.00-1.95 (m, 3H), 1.70-1.59 (m, 5H), 1.66 (s, br, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 203.8 (p), 132.3 (p), 120.3 (p), 116.7 (ap), 49.9 (p), 42.2 (p), 37.9 (ap), 34.1 (p), 32.6 (p), 31.5 (p), 25.9 (p), 24.0 (p), 23.3 (ap); HRMS M^+: 203.1301 (calcd. for $C_{13}H_{17}NO$: 203.1307). Anal. calcd. for $C_{13}H_{17}NO$: C 76.85%, H 8.37%; found: C 76.94%, H 8.12%.

(1S*,3R*,8S*,12R*)-1-Cyano-3,12-dimethylbicyclo[6.4.0]dodec-10-en-2-one (37)



37

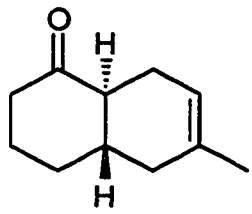
Diels-Alder reaction of dienophile **24** (50 mg, 0.31 mmol) with *trans*-piperylene (0.31 mL, 0.21 g, 3.1 mmol) for 26 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 20) adduct **37** (55.3 mg, 0.24 mmol, 78%): IR (CH_2Cl_2, cast): 1708 (C=O), 2224 cm^{-1} (CN); ^1H NMR (360 MHz, $CDCl_3$): δ 5.72 (m, 1H, **H**C=, C-11), 5.45 (dm, J = 10 Hz, 1H, **H**C=, C-10), 2.82 (m, 1H, CH_3C**H**, C-3), 2.05 (m, 1H, CH_2CHCH_2), 1.90 (m, 1H, CH_3C**H**, C-12), 2.60-2.40 (m, 2H, CH_2CH=, C-9), 1.22 (d, J = 7.5 Hz, 3H, CH_3, C-3), 1.10 (d, J = 7 Hz, 3H, CH_3, C-12); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 204.7 (p), 122.2 (ap), 120.2 (p), 115.8 (ap), 49.6 (p), 41.3 (ap), 40.9 (ap), 33.1 (ap), 30.1 (p), 27.7 (p), 24.3 (p), 24.2 (p), 23.8 (p), 19.0 (ap), 16.2 (ap); HRMS M^+: 231.1624 (calcd. for $C_{15}H_{21}NO$: 231.1617).

General procedure for reductive decyanation and alkylation

Lithium metal (14.8 mg, 2.13 mmol, 6 equivalents) was added to a solution of naphthalene (0.41 g, 3.19 mmol, 9 equivalents) in THF (12 mL). The resulting mixture was stirred at room temperature for 4-5 hours to yield a dark green solution which was then cooled to -25°C and added to a flask containing the adduct (0.35 mmol, 1 equivalent) under argon. The mixture was stirred for 25-30 minutes at -25°C then quenched with methanol (6 mL) and extracted with dichloromethane (2 x 15 mL). The organic extracts were washed successively with water (15 mL) and saturated sodium chloride solution (15 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography, first eluting with Skelly B to remove naphthalene and then with ethyl acetate-Skelly B to give the decyanated product. Addition of an alkylating agent (3.5 mmol, 10 equivalents) to the mixture of the Diels-Alder adduct and lithium naphthalenide followed by

stirring the resulting solution at the appropriate temperature for a period of time (**Table 2-2**) provided the alkylated product(s) after work-up and purification in the same manner as described for the reductive cleavage reaction.

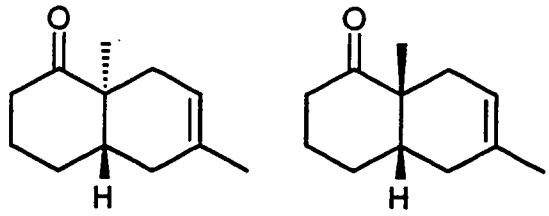
(1S*,6S*)-8-methyl-bicyclo[4.4.0]dec-8-en-2-one (38)



38

Reductive decyanation of adduct **31** (50 mg, 0.26 mmol) gave, after flash chromatography (ethyl acetate-Skelly B 1 : 40), compound **38** as a colorless oil (35 mg, 0.21 mmol, 80%): IR ($CHCl_3$, cast): 1708 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.30 (m, 1H, **H**C=), 2.48 (m, 1H, C**H**C=O), 2.45 (m, 1H, CH_2C=O), 1.85 (ddd, J_1 = 16 Hz, J_2 = 7 Hz, J_3 = 1Hz, 1H, CH_2C=O), 1.72-1.45 (m, 4H), 1.62 (s, br, 3H, CH_3C=), 1.40-1.20 (m, 4H), 1.00 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 209.3 (p), 131.9 (p), 120.7 (ap), 50.1 (ap), 41.8 (p), 40.2 (ap), 38.1 (p), 32.4 (p), 25.9 (p), 24.6 (p), 23.1 (ap); HRMS M^+: 164.1204 (calcd. for $C_{11}H_{16}O$: 164.1200). Anal. calcd. for $C_{11}H_{16}O$: C 80.49%, H 9.76%; found: C 80.33%, H 9.73%.

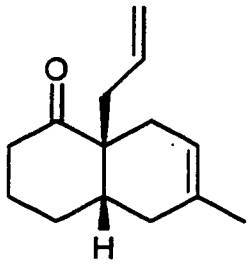
(1S*,6S*)-1,8-dimethylbicyclo[4.4.0]dec-8-en-2-one (39) and (1R*,6S*)-1,8-dimethylbicyclo[4.4.0]dec-8-en-2-one (40)



39 **40**

Methyl iodide was added to a mixture of adduct **31** (100 mg, 0.53 mmol) and lithium naphthalenide in THF. The solution was stirred at -25°C for 12 hours to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 30), an inseparable 4 : 1 mixture of **39** and **40** (71 mg, 0.39 mmol, 75%): IR (mixture, $CHCl_3$, cast): 1705 cm^{-1} (C=O); ^1H NMR (mixture, 300 MHz, $CDCl_3$): δ 5.32 (s, 0.2H, C**H**=, **40**), 5.20 (m, 0.8H, C**H**=, **39**), 2.69-2.10 (m, 5.5H), 2.00 (m, 1.5H), 1.95-1.70 (m, 2.5H), 1.50 (m, 1.5H), 1.67 (s, br, 0.6H, CH_3C=, **40**), 1.63 (s, br, 2.4H, CH_3C=, **39**), 1.10 (s, 0.6H, CH_3, **40**), 1.02 (d, J = 1 Hz, 2.4H, CH_3, **39**); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): for **39**: δ 216.1 (p), 131.8 (p), 119.6 (p), 46.6 (p), 41.7 (ap), 38.3 (p), 34.4 (p), 33.8 (p), 27.7 (p), 26.0 (p), 23.1 (ap), 16.3 (ap); for **40**: δ 214.2 (p), 130.9 (p), 116.9 (ap), 47.5 (p), 41.6 (ap), 37.3 (p), 33.1 (p), 31.7 (p), 27.9 (p), 25.3 (p), 23.7 (ap), 20.4 (ap); HRMS (mixture) M^+: 178.1354 (calcd. for $C_{12}H_{18}O$: 178.1354).

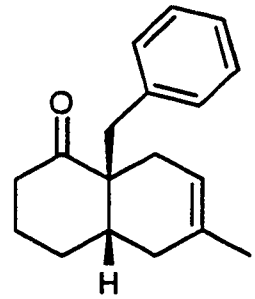
(1R*,6S*)-1-Allyl-8-methylbicyclo[4.4.0]dec-8-en-2-one (41)



41

Reductive alkylation of adduct **31** (60 mg, 0.32 mmol) with allyl bromide for 20 hours at -25°C gave, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **41** as a pale yellow oil (48.6 mg, 0.24 mmol, 75%): IR ($CHCl_3$, cast): 1708 (C=O), 1654 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): δ 5.75 (dm, J = 18 Hz, 1H, C**H**=CH_2), 5.30 (m, 1H, C**H**=CCH_3), 5.04 (dm, J = 18 Hz, 1H, CH=C**H**$_2$), 4.98 (dm, J = 12 Hz, 1H, CH=C**H**$_2$), 2.58 (m, 1H, C**H**$_2$C=O), 2.32 (dm, J = 13 Hz, 1H, C**H**$_2$C=O), 2.52 (dm, J = 18 Hz, 1H, C**H**$_2$CH=CH_2), 2.22 (dd, J_1 = 18 Hz, J_2 = 10 Hz, 1H, C**H**$_2$CH=CH_2), 2.42 (dd, J_1 = 14 Hz, J_2 = 10 Hz, 1H, C**H**$_2$CH=, C-10), 2.12 (dm, J = 14.5 Hz, 1H, C**H**$_2$C=, C-7), 2.02 (m, 1H, CH_2C**H**CH_2), 1.69-1.57 (m, 5H), 1.95 (m, 1H), 1.66 (s, br, 3H, CH_3C=); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 214.4 (p), 135.1 (ap), 131.4 (p), 117.2 (p), 116.8 (ap), 50.7 (p), 38.1 (p), 37.7 (p), 37.3 (ap), 32.3 (p), 31.1 (p), 27.4 (p), 24.6 (p), 23.7 (ap); HRMS M^+: 204.1508 (calcd. for $C_{14}H_{20}O$: 204.1517). Anal. calcd. for $C_{14}H_{20}O$: C 82.35%, H 9.80%; found C 82.11%, H 10.04%.

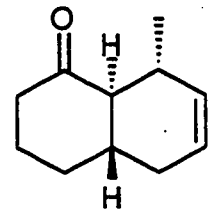
(1S*,6S*)-1-Benzyl-8-methylbicyclo[4.4.0]dec-8-en-2-one (42)



42

Benzyl bromide was added to a mixture of adduct **31** (110 mg, 0.58 mmol) and lithium naphthalenide in THF. The solution was stirred at room temperature for 40 hours to give, after flash chromatography (ethyl acetate-Skelly B : 1 : 25), compound **42** (96 mg, 0.38 mmol, 65%): IR (CH_2Cl_2, cast): 1702 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.15 (m, 5H, phenyl), 5.34 (s, br, 1H, C**H**=), 3.35 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.80 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.46 (m, 1H, C**H**$_2$C=O), 2.32 (m, 1H, C**H**$_2$C=O), 2.26 (dm, J = 14 Hz, 1H, C**H**$_2$CH=, C-10), 1.68 (d, J = 14 Hz, 1H, C**H**$_2$CH=, C-10), 2.20 (dm, J = 13.5 Hz, 1H, C**H**$_2$C=, C-7), 2.10 (m, 1H), 1.84 (m, 1H, CH_2C**H**CH_2), 1.79-1.58 (m, 4H), 1.75 (s, br, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 202.0 (p), 138.8 (p), 131.3 (p), 130.6 (ap), 127.9 (ap), 126.1 (ap), 116.9 (ap), 51.3 (p), 39.2 (p), 37.9 (p), 36.4 (ap), 32.8 (p), 31.6 (p), 27.5 (p), 23.8 (p), 23.6 (ap); HRMS M^+: 254.1169 (calcd. for $C_{18}H_{22}O$: 254.1665).

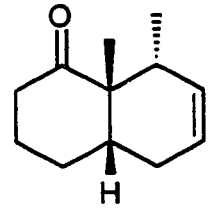
(1R*,6S*,10R*)-10-Methylbicyclo[4.4.0]dec-8-en-2-one (43)



43

Reductive decyanation of adduct **33** (80 mg, 0.42 mmol) afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 40), compound **43** as a colorless oil (56 mg, 0.34 mmol, 80%): IR (CH_2Cl_2, cast): 1709 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.42 (s, br, 2H, C**H**=C**H**), 2.85 (m, 1H, C**H**C=O), 2.80 (m, 1H, CH_2C=O), 2.25 (m, 1H, CH_2C=O), 1.80 (m, 1H, CH_2C**H**CH_2), 1.75 (m, 1H, CH_3C**H**), 1.54 (m, 1H), 1.50-1.25 (m, 4H), 1.03 (d, J = 7.5 Hz, 1H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 209.5 (p), 133.4 (ap), 123.6 (ap), 58.1 (ap), 42.8 (p), 40.8 (ap), 33.2 (p), 33.0 (p), 29.7 (ap), 27.0 (p), 21.3 (ap); HRMS M^+: 164.1195 (calcd. for $C_{11}H_{16}O$: 164.1200).

(1S*,6S*,10R*)-1,10-Dimethylbicyclo[4.4.0]dec-8-en-2-one (44)

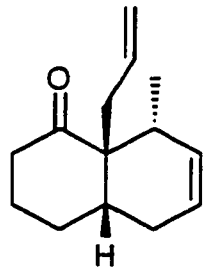


44

Reductive alkylation of adduct **33** (60 mg, 0.32 mg) with methyl iodide at -25°C for 12 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 30),

compound **44** as a colorless oil (39.6 mg, 0.22 mmol, 70%): IR (CH_2Cl_2, cast): 1706 (C=O), 1660 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.55 (s, br, 2H, C**H**=C**H**), 2.65 (m, 1H, CH_2C=O), 2.23 (m, 1H, CH_2C=O), 2.10 (m, 1H, CH_3CH), 1.90 (m, CH_2CHCH_2), 1.75-1.80 (m, 2H, CH_2CH=), 1.50 (m, 1H), 1.49-1.22 (m, 3H), 1.35 (s, 3H, CH_3), 1.17 (d, J = 7 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 214.9 (p), 131.6 (ap), 122.8 (ap), 50.7 (p), 42.5 (ap), 39.5 (p), 39.1 (ap), 27.8 (p), 25.9 (p), 23.9 (p), 23.6 (ap), 17.7 (ap); HRMS M^+: 178.1357 (calcd. for $C_{12}H_{18}O$: 178.1354).

(1S*,6S*,10R*)-1-Allyl-10-methylbicyclo[4.4.0]dec-8-en-2-one (45)

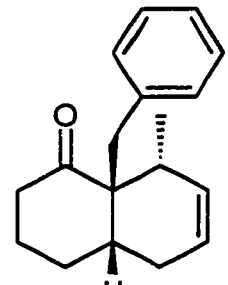


45

Allyl bromide was added to a mixture of adduct **33** (150 mg, 0.79 mmol) and lithium naphthalenide in THF. The mixture was stirred at -25°C for 12 hours to afford, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **45** as a pale yellow oil (129 mg, 0.63 mmol, 80%): IR (CH_2Cl_2, cast): 1707 (C=O), 1661, 1638 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): δ 5.70 (m, 1H, C**H**=CH_2), 5.59 (m, 2H, C**H**=C**H**), 5.10 (dm, J = 17 Hz, 1H, CH=C**H**$_2$), 4.95 (dm, J = 10 Hz, 1H, CH=C**H**$_2$), 2.80 (ddd, J_1 = 12 Hz, J_2 = 6 Hz, J_3 = 1 Hz, 1H, C**H**$_2$CH=CH_2), 2.31 (dd, J_1 = 12 Hz, J_2 = 7 Hz, 1H, C**H**$_2$CH=CH_2), 2.55 (m, 1H, C**H**$_2$C=O), 2.24 (m, 1H, C**H**$_2$C=O), 2.20 (m, 1H, C**H**$_2$CH=CH), 1.88 (m, 1H, C**H**$_2$CH=CH), 2.06

(m, 1H, CH_3CH), 1.98-1.92 (m, 2H), 1.78 (m, 1H, CH_2CHCH_2), 1.70 (m, 2H), 1.12 (d, J = 7 Hz, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 215.0 (p), 134.5 (ap), 133.1 (ap), 122.6 (ap), 117.8 (p), 53.7 (p), 40.1 (p), 40.1 (p), 36.5 (ap), 35.1 (ap), 27.4 (p), 26.2 (p), 22.3 (p), 18.9 (ap); HRMS M^+: 204.1505 (calcd. for $C_{14}H_{20}O$: 204.1517).

(1S*,6S*,10R*)-1-Benzyl-10-methylbicyclo[4.4.0]dec-8-en-2-one (46)

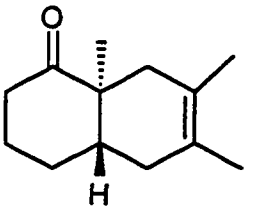


46

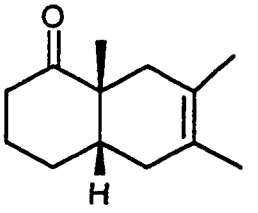
Reductive alkylation of adduct **33** (70 mg, 0.37 mmol) with benzyl bromide at room temperature for 24 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 25) compound **46** (70 mg, 0.28 mmol, 74%): IR (CH_2Cl_2, cast): 1702 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.20-7.15 (m, 5H, phenyl), 5.65 (s, 2H, CH=CH), 3.45 (d, J = 13 Hz, 1H CH_2Ph), 2.72 (d, J = 13 Hz, 1H, CH_2Ph), 2.42 (dm, J = 14 Hz, 1H, $CH_2CH=CH$), 1.88 (dm, J = 14 Hz, 1H, $CH_2CH=CH$), 2.34-2.20 (m, 2H, $CH_2C=O$), 2.16 (m, 1H, CH_3CH), 2.02 (m, 1H, CH_2CHCH_2), 1.75-1.65 (m, 2H), 1.50 (m, 2H), 1.10 (d, J = 7 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHZ, $CDCl_3$): δ 216.8 (p), 138.7 (p), 130.6 (ap), 130.3 (ap), 128.2 (ap), 126.4 (ap), 122.3 (ap), 54.9 (p), 42.4 (p), 40.5 (p), 37.3 (ap), 32.7 (ap), 27.8 (p), 26.5

(p), 20.9 (p), 19.5 (ap); HRMS M^+: 254.1676 (calcd. for $C_{18}H_{22}O$: 254.1665). Anal. calcd. for $C_{18}H_{22}O$: C 85.04%, H 8.66%; found: C 85.37%, H 8.96%.

(1S*,6S*)-1,8,9-Trimethylbicyclo[4.4.0]dec-8-en-2-one (47) and (1R*,6S*)-1,8,9-trimethylbicyclo[4.4.0]dec-8-en-2-one (48)



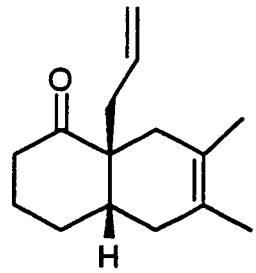
47



48

Methyl iodide was added to a mixture of adduct **34** (110 mg, 0.54 mmol) and lithium naphthalenide in THF. The solution was stirred at -25°C for 12 hours to give, after flash chromatography (ethyl acetate-Skelly B 1 : 40), an inseparable 2 : 1 mixture of **47** and **48** (89 mg, 0.46 mmol, 85%): IR (mixture, CH_2Cl_2, cast): 1706 cm^{-1} (C=O); ^1H NMR (mixture, 300 MHz, $CDCl_3$): δ 2.62-2.20 (m, 3.5H), 2.15-1.83 (m, 2.5H), 1.75-1.46 (m, 5H), 1.62 (s, br, 4H, $CH_3C{=}CCH_3$, **47**), 1.58 (s, br, 2H, $CH_3C{=}CCH_3$, **48**); 1.20 (d, J = 1 Hz, 2H, CH_3, **47**), 1.07 (s, 1H, CH_3, **48**); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): for **47**: δ 216.3 (p), 124.0 (p), 123.2 (p), 47.3 (p), 42.0 (ap), 39.6 (p), 38.1 (p), 35.9 (p), 27.3 (p), 26.1 (p), 19.3 (ap), 18.4 (ap), 16.3 (ap); for **48**: δ 215.5 (p), 122.6 (p), 121.4 (p), 48.5 (p), 41.7 (ap), 37.7 (p), 37.2 (p), 34.7 (p), 27.8 (p), 25.1 (p), 20.7 (ap), 19.0 (ap), 18.8 (ap); HRMS (mixture) M^+: 192.1512 (calcd. for $C_{13}H_{20}O$: 192.1510). Anal. calcd. for $C_{13}H_{20}O$: C 81.25%, H 10.42%; found: C 81.34%, H 10.04%.

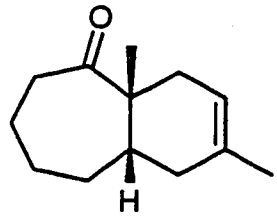
(1R*,6S*)-1-Allyl-8,9-dimethylbicyclo[4.4.0]dec-8-en-2-one (49)



49

Reductive alkylation of adduct **34** (70 mg, 0.34 mmol) with allyl bromide for 12 hours at -25°C provided, after flash chromatography (ethyl acetate-Skelly B 1 : 30), compound **49** as a pale yellow oil (53 mg, 0.24 mmol, 70%): IR (CH_2Cl_2, cast): 1703 (C=O), 1638 cm^{-1} (C=C); ^1H NMR (500 MHz, $CDCl_3$): δ 5.75 (m, 1H, C**H**=CH_2), 5.05 (dm, J = 17 Hz, 1H, CH=C**H**$_2$), 5.00 (dm, J = 9 Hz, 1H, CH=C**H**$_2$), 3.06 (dd, J_1 = 14 Hz, J_2 = 6 HZ, 1H, C**H**$_2$CH=CH_2), 2.65 (dd, J_1 = 14 Hz, J_2 = 6.5 Hz, 1H, C**H**$_2$CH=CH_2), 2.60 (m, 1H, C**H**$_2$C=O), 2.34 (m, 1H, C**H**$_2$C=O), 2.40 (dm, J = 15 Hz, 1H, C**H**$_2$C=, C-10), 2.18 (dm, J = 15 Hz, 1H, C**H**$_2$C=, C-10), 2.06 (m, 1H, CH_2C**H**CH_2), 1.90 (m, 1H), 1.77-1.58 (m, 5H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 214.2 (p), 135.1 (ap), 123.0 (p), 121.4 (p), 117.1 (p), 51.9 (p), 38.4 (p), 37.7 (p), 37.5 (ap), 37.0 (p), 34.1 (p), 27.3 (p), 24.5 (p), 19.1 (ap), 18.9 (ap); HRMS M^+: 218.1617 (calcd. for $C_{15}H_{22}O$: 218.1612).

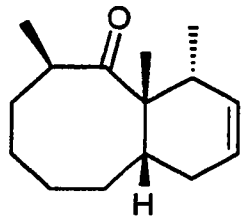
(1R*,7S*)-1,9-Dimethylbicyclo[5.4.0]undec-9-en-2-one (50)



50

Reductive alkylation of adduct **36** (90 mg, 0.44 mmol) with methyl iodide at -25°C for 13 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 45), compound **50** as a colorless oil (68 mg, 0.35 mmol, 80%): IR (CH_2Cl_2, cast): 1698 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 5.06 (s, 1H, C**H**=), 2.82 (m, 1H, C**H**$_2$C=O), 2.28 (m, 1H, C**H**$_2$C=O), 2.36 (dm, J = 12 Hz, 1H, C**H**$_2$C=, C-8), 1.74 (dm, J = 12 Hz, 1H, C**H**$_2$C=, C-8), 2.22 (d, J = 15 Hz, 1H, C**H**$_2$CH=), 2.06 (dm, J = 15 Hz, 1H, C**H**$_2$CH=), 1.98 (m, 1H, CH_2C**H**CH_2), 1.65-1.20 (m, 6H), 1.62 (s, br, 3H, C**H**$_3$C=), 1.02 (s, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.4 (p), 130.3 (p), 118.6 (ap), 47.9 (p), 40.2 (p), 38.9 (ap), 36.1 (p), 33.9 (p), 30.9 (p), 28.9 (p), 26.4 (p), 24.3 (ap), 23.5 (ap); HRMS M^+: 192.1517 (calcd. for $C_{13}H_{20}O$: 192.1510).

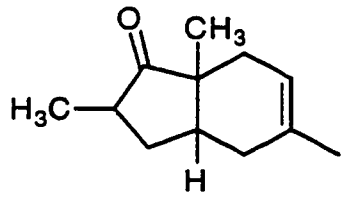
(1S*,3R*,8S*,12R*)-1,3,12-Trimethylbicyclo[6.4.0]dodec-10-en-2-one (51)



51

Treatment of adduct **37** (100 mg, 0.43 mmol) with lithium naphthalenide followed by addition of methyl iodide at -25°C for 14 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 45), compound **51** as a colorless oil (67 mg, 0.30 mmol, 70%): IR (CH_2Cl_2, cast): 1699 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 5.88 (m, 1H, **HC**=, C-10), 5.70 (dm, J = 10 Hz, 1H, **HC**=, C-11), 2.68 (m, 1H, CH_3**CH**, C-3), 2.44 (m, 1H, CH_2**CH**=), 1.90 (m, 1H, CH_2**CH**=), 1.96 (m, 1H, CH_3**CH**, C-12), 1.82 (m, 1H, CH_2**CH**CH_2), 1.72 (m, 1H), 1.42 (m, 1H), 1.38-1.22 (m, 6H), 1.18 (s, 3H, CH_3), 1.25 (d, J = 7 Hz, 3H, CH_3CH, C-3), 0.52 (d, J = 7.5 Hz, 3H, CH_3CH, C-12); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 222.7 (p), 131.9 (ap), 125.7 (ap), 52.3 (p), 42.9 (ap), 41.1 (ap), 40.1 (ap), 39.1 (p), 31.1 (p), 30.8 (p), 26.7 (p), 24.4 (ap), 22.8 (p), 18.7 (ap), 17.3 (ap); HRMS M^+: 220.1828 (calcd. for $C_{15}H_{24}O$, 220.1821). Anal. calcd. for $C_{15}H_{24}O$: C 81.82%, H 10.91; found C 82.02%, H 11.17%.

3,6,8-Trimethylbicyclo[4.3.0]non-3-en-7-one

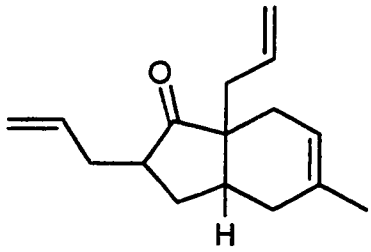


52

Reductive methylation of adduct **35** (90 mg, 0.51 mmol) with methyl iodide at -25°C for 13 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 35), the dialkylated product **52** as an inseparable mixture of two diastereoisomers in a ratio of 2 : 1 (73 mg, 0.41 mmol, 80%): IR (mixture, CH_2Cl_2, cast): 1739 cm^{-1} (C=O); ^1H NMR (mixture, 400 MHz, $CDCl_3$): δ 5.35 (s, br, 1H, **CH**=), 2.48 (m, 1H, CH_3**CH**), 2.28-2.05 (m, 3H), 1.95-1.70 (m, 2.5H),

1.60-1.52 (m, 1.5H), 1.14 (d, J = 7 Hz, 2H, CH_3CH), 1.12 (d, J = 7 Hz, 1H, CH_3CH), 1.68 (s, br, 2H, CH_3C=), 1.56 (s, br, 1H, CH_3C=), 1.04 (s, 2H, CH_3), 0.88 (s, 1H, CH_3); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 229.8 (p), 221.2 (p), 131.5 (p), 130.4 (p), 117.3 (ap), 116.5 (ap), 46.5 (p), 46.1 (p), 39.7 (ap), 39.4 (ap), 39.0 (ap), 38.2 (ap), 33.7 (p), 33.4 (p), 32.7 (p), 32.5 (p), 30.3 (p), 29.4 (p), 23.8 (ap), 23.4 (ap), 20.7 (ap), 16.9 (ap), 16.8 (ap), 13.9 (ap); HRMS M^+: 178.1355 (calcd. for $C_{12}H_{18}O$: 178.1354).

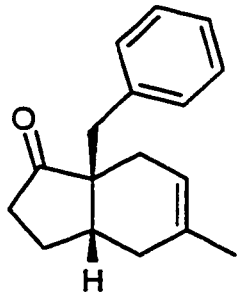
6,8-Diallyl-3-methylbicyclo[4.3.0]non-3-en-7-one (53)



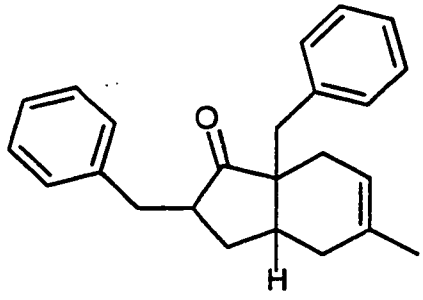
53

Reductive alkylation of adduct **35** (110 mg, 0.63 mmol) with allyl bromide at -25°C for 24 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 40), compound **53** as a single stereoisomer (87 mg, 0.38 mmol, 60%): IR ($CHCl_3$, cast): 1735 (C=O), 1640 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.80-5.63 (m, 2H, CH=CH_2), 5.25 (s, br, 1H, CH_3C=CH), 4.91 (m, 4H, CH=CH_2), 2.45 (m, 1H, $CHCH_2CH$=CH_2), 2.30-1.90 (m, 4H, CH_2CH=CH_2), 1.89-1.76 (m, 2H), 1.62-1.30 (m, 5H), 1.20 (s, br, 3H, CH_3); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 219.1 (p), 136.6 (ap), 134.9 (ap), 131.4 (p), 117.9 (ap), 117.6 (p), 116.4 (p), 49.9 (p), 44.2 (ap), 38.4 (p), 35.4 (p), 34.5 (ap), 30.5 (p), 30.3 (p), 28.8 (p), 23.7 (ap); HRMS M^+: 230.1666 (calcd. for $C_{16}H_{22}O$: 230.1672).

(1R*,6S*)-6-Benzyl-3-methylbicyclo[4.3.0]non-3-en-7-one (54) and 6,8-dibenzyl-3-methylbicyclo[4.3.0]non-3-en-7-one (55)



54

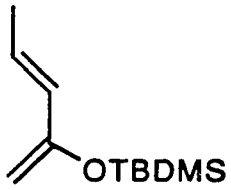


55

Benzyl bromide was added to a solution of adduct **35** (100 mg, 0.57 mmol) and lithium naphthalenide in THF. The resulting solution was stirred at -10°C for 12 hours. Flash chromatography of the crude product, eluting with ethyl acetate-Skelly B (1 : 40), afforded compound **55** (37 mg, 0.11 mmol, 20%). Further elution gave compound **54** (82 mg, 0.34 mmol, 60%). Compound **54**: IR (CH_2Cl_2, cast): 1736 cm^{-1} (C=O); ^1H NMR (300 MHz, C_6D_6): δ 7.30-7.05 (m, 5H, phenyl), 5.10 (s, br, 1H, C**H**=), 3.42 (d, J = 12 Hz, 1H, C**H**$_2$Ph), 2.50 (d, J = 12 Hz, 1H, C**H**$_2$Ph), 2.08 (m, 2H, C**H**$_2$C=O), 1.75 (m, 1H), 1.65-1.33 (m, 3H), 1.20 (m, 2H), 1.54 (s, 3H, C**H**$_3$), 1.82 (m, 1H, CH_2CHCH_2); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 218.6 (p), 139.6 (p), 131.7 (p), 128.9 (ap), 128.7 (ap), 127.64 (ap), 117.72 (ap), 51.43 (p), 39.37 (p), 36.88 (p), 35.92 (ap), 30.29 (p), 29.32 (p), 25.6 (p), 24.2 (ap); HRMS M^+: 240.1140 (calcd. for $C_{17}H_{20}O$: 240.1146). Anal. calcd. for $C_{17}H_{20}O$: C 84.96%, H 8.33%; found: C 85.13%, H 8.11%. Compound **55**: IR (CH_2Cl_2, cast): 1734 cm^{-1} (C=O); ^1H NMR (500 MHz, C_6D_6): δ 7.23-6.90 (m, 10H, phenyl), 5.22 (s, 1H, C**H**=), 3.35 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.50 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 3.05 (dd, J_1 = 14 Hz, J_2 = 5 Hz, 1H, CHC**H**$_2$Ph), 2.05 (dd, J_1 = 14 Hz, J_2 = 10 Hz, 1H, CHC**H**$_2$Ph), 2.47 (m, 1H, C**H**CH$_2$Ph), 1.88 (d, J = 13 Hz,

1H, CH_2CH=), 1.70 (d, J = 13 Hz, 1H, CH_2CH=), 1.85 (m, 1H, CH_2CHCH_2), 1.56 (s, 3H, CH_3); ^{13}C NMR APT (75 MHz, C_6D_6): δ 219.4 (p), 140.2 (p), 138.9 (p), 131.6 (p), 130.7 (ap), 129.2 (ap), 128.7 (ap), 128.4 (ap), 126.6 (ap), 126.3 (ap), 117.5 (ap), 52.3 (p), 47.0 (ap), 39.4 (p), 36.2 (p), 33.1 (ap), 30.3 (p), 30.1 (p), 29.8 (p), 23.7 (ap); HRMS M^+: 330.1965 (calcd. for $C_{24}H_{26}O$: 330.1971).

trans-2-*tert*-Butyldimethylsilyloxy-1,3-pentadiene (78)

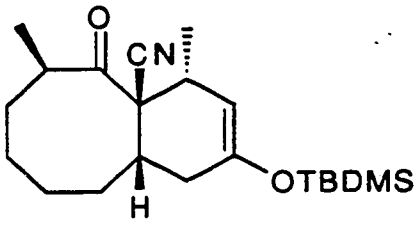


78

Diisopropylamine (8.7 mL, 62.2 mmol) was dissolved in dry THF (100 mL) and cooled to 0°C with stirring under an argon atmosphere. A solution of *n*-butyllithium (2.5 M in THF, 24.8 mL, 62.2 mmol) was added dropwise over a period of 20 minutes. The resulting LDA solution was then cooled to -78°C and a solution of 3-penten-2-one (5.1 mL, 4.36 g, 51.8 mmol) in THF (10 mL) was added dropwise over 20 minutes. After stirring at -78°C for 20 minutes, hexamethylphosphoramide (11.7 mL, 67.3 mmol) and a solution of *tert*-butyldimethylsilyl chloride (1 M in THF, 56.9 mL, 56.9 mmol) were added sequentially. The solution was warmed to room temperature and stirred for 45 minutes. The reaction was then quenched with water (100 mL) and extracted with hexane (2 x 150 mL). The organic extracts were combined and washed with water (3 x 100 mL) and saturated sodium chloride solution (2 x 80 mL), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo.

The crude residue was subjected to Kugelrohr distillation at 60°C/5 mm of Hg to give diene **78** as a colorless oil (7.69 g, 39 mmol, 75%): IR (CH_2Cl_2, cast): 1607 (C=C), 1247 cm^{-1} (Si-C); ^1H NMR (360 MHz, $CDCl_3$): δ 6.02 (dq, J_1 = 16 Hz, J_2 = 7 Hz, 1H, CH_3CH=CH), 5.90 (dq, J_1 = 16 Hz, J_2 = 1.5 Hz, 1H, CH_3CH=C**H**), 4.20 (s, 1H, C**H**$_2$=), 4.18 (s, 1H, C**H**$_2$=), 1.75 (d, J = 1.5 Hz, 3H, C**H**$_3$CH=CH), 1.00 (s, 9H, *tert*-butyl), 0.20 (s, 6H, Si(C**H**$_3$)$_2$); HRMS M^+: 198.1905 (calcd. for $C_{11}H_{22}OSi$: 198.1913).

(1S*,3R*,8S*,12R*)-10-*tert*-Butyldimethylsilyloxy-1-cyano-3,12-dimethylbicyclo[6.4.0]dodec-10-en-2-one (79)

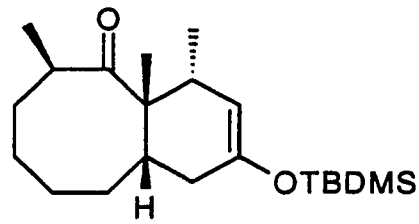


79

Zinc chloride (2.1 g, 15.5 mmol) was flame-fuse dried in a round-bottomed flask under argon. The flask was cooled to room temperature and diethyl ether (70 mL) was added. The suspension was stirred at room temperature for 50 minutes until the zinc chloride was completely dissolved. A solution of dienophile **24** (1.265 g, 7.8 mmol) in ether (5 mL) was then added and the resulting solution was cooled to 0°C. After stirring at 0°C for 20 minutes, diene **78** (6.9 g, 34.9 mmol) dissolved in ether (10 mL) was added and the reaction mixture was stirred at 0°C for 16 hours. After the reaction was complete, the mixture was neutralized with saturated sodium bicarbonate solution (20 mL) and extracted with ether (50 mL). The ether layer was separated and washed with water (2 x

20 mL) and saturated sodium chloride solution (2 x 15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by Kugelrohr distillation, first at 50°C/5 mm of Hg to get ride of impurities and then at 80°C/5 mm of Hg to give compound **79** (1.96 g, 5.43 mmol, 70%): IR (CH_2Cl_2, cast): 1705 (C=O), 2234 cm^{-1} (CN); ^1H NMR (300 MHz, C_6D_6): δ 4.60 (s, 1H, **H**C=), 2.85 (m, 1H, CH_3**C**H, C-3), 2.80-2.43 (m, 4H), 2.20-1.95 (m, 4H), 1.85-1.70 (m, 2H), 1.60 (m, 2H), 1.25 (d, J = 7.5 Hz, 3H, **C**H_3CH, C-3), 1.05 (d, J = 7 Hz, 3H, **C**H_3CH, C-12), 0.92 (s, 9H, *tert*-butyl), 0.20 (s, 6H, Si(**C**H_3)$_2$); ^{13}C NMR APT (75 MHz, C_6D_6): δ 206.9 (p), 148.9 (p), 123.2 (p), 108.9 (ap), 52.9 (p), 51.0 (ap), 42.8 (ap), 41.6 (ap), 38.3 (p), 31.0 (p), 29.6 (p), 27.3 (p), 27.0 (p), 25.9 (ap), 18.4 (p), 18.3 (ap), 17.5 (ap), -4.3 (ap), -4.4 (ap); HRMS M^+: 361.2429 (calcd. for $C_{21}H_{35}O_2SiN$: 361.2433).

(1S*,3R*,8S*,12R*)-10-*tert*-Butyldimethylsilyloxy-1,3,12-trimethylbicyclo[6.4.0]dodec-10-en-2-one (83)

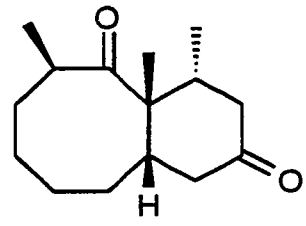


83

Lithium metal (125 mg, 18.1 mmol) was added to a solution of naphthalene (3.4 g, 27 mmol) in THF (70 mL) under argon. The mixture was stirred at room temperature for 5 hours. The resulting dark green solution was cooled to -25°C and transferred to a pre-cooled flask containing compound **79** (1.089 g, 3 mmol) by syringe. After 50 minutes, methyl iodide (1.1 mL, 30 mmol) was

added. The resulting solution was stirred at -25°C for 12 hours and then quenched with water (20 mL). The mixture was extracted with ether (2 x 40 mL). The combined extracts were washed with water (2 x 15 mL) and saturated sodium chloride solution (15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated. The residue was subjected to flash chromatography, first eluting with Skelly B and then with ethyl acetate-Skelly B (1 : 80) to give compound **83** (771 mg, 2.2 mmol, 73%): IR (CH_2Cl_2, cast): 1690 (C=O), 1253 cm^{-1} (Si-C); ^1H NMR (360 MHz, C_6D_6): δ 4.79 (s, 1H, C**H**=), 2.75 (m, 1H, CH_3C**H**, C-3), 2.15 (m, 2H), 1.84 (m, 1H), 1,63-1.50 (m, 2H), 1.45-1.05 (m, 7H), 1.20 (s, 3H, CH_3), 1.13 (d, J = 7 Hz, 3H, CH_3CH, C-3), 1.05 (s, 9H, *tert*-butyl), 0.96 (d, J = 7 Hz, 3H, CH_3CH, C-12), 0.18 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR APT (75 MHz, C_6D_6): δ 220.1 (p), 149.3 (p), 109.9 (ap), 52.4 (p), 43.4 (ap), 42.0 (ap), 39.1 (ap), 37.4 (p), 35.4 (p), 30.3 (p), 26.2 (p), 25.9 (ap), 24.3 (ap), 22.9 (p), 19.0 (ap), 18.4 (ap), 18.2 (p), -4.1 (ap), -3.9 (ap); HRMS M^+: 350.2634 (calcd. for $C_{21}H_{38}O_2Si$: 350.2641). Anal. calcd. for $C_{21}H_{38}O_2Si$: C 71.95%, H 10.86%; found: C 72.04%, H 10.74%.

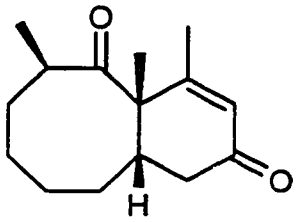
(1R*,3R*,8S*,12R*)-1,3,12-Trimethylbicyclo[6.4.0]dodecane-2,10-dione (84)



84

Compound **83** (106 mg, 0.3 mmol) was dissolved in THF (10 mL). The solution was cooled to -25°C and tetrabutylammonium fluoride (1.0 M in THF, 0.61 mL, 0.61 mmol) was added. The resulting solution was stirred at -25°C for 50 minutes and quenched with water (10 mL). The mixture was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (15 ml) and saturated sodium chloride solution (15 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 (1 : 5), to afford compound **84** (64 mg, 0.27 mmol, 90%): IR (CH_2Cl_2, cast): 1707, 1704 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 2.48 (m, 1H, CH_3CH, C-3), 2.70 (dd, J_1 = 14 Hz, J_2 = 13 Hz, 1H, CH_2C=O, C-9), 2.12 (ddd, J_1 = 14 Hz, J_2 = 6 Hz, J_3 = 2Hz, 1H, CH_2C=O, C-9), 2.32 (dd, J_1 = 15 Hz, J_2 = 14 Hz, 1H, CH_2C=O, C-11), 2.22 (ddd, J_1 = 15 Hz, J_2 = 4.5 Hz, J_3 = 2 Hz, 1H, CH_2C=O, C-11), 1.52 (m, 1H, CH_2CHCH_2), 1.22 (m, 1H, CH_3CH, C-12), 1.05 (s, 3H, CH_3), 0.88 (d, J = 7 Hz, 3H, CH_3CH, C-3), 0.72 (d, J = 7 Hz, 3H, CH_3CH, C-12), 1.45 (m, 1H), 1.27 (m, 1H), 1.19-0.95 (m, 6H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 218.6 (p), 208.1 (p), 53.8 (p), 47.4 (p), 45.8 (ap), 45.7 (ap), 44.7 (p), 43.1 (ap), 36.5 (p), 30.5 (p), 26.9 (p), 23.6 (ap), 21.0 (p), 18.1 (ap), 17.3 (ap), HRMS M^+: 236.1776 (calcd. for $C_{15}H_{24}O_2$: 236.1176). Anal. calcd. for $C_{15}H_{24}O_2$: C 76.27%, H 10.17%; found: C 76.14%, H 10.19%.

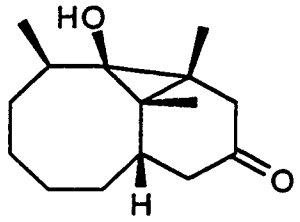
(1S*,3R*,8S*)-1,3,12-Trimethylbicyclo[6.4.0]dodec-11-ene-2,10-dione (85)



85

To a suspension of DDQ (74 mg, 0.32 mmol) and hexamethyldisilazane (0.02 mL, 0.16 mmol) in benzene (3 mL), a solution of compound **83** (57 mg, 0.16 mmol) in benzene (3 mL) was added under argon. The resulting solution was stirred at 15°C for 30 minutes and quenched with water (10 mL). The mixture was extracted with dichloromethane (2 x 15 mL). The organic extracts were washed with water (2 x 10 mL) and saturated sodium chloride solution (15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was subjected to flash chromatography. Elution with ethyl acetate-Skelly B (1 : 5) gave compound **85** (34 mg, 0.15 mmol, 90%): IR (CH_2Cl_2, cast): 1686 (unsaturated C=O), 1704 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.92 (s, 1H, **H**C=), 2.59 (m, 1H, CH_3C**H**), 2.42 (dd, J_1 = 14 Hz, J_2 = 7 Hz, 1H, C**H**$_2$C=O), 2.25 (dd, J_1 = 14 Hz, J_2 = 5 Hz, 1H, C**H**$_2$C=O), 1.29 (s, 3H, C**H**$_3$C=), 1.15 (s, 3H, C**H**$_3$), 0.80 (d, J = 7 Hz, 3H, C**H**$_3$CH), 1.65 (m, 1H), 1.54 (m, 1H), 1.43-1.04 (m, 7H); HRMS M^+: 234.1649 (calcd. for $C_{15}H_{22}O_2$: 234.1653).

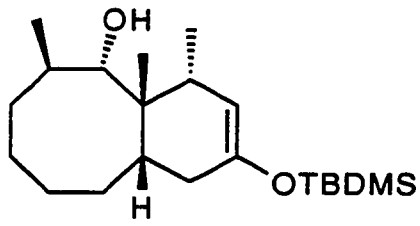
(1R*,2S*,3R*,8S*,12S*)-2-Hydroxy-1,3,12-trimethyltricyclo-[6.3.1.0^{2,12}]dodecan-10-one (86)



86

Lithium metal (17.8 mg, 2.56 mmol) was dissolved in liquid ammonia (20 mL) at -78°C under argon. To the resulting dark blue solution, *tert*-butyl alcohol (0.25 mL, 2.56 mmol) and a solution of **85** (100 mg, 0.43 mmol) in THF (2 mL) were sequentially added. After stirring at -60°C for 2 hours, the reaction was quenched by solid ammonium chloride (0.5 g) and slowly warmed to room temperature. The mixture was then diluted with water (10 mL) and extracted with ether (30 mL). The organic extract was seperated, washed with water (2 x 10 mL) and saturated sodium chloride solution (10 mL), filtered, and concentrated. The crude product was purified by flash chromatography, eluting with ethyl acetate-Skelly B (1 : 3), to give **86** as a white solid (81 mg, 0.34 mmol, 80%): mp 104-105°C (ethyl acetate); IR (CH_2Cl_2, cast): 3422 (OH), 1689 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (d, J = 14 Hz, 1H, C**H**$_2$C=O, C-11), 2.15 (d, J = 14 Hz, 1H, C**H**$_2$C=O, C-11), 2.00 (m, 1H, CH$_3$C**H**), 1.10 (s, 3H, C**H**$_3$), 0.92 (s, 3H, C**H**$_3$), 0.80 (d, J = 7 Hz, 3H, C**H**$_3$CH), 1.54-1.27 (m, 7H), 1.10-1.04 (m, 4H); HRMS M$^+$: 236.1775 (calcd. for $C_{15}H_{24}O_2$: 236.1776).

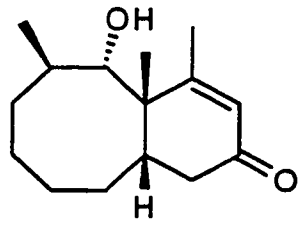
(1S*,2S*,3R*,8S*,12R*)-10-*tert*-Butyldimethylsilyloxy-1,3,4-trimethylbicyclo[6.4.0]dodec-10-en-2-ol (87)



87

To a suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in THF (15 mL), a solution of **83** (370 mg, 1.06 mmol) in THF (10 mL) was added dropwise under argon. The mixture was cooled to 0°C and stirred for 1 hour. After the reaction was complete, the mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with water (2 x 8 mL) and saturated sodium chloride solution (10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. Flash chromatography of the residue eluting with ethyl acetate-Skelly B (1 : 10) provided compound **87** (297 mg, 0.85 mmol, 80%): IR (CH_2Cl_2, cast): 3478 cm^{-1} (OH); ^1H NMR (400 MHz, $CDCl_3$): δ 4.95 (s, 1H, **H**C=), 3.60 (s, br, **H**COH), 1.15 (d, J = 7 Hz, 3H, CH_3CH, C-3), 1.10 (s, 3H, CH_3), 0.90 (s, 9H, *tert*-butyl), 0.80 (d, J = 7 Hz, 3H, CH_3CH, C-12), 0.23 (s, 6H, $Si(CH_3)_2$), 2.29 (m, 1H), 2.20-1.99 (m, 3H), 1.85-1.59 (m, 4H), 1.40-1.00 (m, 5H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 149.2 (p), 110.5 (ap), 72.9 (ap), 48.2 (p), 46.9 (ap), 42.2 (p), 39.1 (ap), 36.7 (p), 29.5 (ap), 28.3 (p), 25.9 (ap), 25.8 (ap), 23.5 (ap), 19.4 (p), 18.9 (ap), 18.2 (p), -4.3 (ap), -4.2 (ap); HRMS M^+: 352.2798 (calcd. for $C_{21}H_{40}O_2Si$: 352.2802). Anal. calcd. for $C_{21}H_{40}O_2Si$: C 71.53%, H 11.36%; found: C 71.55%, H 11.42%.

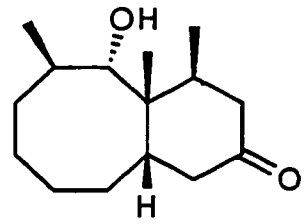
(1S*,2S*,3R*,8S*)-2-Hydroxy-1,3,12-trimethyl[6.4.0]dodec-11-en-10-one (88)



88

Treatment of compound **87** (178 mg, 0.51 mmol) with DDQ (0.23 g, 1 mmol) and hexamethyldisilazane (0.11 mL, 1 mmol) in benzene (20 mL) at 0°C for 18 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 5), compound **88** (99 mg, 0.41 mmol, 80%): IR (CH_2Cl_2, cast): 3426 (OH), 1660 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (s, 1H, **H**C=), 3.28 (s, br, 1H, **H**COH), 2.60 (dd, J_1 = 14 Hz, J_2 = 5 Hz, 1H, CH_2C=O), 2.24 (dd, J_1 = 14 Hz, J_2 = 4 Hz, 1H, CH_2C=O), 1.95 (s, 3H, CH_3C=), 1.62 (s, 3H, CH_3), 0.84 (d, J = 7 Hz, 3H, CH_3CH), 2.03-1.84 (m, 2H), 1.65-1.43 (m, 2H), 1.40-1.10 (m, 5H), 0.85 (m, 1H); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 196.8 (p), 164.8 (p), 128.3 (ap), 79.4 (ap), 48.2 (p), 45.3 (p), 38.2 (ap), 33.8 (p), 31.6 (p), 30.5 (ap), 27.4 (p), 26.5 (ap), 23.7 (p), 22.2 (ap), 20.9 (ap); HRMS M^+: 236.1785 (calcd. for $C_{15}H_{24}O_2$: 236.1176).

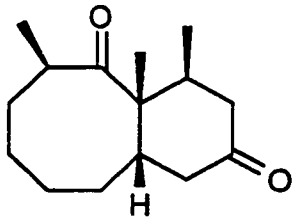
(1R*,2S*,3R*,8S*,12S*)-2-Hydroxy-1,3,12-trimethylbicyclo[6.4.0]-dodecan-10-one (89)



89

Dissolving metal reduction of **88** (100 mg, 0.42 mmol) with lithium (17.6 mg, 2.5 mmol) and liquid ammonia (30 mL) in the presence of *tert*-butyl alcohol (0.24 mL, 2.5 mmol) at -60°C for 12 hours provided, after flash chromatography (ethyl acetate-Skelly B 1 : 3), compound **89** (91 mg, 0.38 mmol, 90%): IR (CH_2Cl_2, cast): 3749 (OH), 1700 cm^{-1} (C=O); ^1H NMR (360 MHz, $CDCl_3$): δ 3.75 (s, 1H, **H**COH), 2.64 (dd, J_1 = 14 Hz, J_2 = 6 Hz), 2.39 (m, 1H), 2.21-2.17 (m, 5H), 2.00 (m, 2H), 1.78 (m, 1H), 1.37-1.25 (m, 5H), 1.20 (s, 3H, CH_3), 1.05 (d, J = 7 Hz, 3H, CH_3CH), 0.92 (d, J = 7 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 208.9 (p), 82.3 (ap), 47.8 (p), 46.9 (p), 42.6 (p), 39.8 (ap), 34.5 (ap), 33.9 (p), 33.1 (ap), 31.1 (p), 28.8 (p), 27.5 (ap), 24.1 (p), 23.1 (ap), 16.5 (ap); HRMS M^+: 238.1928 (calcd. for $C_{15}H_{26}O_2$: 238.1933).

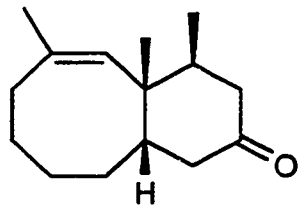
(1R*,3R*,8S*,12S*)-1,3,12-Trimethylbicyclo[6.4.0]dodecane-2,10-dione (90)



90

Compound **89** (98 mg, 0.41 mmol) was mixed with water (10 mL). The mixture was stirred at room temperature while sodium dichromate dihydrate (0.25 g, 0.82 mmol) and concentrated sulfuric acid (0.5 mL) were added. The resulting solution was stirred for 40 minutes and diluted with water (15 mL). The mixture was extrated with ether (2 x 20 mL). The organic extracts were washed with saturated sodium bicarbonate solution (2 x 15 mL), water (2 x 10 mL) and saturated sodium chloride solution (15 mL). Drying with anhydrous magnesium sulfate, filtration and concentration gave the crude product which was subjected to flash chromatography, eluting with ethyl acetate-Skelly B (1 : 5), to give compound **90** (92 mmg, 0.39 mmol, 95%): IR (CH_2Cl_2, cast): 1693, 1715 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$): δ 2.75 (m, 1H, CH_3CH, C-3), 2.25 (dd, J_1 = 14 Hz, J_2 = 5 Hz, 1H, $CH_2C=O$, C-9), 1.85 (dm, J = 14 Hz, 1H, $CH_2C=O$, C-9), 2.05 (ddd, J_1 = 16 Hz, J_2 = 6 Hz, J_3 = 2 Hz, 1H, $CH_2C=O$, C-11), 1.65 (dd, J_1 = 16 Hz, J_2 = 14 Hz, 1H, $CH_2C=O$, C-11), 2.20 (m, 1H, CH_3CH, C-12), 1.50 (m, 1H, CH_2CHCH_2), 1.05 (s, 3H, CH_3), 0.95 (d, J = 7 Hz, 3H, CH_3CH, C-3), 0.50 (d, J = 7 Hz, 3H, CH_3CH, C-12); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 216.8 (p), 209.1 (p), 51.3 (p), 46.9 (p), 45.8 (ap), 44.9 (ap), 44.6 (p), 43.0 (ap), 35.6 (p), 30.5 (p), 27.3 (p), 21.5 (ap), 20.0 (p), 17.6 (ap), 16.3 (ap); HRMS M^+: 236.1778 (calcd. for $C_{15}H_{24}O_2$: 236.1776).

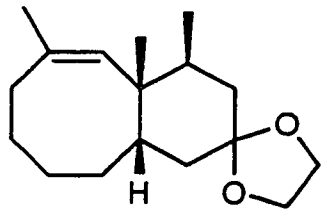
(1R*,8S*,12S*)-1,3,12-Trimethylbicyclo[6.4.0]dodec-2-en-10-one (91)



91

Compound **89** (200 mg, 0.84 mmol) was dissolved in dry pyridine (5 mL) under argon. To this solution, phosphorus oxychloride (0.16 mL, 1.68 mmol) was added. The mixture was stirred at room temperature for 14 hours, then cooled to 0°C and slowly quenched with water (10 mL). The solution was extracted with ether (2 x 20 mL). The organic extracts were washed with aqueous HCl (0.5N, 15 mL), saturated sodium bicarbonate solution (10 mL), water (2 x 10 mL) and saturated sodium chloride solution (15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography, eluting with ethyl acetate-Skelly B (1 : 10), to give compound **91** (129 mg, 0.59 mmol, 70%): IR (CH_2Cl_2, cast): 1716 (C=O), 1652 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.42 (s, 1H, **H**C=), 2.93 (dm, J = 14 Hz, 1H), 2.84 (m, 1H), 2.60 (dd, J_1 = 16 Hz, J_2 = 6 Hz, 1H), 2.54 (m, 1H), 2.46 (m, 2H), 2.20-1.85 (m, 3H), 1.62-1.15 (m, 3H), 1.70 (d, J = 1 Hz, 3H, CH_3C=), 1.20 (s, 3H, CH_3), 0.95 (d, J = 7 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 208.6 (p), 131.2 (ap), 127.7 (p), 48.6 (p), 46.5 (p), 46.5 (ap), 45.9 (p), 36.1 (ap), 31.0 (p), 30.3 (p), 27.3 (ap), 25.3 (p), 25.2 (p), 21.9 (ap), 16.5 (ap); HRMS M^+: 220.1827 (calcd. for $C_{15}H_{24}O$: 220.1821).

(1R*,8S*,12S*)-10,10-Ethylenedioxa-1,3,12-trimethylbicyclo[6.4.0]-dodec-2-ene (80)



80

Ethylene glycol (0.46 mL, 8.2 mmol) and *p*-toluenesulfonic acid (2 mg, 0.011 mmol) were added to a solution of compound **91** (90 mg, 0.41 mmol) in dry benzene (10 mL). The mixture was stirred at 80°C for 6 hours and cooled to room temperature. The solution was then diluted with water (15 mL) and extracted with ether (2 x 25 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (2 x 10 mL), water (2 x 10 mL) and saturated sodium chloride solution (15 mL), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo. Flash chromatography of the residue eluting with ethyl acetate-Skelly B (1 : 50) provided compound **80** (81 mg, 0.31 mmol, 75%): IR (CH_2Cl_2, cast): 1637 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 5.35 (s, 1H, **HC**=), 3.95-3.85 (m, 4H, O**CH$_2$CH$_2$**O), 2.40 (dd, J_1 = 16 Hz, J_2 = 6 Hz, 1H), 2.42-2.30 (m, 2H), 2.20 (dm, J = 16 Hz, 1H), 2.05 (m, 1H), 2.00-1.75 (m, 3H), 1.67-1.40 (m, 4H), 1.32-1.20 (m, 2H), 1.07 (d, J = 1 Hz, 3H, **CH$_3$**C=), 1.05 (s, 3H, **CH$_3$**), 0.92 (d, J = 7 Hz, 3H, **CH$_3$**CH); HRMS M^+: 264.2101 (calcd. for $C_{17}H_{28}O_2$: 264.2107).

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Introduction

In the previous chapters, we described the reductive alkylation of α-cyano ketones using lithium naphthalenide as the reducing agent. In searching for alternative reducing agents which might further enhance the sythetic utility of this process, samarium(II) iodide (SmI_2), one of the most important electron-donating reagents developed in recent years, was explored.

The preparation of SmI_2 was first reported in early 1980s.[1] Since then, this ether-soluble one-electron reducing agent has played an ever-increasing role in organic synthesis. Extensive reactions have been investigated, in which SmI_2 is employed as the reducing agent.[2] The powerful reducing ability of SmI_2 is due to the strong tendency of Sm^{+2} to release an electron to become the more stable Sm^{+3}. In the aqueous solution, the redox potential of Sm^{+3}/Sm^{+2} has been measured as -1.55 v.

In general, there are essentially three types of transformations mediated by SmI_2, including reductions of functional groups, intermolecular reductive coupling reactions and intramolecular reductive coupling reactions. The first type of reactions is usually carried out in THF or some protic solvents such as MeOH and *t*-BuOH. In those solvents, a large number of functional groups can be reduced upon treatment with SmI_2. Those reactions include the reduction of aldehydes, ketones, carboxylic acids and esters into the corresponding alcohols,[1,3,4] the reductive cleavage reaction of alkyl halides and alkyl tosylates,[5] the reduction of diphenyl sulfoxides, *p*-tolylethyl sulfoxide and sulfones into sulfides[6] and the reduction of nitroalkanes into the hydroxyamines or primary amines.[7] SmI_2 has also displayed the ability of promoting the

reductive elimination of epoxides to give the alkenes[8] as well as the reductive cleavage of α,β-epoxy ketones to afford the corresponding β-hydroxy ketones.[9] The reductive elimination of α-heterosubstituted ketones (Br, Cl, SPh, SOPh, SO_2Ph, OAc, OTMS, OH, OCOBn, OTs, HgCl) induced by SmI_2 has been reported as well.[10]

The SmI_2 mediated intermolecular reductive coupling reactions can occur between either the same (self-coupling reaction) or different molecules. The dimerization of allyl bromide and benzyl bromide was the first self-coupling reactions to be investigated.[5] Treatment of allyl bromide and benzyl bromide with SmI_2 can lead to the formation of free radical intermediates. Due to the increased stability, these intermediates can react with each other to provide dimers. The self-coupling reactions can also happen between aldehydes or ketones to give 1,2-diols and between aldimines to afford 1,2-diamines.[11,12] Furthermore, the SmI_2-promoted self-coupling reaction of α,β-unsaturated esters can serve as an useful tool to prepare symmetrical 1,4-diesters.[13]

Among those intermolecular coupling reactions happening between the different compounds, the intermolecular ketyl-olefin coupling reactions have been the most widely studied. This type of reactions is used to couple aldehydes and ketones to alkenes and alkynes. They are believed to occur initially with the reduction of carbonyl group to provide a ketyl radical anion, followed by the addition of radical anion to the substituted alkenes or alkynes. Among the different radical acceptors, α,β-unsaturated esters proved to be the best partners for this type of reactions.[14]

In addition to the reactions described above, SmI_2-promoted intermolecular coupling reactions also include Barbier- and Grignard-Type reactions,[15,16] Aldol-type reaction[17] and Reformatsky-type reaction.[18]

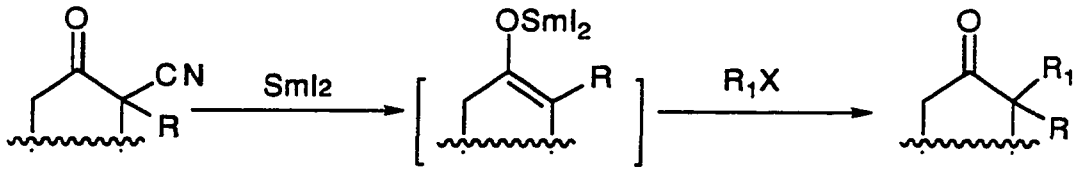
The third type of SmI_2 mediated reactions is the intramolecular reductive coupling reaction. This type of reactions occurs only when two functional groups of an organic compound are properly arranged. For example, with two carbonyl groups in a molecule, a coupling reaction might happen between them upon treatment with SmI_2 to give a vicinal diol. It has been found that the formation of the five-membered diol is highly preferred.[19,20] Other reported intramolecular coupling reactions include ketyl-olefin coupling reaction,[21,22] Barbier-type reaction,[23] Reformatsky-type reaction,[24] and free radical cyclization occurring between a carbon substituted with a halogen atom and a double or triple bond within a molecule.[25]

In the above mentioned reactions, SmI_2 exhibits a remarkable efficiency in promoting the different transformations. Furthermore, the reactivity and/or selectivity of SmI_2 can be modified by the addition of catalysts,[26] by solvent effects,[27] or through other variations of the reaction conditions.[28] The ability to modulate the reactivity of SmI_2 enhances the potential applicability of the reagent in organic synthesis.

The proven versatility of SmI_2 as a reducing agent led us to examine the possibility of applying this reagent to the α-cyano ketone system. The basic idea of this procedure is schematically illustrated in **Scheme 3-1**. The reaction of SmI_2 with an α-cyano ketone might give an anionic intermediate through a reductive decyanation process. The anionic intermediate thus generated might

be trapped with an alkylating agent to yield a dialkylated product, a process which promises to have broad synthetic utility as we discussed in the previous chapters. Preliminary results of this investigation will be reported in the following section.

Scheme 3-1

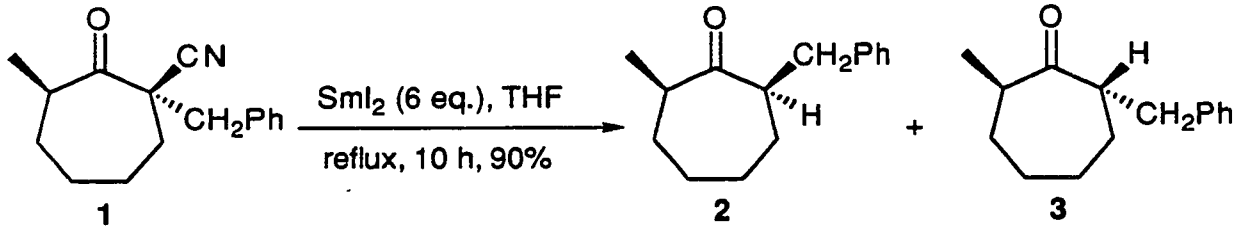


Results and Discussion

Samarium(II) iodide is commercially available as a 0.1 M solution in tetrahydrofuran (THF). However, this reagent was found to decompose over a short period of time as indicated by its color change even under a blank of inert gas. This promoted us to freshly prepare the reagent prior to each experiment using the established procedure[29] which involved the addition of samarium powder to a solution of 1,2-diiodoethane in THF. The resulting mixture was stirred at room temperature for 5 hours to yield a blue-green solution of SmI_2.

Our original investigation was carried out on 2-benzyl-2-cyano-7-methylcycloheptanone (**1**) with SmI_2. It was observed that at room temperature, the starting material was intact even after an extended period of 24 hours. The reductive decyanation, however, did occur at elevated temperature to give a 90% yield of ketones **2** and **3** in 2 : 1 ratio (**Equation 3-1**).

Equation 3-1

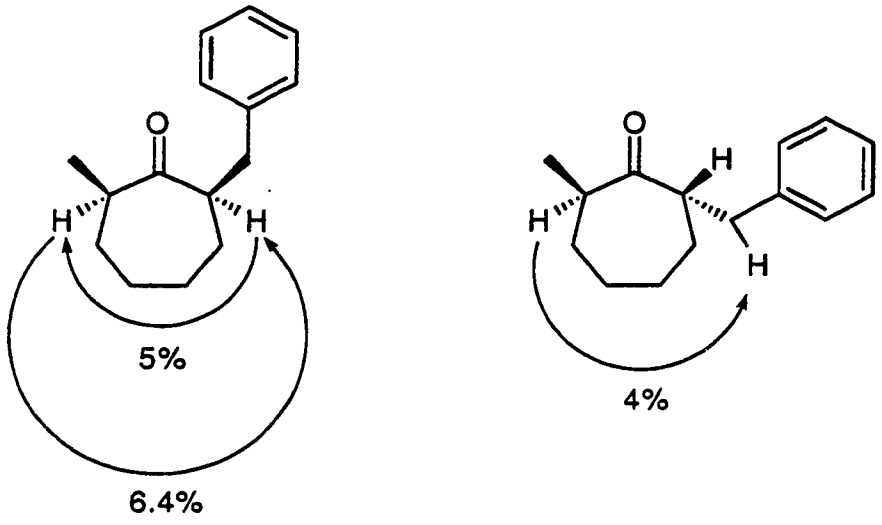


1 **2** **3**

The molecular formulas of **2** and **3** were supported by their high resolution mass spectra. The absence of the nitrile absorption band in the infrared spectra confirmed that the cyano group was removed from adduct **1**. For ketone **2**, the ^1H

NMR spectrum displayed two signals at δ 3.35 (dd, J_1 = 15 Hz, J_2 = 6.5 Hz) and 2.55 (dd, J_1 = 15 Hz, J_2 = 7.5 Hz) for the benzylic protons. Two multiplets at δ 2.73 and 2.20 were assigned to the C-2 and C-7 methine protons. The signal of the methyl group was observed at δ 1.05 as a doublet (J = 7 Hz). The ^{1}H NMR spectrum of ketone **3** showed two signals at δ 3.10 (dd, J_1 = 16 Hz, J_2 = 7 Hz) and 2.54 (dd, J_1 = 16 Hz, J_2 = 7 Hz) for the benzylic protons. The signals of the C-2 and C-7 methine protons were displayed at δ 2.75 and 2.32 as two multiplets. The methyl signal was shown as a doublet at δ 0.85 (J = 6.5 Hz). The stereochemistry of these two products was confirmed by NOE experiments **(Figure 3-1)**.

Figure 3-1 The NOE results of compounds **2** and **3**

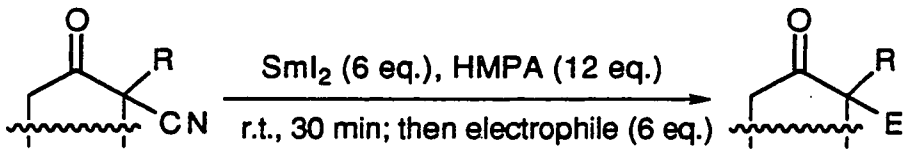


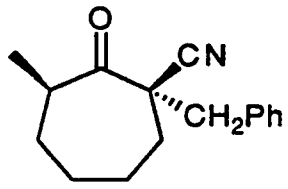
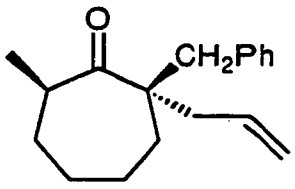
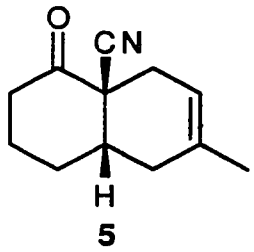
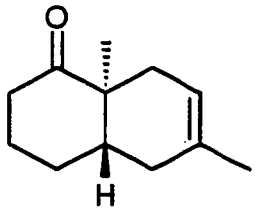
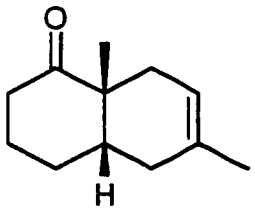
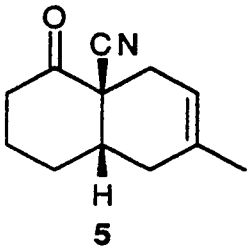
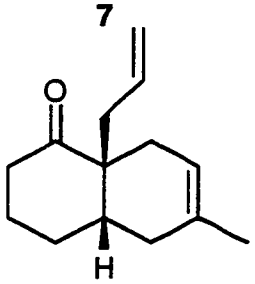
In this case, the long reaction time coupled with the high temperature required to induce the desired reductive decyanation made trapping of the ensuing enolate ion with an alkylating agent virtually impossible. This problem led us to modify the reaction condition to make it suitable for the purpose of reductive alkylation.

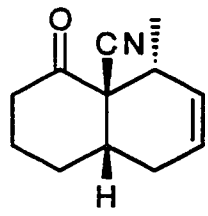
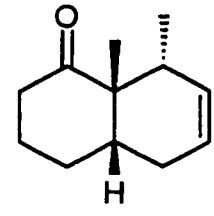
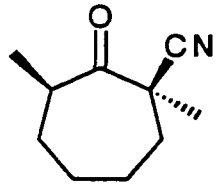
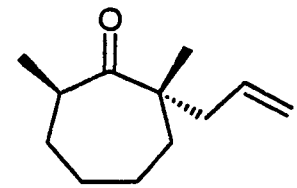
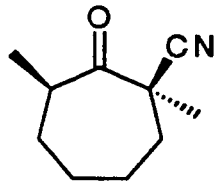
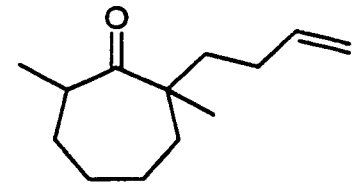
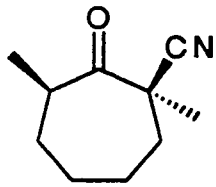
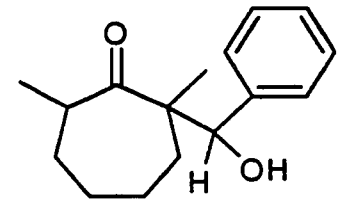
The ability of Sm^{+2} to coordinate many ligands suggests that the redox potential of divalent Sm species will vary depending on the type of ligands bound to it. This is reflected in the fact that the redox potential of SmI_2 can be markedly increased by addition of hexamethylphosphoramide (HMPA) and the extent of the potential increase depends on the concentration of HMPA added.[29,30] A number of examples of using of SmI_2 in combination with HMPA have been reported.[2] In the present investigation, we discovered that SmI_2 containing 2 equivalents of HMPA was effective enough to remove the cyano group in a short period of time (30 minutes) at room temperature, thus making it possible to trap the resulting enolate with an alkylating agent.

The reductive alkylation procedure involved the treatment of an α-cyano ketone with samarium iodide (6 eq.) in THF in the presence of HMPA (12 eq.) at room temperature for 30 minutes followed by the addition of an alkylating agent. The alkylation was carried out at room temperature to afford the desired product. Theoretically, the generation of the anionic intermediate from an α-cyano ketone requires only 2 equivalents of SmI_2. In practice, however, the use of an amount less than 6 equivalents of SmI_2 often resulted in incompletion of the reaction under the specified conditions. The amount of the alkylating agent was adjusted accordingly to cover the expected side reactions with the excess of SmI_2. A number of selected α-cyano ketones described in the previous chapters were examined. Alkylating agents used for the present study include methyl iodide, allyl bromide and 4-bromo-1-butene. Besides, benzaldehyde was also used as a trapping agent in one case. The results of this investigation are compiled in **Table 3-1**.

Table 3-1 Reductive Alkylation of α-Cyano Ketones with Samarium(II) Iodide

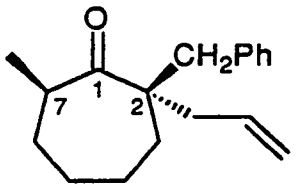


Entry	α-Cyano ketone	Electrophile	Time (h)	Product(s)	Yield (%)
1	 **1**	allyl bromide	10	 **4**	80
2	 **5**	methyl iodide	1	 **6**  **7**	70[a]
3	 **5**	allyl bromide	1.5	 **8**	60

Entry	α-Cyano ketone	Electrophile	Time (h)	Product(s)	Yield (%)
4	 **9**	methyl iodide	2	 **10**	80
5	 **11**	allyl bromide	8	 **12**	75
6	 **11**	4-bromo-1-butene	15	 **13**	60[b]
7	 **11**	benzaldehyde	8	 **14**	74[c]

[a]The ratio between **6** and **7** is 2 : 1. [b]A single diastereomer was formed. Its stereochemistry remains to be determined. [c]Two diastereomers were formed in a ratio of 1 : 1.

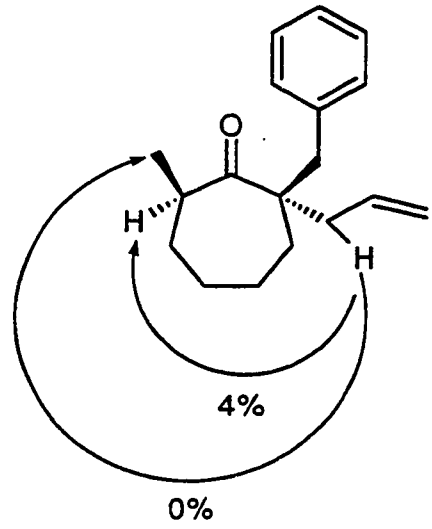
Treatment of cyano ketone **1** with SmI_2 in the presence of HMPA followed by addition of allyl bromide at room temperature for 10 hours provided ketone **4** in 80% yield (Entry 1).



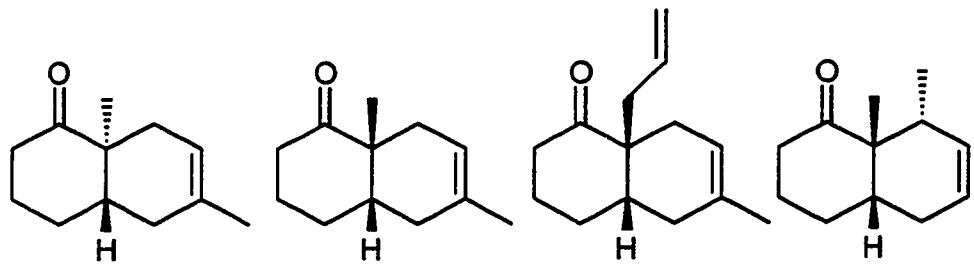
4

The infrared spectrum of this compound displayed an absorption at 1700 cm^{-1} for the carbonyl group. No absorption for the nitrile group was observed. Its high resolution mass spectrum gave a molecular ion peak at m/z 256.1825 in agreement with the molecular formula $C_{18}H_{24}O$. There were a total of 16 carbon signals displayed in the ^{13}C NMR APT spectrum, confirming the formation of a single product. In the ^{1}H NMR spectrum, the aromatic protons were displayed at δ 7.20 as a multiplet. The signal for the non-terminal vinylic proton was shown at δ 5.75 (dm, J = 18 Hz), while the signals of the terminal vinylic protons were displayed at δ 5.05 (dm, J = 18 Hz) and 4.95 (dm, J = 10 Hz). Two mutually coupled doublets (J = 13 Hz) at δ 3.20 and 3.04 were attributed to the benzylic protons. The signal of the C-7 methine proton was found at δ 2.60 as a multiplet. The allylic protons were shown at δ 2.20 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 1Hz) and 1.93 (dd, J_1 = 14 Hz, J_2 = 6.5 Hz). A doublet (J = 7 Hz) at δ 1.13 was assigned to the C-7 methyl group. The stereochemistry of compound **4** was deduced from the results of NOE experiments (**Figure 3-2**).

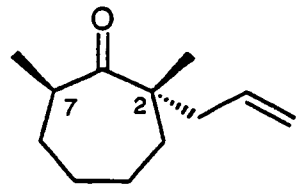
Figure 3-2 The NOE results of compound **4**



Reductive alkylation of Diels-Alder adduct **5** with methyl iodide at room temperature for 1 hour provided a 2 : 1 mixture of ketones **6** and **7** in a yield of 70% (Entry 2). In the case of reductive alkylation of **5** with allyl bromide, ketone **8** was obtained in 60% yield after 1.5 hours at room temperature (Entry 3). When adduct **9** was subjected to reductive alkylation with methyl iodide, ketone **10** was produced in 65% yield after 2 hours (Entry 4). The characterization of compounds **6**, **7**, **8** and **10** was detailed in Chapter 2.



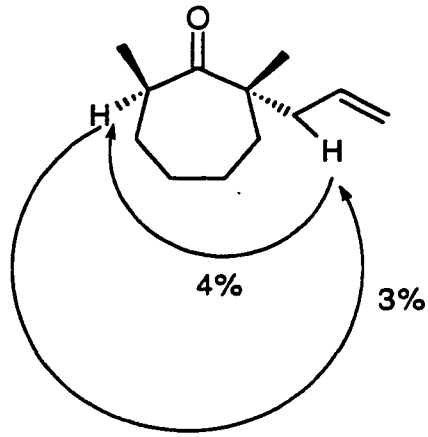
Reductive alkylation of cyano ketone **11** with allyl bromide at room temperature for 8 hours gave compound **12** as a single stereoisomer in 75% yield (Entry 5).



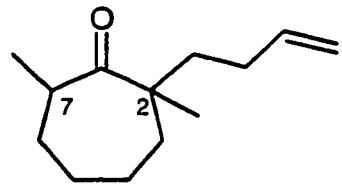
12

The molecular formula of **12**, $C_{12}H_{20}O$, was supported by its high resolution mass spectrum by showing a molecular ion peak at m/z 180.1513. The ^{13}C NMR APT spectrum displayed one set of 12 carbon signals, including a carbonyl signal at δ 218.8 and two vinylic carbon signals at δ 133.7 and 117.9. The ^{1}H NMR spectrum of **12** gave a signal at δ 5.65 (dm, J = 18Hz) for the non-terminal vinylic proton and signals at δ 5.05 (dm, J = 18 Hz) and 4.95 (dm, J = 10 Hz) for the terminal vinylic protons. The signal of the C-7 methine proton was shown as a multiplet at δ 2.92. Two allylic protons appeared as two broad singlets at δ 2.17 and 2.15. A singlet at δ 1.06 represented the C-2 methyl group. The C-7 methyl group was displayed as a doublet at δ 1.00 (J = 7 Hz). The stereochemistry of this compound was confirmed by NOE experiments (**Figure 3-3**)

Figure 3-3 The NOE results of compound **12**



Reductive alkylation of **11** with 4-bromo-1-butene, a less reactive alkylating reagent, proceeded reasonably well to give compound **13** as a single stereoisomer in a yield of 60% (Entry 6).

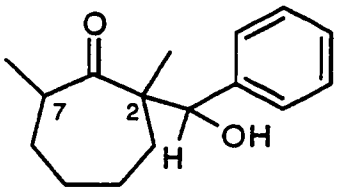


13

The high resolution mass spectrum of **13** gave a molecular ion peak at m/z 194.2176 corresponding to the molecular formula $C_{13}H_{22}O$. The ^{13}C NMR APT spectrum displayed one set of 13 carbon signals, indicating the formation of a single stereoisomer. The ^{1}H NMR spectrum displayed a signal at δ 5.75 (dm, J = 18 Hz) for the non-terminal vinylic proton and signals at δ 5.02 (dm, J = 18 Hz) and 4.95 (dm, J = 9 Hz) for the terminal vinylic protons. Two methyl signals were

observed at δ 1.06 as a singlet and at δ 1.03 as a doublet (J = 7 Hz). Due to the overlapped signals in the ^1H NMR spectrum, we could not confirm the stereochemistry of this compound by NOE experiments.

Finally, an Aldol-type reaction was conducted with cyano ketone **11.** Treatment of **11** with SmI_2 in the presence of HMPA followed by addition of benzaldehyde gave compound **14** as a 1 : 1 mixture of two diastereoisomers in a yield of 74% (Entry 7).



14

For compound **14**, a molecular ion peak was observed at m/z 246.3176 in the high resolution mass spectrum, supporting the molecular formula $C_{16}H_{22}O_2$. The infrared spectrum displayed an absorption at 3475 cm^{-1} for the hydroxyl group and an absorption at 1694 cm^{-1} for the carbonyl group. The ^{13}C NMR spectrum showed two sets of carbon signals representing two isomers. In the ^1H NMR spectrum, the aromatic protons were displayed as 2 multiplets at approximately δ 7.20 and 7.40. Two broad singlets at δ 4.50 and 4.48 were assigned to the proton adjacent to the hydroxyl group. The C-7 methine proton appeared as two multiplets at δ 2.85 and 2.55. The C-2 methyl group was shown as two singlets at δ 1.18 and 1.11. Two doublets at δ 1.22 (J = 7 Hz) and 1.13 (J = 7 Hz) were attributed to the C-7 methyl group.

Compared to the lithium naphthalenide induced reductive alkylation of α-cyano ketones, the current procedure promoted by SmI_2 proved to be equally effective. Hence samarium iodide represents itself as a viable alternative to lithium naphthalenide to effect reductive alkylation of α-cyano ketones and expands the scope of synthetic utility of this process.

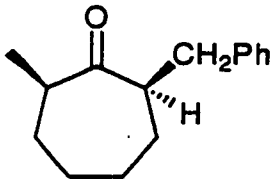
Experimental

For general remarks see Chapter 1 of this thesis

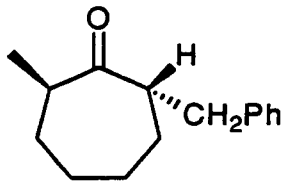
Preparation of tetrahydrofuran solution of SmI_2

A solution of 1,2-diiodoethane (0.54 g, 2 mmol) in absolute tetrahydrofuran (20 mL) was cooled to 0°C and added to samarium powder (0.6 g, 3.99 g-atom) under argon. The resulting mixture was then stirred at room temperature for 5 hours to yield a dark green supernatant as a 0.1 M solution of samarium iodide.

(2R*,7R*)-2-Benzyl-7-methylcycloheptanone (2) and (2S*,7R*)-2-benzyl-7-methylcycloheptanone (3)



2



3

The SmI_2 solution (12.4 mL, 1.24 mmol, 6 equivalents) was added to cyano ketone **1** (50 mg, 0.21 mmol). The resulting solution was refluxed for 24 hours under argon and cooled to room temperature. The reaction mixture was quenched with aqueous saturated ammonium chloride solution (10 mL) and extracted with dichloromethane (2 x 15 mL). The extracts were washed with water (2 x 10 mL) and saturated sodium chloride solution (10 mL), dried with anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was subjected to flash chromatography, eluting with ethyl acetate-Skelly

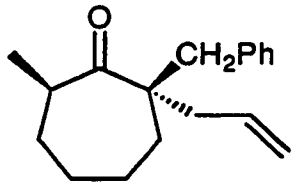
B (1 : 50) to give first compound **2** (27 mg, 0.12 mmol, 60%) and then compound **3** (13 mg, 0.06 mmol, 30%). Compound **2:** IR (CH_2Cl_2, cast): 1705 cm^{-1} (C=O); ^1H NMR (360 MHz, C_6D_6): δ 7.20-7.00 (m, 5H, phenyl), 3.35 (dd, J_1 = 15 Hz, J_2 = 6.5 Hz, 1H, C**H**$_2$Ph), 2.55 (dd, J_1 = 15 Hz, J_2 = 7.5 Hz, 1H, C**H**$_2$Ph), 2.73 (m, 1H, C**H**CH$_2$Ph), 2.20 (m, 1H, CH$_3$C**H**), 1.45-1.43 (m, 3H), 1.36-1.07 (m, 5H), 1.05 (d, J = 7 Hz, 3H, C**H**$_3$CH); ^{13}C NMR APT (75 MHz, C_6D_6): δ 214.0 (p), 141.2 (p), 129.4 (ap), 128.8 (ap), 126.2 (ap), 52.9 (ap), 45.9 (ap), 41.0 (p), 32.5 (p), 30.9 (p), 27.6 (p), 25.8 (p), 16.4 (ap); HRMS M^+: 216.1516 (calcd. for $C_{15}H_{20}O$: 216.1519). Compound **3**: IR (CH_2Cl_2, cast): 1707 cm^{-1} (C=O); ^1H NMR (360 MHz, C_6D_6): δ 7.00 (m, 5H, phenyl), 3.10 (dd, J_1 = 16 Hz, J_2 = 7 Hz, 1H, C**H**$_2$Ph), 2.54 (dd, J_1 = 16 Hz, J_2 = 7 Hz, 1H, C**H**$_2$Ph), 2.75 (m, 1H, C**H**CH$_2$Ph), 2.35 (m, 1H, CH$_3$C**H**), 1.55-1.40 (m, 4H), 1.40-0.87 (m, 4H), 0.85 (d, J = 6.5 Hz, 3H, C**H**$_3$CH); HRMS M^+: 216.1519 (calcd. for $C_{15}H_{20}O$: 216.1519).

General procedure for reductive alkylation

To a 0.1 M solution of SmI_2 in THF (25 mL, 2.49 mmol, 6 equivalents), HMPA (0.86 mL, 4.98 mmol, 12 equivalents) was added. The mixture was stirred at room temperature for 2 minutes under argon and then added to a flask containing the cyano ketone (0.41 mmol, 1 equivalent). The resulting purple solution was stirred for 30 minutes at room temperature then treated with an alkylating agent (6 equivalents) for a period of time. Upon completion, the reaction was quenched with saturated ammonium chloride soution (10 mL) and the resulting mixture was extracted with dichloromethane (3 x 15 mL). The extracts were washed with water (3 x 10 mL) and saturated sodium chloride solution (2 x 10 mL), dried with anhydrous magnesium sulfate, filtered and

concentrated in vacuo. The residue was subjected to flash chromatography. Elution with ethyl acetate-Skelly B gave the desired alkylated product(s).

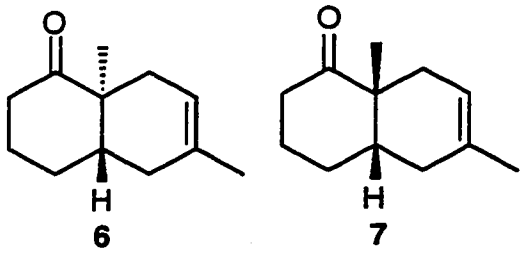
(2S*,7R*)-2-Allyl-2-benzyl-7-methylcycloheptanone (4)



4

Allyl bromide was added to a mixture of cyano ketone **1** (90 mg, 0.37 mmol) and SmI_2 in THF in the presence of HMPA. The solution was stirred at room temperature for 10 hours to give, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **4** as a yellow oil (77 mg, 0.29 mmol, 80%): IR (CH_2Cl_2, cast): 1700 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (m, 5H, phenyl), 5.75 (dm, J = 18 Hz, 1H, CH_2=C**H**), 5.05 (dm, J = 18 Hz, 1H, CH=C**H**$_2$), 4.95 (dm, J = 10 Hz, 1H, CH=C**H**$_2$), 3.20 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 3.04 (d, J = 13 Hz, 1H, C**H**$_2$Ph), 2.60 (m, 1H, CH_3C**H**), 2.20 (ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 1 Hz, 1H, C**H**$_2$CH=CH_2), 1.93 (dd, J_1 = 14 Hz, J_2 = 6.5 Hz, 1H, C**H**$_2$CH=CH_2), 1.50-1.23 (m, 6H), 1.00-0.90 (m, 2H), 1.13 (d, J = 7 Hz, 3H, C**H**$_3$); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 237.4 (p), 138.8 (p), 133.9 (ap), 131.1 (ap), 128.0 (ap), 126.1 (ap), 118.3 (p), 55.6 (p), 43.4 (ap), 43.0 (p), 37.8 (p), 35.7 (p), 32.1 (p), 29.8 (p), 24.2 (p), 17.4 (ap); HRMS M^+: 256.1825 (calcd. for $C_{18}H_{24}O$: 256.1831). Anal. calcd. for $C_{18}H_{24}O$: C 84.38%, H 9.36%; found: C 84.32%, H 9.43%.

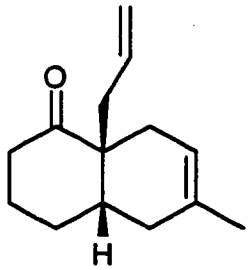
(1S*,6S*)-1,8-Dimethylbicyclo[4.4.0]dec-8-en-2-one (6) and (1R*,6S*)-1,8-dimethylbicyclo[4.4.0]dec-8-en-2-one (7)



6 7

Reductive alkylation of cyano ketone **5** (84 mg, 0.44 mmol) at room temperature for 1 hour provided, after flash chromatography (ethyl acetate-Skelly B 1 : 25), an inseparable 2 : 1 mixture of **6** and **7** (55 mg, 0.31 mmol, 70%).

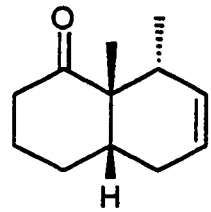
(1R*,6S*)-1-Allyl-8-methylbicyclo[4.4.0]dec-8-en-2-one (8)



8

Reductive alkylation of cyano ketone **5** (100 mg, 0.53 mmol) with allyl bromide at room temperature for 1.5 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 20), compound **8** (65 mg, 0.32 mmol, 60%).

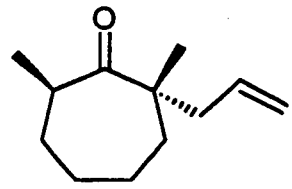
(1S*,6S*,10R*)-1,10-Dimethylbicyclo[4.4.0]dec-8-en-2-one (8)



10

Reductive alkylation of cyano ketone **9** (75 mg, 0.39 mmol) with methyl iodide at room temperature for 2 hours afforded, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **10** ((56 mg, 0.32 mmol, 80%)

(2S*,7R*)-2-Allyl-2,7-dimethylcycloheptanone (12)

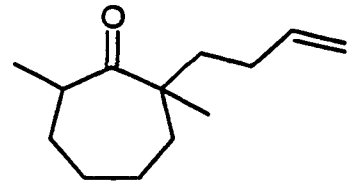


12

Treatment of cyano ketone **11** (49 mg, 0.3 mmol) with SmI_2 in THF in the presence of HMPA for 30 minutes, followed by addition of allyl bromide and reaction for 8 hours at room temperature gave, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **12** as a pale yellow oil (40 mg, 0.22 mmol, 75%): IR (CH_2Cl_2, cast): 1640 (C=C), 1704 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 5.65 (dm, J = 18 Hz, 1H, C**H**=CH_2), 5.05 (dm, J = 18 Hz, 1H, CH=C**H**$_2$), 4.95 (dm, J = 10 Hz, 1H, CH=C**H**$_2$), 2.92 (m, 1H, CH_3C**H**), 2.17 (s, br, 1H, C**H**$_2$CH=CH_2), 2.15 (s, br, 1H, C**H**$_2$CH=CH_2), 1.82-1.53 (m, 4H), 1.45-1.05 (m,

4H), 1.06 (s, 3H, CH_3), 1.01 (d, J = 7 Hz, 3H, CH_3CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): δ 218.8 (p), 133.7 (ap), 117.9 (p), 51.4 (p), 42.6 (ap), 38.2 (p), 37.3 (p), 35.8 (p), 32.0 (p), 29.8 (p), 21.2 (ap), 17.5 (ap); HRMS M^+: 180.1513 (calcd. for $C_{12}H_{20}O$: 180.1517). Anal. calcd. for $C_{12}H_{20}O$: C 79.93%, H 11.10%; found: C 80.03%, H 11.27%.

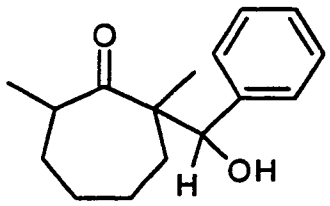
2-(3-Butenyl)-2,7-dimethylcycloheptanone (13)



13

Reductive alkylation of cyano ketone **11** (70 mg, 0.42 mmol) with 4-bromo-1-butene at room temperature for 15 hours gave, after flash chromatography (ethyl acetate-Skelly B 1 : 25), compound **13** as a single diastereoisomer (49.4 mg, 0.25 mmol, 60%): IR (CH_2Cl_2, cast): 1732 (C=O), 1682 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 5.75 (dm, J = 18 Hz, 1H, C**H**=CH_2), 5.02 (dm, J = 18 Hz, 1H, CH=C**H**$_2$), 4.95 (dm, J = 9 Hz, 1H, CH=C**H**$_2$), 2.85 (m, 1H, CH_3C**H**), 2.40-2.24 (m, 2H), 2.00-1.66 (m, 6H), 1.54-0.93 (m, 4H), 1.06 (s, 3H, C**H**$_3$), 1.03 (d, J = 7 Hz, C**H**$_3$CH); ^{13}C NMR APT (75 MHz, $CDCl_3$): 218.8 (p), 133.7 (ap), 117.9 (p), 51.4 (p), 45.7 (p), 42.6 (ap), 37.3 (p), 35.8 (p), 30.4 (p), 29.7 (p), 24.2 (p), 21.2 (ap), 17.6 (ap); HRMS M^+: 194.2176 (calcd. for $C_{13}H_{22}O$: 194.2182).

2-(Hydroxyphenylmethyl)-2,7-dimethylcycloheptanone (14)



14

Benzaldehyde was added to a mixture of cyano ketone **11** (75 mg, 0.45 mmol) and SmI_2 in THF in the presence of HMPA. The solution was stirred at room temperature for 8 hours to give, after flash chromatography (ethyl acetate-Skelly B 1 : 8), compound **14** as a 1 : 1 mixture of 2 diastereoisomers (84 mg, 0.34 mmol, 74%): mp (mixture): 194-199°C; IR (mixture, CH_2Cl_2, cast): 3475 (OH), 1694 cm^{-1} (C=O); ^1H NMR (mixture, 300 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5H, phenyl), 4.50 (s, br, 0.5H, **H**COH), 4.48 (s, br, 0.5H, **H**COH), 2.85 (m, 0.5H, CH_3CH), 2.55 (m, 0.5H, CH_3CH), 2.04-1.56 (m, 3.5H), 1.49-1.12 (m, 4.5H) 1.18 (s, 1.5H, CH_3), 1.11 (s, 1.5H, CH_3), 1.22 (d, J = 7 Hz, 1.5H, CH_3CH), 1.13 (d, J = 7 Hz, 1.5H, CH_3CH); ^{13}C NMR APT (mixture, 75 MHz, $CDCl_3$): δ 218.9 (p), 216.8 (p), 141.5 (p), 140.9 (p), 129.6 (ap), 128.2 (ap), 127.7 (ap), 127.7 (ap), 120.4 (ap), 115.5 (ap), 81.9 (ap), 79.6 (ap), 56.3 (p), 54.9 (p), 46.3 (ap), 43.5 (ap), 35.5 (p), 34.8 (p), 33.0 (p), 30.6 (p), 30.5 (p), 30.3 (p), 23.9 (p), 23.8 (p), 20.9 (ap), 18.2 (ap), 18.1 (ap), 18.0 (ap); HRMS M^+: 246.3176 (calcd. for $C_{16}H_{22}O_2$: 246.3182).

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