UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON TERPENOIDS. PART 1. TOTAL SYNTHESIS OF THE MARINE NATURAL PRODUCT NANAIMOAL. PART 2. TOWARDS THE TOTAL SYNTHESIS OF SOLIDAGO ALCOHOL *VIA* AN INTERMOLECULAR DIELS-ALDER APPROACH

by

TAI WEI LY

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

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 2000

Dedicated to my wife, Winnie Wong, for her unending support and love

Abstract

Chapter one of this thesis describes the total synthesis of the marine natural product nanaimoal (**1**). The key step was the conversion of enone **53** to give bicyclic ketone **60** using a reductive alkylation methodology recently developed in our laboratories. Bicyclic ketone **60** was also synthesized from enone **64** albeit in lower yield.

Enone **53** was readily prepared from *bis*-nitrile **56** as described in Scheme 15 . Wittig olefination followed by acid hydrolysis furnished keto nitrile **54**. Robinson annulation of keto nitrile **54** using ethyl vinyl ketone as the Michael acceptor then yielded enone **53**. Enone **64** was also synthesized following the same route using methyl vinyl ketone as the Michael acceptor.

Bicyclic ketone **60** was reduced under the Huang Minlon modification of the Wolff-Kishner reaction conditions to furnish bicyclic diene **42**. Regioselective hydroboration followed by oxidation of the ensuing alkylborane species with pyridinium chlorochromate then completed the synthesis of nanaimoal in 15% overall yield.

The second chapter reports on our efforts towards the total synthesis of the C-19 oxygenated *cis*-normal clerodane solidago alcohol (**91**) using an intermolecular Diels-Alder approach previously developed in our laboratories. Zinc chloride mediated Diels-Alder reaction of dienone **76** with piperylene (2:1 *trans:cis* mixture) gave keto ester **77** as the major diastereomer. Conjugate addition of lithium dimethylcuprate followed by reduction of the resulting enolate with

lithium aluminum hydride then furnished keto alcohol **78**. Mesylation followed by debenzylation resulted in the isolation of keto mesylate **99** which was treated with sodium hydride to effect the ring closure to give keto ether **93**. Keto ether **93** was also synthesized from benzyl mesylate **79** by the action of sodium iodide in *N*,*N*-dimethylformamide at elevated temperature. Wolff-Kishner reduction of keto ether **93** under Huang Minlon modification conditions then gave tricyclic ether **98**. Ether ring opening followed by benzoylation then gave bromo benzoate **106** which was oxidized under modified Kornblum oxidation conditions to yield benzoyl aldehyde **107**. 1,2-Addition of 3-lithiofuran to the aldehyde moiety of benzoyl aldehyde **107** followed by acetylation gave furyl acetate **113** which was reduced under dissolving metal reduction conditions to yield Δ^2-isomer (**112**) of solidago alcohol (**91**). Rhodium mediated olefin isomerization resulted in the isolation of the Δ^1-isomer (**114**).

ACKNOWLEDGMENTS

First and foremost I would like to convey my utmost gratitude and appreciation to Professor H.J. Liu for his unswerving support, guidance, and assistance throughout my graduate career. His encouragement, meticulous attention to detail, and guidance over these past few years has been invaluable and instilled upon me a greater appreciation of the joy and pains of research.

I would also like to thank all the technical staff of the department for inspirational discussion and without which this work would not have been possible: Dr. A. Morales, L. Harrower, and D. Morgan in the Mass Spectrometry Laboratory, D. Formanski and J. Hoyle in the Spectral Services Laboratory, D. Mahlow and A. Dunn in the Microanalytical Laboratory, Dr. T.T. Nakashima, G. Bigam, L. Kong, and G. Aarts in the NMR Spectroscopy Laboratory, as well as all the personnel in the Electronic, Glass Blowing and Machine Shops.

I would like to acknowledge Dr. J.M. Stryker for invaluable discussions and insights, all the members of our research group (wherever they may be) for a sociable and enjoyable work environment, and the Edmonton Fire Department for timely response to our laboratory fire.

Last of all, the University of Alberta is acknowledged for financial support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SCHEMES (CONT.)

Chapter 2: Towards the Total Synthesis of Solidago Alcohol *via* an Intermolecular Diels-Alder Approach

LIST OF SCHEMES (CONT.)

LIST OF ABBREVIATIONS

Ac	Acetyl
APT	Attached Proton Test
Ar	aryl
Bn	benzyl
br	broad
Bu	butyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
eq	equivalent(s)
Et	ethyl
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
i	iso
IR	infrared
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
min	minutes
m.p.	melting point
Ms	methanesulfonyl

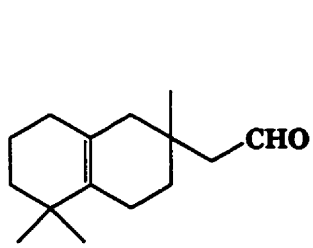
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	propyl
pyr	pyridine
q	quartet
r.t.	room temperature
t	tert
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluenesulfonyl

Chapter One

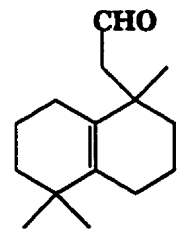
Total Synthesis of the Marine Natural Product Nanaimoal

Introduction

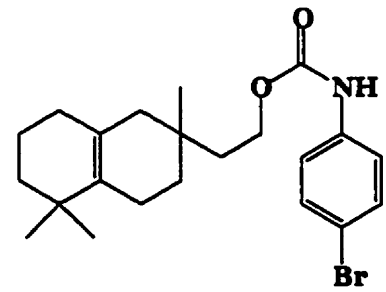
Nanaimoal (**1**), was first isolated and identified by Andersen *et al*[1]. in 1984 as the major component in the methanol extracts of dorid nudibranch *Acanthodoris nanaimoensis*. The structure of this fragrant sesquiterpenoid aldehyde was inferred from its spectroscopic data and the biogenetic isoprene rule. However, the biogenetic isoprene rule suggests two possible structures (**1, 2**) for nanaimoal which were consistent with the structural features as determined by the authors. Given this uncertainty, the authors attempted to synthesize **3** for structural correlation. Their



1



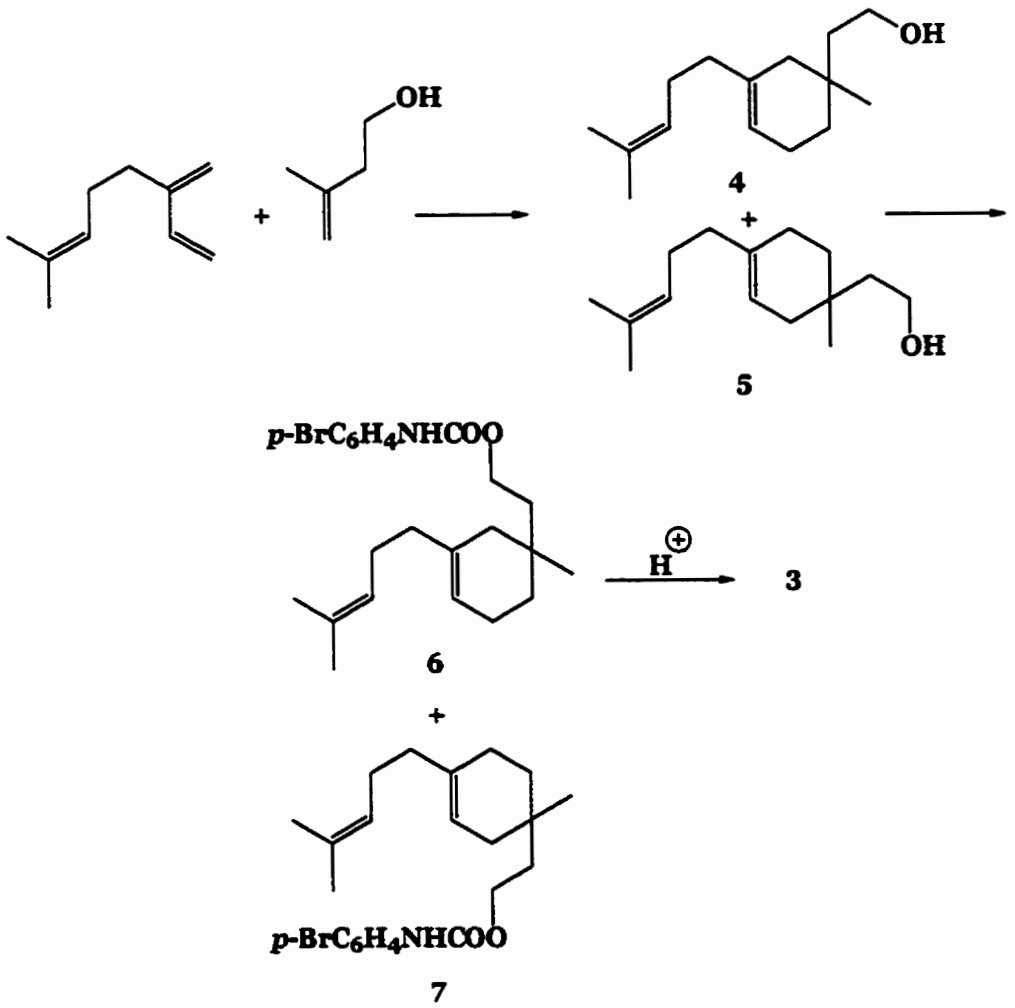
2



3

rationale for choosing structure **1** as the most plausible structure for nanaimoal stems from the fact that a large number of naturally occurring monocyclofarnesane sesquiterpenoids have the same gross structure. Andersen *et al.* embarked on the synthesis of **3** with the Diels-Alder reaction of myrcene and 3-methylbut-3-en-1-ol to give a mixture of regioisomeric Diels-Alder adducts **4** and **5** as diagrammed in Scheme 1. Unfortunately, the spectroscopic data for **4** and **5** did not allow for unambiguous structural assignment and so the authors resorted to derivatizing the hydroxy functionality as their corresponding *p*-

bromophenylurethanes **6** and **7**. With the individual urethanes in hand, structural analysis verified the structural assignment of **7** which served to confirm the structure of **5**. With the structure of **6** indirectly confirmed, its cyclization into **3** was then carried out by heating in 95% formic acid at 60°C for 12 hours. The structure of synthetic **3** was found to be spectroscopically identical to that synthesized from natural nanaimoal.

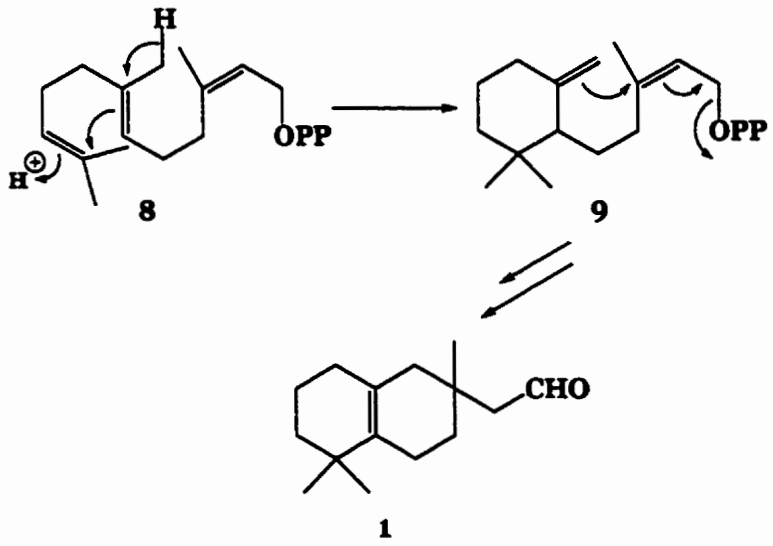


Scheme 1

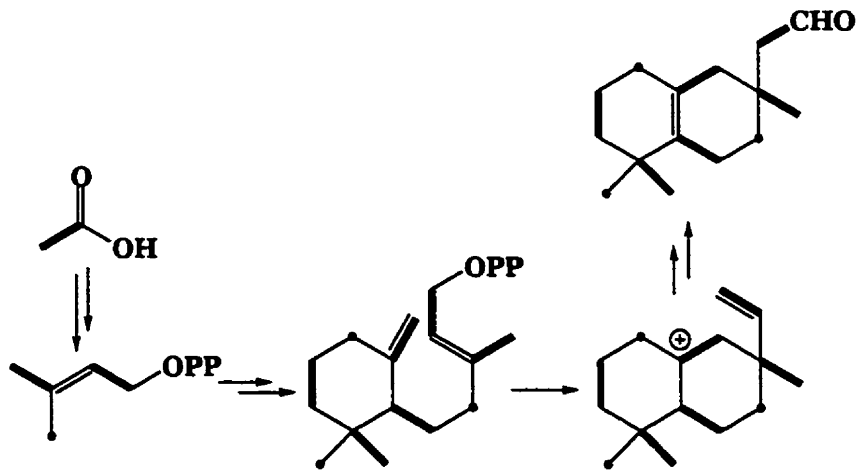
Thus, the inferred structure of **1** was confirmed unambiguously.

The biosynthesis of nanaimoal was proposed by Andersen *et al*[1]. to proceed from farnesyl pyrophosphate (**8**) as depicted in Scheme 2. The authors hypothesized that an acid catalyzed cyclization of farnesyl pyrophosphate would yield cyclohexyl intermediate **9** which was proposed to undergo a second cyclization to give, after elimination and oxidation, nanaimoal. Evidence for this biogenetic pathway to nanaimoal was reported in 1996 by Andersen *et al*[2]. The authors periodically injected specimens of *A. nanaimoensis* with [1,2-$^{13}C_2$]acetate and then extracted the whole animals with methanol. From the methanol extracts, the authors were able to isolate ^{13}C enriched nanaimoal. The labeling pattern found by the authors is depicted in Scheme 3 and is consistent with the proposed biogenesis alluded to above.

Since its isolation and identification in 1984, there have been three



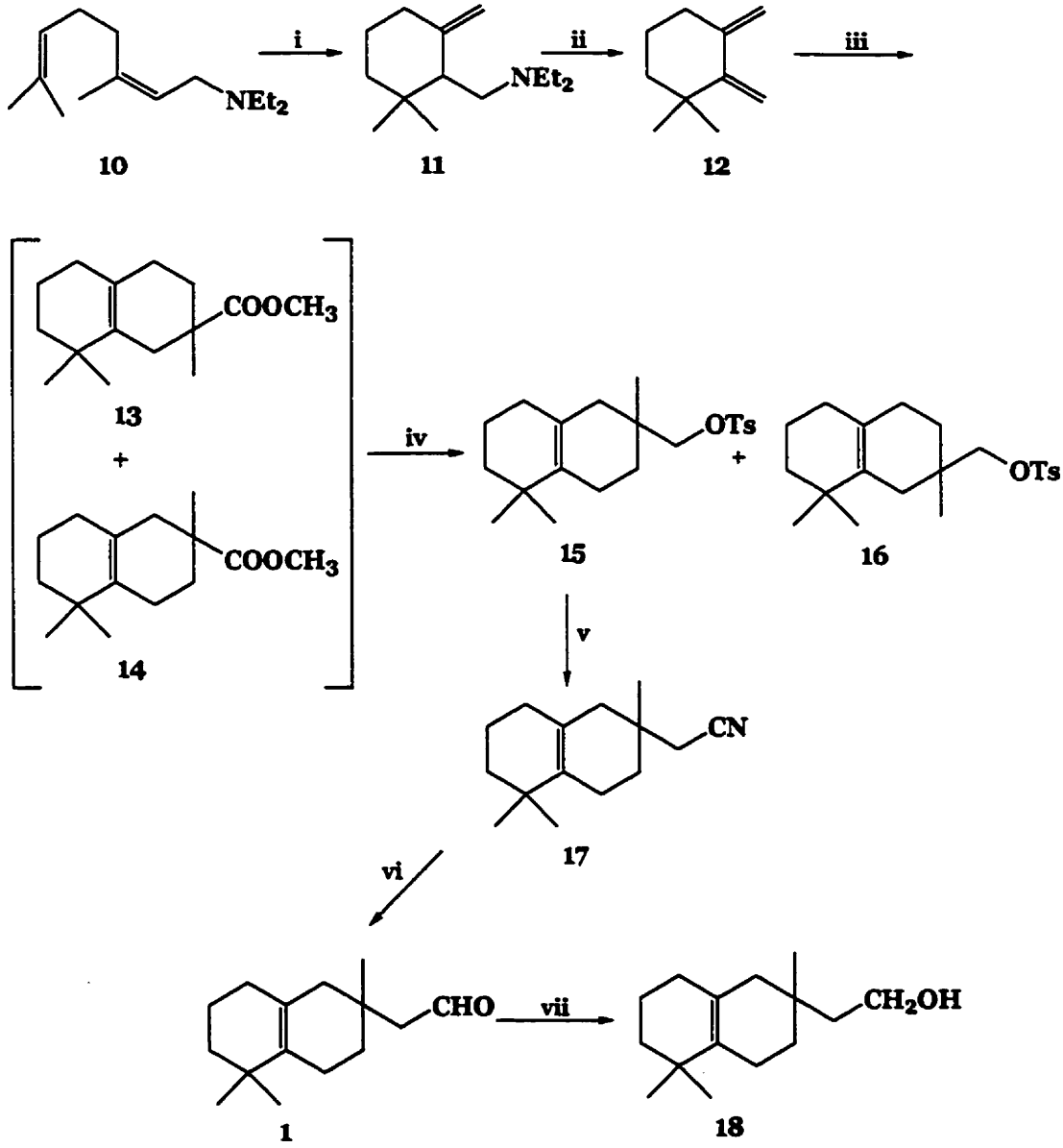
Scheme 2



Scheme 3

independent syntheses of nanaimoal. In 1993, Takabe and Yamada[3] reported the synthesis of racemic **1** and its reduction product nanaimool (**18**). The key step in their synthesis was the Diels-Alder reaction of 1,1-dimethyl-2,3-dimethylenecyclohexane (**12**) with methyl methacrylate (MMA) (Scheme 4). The authors synthesized diene **12** from *N*,*N*-diethylgeranylamine (**10**) in two steps; first reaction involving cyclization to cyclogeranylamine **11** by treatment with boron trifluoride etherate followed by oxidative elimination of **11** with 30% hydrogen peroxide. The Diels-Alder reaction mentioned above was found to yield an inseparable mixture of regioisomers **13** and **14** in excellent yield (91%). The authors then reduced the above regioisomeric mixture with lithium aluminum hydride followed by tosylation to give a mixture of tosylates **15** and **16** which was separated by HPLC. The desired tosylate **15** was then treated with sodium cyanide in dimethyl sulfoxide at elevated temperatures for 3 hours to give nitrile **17** in 85% yield. Finally, reduction of nitrile **17** with diisobutylaluminum hydride completed the total synthesis of **1**. Alcohol

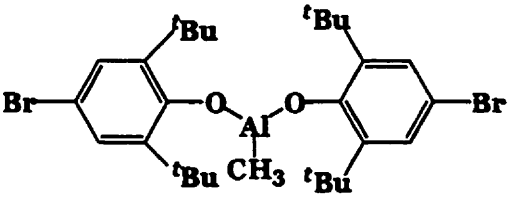
18 was then synthesized quantitatively by reduction of **1** with sodium borohydride.



Scheme 4

Conditions: i. $BF_3 \cdot OEt_2$, 70%; ii. 30% H_2O_2, then heat, 70%; iii. MMA, 170°C, 91%; iv. $LiAlH_4$, then TsCl, base, 98% (**15**:**16** = 56:44); v. NaCN, DMSO, 110-115°C, 85%; vi. DIBAL-H, 80%; vii. $NaBH_4$, quantitative.

The second total synthesis of **1** was achieved in 1994 by Shisido and Omodani[4]. This was also the first enantioselective synthesis of **1** which served to establish its absolute stereochemistry. Shishido's approach relied on the Diels-Alder reaction to construct the carbon skeleton of **1**. The authors' synthetic endeavor began with the Sharpless asymmetric epoxidation of geraniol (**20**) using L-(+)-diethyl tartrate followed by silylation to give the desired starting epoxy silyl ether **21** (Scheme 5). Treatment of epoxide **21** with two equivalents of methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide (**19**) gave the desired aldehyde **22** with (*S*)-configuration in 97% yield and 95% ee. Nitroalkene **25** was then synthesized in 55% overall yield from aldehyde **22** in three steps: nitromethylation, acetylation of the resulting alcohol, and finally, reduction of the acetate by sodium borohydride. When nitroalkene **25** was treated with *p*-chlorophenylisocyanate and triethylamine, isoxazoline **26**

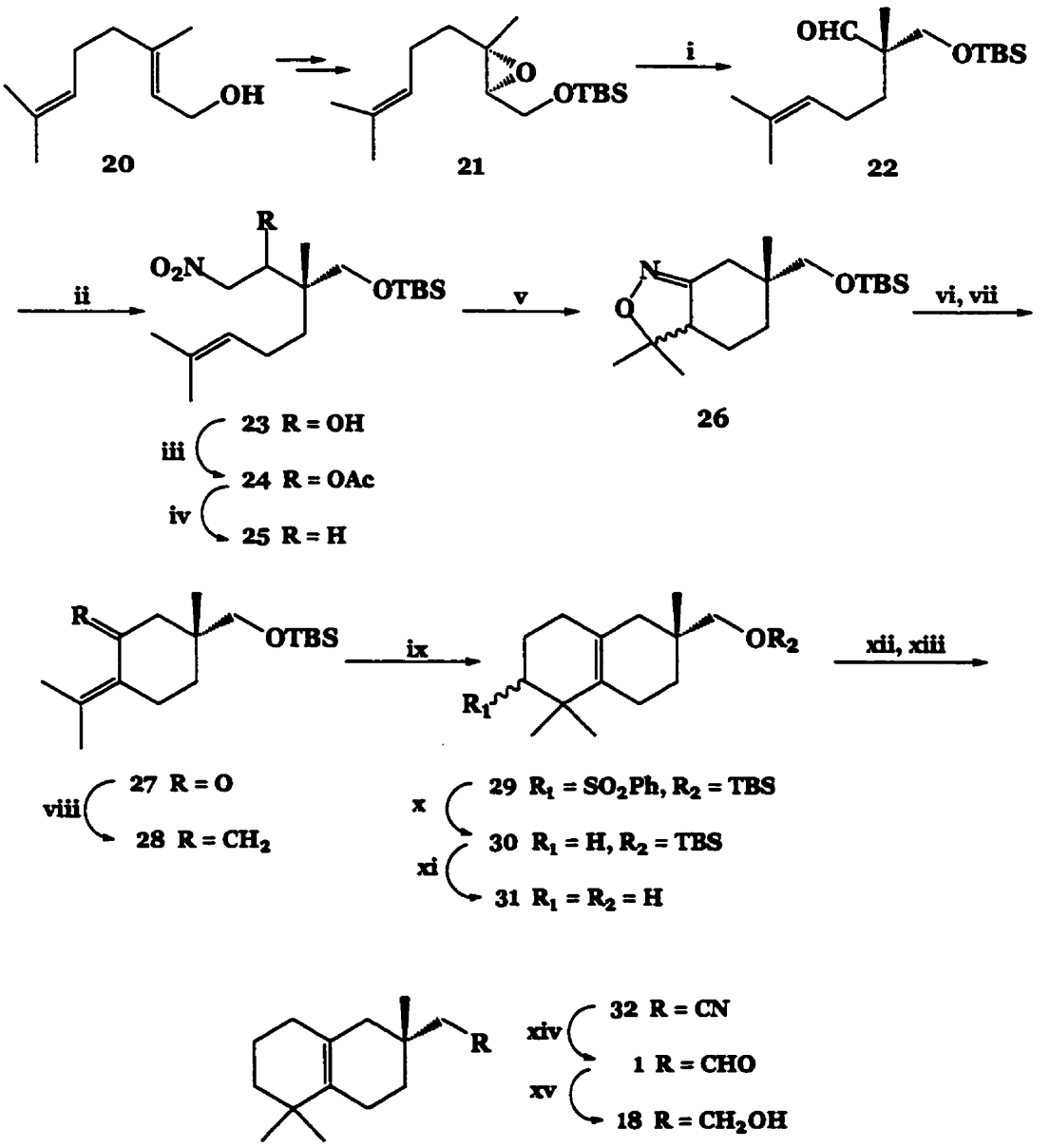


19

was formed quantitatively as an inseparable pair of diastereomers in a ratio of 2:1. Treatment of isoxazoline **26** with Raney nickel in aqueous methanol in the presence of trimethyl borate under an atmosphere of hydrogen achieved the reductive hydrolysis process, yielding a β-hydroxy ketone which was immediately exposed to *d*-10-camphorsulfonic acid in dichloromethane. The desired α,β-unsaturated ketone **27** thus obtained

was then methylenated under Nozaki-Lombardo conditions[5] to give the conjugated dienyl product **28** in 48% yield over three steps. Subsequent thermal Diels-Alder reaction of diene **28** with phenyl vinyl sulfone in benzene yielded cycloadduct **29** as an inseparable 1:1 mixture of diastereomers in 43% yield. Removal of the sulfone functionality was achieved by treating cycloadduct **29** with 5% sodium amalgam in methanol which gave the bicyclic compound **30**. Desilylation of **30** using tetrabutylammonium fluoride in tetrahydrofuran then yielded alcohol **31** in 49% yield over two steps. The authors completed the synthesis of **1** by conversion of alcohol **31** to the tosylate followed by cyanation with sodium cyanide in dimethyl sulfoxide to give the cyano product **32** in 86% yield over two steps. Reduction of the cyano functionality with diisobutylaluminum hydride followed by acid workup then gave the target product **1** in 70% yield. In order to confirm the absolute structure and optical purity of their synthetic **1**, the authors proceeded to treat their synthetic **1** with sodium borohydride in methanol which gave alcohol **18** in 73% yield. Synthetic nanaimool (**18**) was found to have an optical rotation of +10.9° (c 0.2, MeOH)[1] which was consistent to the reported value of +10.4° (MeOH). Thus with this enantioselective synthesis of **1**, the absolute stereochemistry of nanaimoal was established.

In 1996, Engler and co-workers published the most recent total synthesis of nanaimoal[6]. In his approach, Engler utilized a protic acid promoted cycloaddition reaction to form the core carbon skeleton of nanaimoal (Scheme 6). His synthesis began with α-(phenysulfinyl) keto ester **34** formed *via* a two-step, one pot reaction. Thus, treatment of 3-methyl-2-

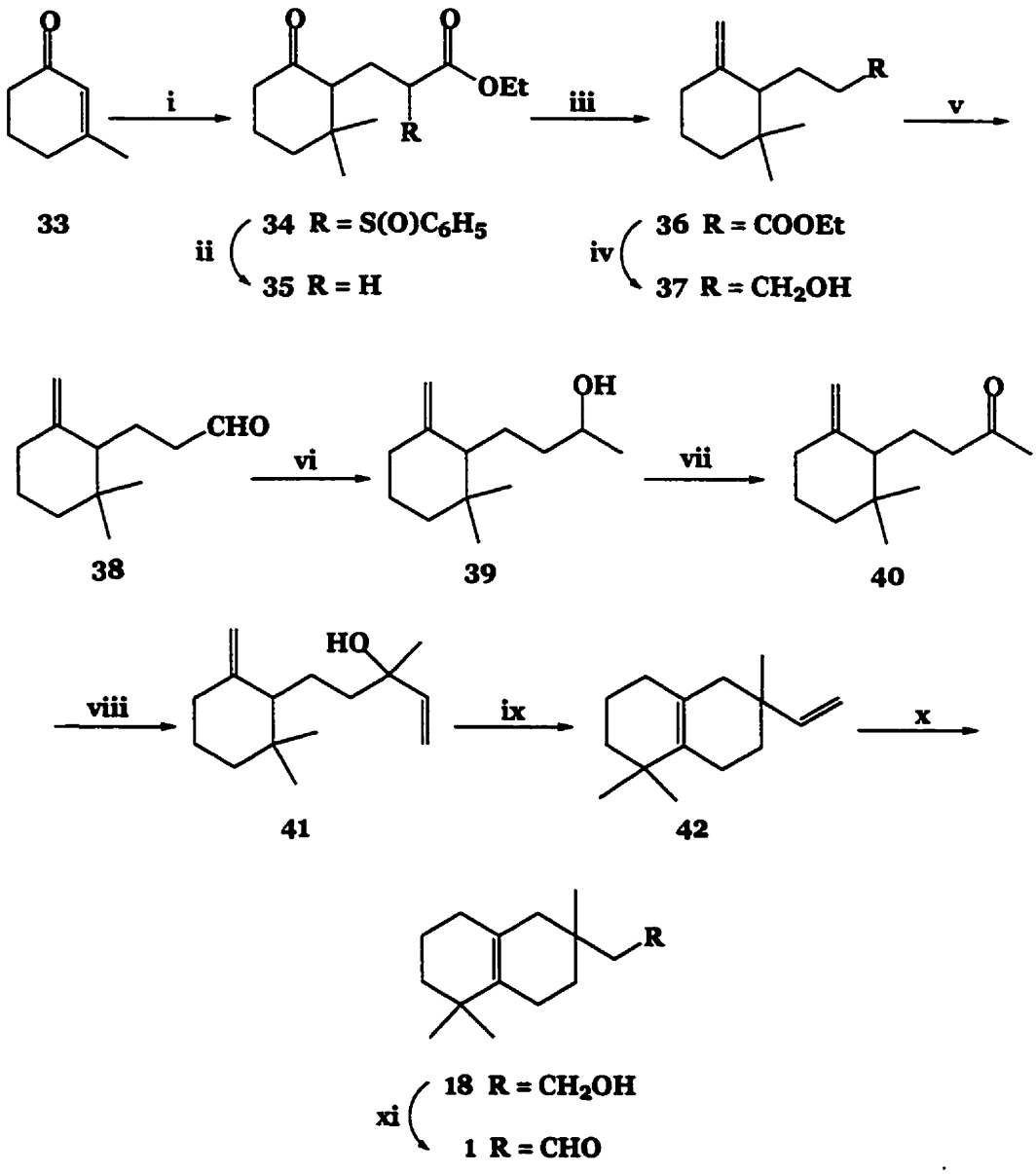


Scheme 5

Conditions: i. **19**, CH_2Cl_2, 97%; ii. $MeNO_2$, KF, 18-crown-6, 2-propanol; iii. Ac_2O, DMAP, Et_2O; iv. $NaBH_4$, EtOH, 55% over 3 steps; v. *p*-ClC_6H_4NCO, Et_3N, benzene, 100%; vi. H_2, Ra-Ni, $(MeO)_3B$, H_2O-MeOH; vii. *d*-10-camphorsulfonic acid, CH_2Cl_2; viii. CH_2Br_2, Zn, $TiCl_4$, THF-CH_2Cl_2, 48% over 3 steps; ix. $PhSO_2CH{=}CH_2$, benzene, sealed tube, 160°C, 43%; x. 5% Na-Hg, MeOH; xi. $^nBu_4NF$, THF, 49% over 2 steps; xii. *p*-TsCl, pyridine; xiii. NaCN, DMSO, 86% over 2 steps; xiv. DIBAL-H, hexane-CH_2CH_2 (1:1), then aq. HCl, 70%; xv. $NaBH_4$, EtOH, 73%.

cyclohexen-1-one (**33**) with lithium dimethylcuprate followed by alkylation of the enolate with ethyl α-(phenylsulfinyl)acrylate gave the desired product **34**. Reduction of the sulfoxy functionality was then achieved by treating **34** with either Raney nickel (98% yield) or aluminum amalgam (75% yield) to give the expected keto ester product **35**. The ketone carbonyl was then chemoselectively methylenated under Nozaki-Lombardo conditions[5] to furnish ester **36** in 71% yield which was then reduced to the primary alcohol **37** in 98% yield by the action of lithium aluminum hydride. Methyl ketone **40** was then synthesized from alcohol **37** *via* a three-step process: Swern oxidation to aldehyde **38** (96%), 1,2-addition using methylmagnesium chloride to give the secondary alcohol **39** (100%), and Swern oxidation to give the desired ketone **40** (98%). Treatment of methyl ketone **40** with vinylmagnesium bromide then resulted in allylic alcohol **41** being isolated in quantitative yield. Acid catalyzed cyclization of allylic alcohol **41** to give intermediate diene **42** in 82% yield was then effected by treatment with aqueous hydrofluoric acid. Diene **42** thus obtained was then hydroborated with 9-borabicyclo[3.3.1]nonane (9-BBN-H) followed by a basic hydrogen peroxide workup to furnish nanaimool in 98% yield. Finally, Swern oxidation of nanaimool to give nanaimoal in 82% yield then completed Engler's total synthesis.

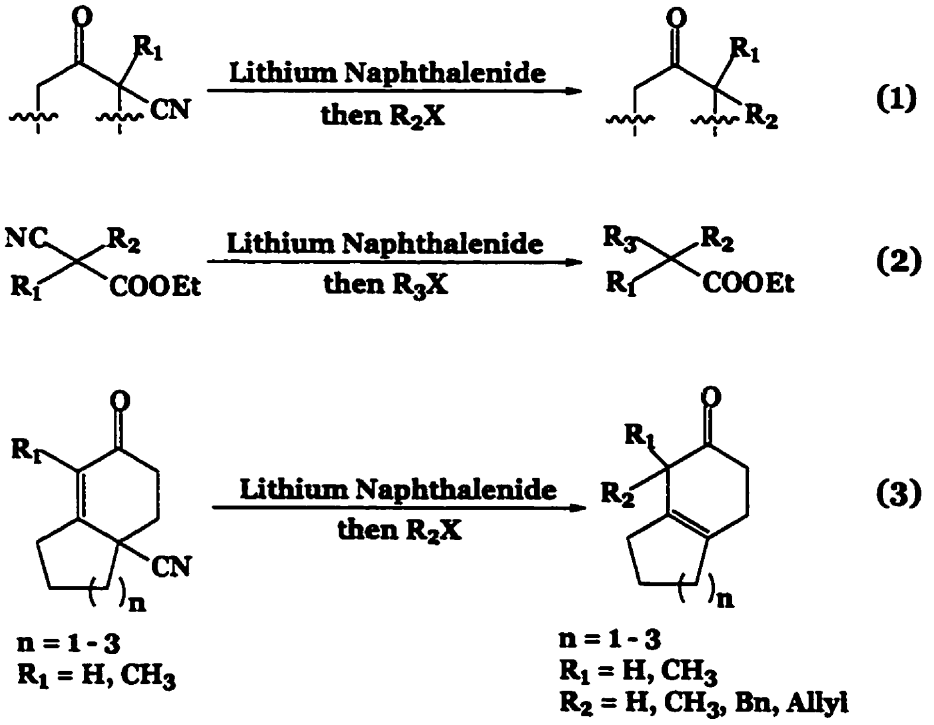
Our interest in nanaimoal stems from a recent reductive alkylation methodology developed in our laboratories[7]. It was discovered that α-cyano ketones and esters can be reductively alkylated with ease by treatment with lithium naphthalenide followed by the addition of an



Scheme 6

Conditions: i. $(CH_3)_2CuLi$, then ethyl α-(phenylsulfinyl)acrylate; ii. $Al(Hg)/H_2O$, 75% or Ra-Ni/H_2O, 98%; iii. $TiCl_4/Zn/CH_2Br_2$, 71%; iv. $LiAlH_4$, 98%; v. Swern oxidation, 96%; vi. CH_3MgCl, 100%; vii. Swern oxidation, 98%; viii. CH_2=CHMgBr, 100%; ix. 48% aqueous HF, 82%; x. 9-BBN-H, then $H_2O_2/NaOH$, 98%; xi. Swern oxidation, 82%.

appropriate alkylating agent to give various α-substituted ketones and esters (Scheme 7, Eq. 1 and 2). The viability of this methodology towards the synthesis of complex organic molecules has been recently demonstrated in the formal syntheses of two *cis*-clerodane natural products, namely 6β-2-oxokolavenool (**52**) and 2-oxo-5α,8α-13,14,15,16-tetranorclerod-3-en-12-oic acid (**51**) (Scheme 8)[8]. The key intermediate

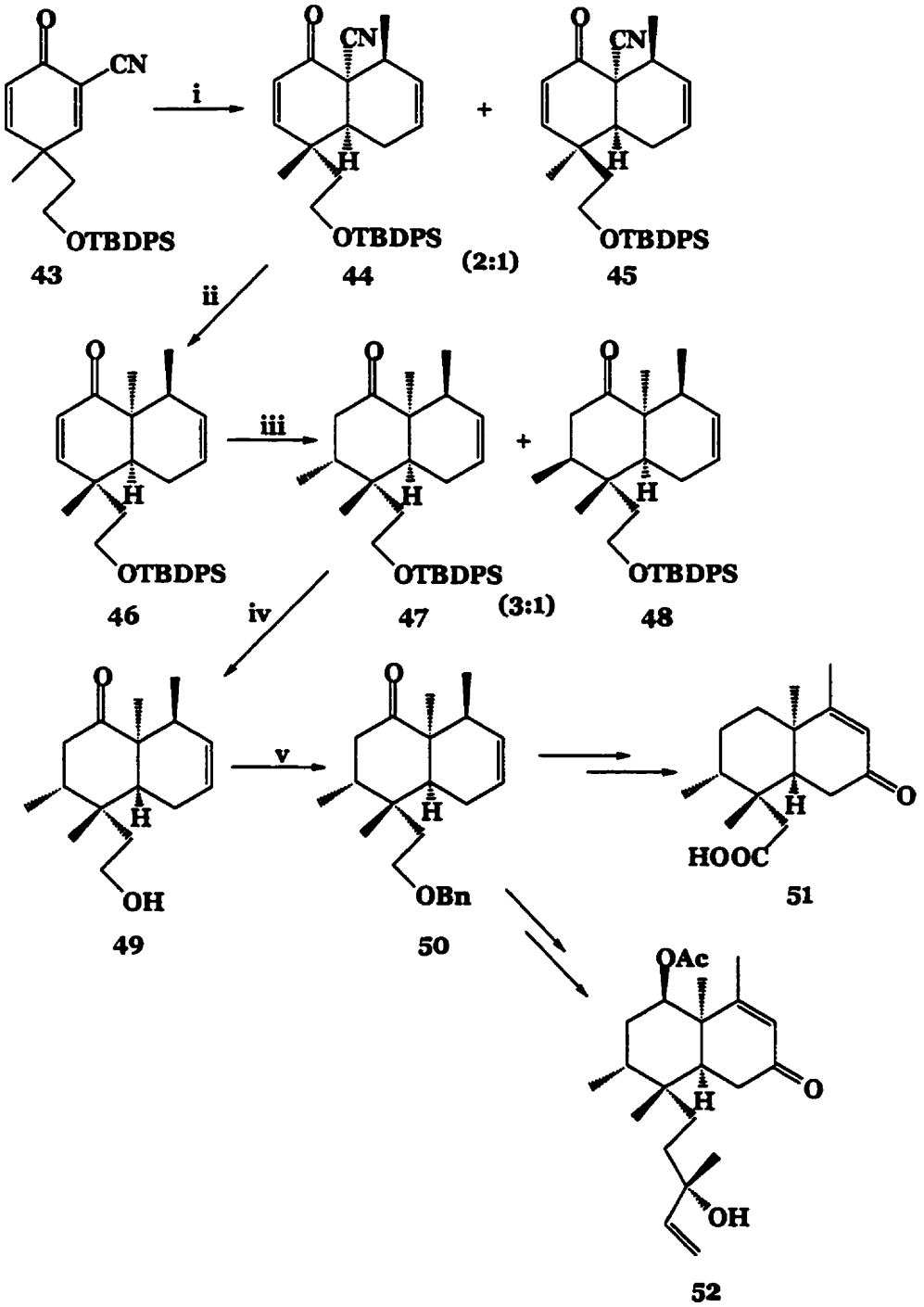


Scheme 7

was the Diels-Alder adduct **44**, the major cycloadduct formed from the zinc chloride catalysed Diels-Alder reaction between dienophile **43** and *trans*-piperylene. Thus, treatment of **43** with fused zinc chloride and *trans*-piperylene in diethyl ether furnished, after 2 days, a 2:1 mixture of cycloadducts **44** and **45** in 90% yield favoring the desired diastereomer **44**. Reductive alkylation of α-cyano ketone **44** using lithium

naphthalenide and methyl iodide then gave the desired compound **46** as the sole product in 86% yield. 1,4-Addition across the enone system in **46** was then achieved by treating **46** with lithium dimethylcuprate in the presence of bromotrimethylsilane followed by hydrolysis of the resulting silyl enol ether to give a 3:1 mixture of diastereomers **47** and **48** in 52% yield favoring the desired stereoisomer **47**. The *tert*-butyldiphenylsilyl protecting group was then removed using tetrabutylammonium fluoride to give the primary alcohol **49** in 59% yield. The formal syntheses were completed by the reprotection of the hydroxy moiety as the benzyl ether. Thus, treatment of keto alcohol **49** with sodium hydride and benzyl bromide furnished the key intermediate **50** in 73% yield after 3 days. Bicyclic ketone **50** was previously used successfully in the total synthesis of the two *cis*-clerodane natural products **51** and **52** mentioned above[9,10].

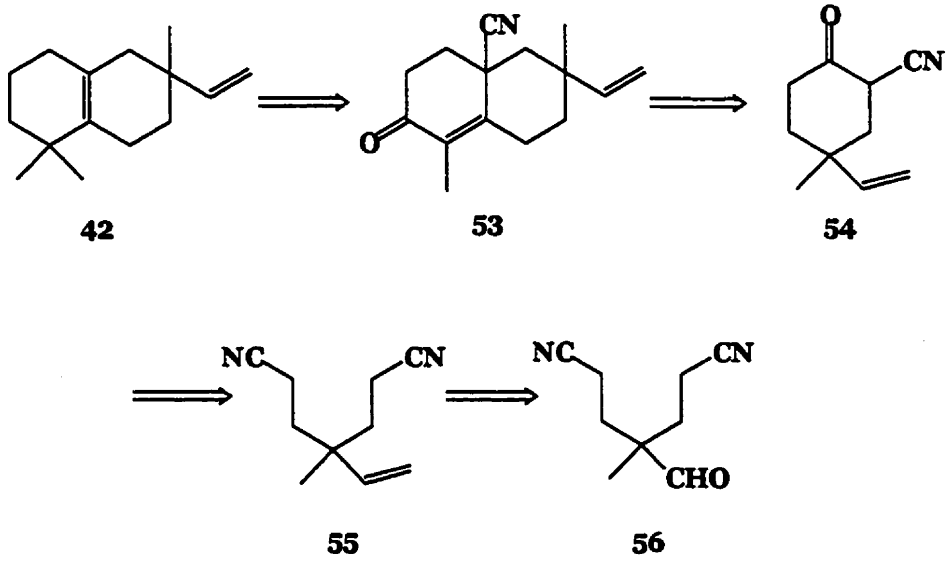
Further development of the aforementioned reductive alkylation methodology led to the discovery that bicyclic systems containing a γ-cyano-α,β-unsaturated ketone moiety can also be reductively alkylated to give α-substituted β,γ-unsaturated ketones (Scheme 7, Eq. 3). Since the viability and scope of this reductive alkylation methodology had been extensively investigated[7], it was our aim to demonstrate its utility in organic synthesis. We chose nanaimoal as the target natural product and as an immediate target, we chose Engler's bicyclic dienyl intermediate (Scheme 6, compound **42**). Our retrosynthetic analysis is depicted in Scheme 9. The immediate precursor to bicyclic diene **42** is envisioned to be cyano ketone **53** which is envisioned to be easily constructed *via* the Robinson annulation[11] of 2-cyano-4-methyl-4-vinylcyclohexanone (**54**)



Scheme 8

Conditions: i. $ZnCl_2$, *trans*-piperylene, 90%; ii. Lithium naphthalenide, then CH_3I, 86%; iii. $(CH_3)_2CuLi$, TMSBr, then aq. NH_4Cl/NH_4OH (pH=9), 52%; iv. TBAF, 59%; v. NaH, BnBr, 73%.

with ethyl vinyl ketone. Cyano ketone **54** is proposed to be synthesized from dicyano alkene **55** by a Thorpe-Ziegler reaction[12] and acid hydrolysis of the cyano enamine thus formed. Dicyano alkene **55** should be readily synthesized from the known aldehyde **56** *via* a Wittig olefination reaction[13]. The next section describes our work towards this end in detail.



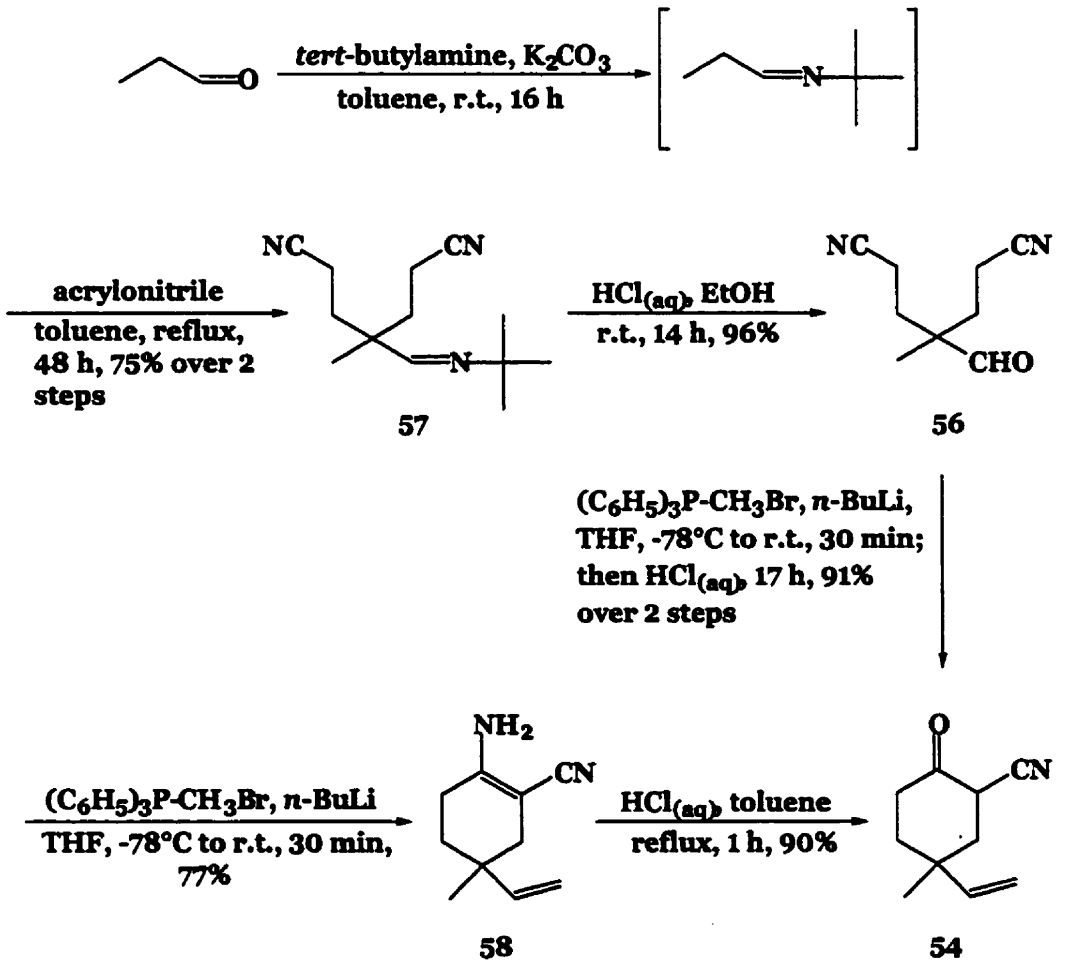
42 **53** **54**

55 **56**

Scheme 9

Results and Discussion

As indicated in scheme 9, our synthetic endeavor towards nanaimoal (**1**) required the efficient and rapid synthesis of bis-cyano aldehyde **56** in order to synthesize α-cyano ketone **54**. Our synthetic sequence is depicted in Scheme 10. A perusal



scheme 10

of the literature led us to two papers[14,15] published in the early 70's in which the authors described a synthesis of the desired aldehyde **56** in two steps *via* it's isopropylimino derivative. Further reading indicated that the synthesis of the

tert-butylimino derivative was the most efficient and operationally simple of the myriad of alkyl imines described. Therefore, we proceeded to synthesize *tert*-butylimino derivative **57** with some modification to the published procedure. Thus, treating a toluene solution of propionaldehyde with *tert*-butylamine in the presence of potassium carbonate gave, presumably, the *N*-propylidene-*tert*-butylamine which was not isolated. To this was then added acrylonitrile and the mixture heated at reflux for two days. Distillation of the crude product then gave the desired bis-cyano imine **57** in 75% yield over two steps. The IR spectrum of compound **57** showed a cyano absorption at 2246 cm^{-1} as well as an imine absorption at 1666 cm^{-1}. Due to the symmetrical nature of the molecule, the proton NMR was quite straight forward. The proton attached to the sp^2 carbon was assigned the singlet at δ 7.30 and the four protons adjacent to the cyano moieties were observed to resonate at δ 2.13 as a multiplet. Since the methylenes beta to the cyano functionality are adjacent to a quaternary center which is stereogenic, it was expected that the four protons be facially differentiated and thus resonate at different chemical shifts. Indeed this was the case. The multiplet observed at δ 1.84-2.03 was attributed to two protons on one face while the signal at δ 1.77 (ddd, J = 16, 10, 10 Hz) was attributed to the remaining two protons. The *tert*-butyl protons appeared at δ 1.15 as a sharp singlet and the remaining methyl group was found to resonate at δ 1.06 also as a sharp singlet. The carbon NMR displayed 8 lines with 5 in-phase and 3 anti-phase signals which corresponds with the structure of imine **57**.

The next transformation involves the acid hydrolysis of imine **57** to give aldehyde **56**. As such, treatment of an ethanolic solution of imine **57** with hydrochloric acid gave, after distillation, the desired aldehyde **56** in 96% yield. The aldehyde functionalities were ascertained by the presence of the weak "w"

shaped absorption in the IR spectrum (2850 and 2750 cm^{-1}) along with the carbonyl stretch found at 1727 cm^{-1}. This was confirmed by the observance of a triplet at δ 9.43 (J = 1 Hz) in the proton NMR spectrum and an anti-phase signal at δ 202.5 in the carbon APT spectrum. The retention of the cyano functionality was indicated by the presence of a sharp absorption in the IR spectrum (2248 cm^{-1}) and confirmed by the in-phase signal at δ 118.8 in the carbon spectrum. High resolution mass spectroscopy yielded a peak at 165.1021 corresponding to the [M+1] ion peak.

With aldehyde **56** in hand, we proceeded with the Wittig olefination reaction[13] in advance of the proposed Thorpe-Ziegler condensation[12]. Surprisingly, it was found that, under the Wittig olefination reaction conditions, the Thorpe-Ziegler condensation also occurred to give cyano enamine **58** in one step. Thus, addition of a tetrahydrofuran solution of aldehyde **56** to a solution of the ylide prepared *in situ* from methyltriphenylphosphonium bromide and *n*-butyllithium in tetrahydrofuran at -78°C gave, after workup and purification, the cyclic enamine **58** in 77% yield. The "primary" enamine functionality was ascertained by the presence of two distinct N-H stretches in the IR spectrum (2444 and 2254 cm^{-1}). It was also confirmed by the broad singlet present in the proton NMR spectrum at δ 4.18. A sharp absorption signal at 2179 cm^{-1} in the IR spectrum indicated the presence of the cyano group which was corroborated by an in-phase resonance in the carbon APT spectrum at δ 120.7. The terminal olefin was shown to be present by the resonances in the proton NMR spectrum characteristic of terminal olefins. As such, the doublet of doublets resonating at δ 5.74 (J = 18, 11 Hz) was attributed to the methine proton whereas the overlapping doublets of doublets centered at δ 5.01 (J = 18, 1 Hz and J = 11, 1 Hz) were attributed to the methylene protons of the olefin. The presence of an anti-phase signal at δ 145.0 along with

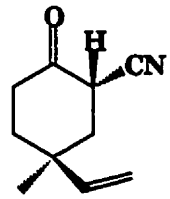
an in-phase signal at δ 111.9 provided collaborative evidence for a terminal olefin. The high resolution mass spectrum indicated the presence of an ion peak at 162.1154 corresponding to a molecular formula of $C_{10}H_{14}N_2$. This was also evidenced for by elemental analysis.

The hydrolysis of cyano enamine **58** was achieved by heating a toluene solution of **58** in the presence of aqueous hydrochloric acid. Thus, after refluxing for 1 hour, the desired α-cyano ketone **54** was isolated, after flash chromatographic purification, in 90% yield. The rapidity of the reaction indicated that the hydrolysis of the enamine may not require such harsh conditions and so it was decided that, given the opportunity, the hydrolysis would be attempted at room temperature. Indeed, it was discovered that the hydrolysis does proceed at ambient temperature albeit requiring a reasonably longer period of time. The hydrolysis reaction was deemed successful by the observance of the absence of the primary amine N-H stretch mentioned above and the presence of a ketone carbonyl stretch at 1728 cm^{-1} in the IR spectrum. Also present in the IR spectrum was a broad OH stretch centered around 3361 cm^{-1} which suggests the presence of an enol tautomer. It was evident from the proton NMR spectrum that apart from the enol tautomer, the keto tautomer actually exists as a mixture of diastereomers. As such, two sets of characteristic terminal olefinic signals were observed along with two sets of signals attributed to the methine proton adjacent to the cyano group. The carbon APT spectrum served to confirm the presence of the two keto diastereomers plus the enol tautomer. Three in-phase resonances were found at δ 200.4, 200.3, and 166.1 which were attributed, respectively, to the carbonyl carbons of the two keto diastereomers and the sp^2 hybridized carbon adjacent to the hydroxy functionality in the enol tautomer. The high resolution

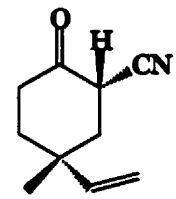
mass spectrum showed an ion peak at 163.0996 which corresponds to a molecular formula of $C_{10}H_{13}NO$.

Detailed analysis of the proton NMR spectrum for cyano ketone **54** resulted in the delineation of the keto:enol ratio being 9:1 and the ratio of the diastereomeric keto isomers to be 7:2. The proton NMR spectrum also lends some clues as to the stereochemistry about the two stereogenic centers present in the keto form of the molecule. A collection of selected proton NMR resonances and their assignments are presented in Table 1.

Table 1. Selected Proton NMR Resonances and Assignments for Compound 54.



54A



54B

Assignment	Major Isomer (δ)	Minor Isomer (δ)
$-CH_3$	1.12	1.30
CN-CH	3.63 (dd, J = 14, 6 Hz)	3.69 (dd, J = 14, 6 Hz)

From the coupling constants of the α-methine proton signal, it can be deduced that the proton is oriented in the axial position for both diastereomers. The difference in chemical shift for the methyl signal suggests that the major isomer has an axial methyl whereas the minor isomer has the methyl oriented in the equatorial position. This conclusion was based on the abundant precedence of

equatorial protons in a rigid cyclohexane ring being deshielded compared to axially oriented protons[16]. From this analysis, we were able to delineate a conformational picture for the major and minor isomers of cyano ketone **54** as depicted in Figure 1.

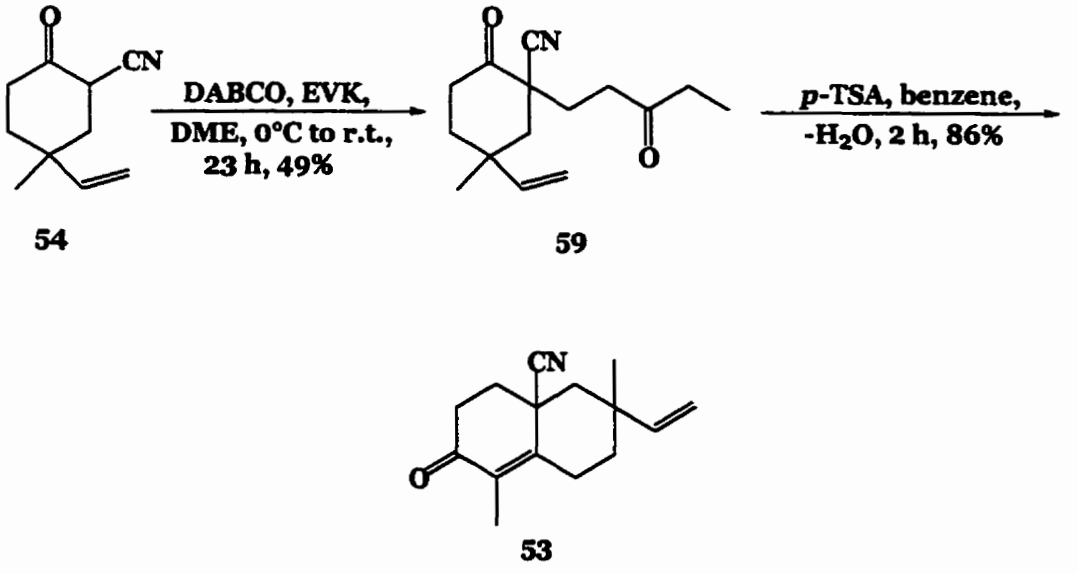
Major isomer 54A **Minor isomer 54B**

Figure 1. Dominating Conformations of Isomers of 54

It was fortuitously discovered during the optimization stage of our project that cyano ketone **54** may be synthesized from aldehyde **56** directly in a one-pot procedure in which enamine **58** was not isolated. With the isolation of the enamine intermediate, the overall yield of cyano ketone **54** over two steps was around 70%. However, when enamine **58** was not isolated but directly hydrolysed during the workup of the Wittig/Thorpe-Ziegler reaction, the yield of cyano ketone **54** increased dramatically to 90% over two steps. This was a significant contribution towards our synthetic scheme in general.

With cyano ketone **54** in hand, the next stage in our synthetic scheme was to complete the bicyclic core of nanaimoal (**1**) and set the stage for the crucial reductive alkylation step. The synthetic sequence leading to bicyclic enone **53** from cyano ketone **54** is outlined in Scheme 11. Thus, treatment of a solution of cyano ketone **54** in 1,2-dimethoxyethane with 1,4-diazabicyclo[2.2.2]octane (DABCO) followed by ethyl vinyl ketone gave, after acidic workup and

purification, the Michael adduct **59** as an inseparable mixture of diastereomers in 49% yield. The IR spectrum of the product showed the absence of the broad



Scheme 11

hydroxy stretch observed in the spectrum of cyano ketone **54** which suggests the absence of the methine proton adjacent to the carbonyl. This was verified by the absence of a methine proton signal centered around δ 3.65 in the proton NMR of the product. Two apparent triplets, one at δ 1.07 (J = 7 Hz) and the other at δ 1.05 (J = 7 Hz), further indicated that the Michael reaction was a success. The high resolution mass spectrum showed an ion peak at 247.1562 which corresponds to a molecular formula of $C_{15}H_{21}NO_2$. This was verified by the combustion analysis. Unfortunately, subsequent attempts at improving the yield of the addition reaction were fruitless.

Although attempts at separating the diastereomeric mixture was unsuccessful, the ratio of the diastereomers was determined by the integration of the olefinic

signals in the proton NMR and corroborated by the integration of the methyl signals. From this simple analysis, the ratio of the diastereomeric mixture was determined to be 7:3. Again, the chemical shifts of the individual methyl groups gave us an indication as to the structure of the major diastereomer. The two possible diastereomers are depicted in Figure 2. Since the methyl singlet of the major diastereomer resonates at δ 1.08 compared to δ 1.36 for the minor diastereomer, we propose that the major diastereomer has an axial methyl group (i.e. **59B**) and the minor diastereomer has an equatorial methyl group (i.e. **59A**).

Minor isomer 59A **Major isomer 59B**

(R = -$CH_2CH_2C(O)CH_2CH_3$)

Figure 2. Dominating Conformations of the Isomeric Diketone 59

The cyano functionality was assumed to be axially oriented due to the fact that the cyano group is known to have a smaller A-value compared to alkyl groups such as methyl and ethyl groups[17].

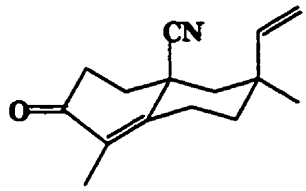
The aldol condensation of diketone **59** was effected under standard conditions. As such, after pre-drying a solution of *para*-toluenesulfonic acid hydrate in benzene by removal of the water-benzene azeotrope, a solution of diketone **59** in benzene was introduced. After refluxing for 2 hours, during which the resulting water-benzene azeotropic distillate was drained, the reaction was worked up under slightly basic conditions. Purification then gave the desired bicyclic enone

53 in 86% yield as a mixture of diastereomers in a 1:1 ratio as determined by proton NMR. Gratifyingly, the individual diastereomers were separable by flash chromatography which eased the characterization dramatically.

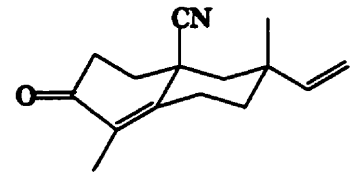
The IR spectrum of cyano enone **53** showed the retention of the cyano functional group (2228 cm^{-1}) and the enone carbonyl was found to stretch at 1676 cm^{-1}. This was confirmed in the carbon APT spectrum with the observance of an in-phase resonance at δ 121.8 for the less polar diastereomer and δ 120.9 for the more polar diastereomer corresponding to the cyano carbon in both cases. The carbonyl carbon was found to resonate at δ 196.4 for both diastereomers. The enone system was also indirectly ascertained by the presence of a singlet at δ 1.84 for the less polar diastereomer and δ 1.83 for the more polar diastereomer in the proton NMR spectrum. These signals were attributed to the vinylic methyl group present in the molecule. The carbon APT spectrum for both diastereomers showed fifteen resonances with 12 in-phase and 3 anti-phase signals. This is in agreement with the structure of cyano enone **53**.

From the chemical shift attributed to the methyl group adjacent to the quaternary center, it was hypothesized that the less polar diastereomer (δ 1.45) has the stereochemistry as depicted for structure **53A** and the more polar diastereomer (δ 1.04) has the stereochemistry as depicted for structure **53B** (Figure 3). The cyano group was assumed to be in the axial position due to consideration of the A-value difference as mentioned before[17]. However, an attempt to determine this experimentally by a heteronuclear nOe experiment failed.

It is well established that Robinson annulation reactions may be achieved without



53A

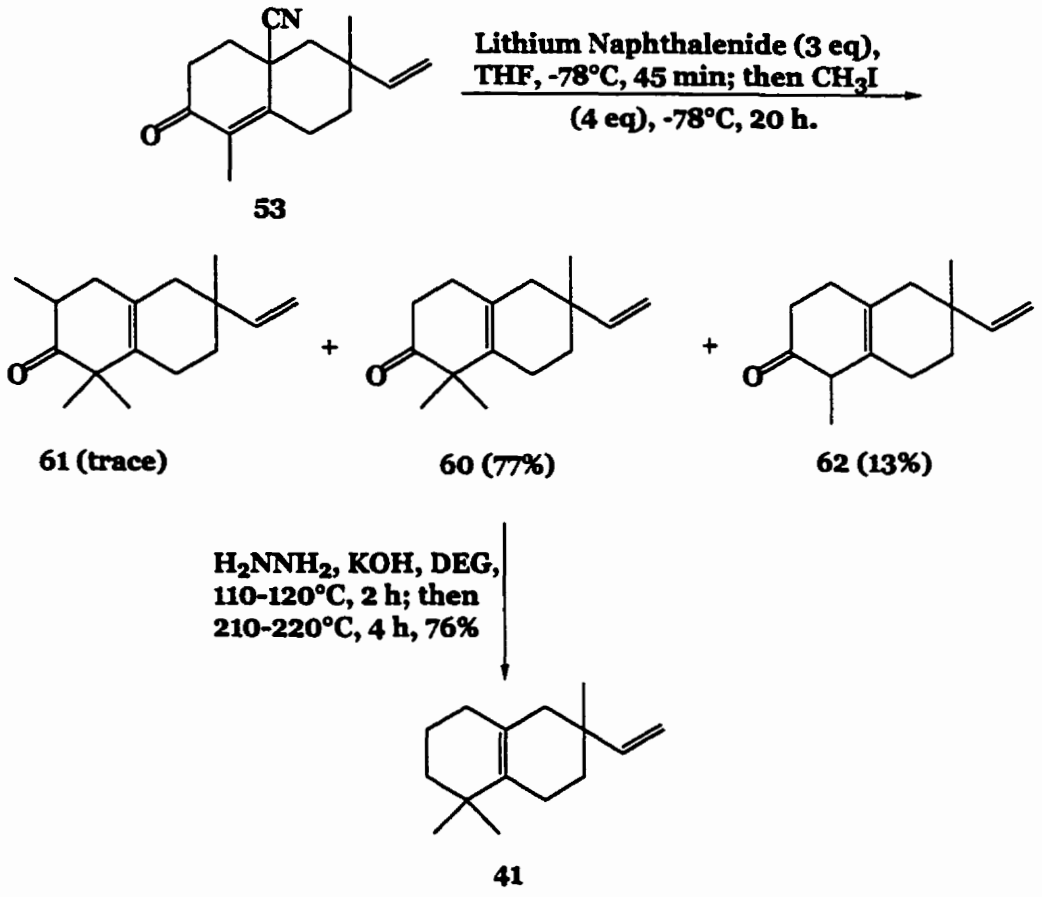


53B

Figure 3. Conformational Structures for 53

prior purification of the Michael adduct[18]. Our synthesis of bicyclic ketone **53** as described above was achieved in an overall yield of 42% over two steps with the purification of Michael adduct **59**. It was reasoned that if bicyclic ketone **53** can be synthesized without the need to purify cyano diketone **59**, the overall yield of **53** may improve. Thus, after the prescribed workup, crude cyano diketone **59** was used as-is in the subsequent aldol condensation reaction. Unfortunately, the yield of bicyclic ketone **53** under this modified procedure did not increase as hoped for; in fact, it decreased slightly to 40%. Nevertheless, this modification does simplify the overall annulation process while not being detrimental to the yield of bicyclic ketone **53**.

With the synthetic route to bicyclic ketone **53** established, our attention turned to the key step in our project. The synthetic route developed for the next phase of our synthetic scheme is portrayed in Scheme 12. Bicyclic ketone **53** was treated with 3 equivalents of lithium naphthalenide reagent at -78°C and 4 equivalents of methyl iodide was then added after the reductive decyanation was deemed complete by TLC analysis. The alkylation reaction was maintained at -78°C and worked up after 20 hours. After flash chromatographic purfication, three



Scheme 12

compounds were isolated from the crude mixture sequentially: the α,α'-dialkylated compound **61** in trace amounts, the desired α-alkylated compound **60** in 77% yield, and the reductive elimination product **62** in 13% yield. The proton NMR spectrum of bicyclic ketone **60** showed three singlets at δ 1.17, 1.14, and 0.98 which confirms that the alkylation occurred on the desired carbon. The retention of the ketone carbonyl was indicated by the observance of a carbonyl stretch in the IR spectrum at 1716 cm^{-1}. This was confirmed by the carbon APT spectrum with an in-phase resonance at δ 215.8. The absence of any absorptions in the IR spectrum attributable to a cyano stretch indicated that the decyanation

occurred and this was confirmed by the lack of an in-phase resonance in the carbon APT spectrum that can be assigned to a cyano carbon. The carbon APT spectrum contained fifteen resonances of which eleven were in-phase and four were anti-phase. This correlated well with the structure assigned to bicyclic ketone **60**. The high resolution mass spectrum of the product showed an ion peak at 218.1671 which corresponds to a molecular formula of $C_{15}H_{22}O$. This was confirmed by an elemental analysis of the product.

Bicyclic ketone **61** was isolated as an inseparable mixture of diastereomers in a 3:2 ratio as determined by proton NMR. Apart from singlets representative of the three methyl groups adjacent to quaternary carbons, the proton NMR spectrum also contained a doublet (J = 7 Hz) at δ 1.07. From a 2D ^1H-^1H correlation spectroscopy (2D-COSY) experiment, it was found that this doublet was coupled to the multiplet found at δ 2.86 which was attributed to the methine proton adjacent to the ketone carbonyl. This led us to believe that compound **61** was indeed the α,α'-dialkylated product. The cyano functionality was deemed to be absent by the same token as described for bicyclic ketone **60**. The high resolution mass spectrum contained an ion peak at 232.1818 in agreement with the molecular formula $C_{16}H_{24}O$. This was confirmed by a combustion analysis of the compound.

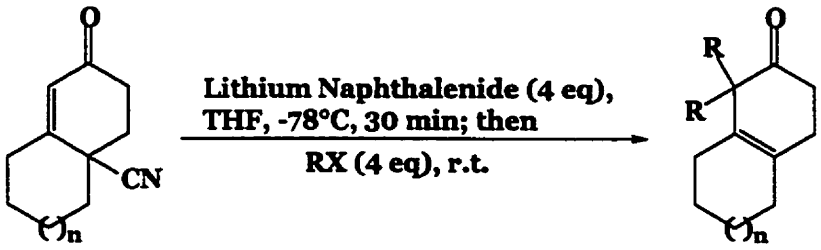
The remaining compound isolated from the crude product mixture was hypothesized to be the reductive elimination product **62** as deemed by TLC. This was rigorously proven by spectroscopic analysis. Again, the absence of the cyano group was suggested by the absence of a cyano stretch in the IR spectrum. The carbon APT spectrum lent credence to this supposition due to the absence of any resonances attributable to a cyano carbon. The proton NMR spectrum displayed

two doublets, one at δ 1.20 and the other at δ 1.16, (J = 7 Hz) and two singlets (δ 1.00 and 0.99) which were assigned to the methyl alpha to the ketone carbonyl and the methyl adjacent to the quaternary carbon respectively. Integration of these resonances resulted in the conclusion that the product contains a mixture of diastereomers in a 1:1 ratio. An absorption at 1714 cm^{-1} in the IR spectrum was characteristic of a ketone carbonyl stretch which was confirmed by an in-phase resonance in the carbon APT spectrum at δ 214.0. The high resolution mass spectrum contained an ion peak at 204.1521 which corresponds to the molecular formula $C_{14}H_{20}O$.

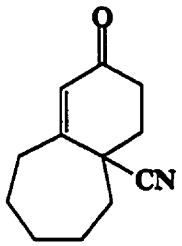
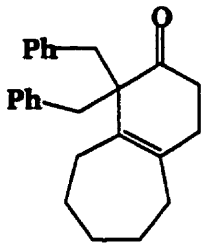
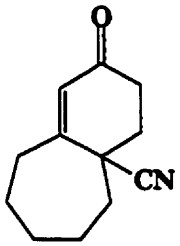
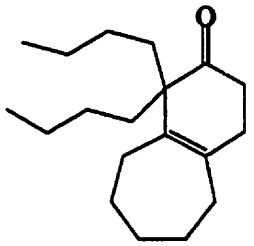
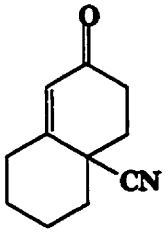
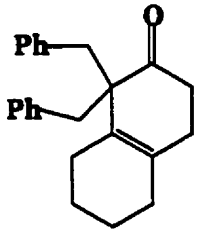
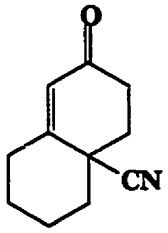
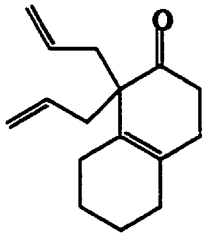
An intriguing alternate route to the desired bicyclic ketone **60** was gleened from the experimental results of a collaborator in our research group in Taiwan[7]. It was observed that γ-cyano α,β-enones with no alkyl groups present in the α carbon may be α,α-dialkylated by treatment with lithium naphthalenide followed by an alkylating agent under modified conditions. A sample of his results are presented in Table 2. The modest modifications necessary to our established reaction conditions are the amount of lithium naphthalenide used (4 equivalents versus 3) and the temperature at which the alkylation part of the reaction is performed. The modification to our synthetic scheme necessary to investigate this possibility is shown in Scheme 13. As can be seen, the only reaction that needs to be modified is the Robinson annulation part; methyl vinyl ketone will replace ethyl vinyl ketone.

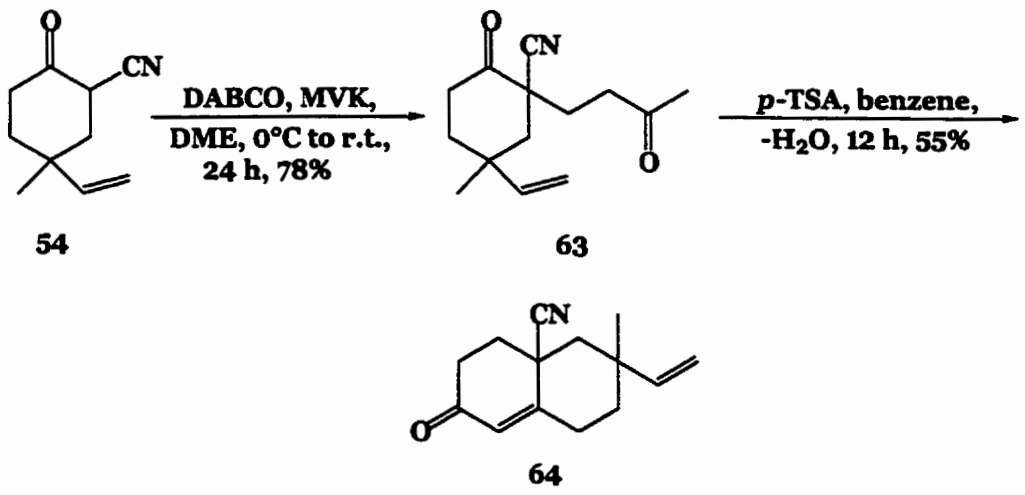
As such, a solution of cyano ketone **54** in 1,2-dimethoxyethane was treated with 1,4-diazabicyclo[2.2.2]octane (DABCO) and then cooled to 0°C. Methyl vinyl ketone was added after 30 minutes and the reaction mixture was stirred at room

Table 2. Selected Data for α,α-Dialkylation of γ-Cyano-α,β-unsaturated Ketones.



n = 1, 2 n = 1, 2

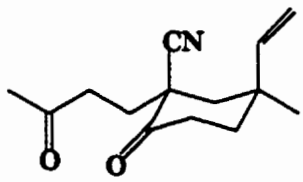
Substrate	Alkylating Agent	Time (h)	Product	Yield (%)
	Benzyl Bromide	20		67
	Butyl iodide	19		63
	Benzyl Bromide	21		81
	Allyl bromide	24		51



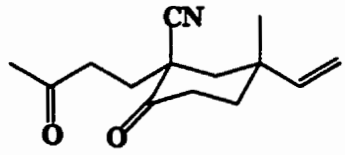
Scheme 13

temperature for 24 hours. After workup and purification, the reaction yielded the expected Michael adduct **63** in 78% yield. Fortuitously, the mixture of diastereomers was separable and so simplified the characterization dramatically. The mixture of diastereomers was deduced to be in a 2:1 ratio as suggested by the proton NMR spectrum. The IR spectrum of the product mixture yielded a cyano stretch at 2232 cm^{-1} and the ketone carbonyls were observed to stretch at 1727 cm^{-1}. The two ketone carbonyl carbons and the cyano carbon of the major isomer were observed to resonate in the carbon APT spectrum at δ 206.6, 203.5, and 119.1 whereas the same carbons in the minor isomer were observed at δ 206.3, 203.5, and 119.7. The carbon APT spectrum for both the major and minor diastereomers contained fourteen resonances, eleven in-phase and three anti-phase, which lent credence to the structure assigned for cyano diketone **63**. The proton NMR also bolstered our confidence in the structural assignments. The methyl adjacent to the carbonyl was found to resonate at δ 2.16 for the minor isomer and δ 2.15 for the major isomer. The singlet for the second methyl group

was observed at δ 1.05 for the major isomer and δ 1.35 for the minor isomer. The chemical shifts of this latter methyl group led us to tentatively assign the stereochemical structure of the major and minor diastereomer as shown in Figure 4. Again, the axial orientation of the cyano group is speculative based on A-values reported[17]. The high resolution mass spectrum displayed an ion peak at 233.1408 corresponding to a molecular formula of $C_{14}H_{19}NO_2$. This was confirmed by an elemental analysis of the isomeric mixture.



Minor isomer of 63



Major isomer of 63

Figure 4. Dominating Conformations of Diketone 63

The aldol condensation of cyano diketone **63** proceeded uneventfully to give cyano enone **64**. Thus, treatment of cyano diketone **63** with a pre-dried solution of *para*-toluenesulfonic acid in benzene gave, after workup and purification, cyano enone **64** as a light yellow solid in 55% yield. The product was found to contain a mixture of diastereomers in a 2:1 ratio as determined by proton NMR. The cyano functionality was found to stretch at 2228 cm^{-1} and the enone carbonyl stretched at 1684 cm^{-1}. Gratifyingly, the two diastereomers were found to be separable by careful flash chromatography. The proton NMR spectrum of the less polar minor diastereomer contained the characteristic resonances for a terminal olefin (δ 5.74, dd, J = 18, 11 Hz, 1 H; δ 5.01, dd, J = 18, 1 Hz, 1 H; and δ 4.98, dd, J = 11, 1 Hz, 1 H) in addition to the olefinic proton adjacent to the ketone carbonyl (δ 5.98, d, J = 2 Hz, 1 H). The quaternary methyl group was

found to resonate at δ 1.46 as a singlet. The carbon APT spectrum confirmed the presence of the cyano group (δ 120.9, in-phase) and the enone carbonyl (196.6, in-phase). In total, the carbon APT spectrum of the minor diastereomer contained fourteen resonances, eleven in-phase and three anti-phase, which supported the structure anticipated for cyano enone **64**.

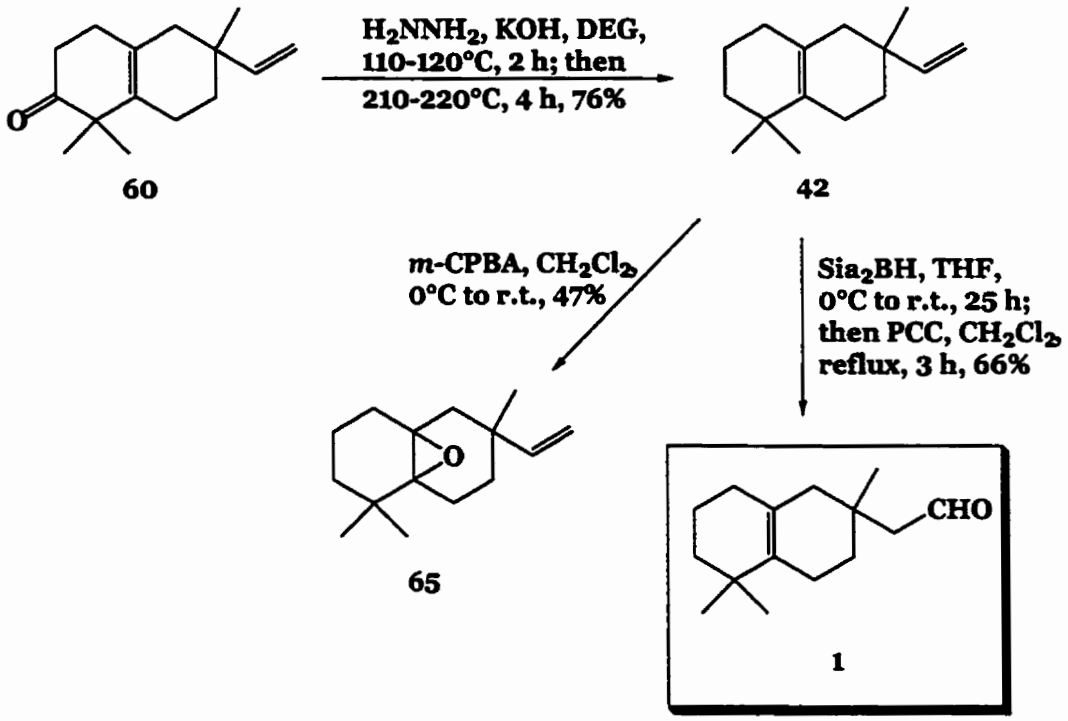
The proton NMR spectrum of the more polar major diastereomer also contained the characteristic terminal olefinic resonances (δ 6.14, ddd, J = 18, 11, 1 Hz, 1 H; δ5.28, d, J = 11 Hz, 1 H; and δ 5.21, d, J = 18 Hz, 1 H) and the enone methine proton (δ 5.95, d, J = 2 Hz, 1 H). The methyl group adjacent to the quaternary carbon was observed as a singlet at δ 1.05. The carbon APT spectrum displayed the enone carbonyl carbon as an in-phase resonance at δ 195.8 and the cyano carbon as an in-phase resonance at δ 119.1. Apart from the two resonances mention, the carbon APT spectrum contained 12 other resonances, nine in-phase and three anti-phase. The high resolution mass spectrum of the product mixture yielded an ion peak at 215.1312 which supports the molecular formula $C_{14}H_{17}NO$. This was further supported by the elemental analysis results.

With the synthesis of cyano enone **64** complete, we began to investigate the reductive dialkylation potential of the compound. A solution of cyano enone **64** in tetrahydrofuran was cooled to -78°C and 4 equivalents of a pre-formed solution of lithium naphthalenide was introduced. After stirring for 30 minutes, the reductive decyanation was confirmed to be complete by TLC and then 4 equivalents of methyl iodide was added. The reaction mixture was allowed to warm to room temperature and worked up after 4 hours when TLC analysis indicated the complete disappearance of the reductive decyanation product. After purification by flash chromatography, the desired bicyclic ketone **60** was

isolated in 41% yield. Various attempts at modifying the reaction conditions and reagent amounts to increase the yield of the reaction met with no success. The bicyclic ketone obtained from this reaction was spectroscopically identical in every respect with that obtained previously from cyano enone **53**.

With the synthetic route to bicyclic ketone **60** established, the successful completion of the project is at hand. All that needs to be accomplished is the deoxygenation of the ketone oxygen in bicyclic ketone **60** to give Engler's intermediate **42**. This would constitute a formal synthesis of nanaimoal (**1**). However, since nanaimoal was only separated from Engler's intermediate **42** by one oxidation level, we also attempted to reach nanaimoal from bicyclic diene **42** *via* an improved route than that taken by Engler and co-workers. Our synthetic scheme for this final stage of the project is depicted in Scheme 14.

The first transformation, the deoxygenation of the ketone oxygen in bicyclic ketone **60** was achieved under standard Huang-Minglon modification[19] of the Wolff-Kishner reaction conditions. Thus, treatment of a solution of bicyclic ketone **60** in diethylene glycol with potassium hydroxide and anhydrous hydrazine and heating at 110-120°C for 2 hours followed by heating at 210-220°C for an additional 4 hours gave the reduced product **42** in 76% yield after purification. The reduction product was found to be quite volatile; the first couple of attempts at the reaction gave disappointingly low yields due to loss of product upon evaporation of solvent *in vacuo*. The proton NMR of the reaction product indicated that the terminal olefin survived the harsh conditions of the reaction; the characteristic resonances for the terminal olefin were observed at δ 5.80 (dd, J = 18, 11 Hz, 1 H) and δ 4.86-4.94 (m, 2 H). The deoxygenation was



Scheme 14

confirmed to have occurred by the absence of any absorption attributable to a ketone carbonyl in the IR spectrum. The absence of a downfield resonance corresponding to carbonyl carbons in the carbon APT spectrum also lends support to the success of the reaction. The high resolution mass spectrum of the product displayed an ion peak at 204.1872 corresponding to a molecular formula of $C_{15}H_{24}$.

Experimental and Engler's reported proton and carbon NMR resonances are tabulated in Table 3 and Table 4 respectively. At first glance, the carbon NMR spectrum appears to match perfectly but the proton NMR spectrum seems to have significant discrepancies between them. The problem was in the assignment of the terminal olefin resonances. Engler and co-worker described, in their

Table 3. Proton NMR Spectral Data for Bicyclic Diene 42.

Proton NMR (ppm)	
Engler (500 MHz)	**Exp'tal (400 MHz)**
0.96, s, 3 H	0.96, s, 3 H
0.97, s, 3 H	0.97, s, 3 H
0.99 s, 3 H	0.99 s, 3 H
	1.44, m, 4 H
1.36-1.71, m, 7 H	1.62, m, 2H
	1.69, bd, 1 H
	1.88, bd, 1 H
1.80-2.00, m, 5 H	1.84, m, 2 H
	1.97, m, 2 H
4.85-4.86. dd, J = 10.5, 1.5, 1 H	
	4.86-4.94 (m, 2 H)
4.90-4.93, dd, J = 18, 1.5, 1 H	
5.74-5.85, dd, J = 18, 10.5, 1 H	5.80, dd, J = 18, 11, 1 H

experimental section, two doublets of doublets, one centered at δ 4.92 with coupling constants of 18 and 1.5 Hz and the other one centered at δ 4.85 with coupling constants of 10.5 and 1.5 Hz. In our spectrum, the only resonances observed at the described chemical shifts were two apparent quartets, one centered at 4.92 and the other one centered at 4.88. What the quartets really represent is the AB part of an ABX spin system. In other words, the two apparent quartets actually is better described as a second order multiplet. Closer analysis

Table 4. Carbon-13 NMR Spectral Data for Bicyclic Diene 42.

Carbon NMR (ppm)	
Engler (75 MHz)	Exp'tal (50 MHz)
19.45	19.4
21.71	21.7
25.67	25.6
27.89	27.9
31.61	31.6
33.52	33.5
34.48	34.5
35.09	35.0
39.83	39.8
42.34	42.3
110.04	110.0
125.42	125.4
133.58	133.6
147.79	147.9

of the doublet of doublets at δ 5.80 reveals the presence of a small peak in between the flanking doublets. This, combined with the two apparent quartets, is an example of a classic ABX spin system[20]. Due to the inconsistency between our spectrum and that described by Engler and co-workers, an attempt was made to obtain their spectrum from microfiche. Our experimental proton NMR spectrum and Engler's are presented in Figure 5 (experimental spectrum) and Figure 6 (Engler's spectrum). A comparison of their spectrum and ours then confirmed

that we have indeed synthesized Engler's bicyclic diene intermediate **42** and that their assignments were in error.

With the synthesis of bicyclic diene **42** confirmed, we turned our attention to improve the transformation of **42** to nanaimoal. As described in Scheme 6, Engler chose to hydroborate the terminal olefin followed by oxidation to the primary alcohol. He then oxidized the primary alcohol using Swern oxidation[21] to give the target compound nanaimoal. We wanted to see whether epoxidation followed by epoxy-ketone rearrangement[22] would also perform the required transformation. Even though peroxy acid epoxidation of olefins epoxidize electron rich olefins much more readily[23], we reasoned that the internal olefin in bicyclic diene **42** may be sterically hindered enough to bias the epoxidation towards the less reactive terminal olefin. Thus, to a solution of bicyclic diene **42** in dichloromethane cooled to 0°C was added *meta*-chloroperoxybenzoic acid and the resulting clear solution was allowed to stir at room temperature for 5 hours. After workup and purification, epoxide **65** was isolated in 47% yield as a 3.5:1 mixture of diastereomers as determined by proton NMR. To our dismay, the reaction produced the undesired epoxide. The first sign of disappointment was evident in the proton NMR. The terminal olefin was shown to have survived the reaction as deemed by the presence of two sets of three doublets of doublets (minor and major isomer) in the proton NMR spectrum; minor diastereomer: δ 5.75 (dd, J = 18, 11 Hz), 4.89 (dd, J = 18, 2 Hz), and 4.86 (dd, J = 11, 2 Hz); major diastereomer: δ 5.65 (ddd, J = 18, 11, 1 Hz), 5.01 (dd, J = 11, 2 Hz), and 4.91 (dd, J = 18, 2 Hz). The three methyl groups were observed at δ 0.97 (6 H) and 0.91 (3 H). The epoxidation was confirmed to have occurred due to the disappearance of the two downfield in-phase resonances in the carbon APT spectrum attributed to

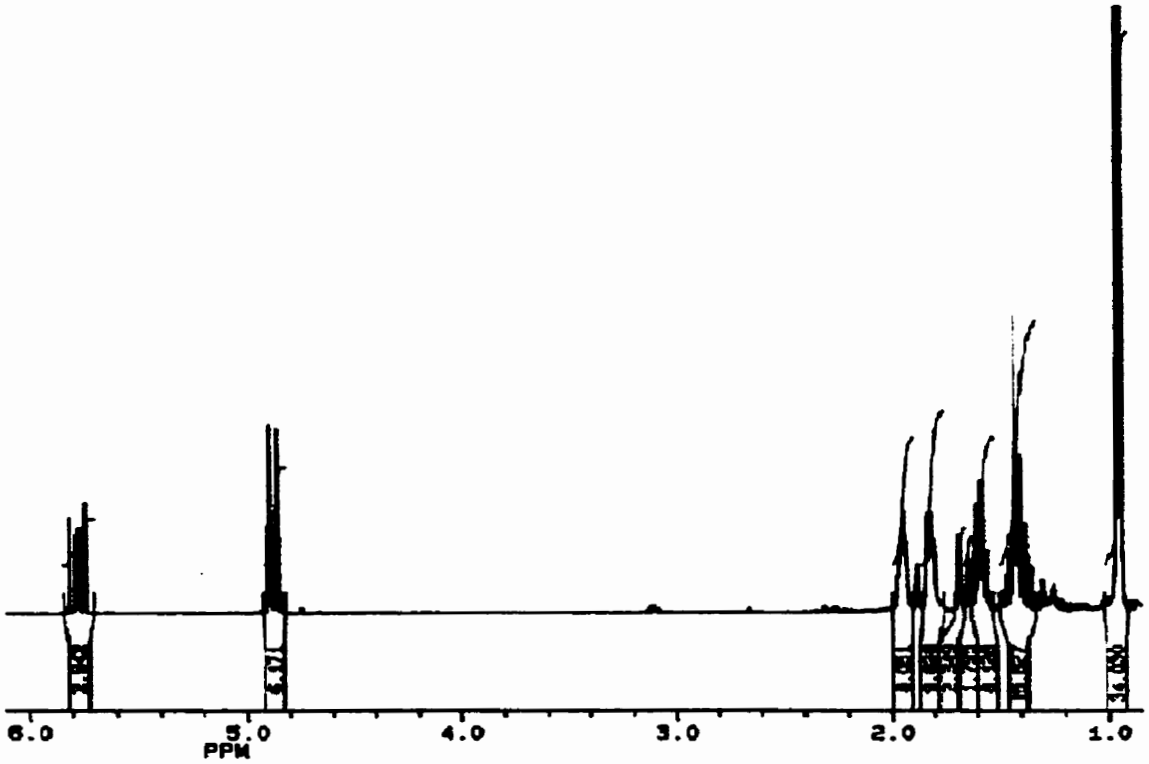


Figure 5. Proton NMR Spectrum of Synthetic 42

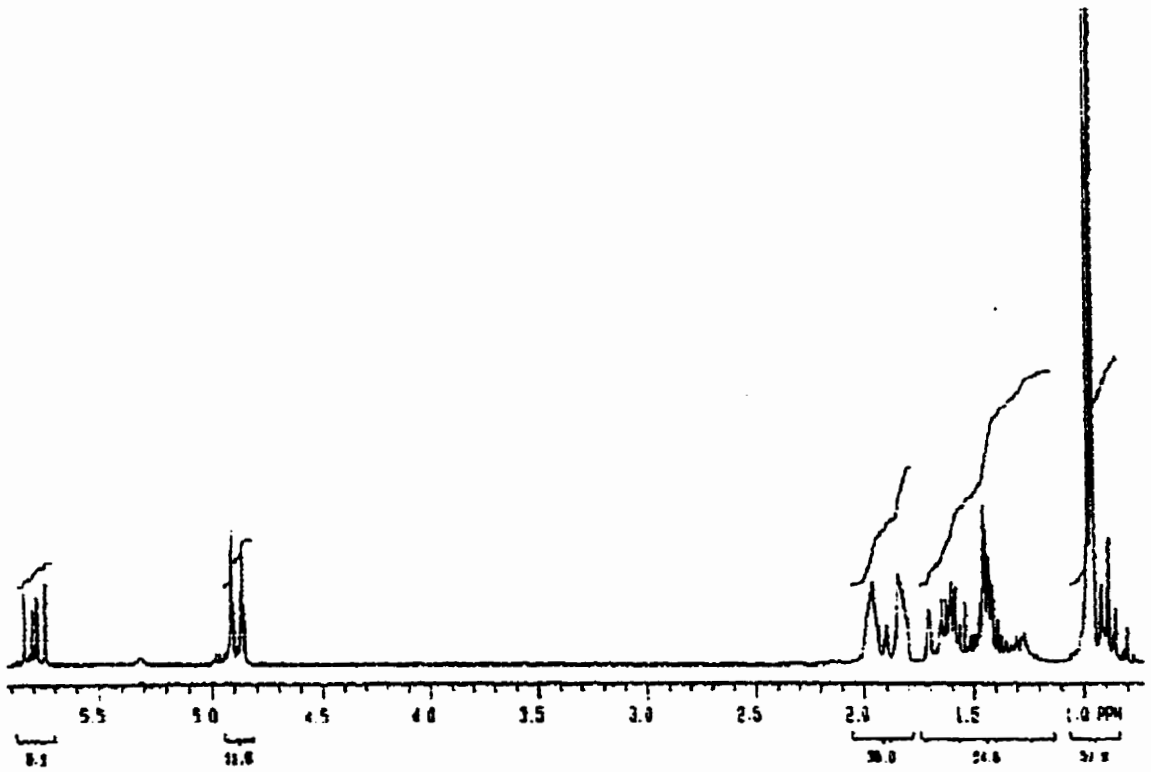


Figure 6. Reported Proton NMR Spectrum of 42

the internal olefin in the starting bicyclic diene **42** (δ 133.6 and 125.4) and the observance of two in-phase resonances in the spectrum of epoxide **65** at δ 62.7 and 43.4. These were attributed to the two epoxide carbons. The high resolution mass spectrum contained an ion peak at 220.1818 corresponding to the molecular formula $C_{15}H_{24}O$, thus further bolstering our confidence that the epoxidation indeed occurred at the internal olefin. Apparently, the steric hindrance hoped for was not adequate to influence the reaction towards the desired outcome.

Given this setback, we abandoned the epoxidation route and settled for the more classical hydroboration/oxidation method. In Engler's synthesis of nanaimoal, he elected to perform the needed oxidation to the aldehyde in two discreet steps; first isolating the alcohol and then oxidizing it to the aldehyde oxidation level. It was not evident why he chose to go this route as there are literature precendents that the oxidation of terminal olefins to the aldehyde can be effected in a one-pot procedure *via* the organoborane species without isolating the intermediate alcohol[24a]. Therefore, we elected to pursue this avenue to see whether the one-pot procedure may be amenable to our synthesis.

We first attempted the hydroboration using 9-borabicyclo[3.3.1]nonane (9-BBN-H) as per Engler's procedure. Since this was our first attempt at the hydroboration, we needed to proceed with caution and so it was decided to repeat Engler's work by isolating the alcohol. Thus, to a solution of bicyclic diene **42** in tetrahydrofuran was added 9-BBN-H and the resulting clear solution was stirred at room temperature for 6 hours. 3 *M* sodium hydroxide was then added followed by 30% aqueous hydrogen peroxide. After stirring for four hours at

room temperature, saturated sodium bicarbonate was added followed by extraction with diethyl ether. Chromatographic purification of the crude product, disappointingly, yielded an unidentifiable product. It was surmised that the bottle of reagent was at fault.

It is well known that disiamylborane exhibits comparable regioselectivity in the hydroboration of olefins as compared to 9-BBN-H in many cases[24b]. Since we had fresh bottles of the reagents needed to synthesize disiamylborane and Brown and co-workers[24b] had reported on the pyridinium chlorochromate oxidation of organoboranes resulting from disiamylborane and various olefins, we sought to investigate whether bicyclic diene **42** would be amenable to the procedure. Thus, to a solution of bicyclic diene **42** in tetrahydrofuran cooled to 0°C was added freshly prepared disiamylborane. After stirring at room temperature for 25 hours, the solvent was removed *in vacuo* and the residue was redissolved in dichloromethane. This was then added to a solution of pyridinium chlorochromate in dichloromethane and the resulting mixture was heated at reflux for 3 hours. After purification, the target natural product nanaimoal (**1**) was isolated in 66% yield. The IR spectrum of the product showed an intense carbonyl stretch at 1721 cm^{-1} and two weak C-H stretches at 2849 and 2730 cm^{-1}. These absorptions suggest the presence of an aldehyde functionality. Confirmation was provided by the proton NMR (δ 9.86, triplet, J = 3 Hz, 1 H) and the carbon APT spectrum (δ 203.9, anti-phase). The acetaldehydic methylene protons were observed to resonate as a pair of doublet of doublets with one proton at δ 2.29 (J = 14, 3 Hz) and the other at δ 2.22 (J = 14, 3 Hz). The three methyl groups were found to resonate at δ 1.05 (3 H) and 0.98 (6 H). The high resolution mass spectrum of the product showed an ion peak at 220.1823 which corresponds to the molecular weight calculated (220.1827) for $C_{15}H_{24}O$ within

acceptable error. The proton and carbon-13 NMR data are presented in Table 5 and 6, respectively. As can be clearly seen, the experimental values of our synthetic nanaimoal is in good agreement with the published results. This then leads us to conclude that we have indeed successfully synthesized the natural product nanaimoal (**1**).

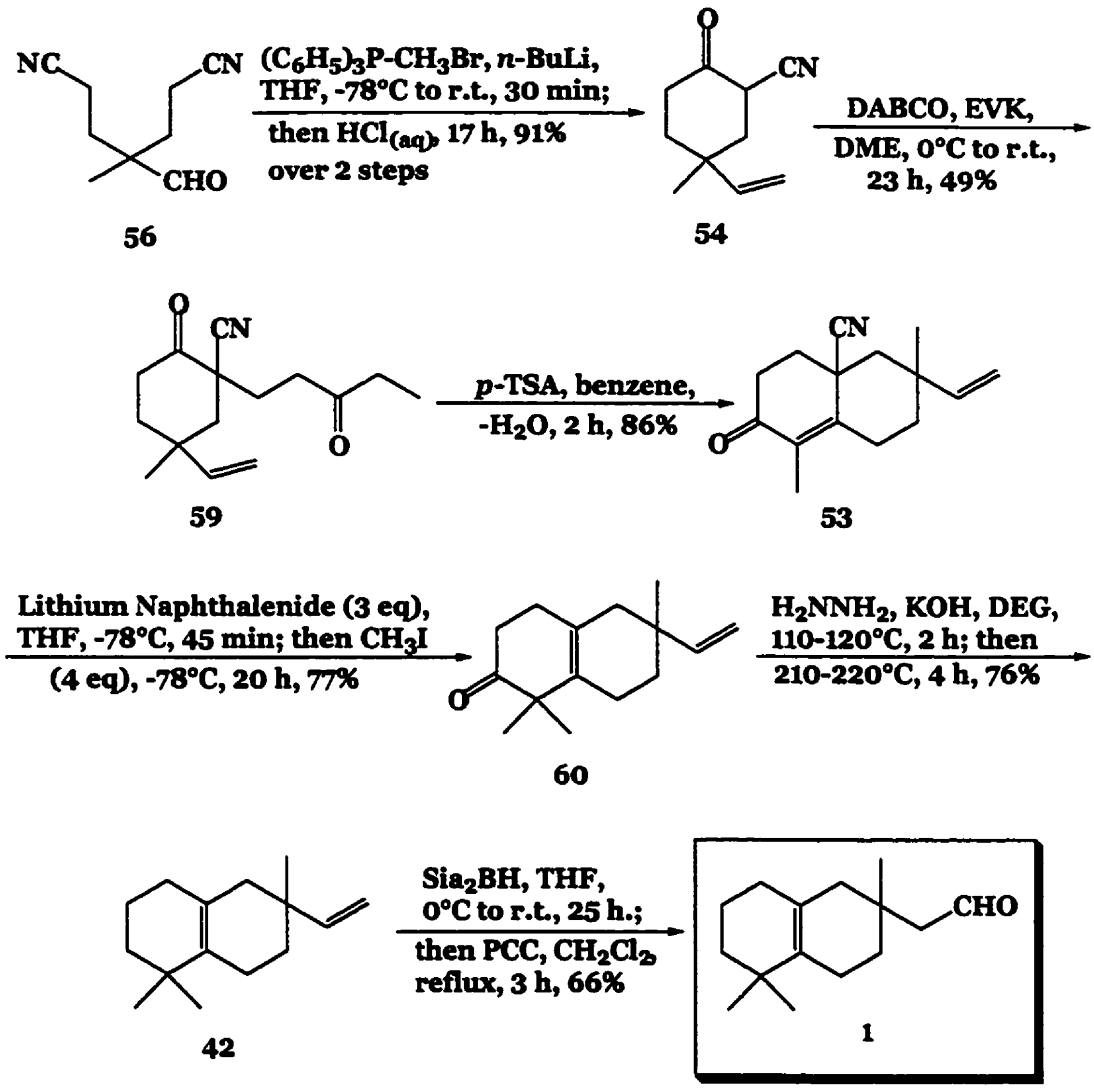
In conclusion, as summarized in Scheme 15, we have achieved the total synthesis of nanaimoal (**1**) starting with the known 3-formyl-3-methyl-1,5-pentanedicarbonitrile (**56**) in a total of eight steps, going through five isolated intermediates, and in an overall yield of 15%. As well, we have, through this synthetic route, demonstrated the utility of the reductive alkylation methodology recently developed in our laboratories.

Table 5. Literature and Corresponding Experimental Proton NMR Data for Nanaimoal (1).

Andersen (400 MHz)	Exp'tal (400 MHz)
0.98, s, 6 H	0.98, s, 6 H
1.05, s, 3 H	1.05, s, 3 H
1.77, d, J = 17.3, 1 H	1.76, d, J = 17, 1 H
1.85, d, J = 17.3, 1 H	1.84, d, J = 17, 1 H
1.81, m, 2 H	1.79, m, 2 H
2.02, m, 2 H	2.01, m, 2 H
2.24, dd, J = 14.5, 3, 1 H	2.22, dd, J = 14, 3, 1 H
2.29, dd, J = 14.5, 3, 1 H	2.29, dd, J = 14, 3, 1 H
9.84, t, J = 3, 1 H	9.86, t, J = 3, 1 H

Table 6. Literature and Corresponding Experimental Carbon-13 NMR Data for Nanaimoal (1).

Andersen (100 MHz)	Exp'tal (100 MHz)
19.4	19.4
21.3	21.3
25.9	26.0
27.9	27.9
31.6	32.2
34.8	34.8
39.8	39.7
43.7	43.7
53.7	53.7
125.3	125.3
133.8	133.8
203.3	203.9


NC
CN
CHO
(C6H5)3P-CH3Br, n-BuLi,
THF, -78°C to r.t., 30 min;
then HCl(aq), 17 h, 91%
over 2 steps
O
CN
DABCO, EVK,
DME, 0°C to r.t.,
23 h, 49%
56
54
O
CN
O
p-TSA, benzene,
-H2O, 2 h, 86%
CN
O
59
53
Lithium Naphthalenide (3 eq),
THF, -78°C, 45 min; then CH3I
(4 eq), -78°C, 20 h, 77%
O
H2NNH2, KOH, DEG,
110-120°C, 2 h; then
210-220°C, 4 h, 76%
60
Sia2BH, THF,
0°C to r.t., 25 h.;
then PCC, CH2Cl2,
reflux, 3 h, 66%
CHO
42
1

Scheme 15

Experimental

General

Melting points were recorded on a Köfler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department using a Carlo Erba EA-1108 Elemental Analyzer. Fourier transform infrared spectra were recorded on a Nicolet Magna 750 instrument. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded using the following spectrometers: Bruker AM-200 (200 MHz), Bruker AM-300 (300 MHz), Varian Inova 300 (300 MHz), Bruker AM-360 (360 MHz), Bruker AM-400 (400 MHz), Varian Unity 500 (500 MHz), and Varian Inova 600 (600 MHz). Coupling constants are reported to within ±0.5 Hertz and 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, and br = broad. Carbon-13 magnetic resonance spectra (^{13}C-NMR) were recorded on the following spectrometers: Bruker AM-200 (50 MHz), Bruker AM-300 (75 MHz), and Bruker AM-400 (100 MHz). Deuteriochloroform or deuteriodichloromethane were used as the solvents for NMR experiments and internal standard. 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 appear as in-phase (p) resonances with respect to the deuterated solvent signal while methyl and methine carbons appear as anti-phase (a) resonances. 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 anti-phase with respect to the irradiated signal. Samples for nOe experiments were deoxygenated with Argon for 10 minutes prior to use. High resolution electron impact mass spectra (HRMS) were recorded using a Kratos MS-50 mass spectrometer. Low resolution chemical ionization mass spectra were run on a Micromass VG7070E with ammonia reagent gas. Electrospray mass spectra (high and low resolution) were run using a Micromass ZABSPEC instrument. Mass spectral data were recorded as m/z values. Bulb-to-bulb distillation were performed using a Kugelrohr distillation apparatus. Eluent systems for flash chromatography are given in volume/volume concentrations.

Materials

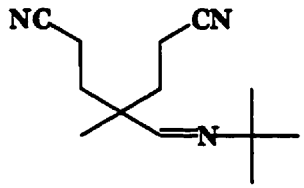
Unless otherwise stated, all materials used were commercially available and used as supplied. All compounds synthesized are racemic. Reactions requiring anhydrous conditions were performed in flame-dried glassware, cooled under an argon atmosphere. Unless otherwise stated, reactions were carried out under argon and monitored by analytical thin-layer chromatography (TLC) performed on aluminum-backed plates precoated with silica gel 60 F_{254} as supplied by Merck. Visualization of the resulting chromatograms were done by looking under an ultraviolet lamp (λ=254 nm) followed by dipping in an ethanol solution of vanillin (5% w/v) containing sulfuric acid 3% v/v) and charring by heat gun.

Solvents for flash chromatography were distilled under normal atmosphere prior to use. Solvent for reactions were dried and distilled under an argon atmosphere prior to use as follows: tetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane from a dark blue solution of sodium benzophenone ketyl; benzene,

dichloromethane, pyridine, diisopropylamine, triethylamine, and carbon tetrachloride from calcium hydride. Purification of reagents, if deemed necessary, was performed using procedures and protocols as described by Perrin, Armarego, and Perrin[25]. Solvents were removed under water aspirator vacuum using a Büchi rotoevaporator. Argon was passed through a column of activated 4Å molecular sieves with self-indicating silica gel (coarse grained) interspersed within.

Flash chromatography developed by Still[26] was used routinely for purification and separation of product mixtures using silica gel of 230-400 mesh size as supplied by Merck.

3-(*tert*-Butyliminomethylidenyl)-3-methyl-1,5-pentanedicarbonitrile (57)

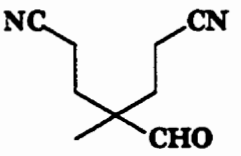


57

To a suspension of *tert*-butylamine (42 mL, 0.420 mol), potassium carbonate (29 g, 0.210 mol) in toluene (40 mL) was added propionaldehyde (15 mL, 0.210 mol). The light yellow suspension was stirred at room temperature for 45 minutes and then filtered. The residue was washed with toluene (3 x 20 mL) and additional potassium carbonate (29 g, 0.210 mol) was added to the combined filtrate. The

resulting light yellow suspension was then stirred at room temperature for 16 hours. The suspension was filtered into a 500 mL round bottom flask and acrylonitrile (70 mL, 1.06 mol) was added to the clear yellow filtrate. The solution was heated to reflux and maintained at refluxing temperature for 48 hours at which time it was cooled to room temperature and filtered over a pad of Celite. The residue was washed with copious amounts of toluene and the solvent was removed *in vacuo* to give a clear light yellow oil which was distilled under reduced presure (178°C/0.5 mm Hg) to give the desired product as a clear light yellow oil (34.508 g, 75%): FTIR (CD_2Cl_2 cast) 2246 (CN) and 1666 cm^{-1} (HC=N); ^{1}H-NMR (CD_2Cl_2, 200 MHz) δ 7.30 (s, 1 H, -CH=N-), 2.13 (m, 4 H, NC-CH_2- x 2), 1.84-2.03 (m, 2 H, NC-CH_2-CHH- x 2), 1.71 (ddd, J = 16, 10, 10 Hz, 2 H, NC-CH_2-CHH- x 2), 1.15 (s, 9 H, -N(CH_3)$_3$), 1.06 (s, 3 H, -CH_3); ^{13}C-NMR (APT, CD_2Cl_2, 50 MHz) δ 159.8 (a), 120.4 (p), 57.5 (p), 41.3 (p), 33.9 (p), 29.5 (a), 21.3 (a), 12.5 (p).

3-Formyl-3-methyl-1,5-pentanedicarbonitrile (56)

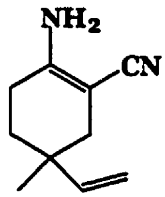


56

To a solution of bis-cyano imine **57** (34.508 g, 0.157 mol) in ethanol (50 mL) was added aqueous hydrochloric acid (2.48 *N*, 50 mL). The resulting homogeneous solution was stirred at room temperature for 14 hours at which time chloroform (100 mL) was added and stirred for an additional 5 minutes at room temperature. The aqueous layer was separated and extracted with chloroform (3 x 100 mL), the combined organic extracts were washed sequentially with water (100 mL),

saturated sodium bicarbonate (100 mL), and brine (100 mL), and then dried over magnesium sulfate. After filtration and evaporation of solvent *in vacuo*, the crude product was isolated as a opaque yellow oil. Vacuum distillation (177°C/0.1 mm Hg) of the crude oil then gave the desired bis-cyano aldehyde **56** as a clear viscous light yellow oil (24.789 g, 96%); FTIR ($CDCl_3$ cast) 2850 and 2750 (OC-H), 2248 (CN), and 1727 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 360 MHz) δ 9.43 (t, J = 1 Hz, 1 H, -CHO), 2.31 (ddd, J = 9, 7, 2 Hz, 4 H, NC-CH_2- x 2), 2.00 (ddd, J = 16, 8, 6 Hz, 2 H, NC-CH_2-CHH- x 2), 1.86 (ddd, J = 16, 8, 6 Hz, 2 H, NC-CH_2-CHH- x 2), 1.16 (s, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 202.5 (a), 118.8 (p), 48.0 (p), 30.1 (p), 17.9 (a), 12.3 (p); HRMS $[M+1]^+$ 165.1021 (calculated for $C_9H_{13}NO_2$: 165.1028).

2-Amino-5-methyl-5-vinyl-1-cyclohexenecarbonitrile (58)

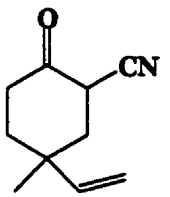


58

To a suspension of methyltriphenylphosphonium bromide (48.069 g, 0.132 mol) in anhydrous tetrahydrofuran (150 mL) cooled to 0°C, was added dropwise *n*-butyllithium (2.5 *M* in hexane, 50 mL, 0.125 mol). The resulting clear reddish orange colored solution was then stirred at 0°C for 1 hour before cooling to -78°C at which time the clear solution became a colored suspension. A solution of the starting bis-cyano aldehyde **56** (10.013 g, 0.061 mol) in anhydrous tetrahydrofuran (50 mL) was then added dropwise *via* a dropping funnel to the suspension at -78°C. After the addition was completed, the cooling bath was

removed and the reaction suspension allowed to warm to room temperature. After 30 minutes, saturated aqueous ammonium chloride was added dropwise until no more precipitate was present and the aqueous layer was extracted with diethyl ether (4 x 100 mL). The combined organic extracts were then washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL). After drying over magnesium sulfate, filtration, and evaporation of solvent *in vacuo*, the crude product was obtained as a clear colorless oil. The crude product was purified by flash chromatography using 20% EtOAc/hexane as eluent to furnish the desired cyano enamine **58** as a white solid (7.640 g, 77%); mp: 88-90°C; FTIR ($CDCl_3$ cast) 3444 and 3354 (NH_2) and 2179 cm^{-1} (CN); ^{1}H-NMR ($CDCl_3$, 360 MHz) δ 5.74 (dd, J = 18, 10 Hz, 1 H, -C**H**=CH_2-), 5.01 (dd, J = 18, 1 Hz, 1 H, -CH=C**H**H-), 5.01 (dd, J = 10, 1 Hz, 1 H, -CH=CH**H**-), 4.18 (br. s, 2 H, -N**H**$_2$), 2.22 (ddd, J = 15, 3, 1 Hz, 1 H, -(CH_3)C-C**H**H-C=), 2.15 (dddd, J = 11, 7, 2, 1 Hz, 2 H, -CH_2-C**H**$_2$-C=), 2.04 (br. d, J = 15 Hz, 1 H, -(CH_3)C-CH**H**-C=), 1.60 (dddd, J = 13, 6, 6, 1 Hz, 1 H, -(CH_3)C-C**H**H-CH_2-), 1.51 (ddd, J = 13, 7, 1 Hz, 1 H, -(CH_3)C-CH**H**-CH_2-), 1.04 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 155.5 (p), 145.0 (a), 120.7 (p), 111.9 (p), 72.4 (p), 35.0 (p), 34.7 (p), 32.4 (p), 25.9 (a), 25.6 (p); HRMS M^+ 162.1154 (calculated for $C_{10}H_{14}N_2$: 162.1157); Anal. calculated for $C_{10}H_{14}N_2$: C 74.03, H 8.70, N 17.27; found: C 74.09, H 8.82, N 17.23.

5-methyl-2-oxo-5-vinylcyclohexanecarbonitrile (54)



54

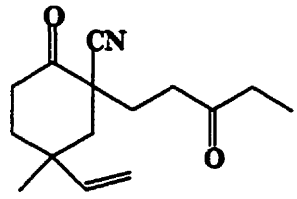
The starting cyano enamine **58** (7.640 g, 0.047 mol) was dissolved in toluene (100mL) and aqueous hydrochloric acid (2.48 *N*, 50 mL) was added. The heterogeneous mixture was heated to reflux and maintained at refluxing temperature for 1 hour followed by cooling to room temperature, at which time the aqueous layer was separated and extracted with diethyl ether (4 x 100 mL). The combined organic layers were then washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product as a light brown oil. Flash chromatography using 20% EtOAc/hexane as eluent yielded the desired cyano ketone **54** as a light yellow oil (6.908 g, 90%); FTIR ($CDCl_3$ cast) 3361 (OH), 2251 (CN), 2210 (=C-CN), 1728 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz, three isomers consisting of an enol tautomer and two keto diastereomers in a respective ratio of 1:2:7); δ 5.87 (dd, J = 18, 11 Hz, 0.7 H, -C**H**=CH_2, major keto), 5.82 (dd, J = 18, 11 Hz, 0.2 H, -C**H**=CH_2, minor keto), 5.74 (dd, J = 18, 11 Hz, 0.1 H, -C**H**=CH_2, enol), 5.35 (d, J = 11 Hz, 0.7 H, -CH=C**H**H-, major keto), 5.25 (d, J = 18 Hz, 0.7 H, -CH=CH**H**-, major keto), 5.08 (d, J = 18 Hz, 0.2 H, -CH=C**H**H, minor keto), 5.07 (d, J = 11 Hz, 0.2 H, -CH=CH**H**, minor keto), 5.03 (dd, J = 11, 1 Hz, 0.1 H, -CH=C**H**H, enol), 5.00 (dd, J = 18, 1 Hz, 0.1 H, -CH=CH**H**, enol), 3.69 (dd, J = 13, 6 Hz, 0.2 H, O=C-C**H**-CN, minor keto), 3.63 (dd, 14, 6 Hz, 0.7 H, O=C-C**H**-CN, major keto), 2.29-2.55 (m,

2.5 H), 2.08-2.18 (m, 0.6 H), 1.99-2.07 (m, 0.9 H), 1.95 (dd, J = 14, 14 Hz, 0.7 H), 1.74-1.81 (m, 0.5 H), 1.70 (ddd, J = 14, 14, 6 Hz, 0.7 H), 1.30 (s, 0.6 H, -CH_3, minor keto), 1.12 (s, 2.1 H, -CH_3, major keto), 1.05 (s, 0.3 H, -CH_3, enol); ^{13}C-NMR (APT, $CDCl_3$, 50 MHz) δ 200.4 (p), 200.3 (p), 166.1 (p), 145.4 (a), 144.7 (a), 142.2 (a), 118.7 (p), 116.4 (p), 115.0 (p), 112.0 (p), 111.9 (p), 79.4 (p), 41.2 (p), 41.0 (p), 40.1 (a), 39.8 (a), 37.2 (p), 36.6 (p), 36.5 (p), 36.2 (p), 35.5 (p), 35.4 (p), 32.4 (p), 29.3 (a), 25.8 (p), 25.6 (a), 21.3 (a); HRMS M^+ 163.0996 (calculated for $C_{10}H_{13}NO$: 163.0997).

Alternatively, the title compound may be synthesized in much higher overall yield directly from 3-formyl-3-methyl-1,5-pentanedicarbonitrile (**56**) without isolating the cyano enamine intermediate **58** in the following manner: To a suspension of methyltriphenylphosphonium bromide (15.590 g, 0.044 mol) in anhydrous tetrahydrofuran (50 mL) cooled to 0°C was added *n*-butyllithium (2.5 *M* in hexane, 16.3 mL, 0.041 mol) dropwise. The resulting clear red solution was stirred at 0°C for 1 hour followed by cooling to -78°C, at which time the solution became an orange colored suspension. A solution of the starting bis-cyano aldehyde **56** (3.192 g, 0.020 mol) in anhydrous tetrahydrofuran (30 mL) was then introduced dropwise *via* a dropping funnel. When addition was complete, the reaction mixture was stirred at -78°C for 15 minutes before the cooling bath was removed. After 1 hour, a 2.48 *N* hydrochloric acid was carefully added dropwise until all precipitate had dissolved. Additional 2.48 *N* hydrochloric acid was then added until the pH of the aqueous layer was approximately 1. The orange colored biphasic mixture was then stirred vigorously at room temperature for 17 hours before the aqueous layer was separated and extracted with diethyl ether (4 x 100 mL). The combined organic layers were then washed sequentially with water (100 mL), saturated sodium bicarbonate (100 mL), and brine (100

mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product thus obtained as a dark brown oil was subjected to vacuum distillation (123-130°C/0.7 mm Hg) to yield the title compound as a clear viscous oil (2.902 g, 91%).

5-Methyl-2-oxo-1-(3-oxopentyl)-5-vinylcyclohexanecarbonitrile (59)

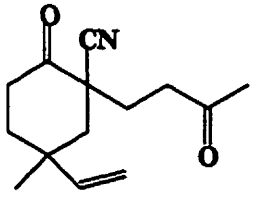


59

To a solution of starting α-cyano ketone **54** (0.706 g, 0.004 mol) in anhydrous dimethoxyethane was added 1,4-diazabicyclo[2.2.2]octane (0.615 g, 0.005 mol) and the resulting clear solution was cooled to 0°C. After stirring at 0°C for 15 minutes, ethyl vinyl ketone (0.7 mL, 0.007 mol) was added dropwise and the resulting clear colorless reaction solution was allowed to warm to room temperature. After stirring at room temperature for 23 hours, the clear light yellow reaction solution was poured into ice-cold dilute hydrochloric acid solution and the slightly acidic aqueous layer was then extracted with ethyl acetate (4 x 50 mL) . The combined organic extracts were washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product as a clear light yellow oil. Flash chromatography using 20% EtOAc/hexane as eluent then gave the title Michael adduct **59** as a clear oil (7:3 inseparable mixture of diastereomers, 0.522 g, 49%): FTIR ($CDCl_3$ cast) 2233 (CN) and 1718 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.16 (ddd, J = 18, 11, 1

Hz, 0.7 H, -C**H**=CH_2, major isomer), 5.82 (dd, J = 18, 11 Hz, 0.3 H, -C**H**=CH_2, minor isomer), 5.31 (d, J = 11 Hz, 0.7 H, -CH=C**H**H-, major isomer), 5.26 (d, J = 18 Hz, 0.7 H, -CH=CH**H**-, major isomer), 5.10 (d, J = 11 Hz, 0.3 H, -CH=C**H**H-, minor isomer), 5.08 (d, J = 18 Hz, 0.3 H, -CH=CH**H**-, minor isomer), 3.02 (ddd, J = 14, 14, 6 Hz, 0.7 H, O=C-C**H**H-), 2.70-2.80 (m, 1.1 H), 2.51-2.68 (m, 1.8 H), 2.25-2.51 (m, 4.0 H), 2.15-2.25 (m, 1.0 H), 1.94-2.08 (m, 0.7 H), 1.64-1.92 (m, 2.7 H), 1.36 (s, 0.9 H, -CH_3, minor isomer), 1.08 (s, 2.1 H, -CH_3, major isomer), 1.07 (dd, J = 7, 7 Hz, 2.1 H, -CH_3, major isomer), 1.05 (dd, J = 7, 7 Hz, 0.9 H, -CH_3, minor isomer); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 209.4 (p), 209.1 (p), 203.5 (p), 145.7 (a), 143.0 (a), 119.8 (p). 119.1 (p), 114.3 (p), 112.3 (p), 49.8 (p), 48.8 (p), 48.3 (p), 47.2 (p), 37.8 (p), 37.6 (p), 36.9 (p), 36.3 (p), 36.0 (p), 35.9 (p), 35.1 (p), 30.3 (a), 29.3 (p), 26.6 (a), 7.8 (a); HRMS M^+ 247.1562 (calculated for $C_{15}H_{21}NO_2$: 247.1572); Anal. calculated for $C_{15}H_{21}NO_2$: C 72.83, H 8.56, N 5.67; found: C 72.80, H 8.76, N 5.60.

5-Methyl-2-oxo-1-(3-oxobutyl)-5-vinylcyclohexanecarbonitrile (63)



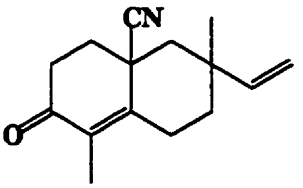
63

To a solution of starting α-cyano ketone **54** (0.254 g, 1.56 mmol) in anhydrous dimethoxyethane (5 mL) was added 1,4-diazabicyclo[2.2.2]octane (0.209 g, 1.86 mmol) and the resulting clear solution was cooled to 0°C. After stirring at 0°C for 30 minutes, methyl vinyl ketone (0.28 mL, 3.36 mmol) was added dropwise and the cooling bath was removed. The slightly cloudy reaction mixture was allowed

to stir at room temperature for 24 hours at which time it was poured into ice-cold dilute hydrochloric acid solution. The aqueous layer was extracted with diethyl ether (4 x 30 mL) and the combined organic extracts were washed sequentially with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting light yellow oil was purified by flash chromatography using 15% EtOAc/hexane as eluent to furnish, after evaporation of solvent, the desired Michael adduct as a light yellow oil in a 2:1 mixture of diastereomers (0.284 g, 78%): FTIR ($CDCl_3$ cast) 2232 (CN) and 1727 cm^{-1} (C=O); HRMS M^+ 233.1408 (calculated for $C_{14}H_{19}NO_2$: 233.1416); Anal. calculated for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00; found C 72.15, H 8.47, N 5.68. An aliquot of the mixture was subjected to flash chromatography using 10% EtOAc/hexane as eluent to furnish the individual diastereomers for characterization; isomer 1 (minor product): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.82 (dd, J = 18, 11 Hz, 1 H, -C**H**=CH_2), 5.09 (d, J = 11 Hz, 1 H, -CH=CH**H**), 5.08 (d, J = 18 Hz, 1 H, -CH=CH**H**), 2.56-2.82 (m, 4 H), 2.30-2.50 (m, 2 H), 2.20 (dd, J = 14, 2 Hz, 1 H, -(CH_3)C-C**H**H-C(CN)), 2.16 (s, 3 H, O=C-CH_3), 1.96 (d, J = 14 Hz, 1 H, -(CH_3)C-CH**H**-C(CN)), 1.80-1.92 (m, 2 H), 1.35 (s, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 206.3 (p), 203.5 (p), 145.8 (a), 119.7 (p), 112.3 (p), 48.3 (p), 42.7 (p), 39.1 (p), 37.4 (p), 36.3 (p), 35.1 (p), 29.9 (a), 29.2 (p), 26.4 (a); isomer 2 (major product): ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 6.12 (ddd, J = 18, 11, 1 Hz, 1 H, -C**H**=CH_2), 5.29 (d, J = 11 Hz, 1 H, -CH=CH**H**), 5.24 (d, J = 18 Hz, 1 H, -CH=CH**H**), 3.00 (ddd, J = 13, 13, 5 Hz, 1 H, O=C-CH**H**-), 2.77 (ddd, J = 18, 1, 5 Hz, 1 H, O=C-CH**H**-), 2.58 (ddd, J = 18, 10, 5 Hz, 1 H, O=C-CH**H**-), 2.37 (ddd, J = 14, 4, 4 Hz, 1 H, O=C-CH_2-CHH-), 2.24-2.33 (m, 2 H, (CH_3)C-CHH- and O=C-CH_2-CH**H**-), 2.13-2.19 (m, 1 H, O=C-CH_2-CH**H**-), 2.15 (s, 3 H, O=C-CH_3), 1.78 (ddd, J = 14, 10, 5 Hz, 1 H, O=C-CH_2-CHH-), 1.70 (dddd, J = 13, 13, 4, 1 Hz, 1 H, O=C-CH**H**-), 1.66 (d, J = 14 Hz, 1 H,

(CH_3)C-CHH-), 1.05 (s, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 206.6 (p), 203.5 (p), 143.0 (a), 119.1 (p), 114.4 (p), 49.8 (p), 47.2 (p), 39.0 (p), 36.9 (p), 36.3 (p), 35.9 (p), 30.3 (a), 30.0 (a), 29.2 (p).

6-Cyano-2,8-dimethyl-8-vinylbicyclo[4.4.0]dec-1-en-3-one (53)



53

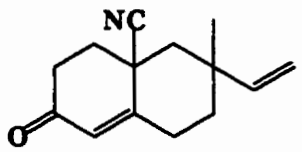
To a 100 mL round bottom flask fitted with a Dean-Stark apparatus was added *p*-toluenesulfonic acid hydrate (0.321 g, 0.0016 mol) and benzene (50 mL). The clear solution was heated to reflux and the water-benzene azeotrope was drained. After no more water was evident in the distillate (~30 mL was drained), the solution was cooled to room temperature and a solution of the starting diketone **59** (0.522 g, 0.002 mol) in anhydrous benzene (30 mL) was quickly introduced. The resulting clear light yellow solution was heated to reflux and the water-benzene azeotrope was drained (~30 mL was drained). After refluxing for 2 hours, the clear red reaction solution was then cooled to room temperature and diethyl ether was added (20 mL). Saturated sodium bicarbonate (30 mL) was added and the aqueous layer was then extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were then washed sequentially with water (50 mL) and brine (50 mL). The pre-dried organic layer thus obtained was then dried further over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product as a light yellow oil. Flash chromatographic purification of the crude product using 20% EtOAc/hexane then gave the title compound as a light

yellow oil in a 1:1 mixture of diastereomers (0.417 g, 86%): FTIR ($CDCl_3$ cast) 2228 (CN) and 1676 cm^{-1} (C=O); HRMS M^+ 229.1463 (calculated for $C_{15}H_{19}NO$: 229.1467). A portion of the mixture was then subjected to flash chromatography using 10% EtOAc/hexane as eluent to give the individual diastereomers for characterization: ^{1}H-NMR ($CDCl_3$, 400 MHz) isomer 1: δ 5.75 (dd, J = 18, 11 Hz, 1 H, -C**H**=CH_2), 4.99 (d, J = 18 Hz, 1 H, -CH=C**H**H), 4.98 (d, J = 11 Hz, 1 H, -CH=CH**H**), 2.72-2.84 (m, 2 H, O=C-C**H**H- and C=C-C**H**H-), 2.47-2.61 (m, 2 H, O=C-CH**H**- and C=C-CH**H**-), 2.34 (ddd, J = 14, 5, 3 Hz, 1 H, O=C-CH_2-C**H**H-), 2.06 (dd, J = 14, 3 Hz, 1 H, -(CH_3)C-C**H**H-), 1.94 (ddd, J = 15, 14, 4 Hz, O=C-CH_2-CH**H**-), 1.84 (s, 3 H, =C-C**H**$_3$), 1.78 (dddd, J = 14, 4, 4, 3 Hz, 1 H, -(CH_3)C-C**H**H-CH_2-), 1.53 (ddd, J = 14, 13, 4 Hz, 1 H, -(CH_3)C-CH**H**-CH_2-), 1.52 (d, J = 14 Hz, -(CH_3)C-CH**H**-), 1.45 (s, 3 H, -C**H**$_3$); isomer 2: 6.16 (ddd, J = 18, 11, 1 Hz, 1 H, -C**H**=CH_2), 5.26 (dd, J = 11, 1 Hz, 1 H, -CH=C**H**H), 5.21 (dd, J = 18, 1 Hz, 1 H, -CH=CH**H**), 2.68-2.81 (m, 2 H, O=C-C**H**H- and C=C-C**H**H-), 2.48-2.60 (m, 2 H, O=C-CH**H**- and C=C-CH**H**-), 2.33 (ddd, J = 14, 5, 3 Hz, 1 H, O=C-CH_2-C**H**H-), 2.21 (dd, J = 14, 3 Hz, 1 H, -(CH_3)C-C**H**H-), 2.14 (ddd, J = 14, 7, 3 Hz, 1 H, -(CH_3)C-C**H**H-CH_2-), 1.92 (ddd, J = 15, 14, 4 Hz, 1 H, O=C-CH_2-CH**H**-), 1.83 (s, 3 H, =C-C**H**$_3$), 1.43 (d, J = 14 Hz, 1 H, (CH_3)C-CH**H**-), 1.39 (dddd, J = 14, 14, 4, 1 Hz, 1 H, -(CH_3)C-CH**H**-CH_2-), 1.04 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) isomer 1: δ 196.4 (p), 150.1 (p), 148.0 (a), 132.7 (p), 121.8 (p), 111.0 (p), 47.9 (p), 36.1 (p), 36.0 (p), 35.6 (p), 35.4 (p), 34.3 (p), 25.2 (p), 22.7 (a), 11.3 (a); isomer 2: 196.4 (p), 150.4 (p), 143.1 (a), 132.3 (p), 120.9 (p), 114.0 (p), 50.0 (p), 36.7 (p), 36.3 (p), 35.3 (p), 34.8 (p), 34.1 (p), 31.1 (a), 25.5 (p), 11.2 (a).

Alternatively, the title compound may be synthesized in directly from cyano ketone **54** without isolating the Michael adduct intermediate **59**. As such, after the prescribed workup for the synthesis of Michael adduct **59**, the crude product

was dried rigorously under high vacuum for 2 hours. This was then used without further purification according to the described procedure for the aldol condensation reaction to give cyano enone **53**. Using this modified procedure, the yield of **53** was 40% over 2 steps.

6-Cyano-8-methyl-8-vinylbicyclo[4.4.0]dec-1-en-3-one (64)

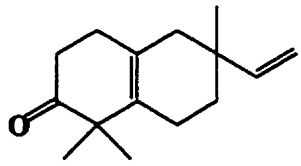


64

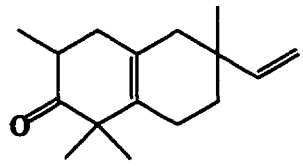
To a 50 mL round bottom flask fitted with a Dean-Stark apparatus was added *p*-toluenesulfonic acid hydrate (0.802 g, 0.0042 mol) and benzene (40 mL). The clear solution was heated to reflux and the water-benzene azeotrope was drained. After no more water was evident in the distillate (~20 mL was drained), the solution was cooled to room temperature and a solution of the starting diketone **63** (1.229 g, 0.0053 mol) in anhydrous benzene (20 mL) was quickly introduced. The resulting clear red solution was heated to reflux and the water-benzene azeotrope was drained (~10 mL). After refluxing for 12 hours, the deep red solution was cooled to room temperature and the reaction was quenched by the addition of saturated sodium bicarbonate (20 mL). The aqueous layer was separated and extracted with diethyl ether (4 x 50 mL) and the combined organic extracts were then washed sequentially with water (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting light yellow oil was subjected to flash chromatography using 20% EtOAc/hexane as eluent to furnish the desired cyano enone **64** as a light yellow solid in a 2:1 mixture of diastereomers (0.623 g, 55%): mp: 54-58°C; FTIR ($CDCl_3$ cast) 2228

(CN) and 1684 cm^{-1} (C=O); HRMS M^+ 215.1312 (calculated for $C_{14}H_{17}NO$: 215.1310); Anal. calculated for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 78.14, H 8.11, N 6.19; A portion of the mixture was subjected to flash chromatographic separation using 10% EtOAc/hexane as eluent to give the individual diastereomers for characterization; isomer 1 (minor product): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.98 (d, J = 2 Hz, 1 H, -C=C**H**-C=O), 5.74 (dd, J = 18, 11 Hz, 1 H, -C**H**=CH_2), 5.01 (dd, J = 18, 1 Hz, 1 H, -CH=C**H**H-), 4.98 (dd, J = 11, 1 Hz, 1 H, -CH=CH**H**-), 2.69-2.85 (m, 2 H), 2.36-2.58 (m, 3 H), 2.12 (dd, J = 14, 3 Hz, 1 H, -(CH_3)C-C**H**H-C(CN)-), 1.98 (ddd, J = 15, 14, 4 Hz, 1 H), 1.74 (ddd, J = 14, 5, 5 Hz, 1 H), 1.74 (dd, J = 14, 5 Hz, 1 H), 1.55 (d, J = 15 Hz, 1 H, -(CH_3)C-CH**H**-C(CN)-), 1.46 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 196.6 (p), 156.9 (p), 147.8 (a), 127.3 (a), 120.9 (p), 111.2 (p), 47.5 (p), 36.5 (p), 36.2 (p), 35.9 (p), 34.4 (p), 31.6 (p), 29.3 (p), 21.9 (a); isomer 2 (major product): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.14 (ddd, J = 18, 11, 1 Hz, 1 H, -C**H**=CH_2), 5.95 (d, J = 2 Hz, 1 H, -C=C**H**-C=O), 5.28 (d, J = 11 Hz, 1 H, -CH=C**H**H), 5.21 (d, J = 18 Hz, 1 H, -CH=CH**H**), 2.65-2.86 (m, 2 H), 2.49 (dddd, J = 17, 4, 4, 1 Hz, 1 H), 2.31-2.44 (m, 2H), 2.26 (dd, J = 14, 3 Hz, 1 H, -(CH_3)C-C**H**H-C(CN)-), 2.12 (ddd, J = 14, 5, 5, Hz, 1 H), 2.12 (dd, J = 14, 5 Hz, 1 H), 1.96 (ddd, J = 15, 14, 4 Hz, 1 H), 1.44 (d, J = 14 Hz, 1 H, -(CH_3)C-CH**H**-C(CN)-), 1.05 (s, 3 H, -C**H**$_3$): ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) 195.8 (p), 156.5 (p), 141.5 (a), 126.0 (a), 119.1 (p), 113.5 (p), 48.5 (p), 35.9 (p), 34.9 (p), 34.2 (p), 33.3 (p), 30.6 (p), 30.4 (a), 28.7 (p).

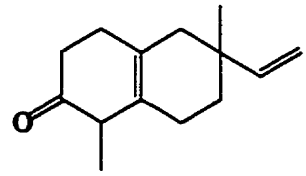
2,2,8-Trimethyl-8-vinylbicyclo[4.4.0]dec-1(6)-en-3-one (60), 2,2,4,8-tetramethyl-8-vinylbicyclo[4.4.0]dec-1(6)-en-3-one (61), and 1,8-dimethy-8-vinylbicyclo[4.4.0]dec-1(6)-en-3-one (62)



60



61



62

To a clear solution of naphthalene (0.331 g, 0.00258 mol) in anhydrous tetrahydrofuran (5 mL) was added lithium wire (0.064 g, 0.009 mol). The resulting mixture was stirred at room temperature for 1 hour at which time it became a dark blue solution. This was used as a stock 0.52 *M* solution of lithium naphthalenide.

To a solution of the starting cyano enone **53** (0.096 g, 0.419 mmol) in anhydrous tetrahydrofuran (5 mL) cooled to -78°C was added dropwise the above pre-formed lithium naphthalenide solution (2.4 mL, 1.25 mmol). The resulting blue solution was stirred at -78°C for 45 minutes followed by rapid addition of methyl iodide (0.11 mL, 0.251 g, 1.77 mmol). The clear light yellow reaction mixture was then stirred at -78°C for 20 hours. Solid ammonium chloride (~100 mg) was then added and the suspension was allowed to warm to room temperature. Water was then introduced dropwise to dissolve all precipitate and the aqueous layer was separated and extracted with diethyl ether (4 x 30 mL). The combined organic extracts were then washed sequentially with water (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The light yellow oil thus obtained was then subjected to flash chromatography using

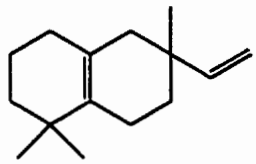
0.4% EtOAc/hexane as eluent to give the α,α'-dialkylated reduction product **61** (trace amount) as an inseparable mixture of two diastereomers in a 3:2 ratio: FTIR ($CHCl_3$ cast) 1710 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 360 MHz) δ 5.84 (dd, J = 18, 11 Hz, 0.4H, -C**H**=CH_2, minor isomer), 5.71 (dd, J = 18, 11 Hz, 0.6 H, -C**H**=CH_2, major isomer), 4.95 (dd, J = 18, 1 Hz, 0.4 H, -CH=C**H**H, minor isomer), 4.93 (dd, J = 11, 1 Hz, 0.4 H, -CH=CH**H**, minor isomer), 4.90 (dd, J = 11, 1 Hz, 0.6 H, -CH=C**H**H, major isomer), 4.81 (dd, J = 18, 1 Hz, 0.6 H, -CH=CH**H**, major isomer), 2.86 (m, 1 H, O=C-C**H**-), 2.26 (dd, J = 16, 7 Hz, 1 H, O=C-CH-CHH-), 1.81-2.11 (m, 4.6 H), 1.71 (d, J = 16 Hz, 0.4 H, O=C-CH-CH**H**-, minor isomer), 1.36-1.60 (m, 3 H), 1.19 (s, 3 H, -C**H**$_3$), 1.14 (s, 1.2 H, -C**H**$_3$, minor isomer), 1.08 (s, 1.8 H, -C**H**$_3$, major isomer), 1.07 (d, J = 7 Hz, 3 H, O=C-CH-C**H**$_3$), 1.03 (s, 1.8 H, -C**H**$_3$, major isomer), 0.94 (s, 1.2 H, -C**H**$_3$, minor isomer); ^{13}C-NMR (APT, $CDCl_3$, 50 MHz) δ 193.7 (p), 148.4 (a), 145.7 (a), 133.4 (p), 125.7 (p), 111.0 (p), 110.1 (p), 47.2 (p), 41.7 (p), 41.3 (p), 40.0 (p), 39.8 (p), 38.9 (a), 38.8 (a), 35.1 (p), 34.8 (p), 34.1 (p), 33.3 (p), 27.8 (a), 26.7 (a), 23.7 (a), 22.0 (a), 21.9 (p), 21.5 (p), 14.1 (a); HRMS M^+ 232.1818 (calculated for $C_{16}H_{24}O$: 232.1827); Anal. calculated for $C_{16}H_{24}O$: C 82.70, H 10.41; found: C 82.36, H 10.57. Further elution gave the desired bicyclic ketone **60** (0.070 g, 77%): FTIR ($CDCl_3$ cast) 1716 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.77 (dd, J = 18, 11 Hz, 1 H, -C**H**=CH_2), 4.92 (dd, J = 11, 2 Hz, 1 H, -CH=C**H**H), 4.89 (dd, J = 18, 2 Hz, 1 H, -CH=CH**H**), 2.49-2.60 (m, 2 H, O=C-C**H**$_2$-), 2.28 (mt, J = 8 Hz, 2 H, O=C-CH_2-C**H**$_2$-), 2.00 (m, 3 H, =C-C**H**$_2$-CH_2- and -(CH_3)C-C**H**H-C=), 1.81 (md, J = 18 Hz, 1 H, -(CH_3)C-CH**H**-C=), 1.52 (dddd, J = 13, 6, 6, 1 Hz, 1 H, -(CH_3)C-C**H**H-), 1.44 (dddd, J = 13, 6, 6, 1 Hz, 1 H, -(CH_3)C-CH**H**-), 1.17 (s, 3 H, -C**H**$_3$), 1.14 (s, 3 H, -C**H**$_3$), 0.98 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 50 MHz) δ 215.8 (p), 146.9 (a), 133.0 (p), 126.2 (p), 110.6 (p), 47.0 (p), 41.7 (p), 35.9 (p), 34.9 (p), 33.8 (p), 30.9 (p), 29.7 (p), 25.8 (a), 24.1 (a), 23.8 (a); HRMS M^+ 218.1671

(calculated for $C_{15}H_{22}O$: 218.1671); Anal. calculated for $C_{15}H_{22}O$: C 82.52, H 10.16; found: C 82.22, H 9.91. Final elution with the same solvent system gave the reduction product **62** (0.011 g, 13%) as a 1:1 mixture of diastereomers: FTIR ($CDCl_3$ cast) 1714 cm^{-1} (C=O); ^1H-NMR ($CDCl_3$, 360 MHz) δ 5.79 (dd, J = 18, 11 Hz, 0.5 H, -C**H**=CH_2), 5.77 (dd, J = 18, 11 Hz, 0.5 H, -C**H**=CH_2), 4.85-4.95 (m, 2 H, -CH=CH_2), 2.50-2.67 (m, 2 H), 2.20-2.47 (m, 3 H), 2.05-2.20 (m, 1 H), 1.94-2.05 (m, 1 H), 1.70-1.87 (m, 2 H), 1.39-1.57 (m, 2 H), 1.20 (d, J = 7 Hz, 1.5 H, -CH-CH_3), 1.16 (d, J = 7 Hz, 1.5 H, -CH-CH_3), 1.00 (s, 1.5 H, -CH_3), 0.99 (s, 1.5 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) 214.0 (p), 147.7 (a), 146.3 (a), 129.8(p), 129.6 (p), 126.8 (p), 110.9 (p), 110.4 (p), 47.3 (a), 47.2 (a), 41.4 (p), 41.2 (p), 37.0 (p), 36.9 (p), 35.4 (a), 35.2 (a), 33.8 (p), 33.4 (p), 30.9 (p), 30.8 (p), 26.9 (a), 25.6 (p), 25.3 (p), 24.9 (a), 16.0 (a), 15.8 (a); HRMS M^+ 204.1521 (calculated for $C_{14}H_{20}O$: 204.1514).

Alternatively, the desired bicyclic ketone **60** may also be synthesized from bicyclic ketone **64** in the following manner: To a solution of ketone **64** (0.082 g, 0.381 mmol) in anhydrous tetrahydrofuran (4 mL) cooled to -78°C was added pre-formed lithium naphthalenide solution (1.0 *M* in tetrahydrofuran, 1.6 mL, 1.6 mmol) dropwise. The resulting blue solution was stirred at -78°C for 30 minutes followed by the rapid introduction of methyl iodide (0.085 mL, 1.4 mmol). The clear light yellow solution was removed from the cooling bath and warmed to room temperature. After stirring at room temperature for 4 hours, saturated aqueous ammonium chloride was added (10 mL). The aqueous layer was extracted with diethyl ether (4 x 20 mL) and the combined organic extracts were washed with water (20 mL) followed by brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography of the

resulting light yellow oil using 0.25% EtOAc as eluent gave, after evaporation of solvent, bicyclic ketone **60** as the only isolable product in 41% yield.

2,2,8-Trimethyl-8-vinylbicyclo[4.4.0]dec-1(6)-ene (42)

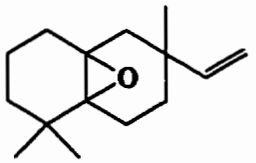


42

To a solution of the starting bicyclic ketone **60** (0.110 g, 0.504 mmol) in diethylene glycol (8 mL) was added potassium hydroxide pellets (80% wt/wt, 0.191 g, 2.72 mmol) and anhydrous hydrazine (0.15 ml, 4.78 mmol). A Dean-Stark apparatus containing 4Å molecular sieves was then fitted onto the round bottom flask and the clear light yellow reaction mixture was then heated to 110-120°C. After 2 hours at 110-120°C, the temperature was gradually raised to 210-230°C and maintained there for a further 4 hours. The clear solution was then cooled to room temperature, diluted with water (20 mL), and extracted with petroleum ether (4 x 50 mL). The combined organic extracts were then washed with water (30 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and carefully concentrated *in vacuo* **(the product is appreciably volatile).** Flash chromatography through a short column using petroleum ether as eluent then furnished the desired deoxygenated product **42** as a clear colorless oil (0.078 g, 76%): FTIR ($CDCl_3$ cast) 1641 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.80 (dd, J = 18, 11 Hz, 1 H, -C**H**=CH_2), 4.86-4.94 (m, 2 H, -CH=C**H**$_2$), 1.97 (m, 2 H), 1.84 (m, 2 H), 1.88 (br. d, J = 17 Hz, 1 H, -(CH_3)C-C**H**H-C=), 1.69 (br. d, J = 17 Hz, 1 H, -(CH_3)C-CH**H**-C=), 1.62 (m, 2 H), 1.44 (m, 4 H), 0.99 (s, 3 H, -C**H**$_3$), 0.97 (s, 3 H, -C**H**$_3$), 0.96 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 50 MHz) δ 147.9

(a), 133.6 (p), 125.4 (p), 110.0 (p), 42.3 (p), 39.8 (p), 35.0 (p), 34.5 (p), 33.5 (p), 31.6 (p), 27.9 (a), 25.6 (a), 21.7 (p), 19.4 (p); HRMS M^+ 204.1872 (calculated for $C_{15}H_{24}$: 204.1878).

2,2,8-Trimethyl-11-oxa-8-vinyltricyclo[4.4.1.$0^{1,6}$]undecane (65)

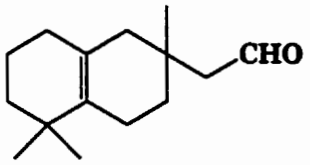


65

To a solution of the starting bicyclic diene **42** (0.008 g, 0.0372 mmol) in anhydrous dichloromethane (2 mL) cooled to 0°C was added *m*-chloroperbenzoic acid (0.012 g, 0.0695 mmol) and the clear solution was stirred at 0°C for 15 minutes before being allowed to warm to room temperature. After 5 hours at room temperature, saturated sodium bicarbonate (5 mL) was added and the aqueous layer was extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The clear oil thus obtained was subjected to flash chromatography using 5% EtOAc/hexane as eluent to give the title epoxide **65** (0.004 g, 47%)as a clear oil in a 3.5:1 mixture of diastereomers : FTIR ($CDCl_3$ cast) 1640 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$, 360 MHz) δ 5.75 (dd, J = 18, 11 Hz, 0.22 H, -C**H**=CH_2, minor isomer), 5.65 (ddd, J = 18, 11, 1 Hz, 0.78 H, -C**H**=CH_2, major isomer), 5.01 (dd, J = 11, 2 Hz, 0.78 H, -CH=C**H**H, major isomer), 4.91 (dd, J = 18, 2 Hz, 0.78 H, -CH=CH**H**, major isomer), 4.89 (dd, J = 18, 2 Hz, 0.22 H, -CH=C**H**H, minor isomer), 4.86 (dd, J = 11, 2 Hz, 0.22 H, -CH=CH**H**, minor isomer), 1.62-2.02 (m, 8 H), 1.34-1.46 (m, 4

H), 0.97 (s, 6 H, -CH_3 x 2), 0.91 (s, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 146.5 (a), 111.2 (p), 109.6 (p), 62.7 (p), 43.4 (p), 41.4 (p), 37.0 (p), 32.0 (p), 31.6 (p), 31.2 (p), 29.3 (a), 26.2 (a), 24.8 (a), 22.7 (p), 21.9 (p), 21.2 (p), 17.1 (p), 17.0 (p), 14.1 (a); HRMS M^+ 220.1818 (calculated for $C_{15}H_{24}O$: 220.1827).

Nanaimoal (1)



1

To a solution of the starting diene **42** (0.021 g, 0.103 mmol) in anhydrous tetrahydrofuran (3 mL) cooled to 0°C, was added dropwise a pre-formed solution of disiamylborane in anhydrous tetrahydrofuran (0.5 *M*, 0.82 mL, 0.410 mmol). The resulting clear colorless solution was allowed to warm to room temperature and stirred for 25 hours. The solvent was then removed *in vacuo* and the residue redissolved in anhydrous dichloromethane (2 mL). This clear colorless solution was then added to a bright orange solution of pyridinium chlorochromate (0.443 g, 2.06 mmol) in anhydrous dichloromethane (3 mL) and the resulting dark brown suspension was then heated to reflux. After refluxing for 3 hours, the dark suspension was cooled to room temperature, diluted with diethyl ether (~20 mL), and the resulting dark suspension was filtered over a pad of Celite. The residue was rinsed with copious amounts of diethyl ether and the filtrate was concentrated *in vacuo*. Flash chromatography of the resulting clear oil using 5% Et_2O/hexane as eluent then yielded the desired aldehyde **1** as a fragrant clear colorless oil (0.012 g, 66%): FTIR ($CDCl_3$ cast) 2849 and 2730 (OC-H) and 1721

cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) 9.86 (t, J = 3 Hz, 1 H, -C**H**O), 2.29 (dd, J = 14, 3 Hz, 1 H, -C**H**H-CHO), 2.22 (dd, J = 14, 3 Hz, 1 H, -CH**H**-CHO), 2.01 (m, 2 H), 1.84 (d, J = 17 Hz, 1 H, -(CH_3)C-C**H**H-C=), 1.79 (m, 2 H), 1.76 (d, J = 17 Hz, -(CH_3)C-CH**H**-C=), 1.59 (m, 4 H), 1.44 (m, 2 H), 1.05 (s, 3 H, -C**H**$_3$), 0.98 (s, 6 H, -C**H**$_3$ x 2); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 203.9 (a), 133.8 (p), 125.3 (p), 53.7 (p), 43.7 (p), 39.7 (p), 34.8 (p), 33.6 (p), 32.2 (p), 31.6 (p), 27.9 (a), 26.0 (a), 21.3 (p), 19.4 (p); HRMS M^+ 220.1823 (calculated for $C_{15}H_{24}O$: 220.1827).

References

1. Ayer, S.W.; Hellou, J.; Tischler, M.; Andersen, R.J. *Tetrahedron Lett.* **1984**, *25*, 141.
2. Grazianni, E.I.; Andersen, R.J. *J. Am. Chem. Soc.* **1996**, *118*, 4701.
3. Yamada, T.; Takabe, K. *Chem. Lett.* **1993**, 29.
4. Omodani, T.; Shishido, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2781.
5. Takai, K; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.; Lombardo, L. *Org. Synth.* **1987**, *65*, 81.
6. Engler, T.A.; Ali, M.H.; Takusagawa, F. *J. Org. Chem.* **1996**, *61*, 8456.
7. Tai, C.L. Masters Thesis, Department of Chemistry, National Tsing-Hua University, Taiwan, 1999.
8. Yip, J. Ph.D. Thesis, Department of Chemistry, University of Alberta, Canada, 1998.
9. Liu, H.J.; Shia, K.S. *Tetrahedron* **1998**, *54*, 13449.
10. Liu, H.J.; Shia, K.S.; Han, Y.; Sun, D.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 646.
11. Bergmann, E.D.; Ginsburg, D.; Pappo, R. *Org. React.* **1950**, *10*, 179.; Cornforth, J.W.; Robinson, R. *J. Chem. Soc.* **1949**, 1855.; Gawley, R. *Synthesis* **1976**, 777.; Jung, M.E. *Tetrahedron* **1976**, *32*, 3.; Mundy, B.P. *J. Chem. Educ.* **1973**, *50*, 110.
12. Baron, H.; Remfry, F.G.P.; Thorpe, Y.F. *J. Chem. Soc.* **1904**, *85*, 1726.; Ziegler, K.; Eberle, E.; Ohlinger, M. *Ann.* **1933**, *504*, 94.; Schaefer, J.P.; Bloomfield, J.J. *Org. React.* **1967**, *15*, 1.
13. Wittig, G.; Schöllkopf, U. *Ber.* **1954**, *87*, 1318.; Wittig, G.; Haag, W. *Ber.* **1955**, *88*, 1654.

14. Zondler, H.; Pfleiderer, W. *Liebigs Ann. Chem.* **1972**, *759*, 84.

15. Zondler, H.; Pfleiderer, W. *Helv. Chim. Acta* **1975**, *58*, 2261.

16. Silverstein, R.M.; Webster, F.X. *Spectrometric Identification of Organic Compounds*, 6th ed., John Wiley & Sons, 1998.

17. Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 3rd ed., Plenum Press, 1990.

18. Wieland, P.; Ueberwasser, H.; Amuer, G.; Miescher, K. *Helv. Chim. Acta* **1953**, *36*, 376.; Liu, H.J.; Wynn, H. *Can. J. Chem.* **1986**, *64*, 658.

19. Huang-Minlon *J. Am. Chem. Soc.* **1946**, *68*, 2487.; Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301.

20. Abraham, R.J.; Fisher, J.; Loftus, P. *Introduction of NMR Spectroscopy*, John Wiley & Sons, 1988.

21. Mancuso, A.J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

22. Coxon, J.N.; Hartshorn, M.P.; Rae, W.J. *Tetrahedron* **1970**, *26*, 1091; Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1971**, *93*, 2080.

23. Lynch, B.M.; Pausacker, K.H. *J. Chem. Soc.* **1955**, 1525.

24. a) Rao, C.G.; Kulkarni, S.U.; Brown, H.C. *J. Organometal. Chem.* **1979**, *172*, C20.; b) Brown, H.C.; Kulcarni, S.U.; Rao, C.G. *Synthesis* **1980**, 151.

25. Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of Laboratory Chemicals*, 2nd edition, Pergamon Press, 1987.

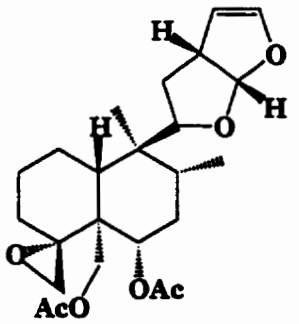
26. Still, W.C.; Kahn, M.; Mitra, A *J. Org. Chem.* **1978**, *43*, 2923.

Chapter Two

Towards the Total Synthesis of Solidago Alcohol *via* an Intermolecular Diels-Alder Approach

Introduction

The clerodanes constitute one of the largest families of diterpenoid natural products known. Ever since the isolation of clerodin (1) by Barton[1] and co-workers, there has been an ever increasing number of isolated and identified



1

natural products possessing the clerodane carbon skeleton (Figure 1)[2]. The clerodane natural products may be categorized into two distinct series, namely the *cis* and the *trans* series depending upon the stereochemistry of the ring junction. These two series are proposed to be descended from the same biosynthetic pathway.

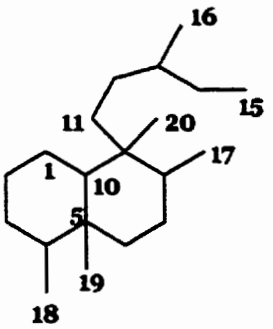
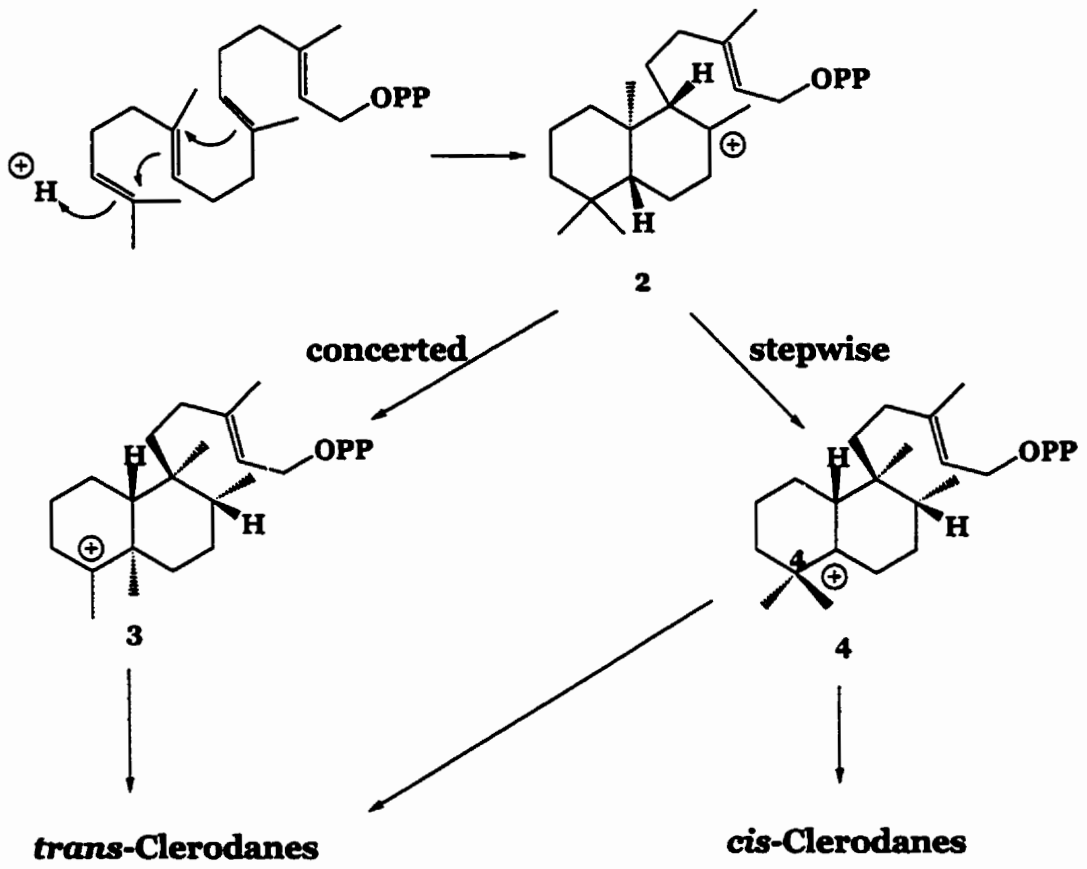


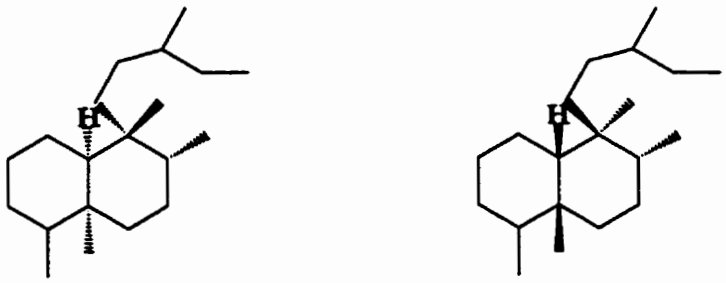
Figure 1. Clerodane Carbon Skeleton

The proposed biosynthetic pathway leading to the clerodanes is depicted in Scheme 1. Starting from geranyl geranyl pyrophosphate (GGPP), cyclization to the labdane skeleton **2** starts off a cascade of methyl and hydride shifts leading to the *cis* and *trans* clerodanes. The *trans* clerodanes can arise *via* a concerted migration process to intermediate **3** whereas the *cis* clerodanes require that the migrations proceed in a stepwise manner, with a "pause" at intermediate **4**. Intermediate **4** can then lead either to the *trans*- or the *cis*- clerodanes depending



Scheme 1

upon which C-4 methyl group migrates. As depicted in Figure 2, the *cis*-clerodanes can be further categorized into the *cis*-normal- and *cis*-ent-clerodanes

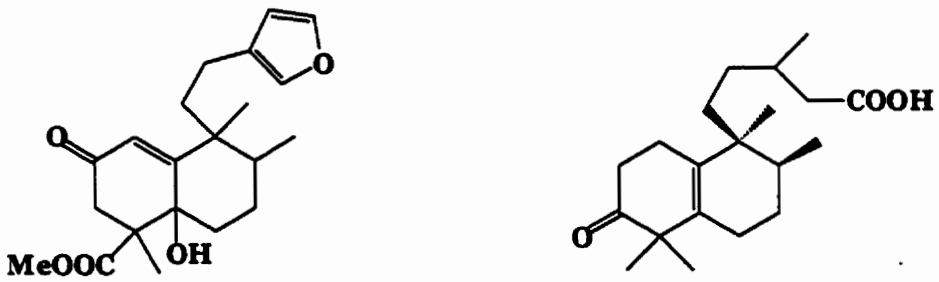


***cis*-normal** ***cis*-ent**

Figure 2. Conformational Structures of *cis*-Clerodanes

by virtue of the relative stereochemistry between the substituents on C-9 (clerodane numbering) and the ring junction.

The proposed biosynthetic pathway to the clerodanes is supported by the isolation and identification of the partially rearranged labdane compounds chettaphanin[3] (**5**) and salmantic acid[4] (**6**).

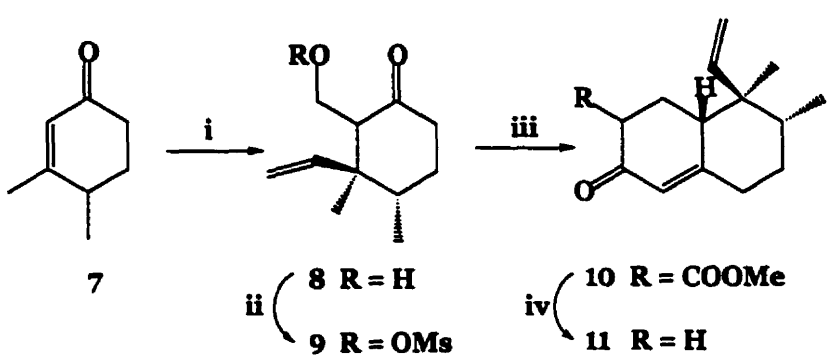


5 **6**

The clerodane natural products have been found to exhibit a wide variety of interesting biological activity. Although they are best known for their insect antifeedant properties[5], many are known to exhibit piscicidal[6], psychotropic[7], antibiotic[8], antiviral[9], antitumor[10], antiamoebic[11], antimicrobial[12], and anti-peptic ulcer[13] activities. In view of this broad array of biological activity and the structural complexity of the clerodanes, there have been numerous attempts

towards the synthesis of these natural products. Up to now, there have been less than thirty reported total syntheses[14-40] of clerodane natural products of which only seven have been directed towards the synthesis of *cis*-clerodanes[33-40]. This is most likely due to the lack of general approaches towards the construction of the *cis*-decalin carbon skeleton as compared to the *trans*-decalin system.

In 1983, Tokoroyama and co-workers achieved the first total synthesis of a *cis*-clerodane natural product, namely 15,16-epoxy-*cis*-cleroda-3,13(16),14-triene (**18**)[33,34]. The key intermediate in their synthesis was the octanone derivative **11** which was readily synthesized from 3,4-dimethyl-2-cyclohexen-1-one (Scheme 2). Their synthetic approach to *cis*-clerodane **18** started with a stereospecific

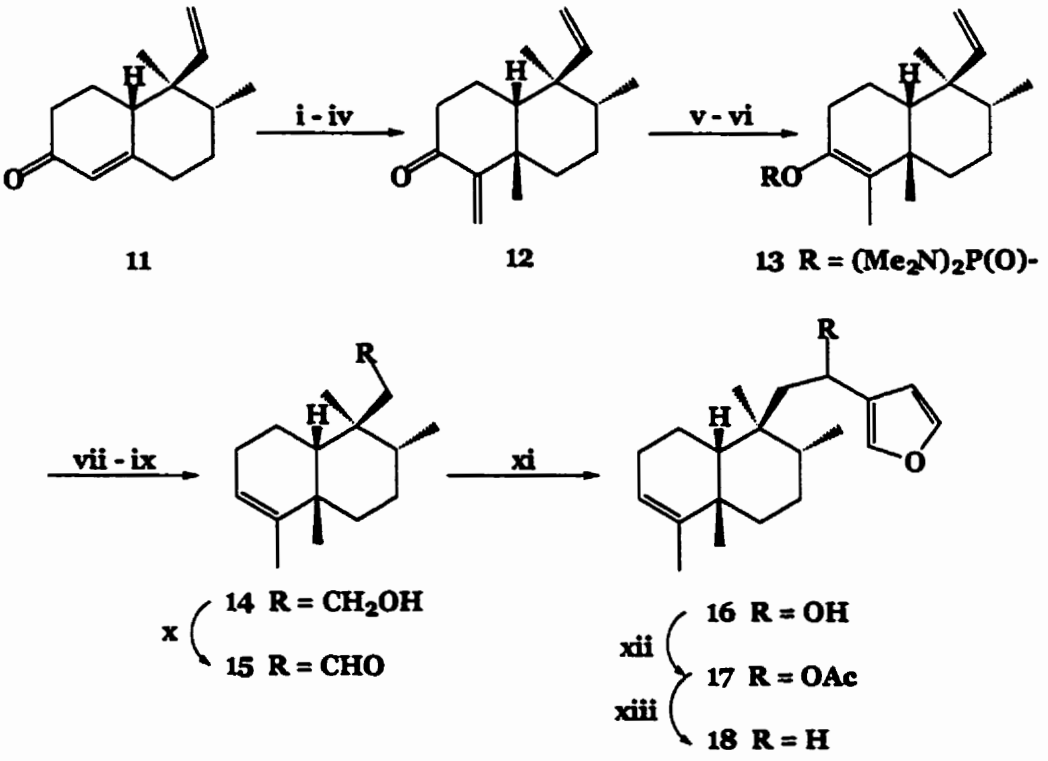


Scheme 2

Conditions: i. CH_2=CHMgBr·(nBu$_3$PCuI)$_4$, -70 to 0°C, 5 h; then HCHO; ii. MsCl, Et_3N, CH_2Cl_2, 0°C; iii. $CH_3C(O)CH_2COOCH_3$, $NaOCH_3$, CH_3OH-benzene, r.t., 15 h; then 40-50°C, 3 h; iv. 2 *M* HCl-CH_3OH, reflux, 7 h, 60% over 6 steps.

conjugate addition[41] to enone **7** and trapping of the ensuing enolate with formaldehyde to give keto alcohol **8** (Scheme 2). Derivatization of the hydroxy group as the mesylate followed by a one-pot Robinson annulation reaction gave the desired enone ester **10**. Acid promoted decarboxylation then gave bicyclic enone **11** in 60% yield over 6 steps. Their synthetic endeavor to target molecule

18 from enone **11** is depicted in Scheme 3 and began with a stereospecific conjugate addition[42] of lithium dimethylcuprate to the enone moiety followed by trapping of the ensuing enolate with formaldehyde gas. The β-hydroxy ketone thus produced in 46% yield was first treated with methanesulfonyl chloride and triethylamine in dichloromethane and then with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing tetrahydrofuran to give the α,β-unsaturated ketone **12**. Reduction of enone **12** followed by quenching of the resulting enolate with tetramethylphosphorodiamidic chloride gave bicyclic phosphorodiamidate **13**



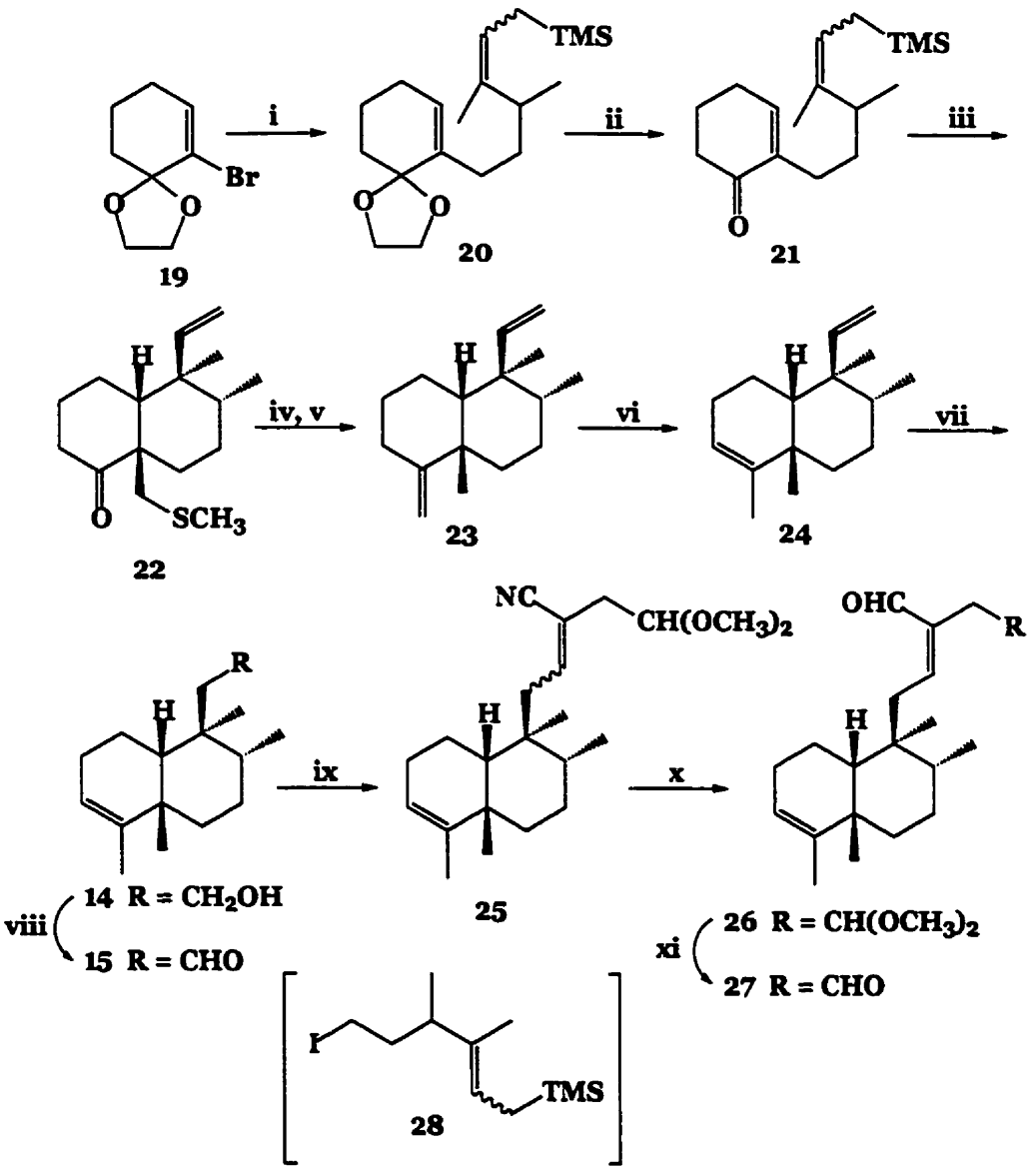
Scheme 3

Conditions: i. $(CH_3)_2CuLi$, Et_2O-pentane, -20°C, 2 h; ii. HCHO, 46% over 2 steps; iii. MsCl, Et_3N, CH_2Cl_2, 0°C; iv. DBU, THF, reflux, 80% over 2 steps; v. $LiB(CHMeEt)_3H$, THF, -78°C; vi. $(Me_2N)_2POCl$, Et_3N, THF-HMPA, 49% over 2 steps; vii. B_2H_6, THF, r.t., 7 h; viii. H_2O_2, NaOH ; ix. Li, $EtNH_2$, *t*-BuOH, 56% over 3 steps; x. Swern oxidation; xi. 3-furyllithium, Et_2O, -17 to -5°C; xii. Ac_2O, pyridine; xiii. Li, liq. NH_3, -78°C, 45% over 4 steps.

which was subjected to hydroboration/oxidation followed by dissolving metal reduction to give alcohol **14**. Swern oxidation of **14** then yielded aldehyde **15** which was then treated with 3-furyllithium to give furyl alcohol **16**. Acetylation followed by dissolving metal reduction of the resulting furyl acetate **17** then completed their synthesis of the target *cis*-clerodane natural product **18**.

In 1987 Tokoroyama and co-workers reported another approach to bicyclic alcohol **14** (Scheme 4) and used this revised approach to synthesize another *cis*-clerodane natural product, namely linaridial (**27**)[35]. Their approach to the key bicyclic alcohol **14** utilized the stereocontrolled cyclization of allyl silane **21** promoted by titanium(IV) chloride[43] followed by treatment of the enolate with chloromethylmethyl sulfide to give keto thioether **22**. Reductive desulfurization effected by Raney nickel, followed by Nozaki-Lombardo olefination[44] of the ketone carbonyl gave exocylic olefin **23** which was isomerized to endocyclic olefin **24** *via* Brown's method[45]. Selective hydroboration followed by basic peroxide workup resulted in the isolation of key intermediate **14** which was then oxidized as before to aldehyde **15**. Horner-Emmons condensation of aldehyde **15** with diethyl (1-cyano-3,3-dimethoxypropyl)phosphonate[46] then gave bicyclic olefin **25** as a mixture of stereoisomers. Reduction of the cyano functionality followed by acid promoted hydrolysis of the acetal then completed the synthesis.

Also in 1987, the same laboratory reported another total synthesis of *cis*-clerodane natural product **18** *via* a completely different route[36] (Scheme 5). Their new approach utilized the Diels-Alder cycloaddition reaction to set up the correct relative stereochemistry of C-8, C-9, and C-10 (clerodane numbering).

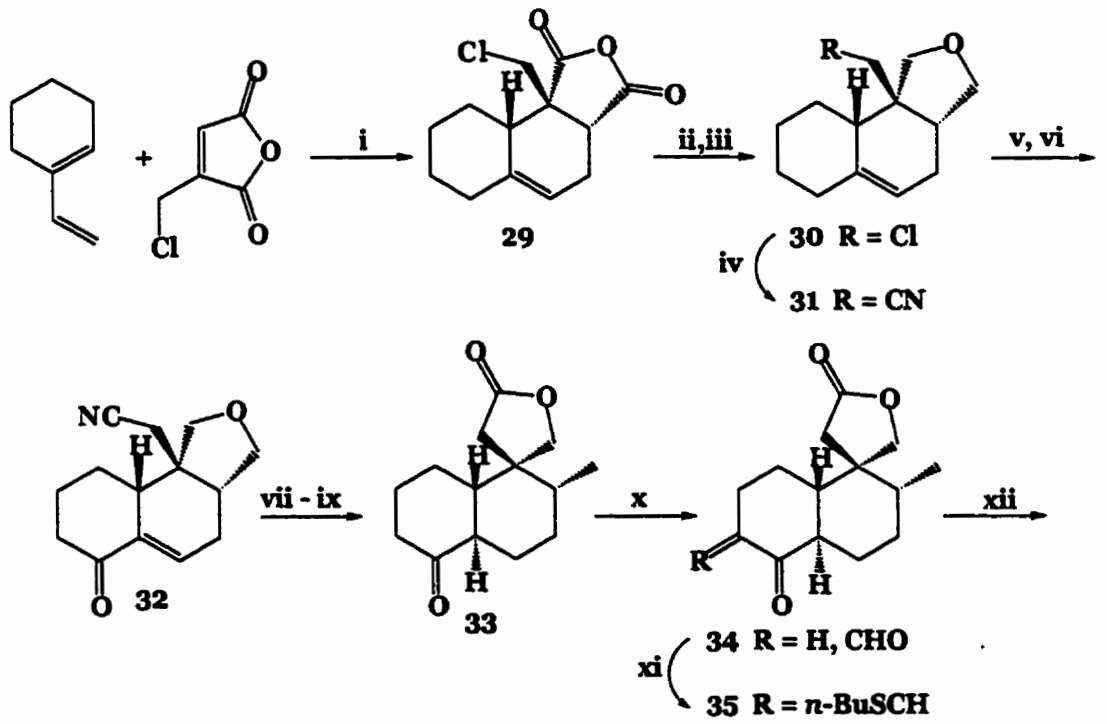


Scheme 4

Conditions: i. *n*-BuLi, HMPA, **28**; ii. H_3O^+; iii. $TiCl_4$, $ClCH_2SCH_3$, 0°C; iv. Ra-Ni, EtOH; v. CH_2Br_2, Zn, $TiCl_4$, THF; vi. $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$, r.t., 5 h; vii. $(CH_3)_2CH(CH_3)_2C\text{-}BH_2$, THF; then, H_2O_2, NaOH; viii. Swern oxidation; ix. diethyl (1-cyano-3,3-dimethoxypropyl)phosphonate, NaH, THF; x. DIBAL-H, Et_2AlCl, Et_2O-toluene, -78 to 40°C; xi. 1 *M* HCl, THF, 73% over 2 steps.

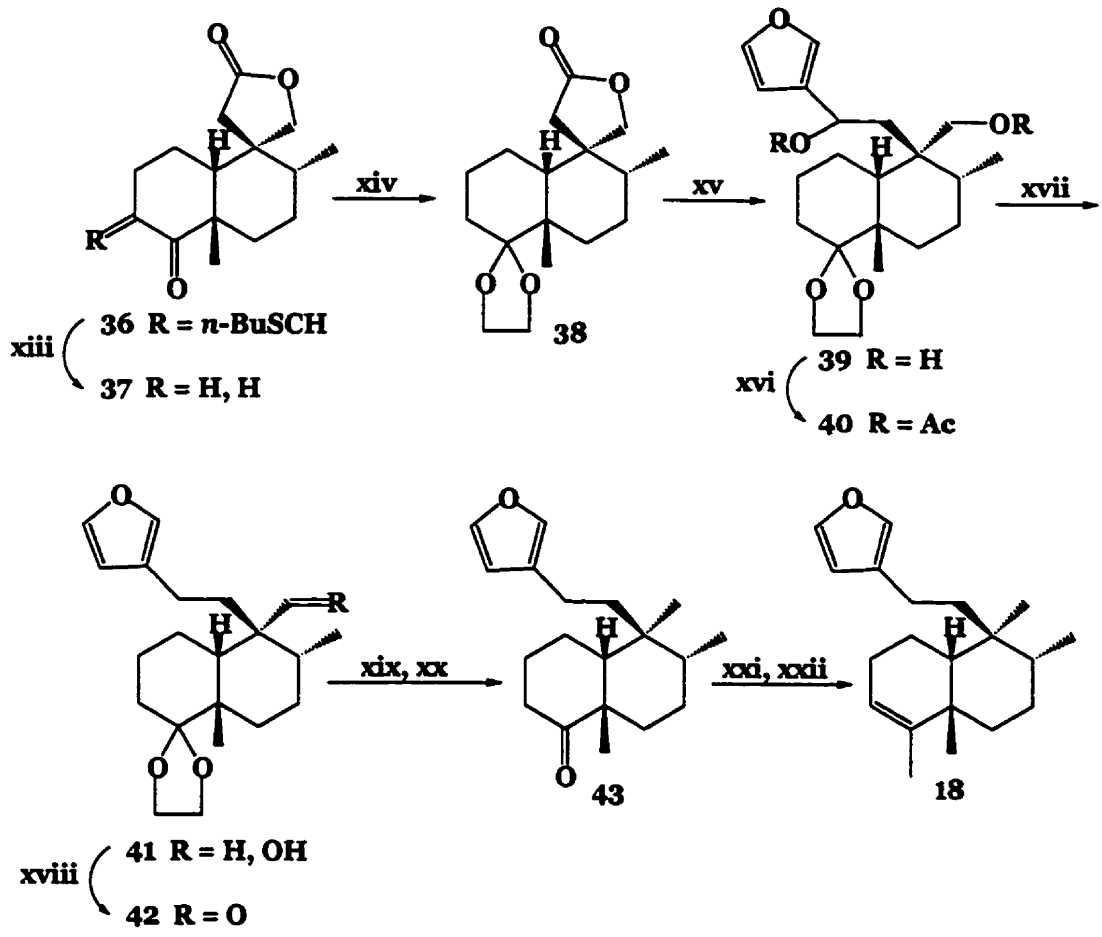
Thus, the Diels-Alder reaction between 1-vinylcyclohexene and (chloromethyl)-maleic anhydride gave cycloadduct **29** which was reduced by treatment with

lithium aluminum hydride. The resulting diol was then treated with a slight excess of *para*-toluenesulfonyl chloride to furnish tetrahydrofuran **30**. The halide was exchanged for the cyano functionality to give nitrile **31** which was oxidized by treatment with selenium dioxide. Manganese dioxide oxidation of the resulting allylic alcohol then gave enone **32**. Hydrogenation followed by ether ring opening with concomitant cyclization and hydrolysis then furnished lactone **33**. Formylation of lactone **33** followed by treatment with *n*-butylthiol resulted in the isolation of the methylene-protected ketone **35**. Alkylation of **35** using a



Scheme 5

Conditions: i. dioxane, sealed tube, 70°C, 23 h; ii. $LiAlH_4$, Et_2O, 92%; iii. TsCl, pyridine, 100%; iv. NaCN, NaI, DMSO, 120-125°C, 94%; v. SeO_2, py-H_2O, 80°C, 49%; vi. MnO_2, $CHCl_3$, r.t., 54%; vii. H_2, Pd-C, EtOH, 21 h, 93%; viii. 57% HI-H_2O, P, AcOH, 120-130°C, 4 h; ix. Zn, AcOH, r.t., 16 h, 79% over 2 steps; x. HCOOEt, NaH, C_6H_6, r.t., 3 h; xi. *n*BuSH, *p*-TSA, C_6H_6, reflux, -H_2O, 3 h, 82% over 2 steps; xii. CH_3I, *t*-$C_5H_{11}OK$, *t*-$C_5H_{11}OH$, r.t., 16 h, 74%;



Scheme 5 (cont.)

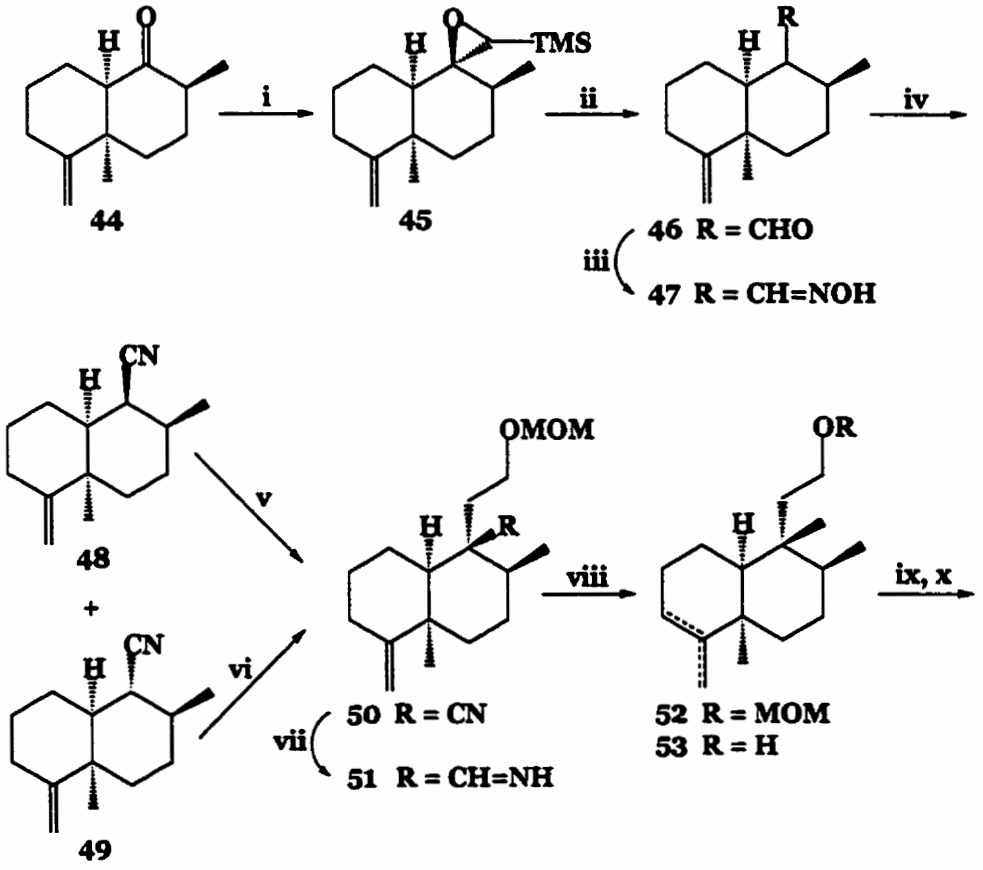
Conditions: xiii. KOH, $HOCH_2CH_2OH$, H_2O, reflux, 16 h, 68%; xiv. $HOCH_2CH_2OH$, *p*-TSA, C_6H_6, reflux, -H_2O, 3 h, 100%; xv. 3-furyllithium, Et_2O, -10°C, 40 min; then $NaAl(OCH_2CH_2OCH_3)_2H_2$, C_6H_6, 1 h, 94%; xvi. Ac_2O, py, 87%; xvii. Li, liq. NH_3, 94%; xviii. CrO_3·2py, CH_2Cl_2, 6 h, 92%; xix. Wolff-Kishner reduction, 54%; xx. 1 *M* HCl, 94%; xxi. CH_2Br_2, Zn, $TiCl_4$, CH_2Cl_2, 24 h, 62%; xxii. $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$, 91%.

large excess of base successfully installed the methyl group into the bridgehead position in a *cis* manner to give keto lactone **36**. Alkaline hydrolysis of keto lactone **36** followed by protection of the ketone carbonyl as the ethylene acetal gave lactone **38**. Lactone ring opening with 3-furyllithium followed by *in situ* reduction using sodium bis(2-methoxyethoxy)aluminum hydride then gave diol

39. Acetylation under standard conditions yielded diacetate **40** which was treated under dissolving metal reduction conditions to furnish alcohol **41**. Oxidation, Wolff-Kishner reduction, and deprotection then gave furyl ketone **43** which was olefinated under Nozaki-Lombardo[44] olefination conditions. Finally, olefin isomerization using Brown's method[45] achieved the total synthesis of **18**.

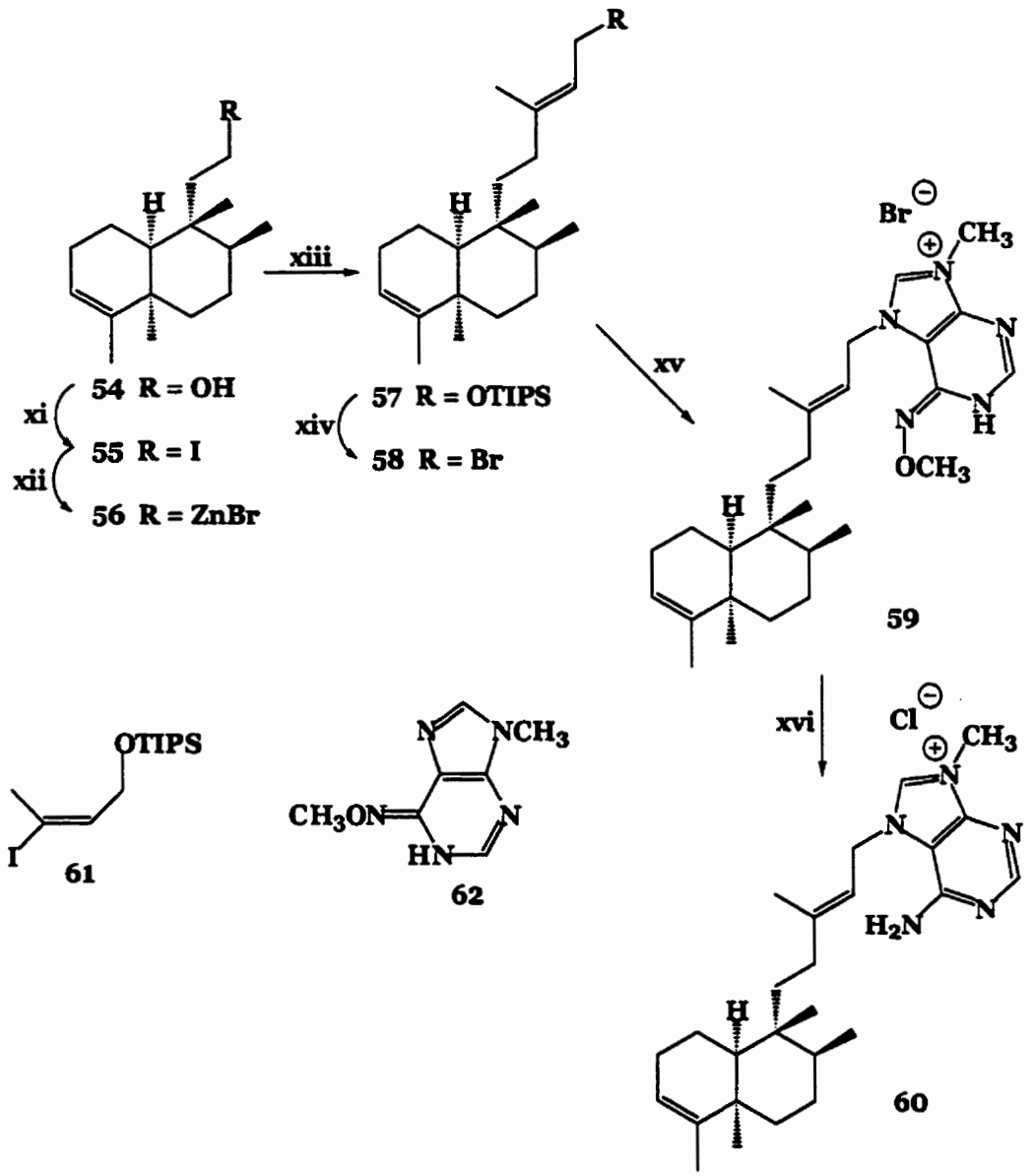
In 1991, Piers and Roberge reported the synthesis, in enantiomerically pure form, of *cis*-bicyclic ketone **44**[47]. This work culminated in the total synthesis of a *cis*-clerodane natural product, (-)-agelasine A (**60**), which was published in 1995 (Scheme 6)[37]. As such, treatment of ketone **44** with the lithium salt of (dichloromethyl)trimethylsilane[48] resulted in the formation of epoxide **45**. Boron trifluoride etherate mediated rearrangement followed by hydroxylamine treatment then gave oxime **47**. Dehydration of oxime **47** by treatment with thionyl chloride and 4-(dimethylamino)pyridine gave bicyclic nitriles **48** and **49**. Deprotonation (lithium diisopropylamide for nitrile **48** and potassium diisopropylamide for nitrile **49**) followed by alkylation with 1-iodo-2-(methoxymethoxy)ethane then furnished nitrile **50**. DIBAL-H reduction of the cyano moiety followed by Wolff-Kishner reduction resulted in the isolation of a mixture consisting of isomeric MOM ethers **52** and isomeric alcohols **53**. This mixture was treated with pyridinium *para*-toluenesulfonate in *tert*-butyl alcohol (to hydrolyse the MOM ether) and then with anhydrous *para*-toluenesulfonic acid in chloroform (to isomerize the olefin) to give alcohol **54**. Iodination under standard condition furnished iodide **55** which was subjected to lithium-iodine exchange followed by transmetallation with zinc bromide. Organozinc compound **56** was then cross coupled with vinyl iodide **61** to furnish silyl ether **57**. Treating silyl ether **57** with triphenylphosphine dibromide in dichloromethane yielded bicyclic bromide **58**. Ammonium bromide salt **59** was then synthesized by

treatment of bicyclic bromide **58** with adenine derivative **62** in the presence of tetrabutylammonium iodide. In a paper describing a total synthesis of (-)-agelasine B, the reductive removal of the methoxy moiety was achieved by electrochemical means[49], however, the authors opted to achieve the desired reduction using zinc in glacial acetic acid. Subsequent anion exchange followed by chromatographic purification then furnished *cis*-clerodane natural product (-)-agelasine A (**60**).



Scheme 6

Conditions: i. $[(CH_3)_3Si(Cl)CH]Li$, THF, TMEDA, 94%; ii. $BF_3{\cdot}OEt_2$, CH_2Cl_2; then CH_3OH, dil. HCl, 84%; iii. $H_2NOH{\cdot}HCl$, pyridine, DMF, 98%; iv. $SOCl_2$, DMAP, CH_2Cl_2, 95%; v. LDA, THF, HMPA, ICH_2CH_2OMOM, 79%; vi. KDA, THF, ICH_2CH_2OMOM, 93%; vii. DIBAL-H, DME; viii. H_2NNH_2, DEG, 120-140°C; then KOH, DEG, 220-230°C, 61% from **50**; ix. PPTS, *t*-BuOH, 84%; x. *p*-TSA, $CHCl_3$, 91%.

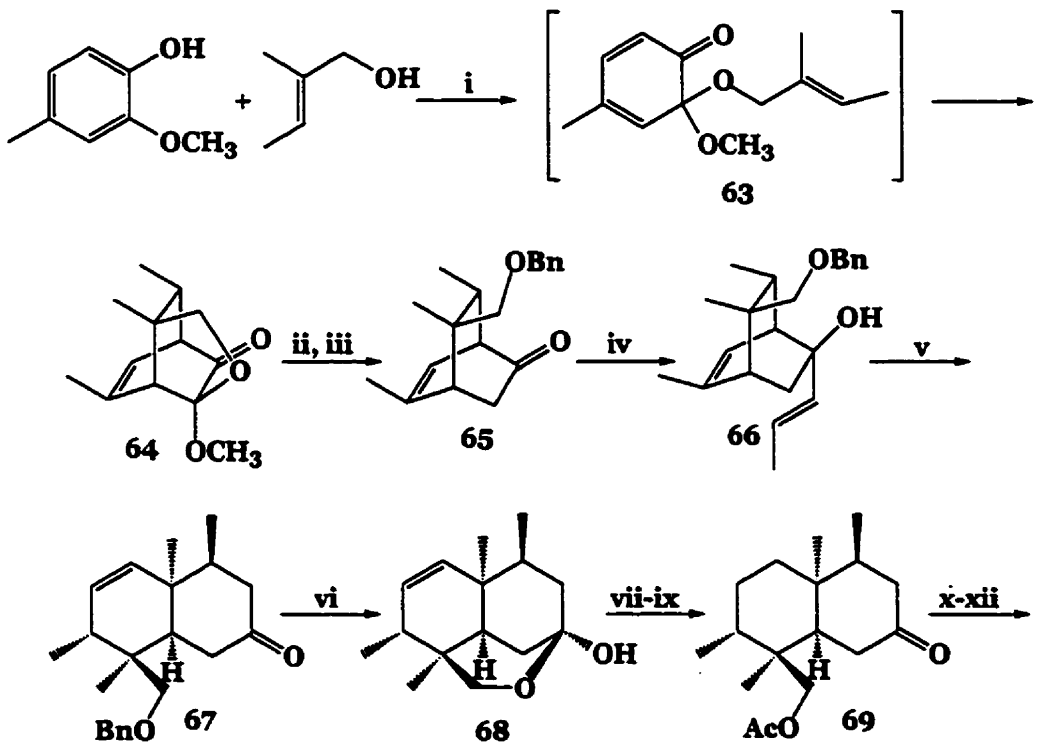


Scheme 6 (cont.)

Conditions: xi. Ph_3P, I_2, imidazole, CH_2Cl_2, 97%; xii. *t*-BuLi, Et_2O; then $ZnBr_2$, THF-Et_2O; xiii. **61**, $Pd_2(dba)_3$, Ph_3As, THF-Et_2O, 73%; xiv. Ph_3PBr_2, CH_2Cl_2; xv. **62**, Bu_4NI, DMA, 47% from **57**; xvi. Zn, HOAc, CH_3OH, H_2O; then, NaCl, H_2O, 88%.

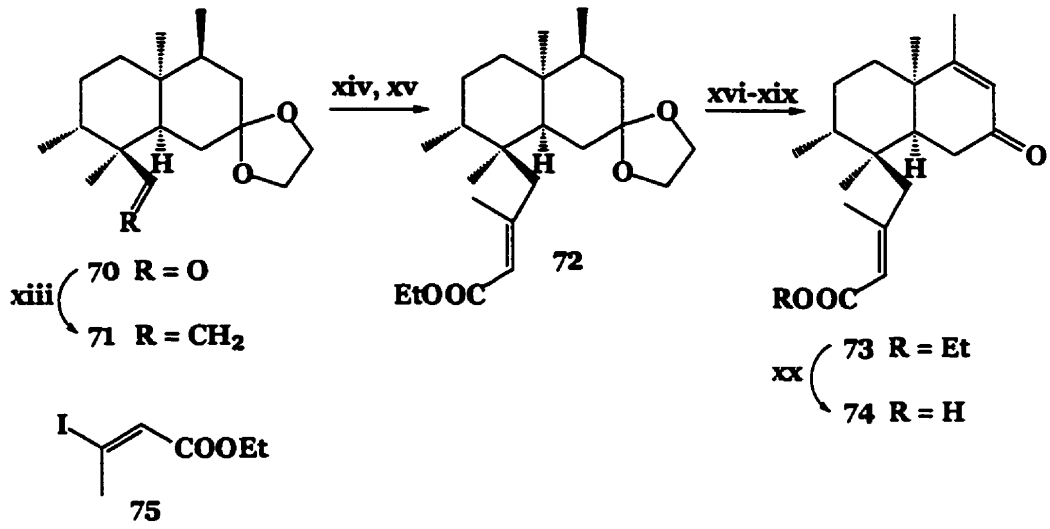
In 1996, Liao and co-workers published a new approach to establish the key bicyclic core of the *cis*-clerodane system based on an anionic oxy-Cope rearrangement reaction[50]. This newly developed methodology led them to

synthesize (±)-(13*E*)-2-oxo-5α-*cis*-17α,20α-cleroda-3,13-dien-15-oic acid (**74**), a compound bearing all the characteristics of a *cis*-clerodane diterpene[38]. Their synthesis began with the oxidation of 2-methoxy-4-methylphenol with iodobenzene diacetate in the presence of *trans*-2-methyl-2-buten-1-ol (Scheme 7) to form keto acetal **63** which undergoes an intramolecular Diels-Alder cycloaddition reaction to furnish tricyclic keto acetal **64**. Reduction of keto acetal **64** with samarium diiodide followed by benzylation of the neopentyl alcohol thus formed resulted in the formation of bicyclic ketone **65**. Upon exposure to *trans*-1-lithiopropene, 1,2-adduct **66** was isolated in 82% yield along with a 6% yield of



Scheme 7

Conditions: i. $PhI(OAc)_2$, $NaHCO_3$, CH_2Cl_2, 50%; ii. SmI_2, THF, CH_3OH, 89%; iii. NaH, BnBr, Bu_4NI, THF, 92%; iv. 1-Bromopropene, *t*-BuLi, $MgBr_2$, THF, 82%; v. KH, 18-cr-6, 1,4-dioxane, 110°C, 83%; vi. H_2, Pd/C, HOAc; vii. Ac_2O, pyridine, DMAP; viii. H_2, PtO_2, HOAc; ix. Jones oxidation, 78% from **67**; x. $TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, 83%; xi. KOH, CH_3OH, 96%; xii. PDC, CH_2Cl_2, 88%;



Scheme 7 (cont.)

Conditions: xiii. $Ph_3P{=}CH_2$, 93%; xiv. 9-BBN-H, THF; xv. **75**, Cs_2CO_3, $PdCl_2(dppf)$, Ph_3As, H_2O, THF, DMF, 65% over 2 steps; xvi. 10% HCl; xvii. LDA, TMSCl; xviii. $PhN(CH_3)_3Br_3$; xix. LiBr, Li_2CO_3, DMF, 68% from **72**; xx. KOH, 98%.

the epimeric alcohol. Alcohol **66** was then treated with potassium hydride and 18-crown-6 to effect the oxy-Cope rearrangement reaction to furnish bicyclic ketone **67**. Debenzylation of ketone **67** resulted in the isolation of hemiacetal **68** which was acetylated, hydrogenated, and oxidized to give keto acetate **69**. Protection of the ketone carbonyl as the ethylene acetal using Noyori's condition[51] followed by hydrolysis of the acetate and subsequent oxidation gave aldehyde **70**. Aldehyde **70** was then olefinated under Wittig conditions to furnish acetal **71**. Hydroboration followed by palladium catalyzed cross coupling of the resulting organoborane with vinyl iodide **75** then gave α,β-unsaturated ester **72**. Hydrolysis of the ethylene acetal followed by the installation of the α,β-unsaturation *via* the bromide resulted in the isolation of bicyclic enone **73** which was converted to the target carboxylic acid by treatment with potassium hydroxide.

All the synthetic endeavors described to this point had target molecules bearing the *cis*-ent clerodane skeleton as depicted in Figure 2. The first synthetic approach towards the *cis*-normal clerodane skeleton was published in 1995 by our research group[39]. It was reasoned that an intermolecular Diels-Alder reaction between the doubly activated dienophile of the type depicted in Figure 3 with a suitably functionalized diene would facilitate the rapid construction of the *cis*-decalin core found in *cis*-clerodane natural products. By suitable choice of substituents in the dienophile, it was envisioned that the C-5, C-9, and C-10 (clerodane numbering) stereocenters of the *cis*-normal clerodanes will be established by facial selectivity based on steric differentiation. The last

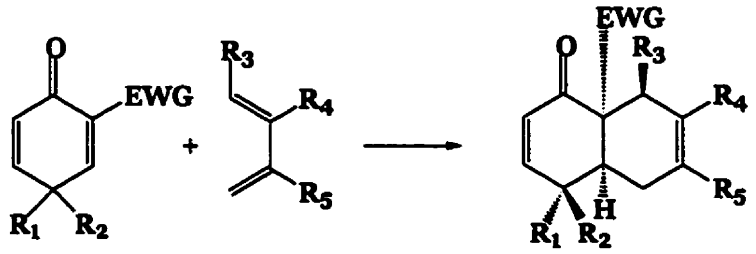
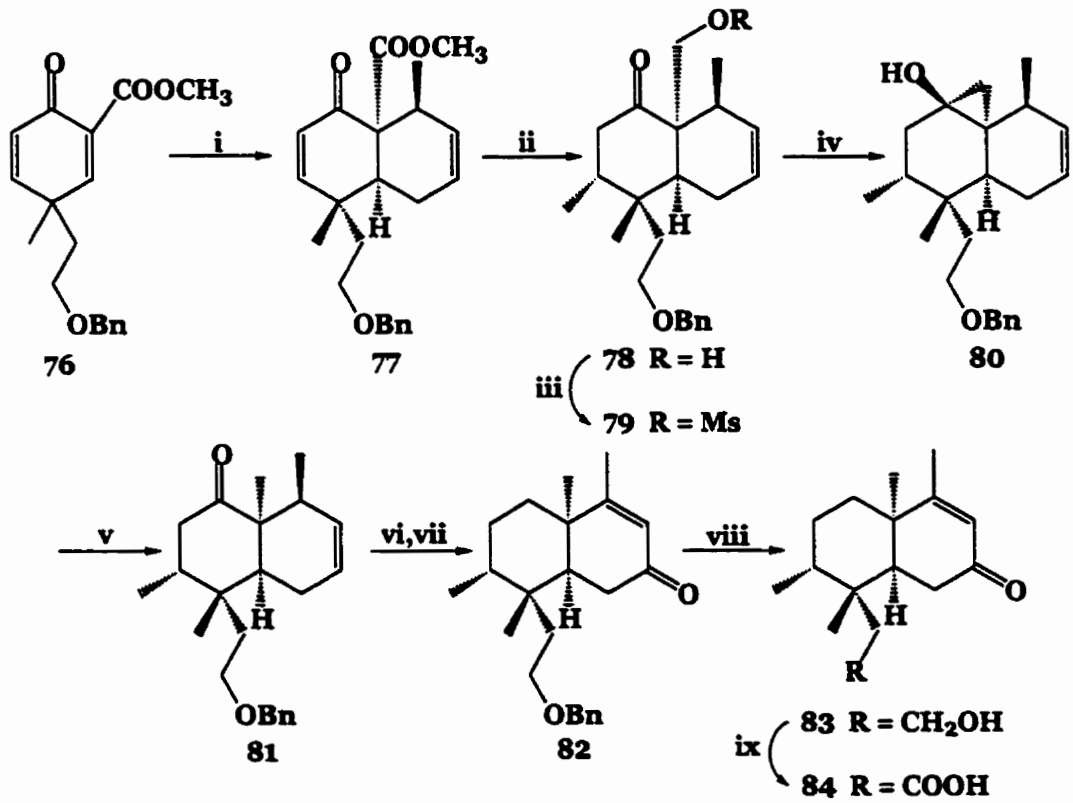


Figure 3. Conceptual Intermolecular Diels-Alder Approach to *cis*-Normal Clerodanes

stereocenter, C-8, will then be installed subsequently *via* a dimethyl cuprate 1,4-addition reaction. This approach has culminated in the total synthesis, in racemic form, of two *cis*-normal clerodane natural products, namely 2-oxo-5α,8α-12,14,15,16-tetranorclerod-3-en-12-oic acid[39] (Scheme 8, **84**) and 6β-acetoxy-2-oxokolavenool[40] (Scheme 9, **90**). The synthetic endeavor for both begins with an intermolecular Diels-Alder reaction between dienone **76** and *trans*-piperylene under zinc(II) chloride catalysis to form a mixture of diastereomeric cycloadducts in a 6:1 ratio with the desired cycloadduct **77** being the major adduct. Treating Diels-Alder adduct **77** with lithium dimethylcuprate

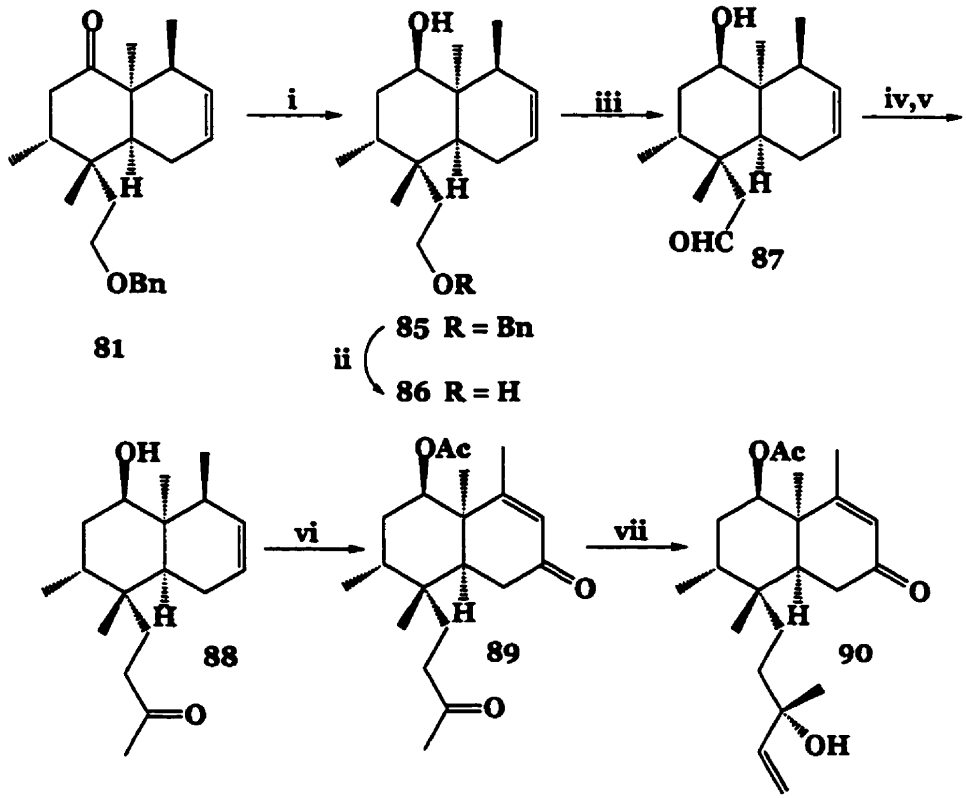
followed by reduction of the ensuing enolate with lithium aluminum hydride then furnished keto alcohol **78**. Derivatization of the hydroxy group to the mesylate under standard conditions followed by zinc mediated reduction of the mesylate then yielded cyclopropyl alcohol **80**. Bicyclic ketone **81** was then synthesized by treating cyclopropyl alcohol **80** with *para*-toluenesulfonic acid. Wolff-Kishner reduction of the ketone carbonyl followed by photooxygenation of the resulting bicyclic olefin then furnished enone **82**. Finally, debenzylation with ferric chloride gave alcohol **83** which was oxidized to the target carboxylic acid **84** by Jones' reagent.



Scheme 8

Conditions: i. *trans*-piperylene, $ZnCl_2$, Et_2O, 85%; ii. $(CH_3)_2CuLi$, Et_2O; then $LiAlH_4$, 62%; iii. MsCl, Et_3N, THF, 98%; iv. NaI, Zn, DMF, 55%; v. *p*-TSA, CH_2Cl_2, 97%; vi. Wolff-Kishner reduction, 45%; vii. TPP, Ac_2O, DMAP, O_2, pyridine, CCl_4, hv, 56%; viii. $FeCl_3$, CH_2Cl_2, 82%; ix. Jones oxidation, 63%.

The total synthesis of 6β-acetoxy-2-oxokolavenool (Scheme 9, **90**) began with bicyclic ketone intermediate **81**. Reduction of **81** with lithium aluminum hydride resulted in the isolation of alcohol **85** which was debenzylated with lithium naphthalenide[52] to furnish diol **86**. Oxidation of the primary hydroxyl functionality in preference to the secondary hydroxy group was achieved by treatment with dichlorotris(triphenylphosphine)ruthenium(II) in benzene[53]. Hydroxy aldehyde **87** thus obtained was treated with the ylide resulting from the



Scheme 9

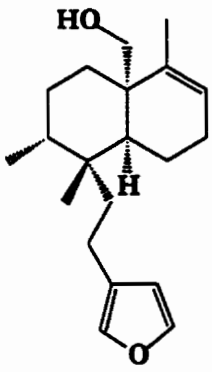
Conditions: i. $LiAlH_4$, THF, 95%; ii. Lithium naphthalenide, THF, 94%; iii. $(Ph_3P)_3RuCl_2$, C_6H_6, 90%; iv. $Ph_3P{=}C(CH_3)OCH_3$, THF; v. 20% $HClO_4$, Et_2O, 65% from **96**; vi. TPP, Ac_2O, DMAP, O_2, pyridine, CCl_4, hv, 61%; vii. $CH_2{=}CHMgBr$, THF, 66% (1:1 mixture of epimers).

reaction between α-methoxyethyltriphenylphosphonium chloride and *n*-butyllithium to give an unstable enol ether which was hydrolyzed by the action of 20% perchloric acid in diethyl ether to yield hydroxy ketone **88**. Photooxygenation of hydroxy ketone **88** gave enone **89** which was then treated with vinylmagnesium bromide to complete the synthesis.

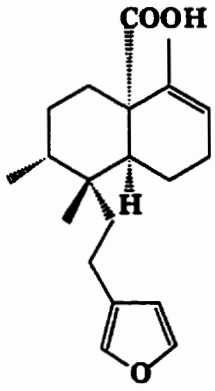
As can be seen from Schemes 8 and 9, the intermolecular Diels-Alder approach developed in our laboratories constitutes a highly flexible approach towards the vast number of *cis*-normal clerodanes isolated thus far[2]. Apart from *cis*-normal clerodanes containing an α-methyl group in the C-5 (clerodane numbering) position, our general approach, by virtue of the ester group present in the adduct **77**, was also envisioned to be amenable towards the total synthesis of *cis*-normal clerodanes containing oxygenated functionalities on the C-19 (clerodane numbering) carbon. This would greatly broaden the generality of our approach and further bolster our claim to have a truly general scheme into the *cis*-normal clerodane series of natural products. In order to substantiate this claim, we chose the *cis*-normal clerodane natural product solidago alcohol (**91**) as the total synthesis target.

In 1972 McCrindle and co-workers investigated the ethyl acetate extracts of the roots of *Solidago gigantea* Ait. var. *serotina* (Kuntze) Cronqu. and identified solidago alcohol as a constituent of the neutral fractions thereof[54]. The structure of solidago alcohol was identified primarily on spectroscopic comparison of the lithium aluminum hydride reduction product of the methyl ester of solidagoic acid A (**92**) with that of the natural product[55]. The structure of solidagoic acid A was identified unequivocably by the same authors based on spectroscopic

evidence of the natural product itself along with that of several simple derivatives[55].

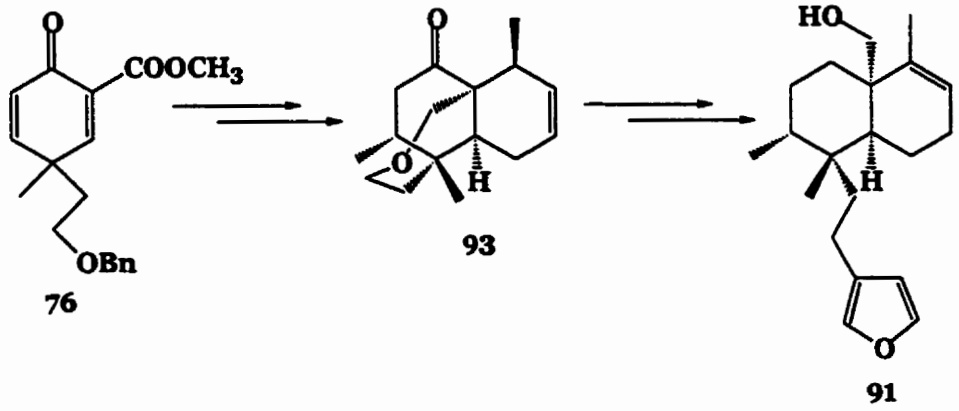


91



92

Our synthetic strategy is as depicted in Scheme 10. In the synthesis of 2-oxo-5α,8α-12,14,15,16-tetranorclerod-3-en-12-oic acid (**84**) and 6β-acetoxy-2-oxokolavenool (**90**) described above, the by-product of the zinc mediated reduction of mesylate **79** was identified to be tricyclic keto ether **93**. It

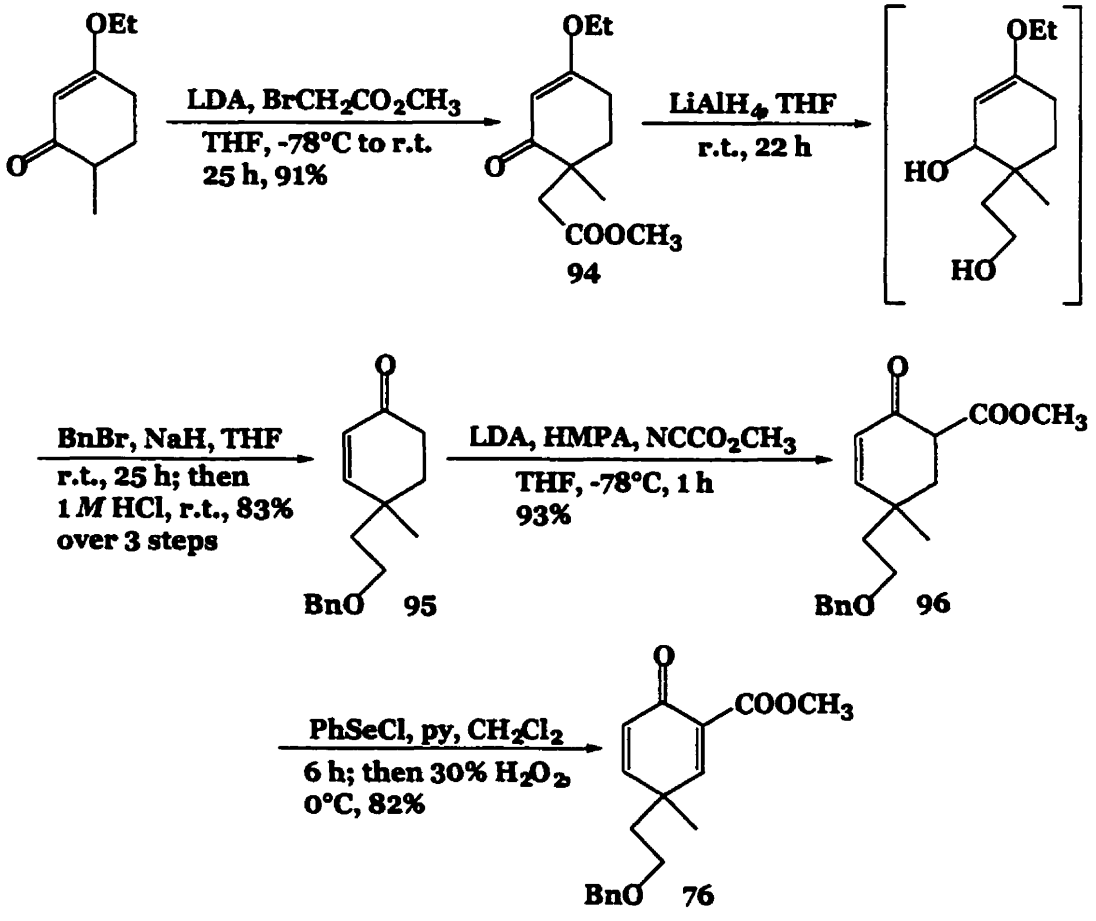


Scheme 10

was envisioned that this compound will be well-suited as the key intermediate for the subsequent transformations needed to achieve the synthesis of solidago

alcohol (**91**). The ether linkage may serve as a robust protecting group under Wolff-Kishner reduction conditions and also as a masked angular hydroxymethyl group and a haloethyl group which may be realized upon ether ring cleavage. As such, the problems that needed to be tackled include the synthesis of tricyclic keto ether **93** in a high yielding manner and its subsequent deoxygenation, regioselective ether cleavage, functional group manipulation to install the required functionalities, and olefin isomerization to the more stable tri-substituted position. Our efforts towards this end are described in detail in the following section.

In the synthesis of 2-oxo-5α,8α-12,14,15,16-tetranorclerod-3-en-12-oic acid (**84**)[39] and 6β-acetoxy-2-oxokolavenool (**90**)[40], the synthetic route employed to furnish dienophile **76** is depicted in Scheme 11. In our synthetic endeavor



Scheme 11

towards dienophile **76**, we utilized this well documented synthetic scheme with some minor modifications. As such, Stork-Danheiser alkylation[56] of 3-ethoxy-6-methyl-2-cyclohexen-1-one with methyl bromoacetate gave enone ester **94** in 92% yield after vacuum distillation (152-154°C/0.8 mm Hg). The IR spectrum of

the product showed carbonyl absorptions at 1737 (ester carbonyl) and 1654 cm^{-1} (enone carbonyl). This was confirmed in the carbon APT spectrum with two in-phase resonances at δ 200.2 and 175.8. The proton NMR spectrum indicated the presence of the methyl acetate group with a singlet at δ 3.63, attributed to the carbomethoxy methyl group, and two doublets, δ 2.78 and 2.37 (J = 16 Hz), due to the methylene protons adjacent to the carbomethoxy carbonyl group. The high resolution mass spectrum of the product contained an ion peak at 226.1200, corresponding to the molecular formula of $C_{12}H_{18}O_4$.

Reduction of enone ester **94** to give the corresponding diol was then achieved by treatment with lithium aluminum hydride in tetrahydrofuran. Since the desired diol was quite unstable, it was subjected to benzylation conditions immediately after workup and vigorous drying. Thus, to a suspension of sodium hydride in tetrahydrofuran was added a tetrahydrofuran solution of the above crude diol followed by benzyl bromide. The reaction was monitored by TLC and when no more starting material was evident, the reaction mixture was quenched with 2.48 *N* hydrochloric acid to both destroy excess sodium hydride and effect the subsequent hydrolysis of the enol ether. In this fashion, the desired benzyloxy enone **95** was isolated in 77% over three steps after vacuum distillation (150°C/0.4 mm Hg). The IR spectrum indicated the success of the reduction/hydrolysis process by the presence of only one carbonyl absorption at 1680 cm^{-1} which was attributed to the enone carbonyl. This was confirmed by the carbon APT spectrum which contained only one in-phase resonance in the carbonyl region (δ 199.3). The proton NMR spectrum showed the olefinic protons of the enone moiety as a pair of doublets (J = 10 Hz), one at δ 6.75 and the other at δ 5.88. The benzylation was also deemed a success by the presence of aromatic proton resonances in the proton NMR spectrum as well as the presence

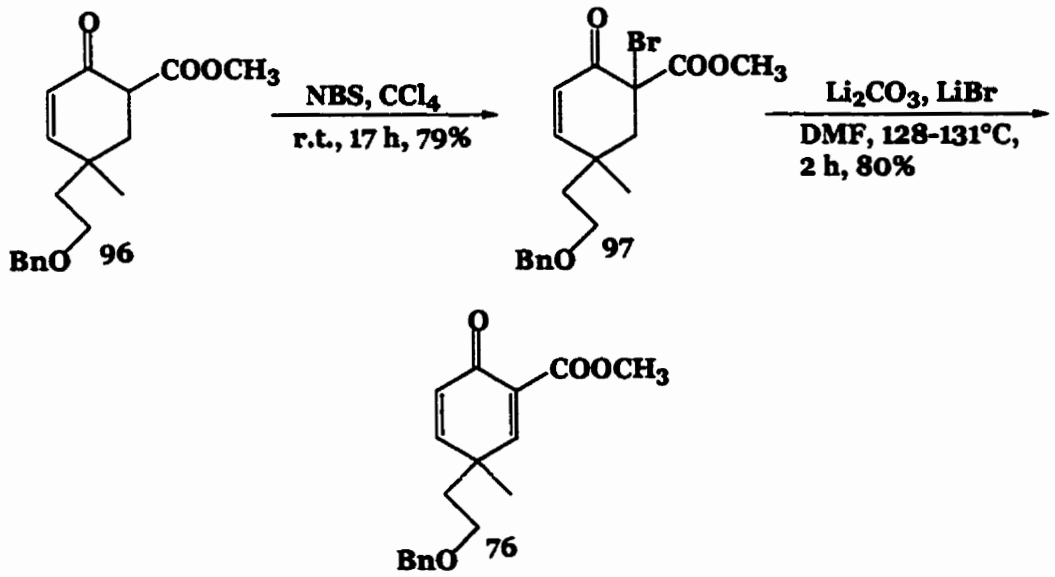
of aromatic carbon resonances in the carbon APT spectrum. The benzylic methylene protons were found to resonate at δ 4.50 as a sharp singlet. The high resolution mass spectrum showed an ion peak at 244.1459 indicative of the desired molecular formula of $C_{16}H_{20}O_2$.

The next transformation required was to install the carbomethoxy group. As indicated in Scheme 11, the desired transformation was previously achieved in our research group by acylation of enone **95** with methyl cyanoformate in the presence of lithium diisopropylamide (LDA) and hexamethylphosphoramide (HMPA). In view of the extreme toxicity of HMPA and methyl cyanoformate, it was deemed advantageous if the carbomethoxylation can be achieved without the use of these toxic reagents. It was reported that the desired reaction can be achieved in 54% yield by treating a refluxing suspension containing sodium hydride and dimethyl carbonate in tetrahydrofuran with a tetrahydrofuran solution of enone **95**[57]. This was repeated and confirmed to be the case. Gratifyingly, after much experimentation, it was found that if the reaction was performed in neat dimethyl carbonate, the yield of the desired β-keto ester **96** could be increased dramatically to 84%. Although the yield was not as high as that achieved by the original procedure, the elimination of the use of HMPA and methyl cyanoformate coupled with the ease of manipulation led us to accept this slight loss in yield. As such, by treating a refluxing suspension of sodium hydride in dimethyl carbonate with a dimethyl carbonate solution of enone **95** gave, after purification, the desired β-keto ester **96** in 84% yield. β-Keto ester **96** was found to exist as a mixture of 3 isomers (a pair of diastereomers and an enol ester) in a respective ratio of 0.3:0.2:0.5 as indicated by the proton NMR spectrum. Even though the characteristic absorption band of an hydroxy group was too weak to be observed in the IR spectrum, the existence of a resonance at δ 11.88 in the

proton NMR spectrum was indicative of the enol tautomer. The enone carbonyl was found to stretch at 1681 cm^{-1} whereas the ester carbonyl was found to stretch at 1744 cm^{-1}. The high resolution mass spectrum contained an ion peak at 302.1515 corresponding to the desired molecular formula of $C_{18}H_{22}O_4$.

With β-keto ester **96** in hand, we briefly investigate the dehydrogenation process. As indicated in Scheme 11, the desired transformation was performed *via* the selenoxide elimination method. Again, due to the toxic nature of selenium reagents, it would be beneficial if an alternate route could be undertaken. The first route investigated was the bromination-dehydrobromination[58] sequence of reactions as depicted in Scheme 12.

As such, a solution of β-keto ester **96** in carbon tetrachloride was treated with *N*-bromosuccinimide (NBS) and the reaction was protected from light. After 17 hours, the reaction mixture was filtered and the desired bromo keto ester **97** was



Scheme 12

isolated in 79% yield after chromatographic purification. The proton NMR spectrum of the purified product was much "cleaner" as compared to the starting enone ester **96**. The disappearance of the enol resonance indicated that the bromination reaction proceeded as expected. Since a high resolution mass spectrum did not show the presence of any ion peaks corresponding to that of the desired molecular formula, a low resolution FAB-MS was performed. Gratifyingly, in the low resolution FAB-MS spectrum, two peaks with almost equal intensities were found at 381.2 and 383.2 corresponding to the ^{79}Br and ^{81}Br isotopic molecules for the desired molecular formula of $C_{18}H_{21}O_3Br$.

The subsequent dehydrobromination reaction of bromo keto ester **97** was initially attempted with tertiary amine bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO). However, the yields of the dehydrobromination product **76** were only achieved in the low 50% range for a variety of conditions tried. This led us to attempt the dehydrobromination as reviewed by Schlosser[59]. Thus a solution of bromo keto ester **97** in anhydrous *N,N*-dimethylformamide was treated with lithium bromide and lithium carbonate. The ensuing suspension was stirred at room temperature to complete dissolution before warming to 123-131°C. After dilute acidic workup and chromatographic purification, the desired dienone ester **76** was isolated in 80% yield. The appearance of absorptions at 1741 and 1664 cm^{-1} indicated the survival of the ester and ketone functionalities respectively. This was confirmed from the carbon APT spectrum with the observance of two in-phase resonances at δ 181.6 (ketone carbonyl) and 165.0 (ester carbonyl). The dehydrobromination was confirmed to be successful by the proton NMR spectrum with the presence of a doublet at δ 7.59 (J = 3 Hz) along with the other two enone protons at δ 6.79 (dd, J = 10, 3 Hz) and 6.29 (d, J = 10 Hz). The

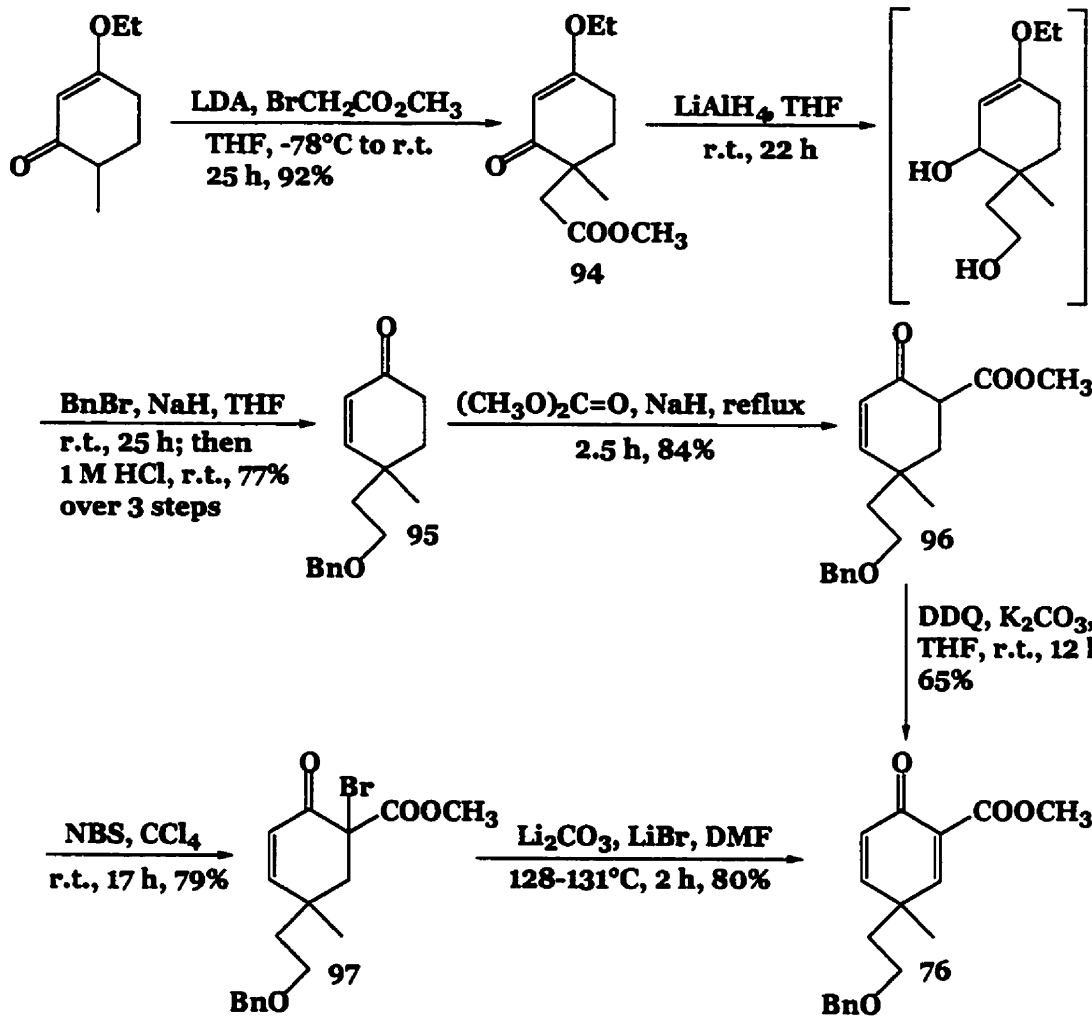
benzylic methylene protons appeared as a sharp singlet at δ 4.35 and the carbomethoxy methyl group was found to resonate as a sharp singlet at δ 3.80. The remaining methyl group adjacent to the quaternary center was observed at δ 1.32 also as a sharp singlet. Unfortunately, at the field strength of the NMR machine (200 MHz), the remaining protons of the benzyloxy ethyl side chain were not resolved but appeared as two complex second order multiplets centered about δ 3.34 (2 H, -CH_2-CH_2-OBn) and 2.04 (2 H, -CH_2-CH_2-OBn). The high resolution mass spectrum contained an ion peak at 300.1353 corresponding to the desired molecular formula of $C_{18}H_{20}O_4$.

It is known in the literature that dehydrogenation of cyclic ketones to their α,β-unsaturated counterparts may be induced by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[60]. It was anticipated that keto ester **96** may be amenable to such a reaction since there were precedents at the time from our research group that the DDQ dehydrogenation reactions of similar substrates were successful. However, under various standard conditions, the dehydrogenation of keto ester **96** with DDQ gave a complex mixture of products of which the desired dienophile **76** was isolated in poor yields. Presumably, the acidic hydroquinone by-product was causing problems. There are literature precedents whereby the addition of a base to remove the hydroquinone by-product from the medium led to improved yields of the desired α,β-unsaturated ketones[61] and so we attempted the DDQ dehydrogenation reaction in the presence of added potassium carbonate. Gratifyingly, after stirring a mixture containing DDQ, potassium carbonate, and keto ester **96** in tetrahydrofuran at room temperature for 12 hours, the desired dienophile **76** was isolated as a light yellow oil in 65% yield. This compared favorably to the bromination/dehydrobromination series of reactions which had a combined yield

of 63%. It was also fortuitously discovered that the dehydrogenation reaction may be carried out without prior purification of keto ester **96** without loss of yield. The success of the DDQ dehydrogenation reaction was viewed as an improvement upon the alternative bromination/dehydrobromination series of reactions since it reduced the number of synthetic steps by one and also removes the need to use carbon tetrachloride which has been deemed environmentally harmful enough to not be commercially available in many localities.

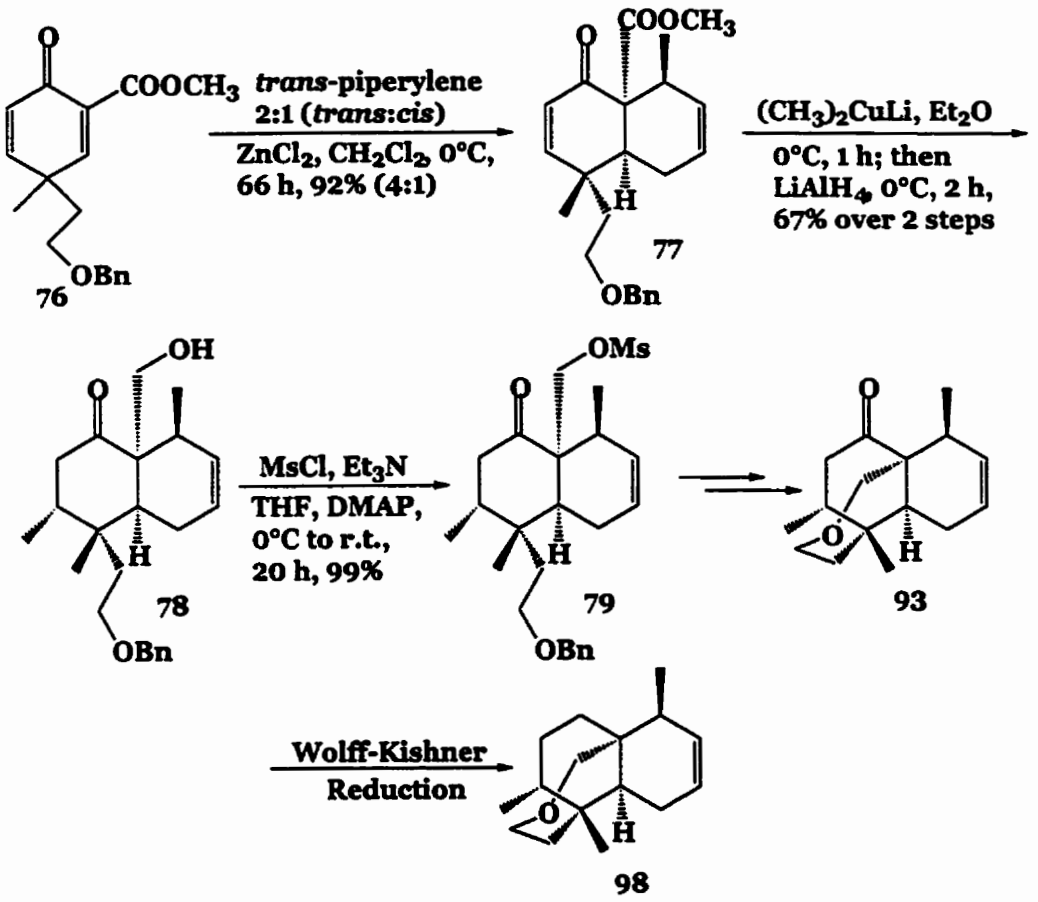
A summary of our revised approach to dienophile **76** is depicted in Scheme 13. Compared to the established sequence of reactions depicted in Scheme 11 which achieved the synthesis of dienophile **76** in 58% overall yield, our modified approach furnished the target dienophile **76** in a somewhat lower overall yield of 39%. However, we have removed one chromatographic step and also negated the need of some highly toxic and potentially harmful reagents and solvents. These two points were deemed sufficient enough to justify the reduction in overall yield, especially in large scale preparation.

With the synthesis of the desired dienophile achieved, we turned to the crucial Diels-Alder reaction of dienophile **76** with *trans*-piperylene and its subsequent transformations as depicted in Scheme 14. Since the Diels-Alder reaction of dienophile **76** had already be investigated extensively by a previous member of our research group[57] and our main focus now was to economically synthesize the required Diels-Alder adduct **77**, we investigated the Diels-Alder reaction of dienophile **76** with piperylene supplied as a 2:1 mixture of *trans*:*cis* isomers. This reagent was much cheaper than the isomerically pure reagent and thus more appropriate to future scale up potential. Thus, this isomerically impure



Scheme 13

reagent was added to a dichloromethane suspension containing fused zinc chloride and dienophile **76** pre-cooled to 0°C. After workup and chromatographic purification, the desired Diels-Alder adduct was isolated as a mixture of diastereomers in a 4:1 ratio as determined by proton NMR favoring the desired diastereomer **77**. Repeated flash chromatography of the product mixture gave pure Diels-Alder adduct **77** for characterization and subsequent reactions. The *ortho*-addition of the diene was confirmed by the proton NMR spectrum. The splitting pattern of the resonance centered at δ 2.78,



Scheme 14

ascribed to the bridgehead proton, was found to be a doublet of doublets of doublets (J = 10, 7, 2 Hz) which can only arise if the addition occurred in an *ortho* fashion. The benzyloxy side chain was confirmed to be present by the observance of aromatic protons resonating at δ 7.35 (m, 5 H) and benzylic protons at δ 4.52. The benzylic protons were found to be an apparent sharp singlet but upon closer analysis, flanking signals were found. Thus, at the field strength of the NMR machine used, the signal due to the benzylic protons are more aptly described as a second order multiplet. The vinylic protons of the enone system were found at δ 6.31 (dd, J = 10, 2 Hz) and 5.93 (d, J = 10 Hz). The other vinylic protons were found as a pair of complex doublets centered at δ 5.66 (J = 10 Hz) and 5.53 (J =

10 Hz). The methoxy group of the ester functionality was found to resonate as a sharp singlet at δ 3.71 while the methyl group adjacent to the quaternary center was found as a singlet at δ 1.12. The allylic methyl group was observed at δ 1.24 as a doublet (J = 7 Hz). The IR spectrum of the product showed carbonyl absorptions at 1726 and 1689 cm^{-1}, corresponding to the ester and enone carbonyls respectively. This was corroborated by the carbon APT spectrum which showed two in-phase resonances in the carbonyl region (δ 196.2 and 174.7). Apart from the two carbonyl carbon resonances, the carbon APT spectrum revealed eight resonances between δ 123 and 153, one in-phase and seven anti-phase, attributed to the benzene moiety and the four olefinic carbons. The remainder of the spectrum contained eleven resonances, six in-phase and five anti-phase, which was in agreement with the structure assigned for bicyclic keto ester **77**. The high resolution mass spectrum also corroborated the desired molecular formula of $C_{23}H_{28}O_4$ with an ion peak at 368.1984.

The experimental proton NMR spectrum matched closely with that reported previously[57] and is tabulated in Table 1. As a result of this close agreement, we were confident that the isolated Diels-Alder adduct was the desired one in terms of stereochemistry. With the synthesis of the key Diels-Alder adduct confirmed, the final stereochemical hurdle was ready to be breached. Lithium dimethylcuprate induced conjugate addition of bicyclic keto ester **77** followed by reduction of the ensuing enolate by lithium aluminum hydride then yielded, after workup and chromatographic purification, the desired bicyclic keto alcohol **78** in 67% yield over two steps. It was after numerous experimentation before the yields could be reliably reproduced. It was discovered that the resulting black residue needed to be vigorously stirred until the majority of it has turned into a grey colored suspension before filtering over Celite. Without this added step in

the workup procedure, the yield of the desired keto alcohol **78** was greatly depressed. In the IR spectrum of keto alcohol **78**, the appearance of a strong absorption band at 1696 cm^{-1} and a sharp strong absorption centered at 3460 cm^{-1} suggested the survival of the ketone carbonyl while successfully reducing the

Table 1: Selected Experimental and Reported Proton NMR data for Diels-Alder Adduct 77.

Selected Experimental Values (200 MHz)		Selected Reported Values (300 MHz)	
δ (ppm)	Multiplicity (J in Hz)	δ (ppm)	Multiplicity (J in Hz)
6.31	dd (10,2)	6.29	dd (10, 2)
5.93	d (10)	5.92	d (10)
5.66	dm (10)	5.57	ddd (10, 4, 2)
5.53	dm (10)	5.50	ddd (10, 7, 3)
3.71	s	3.69	s
3.64	m	3.58-3.66	m
2.81	m	2.83	m
2.78	ddd (10, 7, 2)	2.75	ddd (10, 7, 2)
2.19	dm (18)	2.19	dm (18)
1.96	(dm (18)	1.95	dm (18)
		1.78	dd (14, 7)
1.76	m		
		1.72	dd (14, 7)
1.24	d (7)	1.22	d (7)
1.12	s	1.10	s

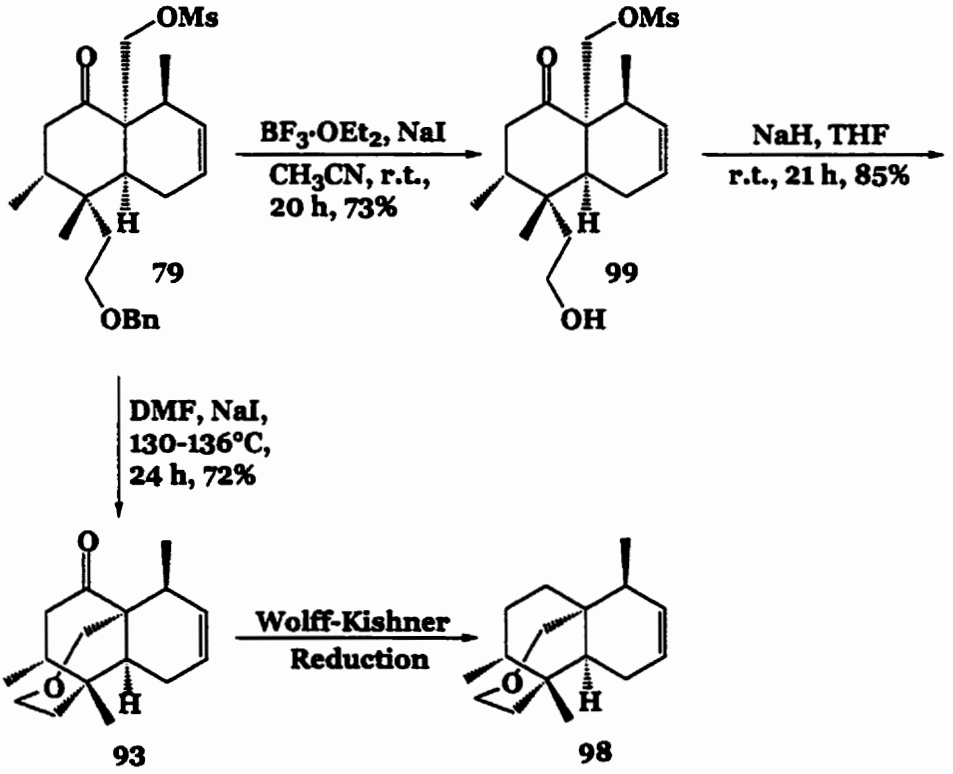
ester moiety. This was confirmed by the carbon APT spectrum which showed the presence of an in-phase resonance at δ 219.9 attributed to the ketone carbonyl carbon while the ester carbonyl resonance was absent. The remaining resonances found in the carbon APT spectrum were in agreement, in terms of the number of in-phase and anti-phase signals, with the structure assigned. The conjugate addition of the methyl group was confirmed by the observance of an additional methyl doublet in the proton NMR spectrum at δ 0.89 (J = 7 Hz) along with the absence of any resonances attributable to vinylic protons of an enone system. The methylene protons adjacent to the hydroxy functionality were found to resonate as a pair of doublets, one at δ 3.58 (J = 11 Hz) and the other at δ 3.45 (J = 11 Hz). Again, the benzylic methylene protons appeared as an apparent singlet but were found, upon closer inspection, to be flanked by two small signals and thus should be quoted as a second order multiplet. The high resolution mass spectrum contained a very weak ion peak (0.71%) at 356.2351 which corresponded well with the calculated mass of the desired molecular formula of $C_{23}H_{32}O_3$. As before, a detailed comparison of the experimentally obtained proton NMR spectrum with the reported spectrum resulted in close agreement. This led us to confidently conclude that the desired stereochemistry of the conjugate addition was achieved.

Derivatization of the hydroxy functionality to the mesylate under standard conditions then yielded the required keto mesylate **79** in near quantitative yield. The IR spectrum showed the absence of the broad hydroxyl stretch previously observed for keto alcohol **78** and the presence of two stretching bands due to the sulfonate functionality (1357 and 1176 cm^{-1}). The ketone carbonyl was observed to stretch at 1700 cm^{-1} which was corroborated by the carbon APT spectrum with the observance of an in-phase resonance at δ 213.4. In the proton NMR

spectrum, the methyl protons of the mesylate was found to resonate at δ 2.95 as a sharp singlet while the methylene protons adjacent to the mesyloxy group were observed as doublets at δ 4.48 (J = 9 Hz) and 4.03 (J = 9 Hz). The benzylic methylene protons were observed as well resolved doublets at δ 4.51 (J = 12 Hz) and 4.43 (J = 12 Hz). The carbon APT spectrum contained twenty-two resonances, ten in-phase and twelve anti-phase, which is in agreement with the structure assigned. The high resolution mass spectrum contained an ion peak at 434.2127 which corroborated the desired molecular formula of $C_{24}H_{34}O_5S$.

The next transformation required was to form the seven membered ether linkage. The obvious synthetic sequence was to remove the benzyl protecting group to give keto alcohol **99** followed by treating the resulting primary alcohol with a base to effect the cyclization. The established sequence of reactions is depicted in Scheme 15. As such, debenzylation of keto mesylate **79** was achieved by treatment with boron trifluoride etherate and sodium iodide in acetonitrile[62]. After stirring for twenty hours at room temperature the reaction was worked up and chromatographed to afford the desired keto alcohol **99** in 73% yield. The IR spectrum contained a strong hydroxyl stretching band centered at 3441 cm^{-1} along with the characteristic ketone carbonyl stretch at 1698 cm^{-1}. The characteristic sulfonate stretching bands were found at 1353 and 1174 cm^{-1}. The proton NMR spectrum contained no resonances attributable to a benzyl group, thus confirming the desired debenzylation. The methyl protons of the mesylate was observed at δ 3.06 as a sharp singlet. The methylene protons adjacent to the mesyloxy functionality were observed as doublets at δ 4.56 (J = 9 Hz) and 3.90 (J = 9 Hz) whereas those adjacent to the hydroxy group were found as doublet of doublets of doublets at δ 3.76 (J = 11, 11, 5 Hz) and 3.56 (J = 11, 11, 5 Hz). Although the high resolution mass spectrum contained no ion peak resembling

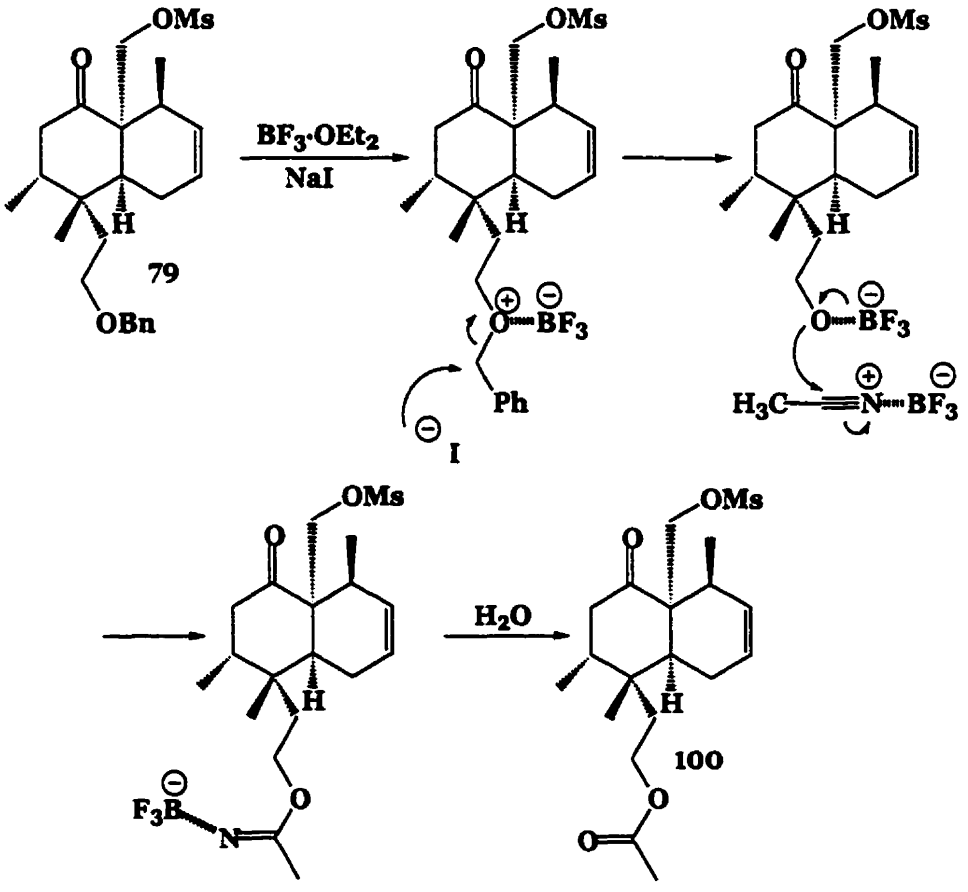
that of the molecular formula desired, a peak at 326.1562, corresponding to the [M-H_2O] molecular formula, and a peak at 248.1777, corresponding to the [M-CH_3SO_3H] molecular formula, provided indirect evidence for the desired molecular formula of $C_{17}H_{28}O_5S$.



Scheme 15

The crude product of the above debenzylation reaction yielded a by-product which was analyzed spectroscopically. The IR spectrum revealed two carbonyl stretches, one at 1738 and the other at 1706 cm^{-1}, which suggested the presence of an ester carbonyl in addition to the ketone carbonyl. This was confirmed by the carbon APT spectrum with two in-phase resonances at δ 213.0 and 171.2. The proton NMR spectrum revealed the presence of four methyl groups in the molecule due to resonances observed at δ 3.00 (s), 2.01 (s), 1.02 (d, J = 7 Hz), and 1.01 (s). The sum of the integrals in the proton NMR spectrum revealed that the

molecule most likely contains thirty protons. The singlet at δ 2.01 along with the ester carbonyl stretch found in the IR spectrum suggested that this by-product contains an acetate group. The carbon APT spectrum contained a total of nineteen resonances, nine in-phase and ten anti-phase. The high resolution mass spectrum contained an ion peak at 387.1825 which translates to a molecular formula of $C_{19}H_{31}O_6S$ which suggests that this is the [M+1] ion peak. After taking all the data into consideration, the by-product was concluded to be keto acetate **100**. Keto acetate **100** was proposed to be formed by the mechanism as depicted in Scheme 16. After the iodide mediated debenzylation occurs, the



Scheme 16

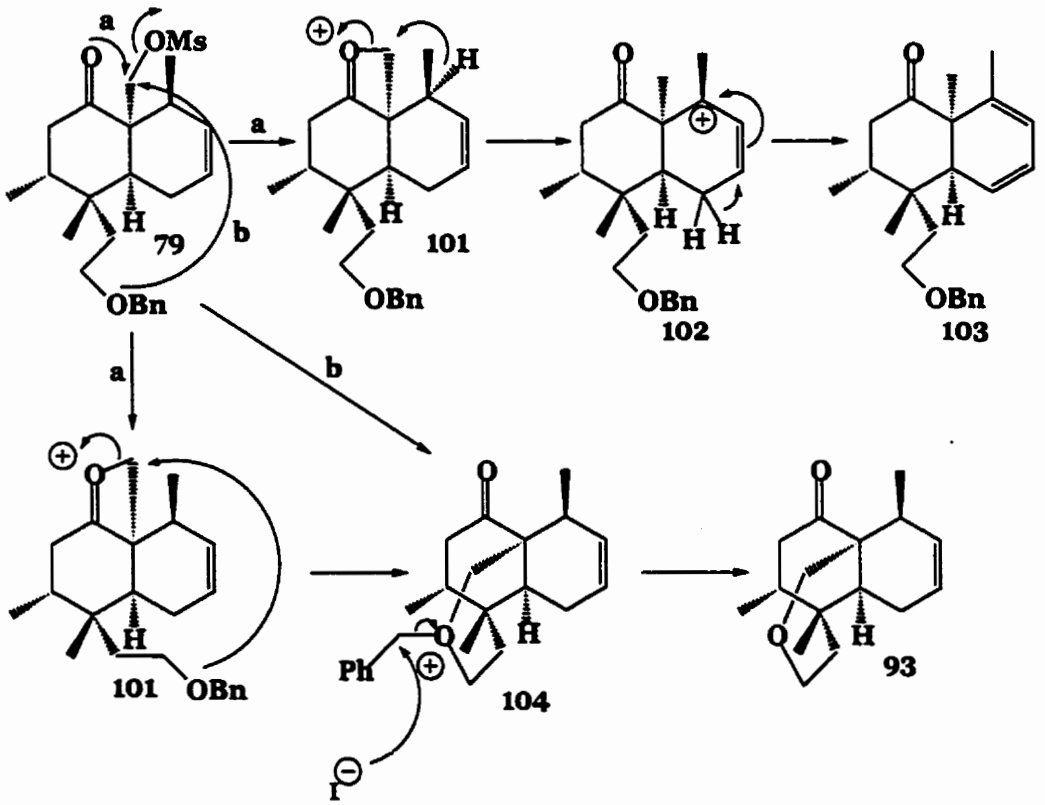
ensuing alkoxy-boron trifluoride complex may attack the nitrile carbon of the solvent. This would then result in the formation of the imino ether shown which would, upon hydrolysis, yield the proposed keto acetate **100**.

With keto alcohol **99** in hand, treatment with sodium hydride in tetrahydrofuran then gave the desired tricyclic keto ether **93** in 85% yield. The IR spectrum showed the presence of a carbonyl stretch at 1706 cm^{-1}. This was confirmed by the carbon APT spectrum with an in-phase resonance at δ 211.9. The neopentyl protons adjacent to the ether oxygen were observed as doublets at δ 4.18 (J = 13 Hz) and 3.58 (J = 13 Hz). The methylene protons on the other side of the ether oxygen were observed as a multiplet centered at δ 3.98. The two vinylic protons were found to resonate as a multiplet at δ 5.50 and the three methyl groups present in the molecule were observed at δ 1.23 (d, J = 7 Hz), 1.02 (s), and 0.95 (d, J = 7 Hz). The carbon APT spectrum revealed sixteen resonances, eight in-phase and eight anti-phase, which is consistent with the structure assigned. The high resolution mass spectrum lent credence to the molecular formula of $C_{16}H_{24}O_2$ by the presence of an ion peak at 248.1788.

As was mentioned before, the zinc promoted reduction of mesylate **79** to give cyclopropyl alcohol **80** was accompanied by the isolation of tricyclic keto ether **93** as a by-product. This led us to hypothesize that if the reducing agent, in this case zinc powder, was removed from the reaction conditions, then maybe the desired tricyclic keto ether **93** may become the major product of the reaction. Gratifyingly, this was found to be the case. As such, a solution of keto mesylate **79** in *N,N*-dimethylformamide was treated with sodium iodide alone and the resulting solution was heated to 130-136°C for 24 hours. After cooling, workup, and purification, the desired tricyclic keto ether **93** was isolated in 72% yield.

The crude product, in this case, also yielded a by-product which was fully characterized spectroscopically. The IR spectrum revealed the presence of a carbonyl group (1706 cm^{-1}) and the absence of the sulfonate stretching bands. The carbon APT spectrum confirmed the presence of the carbonyl by the observance of an in-phase resonance at δ 214.4. The benzyloxy side chain was intact as revealed by the presence, in the proton NMR spectrum, of aromatic protons (δ 7.30, m, 5 H) and benzylic methylene protons (δ 4.48, s, 2 H). The absence of any resonance attributable to the methyl protons of a mesylate functionality confirmed the absence of the mesylate group. In addition to the aromatic protons, three distinct sets of resonances were observed in the vinylic region of the proton NMR spectrum which integrated to three protons. A vinylic methyl signal was observed at δ 1.57 as a doublet (J = 1 Hz) in addition to three other methyl signals observed at δ 1.21 (s), 1.09 (s), and 0.87 (d, J = 7 Hz). This would suggest that the mesyloxymethyl group has been reduced to a methyl group. The presence of the three vinylic protons along with the fact that a vinylic methyl group was also present suggested that the "1-methyl-2-cyclohexenyl" system present in the starting material has been converted into a "1-methyl-1,3-cyclohexadienyl" system. The carbon APT spectrum contained a total of twenty resonances, nine in-phase and eleven anti-phase. The high resolution mass spectrum contained an ion peak corresponding to the characteristic tropylinium ion ($C_7H_7^+$) as the base peak which confirms the presence of a benzyl group. The highest ion peak observed in the high resolution mass spectrum was 338.2244, which corresponded within acceptable error to the molecular formula of $C_{23}H_{30}O_2$. With all the pertinent data accumulated and analysed, a detail picture of the structure of this by-product began to emerge. The proposed structure and mechanism of its formation are depicted in Scheme 17. The main obstacle in deducing the structure of the by-product was the fact that the mesyloxymethyl

substituent had apparently been reduced to the methyl level without the benefit of any reducing agent. However, the formation of the 1,3-dienyl system from the olefinic function constitutes an oxidation. Therefore, in the global sense, there is no net change in oxidation level of the molecule; the mesyloxymethyl was reduced to the methyl level, but the olefin was oxidized to the 1,3-diene. With this mental block out of the way, we became more comfortable concerning the proposed structure of the by-product. As far as the mechanism leading to the dienyl by-product **103** is concerned, we can only speculate. One thing we know for certain was that the mesylate was removed prior to debenzylation. This led us to propose the following mechanism: under the conditions of the reaction, the ketone oxygen displaces the mesylate to form



Scheme 17

the oxonium ion **101** (Scheme 17, path a). This strained oxonium ion then can be opened up by a 1,3-hydride shift, forming the stable tertiary and allylic carbocationic intermediate **102**. Elimination of a proton in the manner as shown then yields dienyl by-product **103**. Oxonium intermediate **101** may also be opened up by the attack of the benzyloxy oxygen to give oxonium ion **104** which may be formed directly by attack of the benzyloxy oxygen onto the mesyloxy containing bridgehead carbon (Scheme 17, path b). This intermediate then is well suited to attack by the iodide to give the desired tricyclic keto ether **93**.

Although dienyl ketone **103** is of no immediate use in our synthetic endeavor, it is actually quite amenable towards elaboration to other *cis*-normal clerodane natural products. The above reaction, if optimized towards the synthesis of dienyl ketone **103**, will achieve the reduction of the mesylate and the installation of the olefin in the correct position observed in *cis*-normal clerodanes in one step. Selective hydrogenation of the less substituted olefin without modifying the benzyl group nor the more substituted olefin may present an obstacle but is not without precedence[63]. All in all, this by-product presents itself as a potential candidate in the further elaboration of our general scheme towards *cis*-normal clerodanes.

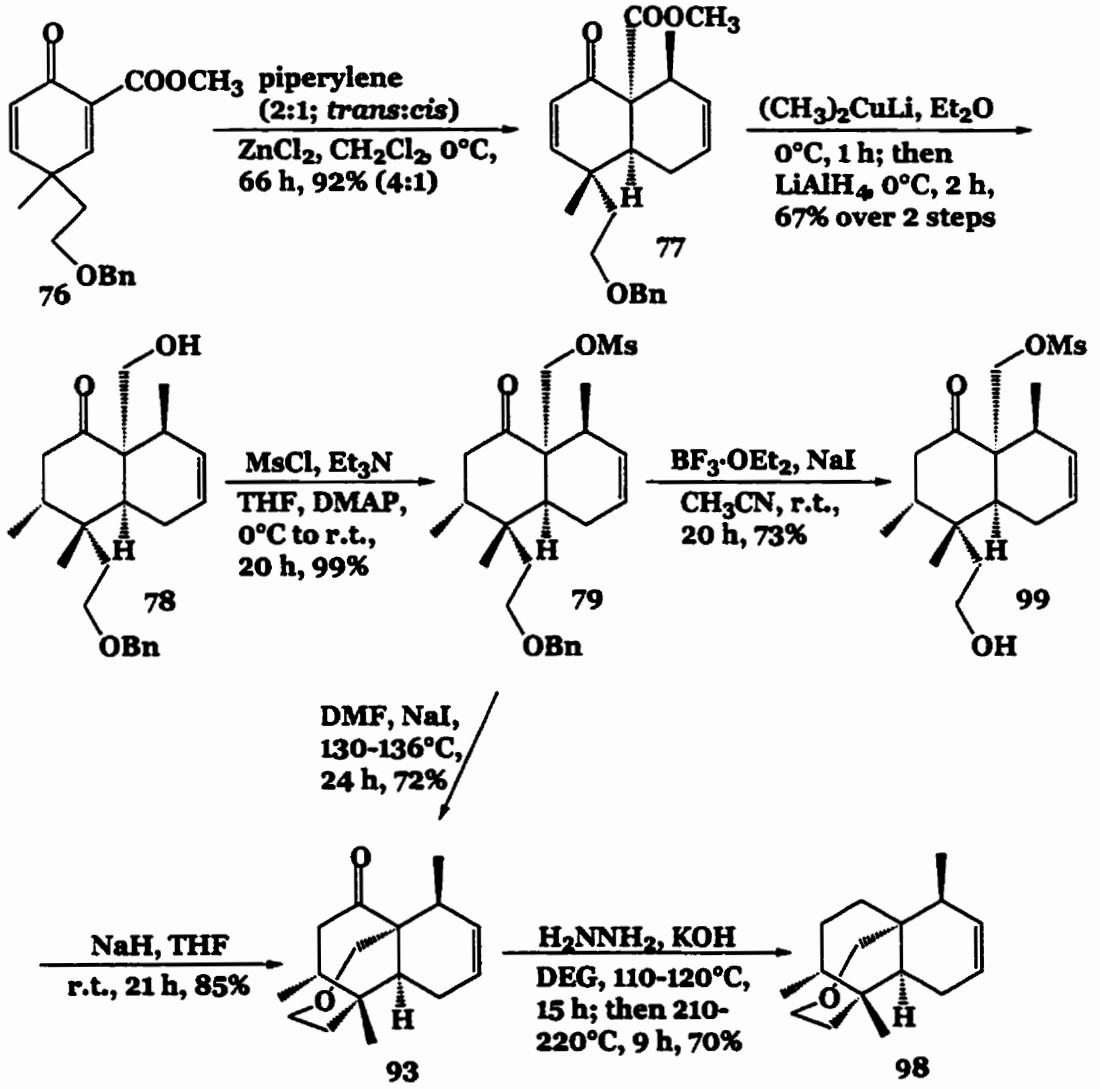
With tricyclic keto ether **93** synthesized, the deoxygenation to give tricyclic ether **98** was achieved *via* a Wolff-Kishner reaction. As such, treatment of a diethylene glycol solution of keto ether **93** with potassium hydroxide and anhydrous hydrazine at 110-120°C for 15 hours followed by heating to 210-230°C for 9 hours effected the desired transformation in 70% yield. The absence of any stretching bands in the IR spectrum of the product attributable to a carbonyl group confirmed the success of the reaction. This was also corroborated by the

absence of any carbonyl carbon resonances in the carbon APT spectrum. The proton NMR spectrum displayed two vinylic proton resonances at δ 5.59 (dddd, J = 10, 5, 3, 3 Hz) and 5.33 (ddd, J = 10, 5, 2 Hz) which suggested that no olefin scrambling had occurred. The neopentyl protons adjacent to the ether oxygen were observed as doublets at δ 3.86 (J = 13 Hz) and 3.41 (J = 13 Hz) while the methylenic protons on the other side of the ether oxygen were observed at δ 3.92 as a multiplet. The three methyl groups were observed at δ 0.96 (s), 0.84 (d, J = 7 Hz), and 0.83 (d, J = 7 Hz). In the carbon APT spectrum, a total of sixteen resonances were observed, eight in-phase and eight anti-phase, which agrees with the structure assigned for tricyclic ether **98**. The high resolution mass spectrum contained an ion peak at 234.1987 which corresponded well within acceptable error with the desired molecular formula of $C_{16}H_{26}O$.

A summary of the synthetic route beyond dienophile **76** is depicted in Scheme 18. In this phase of the project, we have successfully achieved the synthesis of tricyclic keto ether **93** in synthetically useful yields with each transformation being optimized. An unexpected significant result was the isolation of bicyclic dienyl ketone **103** which is viewed as an important extension of our overall synthetic strategy towards the *cis*-normal clerodanes.

With tricyclic ether **98** in hand, the next crucial transformation was to regioselectively open the ether linkage (Scheme 19). Two conditions needed to be met for this reaction; the opening must be regiospecific, leaving the ring juncture with a hydroxymethyl group, and it must attach a manipulable functionality on the ethyl side chain for further elaboration to a 3-furyl functionality. With these considerations in mind, we concluded that a halide containing nucleophilic reagent that can cleave the ether in a S_N2 fashion would be the most likely

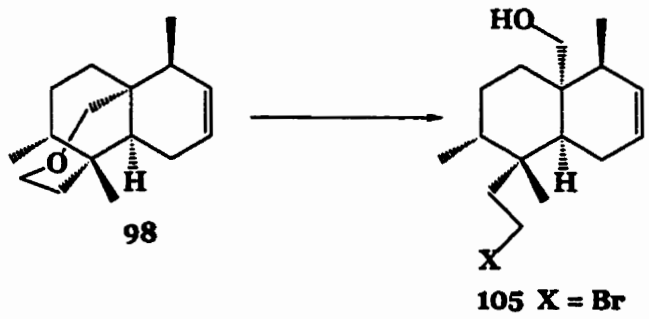
candidate. Regioselectivity was not envisioned to be a major obstacle due to the fact that the stereochemical environment about the two *alpha* methylenes flanking the oxygen are vastly different; one is a neopentyl methylene while the



Scheme 18

other is a homoneopentyl methylene. It was hypothesized that the incoming halide would attack the homoneopentyl methylene carbon preferentially, thus opening the cyclic ether in the desired fashion. From the above analysis, we

concluded that the reagent of choice would be halide containing Lewis acidic reagents.



98

105 X = Br

Scheme 19

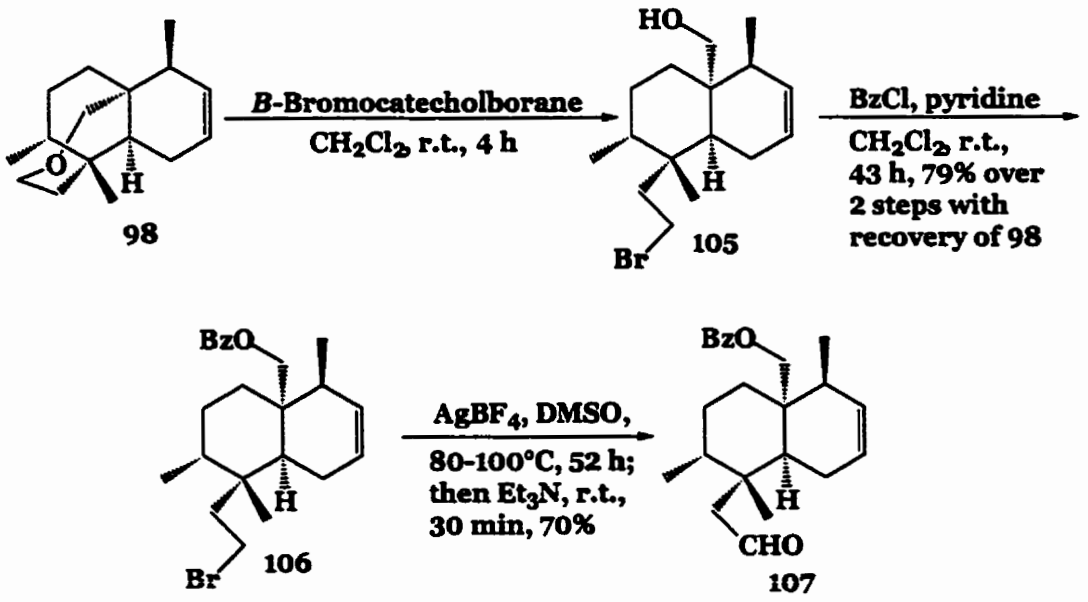
In 1983, Bhatt and Kulkarni published a review on the scope and limitations of reagents for the cleavage of ethers[64]. This invaluable resource revealed a plethora of reagents available for effecting the desired transformation. Of the many reagents cited, we were drawn towards the silicon and boron based reagents since the oxophilicity of these elements is well documented. Silicon based reagents were investigated first[65]. As such, a solution of tricyclic ether **98** in carbon tetrachloride was treated with iodotrimethylsilane. At completion (as monitored by TLC), water was introduced to quench the reaction and, after chromatographic purification, the only isolated product was the starting material. From the TLC analysis, a reaction had indeed occurred. The only explanation for this surprising result is that the resulting iodo alcohol is just too labile and cyclized back to the starting material during workup or chromatography. Due to this result, we chose to abandon silicon based reagents and turned our attention to boron based reagents.

The first reagent investigated was boron tribromide[66]. Thus, boron tribromide was introduced to a solution of tricyclic ether **98** in dichloromethane and the

reaction was carefully monitored as before. Unfortunately, after an extended period of time, no reaction was observed to have occurred and the starting material was recovered. The next reagent investigated was the bulky *B*-bromo-9-borabicyclo[3.3.1]nonane (*B*-Br-9-BBN)[67]. Thus, *B*-Br-9-BBN was added to a solution of tricyclic ether **98** in dichloromethane and the reaction was stirred at room temperature for two hours. The solvent was then removed under aspirator vacuum and the residue redissolved in pentane followed by the addition of 2-aminoethanol. The resulting suspension was then stirred for an additional hour at which time it was filtered over Celite and the residue was washed with copious amounts of pentane. After chromatographic purification, a mixture containing the desired bromo alcohol **105** and the starting material was isolated. The IR spectrum of the mixture clearly indicated the presence of an alcohol functionality by the observance of a broad strong hydroxyl stretch centered about 3442 cm^{-1}. The proton NMR spectrum contained, in addition to the resonances observed in that of the starting material, the neopentyl methylene protons of the product observed as doublets at δ 4.08 (J = 11 Hz) and 3.59 (J = 11 Hz) which are downfield shifted with respect to the corresponding signals in the starting tricyclic ether **98**. The high resolution mass spectrum contained two ion peaks of almost equal intensities separated by two mass units (314.1244 and 316.1226), indicating that they were due to isotopic bromides. These corresponded well with the desired molecular formula of $C_{16}H_{27}OBr$. The carbon APT spectrum of the mixture was too complex and overlapped to allow for any meaningful interpretation. At this point the regiochemistry of the ring opening reaction was assumed to be in the desired direction.

Due to the amount of precipitation present in the reagent bottle and the inability of Aldrich to supply any new bottles of *B*-Br-9-BBN at the time, we were forced to

search for another boron based reagent to effect the ether ring opening reaction. A search of the literature yielded the reagent *B*-bromocatecholborane which was reported to effect ether cleavage reactions upon dialkyl and benzyl alkyl ethers[68]. As such, to a solution of the tricyclic ether **98** in dichloromethane was added *B*-bromocatecholborane and the resulting clear solution was stirred at room temperature for 4 hours. After quenching with water, extraction, and mild basic washing of the organic extracts, the crude product was found to exhibit the same spectroscopic (IR, proton NMR, HRMS) properties as that described above. One thing to note is that the TLC of the crude product mixture was very clean; only the two spots due to the starting material and what was assumed to be the desired product was visible. This compared favorably with the reaction using *B*-Br-9-BBN whose crude product yielded a TLC chromatogram which was significantly more "spotted". Scheme 20 diagrams the ether cleavage reaction and subsequent transformations thereof.



Scheme 20

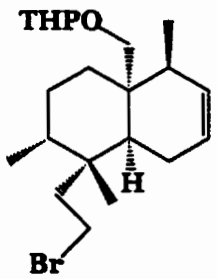
The crude product obtained above was dissolved in dichloromethane and treated with benzoyl chloride and pyridine. After workup and chromatographic purification, the only isolable product was found to consist of an inseparable mixture of tricyclic ether **98** and the desired bromo benzoate **106**. The IR spectrum of the mixture revealed the absence of the hydroxy stretching band observed before and presence of a carbonyl stretch at 1720 cm^{-1}. The proton NMR spectrum displayed three sets of aromatic resonances characteristic of a benzoate functionality. The neopentyl methylene protons were observed as doublets at δ 4.64 (J = 13 Hz) and 4.41 (J = 13 Hz) which are downfield shifted with respect to the corresponding resonances observed for bromo alcohol **105**. This supported the contention that the ether ring opening was regiospecific and the nucleophilic bromide attacked the less hindered methylene. The methylene protons adjacent to the terminal bromide were observed to resonate as doublet of doublets of doublets at δ 3.59 (J = 13, 9, 4 Hz) and 3.31 (J = 14, 9, 5 Hz).

The following transformation needed was to oxidize the terminal bromide functionality to the corresponding aldehyde. In 1974, Ganem and Boeckman Jr. reported on a modification[69] of the well-known Kornblum oxidation[70] in which alkyl iodides and tosylates were found to be displaced by dimethyl sulfoxide at elevated temperatures. Ganem reported that primary bromides can be prompted to undergo the same reaction if a soluble, non-nucleophilic silver salt was added to promote the reaction. Thus, silver tetrafluoroborate was added to a solution of the above purified mixture in dimethyl sulfoxide and the clear solution was heated to 80-100°C for 52 hours at which time, the reaction mixture was cooled to room temperature and triethylamine was added. After stirring the resulting black suspension for 30 minutes at room temperature, water was added and the mixture was extracted with diethyl ether. After washing, drying, concentration,

and chromatographic purification, the desired benzoyl aldehyde **107** was isolated in 70% yield as a clear colorless oil. The IR spectrum of the product showed the carbonyl stretch of the benzoate and the aldehyde functionality to overlap at 1717 cm^{-1}. The proton NMR spectrum contained a resonance at δ 9.75 (triplet, J = 2 Hz) which indicated the presence of an aldehydic proton. The carbon APT spectrum corroborated the success of the oxidation reaction due to the observance of an anti-phase resonance at δ 202.5 attributed to the aldehydic carbonyl carbon. The benzoate protecting group was revealed to be present by the observance of three sets of aromatic proton resonances characteristic of a benzoate group. The carbonyl carbon of the benzoate was observed to resonate as an in-phase resonance at δ 166.9 in the carbon APT spectrum. The methylene protons adjacent to the aldehyde functionality were observed as doublet of doublets at δ 2.76 (J = 18, 2 Hz) and 2.24 (J = 18, 2 Hz) while the neopentyl methylene protons were observed as two sets of doublets at 4.54 (J = 13 Hz) and 4.35 (J = 13 Hz). The vinylic protons were found at δ 5.61 (m) and 5.34 (ddd, J = 10, 4, 1 Hz). The ring junction proton was found to resonate as a multiplet at δ 1.80 and the three methyl groups present in the molecule were observed at δ 1.17 (d, J = 1 Hz), 0.89 (d, J = 7 Hz), and 0.85 (d, J = 7 Hz). The carbon APT spectrum contained a total of twenty-one resonances, nine in-phase and twelve anti-phase, which agrees well with the desired structure. The high resolution electrospray mass spectrum revealed the presence of a $[M + Na]^+$ ion signal at 377.2092 which corresponded well within error to the desired molecular formula of $C_{23}H_{30}O_3$.

Since bromo benzoate **106** was found to be chromatographically inseparable from tricyclic ether **98**, we attempted to protect the hydroxy group in bromo alcohol **105** as the corresponding tetrahydropyranyl moiety to see if the resulting

bromo acetal **108** would be separable. As such, to a solution of bromo alcohol **105** in dichloromethane was added pyridinium *para*-toluenesulfonate and 3,4-

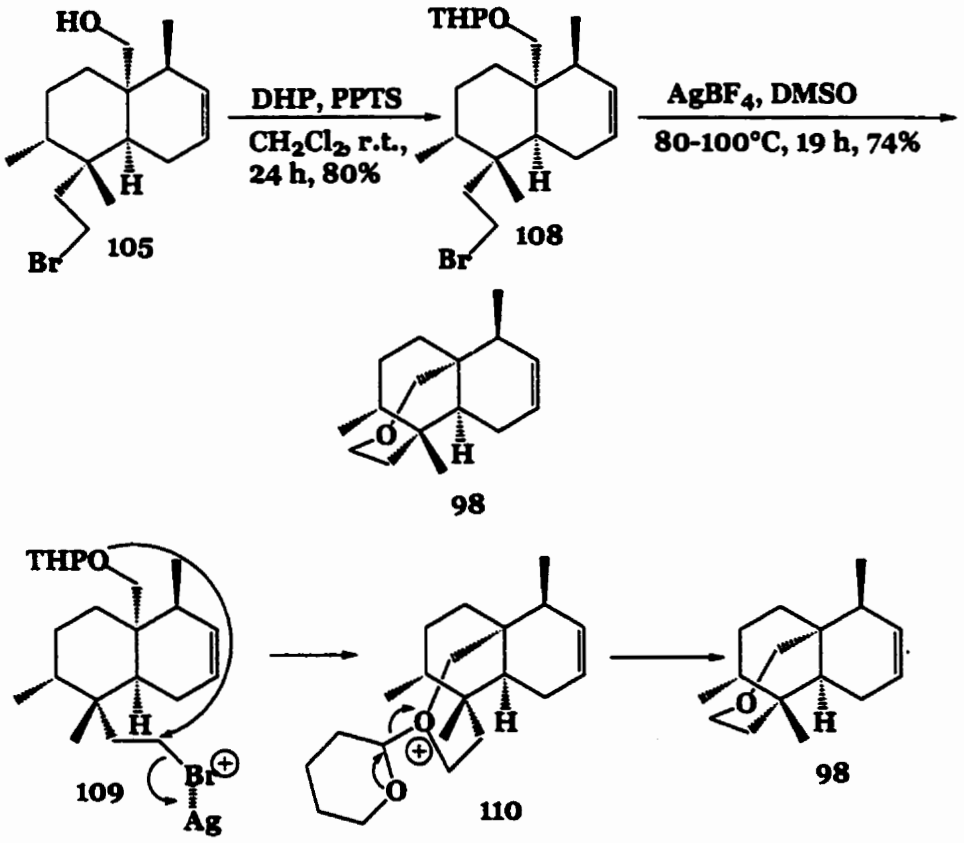


108

dihydro-2*H*-pyran[71]. The clear colorless mixture was stirred at room temperature for 12 hours before workup and purification. The desired tetrahydropyranyl ether **108** was thus isolated in 80% yield (accounting for recovered tricyclic ether **98**) as a colorless oil. The proton NMR spectrum suggested the presence of a diastereomeric mixture of approximately equal amounts which was expected. The acetal methine proton was observed to resonate at δ 4.73 for one isomer and δ 4.49 for the other. Both were found to be apparent triplets with a coupling constant of 3 Hz. The neopentyl methylene protons were observed as two sets of doublets at δ 4.17 (J = 12 Hz) and 3.27 (J = 12 Hz). The allylic methine proton was observed as multiplets at δ 2.75 for one diastereomer and 2.44 for the other. The carbon APT spectrum clearly contained two sets of signals of approximate equal intensity, thus corroborating the diastereomeric nature of the mixture. High resolution mass spectroscopic experiments failed to reveal any ion peaks attributable to the desired molecular formula, however, the low resolution electrospray spectrum revealed the presence of two ion signals, 422.2 and 424.2, which were two mass units apart. The mass separation and relative intensities clearly indicated that the two signals were due

to isotopic bromides and the mass value registered corresponded well with the $[M+Na]^+$ of the desired molecular formula of $C_{21}H_{35}O_2Br$.

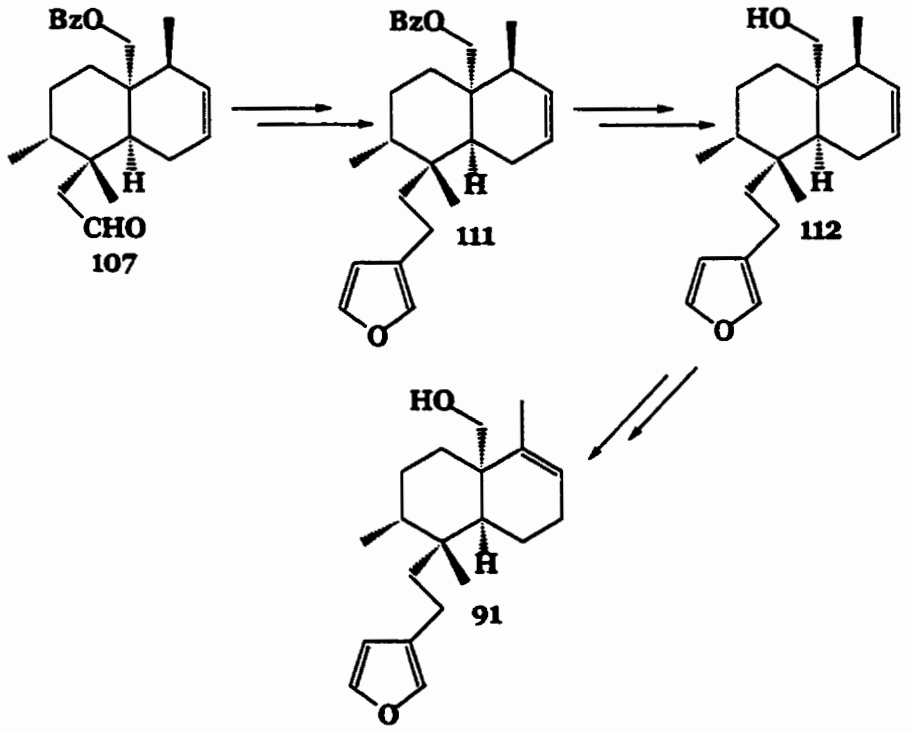
Subsequent attempts at oxidizing the terminal bromide of bromo acetal **108** resulted in a very surprising outcome. The only isolable product of the reaction was found to be spectroscopically identical to tricyclic ether **98**. This unexpected result is mechanistically rationalized in Scheme 21. It is hypothesized that, upon activation of the terminal bromide moiety by the silver salt (**109**), the acetal



Scheme 21

oxygen can displace the activated bromide in an intramolecular fashion to give oxonium ion **110**. This oxonium ion can then eliminate the tetrahydropyranyl moiety in the fashion diagrammed to give tricyclic ether **98**.

With benzoyl aldehyde **107** in hand, the end of our synthetic endeavor is at hand. All that is required now is to install the 3-furyl moiety followed by deoxygenation, removal of the benzoate protecting group, and finally, the isomerization of the olefin to the more substituted position (Scheme 22). As such, 3-lithiofuran, formed by treating a solution of 3-bromofuran in diethyl ether with *tert*-butyllithium at -78°C, was added to a solution of benzoyl aldehyde **107** in diethyl ether cooled to -78°C. After stirring at -78°C for 2 hours, the reaction was quenched by the addition of solid ammonium chloride and allowed to warm to



Scheme 22

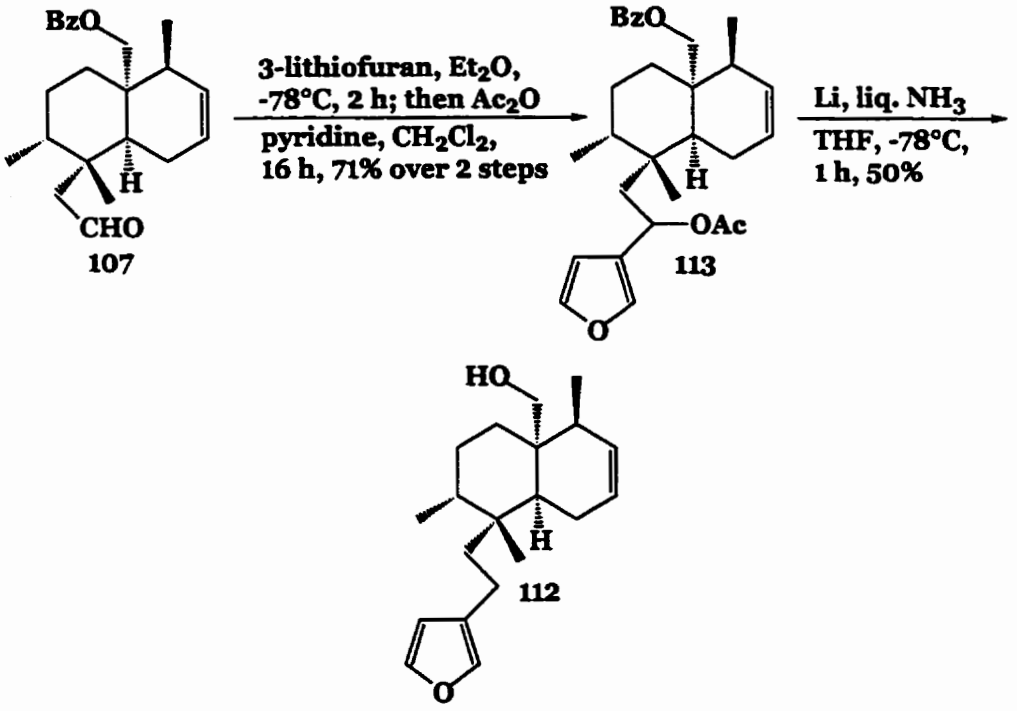
room temperature. Since the resulting furyl alcohol was deemed to be unstable due to the presence of a benzylic-like hydroxy group, the crude product was subjected to standard acetylation conditions after partial characterization. The IR spectrum of the crude product of the furan addition reaction revealed the

presence of a hydroxy group as evidenced by a strong absorption band centered about 3400 cm^{-1}. The carbonyl stretching band of the benzoate moiety was observed at 1693 cm^{-1}. The high resolution mass spectrum contained an ion peak at 422.2442 which corresponded well within error to the desired molecular formula of $C_{24}H_{34}O_4$. The crude furyl alcohol product was dissolved in dichloromethane and treated with acetic anhydride and pyridine. After workup and chromatographic purification, the desired benzoyl acetate **113** was isolated in 71% over two steps as a 1:1 mixture of diastereomers. The proton NMR spectrum revealed the retention of the benzoate protecting group by the presence of aromatic proton resonances at δ 8.11 (ddd, J = 7, 7, 1 Hz), 7.56 (m), and 7.46 (m). The *alpha*-furyl protons were observed at δ 7.29, 7.25, 7.07, and 6.89 as unresolved multiplets while the lone *beta*-furyl proton was observed as a pair of doublets, one at δ 6.19 (J = 1 Hz) and the other at δ 5.99 (J = 1 Hz). The methine proton adjacent to the acetoxy group was found at δ 6.36 and 5.85 as doublet of doublets (J = 9, 3 Hz) while the methyl protons of the acetate group were noticed at δ 1.96 and 1.82 as two singlets. The neopentyl methylene protons adjacent to the benzoyloxy functionality were observed to resonate as doublets at δ 4.52 (J = 13 Hz) and 4.28 (J = 13 Hz) for one diastereomoer and δ 4.50 (J = 12 Hz) and 4.38 (J = 12 Hz) for the other while the three methyl groups were observed at δ 0.95 (d, J = 7 Hz), 0.92 (s), and 0.90 (d, J = 7 Hz).

The acetoxy functional group of benzoyl acetate **113** was removed under dissolving metal reduction conditions. Gratifyingly, the benzoate protecting group was also removed under the reaction conditions as was hoped for. Thus, a solution of benzoyl acetate **113** in tetrahydrofuran was added to a dark blue solution of lithium metal in liquid ammonia cooled to -78°C. After stirring at -78°C for 1 hour, solid ammonium chloride was introduced and the liquid

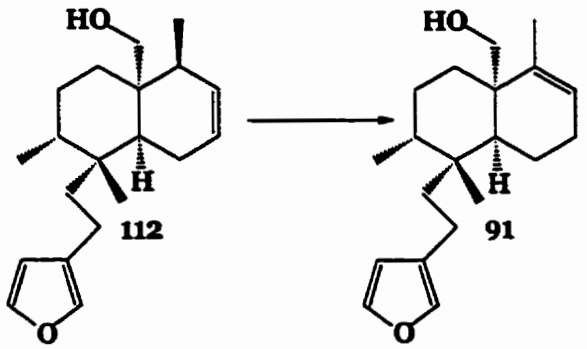
ammonia was allowed to evaporate by warming slowly to 0°C. The residue was diluted with ethyl acetate followed by the addition of water to dissolve the solid residue. After standard workup procedures, the crude product was subjected to chromatographic purification to furnish the desired furyl alcohol **112** as a colorless oil in 50% yield. In the proton NMR spectrum, the *alpha* protons of the furan moiety were observed as doublet of doublets at δ 7.33 (J = 2, 2 Hz) and 7.23 (J = 2, 1 Hz) while the *beta* proton was observed at 6.31 as a doublet of doublet (J = 2, 1 Hz). The two vinylic protons were found as two sets of complex doublets, one at δ 5.56 (J = 10 Hz) and the other at δ 5.34 (J = 10 Hz). The neopentyl methylene protons adjacent to the hydroxy group were found as doublets at δ 4.05 (J = 12 Hz) and 3.52 (J = 12 Hz) whereas the methylene protons adjacent to the furan ring were observed at δ 2.81 and 1.88, both signals being a doublet of doublets of doublets with coupling constants 14, 14, and 4 Hz. The three methyl groups were observed to resonate at δ 0.96 (s), 0.88 (d, J = 7 Hz), and 0.83 (d, J = 7 Hz). The reaction sequence since benzoyl aldehyde **107** as described above is summarized in Scheme 23.

With furyl alcohol **112** in hand, the last transformation required was to migrate the 1,2-disubstituted olefin to the more substituted 1,1,2-trisubstituted position present in *cis*-normal clerodane natural products (Scheme 24). Although many reagents[72] are available to effect the isomerization of olefins to what is predicted to be the thermodynamically more stable position, previous research in our group have had success with rhodium trichloride hydrate[57]. As such, rhodium trichloride hydrate was added to a solution of furyl alcohol **112** in absolute ethanol. The resulting suspension was stirred at room temperature until a clear pink solution was obtained after which it was heated to refluxing temperature



Scheme 23

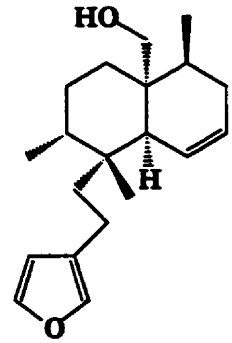
and maintained at reflux until a bluish purple solution was achieved. Reflux was continued for 45 minutes at which time, the reaction was quenched, worked up,



Scheme 24

and purified by flash chromatography. Spectroscopic analysis of the only isolable product revealed that it was not the desired product. Spectroscopic comparison with the literature values reported by McCrindle and co-workers[54]

were disappointingly inconsistent. The furan ring was intact as evidenced by resonances at δ 7.48 (dd, J = 2, 2 Hz), 7.38 (m), and 6.43 (apparent singlet) in the proton NMR spectrum. A hydroxy stretching band was observed in the IR spectrum of the product at 3453 cm^{-1} and the hydroxy proton was found to resonate at δ 1.19 as a broad singlet. In the olefin region of the proton NMR spectrum, two vinylic protons resonances were observed as complex doublets at δ 5.89 (J = 11 Hz) and 5.81 (J = 11 Hz). The neopentyl methylene protons adjacent to the hydroxyl were observed as broad doublets at δ 4.22 (J = 11 Hz) and 3.78 (J = 11 Hz) while the methylene protons adjacent to the furan ring were observed as doublet of doublets of doublets at δ 3.06 (J = 13, 13, 4 Hz) and 2.49 (J = 13, 13, 5 Hz). Other readily discernible signals were three methyl resonances which were observed at δ 1.37 (s), 1.08 (d, J = 7 Hz) and 1.04 (d, J = 7 Hz). The carbon APT spectrum contained a total of twenty resonances, nine in-phase and eleven anti-phase. Of the twenty resonances, six were attributable to sp^2 hybridized carbons which were consistent with the molecule containing a furan ring in addition to an olefin. Apart from the resonances attributable to the *beta*-substituted furan ring (δ 142.9 (a), 138.9 (a), 126.6 (p), and 111.6 (a)), the olefinic carbon resonances were anti-phase resonances observed at δ 130.7 and 127.2. This confirms that the unsaturation in the molecule is a 1,2-disubstituted olefin as suggested in the proton NMR spectrum. From the above spectroscopic data, it was not entirely



114

clear whether any reaction had occurred. If an isomerization reaction did indeed occur, a possible product would be furyl alcohol **114** which contains all the features consistent with the above spectroscopic data. A COSY experiment revealed cross peaks between the olefinic protons and the multiplet found at δ 2.84 which integrated to one proton. This one proton multiplet was correlated to the in-phase resonance at δ 40.9 in the carbon APT spectrum as evidenced by a HMQC experiment. These two pieces of information coupled with the nOe results as diagrammed in Figure 4 confirms the assignment of the ring junction proton to the resonance at δ 2.84 and thus the position of the olefin.

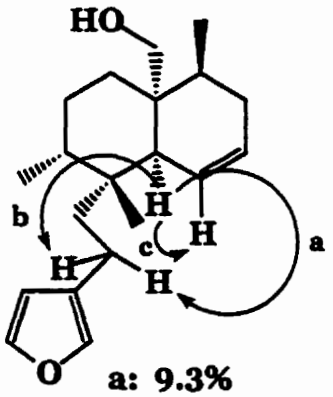


Figure 4. Selected nOe Data of Furyl Alcohol 114

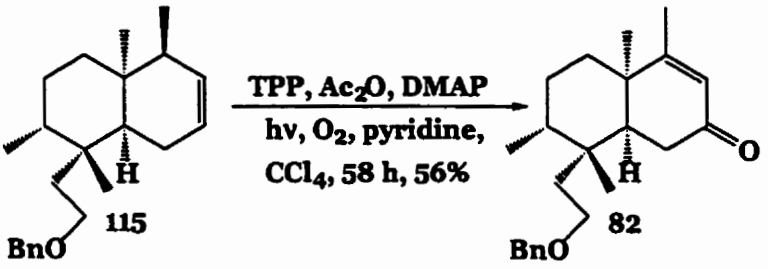
Since the olefin isomerization reaction was assumed to be an equilibration process in which the metal hydride reversibly inserts and β-eliminates until the β-elimination occurs only in one direction to give the thermodynamically more stable product, it seemed that prolonging the reaction time may allow the desired 1,1,2-trisubstituted olefin to be produced. Unfortunately, the undesired furyl alcohol **114** was the exclusive product in all reaction times attempted. Our

hypothesis to explain this interesting, albeit disappointing, result is that the furan moiety may be complexing with the rhodium center and thus biasing the β-elimination towards the observed position. Another explanation may be that, even though the desired olefin **91** may be thermodynamically more stable than olefin **114**, the transition state leading to olefin **114** may lie at a much lower energy level due to the added complexation effect afforded by the furan ring, thus leading to the observed product. Whatever the case may be, this final step needs to be further investigated in the future. If the complexation hypothesis is true, the obvious solution would be to remove the use of transition metals for the isomerization. Various basic and acidic reagents are known to isomerize olefins and this avenue of approach will be investigated thoroughly in the future.

Another modification would be to perform the isomerization earlier on in the synthetic scheme. The only intermediate which was thought to be amenable to the rhodium isomerization conditions was tricyclic ether **98**. As such, rhodium trichloride hydrate was added to a solution of tricyclic ether **98** in absolute ethanol and heated as outlined above. Unfortunately, after workup and chromatographic purification, tricyclic ether **98** was recovered almost quantitatively. Various reaction times and reagent equivalents failed to effect any isomerization.

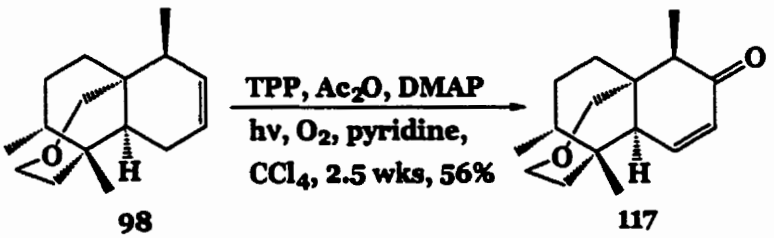
In the synthesis of 2-oxo-5α,8α-12,14,15,16-tetranorclerod-3-en-12-oic acid (**84**)[39], the photooxygenation reaction of bicyclic olefin **115** , which has similar gross structure as tricyclic ether **98**, resulted in the isolation of the enone **82** which has the unsaturation in the desired position (Scheme 25). This prompted us to investigate the photooxygenation of tricyclic ether **98** under identical conditions. Thus, to a solution of tricyclic ether **98** in carbon tetrachloride was

added 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine, acetic anhydride, pyridine, and 4-(*N*,*N*-dimethylamino)pyridine. The resulting dark purple mixture was stirred under an atmosphere of oxygen while being irradiated with two 500W tungsten lamps. After an extended length of time (2.5 weeks!), the reaction was worked up



Scheme 25

and purified to yield a product which was deduced to be enone **117** (Scheme 26) based on spectroscopic evidence. The IR spectrum of enone **117** revealed the presence of an enone carbonyl by virtue of a carbonyl absorption band at 1678 cm^{-1}. This was confirmed by the carbon APT spectrum by the observance of an in-phase resonance at δ 210.8. The proton resonance contained two vinylic

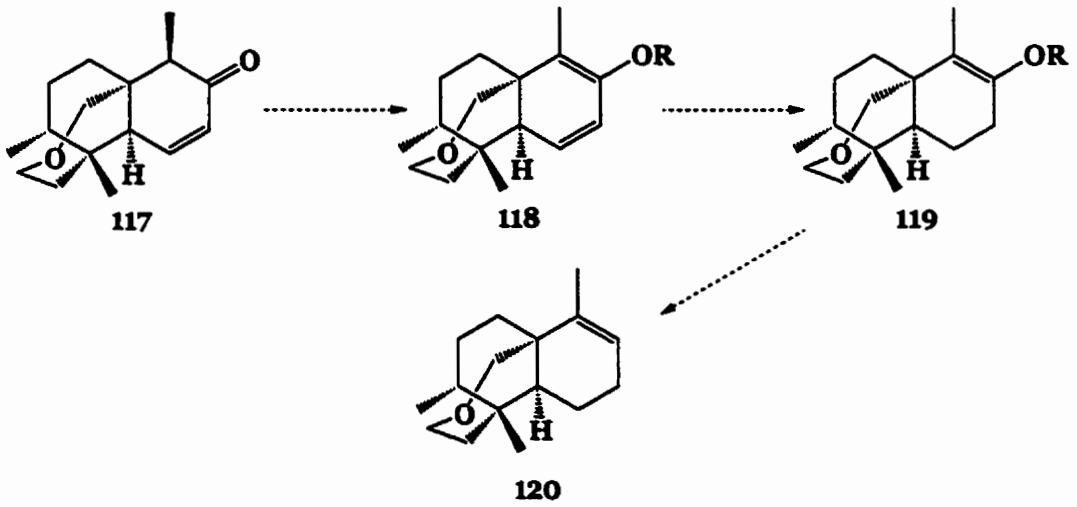


Scheme 26

proton resonances at δ 6.91 (dd, J = 11, 2 Hz) and 6.08 (dd, J = 11, 3 Hz). This fact, coupled with the observance of two anti-phase resonances (δ 149.6 and 129.5) in the olefin region of the carbon APT spectrum, constitutes evidence for the enone olefin being in the position as depicted and not in the desired position. The neopentyl methylene protons adjacent to the ether oxygen were observed to

resonate as doublets at δ 3.88 (J = 13 Hz) and 3.58 (J = 13 Hz) while the homoneopentyl methylene protons adjacent to the ether oxygen were observed at δ 3.97 (ddd, J = 13, 5, 3 Hz) and 3.81 (ddd, J = 13, 13, 3 Hz). The remainder of the proton NMR spectrum were consistent with the structure of enone **117**. The carbon APT spectrum contained a total of sixteen resonances, eight in-phase and eight anti-phase, which is in agreement with the structure assigned.

Although enone **117** was not the desired product, nevertheless it is considered to be a possible intermediate towards our synthetic goal. A possible route of achieving the desired olefin is depicted in Scheme 27. Enone **117** may be



117 **118** **119** **120**

Scheme 27

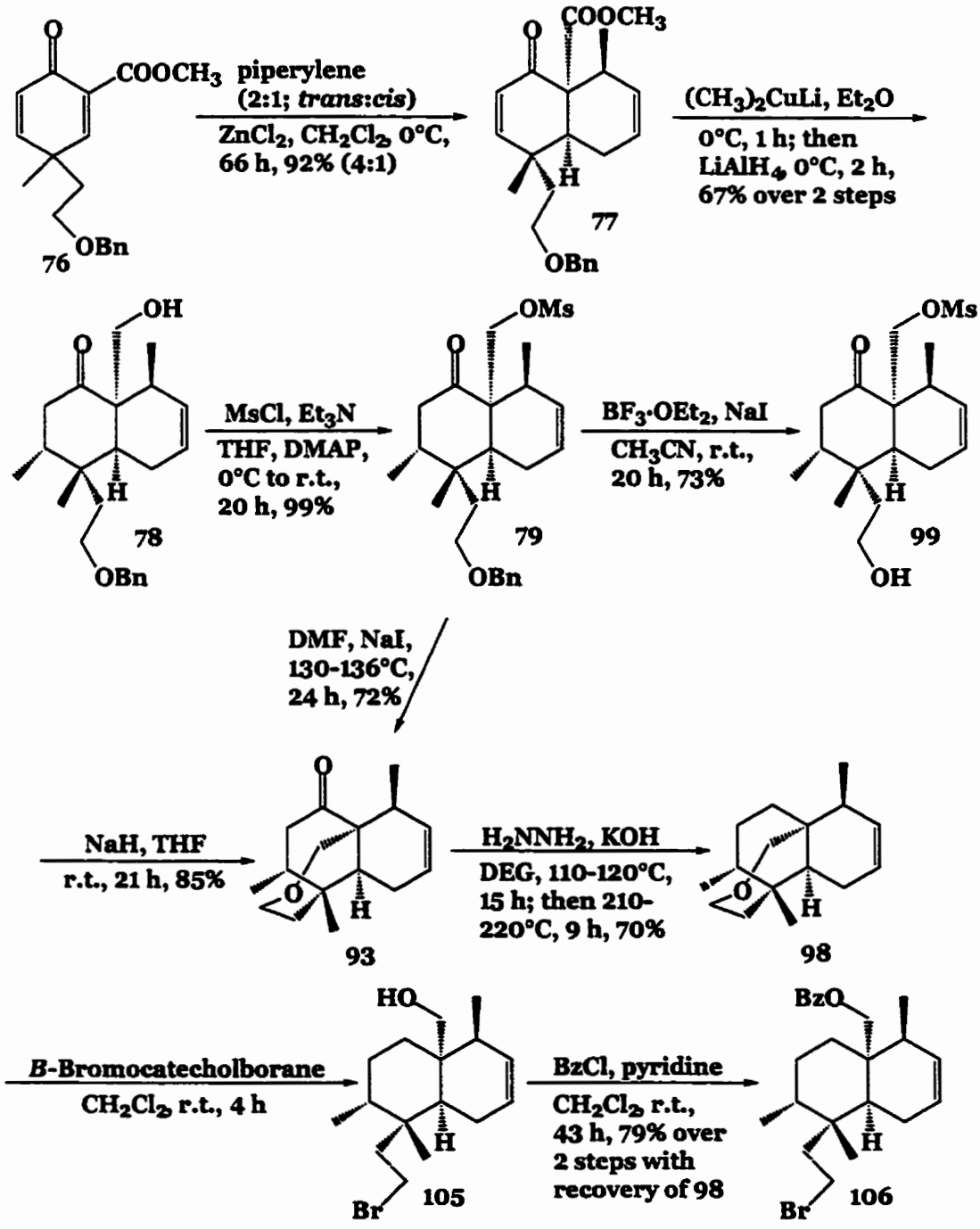
converted to a variety of enol derivatives with the general structure of **118** by base treatment followed by trapping of the ensuing enolate with an appropriate electrophile. Selective hydrogenation of the less sterically encumbered olefin would remove the undesired unsaturation to give enol ether **119**. Finally, reduction of the enol ether moiety will give the desired tricyclic ether **120** with the olefin in the desire position. Various types of enol derivatives are known in

the literature to be reductively removed while maintaining the olefin. Examples include silyl[73], triflate[74], phosphate[75], and *N,N,N',N'*-tetramethylphosphorodiamidate[76] enol derivatives. Research towards this end will be carried out in the future.

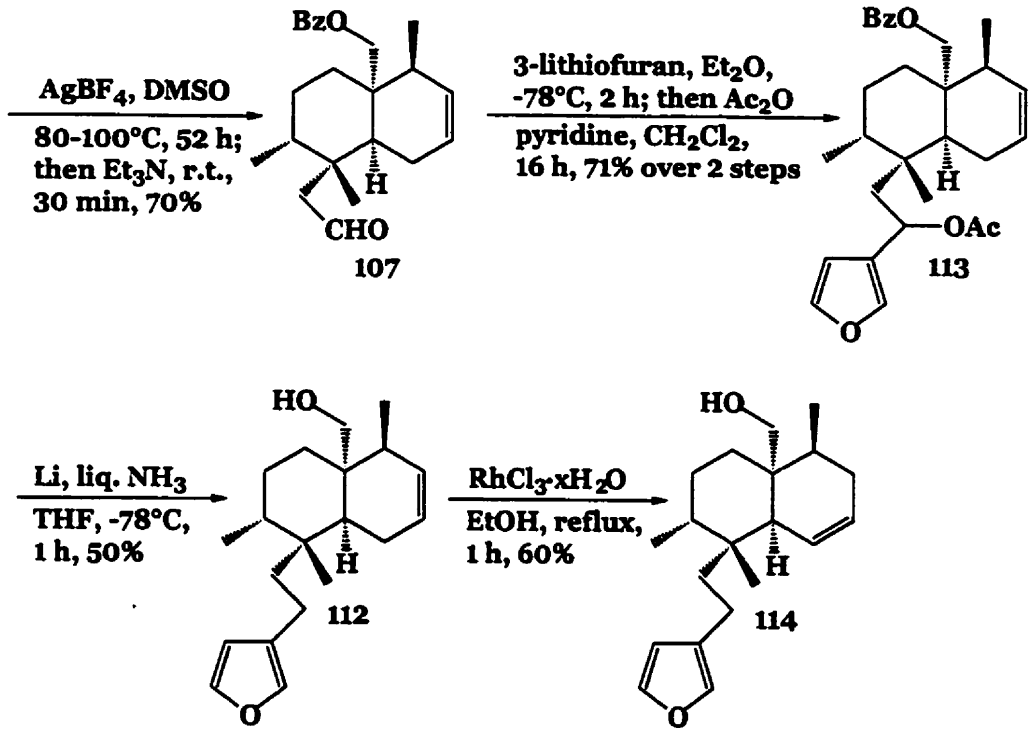
In late April of this year, a fire of serious proportions broke out in our laboratories. All three laboratories under our research group were extensively damaged. Afterwards it was discovered, to our dismay, that a significant portion of our spectral data of the most recent synthetic products had been destroyed or were discarded during the ensuing cleanup. As well, our spectroscopic samples and bulk intermediates were also either destroyed or discarded. Due to the lack of equipment, lab space, reagents, and most importantly time, we were unable to repeat the synthetic sequence to replenish those data that were unaccounted for. However, it is our intention to be able to replace these important spectroscopic data in the near future as this work will be continued.

In conclusion, as summarized in Scheme 28, we have developed a new synthetic route towards *cis*-normal clerodane natural products with oxygenated C-19 (clerodane numbering) functionalities as demonstrated by the successful synthesis of furyl alcohol **112**. Although furyl alcohol **112** has not been isolated from natural sources, it contains all the key constituents of a variety of *cis*-normal clerodane natural products and thus can be considered as an advanced intermediate. During our synthetic endeavor, the isolation and identification of the dienyl by-product **103** was viewed as quite significant. This compound is postulated to be amenable towards the synthesis of *cis*-normal clerodanes containing C-19 (clerodane numbering) methyl groups and our work towards this end is continuing. Finally, with the synthesis of advanced intermediate **113**, we

believe we have further demonstrated that our general synthetic scheme, starting with the Diels-Alder reaction of dienophile **76**, is one of the more flexible and easily manipulated schemes towards the synthesis of *cis*-normal clerodanes.



Scheme 28



Scheme 28 (cont.)

Experimental

General

Melting points were recorded on a Köfler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department using a Carlo Erba EA-1108 Elemental Analyzer. Fourier transform infrared spectra were recorded on a Nicolet Magna 750 instrument. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded using the following spectrometers: Bruker AM-200 (200 MHz), Bruker AM-300 (300 MHz), Varian Inova 300 (300 MHz), Bruker AM-360 (360 MHz), Bruker AM-400 (400 MHz), Varian Unity 500 (500 MHz), and Varian Inova 600 (600 MHz). Coupling constants are reported to within ±0.5 Hertz and 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, and br = broad. Carbon-13 magnetic resonance spectra (^{13}C-NMR) were recorded on the following spectrometers: Bruker AM-200 (50 MHz), Bruker AM-300 (75 MHz), and Bruker AM-400 (100 MHz). Deuteriochloroform or deuteriodichloromethane were used as the solvents for NMR experiments and internal standard. 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 appear as in-phase (p) resonances with respect to the deuterated solvent signal while methyl and methine carbons appear as anti-phase (a) resonances. 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 anti-phase with respect to the irradiated signal. Samples for nOe experiments were deoxygenated with argon for 10 minutes prior to use. High resolution electron impact mass spectra (HRMS) were recorded using a Kratos MS-50 mass spectrometer. Low resolution chemical ionization mass spectra were run on a Micromass VG7070E with ammonia reagent gas. Electrospray mass spectra (high and low resolution) were run using a Micromass ZABSPEC instrument. Mass spectral data were recorded as m/z values. Bulb-to-bulb distillation were performed using a Kugelrohr distillation apparatus. Eluent systems for flash chromatography are given in volume/volume concentrations.

Materials

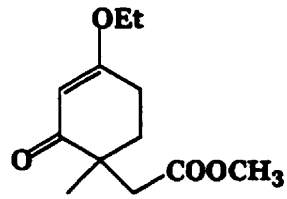
Unless otherwise stated, all materials used were commercially available and used as supplied. All compounds synthesized are racemic. Reactions requiring anhydrous conditions were performed in flame-dried glassware, cooled under an argon atmosphere. Unless otherwise stated, reactions were carried out under argon and monitored by analytical thin-layer chromatography (TLC) performed on aluminum-backed plates precoated with silica gel 60 F_{254} as supplied by Merck. Visualization of the resulting chromatograms were done by looking under an ultraviolet lamp (λ=254 nm) followed by dipping in an ethanol solution of vanillin (5% w/v) containing sulfuric acid 3% v/v) and charring by heat gun.

Solvents for flash chromatography were distilled under normal atmosphere prior to use. Solvent for reactions were dried and distilled under an argon atmosphere prior to use as follows: tetrahydrofuran, diethyl ether, and 1,2-dimethoxyethane from a dark blue solution of sodium benzophenone ketyl; benzene,

dichloromethane, pyridine, diisopropylamine, triethylamine, and carbon tetrachloride from calcium hydride. Purification of reagents, if deemed necessary, was performed using procedures and protocols as described by Perrin, Armarego, and Perrin[77]. Solvents were removed under water aspirator vacuum using a Büchi rotoevaporator. Argon was passed through a column of activated 4Å molecular sieves with self-indicating silica gel (coarse grained) interspersed within.

Flash chromatography developed by Still[78] was used routinely for purification and separation of product mixtures using silica gel of 230-400 mesh size as supplied by Merck. 3-Ethoxy-6-methyl-2-cyclohexen-1-one was prepared according to the procedure by Kende and co-workers[79].

6-(Carbomethoxymethyl)-3-ethoxy-6-methyl-2-cyclohexen-1-one (94)

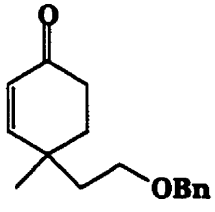


94

To a solution of diisopropylamine (15 mL, 0.107 mol) in anhydrous tetrahydrofuran (10 mL) cooled to 0°C, was added dropwise *n*-butyllithium (2.5 *M* in hexane, 39 mL, 0.098 mol). The resulting clear yellow solution was stirred at 0°C for 30 minutes followed by cooling to -78°C. To this was added, *via* a dropping funnel, a solution of 3-ethoxy-6-methyl-2-cyclohexen-1-one (13.731 g, 0.089 mol) in anhydrous tetrahydrofuran (20 mL). The resulting mixture was

allowed to stir at -78°C for 1 hour before methyl bromoacetate (17 mL, 0.180 mol) was added in one portion. The reaction vessel was removed from the cooling bath and allowed to warm to room temperature. After stirring at room temperature for 29 hours, saturated ammonium chloride (100 mL) was added and the aqueous layer extracted with diethyl ether (4 x 100 mL). The combined organic extracts were washed sequentially with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the crude product as a dark brown oil. Vacuum distillation (152-154°C/0.8 mm Hg) of the crude oil then yielded the desired enone ester **94** as a viscous light yellow oil (18.584 g, 92%): FTIR ($CDCl_3$ cast) 1737 (C=O ester), 1654 cm^{-1} (C=O enone); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 5.29 (d, J = 1 Hz, 1 H, =C-**H**), 3.90 (q, J = 7 Hz, 1 H, -O-C**H**H-CH_3), 3.89 (q, J = 7 Hz, 1 H, -O-CH**H**-CH_3), 3.63 (s, 3 H, -COOC**H**$_3$), 2.78 (d, J = 16 Hz, 1 H, -C**H**H-$COOCH_3$), 2.14-2.64 (m, 3 H), 2.37 (d, J = 16 Hz, 1 H, -CH**H**-$COOCH_3$), 1.75 (ddd, J = 14, 5, 5 Hz, 1 H, =C-C**H**H-), 1.35 (t, J = 7 Hz, 3 H, -CH_2C**H**$_3$), 1.16 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 50 MHz) δ 200.2 (p), 175.8 (p), 172.0 (p), 101.0 (a), 64.2 (p), 51.4 (a), 42.2 (p), 41.7 (p), 31.4 (p), 26.0 (p), 22.4 (a), 14.1 (a); HRMS M^+ 226.1200 (calculated for $C_{12}H_{18}O_4$: 226.1205)

4-(2-Benzyloxyethyl)-4-methyl-2-cyclohexen-1-one (95)



95

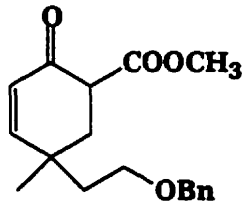
Lithium aluminum hydride (7.442 g, 0.196 mol) was suspended in anhydrous tetrahydrofuran (50 mL) and the resulting grey suspension was cooled to 0°C. A

solution of enone ester **94** (14.052 g, 0.062 mmol) in anhydrous tetrahydrofuran (50 mL) was then introduced dropwise. The reaction mixture was stirred at 0°C for 30 minutes before warming to room temperature. After stirring at room temperature for 18 hours, the reaction mixture was cooled to 0°C followed by careful sequential addition of water (8 mL), 15% aqueous sodium hydroxide solution (8 mL), and water (24 mL). The resulting milky white suspension was then warmed to room temperature and stirred vigorously for a further 15 minutes after which the solid precipitate was filtered off. After washing the filter residue with copious amounts of ethyl acetate, any aqueous layer was separated and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude diol thus obtained was then rigorously dried under high vacuum and used without further purification.

To a suspension of sodium hydride (6.210 g, 60% in oil, 0.155 mol) in anhydrous tetrahydrofuran (50 mL) cooled to 0°C, was added dropwise a solution of the above crude diol in anhydrous tetrahydrofuran (50 mL). After stirring for 1 hour at 0°C, benzyl bromide (19 mL, 0.160 mol) was introduced rapidly. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature for 8 hours. Hydrochloric acid (2.5 *N*) was then carefully added until the reaction solution was acidic followed by a further aliquot of 2.5 *N* hydrochloric acid of the same volume. The resulting biphasic solution was allowed to stir at room temperature for 8 hours at which time the aqueous layer was separated and extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were then washed sequentially with water (100 mL), saturated sodium bicarbonate (100 mL), and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product thus obtained was then purified by vacuum distillation (150°C/0.4 mm Hg) to yield the desired

product as a clear colorless oil (11.730 g, 77% over 3 steps): FTIR ($CDCl_3$ cast) 1680 cm^{-1} (C=O), 738 and 698 cm^{-1} (C-H bending, aromatic); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.34 (m, 5 H, aromatic **H**), 6.75 (d, J = 10 Hz, 1 H, O=C-CH=C**H**-), 5.88 (d, J = 10 Hz, 1 H, O=C-C**H**=CH-), 4.50 (s, 2 H, -C**H**$_2$-Ph), 3.59 (m, 2 H, -C**H**$_2$-OBn), 2.47 (m, 2 H), 2.00 (ddd, J = 15, 7, 7 Hz, 1 H, O=C-C**H**H-), 1.70-1.87 (m, 3 H), 1.18 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 199.3 (p), 158.8 (a), 138.1 (p), 128.3 (a), 127.7 (a), 127.5 (a), 127.1 (a), 73.0 (p), 66.6 (p), 40.2 (p), 34.9 (p), 34.0 (p), 25.2 (a); HRMS M^+ 244.1459 (calculated for $C_{16}H_{20}O_2$: 244.1463).

4-(2-Benzyloxyethyl)-6-carbomethoxy-4-methyl-2-cyclohexen-1-one (96)

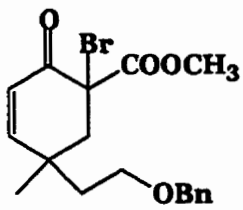


96

To a refluxing suspension of sodium hydride (95%, 0.321 g, 12.7 mmol) in anhydrous dimethyl carbonate (freshly distilled from calcium hydride, 5 mL), was added dropwise a solution of the starting enone **95** (1.479 g, 6.05 mmol) in anhydrous dimethyl carbonate (5 mL) while maintaining mild reflux. The resulting bright red suspension was then allowed to stir at reflux for 2.5 hoursat which time, the reaction was cooled to 0°C and quenched by the careful dropwise addition of 2.5 *N* hydrochloric acid. When all precipitate had dissolved, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 x 50 mL). The combined organic layers were then washed sequentially

with water (50 mL), saturated sodium bicarbonate (50 mL), and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a light brown oil. Purification of the crude product by flash chromatography using 15% EtOAc/hexane as eluent gave the desired keto ester **96** as a light yellow oil (1.537 g, 84%) : FTIR ($CDCl_3$ cast) 1744 (C=O ester), 1681 (C=O enone), 1670 (C=O···H-O-, enol ester), 1625 and 1590 (C=C, enol ester), 738 and 699 cm^{-1} (C-H bending, aromatic); ^{1}H-NMR ($CDCl_3$, 200 MHz, three isomers consisting of an enol tautomer and two keto diastereomers in a respective ratio of 0.5:0.3:0.2) δ 11.88 (s, 0.5 H, =C-O**H**), 7.35 (m, 5 H, aromatic **H**), 6.83 (dd, J = 10, 2 Hz, 0.3 H, O=C-CH=C**H**-, major keto), 6.74 (dd, J = 10, 2 Hz, 0.2 H, O=C-CH=C**H**-, minor keto), 6.13 (d, J = 10 Hz, 0.5 H, O=C-CH=C**H**-, enol), 5.94 (d, J = 10 Hz, 0.2 H, O=C-C**H**=, minor keto), 5.92 (d, J = 10 Hz, 0.3 H, O=C-C**H**=, major keto), 5.90 (d, J = 10 Hz, 0.5 H, O=C-C**H**=, enol), 4.51 (s, 0.4 H, -O-C**H**$_2$-Ph, minor keto), 4.50 (s, 0.6 H, -O-C**H**$_2$-Ph, major keto), 4.48 (s, 1.0 H, -O-C**H**$_2$-Ph, enol), 3.80 (s, 0.6 H, -COOC**H**$_3$, minor keto), 3.77 (s, 0.9 H, -COOC**H**$_3$, major keto), 3.76 (s, 1.5 H, -COOC**H**$_3$, enol), 3.50-3.70 (m, 2 H, -C**H**$_2$-OBn), 2.50 (d, J = 16 Hz, 0.5 H, -(CH$_3$)C-C**H**H-, enol), 2.29 (d, J = 16 Hz, 0.5 H, -(CH$_3$)C-CH**H**-, enol), 1.60-2.00 (m, 3.5 H), 1.24 (s, 0.9 H, -C**H**$_3$, major keto), 1.21 (s, 0.6 H, -C**H**$_3$, minor keto), 1.09 (s, 1.5 H, -C**H**$_3$, enol); HRMS M^+ 302.1515 (calculated for $C_{18}H_{22}O_4$: 302.1518).

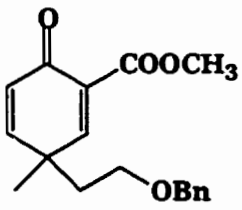
4-(2-Benzyloxyethyl)-6-bromo-6-carbomethoxy-4-methyl-2-cyclohex-en-1-one (97)



97

To a solution of the starting keto ester **96** (1.425 g, 4.712 mmol) in anhydrous carbon tetrachloride (5 mL) was added *N*-bromosuccinimide (2.516 g, 14.14 mmol). The reaction vessel was wrapped in aluminum foil and stirred at room temperature for a period of 17 hours. The reaction suspension was then filtered over Celite and the residue was washed with copious amounts of carbon tetrachloride. After evaporation of solvent under aspirator vacuum, the crude product was obtained as a dark brown oil which was subjected to flash chromatography using 10% EtOAc/hexane as eluent. The pure α-bromo keto ester **97** was thus obtained as a light yellow oil (1.414 g, 79%): FTIR ($CDCl_3$ cast) 1744 (C=O ester) and 1685 cm^{-1} (C=O enone); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.33 (m, 5 H, aromatic **H**), 6.73 (d, J = 10 Hz, 1 H, O=C-CH=C**H**-), 5.84 (d, J= 10 Hz, 1 H, O=C-C**H**=), 4.45 (s, 2 H, -OC**H**$_2$Ph), 3.53 (m, 2 H, -C**H**$_2$-OBn), 2.43 (m, 2 H, -C**H**$_2$-CH_2OBn), 2.00 (s, 3 H, -COOC**H**$_3$), 1.65-1.88 (m, 2 H,- (CH_3)C-C**H**$_2$-), 1.18 (s, 3 H, -C**H**$_3$); FAB-MS M^+ 381.2 and 383.2 (calculated for $C_{18}H_{21}O_3Br$: 381.27).

4-(2-Benzyloxyethyl)-2-carbomethoxy-4-methyl-2,5-cyclohexadien-1-one (76)



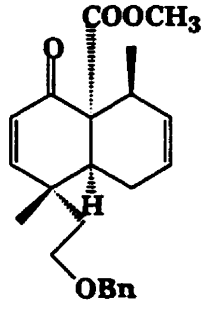
76

To a solution of the starting α-bromo keto ester **97** (2.657 g, 6.968 mmol) in anhydrous *N,N*-dimethylformamide (20 mL) was added lithium bromide (1.029 g, 11.85 mmol) and lithium carbonate (1.287 g, 17.42 mmol). The white suspension thus obtained was heated to 128-131°C and maintained at that temperature range for 2 hours. The reaction was subsequently cooled to room temperature and 2.5 *N* hydrochloric acid was carefully added until no more gas evolution was observed. The cloudy mixture was extracted with diethyl ether (4 x 80 mL) and the combined organic extracts were washed sequentially with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The dark brown oily crude product thus obtained was subjected to flash chromatography using 20% EtOAc/hexane as eluent to furnish the desired dienyl keto ester **76** as a light yellow oil (1.674 g, 80%): FTIR ($CDCl_3$ cast) 1741 (C=O ester), 1664 (C=O enone), 1635 (C=C), 737 and 699 cm^{-1} (C-H bending, aromatic); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.59 (d, J = 3 Hz, 1 H, CH_3OOC-C=C**H**-), 7.20-7.39 (m, 5 H, aromatic **H**), 6.79 (dd, J = 10, 3 Hz, 1 H, O=C-CH=C**H**-), 6.29 (d, J = 10 Hz, 1 H, O=C-C**H**=CH-), 4.35 (s, 2 H, -O-CH_2-Ph), 3.80 (s, 3 H, -$COOCH_3$), 3.34 (m, 2 H, -CH_2-OBn), 2.04 (m, 2 H, -CH_2-CH_2OBn), 1.32 (s, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) 181.6 (p), 165.0 (p), 160.9 (a), 153.5 (a), 137.8 (p), 130.5 (p), 129.2 (a), 128.3 (a), 127.6 (a), 73.2

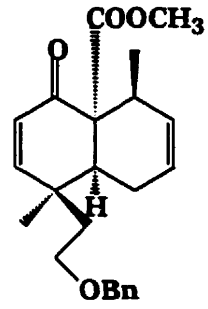
(p), 66.7 (p), 52.2 (a), 41.0 (p), 40.5 (p), 26.0 (a); HRMS M^+ 300.1353 (calculated for $C_{18}H_{20}O_4$: 300.1361).

Alternatively, the titled compound may be synthesized from 4-(2-benzyloxyethyl)-6-carbomethoxy-4-methyl-2-cyclohexen-1-one (**96**) using the procedure outlined below: To a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.656 g, 11.70 mmol) in anhydrous tetrahydrofuran (10 mL) was added anhydrous potassium carbonate (1.617 g, 11.70 mmol) and the resulting dark brown suspension was stirred at room temperature for 30 minutes. A solution of 4-(2-benzyloxyethyl)-6-carbomethoxy-4-methyl-2-cyclohexen-1-one (**96**) (1.769 g, 5.850 mmol) in anhydrous tetrahydrofuran (10 mL) was then added dropwise *via* a dropping funnel and the reaction suspension was stirred at room temperature for 12 hours. Aqueous sodium hydroxide (1 *M*) was added and the separated aqueous layer was extracted with ethyl acetate (4 x 80 mL). The combined organic extracts were washed sequentially with 1 *M* sodium hydroxide (2 x 50 mL), water (50 mL), and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield the crude product as a dark brown oil. Flash chromatography of the crude product using 20% EtOAc/hexane as eluent gave the desired dienyl keto ester **76** as a light yellow oil (1.136 g, 65%).

(1R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (77) and (1R*, 5S*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1-carbomethoxy-5,10-dimethylbicyclo[4.4.0]deca-3,8-dien-2-one (77A)



77

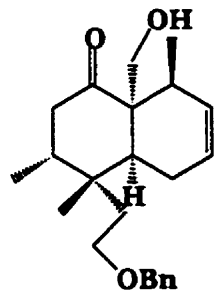


77A

Zinc chloride (1.403 g, 0.010 mol) was heat-fused under vacuum and cooled to room temperature while under a gentle stream of argon. Anhydrous dichloromethane (5 mL) was introduced and the fused zinc chloride was crushed using a thin spatula. The resulting mixture was cooled to 0°C and a solution of dienyl keto ester **76** (1.031 g, 0.003 mol) in anhydrous dichloromethane (1 mL) was added dropwise. The resulting light yellow suspension was stirred at 0°C for 15 minutes followed by a rapid introduction of piperylene (cis:trans = 1:2, 5.14 mL, 0.034 mol trans). The cloudy yellow reaction mixture was stirred vigorously (to prevent clogging) at 0°C for 66 hours after which saturated aqueous sodium bicarbonate (20 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 100 mL) and the combined organic extracts were washed with water (100 mL) followed by brine (100 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was thus obtained as a cloudy yellow oil. Flash chromatography using 5% EtOAc/hexane as eluent then yielded the desired Diels-Alder product as a mixture of two diastereomers whose

ratio was determined by GC analysis (**77**:**77A** =4.2:1, 1.158 g, 92%): FTIR ($CDCl_3$ cast) 1726 (C=O ester) and 1689 (C=O enone), 739 and 699 cm^{-1} (C-H bending, aromatic); HRMS M^+ 368.1984 (calculated for $C_{23}H_{28}O_4$: 368.1987); An aliquot of the diastereomeric mixture was subjected to repeated flash chromatographic separation using 5% EtOAc/hexane as eluent to furnish the desired diastereomer **77** individually for characterization: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.35 (m, 5 H, aromatic **H**), 6.31 (dd, J = 10, 2 Hz, 1 H, O=C-CH=C**H**-), 5.93 (d, J = 10 Hz, 1 H, O=C-C**H**=CH-), 5.66 (complex d, J = 10 Hz, 1 H, CH_3-CH-C**H**=CH-), 5.53 (complex d, J = 10 Hz, 1 H, CH_3-CH-CH=C**H**-), 4.52 (s, 2 H, -O-C**H**$_2$-Ph), 3.71 (s, 3 H, -COOC**H**$_3$), 3.64 (m, 2 H, -C**H**$_2$-OBn), 2.81 (m, 1 H, CH_3-C**H**-), 2.78 (ddd, J = 10, 7, 2 Hz, 1 H, (CH_3)C-C**H**-CH_2-), 2.19 (dm, J = 18 Hz, 1 H, =CH-C**H**H-), 1.96 (dm, J = 18 Hz, 1 H, =CH-CH**H**-), 1.76 (m, 2 H, -C**H**$_2$-CH_2OBn), 1.24 (d, J = 7 Hz, 3 H, -CH-C**H**$_3$), 1.12 (s, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz)δ 196.2 (p), 174.7 (p), 152.0 (a), 138.2 (p), 130.6 (a), 128.5 (a), 127.7 (a), 127.6 (a), 127.0 (a), 123.4 (a), 73.3 (p), 65.7 (p), 59.2 (p), 52.2 (a), 46.3 (a), 39.8 (p), 38.8 (a), 38.7 (p), 27.0 (p), 24.8 (a), 16.9 (a); diastereomer **77A** could not be obtained isomerically pure for characterization; ^{1}H-NMR ($CDCl_3$, 200 MHz, selected data) δ 5.87 (d, J = 10 Hz, 1 H, O=C-C**H**=CH-), 4.53 (s, 2 H, -O-C**H**$_2$-Ph), 3.73 (s, 3 H, -COOC**H**$_3$), 1.28 (d, J = 7 Hz, 3 H, -CH-C**H**$_3$), 1.17 (s, 3 H, -C**H**$_3$). The spectral data are in good agreement with those reported previously[57].

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1-hydroxymethyl-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (78)

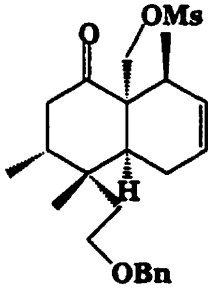


78

To an off-white suspension of copper(I) iodide (0.260 g, 1.37 mmol) in anhydrous diethyl ether (5 mL) cooled to 0°C, was added dropwise methyllithium (1.4 *M* in diethyl ether, 1.88 mL, 2.63 mmol). The resulting clear colorless solution was stirred at 0°C for 1 hour followed by the dropwise introduction of a solution of enone ester 77 (0.162 g, 0.440 mmol) in anhydrous diethyl ether (1 mL). The subsequent yellow suspension was stirred at 0°C for 1 hour, at which point lithium aluminum hydride (0.050 g, 1.32 mmol) was added in one portion. The reaction mixture immediately turned into a black suspension which was then stirred at 0°C for 2 hours. Saturated ammonium chloride was then added dropwise and when gas no longer evolved, 2.5 *N* hydrochloric acid (10 mL) was introduced. The resulting grey suspension was filtered over Celite and the residue was rinsed with copious amounts of diethyl ether. The aqueous layer in the filtrate was separated and extracted with diethyl ether (4 x 20 mL) and the combined organic extracts were washed sequentially with water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product thus obtained as a clear yellow oil was subjected to flash chromatography using 15%

EtOAc/hexane as eluent to yield, after evaporation of solvent, the desired keto alcohol **78** as a clear colorless oil (0.105 g, 67%): FTIR ($CDCl_3$ cast) 3460 (br, OH) and 1696 (C=O), 736 and 698 cm^{-1} (C-H bending, aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5 H, aromatic **H**), 5.85 (ddd, J = 10, 5, 1 Hz, 1 H, CH_3CH-CH=C**H**-), 5.75 (dd, J = 10, 5 Hz, 1 H, CH_3CH-C**H**=CH-), 4.50 (s, 2 H, -O-C**H**$_2$-Ph), 3.58 (d, J = 11 Hz, 1 H, HO-CH**H**-), 3.54 (dd, J = 7, 7 Hz, 2 H, -C**H**$_2$-OBn), 3.45 (d, J = 11 Hz, HO-CH**H**-), 2.80 (br. s, 1 H, -O**H**), 2.50 (m, 1 H, =CH-C**H**-CH_3), 2.35 (dd, J = 11, 11 Hz, 1 H, O=C-C**H**H-), 1.96-2.20 (m, 5 H), 1.60 (m, 2 H), 1.01 (d, J = 7 Hz, 3 H, =CH-CH-C**H**$_3$), 0.98 (s, 3 H, -C**H**$_3$), 0.89 (d, J = 7 Hz, 3 H, -CH_2-CH-C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 219.9 (p), 138.3 (p), 132.2 (a), 128.4 (a), 127.7 (a), 126.6 (a), 73.3 (p), 69.4 (p), 67.0 (p), 55.2 (p), 46.0 (p), 41.6 (a), 37.3 (p), 35.1 (a), 34.8 (p), 33.0 (a), 22.9 (p), 22.5 (a), 17.3 (a), 15.5 (a); HRMS M^+ 356.2355 (calculated for $C_{23}H_{32}O_3$: 356.2351).

(1S*, 4R*, 5R*, 6S*, 10S*)-5-(2-Benzyloxyethyl)-1-mesyloxymethyl-4,5,10-trimethylbicyclo[4.4.0]dec-8-en-2-one (79)

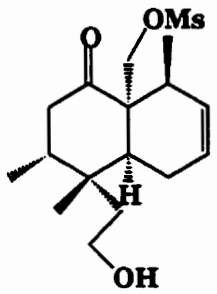


79

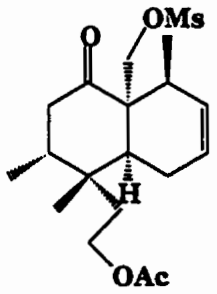
To a solution of keto alcohol **78** (0.212 g, 0.595 mmol) in anhydrous tetrahydrofuran (5 mL) cooled to 0°C was added 4-(*N*,*N*-dimethylamino)pyridine (0.010 g, 0.082 mmol) and triethylamine (0.45 mL, 3.23 mmol). To this mixture

was then added methanesulfonyl chloride (0.23 mL, 2.97 mmol). The resulting white suspension was stirred at 0°C for 5 minutes followed by warming to room temperature. After stirring at room temperature for 20 hours, 5% hydrochloric acid was added dropwise until all the precipitate had dissolved. Water (20 mL) was added and the mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed sequentially with water (30 mL), saturated sodium bicarbonate (30 mL), and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The clear light yellow oil thus obtained was then subjected to flash chromatography using 5% EtOAc/hexane as eluent to yield the desired keto mesylate **79** as a clear colorless oil (0.256 g, 99%): FTIR ($CDCl_3$ cast) 1700 (C=O), 1357 and 1176 (-SO_2-), 737 and 699 cm^{-1} (C-H bending, aromatic); ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 7.35 (m, 5 H, aromatic **H**), 6.64 (dddd, J = 10, 4, 2, 2 Hz, 1 H, CH_3-CH-C**H**=CH-), 5.88 (m, 1 H, CH_3-CH-CH=C**H**-), 4.51 (d, J = 12 Hz, 1 H, -O-C**H**H-Ph), 4.48 (d, J = 9 Hz, 1 H, -C**H**H-OMs), 4.43 (d, J = 12 Hz, 1 H, -O-CH**H**-Ph), 4.03 (d, J = 9 Hz, 1 H, -CH**H**-OMs), 3.56 (m, 2 H, -C**H**$_2$-OBn), 2.95 (s, 3 H, -OSO_2-C**H**$_3$), 2.41 (dd, J = 7, 4 Hz, 1 H, O=C-C**H**H-), 2.29 (dd, J = 15, 5 Hz, 1 H), 2.01-2.22 (m, 4 H), 1.98 (m, 1 H, -(CH_3)C-C**H**-CH_2-), 1.60 (m, 2 H, -C**H**$_2$-CH_2OBn), 1.01 (d, J = 7 Hz, 3 H, =CH-CH-C**H**$_3$), 0.98 (s, 3 H, -C**H**$_3$), 0.88 (d, J = 7 Hz, 3 H, -CH_2-CH-C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 213.4 (p), 138.5 (p), 130.9 (a), 128.4 (a), 127.8 (a), 127.6 (a), 127.4 (a), 74.0 (p), 73.3 (p), 67.0 (p), 54.2 (p), 45.2 (p), 39.6 (a), 37.3 (p), 37.1 (a), 35.6 (a), 35.2 (p), 34.4 (a), 22.9 (p), 22.8 (a), 17.1 (a), 15.7 (a); HRMS M^+ 434.2127 (calculated for $C_{24}H_{34}O_5S$: 434.2127).

(1S*, 4R*, 5R*, 6R*, 10S*)-5-(2-Hydroxyethyl)-4,5,10-trimethyl-1-mesyloxymethylbicyclo[4.4.0]dec-8-en-2-one (99) and (1S*, 4R*, 5R*, 6R*, 10S*)-5-(2-acetoxyethyl)-4,5,10-trimethyl-1-mesyloxymethylbicyclo[4.4.0]dec-8-en-2-one (100).



99

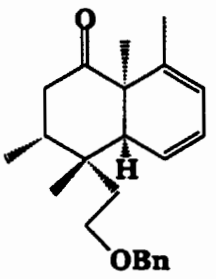


100

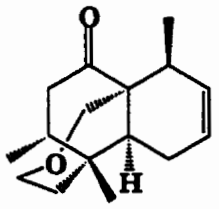
To a solution of benzyl ether **79** (0.145 g, 0.334 mmol) in anhydrous acetonitrile (5 mL) was added sodium iodide (0.330 g, 2.20 mmol) and the resulting clear colorless solution was cooled to 0°C. Boron trifluoride etherate (0.26 mL, 2.05 mmol) was then added dropwise to the reaction mixture. The light yellow solution was stirred at 0°C for 1 hour before warming to room temperature. After stirring at room temperature for 20 hours, the reaction solution was poured into ice and diluted with diethyl ether (20 mL). Saturated sodium thiosulphate was added dropwise until no more discoloration occurs and the aqueous layer was extracted with diethyl ether (4 x 20 mL). The combined organic extracts were washed with water (20 mL) followed by brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product thus obtained as a light yellow oil was subjected to flash chromatography using 30% EtOAc/hexane as eluent to give the by-product acetyl mesylate **100** (0.026 g, 20%): FTIR ($CDCl_3$ cast) 1738 (C=O ester), 1706 (C=O ketone), and 1360 and 1210 cm^{-1} (-SO_2-); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.88 (m, 1 H, -CH_2-CH=CH-), 5.63 (m, 1 H,

-CH_2-CH=C**H**-), 4.48 (d, J = 9 Hz,1 H, -C**H**H-OMs), 4.12 (m, 2 H, -C**H**$_2$-OAc), 4.02 (d, J = 9 Hz, 1 H, -CH**H**-OMs), 3.00 (s, 3 H, -OSO_2-C**H**$_3$), 2.30-2.40 (m, 2 H), 1.90-2.23 (m, 5 H), 2.01 (s, 3 H, C**H**$_3$-C(O)-), 1.60 (m, 2 H), 1.02 (d, J = 7 Hz, 3 H, -C**H**$_3$), 1.01 (s, 3 H, -C**H**$_3$), 0.91 (d, J = 7 Hz, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 213.0 (p), 171.2 (p), 130.7 (a), 127.0 (a), 74.0 (p), 61.3 (p), 54.0 (p), 45.2 (p), 39.2 (a), 37.3 (p), 37.0 (a), 35.8 (a), 34.3 (p), 34.2 (a), 22.6 (p), 22.5 (a), 21.1 (a), 17.3 (a), 15.7 (a); HRMS $[M+1]^+$ 387.1825 (calculated for $C_{19}H_{31}O_6S$: 387.1841). Further elution then gave the desired mesyl alcohol **99** as a clear colorless oil (0.084 g, 73%): FTIR ($CDCl_3$ cast) 3441 (br, OH), 1698 (C=O), 1353 and 1174 cm^{-1} (-SO_2-); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.97 (m, 1 H, -CH_2-C**H**=CH-), 5.79 (ddm, J = 10, 5 Hz, 1 H, -CH_2-CH=C**H**-), 4.56 (d, J = 9 Hz, 1 H, -C**H**H-OMs), 3.90 (d, J = 9 Hz, 1 H, -CH**H**-OMs), 3.76 (ddd, J = 11, 11, 5 Hz, 1 H, -C**H**H-OH), 3.56 (ddd, J = 11, 11, 5 Hz, 1 H, -CH**H**-OH), 3.06 (s, 3 H, -OSO_2-C**H**$_3$), 2.05-2.40 (m, 7 H), 1.98 (m, 1 H, =CH-C**H**-CH_3), 1.64 (ddd, J = 13, 11, 6 Hz,1 H, -C**H**H-CH_2OH), 1.23 (m, 1 H, -CH**H**-CH_2OH), 0.99 (d, J = 7 Hz, 3 H, =CH-CH-C**H**$_3$), 0.91 (s, 3 H, -C**H**$_3$), 0.88 (d, J = 7 Hz, 3 H, -C**H**$_3$); HRMS [M-H_2O]$^+$ 326.1562 (calculated for $C_{17}H_{26}O_4S$: 326.1552) and [M-CH_3SO_3H]$^+$ 248.1777 (calculated for $C_{16}H_{24}O_2$: 248.1776).

(1R*, 4R*, 5R*, 6S*)-5-(2-Benzyloxyethyl)-1,4,5,10-tetramethylbicyclo-[4.4.0]deca-7,9-dien-2-one (103) and (1S*, 2S*, 6S*, 7R*, 14R*)-2,7,14-trimethyl-10-oxatricyclo[5.4.3.0^{1,6}]tetradec-3-en-12-one (93)



103



93

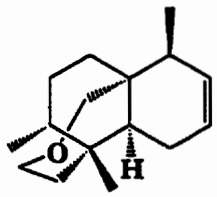
To a solution of starting keto mesylate **79** (0.145 g, 0.334 mmol) in anhydrous *N,N*-dimethylformamide (2.5 mL) was added sodium iodide (0.100 g, 0.667 mmol) and the suspension was stirred at room temperature until a clear light yellow solution was achieved. The mixture was heated to 130-136°C and maintained at that temperature range for 24 hours before cooling to room temperature. Diethyl ether (50 mL) was added followed by water (20 mL) and dropwise addition of saturated aqueous sodium thiosulfate until the mixture no longer discolors. The organic layer was separated and the aqueous layer was extracted with diethyl ether (4 x 30 mL). The combined organic extracts were washed with water (20 mL) followed by brine (20 mL), dried over magnesium sulfate, and filtered. Concentration *in vacuo* gave the crude product as a light yellow oil. Flash chromatography of the crude product using 10% EtOAc/hexane as eluent gave the dienyl by-product **103** (0.026 g, 23%): FTIR ($CDCl_3$ cast) 1706 (C=O), 736 and 697 cm^{-1} (C-H bending, aromatic); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5 H, aromatic **H**), 6.01 (dd, J = 10, 5 Hz, 1 H, -CH=C**H**-CH=), 5.69 (ddd, J = 5, 1, 1 Hz, 1 H, -(CH_3)C=C**H**-), 5.63 (ddd, J = 10, 5, 1 Hz, 1 H, -CH=C**H**-), 4.48 (s, 2 H, -O-CH_2-Ph), 3.49 (m, 2 H, -CH_2-OBn), 2.65 (dd, J = 14, 5 Hz, 1 H, O=C-

CHH-), 2.20 (d, J = 5 Hz, 1 H, =CH-CH-), 2.09 (dd, J = 14, 5 Hz, 1 H, O=C-CHH-), 2.02 (m, 1 H, O=C-CH_2-CH-), 1.79 (m, 1 H, -CHH-CH_2OBn), 1.67 (m, 1 H, -CHH-CH_2OBn), 1.57 (d, J = 1 Hz, 3 H, =C-CH_3), 1.21 (s, 3 H, -CH_3), 1.09 (s, 3 H, -CH_3), 0.87 (d, J = 7 Hz, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 214.4 (p), 138.4 (p), 136.9 (p), 128.4 (a), 127.6 (a), 127.5 (a), 125.2 (a), 123.2 (a), 120.9 (a), 73.1 (p), 66.1 (p), 52.4 (p), 48.7 (a), 44.9 (p), 39.3 (p), 38.7 (a), 37.3 (p), 20.5 (a), 19.1 (a), 15.0 (a); HRMS M^+ 338.2244 (calculated for $C_{23}H_{30}O_2$: 338.2246). Further elution then yielded the desired tricyclic keto-ether **93** (0.046 g, 72%): FTIR ($CDCl_3$ cast) 1704 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.50 (m, 2 H, -CH=CH-), 4.18 (d, J = 13 Hz, 1 H, -CHH-O-), 3.98 (m, 2 H, -CH_2CH_2O-), 3.58 (d, J = 13 Hz, 1 H, -CHH-O-), 2.59 (complex dd, J = 17, 14 Hz, 1 H, -CHH-C=O), 2.07-2.33 (m, 6H), 1.91 (m, 1 H, -CH-CH_2CH=), 1.51 (ddd, J = 16, 6, 5 Hz, 1 H, -CHH-CH_2O-), 1.23 (d, J = 7 Hz, 3 H, -CH_3), 1.02 (s, 3 H, -CH_3), 0.95 (d, J = 7 Hz, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 211.9 (p), 131.9 (a), 123.0 (a), 69.5 (p), 65.7 (p), 58.1 (p), 49.8 (a), 46.8 (p), 38.8 (p), 38.7 (a), 36.6 (a), 35.5 (p), 27.2 (a), 25.2 (p), 16.7 (a), 15.9(a); HRMS M^+ 248.1788 (calculated for $C_{16}H_{24}O_2$: 248.1778).

Alternatively, tricyclic keto ether **93** may be synthesized from keto alcohol **99** using the following procedure: To a solution of keto alcohol **99** (0.084 g, 0.244 mmol) in anhydrous tetrahydrofuran (5 mL) was added sodium hydride (95%, 0.009 g, 0.356 mmol) and the resulting grey suspension was stirred at room temperature for 21 hours. 5% Hydrochloric acid was then added dropwise until no more gas was observed. Water (10 mL) was then introduced and the mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed sequentially with water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL). The organic solution thus obtained was dried over

magnesium sulfate, filtered, and concentrated *in vacuo* to afford the crude product as a clear colorless oil. Flash chromatography as detailed above then yielded the titled compound in 85% yield.

(1S*, 2S*, 6S*, 7R*, 14R*)-2,7,14-Trimethyl-10-oxatricyclo[5.4.3.$0^{1,6}$]-tetradec-3-ene (98)

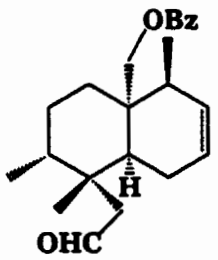


98

To a solution of starting tricyclic keto ether **93** (0.179 g, 0.721 mmol) in diethylene glycol (6 mL) was added potassium hydroxide (85%, 0.285 g, 4.32 mmol) and the resulting suspension was stirred at room temperature until most of the potassium hydroxide has dissolved. Anhydrous hydrazine (0.91 mL, 29.0 mmol) was then added and the reaction mixture was warmed to 110-120°C. After 15 hours at 110-120°C, the temperature was gradually increased to 210-230°C and maintained at that temperature range for 9 hours. After cooling to room temperature, water (20 mL) was added and resulting cloudy solution was then extracted with diethyl ether (4 x 30 mL). The combined extracts were washed sequentially with water (20 mL), 5% hydrochloric acid (20 mL), and brine (20 mL) followed by drying over magnesium sulfate. Filtration and evaporation of solvent *in vacuo* then yielded a clear oil which was subjected to flash chromatography using 5% EtOAc/hexane as eluent to give the desired tricyclic ether **98** (0.119 g, 70%). FTIR (CH_2Cl_2 cast) 3015 cm^{-1} (=CH); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.59 (dddd, J = 10, 5, 3, 3 Hz, 1 H, -CH_2**C**H=), 5.33 (ddd, J = 10, 5, 2

Hz, 1 H, -(CH_3)CHC**H**=), 3.92 (m, 2 H, -CH_2C**H**$_2$O-), 3.86 (d, J = 13 Hz, 1 H -C**H**HO-), 3.41 (d, J = 13 Hz, 1 H, -CH**H**O-), 2.23 (ddd, J = 16, 12, 5 Hz, 1 H -CH**H**CH_2O-), 2.21 (m, 1 H, -(CH_3)C**H**CH=), 2.05 (m, 2 H, -C**H**$_2$CH=), 1.76 (m, 1 H, -C**H**CH_2CH=), 1.75 (m, 1 H, -(CH_3)C**H**CH_2-), 1.43-1.56 (m, 2 H), 1.26 (ddd, J = 13, 13, 6 Hz, 1 H), 1.17 (ddd, J = 16, 4, 4 Hz, 1 H, -C**H**HCH_2O-), 1.10 (complex d, J = 14 Hz, 1 H), 0.96 (s, 3 H, -C**H**$_3$), 0.84 (d, J = 7 Hz, 3 H, -C**H**$_3$), 0.83 (d, J = 7 Hz, 3 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 131.3 (a), 124.1 (a), 68.8 (p), 65.3 (p), 42.6 (a), 40.2 (p), 38.1 (p), 37.8 (a), 33.9 (a), 33.7 (p), 28.1 (p), 27.8 (a), 24.4 (p), 22.5 (p) , 15.6 (a), 15.5 (a); HRMS M^+ 234.1987 (calculated for $C_{16}H_{26}O$: 234.1984).

(1R*, 2S*, 6S*, 7R*, 8R*)-1-Benzoyloxymethyl-2,7,8,-trimethyl-7-(2-oxoethyl)bicyclo[4.4.0]dec-3-ene (107)



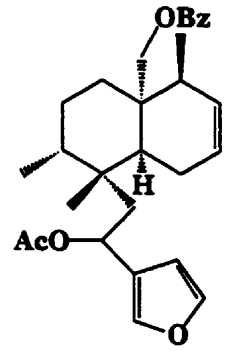
107

To a solution of tricyclic ether **98** (0.104 g, 0.444 mmol) in anhydrous dichloromethane (5 mL) was added *B*-bromocatecholborane (0.182 g, 0.915 mmol) and the resulting colorless solution was stirred at room temperature for 4 hours. The reaction was then diluted with dichloromethane (10 mL) and quenched with water (10 mL). The biphasic mixture was stirred at room temperature for 30 minutes after which the aqueous phase was extracted with dichloromethane (4 x 30 mL). The combined organic extracts were then washed

sequentially with dilute sodium hydroxide (20 mL), water (20 mL), and brine (20 mL) followed by drying over magnesium sulfate. Filtration followed by concentration *in vacuo* afforded a clear colorless oil which was further dried under high vacuum. Selected spectroscopic data: FTIR ($CHCl_3$ cast) 3442 cm^{-1} (br, OH); 1H-NMR (CDCl3, 200 MHz) δ 4.10 (m, 1 H, -CHH-Br), 4.08 (d, J = 11 Hz, 1 H, -CHH-O-), 3.59 (d, J = 11 Hz, 1 H, -CHH-O-), 3.40 (m, 1 H, -CHH-Br); HRMS M^+ 314.1244 and 316.1226 (calculated for $C_{16}H_{27}O^{79}Br$: 314.1245; calculated for $C_{16}H_{27}O^{81}Br$: 316.1225). The crude bromo alcohol thus obtained was dissolved in anhydrous dichloromethane (2 mL) followed by the sequential addition of benzoyl chloride (1.5 mL, 12.9 mmol) and anhydrous pyridine (2.0 mL, 24.7 mmol). The clear light yellow reaction mixture was stirred at room temperature for 43 hours at which time, the reaction mixture was diluted with dichloromethane (30 mL) and quenched with 5% hydrochloric acid (10 mL). The aqueous layer was separated and extracted with dichloromethane (4 x 30 mL) followed by washing of the combined organic extracts sequentially with water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL). Drying over magnesium sulfate, filtration, and concentration *in vacuo* then gave a clear colorless oil which was subjected to flash chromatography using 5% EtOAc/hexane as eluent to afford an inseparable mixture of the desired bromo benzoate **106** along with tricyclic ether **98** in a 2:1 ratio as determined by ^{1}H-NMR (0.129 g, 79% over 2 steps accounting for tricyclic ether **98**). Selected spectroscopic data: FTIR (CDCl3 cast) 1720 (C=O) and 1269 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$, 360 MHz) δ 8.06 (m, 2 H, aromatic **H**), 7.58 (m, 1 H, aromatic **H**), 7.46 (m, 2 H, aromatic **H**), 4.64 (d, J = 13 Hz, 1 H, -CHH-OBz), 4.41 (d, J = 13 Hz, 1 H, -CHH-OBz), 3.59 (ddd, J = 13, 9, 4 Hz, 1 H, Br-CHH-), 3.31 (ddd, J = 14, 9, 5 Hz, 1 H, Br-CHH-), 2.58 (m, 1 H, =CH-CH-CH_3). The above purified mixure (0.118 g) was then dissolved in anhydrous dimethyl sulfoxide (2 mL) and silver

tetrafluoroborate (0.084 g, 0.431 mmol) was introduced. The suspension was stirred at room temperature until complete dissolution was achieved followed by warming to 80-100°C. After heating for 52 hours, the reaction mixture was cooled to room temperature and triethylamine (1 mL) was introduced. The resulting black suspension was stirred at room temperature for a further 30 minutes. Water (30 mL) was added and the mixture was extracted with diethyl ether (4 x 30 mL). The combined organic extracts were washed sequentially with 5% hydrochloric acid (20 mL), water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL) followed by drying over magnesium sulfate. Filtration and concentration of the filtrate *in vacuo* afforded the crude product as a clear oil. Flash chromatography of the crude product using 5% EtOAc/hexane as eluent then gave the desired benzoyl aldehyde **107** (0.047 g, 70%). FTIR ($CDCl_3$ cast) 1717 cm^{-1} (C=O aldehyde and ester); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.75 (t, J = 2 Hz, 1 H, C**H**O), 7.98 (m, 2 H, aromatic **H**), 7.55 (m, 1 H, aromatic **H**), 7.43 (m, 2 H, aromatic **H**), 5.61 (m, 1 H, -CH=C**H**-), 5.34 (ddd, J = 10, 4, 1 Hz, 1 H, -C**H**=CH-), 4.54 (d, J = 13 Hz, 1 H, -CH**H**-O-), 4.35 (d, J = 13 Hz, 1 H, -C**H**H-O-), 2.76 (dd, J = 18, 2 Hz, 1 H, -C**H**H-CHO), 2.51 (m, 2 H, -C**H**-CH_2-CH= and -(CH_3)C**H**-CH=), 2.24 (dd, J = 18, 2 Hz, 1 H, -CH**H**-CHO), 2.22 (m, 2 H, -C$\mathbf{H}_2$-CH=), 1.80 (m, 1 H), 1.80 (m, 1 H, -(CH_3)C**H**-CH_2), 1.20-1.70 (m, 3 H), 1.17 (d, J = 1 Hz, 3 H, -C$\mathbf{H}_3$), 0.89 (d, J = 7 Hz, 3 H, -C$\mathbf{H}_3$), 0.85 (d, J = 7 Hz, 3 H, -C$\mathbf{H}_3$); ^{13}C-NMR (APT, $CDCl_3$, 100 MHz) δ 202.5 (a), 166.9 (p), 133.1 (a), 130.5 (a), 130.0 (p), 129.6 (a), 128.5 (a), 123.8 (a), 67.4 (p), 49.7 (p), 39.1 (p), 38.3 (a), 35.7 (a), 35.0 (a), 29.7 (p), 27.8 (p), 27.5 (a), 25.7 (p), 23.2 (p), 16.1 (a), 15.6 (a); High Resolution Electrospray $[M + Na]^+$ 377.2092 (calculated for $C_{23}H_{30}O_3Na$: 377.2093).

(1R*, 2S*, 6S*, 7R*, 8R*)-7-(2-Acetoxy-2-(3-furyl)ethyl)-1-benzoyloxymethyl-2,7,8-trimethylbicyclo[4.4.0]dec-3-ene (113)

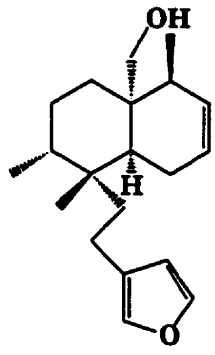


113

To a solution of *t*-butyllithium (1.7 *M* in pentane, 1.4 mL, 2.38 mmol) in anhydrous diethyl ether (8.5 mL) cooled to -78°C, was added dropwise 3-bromofuran (0.1 mL, 1.11 mmol) and the resulting clear yellow solution was stirred at -78°C for 1 hour. The 3-lithiofuran thus prepared was used as a 0.1 *M* stock solution. To a solution of the starting benzoyl aldehyde **107** (0.047 g, 0.133 mmol) in anhydrous diethyl ether (8 mL) cooled to -78°C was added 3-lithiofuran (freshly prepared, 0.1 *M* in diethyl ether, 2 mL, 0.200 mmol) and the resulting clear light yellow solution was stirred at -78°C for 2 hours. Solid ammonium chloride was then introduced and the reaction suspension was allowed to warm to room temperature followed by dropwise addition of water until all the white solid had dissolved. The aqueous layer was extracted with diethyl ether (4 x 20 mL) and the combined organic extracts were washed sequentially with water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL) followed by drying over magnesium sulfate. Filtration and subsequent concentration *in vacuo* of the filtrate gave the crude product as a clear colorless oil. Partial spectroscopic data: FTIR ($CHCl_3$ cast) 3400 (br, OH) and 1693 cm^{-1} (C=O); HRMS M^+ 422.2442 (calculated for $C_{27}H_{34}O_4$: 422.2457). The above crude

furyl alcohol was then dissolved in anhydrous dichloromethane (3 mL) followed by the addition of anhydrous pyridine (1 mL, 12.4 mmol) and acetic anhydride (1 mL, 10.6 mmol). The reaction mixture was stirred at room temperature for 16 hours at which time additional dichloromethane (20 mL) was added followed by water (10 mL). The aqueous layer was separated and extracted with dichloromethane (4 x 20 mL) and the combined organic extracts were washed sequentially with 5% hydrochloric acid (20 mL), water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL). After drying over magnesium sulfate, filtration, and concentration *in vacuo*, the crude product was obtained as a clear light yellow oil. Flash chromatography using 5% EtOAc/hexane as eluent then afforded the desired furyl acetate **113** as a 1:1 mixture of diastereomers (0.044 g, 71% over 2 steps). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.11 (ddd, J = 7, 7, 1 Hz, 2 H, aromatic **H**), 7.56 (m, 1 H, aromatic **H**), 7.46 (m, 2 H, aromatic **H**), 7.29 (m, 0.5 H, furan α-**H**), 7.25 (m, 0.5 H, furan α-**H**), 7.07 (m, 0.5 H, furan α-**H**),6.86 (m, 0.5 H, furan α-**H**), 6.36 (dd, J = 9, 3 Hz, 0.5 H, -C**H**-OAc), 6.19 (d, J = 1, 0.5 H, furan β-**H**), 5.99 (d, J = 1, 0.5 H, furan β-**H**), 5.85 (dd, J = 9, 3 Hz, 0.5 H, -C**H**-OAc), 5.60 (m, 1 H, -C**H**=CH-), 5.32 (m, 1 H, -CH=C**H**-), 4.52 (d, J = 13 Hz, 0.5 H, -CH**H**-OBz), 4.50 (d, J = 12 Hz, 0.5 H, -CH**H**-OBz), 4.38 (d, J = 12 Hz, 0.5 H, -C**H**H-OBz), 4.28 (d, J = 13 Hz, 0.5 H, -C**H**H-OBz), 2.55 (m, 1 H), 2.00-2.45 (m, 5 H), 1.96 (s, 1.5 H, C**H**$_3$-C(O)-), 1.82 (s, 1.5 H, C**H**$_3$C(O)-), 1.10-1.60 (m, 5 H), 0.95 (d, J = 7 Hz, 3 H, -CH-C**H**$_3$), 0.92 (s, 3 H, -C**H**$_3$), 0.90 (d, J = 7 Hz, 3 H, -CH-C**H**$_3$).

(1R*, 2S*, 6S*, 7R*, 8R*)-7-(2-(3-Furyl)ethyl)-1-hydroxymethyl-2,7,8,-trimethylbicyclo[4.4.0]dec-3-ene (112)

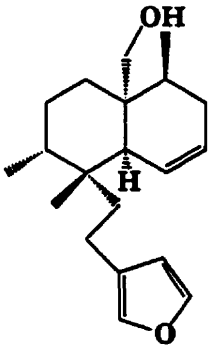


112

To a dark blue solution of lithium (0.066 g, 9.51 mmol) in liquid ammonia cooled to -78°C was added a solution of the starting furyl acetate **113** (0.009 g, 0.019 mmol) in anhydrous tetrahydrofuran (3 mL) and the reaction mixture was maintained at -78°C for 1 hour. Solid ammonium chloride was then added and the liquid ammonia was allowed to evaporate by warming the reaction slowly to 0°C. When no more bubbling was observed, ethyl acetate (10 mL) was added followed by dropwise addition of water until all precipitate had dissolved. 5% Hydrochloric acid was then added until just acidic and the aqueous layer was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were then washed sequentially with water (20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL) and then dried over magnesium sulfate. Filtration and concentration *in vacuo* then gave the crude product as a clear colorless oil which was subjected to flash chromatography using 3% EtOAc/hexane as eluent to give the desired furyl alcohol **112** (0.003 g, 50%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.33 (dd, J = 2, 2 Hz, 1 H, furan α-**H**), 7.23 (dd, J = 2, 1 Hz, 1 H, furan α-**H**), 6.31 (dd, J = 2, 1 Hz, 1 H, furan β-**H**), 5.56 (complex d, J= 10 Hz, 1 H, -C**H**=CH-), 5.34 (complex d, J = 10 Hz, 1 H, -CH=C**H**-), 4.05 (d, J = 12 Hz, 1 H, -C**H**H-OH), 3.52

(d, J = 12 Hz, 1 H, -CH**H**-OH), 2.81 (ddd, J = 14, 14, 4 Hz, 1 H, furan-CH**H**-), 2.51 (m, 1 H), 2.31 (ddd, J = 13, 13 Hz, 5, 1 H,), 1.88 (ddd, J = 14, 14, 4 Hz, 1 H, furan-CH**H**-), 1.73 (m, 1 H), 1.52 (ddd, J = 13, 13, 5 Hz, 1 H), 1.50 (m, 1 H), 1.20-1.42 (m, 5 H), 1.12 (dm, J = 11 Hz, 2 H), 0.96 (s, 3 H, -CH_3), 0.88 (d, J = 7 Hz, 3 H, -CH_3), 0.83 (d, J = 7 Hz, 3 H, -CH_3).

(1R*, 2S*, 6S*, 7R*, 8R*)-7-(2-(3-Furylethyl)-1-hydroxymethyl-2,7,8,-trimethylbicyclo[4.4.0]dec-4-ene (114)

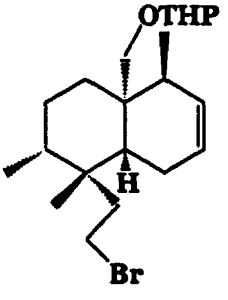


114

To a solution of the starting furyl alcohol **112** (0.005 g, 0.0100 mmol) in absolute ethanol (2 mL) was added rhodium trichloride hydrate (40.1% Rh, 0.005 g, 0.0194 mmol Rh) and the suspension was stirred until a clear pink solution was obtained. The reaction was then brought to reflux and maintained at reflux until a deep blue/purple color was achieved (ca. 1 hr) at which time reflux was continued for an additional 45 minutes. The reaction was then cooled to room temperature, quenched with water (5 mL), and extracted with diethyl ether (4 x 20 mL). The combined organic extracts were then washed with water (20 mL) followed by brine (20 mL) Drying over magnesium sulfate, filtration, and concentration *in vacuo* then afforded the crude product as a clear oil. Flash chromatography of the crude product using 2% EtOAc/hexane as eluent afforded

furyl alcohol **114** (0.003 g, 60%). FTIR (CCl_4 cast) 3453 cm^{-1} (br, OH); ^{1}H-NMR (CCl_4, 400 MHz) δ 7.48 (dd, J = 2, 2 Hz, 1 H, furan α-**H**), 7.38 (m, 1 H, furan α-**H**), 6.43 (apparent s, 1 H, furan β-**H**), 5.89 (complex d, J = 11 Hz, 1 H, -CH=C**H**-), 5.81 (complex d, J = 11 Hz, 1 H, -C**H**=CH-), 4.22 (dm, J = 11 Hz, 1 H, -CH**H**-OH), 3.78 (dm, J = 11 Hz, 1 H, -C**H**H-OH), 3.06 (ddd, J = 13, 13, 4 Hz, 1 H, furan-C**H**H-), 2.84 (m, 1 H, -C**H**CH=CH-), 2.49 (ddd, J = 13, 13, 5 Hz, 1 H, furan-CH**H**-), 2.10-2.32 (m, 3 H), 1.90-2.08 (m, 2 H), 1.62-1.72 (m, 3 H), 1.46-1.53 (m, 2 H), 1.37 (s, 3 H, -CH_3), 1.19 (br. s, 1 H, -O**H**), 1.08 (d, J = 7 Hz, 3 H, -CH_3), 1.04 (d, J = 7 Hz, 3 H, -CH_3); ^{13}C-NMR (APT, CCl_4, 125 MHz) δ 142.9 (a), 138.8 (a), 130.7 (a), 127.2 (a), 126.6 (p), 111.6 (a), 66.3 (p), 40.9 (a), 40.3 (p), 39.3 (a), 37.6 (p), 33.3 (a), 32.0 (p), 30.2 (a), 27.7 (p), 27.6 (p), 23.6 (p), 19.5 (p), 16.3 (a), 15.7 (a).

(1S*, 4R*, 5R*, 6R*, 10S*)-7-(2-Bromoethyl)-1-((2-tetrahydro-pyranyloxy)methyl)-2,7,8-trimethylbicyclo[4.4.0]dec-3-ene (108).

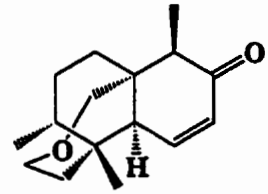


108

To a solution of starting bromo alcohol **105** (0.009 g, 0.029 mmol) in anhydrous dichloromethane (5 mL) was added 3,4-dihydro-2*H*-pyran (0.005 mL, 0.055 mmol) and pyridinium *para*-toluenesulfonate (0.001 g, 0.004 mmol). The resulting clear colorless solution was stirred at room temperature for 12 hours before diluting with diethyl ether (50 mL) and washing with half saturated

sodium chloride solution (30 mL). The aqueous layer was extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography using 3% EtOAc/hexane as eluent then yielded the desired tetrahydropyranyl ether **108** (mixture of diastereomers in a 1:1 ratio) as a clear colorless oil (0.005 g, 80% accounting for recovered tricyclic ether **98**): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.54 (m, 1 H, -CH_2-C**H**=CH-), 5.32 (m, 1 H, -CH_2-CH=C**H**-), 4.73 (t, J = 3 Hz, 0.5 H, -O-C**H**-O-), 4.49 (t, J = 3 Hz, 0.5 H, -O-C**H**-O-), 4.17 (d, J = 12 Hz, 1 H, -C**H**H-OTHP), 3.70-4.18 (m, 2 H), 3.32-3.56 (m, 2 H), 3.27 (d, J = 12 Hz, 1 H, -CH**H**-OTHP), 2.75 (m, 0.5 H, -(CH_3)C-C**H**-), 2.44 (m, 0.5 H, -(CH_3)C-C**H**-), 2.41 (ddd, J = 13, 13, 4 Hz, 0.5 H), 2.27 (ddd, J = 13, 13, 4 Hz, 0.5 H), 1.62-1.90 (m, 9 H), 1.07-1.42 (m, 6 H), 0.97 (s, 1.5 H, -C**H**$_3$), 0.94 (s, 1.5 H, -C**H**$_3$), 0.88 (d, J = 7 Hz, 1.5 H, -C**H**$_3$), 0.85 (d, J = 7 Hz, 1.5 H, -C**H**$_3$), 0.83 (d, J = 7 Hz, 1.5 H, -C**H**$_3$), 0.82 (d, J = 7 Hz, 1.5 H, -C**H**$_3$); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 131.2 (a), 131.0 (a), 123.8 (a), 123.6 (a), 100.9 (a), 98.3 (a), 70.7 (p), 69.6 (p), 62.6 (p), 61.9 (p), 41.2 (p), 41.1 (p), 39.9 (p), 39.6 (p), 36.6 (a), 36.3 (a), 34.4 (a), 34.3 (a), 32.2 (p), 31.9 (p), 30.6 (p), 30.5 (p), 27.9 (p), 37.8 (p), 27.5 (a), 35.9 (p), 35.7 (p), 25.6 (p), 25.4 (p), 24.1 (p), 24.0 (p), 19.6 (p), 19.4 (p), 16.1 (a), 15.9 (a), 15.5 (a).; Low Resolution Electrospray $[M+Na]^+$ 422.2 and 424.2 (calculated for $C_{21}H_{35}O_2{}^{79}BrNa$: 422.2 and $C_{21}H_{35}O_2{}^{81}BrNa$: 424.2). Further elution with the same solvent system furnished tricyclic keto ether **98** (0.003 g).

(1S*, 2R*, 6S*, 7R*, 14R*)-6,11,14-Trimethyl-3-oxatricyclo[5.4.3.0^{1,6}]-tetradec-4-en-3-one (117).



117

To a solution of starting tricyclic ether **98** (0.092 g, 0.400 mmol) in anhydrous carbon tetrachloride (40 mL) was added 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (0.042 g, 0.068 mmol), acetic anhydride (0.17 mL, 1.80 mmol), pyridine (0.13 mL, 1.61 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.008 g, 0.065 mmol). The resulting dark purple solution was stirred under an atmosphere of oxygen and irradiated by two 500W tungsten lamps. After 2.5 weeks, the reaction mixture was diluted with dichloromethane (50 mL) and washed sequentially with saturated sodium bicarbonate (30 mL), 1 *M* aqueous hydrochloric acid (30 mL), saturated copper sulfate solution (30 mL), and brine (30 mL). The organic layer thus obtained was then dried over magnesium sulfate, filtered, and concentrated *in vacuo* to furnish the crude product as a light brown oil. Flash chromatography using 5% EtOAc/hexane as eluent then yielded the starting tricyclic ether **98** (0.043 g). Further elution then gave enone product **117** as a colorless oil (0.030 g, 56% accounting for recovered starting material): FTIR ($CDCl_3$ cast) 1672 cm^{-1} (enone C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.91 (dd, J = 11, 2 Hz, 1 H, -C**H**=CH-C=O), 6.08 (dd, J = 11, 3 Hz, 1 H, -CH=C**H**-C=O), 3.97 (ddd, J = 13, 5, 3 Hz, 1 H, -O-C**H**H-CH_2-), 3.88 (d, J = 13 Hz, 1 H, -O-C**H**H-C-), 3.81 (ddd, J = 13, 13, 3 Hz, 1 H, -O-CH**H**-CH_2-), 3.58 (d, J = 13 Hz, 1 H, -O-CH**H**-C-), 2.82 (dd, J = 2, 2 Hz, 1 H, -CH=CH-C**H**-), 2.46 (q, J = 7 Hz, 1 H, CH_3-

CH-C=O), 2.31 (ddd, J = 16, 13, 5 Hz, 1 H, -O-CH_2-CHH-), 1.50-1.70 (m, 2 H), 1.30-1.45 (m, 4 H), 1.21 (s, 3 H, -CH_3), 1.03 (d, J = 7 Hz, 3 H, -CH_3), 0.84 (d, J = 7 Hz, 3 H, -CH_3); ^{13}C-NMR (APT, $CDCl_3$, 75 MHz) δ 210.8 (p), 149.6 (a), 129.5 (a), 74.3 (p), 67.3 (p), 49.8 (a), 48.3 (a), 46.7 (p), 39.2 (p), 37.7 (a), 34.2 (p), 29.3 (a), 28.0 (p), 243.9 (p), 15.3 (a), 7.5 (a).

References

1. Barton, D.H.R; Cheung, H.T.; Cross, A.D.; Jackman, L.M.; Martin-Smith, M. *J. Am. Chem. Soc.* **1961**, *82*, 5061.
2. Merritt, A.T.; Ley, S.V. *Nat. Prod. Rep.* **1992**, *9*, 243.
3. Sato, A.; Kurabayashi, M.; Nagahori, H.; Ogisa, A.; Mishima, H. *Tetrahedron Lett.* **1970**, 1095.
4. De Pascuale Teresa, J.; Urones, J.G.; Marcos, I.S.; Bermejo, F.; Basabe P. *Phytochemistry* **1983**, *22*, 2783.
5. Nakanishi, K. *Insect Biology of the Future*, Locke, M. and Smith, D.S. ed., Academic Press, New York, 1980.; Philogene, B.J.R. *Ann. de la Société Entomologique du Québec* **1974**, *19*, 121.
6. Manabe, S.; Nishino, C. *Tetrahedron* **1986**, *42*, 3461.
7. Valdes III, L.J.; Butler, W.M.; Hatfield, G.M.; Paul, A.G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716.
8. Andersen, N.R.; Rasmussen, P.R.; Falshaw, C.P.; King, T.J. *Tetrahedron Lett.* **1984**, *25*, 469.
9. Wagner, H.; Seitz, R.; Lotter, H.; Herz, W. *J. Org. Chem.* **1978**, *48*, 3339.
10. Tamamura, T.; Sawa, T.; Isshiki, K.; Masuda, T.; Homma, Y.; Iinuma, H.; Naganawa, H.; Hamada, M.; Takeuchi, T; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1664.; Isshiki, K.; Tamamura, T.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1819.
11. Rojas-Garciduenas, M.; Dominguez, X.A. *Turrialba* **1976**, *26*, 10.
12. Tsuji, H.; Tani, Y.; Ueda, H. *Nippon Kagaku Kaishi* **1977**, *51*, 609.; Tsuji, H.; Tani, Y.; Ueda, H. *Bokin Bobai* **1978**, *6*, 170.
13. Kitazawa, E.; Sato, A.; Takahashi, S.; KuKuwano, H.; Ogiso, A. *Chem. Pharm. Bull.* **1980**, *28*, 227.

14. Hagiwara, H.; Inome, K.; Uda, H. *Tetrahedron Lett.* **1994**, *35*, 8189.

15. Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc. Perkin Trans. 1* **1995**, 757.

16. Jones, P.S.; Ley, S.V.; Simpkins, N.S.; Whittle, A.J. *Tetrahedron* **1986**, *42*, 6519.

17. Ley, S.V.; Simpkins, N.S.; Whittle, A.J. *J. Chem. Soc. Chem. Commun.* **1983**, 503.

18. Bruner, S.D.; Radeke, H.S.; Tallarico, J.A.; Snapper, M.L. *J. Org. Chem.* **1995**, *60*, 1114.

19. Luteijn, H.M.; de Groot, A.E. *Tetrahedron Lett.* **1982**, *3*, 3421.

20. Piers, E.; Fleming, F.F. *J. Chem. Soc. Chem. Commun.* **1989**, 1665.

21. Iio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc. Chem. Commun.* **1987**, 358.

22. Piers, E.; Wai, J.S.M. *Can. J. Chem.* **1994**, *72*, 146.

23. Piers, E.; Wai, J.S.M. *J. Chem. Soc. Chem. Commun.* **1987**, 1342.

24. Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515.

25. Kende, A.S.; Roth, B.; Kubo, I. *Tetrahedron Lett.* **1982**, *23*, 1751.

26. Goldsmith, D.J.; Deshpande, R. *Synlett.* **1995**, 495.

27. Sharma, A.S.; Gayen, A.K. *Tetrahedron* **1985**, *41*, 4581.

28. Sharma, A.S.; Chattopadhyay, P. *J. Org. Chem.* **1982**, *47*, 1727.

29. Piers, E.; Wai, J.S.M. *J. Chem. Soc. Chem. Commun.* **1988**, 1245.

30. Tokoroyama, T.; Matsuo, K.; Kubota. T. *Tetrahedron* **1978**, *34*, 1907.

31. Tokoroyama, T; Matsuo, K.; Kotsuki, H.; Kanazawa, R. *Tetrahedron* **1980**, *36*, 3377.

32. Liu, H.J.; Shia, K.S.; Han, Y.; Wang, Y. *Synlett.* **1995**, 545.

33. Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M; Iio, H. *J. Chem. Soc. Chem. Commun* **1983**, 1516.

34. Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M; Iio, H. *Tetrahedron* **1988**, *44*, 6607.

35. Tokoroyama, T.; Tsukamoto, M.; Asada, T.; Iio, H. *Tetrahedron Lett.* **1987**, *28*, 6645.

36. Tokoroyama, T.; Kanazawa, R.; Yamamoto, S.; Kamikawa, T.; Suenaga, H.; Miyabe, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1720.

37. Piers, E.; Breau, M.L.; Han, Y.; Plourde, G.L.; Yeh, W.L. *J. Chem. Soc. Perkin Trans. 1* **1995**, 963.

38. Liao, C.C.; Lee, T.H. *Tetrahedron Lett.* **1996**, 6869.

39. Liu, H.J.; Shia, K.-S.; Han, Y.; Sun, D.; Wang, Y. *Can. J. Chem.* **1997**, *75*, 646.

40. Liu, H.J.; Shia, K.-S. *Tetrahedron* **1998**, *54*, 13449.

41. Ziegler, F.E.; Reid, G.R.; Studt, W.L.; Wender, P.A. *J. Org. Chem.* **1977**, *42*, 1991.

42. Posner, G.H. *Org. React.* **1972**, *19*, 1.

43. Tokoroyama, T.; Tsukamoto, M.; Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067.

44. Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.; Lombardo L. *Org. Synth.* **1987**, *65*, 81.

45. Brown, C.A. *J. Chem. Soc. Chem. Commun.* **1975**, 222.; Brown, C.A. *Synthesis* **1976**, 754.; Brown, C.A.; Jadhav, P.K. *Org. Synth.* **1987**, *65*, 224.

46. Kandil, A.A.; Slessor, K.N. *J. Org. Chem.* **1985**, *50*, 5649.; Kandil, A.A.; Porter, T.M.; Slessor, K.N. *Synthesis* **1987**, 411.

47. Piers, E.; Roberge, J.Y. *Tetrahedron Lett.* **1991**, *32*, 5219.

48. Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867.

49. Piers, E.; Roberge, J.Y. *Tetrahedron Lett.* **1992**, *33*, 6923.

50. Lee, T.H.; Liao, C.C; Liu, W.C. *Tetrahedron Lett.* **1996**, *37*, 5897.

51. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

52. Liu, H.J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253.

53. Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

54. Anthonsen, T.; Henderson, M.S.; Martin, A.; McCrindle, R.; Murray, R.D.H. *Acta. Chem. Scand.* **1968**, *22*, 351.; Henderson, M.S.; McCrindle, R.; McMaster, D. *Can. J. Chem.* **1973**, *51*, 1346.

55. Anthonsen, T.; Henderson, M.S.; Martin, A.; Murray, R.D.H.; McCrindle, R.; McMaster, D. *Can. J. Chem.* **1973**, *51*, 1332.

56. Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

57. Shia, K.-S. Ph.D. Thesis, Department of Chemistry, University of Alberta, Canada, 1996.

58. Ulibarri, G. Ph.D. thesis, Department of Chemistry, University of Alberta, Canada, 1991.

59. Schlosser, M. *Methoden Org. Chem. (Houben-Weyl)* **1972**, *5/1b*, 134.

60. Orr, J.; de la Roz, A.; Bowers, A. *J. Org. Chem.* **1964**, *29*, 3300.

61. Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.

62. Mandal, A.K.; Soni, N.R.; Ratnam, K.R. *Synthesis* **1985**, 275.; Vankar, Y.D.; Rao, C.T. *J. Chem. Research (S)* **1985**, 232.

63. Brown, M; Piszkiewicz, L.W. *J. Org. Chem.* **1967**, *32*, 2013.

64. Bhatt, M.V.; Kulkarni, S.U. *Synthesis* **1983**, 249.

65. Schmidt, A.H. *Aldrichimica Acta* **1981**, *14*, 31.; Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.; Jung, M.E.; Lyster, M.A. *J. Org. Chem.* **1977**, *42*, 3761.

66. Niwa, H.; Hida, T; Yamada, K *Tetrahedron Lett.* **1981**, *42*, 4239.; Kulkarni, S.U.; Patil, V.D. *Heterocycles* **1982**, *18*, 163.

67. Bhatt, M.V. *J. Organometal. Chem.* **1978**, *156*, 221.

68. Boekman Jr., R.K.; Potenza, J.C. *Tetrahedron Lett.* **1985**, *26*, 1411.; King, P.F.; Stroud, S.G. *Tetrahedron Lett.* **1985**, *26*, 1415.

69. Ganem, B.; Boeckman Jr., R.K. *Tetrahedron Lett.* **1974**, 917.

70. Kornblum, N.; Jones, W.J.; Anderson, G.J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.; Johnson, A.P.; Pelter, A. *J. Chem. Soc.* **1964**, 520.

71. Miyashita, N; Yoshikoshi, A.; Grieco, P.A. *J. Org. Chem.* **1977**, *42*, 3772.

72. Kircher, H.W.; Rosenstein, F.U. *J. Org. Chem.* **1987**, *52*, 2586.; Bond, G.C. *Ann. Reports* **1966**, *63*, 27.; Cramer, R. *Acc. Chem. Res.* **1968**, *1*,186.; Andrieux, J.; Barton, D.H.R.; Patin, H. *J. Chem. Soc. Perkin Trans. 1* **1977**, 359.; Hudson, B.; Webster, D.E.; Wells, P.B. *J. Chem. Soc. Dalton* **1972**, 1204.; Gent, P.A.; Gigg, R. *J. Chem. Soc. Chem. Commun.* **1974**, 277.; Sakaki, S.; Kanai, H.; Tamara, K. *Can. J. Chem.* **1974**, *52*, 2857.

73. Larson, G.L.; Hernández, E.; Alonso, C.; Nieves, I. *Tetrahedron Lett.* **1975**, 4005.

74. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821.; Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.; Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

75. Heathcock, C.H.; DelMar, E.G.; Graham, S.L. *J. Am. Chem. Soc.* **1982**, *104*, 1907.; Roush, W.R.; Walts, A.E. *J. Am. Chem. Soc.* **1984**, *106*, 721.; Doering, W. von E.; Schmidhauser, J.C. *J. Am. Chem. Soc.* **1984**, *106*, 5025.; Crimmins, M.T.; Mascarella, S.W. *J. Am. Chem. Soc.* **1986**, *108*, 3435.

76. Ireland, R.E.; Muchmore, D.C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

77. Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of Laboratory Chemicals*, 2nd edition, Pergamon Press, 1987.

78. Still, W.C.; Kahn, M.; Mitra, A *J. Org. Chem.* **1978**, *43*, 2923.

79. Kende, A.S.; Fludzinski, P. *Org. Synth.* **1985**, *64*, 68.