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Novel ring forming reactions for organic synthesis

Jeffrey J. Thurston
Iowa State University

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Novel ring forming reactions for organic synthesis

Thurston, Jeffrey J., Ph.D.

Iowa State University, 1988

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Novel ring forming reactions for organic synthesis

by

Jeffrey J. Thurston

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

In Charge of Major Work

For the Major Department

For the Graduate College

Iowa State University
Ames, Iowa

1988

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DEDICATION

For the friendly environment and the devotion and enthusiasm given to teaching I would like to dedicate this thesis to the Chemistry Department at Winona State University.

GENERAL INTRODUCTION

Almost all biologically important molecules contain a ring in their structure. The first two sections of this manuscript deal with general methodology which will facilitate the construction of certain rings. The last part of this manuscript deals with the total synthesis of a natural product containing a tricyclic structure.

Part I deals with the preparation of cyclic 1,2-aminoalcohols. Many important natural products contain this substructure. Several recent synthetic methods have been reported for the synthesis of 1,2-aminoalcohols, attesting to the high interest in this area and also to the need for additional methods. Part I deals with the cycloaddition of dienes with E-1-benzoyloxy-2-nitroethene. The nitro group is then reduced to yield the cyclic 1,2-aminoalcohols.

Part II deals with the intramolecular cyclization of cyclic hemiketals with alkenes to yield bicyclic ketals. This reaction proceeds via an alkoxy radical. Many important natural products such as the ginkolides contain the bicyclic ketal moiety. Research is in progress on the application of this methodology to the total synthesis of these biologically important natural products.

The last part of this manuscript deals with the total synthesis of a 9-hydroxy substituted iridoid, which was recently isolated from Gelsemium Sempervirens.

Explanation of Thesis Format

This thesis is divided into three sections which are entirely nonrelated. The thesis is written so that each section can be regarded as a separate article in published form. Therefore, the numbering of the schemes, tables, and references is independent in each part.
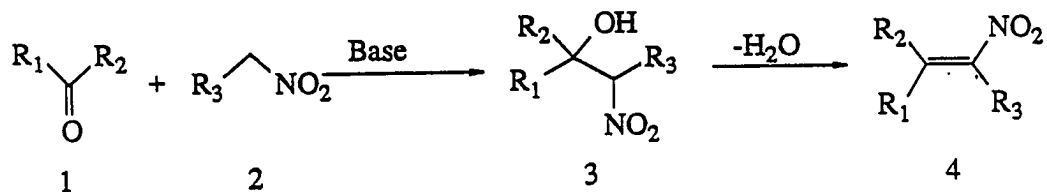
PART I. E-1-BENZOYLOXY-2-NITROETHENE AS A

CIS-2-AMINOETHENOL EQUIVALENT

HISTORICAL

The nitro group is a powerful electron withdrawing group. This property dominates the chemistry of molecules containing this functional group. For example, nitroalkenes are powerful dienophiles in the Diels-Alder reaction. Alternatively, these electrophilic alkenes readily undergo a variety of addition reactions with many different nucleophiles. The nitro group is particularly versatile in synthesis as it can be transformed into a variety of functional groups. It can readily be replaced by a hydrogen atom or converted into a carbonyl group by the classical Nef reaction. Additionally, primary nitro groups can be dehydrated to produce nitrile oxides or oxidized to produce carboxylic acids. Finally, the nitro group can be reduced to produce oximes, hydroxylamines, or amines.[1]

Synthesis of Nitroalkenes

Nitroalkene 4 can be prepared in a variety of ways. One of the more classical preparations is the Henry reaction of an aldehyde or ketone 1 with a nitroalkane 2, followed by dehydration of the resulting β-nitroalcohol 3.[2]

$$R_1 \underset{O}{\overset{R_2}{\bigg\Vert}} + R_3\diagup NO_2 \xrightarrow{Base} R_1 \overset{R_2\diagdown OH}{\underset{NO_2}{\bigg\vert}} R_3 \xrightarrow{-H_2O} R_1 \overset{R_2\diagdown \quad NO_2}{\underset{R_3}{=}}$$

    1   2   3   4

The Henry reaction is not a convenient source of cyclic nitroalkenes. Dampawan and Zajac have reported a synthesis of cyclic nitroalkenes from β-nitroketones.[3] For example, 1-nitrocyclohexene 8 was readily prepared from 2-nitrocyclohexanone 6 via sodium borohydride reduction in ethanol to yield the β-nitroalcohol 7. Elimination, using sodium hydride, yielded 1-nitrocyclohexene. The β-nitroketone 6 was conveniently prepared by nitration of the enol acetate 5.

The reaction scheme shows compounds 5, 6, 7, and 8 with reagents NO_2^+, $NaBH_4$, and NaH.
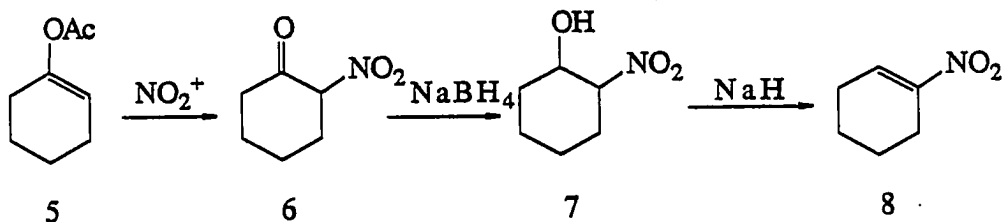
Another route to cyclic nitroalkenes developed by Corey and Estreicher also began with a cyclic ketone.[4] For example, cycloheptanone 2,4,6-triisopropylbenzenesulfonylhydrazone 9 was reacted with sec-butyllithium to produce the vinyl anion, which was trapped with chlorotrimethylstannane to afford 10. The resulting stannane reacted smoothly with tetranitromethane to give 1-nitrocycloheptene 11. These researchers have also shown that olefins are rapidly converted to nitroalkenes by nitromercuration followed by treatment with base.[4]
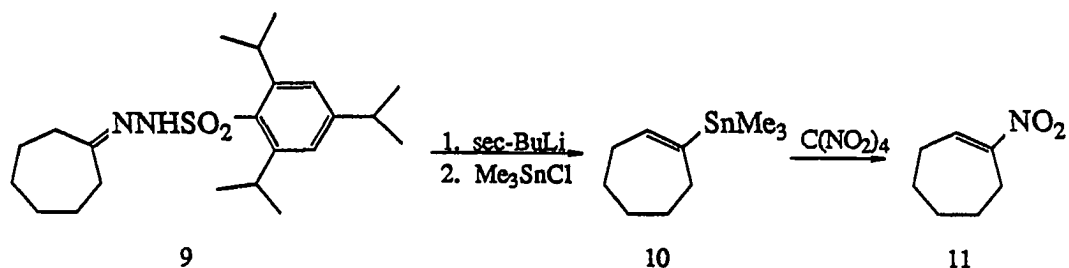
Hayama et al.[5] and Seebach et al.[6] have utilized selenium chemistry in the preparation of nitroalkenes. Hayama et al. have shown that unactivated alkenes can be converted into β-nitroselenides. For example, cyclohexene reacted with phenylselenenyl bromide and silver nitrite to give the trans-nitroselenide 13. On oxidation with hydrogen peroxide, 1-nitrocyclohexene 8 was obtained. Seebach et al. have used phenylselenenyl trifluoroacetate for the function-alization of nitroalkenes. For example, nitroalkene 14 was reacted with phenylselenenyl trifluoroacetate to yield adduct 15. Methanolysis in the presence of sodium bicarbonate and subsequent hydrogen peroxide oxidation afforded 16.
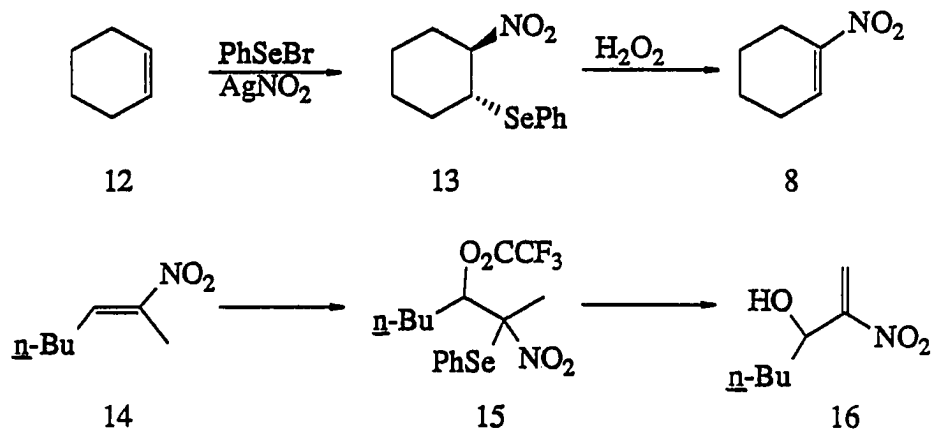
Nitroalkenes are also readily available from halo oximes. Halo oximes are available via the addition of a nitrosyl halide to alkenes. Sakakibara and co-workers reported that trifluorperoacetic acid oxidation of such oximes produced the corresponding alkenes.[7] For example, oxidation of 17 produced 8.
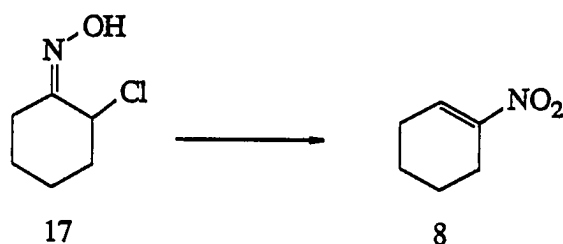
Nitroalkanes are also convenient precursors to nitroalkenes. Formation of the anion of nitroalkane 18 and reaction with phenylselenenyl bromide gave the nitroselenide

19. Oxidation with hydrogen peroxide provided the nitroalkene **20**.[8]
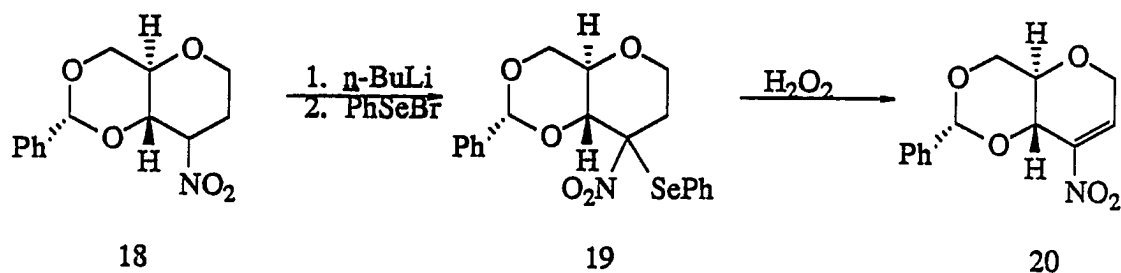
In a more complex synthesis of a nitroalkene, Ono and co-workers have used nitroacetate **21**.[9] Reaction of **21** with thiophenol and base produced **22**. Chlorination of **22** and elimination of hydrogen chloride produced the nitroalkene **23**. Oxidation of the sulfide produced the sulfoxide **24**. The nitroalkene **24** was found to be a good dienophile for the Diels-Alder reaction and underwent an elimination reaction using tri-n-butyltin hydride to produce the alkene **26**. This
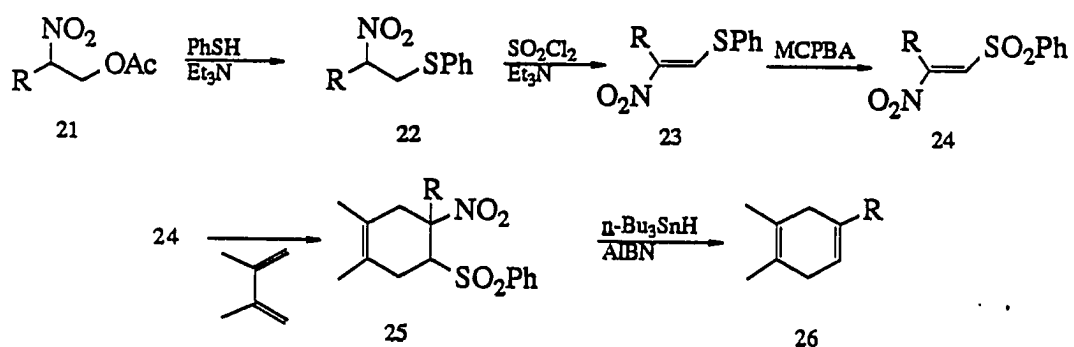
compound is an unactivated acetylene equivalent for the Diels-Alder reaction.

Another interesting route to nitroalkenes involves the condensation of triethyl orthoformate, nitromethane, and secondary amines to produce a β-nitroenamine. β-Nitro-enamines have proven to be useful synthetic intermediates.[10] This reaction will be presented in more detail in the Results and Discussion section.
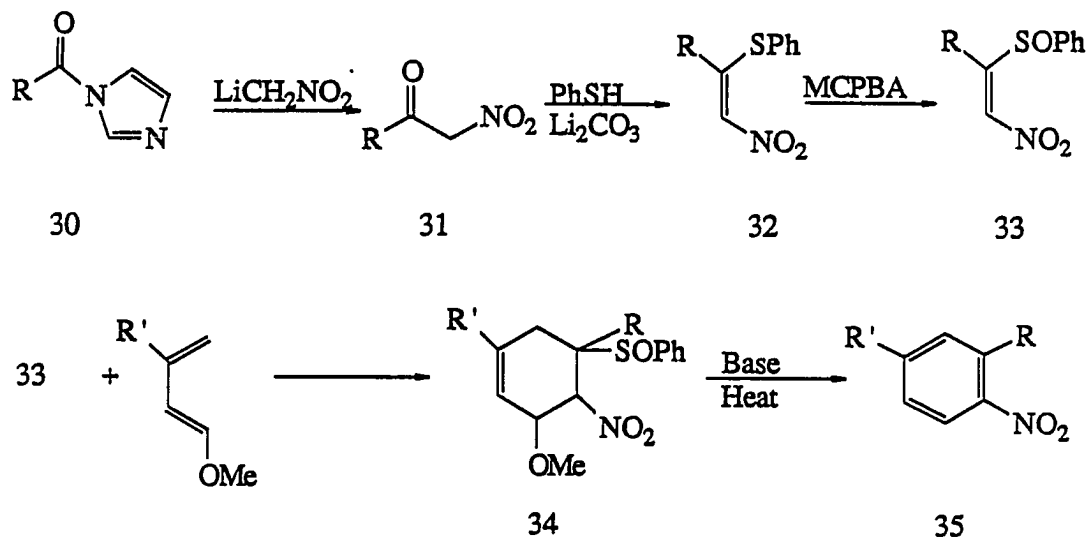
Nitroacetylenes and Their Equivalents

Nitroacetylenes would be useful intermediates for organic synthesis. The use of nitroacetylenes as dienophiles in the Diels-Alder reaction would directly provide cyclic nitroalkenes. Nitroacetylenes have seen limited use in synthesis because their preparation is difficult and they are unstable. Therefore, nitroacetylene equivalents are attractive synthetic objectives.

There have been a few reported syntheses of nitro-acetylenes by the reaction of trimethylstannylacetylenes with nitronium tetrafluoroborate or nitrogen pentoxide in an inert solvent.[11-15] Another route to nitroacetylenes involves the addition of nitryl iodide to the acetylene followed by hydrogen iodide elimination.[16] All of the nitroacetylenes were reported to be thermally unstable.

Recently, Schmitt et al. have reported the synthesis of 1-nitro-2-(trialkylsilyl)acetylenes by treatment of

bis(trialkylsilyl)acetylenes with nitronium tetra-
fluoroborate.[17] The 1-nitro-2-(trialkylsilyl)acetylenes are
thermally stable and undergo Diels-Alder reactions.

Since nitroacetylenes are difficult to prepare, the
synthesis of a nitroacetylene equivalent is desirable. At
present, only two synthetic equivalents have been reported.
Verbruggen and Viehe have reported the synthesis of
2-chloronitroethylene and its 1,3-dipolar and Diels-Alder
cycloaddition reactions.[18] In a more recent publication,
Jung and Grove have reported the synthesis of
2-phenylsulfinyl-1-nitroalkenes.[19] These compounds were
prepared by the reaction of acyl imidazoles 30 with the
anion of nitromethane. Thioketalization followed by
elimination provided the nitroalkene 32. Oxidation of the
sulfide to the sulfoxide afforded the target molecule 33.
The 2-phenylsulfinyl-1-nitroalkenes were found to be very
reactive dienophiles in the Diels-Alder reaction. The
Diels-Alder adducts could also be aromatized to
nitrobenzenes 35 if appropriately substituted dienes were
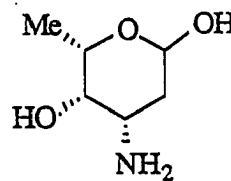used.

Synthesis of 1,2-Aminoalcohols

Many important natural products contain a 1,2-aminoalcohol subunit. Biologically significant examples include retronecine (36) and many other pyrrolizidine alkaloids,[20] slaframine (37),[21] daunosamine (38),[22] and
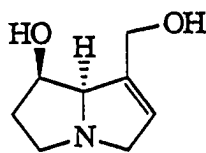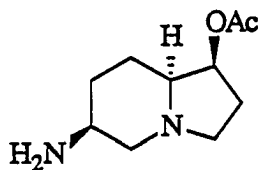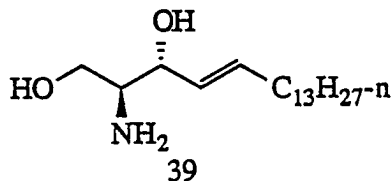
sphingosine ($\underset{\sim}{39}$).[23] Several recent methods for the
synthesis of 1,2-aminoalcohols have been reported, attesting
to the high interest in this area and the need for
additional routes.

Gassman and Guggenheim have reported that the reaction
of trimethylsilyl cyanide with epoxides like $\underset{\sim}{40}$ in the
presence of a Lewis acid produced the β-hydroxyisonitriles
$\underset{\sim}{41}$ after removal of the silyl group.[24] Hydrolysis of the
isonitrile $\underset{\sim}{41}$ in methanolic hydrogen chloride provided the
amino hydrochloride $\underset{\sim}{42}$.
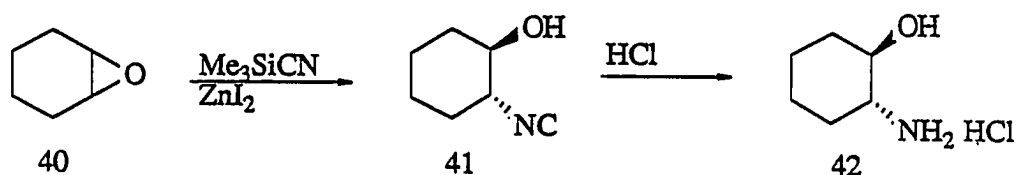

Claremon and co-workers have reported that the reaction
of α-alkoxyhydrazones $\underset{\sim}{43}$ with organolithium reagents
produced hydrazines $\underset{\sim}{44}$. Hydrogenation of the hydrazine $\underset{\sim}{44}$
produced the desired 1,2-aminoalcohols $\underset{\sim}{45}$.[25]
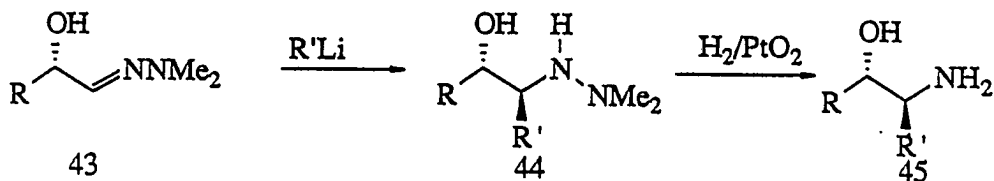
Although there have been many advances in the
stereocontrolled construction of 1,3-aminoalcohols via

cycloaddition reactions;[26] the synthesis of 1,2-amino-

alcohols via concerted reactions has received much less

attention. One notable exception is the use of

N-acetyloxazol-2-one 46 as a cis-1,2-aminoalcohol

equivalent.[26] The Diels-Alder reaction with this compound

provides the intermediate 47 which can be hydrolyzed to
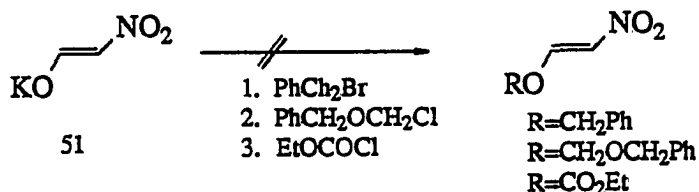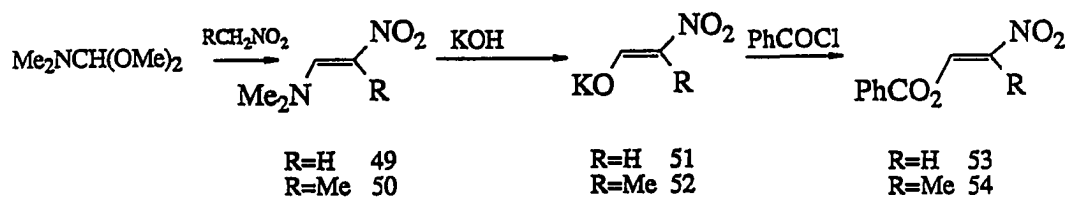
yield the desired aminoalcohol 48.
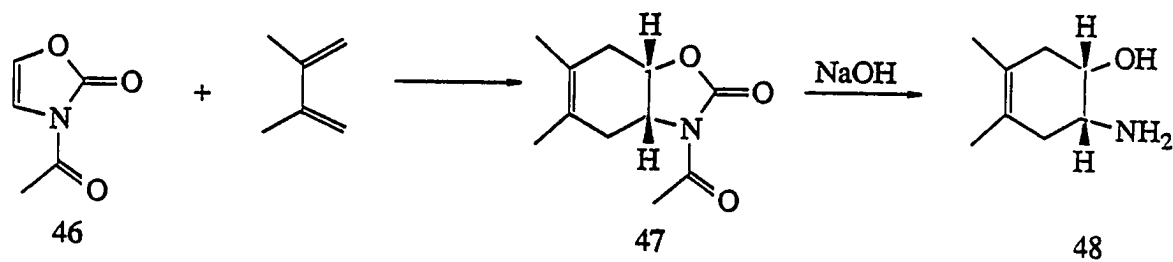
RESULTS AND DISCUSSION

While there have been advances in the synthesis of nitroalkenes, 1,2-aminoalcohols, and nitroacetylene equivalents, these are still active areas of research. There is a need for new synthetic methods which will allow for the expedient synthesis of highly substituted compounds. These compounds could then be used for the synthesis of biologically significant natural products.

General Strategy

E-1-Benzoyloxy-2-nitroethene 53 and its homolog 54 appeared to be attractive intermediates for the synthesis of 1,2-aminoalcohols, as well as useful nitroacetylene equivalents, if they would undergo Diels-Alder reactions. Compound 53 was readily prepared by the reaction of nitromethane with dimethylaminodimethoxymethane to afford dimethylaminonitroethene 49.[27] If nitroethane is used, compound 50 is obtained. Substitution of the dimethylamino group in 49 and 50 with hydroxide proceeded smoothly to afford the potassium salt of the nitroaldehydes 51 and 52. These anions are readily esterified using benzoyl chloride in the presence of 18-crown-6 to produce the desired benzoyloxynitroalkenes 53 and 54. Other attempts to make derivatives of the nitroacetaldehyde 51, including reacting this salt with benzyl bromide, ethyl chloroformate, or

chloro methylbenzyl ether failed. Compounds 53 and 54 are the first nitroalkenes bearing an alkoxy or acyloxy group which have been reported.

$$Me_2NCH(OMe)_2 \xrightarrow{RCH_2NO_2} \underset{Me_2N}{\overset{NO_2}{\diagup}}R \xrightarrow{KOH} \underset{KO}{\overset{NO_2}{\diagup}}R \xrightarrow{PhCOCl} \underset{PhCO_2}{\overset{NO_2}{\diagup}}R$$

R=H 49	R=H 51	R=H 53
R=Me 50	R=Me 52	R=Me 54

$$\underset{KO}{\overset{NO_2}{\diagup}} \xrightarrow[\text{2. PhCH}_2\text{OCH}_2\text{Cl}]{\text{1. PhCh}_2\text{Br}} \underset{RO}{\overset{NO_2}{\diagup}}$$

51   3. EtOCOCl   R=CH₂Ph
                            R=CH₂OCH₂Ph
                            R=CO₂Et

Diels-Alder Reactions of E-1-Benzoyloxy-2-nitroethene

With the syntheses of the nitroalkenes 53 and 54 complete, the next step was to study their reactivity in the Diels-Alder reaction. The reaction of 53 with representative dienes afforded the Diels-Alder adducts 55-62. The results of this study are given in Table 1.

The reaction of 53 with 2-acetoxyfuran to afford 62 at ambient temperature is significant because furans are generally poor dienophiles. The adduct of this reaction 62 also provided some necessary information on the stereochemical relationship between the benzoyloxy and nitro

Table 1. Diels-Alder reactions of 1-benzoyloxy-2-
        nitroethene

| Diels-Alder | Diene | | | | Endo/Exo |
Adduct	R	R'	% Yield	ratio
55	H	$OSiMe_3$	95	. . .
56	$OSiMe_3$	H	90	6:1
57	H	H	45	. . .
58	$\underline{t}$-$BuMe_2SiOCH_2CH_2$	H	57	1:1
59	CH_3	H	62	1:1
60	H	CH_3	50	. . .
61	2,3-dimethyl-1,3-butadiene			53. . .
62	2-acetoxyfuran		75	6:1

62
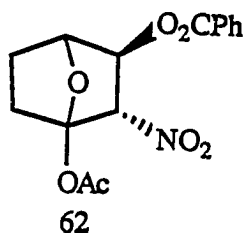
stereochemistry of 53 could not be determined from the
proton NMR spectrum. The rigid bicyclic structure of 62
allowed us to determine the coupling constant of 2 Hz for
the methine proton alpha to the nitro group. A coupling

constant of this magnitude confirms the expected trans
relationship between the nitro and benzoyloxy groups in 53.

Another interesting result occurred when compound 53 was
reacted with 2-methoxyfuran. Instead of generating a
Diels-Alder adduct, a compound was obtained that resulted
from the Michael addition of 2-methoxyfuran to 53.
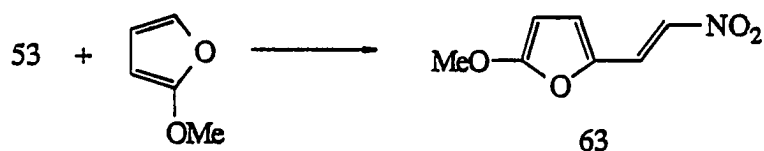
In another study, attempts were made to react 54 with
various dienes. Unfortunately, the methyl group in 54
prevents this compound from undergoing this reaction.

1-Benzoyloxy-2-nitroethene as a Nitroacetylene Equivalent

The Diels-Alder reaction conditions proceeded under
sufficiently mild conditions that loss of benzoic acid did
not occur. However, in the presence of a slight excess of
base, benzoic acid was eliminated from the Diels-Alder
adducts to produce compounds which aromatized to nitro-
benzenes. While several bases including sodium acetate
could be used, potassium tert-butoxide was the most
convenient and provided the best yields of the aromatic
products. The results of the treatment of adducts 57, 58,
and 59 with potassium tert-butoxide are given in Table 2.

1-Benzoyloxy-2-nitroethene as a 1,2-Aminoalcohol Equivalent

One of the original goals of this research was the
synthesis of biologically important natural products
containing a 1,2-aminoalcohol unit. For the formation of
these products, the nitro group would have to be reduced to
the amine in the presence of the double bond. The study was
carried out on the Diels-Alder adduct 57. Many different
reagents are known to reduce nitro groups to amines
including Pd/C in the presence of ammonium formate,[28] Raney
nickel,[29] aluminum amalgam,[30] sodium borohydride in the
presence of cobaltous chloride,[31] and lithium aluminum
hydride.[32] However, none of these reagents successfully
converted 57 into the amine 67 or aminoalcohol 68.


57

R=O$_2$CPh 67
R=H   68
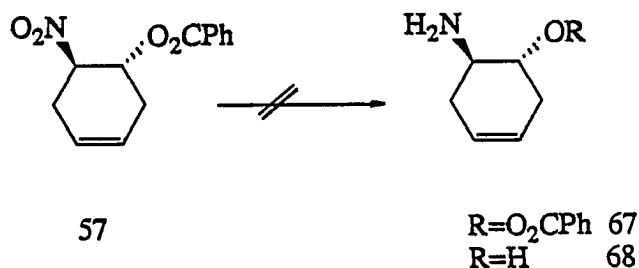
Although we knew from the nitroacetylene equivalent
study that the benzoate group was extremely labile in 57, we
felt that perhaps the double bond in 57 was creating the
problem. We, therefore, transformed the double bond in 57

Table 2. Formation of nitrobenzenes from 1-benzoyloxy-2-
nitroethene

| Diels-Alder Adduct	% Yield	Nitrobenzene Derivative R =	Nitrobenzene Adduct
		R	
57	85	H	64
58	75	$\underline{t}$-BuMe$_2$SiOCH$_2$CH$_2$	65
59	95	CH$_3$	66

into a mixture of diols which were converted directly to the
acetonides 69.[33,34] Again, the reduction of the nitro group
to the amine 70 was unsuccessful.


69   70
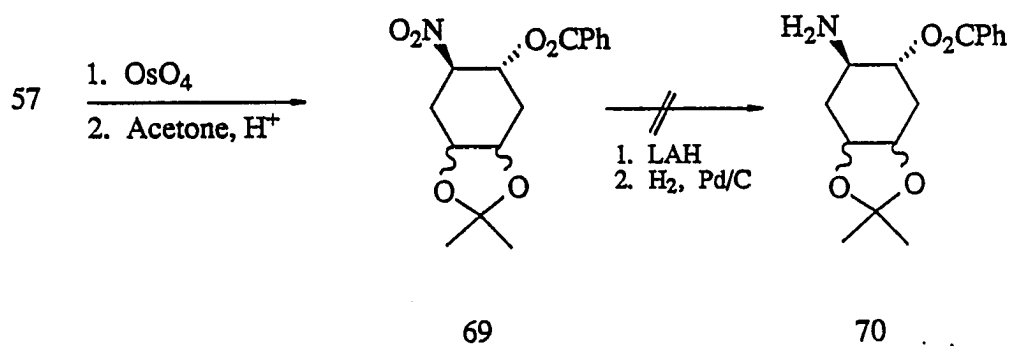
In a final attempt to use the benzoate 57 to produce a
cyclic aminoalcohol, we decided to make the oxime 71 under
acidic conditions using chromium trichloride and zinc metal
in hydrochloric acid.[35] The preparation of 71 was
successful, but the reduction using sodium cyanoborohydride
in acidic methanol[36] failed to produce the desired amine 72.
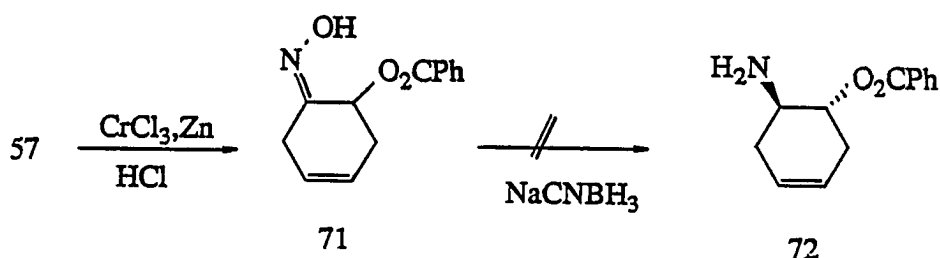

The last attempt to create an aminoalcohol from 57 that
could be used in the preparation of natural products
involved the opening of the cyclohexene ring. We decided
that the benzoate group would perhaps be less labile if it
were in an acyclic system. Therefore, 57 was treated with
ozone to create the dialdehyde, which was protected as the
bisdimethylacetal 73. The reduction of the nitro group
in 73 again was unsuccessful.
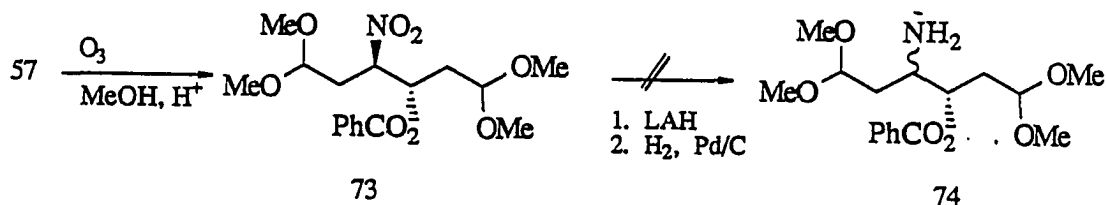
At this stage we realized we could not reduce the nitro group to the amine with the benzoate group present in the molecule. We went back to the salt of nitroacetaldehyde 51 and tried unsuccessfully to make other derivatives. We then decided to remove the benzoyl group after the formation of the Diels-Alder adduct 57. Hydrolysis of the benzoate in 57 using anhydrous hydrochloric acid in methanol provided the alcohol 75. All attempts to reduce 75 directly to the aminoalcohol failed.
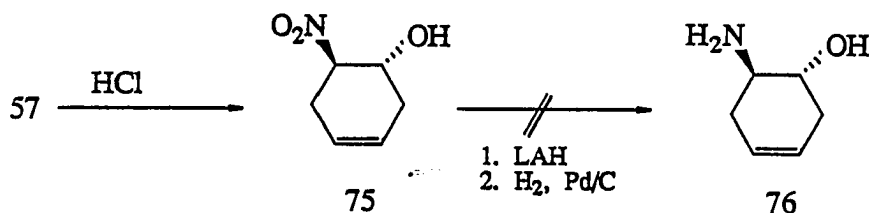
Compound 75 was protected as the methoxymethyl ether 77 using dimethoxymethane and phosphorus pentoxide.[36] The reduction of the nitro group proceeded smoothly with lithium aluminum hydride[32] which provided 78.
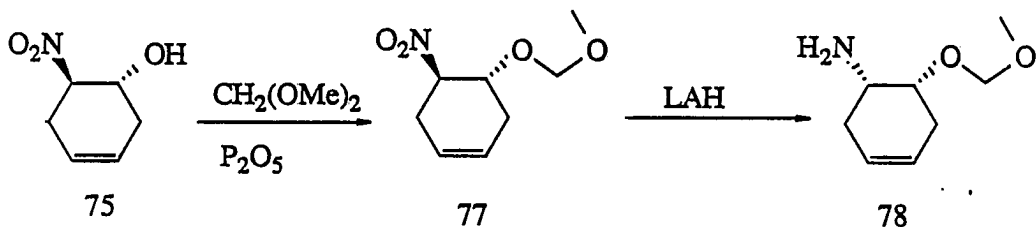
Originally, we had assumed that the amine and the
protected alcohol group in 78 would be trans. However,
decoupling of the allylic methylene groups in 78 gave a
vicinal coupling constant of only 3 Hz. A coupling constant
of this magnitude is not consistent with a trans
relationship unless both the amine and protected alcohol are
axial. In order to secure the structure of 78, the
benzamide derivative 79 was prepared by reaction of 78 with
benzoyl chloride. Hydrogenation of the double bond in 79
produced benzamide 80. The methoxymethyl ether in 80 was
removed using methanolic hydrogen chloride to produce the
benzamide alcohol 81. The melting point of 81 was
184-185°C, in good agreement with the authentic cis isomer
(189-190°C), but different from the authentic trans isomer
(175-176°C).[37] As a final proof, the structure of 81 was
confirmed by x-ray crystallography. This confirmed the cis
relationship of the benzamide and hydroxyl groups.

It seems unlikely that epimerization occurred during the
debenzoylation or protecting steps. We, therefore,
postulate that the nitro group in 77 was first reduced to
the oxime 82. The oxime 82 could then be reduced to the cis
alkoxyamine 78, possibly via a chelated Cram transition
state.
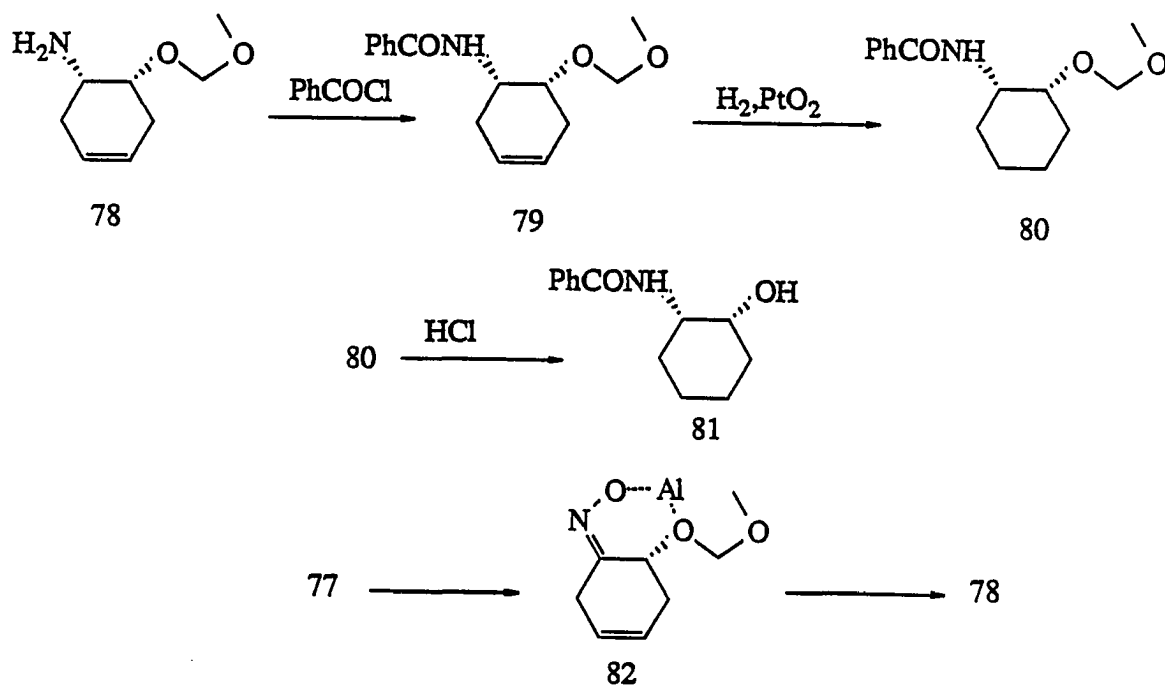
This research demonstrates the utility of 53 as a useful aminoalcohol equivalent, as well as a nitroacetylene equivalent. Given the many biologically active natural products which contain vicinal aminoalcohols, compound 53 should become a useful complement to existing methodology. This work has been recently published.[38]

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under a nitrogen atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. High field proton nuclear magnetic resonance spectra (300 MHz) were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023

mass spectrometer. Silica gel used for flash chromatography was 230-400 mesh (Kieselgel 60) purchased from EM Science.

Potassium Nitroacetaldehyde (51)

Potassium hydroxide (2.24 g, 34.48 mmole) was dissolved in 25 mL of absolute ethanol. The solution was cooled to 0°C and dimethylaminonitroethene 49 (2.00 g, 17.24 mmol) was added to the solution. The solution was stirred for one hour in which time a white solid precipitated. The solution was filtered and the solid was washed once with 10 mL of ice cold ethanol to afford a quantitative yield of 51. This compound was taken immediately on to the next step because of its instability.

Potassium 2-Nitropropanal (52)

Potassium hydroxide (0.47 g, 7.24 mmol) was dissolved in 20 mL of absolute ethanol. The solution was cooled to 0°C and the dimethylaminonitropropene 50 (0.47 g, 3.62 mmol) was added to the solution. The solution was stirred for one hour then the solvent was removed and the resulting solid was washed twice with ether to yield a compound that was contaminated with excess potassium hydroxide. This compound was taken immediately on to the next step because of its instability.

1-Benzoyloxy-2-nitroethene (53)

To potassium nitroacetaldehyde 51 (2.33 g, 18.35 mmol) in 50 mL of methylene chloride was added benzoyl chloride (3.61 g, 25.68 mmol) and 18-crown-6 (0.24 g, 0.92 mmol). The solution was stirred at room temperature overnight. The methylene chloride was removed to yield a dark solid. The solid was washed three times with 50 mL of hot hexane. The hexane solutions were combined and cooled to afford 1.86 g (54%) of 53 as pale yellow crystals. Mp 88-91°C; 300 MHz ^{1}H NMR δ 7.2-7.8 (m, 5 H), 8.10 (d, 1 H, J = 12.5 Hz), 9.10 (d, 1 H, J = 12.5 Hz); IR (film) 1756, 1655, 1515, 1312, 1162 cm^{-1}; ^{13}C NMR 126.47, 128.38, 128.76, 130.61, 135.15, 148.33, 161.54 ppm. MS: m/e 77, 105, 122.

1-Benzoyloxy-2-nitropropene (54)

To the potassium salt 52 (1.69 g, 12.0 mmol) in 40 mL of methylene chloride was added benzoyl chloride (2.02 g, 14.4 mmol) and 18-crown-6 (0.02 g, 0.06 mmol). The solution was stirred at room temperature overnight. The solvent was removed to yield a solid which was purified by chromatography using 5:1 hexane:ethyl acetate to afford 1.24 g (50%) of 54. 300 MHz ^{1}H NMR δ 3.90 (s, 1 H), 7.40-7.70 (m, 3 H), 8.00 (d, 2 H, J = 10 Hz), 8.15 (m, 1 H); IR (film) 1720, 1580, 1450, 1275 cm^{-1}. MS: m/e 77, 105, 122.

2-Nitro-5-trimethylsilyloxy-4-cyclohexen-1-ol
Benzoate Ester (55)

Compound 53 (0.10 g, 0.52 mmol) was dissolved in 1 mL of degassed benzene in a tube that could be sealed. To this tube, 2-trimethylsilyloxy-1,3-butadiene (0.11 g, 0.78 mmol) was added. The .tube was sealed and the solution was heated at 90°C for 12 hours. The solvent was removed and the product purified by chromatography using chloroform to afford 0.16 g (94%) of 55 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.21 (s, 9 H), 2.20-2.40 (m, 1 H), 2.70-2.90 (m, 3 H), 4.80 (bs, 1 H), 4.90 (m, 1 H), 5.70 (m, 1 H), 7.3-8.0 (m, 5 H); IR (film) 2960, 1725, 1555, 1260, 1108 cm^{-1}. MS: m/e 73, 105, 151, 167, 198, 213, 253, 305.

2-Nitro-3-trimethylsilyloxy-4-cyclohexen-1-ol
Benzoate Ester (56)

Compound 53 (0.3 g, 1.55 mmol) was dissolved in 4 ml of degassed benzene in a tube that could be sealed. To this tube, 1-trimethylsilyloxy-1,3-butadiene (0.49 g, 3.42 mmol) was added. The tube was sealed and the solution heated at 100°C for 12 hours. The solvent was removed and the product purified by chromatography using benzene to afford 0.47 g (90%) of 56 as a colorless oil. 300 MHz ^{1}H NMR CDCl$_3$ δ 0.15 (s, 9 H), 2.23 (m, 1 H), 2.98 (m, 1 H), 4.82-4.96 (m, 2 H), 5.53-5.75 (m, 3 H), 7.40-8.00 (m, 5 H); IR (film) 2952, 1720, 1545, 1245 cm^{-1}. MS: m/e 75, 105, 151, 166, 179, 198, 213, 279, 320.

2-Nitro-4-cyclohexen-1-ol Benzoate Ester (57)

Compound 53 (1.83 g, 9.48 mmol) was dissolved in 7 mL of degassed THF in a Parr bomb apparatus. Ten mL of 1,3-butadiene, which was previously condensed by bubbling the gas into a test tube at -78°C, was added. The bomb was sealed and heated at 110°C for 24 hours. The solvent was removed and the product purified by chromatography using 6:1 hexane:ethyl acetate to afford 1.29 g (55%) of 57 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.25 (m, 1 H), 2.65-3.05 (m, 3 H), 4.95-5.05 (m, 1 H), 5.55-5.75 (m, 3 H), 7.40-7.80 (m, 5 H); IR (film) 2960, 1720, 1540, 1450 cm^{-1}. MS: m/e 79, 105, 123, 198, 217, 248.

3-(2-tert-butyldimethylsilyloxyethyl)-2-nitro-4-cyclohexen-1-ol Benzoate Ester (58)

Compound 53 (1.00 g, 5.18 mmol) was dissolved in 15 mL of degassed benzene in a tube that could be sealed. To this tube, the diene[39] (1.64 g, 7.77 mmol) was added. The tube was sealed and the solution heated at 110°C for 24 hours. The solvent was removed and the product was purified by chromatography using 5:1 hexane:ethyl acetate to afford 1.15 g (55%) of 58 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.03 (s, 6 H), 0.90 (s, 9 H), 1.21-1.39 (m, 2 H), 2.31 (m, 2 H), 2.81-3.21 (m, 1 H), 3.63 (m, 2 H), 4.95-5.05 (m, 1 H), 5.55-5.95 (m, 3 H), 7.40-8.20 (m, 5 H); IR (film) 2960, 1725, 1552, 1260 cm^{-1}. MS: m/e 105, 123, 226, 284, 406.

3-Methyl-2-nitro-4-cyclohexen-1-ol Benzoate Ester (59)

Compound 53 (0.25 g, 1.30 mmol) was dissolved in 3 mL of degassed benzene in a tube that could be sealed. Piperylene (0.36 g, 5.20 mmol) was added. The tube was sealed and the solution was heated at 110°C for 24 hours. The solvent was removed and the product purified by chromatography using 6:1 hexane:ethyl acetate to afford 0.23 g (68%) of 59 as a colorless oil as a 1:1 mixture of endo:exo adducts which were unseparable. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.05 and 1.15 (d, 3 H, J = 8.6 Hz), 2.25 (m, 1 H), 30 (m, 2 H), 5.00 (m, 1 H), 5.65 (m, 3 H), 7.3-8.0 (m, 5 H); IR (film) 2960, 1722, 1540, 1445 cm^{-1}. Structure confirmed by formation of o-nitrotoluene (66).

5-Methyl-2-nitro-4-cyclohexen-1-ol Benzoate Ester (60)

Compound 53 (0.10 g, 0.52 mmol) was dissolved in 1 mL of degassed benzene in a tube that could be sealed. Isoprene (0.18 g, 2.60 mmol) was added. The tube was sealed and the solvent heated at 80°C for 24 hours. The solvent was removed and the product was purified by chromatography using 6:1 hexane:ethyl acetate to afford 0.068 g (50%) of 60 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.72 (s, 3 H), 2.23 (m, 1 H), 2.81 (m, 3 H), 4.96 (m, 1 H), 5.30 (m, 1 H), 5.72 (m, 1 H), 7.40-8.20 (m, 5 H); IR (film) 2960, 1720, 1550, 1450, 1270 cm^{-1}. MS: m/e 105, 123, 140, 217, 262.

4,5-Dimethyl-2-nitro-4-cyclohexen-1-ol Benzoate Ester (61)

Compound 53 (0.50 g, 2.59 mmol) was dissolved in 6 mL of degassed benzene in a tube that could be sealed. To this tube, 2,3-dimethyl-1,3-butadiene (0.42 g, 5.18 mmol) was added. The tube was sealed and the solution heated at 110°C for 24 hours. The solvent was removed and the product purified by chromatography using 5:1 hexane:ethyl acetate to yield 0.38 g (53%) of 61 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.65 (s, 3 H), 1.70 (s, 3 H), 2.25 (m, 1 H), 2.75 (m, 3 H), 4.90 (m, 1 H), 5.60 (m, 1 H), 7.40-7.80 (m, 5 H); IR (film) 2955, 1720, 1550, 1445, 1260 cm^{-1}.

1-Acetoxy-6-nitro-7-oxobicyclo[2.2.1]hept-2-en-5-ol Benzoate Ester (62)

Compound 53 (0.10 g, 0.52 mmol) was dissolved in 2 mL of degassed methylene chloride. 2-Acetoxyfuran (0.11 g, 1.04 mmol) was added and the solution stirred at 25°C for four days. The solvent was removed and the product purified by chromatography using 3:1 hexane:ethyl acetate to afford 0.12 g (75%) of 62 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.22 (s, 3 H), 4.95 (d, 1 H, J = 1.90 Hz), 5.33 (m, 1 H), 5.96 (m, 1 H), 6.85 (m, 2 H), 7.40-7.90 (m, 5 H). MS: m/e 77, 84, 105, 126, 147, 230, 260, 273.

2-Methoxy-5-(2-nitroethene)furan (63)

Compound 53 (0.22 g, 1.15 mmol) was mixed with 2-methoxyfuran (0.23 g, 2.34 mmol) in the absence of solvent

and the solution was stirred at 25°C for 12 hours. The
product was purified by chromatography using 3:1
hexane:ethyl acetate to afford 0.17 g (87%) of 63 as a red
solid. Mp 33-36°C; 300 MHz ^{1}H NMR (CDCl$_3$) δ 3.92 (s, 3 H),
5.40 (d, 1 H, J = 3 Hz), 6.80 (d, 1 H, J = 3 Hz), 7.30 (d, 1
H, J = 15 Hz), 7.60 (d, 1 H, J = 15 Hz); IR (film) 3040,
1572, 1538, 1315, 1260 cm^{-1}. High resolution mass spectrum
for C$_7$H$_7$NO$_4$ requires 169.03571, determined 169.03781.

Nitrobenzene (64)

Diels-Alder adduct 57 (0.10 g, 0.41 mmol) was dissolved
in 2 mL of THF. Potassium tert-butoxide (0.051 g, 0.46
mmol) was added which caused the solution to immediately
turn red. After 10 minutes the solvent was removed and the
product purified by chromatography using 10:1 hexane:ethyl
acetate to afford 0.042 g (88%) of nitrobenzene which was
characterized by comparing spectra with those of an
authentic sample.

1-Tert-butyldimethylsilyloxy-2-(2-nitrophenyl)ethane (65)

Diels-Alder adduct 58 (0.0673 g, 0.166 mmol) was
dissolved in 2 ml of THF. Potassium tert-butoxide (0.0223
g, 0.199 mmol) was added which caused the solution to
immediately turn red. After 10 minutes the solvent was
removed and the product purified by chromatography using
10:1 hexane:ethyl acetate to afford 0.0347 g (75%) of 65 as

a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.09 (s, 6 H),
0.93 (s, 9 H), 3.22 (t, 3 H, J = 7.5 Hz), 4.02 (t, 3 H, J =
7.5 Hz), 7.40-7.68 (m, 3 H), 8.02 (m, 1 H); IR (film) 3022,
2960, 1523, 1347, 1260 cm^{-1}. MS: m/e 150, 224, 252, 266,
282.

o-Nitrotoluene (66)

Diels-Alder adduct 59 (0.0467 g, 0.18 mmol) was
dissolved in 4 ml of THF. Potassium <u>tert</u>-butoxide (0.0241
g, 0.215 mmol) was added which caused the solution to turn
immediately red. After 10 minutes the solvent was removed
and the product purified by chromatography using 10:1
hexane:ethyl acetate to afford 0.0242 g (97%) of
o-nitrotoluene which was characterized by comparing spectra
with those of an authentic sample.

Hexahydro-5-benzoyloxy-2,2-dimethyl-6-nitro-1,3-benzodioxal (69)

The Diels-Alder adduct 57 (0.25 g, 1.01 mmol) was
dissolved in 2 mL of acetone and 1 mL of water. OsO$_4$ was
added (0.010 g), followed by 4-methylmorpholine N-oxide
(0.15 g, 1.11 mmol) and the resulting solution was stirred
overnight. The solution was saturated with sodium sulfate
and extracted with ethyl acetate. The ethyl acetate
extracts were dried with magnesium sulfate and then the
solvent was removed to afford 0.16 g (56%) of the crude diol
as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.05 (m, 1 H),

2.50 (m, 2 H), 2.89 (m, 1 H), 4.05-4.20 (m, 2 H), 5.10 (m, 1 H), 5.50 (m, 1 H), 7.40-8.15 (m, 5 H). The crude diol (0.1583 g, 0.563 mmol) was dissolved in 10 mL acetone and one drop of concentrated H_2SO_4 was added and the solution stirred for 12 hours. Sodium bicarbonate (0.25 g) was added and the acetone removed. The product was purified by chromatography 3:1 hexane:ethyl acetate to afford 0.16 g (90%) of 69 as a colorless oil which is a 1:1 mixture of diastereomers. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.33 (2s, 3 H), 1.51 (2s, 3 H), 1.90 (m, 1 H), 2.21 (m, 1 H), 2.40 (m, 1 H), 2.70 (m, 1 H), 4.40 (m, 2 H), 5.05 (m, 1 H), 5.50 (m, 1 H), 7.40-8.10 (m, 5 H); IR (film) 2990, 1725, 1550, 1260 cm^{-1}.

2-Benzoyloxy-4-cyclohexen-1-one Oxime (71)

$CrCl_3 \cdot 6H_2O$ (4.00 g, 15 mmol) was dissolved in 3 mL of water. After the salt dissolved, 5.0 mL of 6N HCl was added to the solution. Zinc metal (2.00 g, 30 mmol) was added which caused the solution to turn from green to blue. The blue solution was then decanted into a solution of the Diels-Alder adduct 57 (0.10 g, 0.405 mmol) which had previously been dissolved in 10 ml of acetone. After 12 hours the solution was extracted three times with 30 mL portions of ether. The combined ether extracts were dried and concentrated. The product was purified by chromatography using 5:1 hexane:ethyl acetate to afford 0.032 g (34%) of 71 as a colorless oil. 300 MHz ^{1}H NMR

(CDCl$_3$) δ 2.60 (m, 2 H), 3.05-3.15 (m, 1 H), 3.30-3.45 (m, 1 H), 5.70 (m, 3 H), 7.40-8.0 (m, 5 H); IR (film) 3560, 3040, 1720, 1260, 1110 cm^{-1}. MS: m/e 51, 77, 91, 105, 122, 149, 167, 214, 231.

1,1,6,6-Tetramethoxy-4-nitrohexan-3-ol Benzoate Ester (73)

The Diels-Alder adduct 57 (0.10 g, 0.405 mmol) was dissolved in 15 ml of 1:1 methylene chloride:methanol. The solution was cooled to -78°C and ozone was bubbled in until the blue color persisted. Nitrogen was then bubbled in to remove the excess ozone. Triphenylphosphine (0.11 g, 0.405 mmol), trimethyl orthoformate (0.13 g, 1.23 mmol), and one drop of concentrated H$_2$SO$_4$ were added and the solution was stirred for 12 hours. The solution was neutralized to pH 7 with sodium bicarbonate and the solvent was removed. The product was purified by chromatography using 5:1 hexane:ethyl acetate to afford 0.11 g (75%) of 73 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.05 (m, 3 H), 2.45 (m, 1 H), 3.35 (m, 12 H), 4.35 (m, 1 H), 4.50 (m, 1 H), 4.95 (m, 1 H), 5.55 (m, 1 H), 7.40-8.10 (m, 5 H); IR (film) 2960, 2912, 1725, 1550, 1450, 1260 cm^{-1}. MS: m/e 75, 101, 127, 308, 340.

2-Nitro-4-cyclohexen-1-ol (75)

Compound 57 (1.00 g, 4.05 mmol) was dissolved in 8 mL of methanol and cooled to 0°C. Hydrogen chloride gas was

bubbled into the solution until it was saturated. The solution was heated at 70°C for 24 hours and then cooled. Most of the methanol was removed and then 10 ml of saturated sodium chloride was added. The resulting solution was extracted three times with 30 mL portions of ether. The ether extracts were dried and concentrated. The product was purified by chromatography using 3:2 hexane:ethyl acetate to afford 0.35 g (60%) of 75 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.18 (m, 1 H), 2.50-2.90 (m, 3 H), 4.35 (m, 1 H), 4.60 (m, 1 H), 5.65 (m, 2 H); IR (film) 3440, 2970, 1545, 1068 cm^{-1}.

2-Nitro-4-cyclohexen-1-ol Methoxymethyl Ether (77)

The nitroalcohol 75 (0.070 g, 0.49 mmol) was dissolved in 4 mL of methylene chloride. Dimethoxymethane (2 mL) and phosphorus pentoxide were added and the solution was stirred for one hour. Saturated sodium carbonate (3 mL) was added and the methylene chloride layer was removed. The water layer was washed twice with 5 mL of methylene chloride and the methylene chloride layers were combined, dried, and concentrated. The product was purified by chromatography to afford 0.080 g (88%) of 77. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.20 (m, 1 H), 2.70 (m, 3 H), 3.34 (s, 3 H), 4.70 (m, 3 H), 5.60 (m, 2 H); IR (film) 2960, 1550, 1440, 1250, 1030 cm^{-1}.

2-Amino-4-cyclohexen-1-ol Methoxymethyl Ether (78)

To compound 77 (0.08 g, 0.428 mmol) in 3 mL of ether
lithium aluminum hydride (0.065 g, 1.71 mmol) was added and
the solution was stirred for 24 hours. Saturated sodium
sulfate was added to quench the excess hydride and the
aluminum salts were removed by filtration. Evaporation of
the ether afforded 0.60 g (89%) of the crude amine 78 which
was converted directly to the benzamide 79.

N-(2-Hydroxy-4-cyclohexene)benzamide Methoxymethyl

Ether (79)

The amine 78 (0.11 g, 0.71 mmol) was dissolved in 5 mL
of benzene. Pyridine (1 mL) and benzoyl chloride (0.10 g)
were added and the solution was heated at 70°C for 90
minutes. The solution was cooled and the benzene layer was
washed with 2 mL of 2N HCl and then 2 mL of 10% NaHCO$_3$. The
benzene layer was dried and concentrated to afford the crude
product. The product was purified by chromatography using
5:1 hexane:ethyl acetate to afford 0.083 g (45%) of the
benzamide 79. 300 MHz ^{1}H NMR (CDCl$_3$) δ 2.15-2.25 (m, 4 H),
3.40 (s, 3 H), 3.98 (m, 1 H), 4.40 (m, 1 H), 4.79 (s, 2 H),
5.60 (m, 1 H), 5.72 (m, 1 H), 7.20 (m, 1 H), 7.40-7.80 (m, 5
H); IR (film) 3440, 3350, 2960, 1650, 1510, 1480, 1030 cm^{-1}.
High resolution mass spectrum for C$_{15}$H$_{19}$NO$_3$ requires
261.13650, determined 261.13631.

N-(2-Hydroxycyclohexyl)benzamide Methoxymethyl Ether (80)

Compound 79 (0.090 g, 0.35 mmol) was dissolved in 5 mL of methanol. PtO_2 (0.0025 g) was added and the compound hydrogenated under 60 psi for one hour. The solution was filtered through Celite to afford a quantitative yield of 80. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.3-2.1 (m, 8 H), 3.40 (s, 3 H), 3.80 (m, 1 H), 4.10 (m, 1 H), 4.70 (s, 2 H), 7.0 (m, 1 H), 7.40-7.80 (m, 5 H).

N-(2-Hydroxycyclohexyl)benzamide (81)

Compound 80 (0.090 g, 0.35 mmol) was dissolved in 5 mL of methanol. One drop of concentrated HCl was added and the solution was refluxed for one hour. Most of the methanol was removed and 3 mL of water was added. The water was extracted three times with 5 mL of ether. The ether extracts were combined, dried, and concentrated to afford the crude product. The product was recrystalized from methanol to afford 0.038 g (50%) of 81 as a white solid. Mp 184-185°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.40-1.90 (m, 8 H), 4.05 (m, 1 H), 4.15 (m, 1 H), 6.50 (m, 1 H), 7.40-7.80 (m, 5 H). The structure was confirmed by the x-ray spectrum which is shown below.
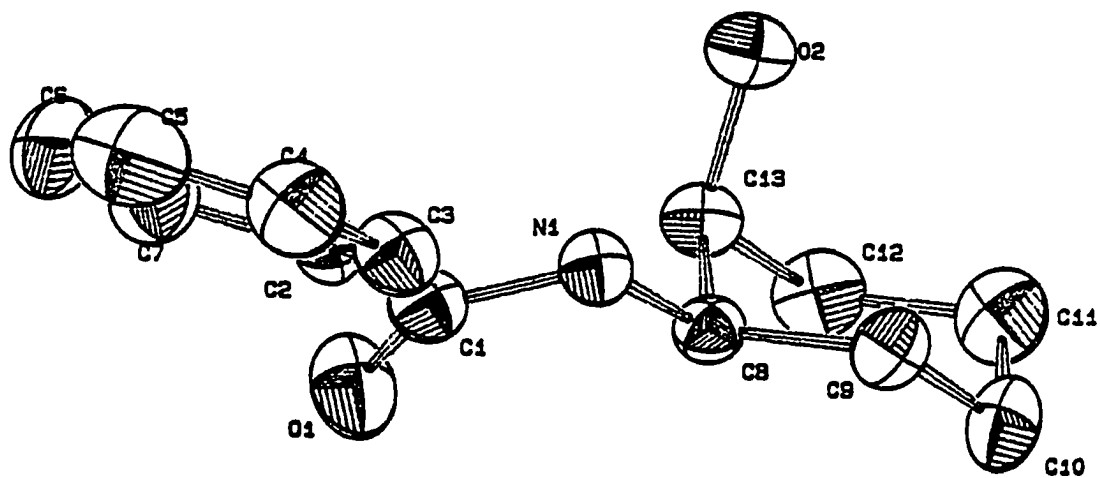
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PART II. ALKOXY RADICALS IN ORGANIC SYNTHESIS.

A NOVEL APPROACH TO SPIROKETALS

HISTORICAL

The use of radical chemistry in organic synthesis has seen explosive growth in recent years. Radical cyclizations have been employed in the synthesis of alkaloids, terpenes and other natural products. Most of the research has been collated in reviews[1-3] and a timely monograph.[4] In contrast to the volume of work on carbon centered radicals, the use of alkoxy radicals in synthesis has been limited.

There are a wide variety of methods available for the production of alkoxy radicals including the decomposition of alkyl hydroperoxides, dialkyl peroxides, peroxy oxalates, dialkyl peroxydicarbonates, peresters, alkyl hypohalites, alkyl nitrosohydroxylamines, and alkyl hyponitrites. Other methods include the photolysis of alkyl nitrites, the oxidation of alcohols and hydroperoxides by heavy metals, and the disproportionation of alkylperoxy radicals during autoxidation.[5,6]

More recently, Beckwith and Hay have used N-alkoxy-pyridinethiones for the formation of alkoxy radicals. Treatment of the pyridine thione 1 with tri-n-butyltin hydride forms the alkoxy radical 2.
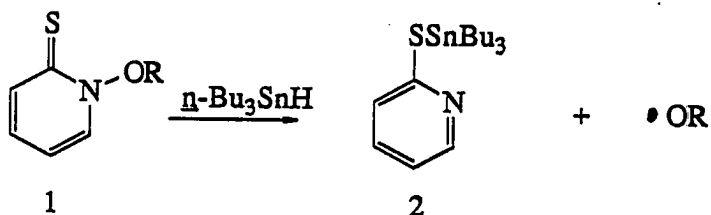
β-Fission and hydrogen atom abstraction, both inter- and intramolecular, are important characteristic reactions of alkoxy radicals. For example, Mihailovic and Cekovic have demonstrated that saturated alcohol 3 readily cyclizes in the presence of lead tetraacetate to tetrahydrofuran 4.[7]
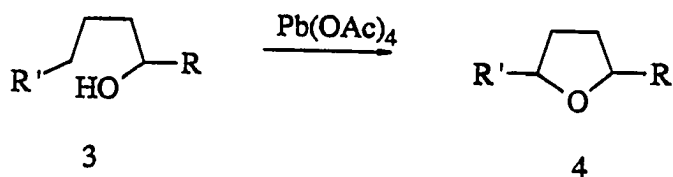
Barton and co-workers have also taken advantage of hydrogen abstraction by alkoxy radicals for remote functionalization in steroids and other molecules. They
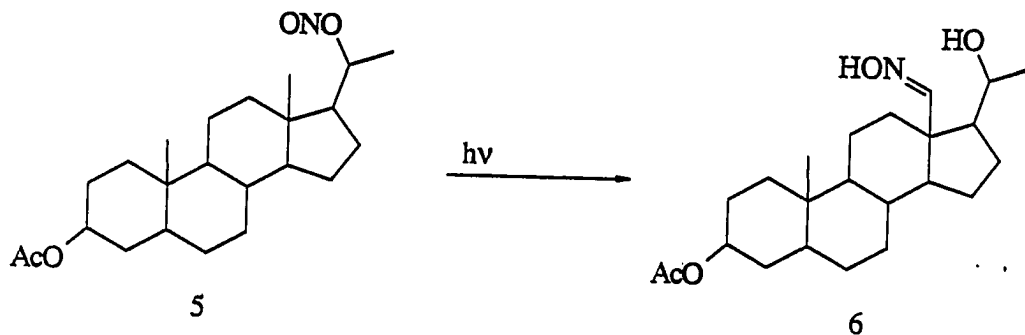
found that photolysis of the nitrite ester $\underset{\sim}{5}$ caused it to rearrange to the oxime $\underset{\sim}{6}$.[8]

Alkoxy radicals also undergo unimolecular fragmentation by scission of the C_∂-C_β bond. This chemistry has been used extensively in the opening of steroid rings. Suginome and Yamada have opened steroid $\underset{\sim}{7}$ by formation of the alkoxy radical to generate the formate $\underset{\sim}{8}$. Reduction of the formate to the alcohol resulted in formation of the cyclic ether $\underset{\sim}{9}$.[9]
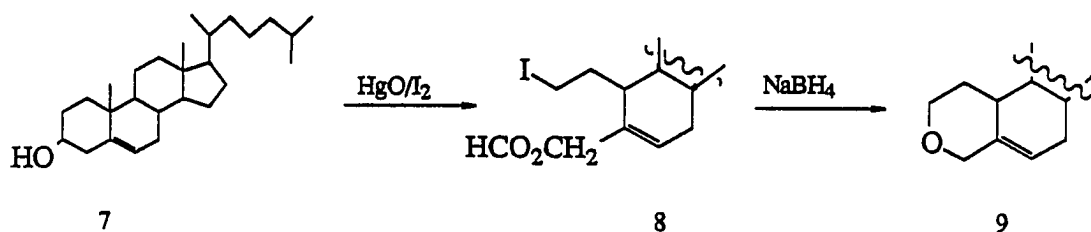
Binkley and Koholic have used the β-fission reaction of alkoxy radicals for epimerization of sugars. They found that photolysis of the nitrate ester $\underset{\sim}{10}$ caused fragmentation to the intermediate $\underset{\sim}{11}$. This intermediate reclosed to give the alcohol $\underset{\sim}{12}$ as the sole product.[10]
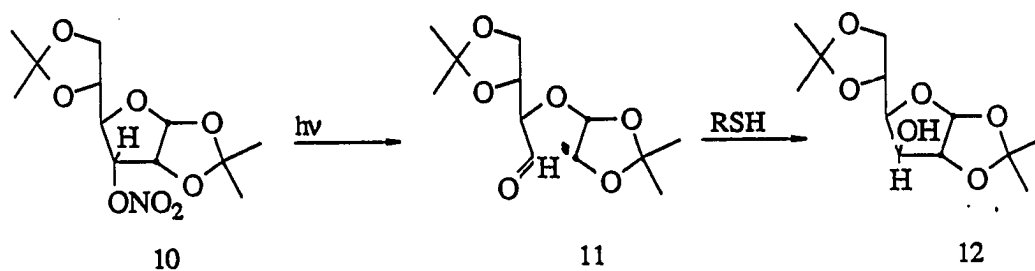
The use of carbon radicals for C-C bond formation is well known and has been reviewed.[11] However, the use of alkoxy radicals for C-O bond formation is limited, in part because of the competitive hydrogen atom abstraction that often ensues. Bertrand and Surzur have shown that the intermolecular reaction of an alkoxy radical with an alkene affords largely products derived from hydrogen abstraction.[12] However, when the alkoxy radical is generated in a molecule bearing a proximate alkene, the addition reaction to afford a cyclic ether can become the sole pathway. An example of this reaction has been described by Riecke and Moore using the nitrite ester 13, which rearranged to the furan derivative 14 on photolysis.[13]

13   14

15   16   17

2   :   1
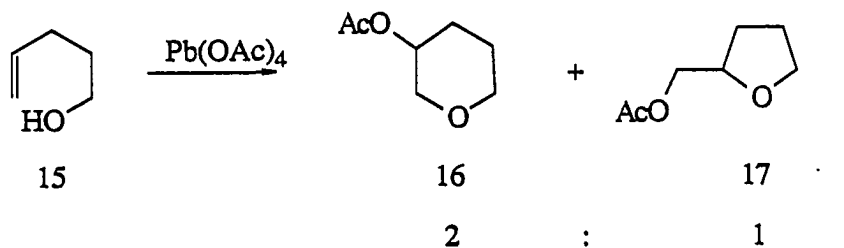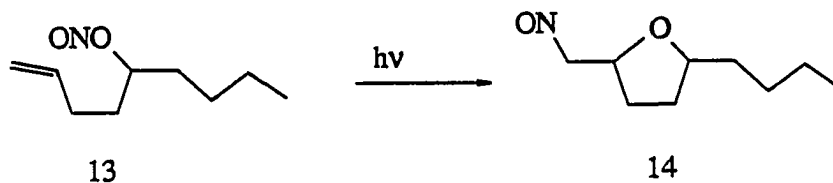
Surzur and Michele have also tried this reaction on the alcohol 15 using lead tetraacetate for radical initiation, but obtained a mixture of the tetrahydropyran 16 and tetrahydrofuran 17.[14]

Peroxy radicals have also been used in synthesis. Porter et al. have shown that peroxy radicals cyclize to form cyclic peroxides. Thus, the peroxide 18 cyclized in the presence of di-tert-butyl peroxyoxalate (DBPO) to the peroxide 19. The hydroperoxide was readily cleaved by triphenylphosphine to the alcohol 20.[15]
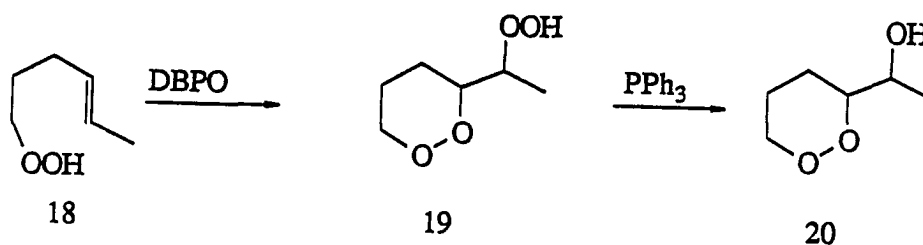
Peroxy radicals have also been used by Feldman et al. for the synthesis of polyoxygenated hydrocarbons from vinylcyclopropanes. Thus, treatment of the cyclopropane 21 with diphenyl disulfide and a radical initiator in the
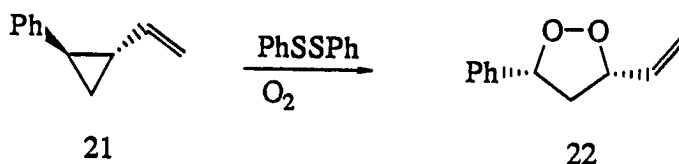
presence of oxygen resulted in formation of the
1,2-dioxolane 22.[16]

RESULTS AND DISCUSSION

The formation of ethers by a radical reaction has some advantages over its ionic counterparts. Ether formation from alcohols and alkenes has been accomplished by oxymercuration,[17] iodoetherification,[18] and selenoetherification.[19,20] With many intramolecular examples, the ring size is dictated by the substitution pattern on the alkene. In some cases the reaction fails or proceeds in poor yields when electron withdrawing substituents are conjugated with the alkene. In contrast, the intramolecular addition of radicals to alkenes affords products derived from a 5-exo-trig type attack. The electronic effect of a substituent is not as important as its steric effect.

In connection with a synthetic approach to the ginkgolides 23,[21] the synthesis of certain spiroketals
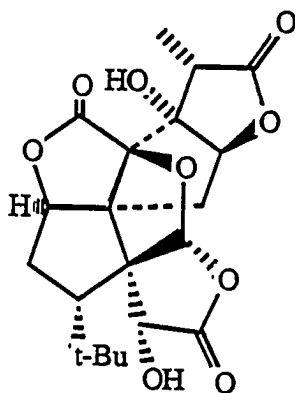
23

became necessary. Because we envisioned C-O bond formation to an electron-deficient alkene, we became interested in studying the addition of alkoxy radicals made from cyclic hemiketals cyclizing with olefins.

General Strategy

Alkoxy radicals are readily generated by photolysis of nitrite esters, which are formed from alcohols, and also by the action of lead tetraacetate with alcohols. We attempted to use these conditions in the model system 25 with little success. The model system 25 was readily prepared by the addition of butyrolactone 24 to a solution of 3-butenyl-magnesium bromide. Despite several attempts, the nitrite ester of 25 could not be prepared. The reaction of lead tetraacetate also failed to produce the desired spiroketal 26. After other unsuccessful ventures, the photochemically initiated reaction of 25 with mercuric oxide and iodine afforded the spiroketal 26. This compound unexpectedly
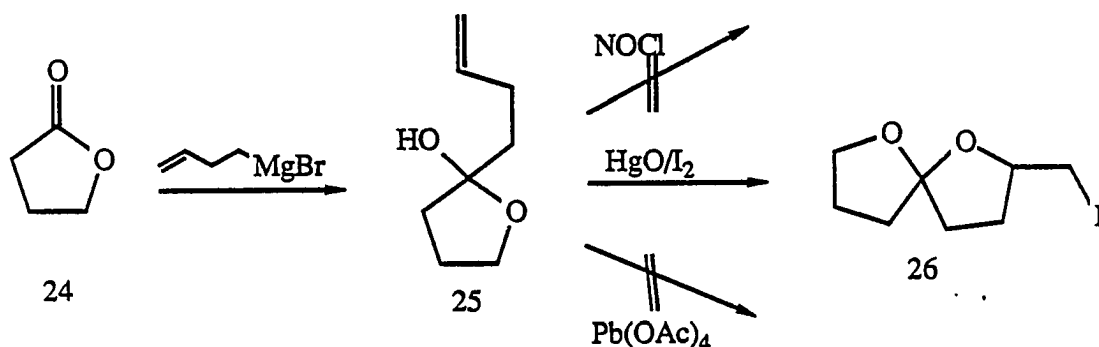
proved to be only one diastereomer as evidenced by proton and carbon NMR spectroscopy.

Many attempts were made to convert 26 into the natural product chalcogran 27[21] using organometallic reagents, but this transformation was unsuccessful.
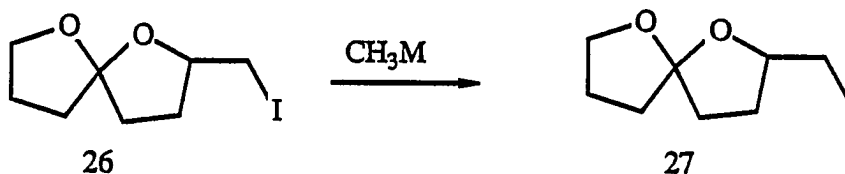
Although Suginome and Yamada have shown that mercuric oxide and iodine generate alkoxy radicals, these conditions have not been used to effect alkoxy radical additions to alkenes. Therefore, we examined several representative olefinic alcohols to assess the scope of this procedure. The results are given in Table 1.

From the results in Table 1, the HgO/I_2 conditions appear to be the most general yet found. In most cases the formation of five-membered ring ethers proceeds well. It is possible that 3-hydroxyethylcyclopentene 36 cyclized in low yield because of competing intramolecular hydrogen atom abstraction. The transition state for the alkoxy radical addition reflects the strain inherent in a bicyclo[3.3.0]-octane, thereby allowing the less strained hydrogen atom abstraction to intervene. Fragmentation of the alkoxy
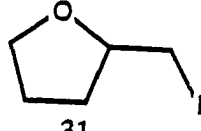
Table 1. Alkoxy radical cyclizations
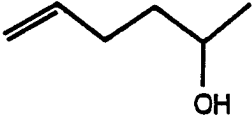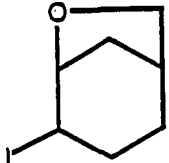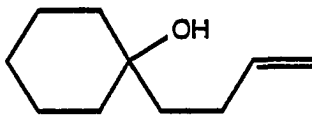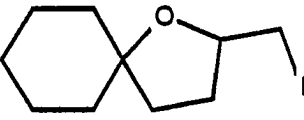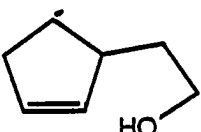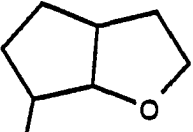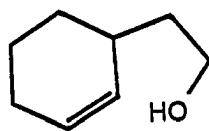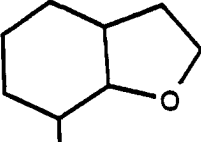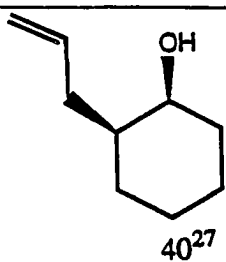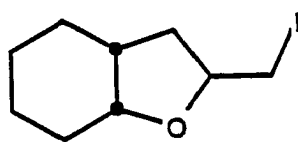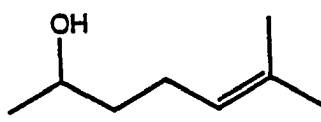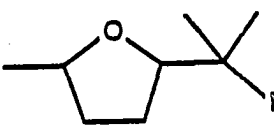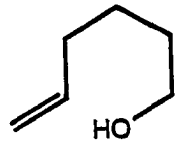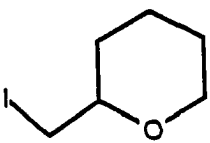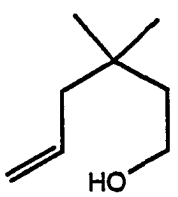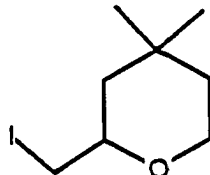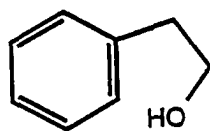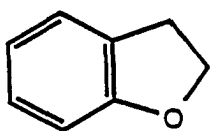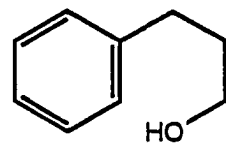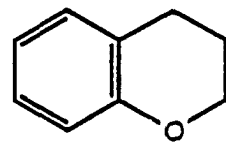
Entry	Alcohol	Product	% Yield
1	28[22]	29	60
2	30	31	50
3	32[23]	33 One Stereoisomer	55
4	34[24]	35	34
5	36[25]	37 One Stereoisomer	17
6	38[26]	39 One Stereoisomer	60

Table 1. Continued

Entry	Alcohol	Product	% Yield
7	**40**[27]	**41**	0
8	**42**[28]	**43**	0
9	**44**	**45**	39
10	**46**[29]	**47**	17
11	**48**	**49**	0
12	**50**	**51**	0

radical to formaldehyde and an alkyl radical might also have occurred. Formation of the six-membered ring ethers 45 and 47 proceeded in modest yield. This could be caused by hydrogen atom abstraction which would produce an allylic radical. Addition of alkoxy radicals to aromatic systems proved to be unsuccessful.

The structure of compound 33 was proven by dehalogenation using tri-n-butyltin hydride which produced the known compound 52.[30]

33   52
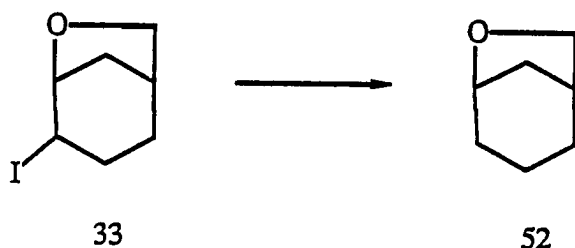
In view of the encouraging results from Table 1, we synthesized hemiketal 54 from gluconolactone 53.[31] Cyclization of the hemiketal 54 afforded the spiroketal 55.

53   54

55
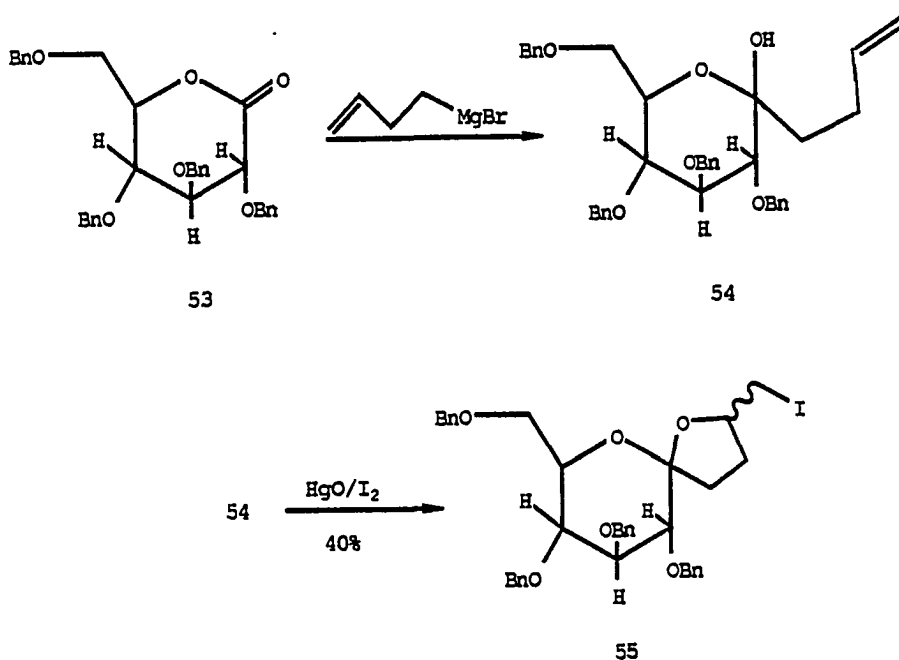
While the intermediacy of alkoxy radicals is likely, particularly in light of Suginome and Yamada's results,[9] one cannot rule out an extremely rapid ionic addition of a hypoiodite to the alkene. The intramolecular addition to compound 61 would provide some insight into this question. Treatment of valerolactone 56 with magnesium methoxide in methanol afforded 57. The resulting primary alcohol was silylated with tert-butyldimethylsilyl (TBS) chloride to afford 58. This ester was deprotonated and reacted with acetyl cyanide to afford the ketoester 59. The ketoester 59 was O-alkylated with chloromethyl methyl ether which after deprotection of the silyl group afforded 61. When 61 was

treated with our standard conditions, compound 62 was

obtained. The methoxymethyl ether was selected because

it should promote the fragmentation which afforded the

ketone 62. The cyclization to produce the five-membered

ring ether is consistent with a radical addition. An ionic

addition would produce the six-membered ring ether.
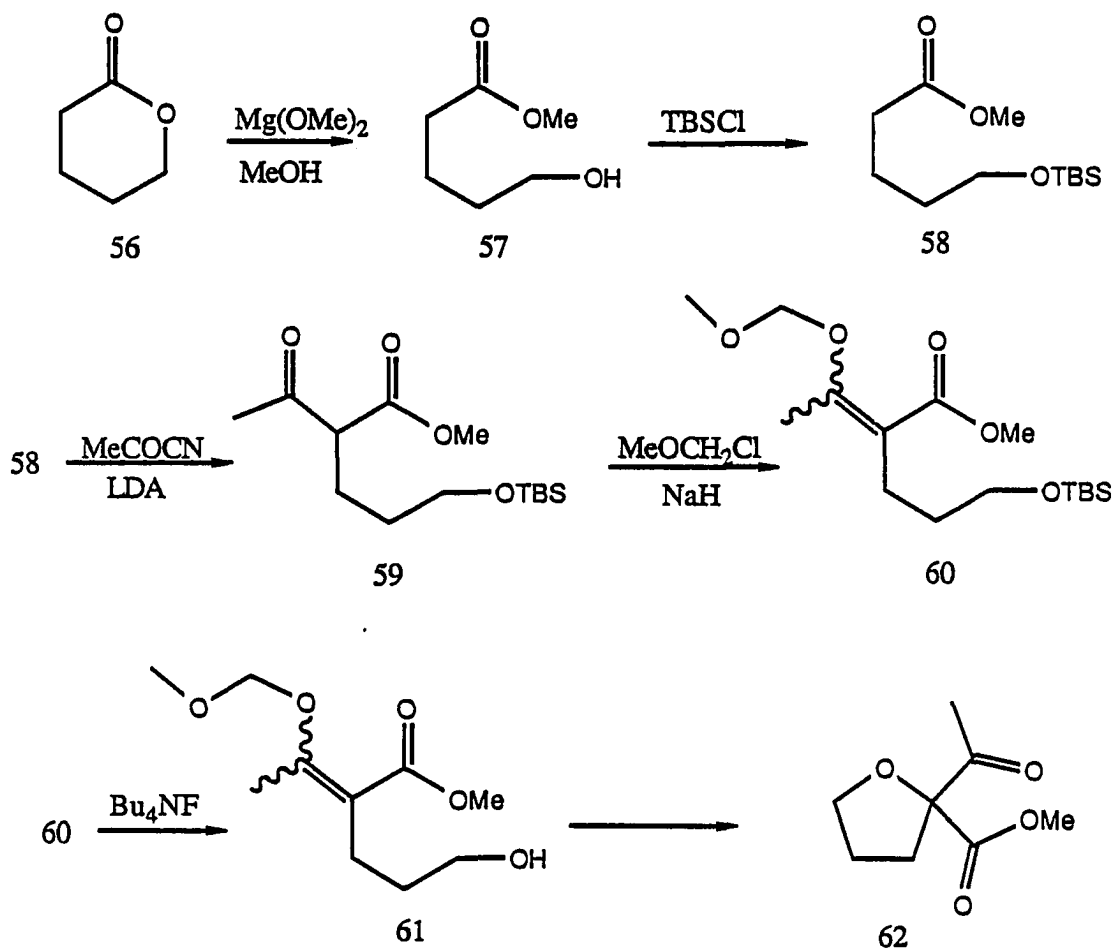
The synthesis of 62 proceeded smoothly except for the removal of the tert-butyldimethylsilyl group. Deprotection gave 61 plus a lactone and other undesired compounds. We attempted to circumvent this problem by using dilute hydrofluoric acid and the salt of triethylamine and hydrofluoric acid, but these conditions were less successful than the tetra-n-butylammonium fluoride conditions. We also protected the alcohol 57 using ethyl vinyl ether (EVE) which can be removed under acidic conditions. However, later deprotection was again unsuccessful.

The chemistry herein provides a mild and reliable method for the generation of alkoxy radicals and extends their synthetic utility. The radical-based approach to the spiroketals is distinctly different from previous methods and offers a useful alternative. The conversion of 61 to the ether 62 supports our projected synthesis of the ginkgolides which involves the same type of cyclization in a more complex system. The work on the synthesis of the ginkgolides will continue. This work has been published recently.[32]

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under a nitrogen atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. High field proton nuclear magnetic resonance spectra (300 MHz) were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023

mass spectrometer. Silica gel used for flash chromatography was 230-400 mesh (Kieselgel 60) purchased from EM Science.

2-(3-Butenyl)tetrahydro-2-furanol (25)

Magnesium (0.18 g, 7.41 mmol) was suspended in 10 mL of THF. To this suspension, 1-bromo-3-butene (1.00 g, 7.41 mmol) was added and the suspension was sonicated until all of the magnesium dissolved. The butyrolactone (0.64 g, 7.41 mmol) in 2 mL of THF was added and the resulting solution was stirred at room temperature for three hours. The reaction was quenched with 20 mL of 2N HCl and extracted three times with 30 mL of ethyl acetate. The ethyl acetate extracts were combined and dried with magnesium sulfate and concentrated. The product was purified by chromatography using 1:1 hexane:ethyl acetate to afford 0.89 g (85%) of 25. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.60 (m, 4 H), 2.10 (m, 3 H), 2.30 (m, 1 H), 2.50 (m, 1 H), 3.60 (m, 1 H), 4.35 (m, 1 H), 5.0 (m, 2 H), 5.80 (m, 1 H); IR (film) 3400, 2970, 1710 cm^{-1}.

General Procedure for the Alkoxy Radical Cyclization

To the alcohol or hemiketal (1 mmol) in 10 mL of degassed benzene was added mercuric oxide (3 mmol) and iodine (3 mmol). The solution was cooled to 0°C and irradiated for three hours using a medium pressure Hanovia lamp. The crude product was poured into 30 mL of ether and then filtered. The ether was washed twice with 10 mL of 10%

sodium bisulfite solution, concentrated and purified by chromatography.

2-(Iodomethyl)-1,6-Dioxaspiro[4.4]nonane (26)

Purified by chromatography using 5:1 hexane:ethyl acetate. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.30-2.00 (m, 8 H), 3.20 (m, 2 H), 3.70 (m, 1 H), 3.80 (m, 2 H); ^{13}C NMR δ 84.87, 80.47, 66.84, 38.56, 34.09, 30.39, 25.55, 11.22; IR (film) 2944, 2922, 2562, 1262, 1150, 738 cm^{-1}. High resolution mass spectrum for C$_8$H$_{13}$O$_2$I requires 267.99603, determined 267.99532.

Tetrahydro-2-(iodomethyl)-5-methylfuran (29)

Purified by chromatography using 5:1 hexane:ethyl acetate to afford 29 as a 1:1 mixture of diastereomers. 300 MHz ^{1}H NMR (CDCl$_3$) δ 4.1-4.3 (m, 2 H), 3.1-3.3 (m, 2 H), 1.9-2.3 (m, 2 H), 1.45-1.8 (m, 2 H), 1.2-1.3 (m, 3 H); IR (film) 2980, 2932, 1730, 1080 cm^{-1}. High resolution mass spectrum m/e for C$_6$H$_{11}$OI requires 226.9915, determined 226.9935.

Tetrahydro-2-(iodomethyl)furan (31)

Purified by chromatography using 5:1 hexane:ethyl acetate. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.1-1.25 (m, 1 H), 1.4-1.7 (m, 3 H), 2.7 (m, 2 H), 3.33 (m, 1 H), 3.46 (m, 2 H); ^{13}C NMR δ 10.38, 25.98, 31.77, 68.75, 78.30; IR (film) 2982, 2932, 1731, 1180, 1098, 1051, 730 cm^{-1}. High

resolution mass spectrum m/e for C_5H_9OI requires 212.0300, determined 211.9552.

4-Iodo-6-oxabicyclo[3.2.1]octane (33)

Purified by chromatography using 5:1 hexane:ethyl acetate. 300 MHz ^1H NMR $(CDCl_3)$ δ 1.50 (m, 1 H), 1.7-2.0 (m, 3 H), 2.35 (m, 2 H), 2.60 (d, 1 H, J = 11.2 Hz), 3.90 (m, 2 H), 4.35 (m, 2 H); ^{13}C NMR δ 26.27, 29.80, 31.17, 34.85, 34.94, 73.12, 79.30; IR (film) 2970, 2932, 1710, 1440, 1218, 1180, 1075, 1015 cm^{-1}.

2-(Iodomethyl)-1-oxaspiro[4.5]decane (35)

Purified by chromatography using 10:1 hexane:ethyl acetate. 300 MHz ^1H NMR $(CDCl_3)$ δ 1.2-1.8 (m, 13 H), 2.1-2.2 (m, 1 H), 3.1 (m, 1 H), 3.3 (m, 1 H), 4.05 (m, 1 H); IR (film) 2962, 2925, 1440, 1020 cm^{-1}. High resolution mass spectrum for $C_{10}H_{17}OI$ requires 280.1482, determined 280.0176.

8-Iodo-2-oxabicyclo[3.3.0]octane (37)

Purified by chromatography using 5:1 hexane:ethyl acetate. 300 MHz ^1H NMR $(CDCl_3)$ δ 1.3-1.7 (m, 2 H), 1.9-2.3 (m, 4 H), 2.9 (m, 1 H), 3.7 (m, 2 H), 4.30 (m, 1 H), 4.70 (m, 1 H); ^{13}C NMR δ 31.6, 34.2, 34.4, 36.3, 41.1, 69.1, 93.2; IR (film) 2980, 2930, 1450, 1062, 1032 cm^{-1}. High resolution mass spectrum m/e for $C_7H_{11}OI$ requires 238.0678, determined 237.9563.

5-Iodo-7-oxabicyclo[4.3.0]nonane (39)

Purified by chromatography using 5:1 hexane:ethyl
acetate. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.85-1.60 (m, 6 H),
1.9-2.0 (m, 2 H), 3.35 (m, 1 H), 3.50 (m, 1 H), 3.60 (m, 1
H), 3.90 (m, 1 H); ^{13}C NMR δ 21.99, 26.09, 30.38, 32.72,
32.85, 36.15, 66.78, 83.31; IR (film) 2962, 2935, 1725,
1150, 1018, 908, 730 cm^{-1}. High resolution mass spectrum
m/e for C$_8$H$_{13}$OI requires 252.00112, determined 252.00063.

Tetrahydro-2-(iodomethyl)-2H-pyran (45)

Purified by chromatography using 5:1 hexane:ethyl
acetate. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.2-1.9 (m, 6 H), 3.15
(m, 2 H), 3.30 (m, 1 H), 3.50 (m, 1 H), 4.0 (m, 1 H); [13]C
NMR δ 9.91, 23.15, 25.57, 31.68, 68.72, 76.91; IR (film)
2965, 2920, 1165, 1030 cm^{-1}. MS: m/e 55, 67, 85, 99, 170,
226.

6-Oxabicyclo[3.2.1]octane (52)

Compound 33 (0.16 g, 0.65 mmol) was dissolved in 5 mL of
degassed benzene. Tri-n-butyltin hydride (0.56 g, 1.95
mmol) was added along with 0.02 g of AIBN. The solution was
refluxed for three hours under nitrogen. The solvent
was removed and the product purified by chromatography to
yield 52 which was contaminated with tri-n-butyltin hydride.
The proton spectra was clean enough that by comparison with

the known spectra[30] it was determined to be the right compound.

1,2,3,4-Tetradeoxy-6,7,8,10-tetrakis-o-(phenylmethyl)-β-D-gluco-dec-1-en-5-ulo-5,9-pyranose (54)

Magnesium (0.0066 g, 0.27 mmol) was suspended in 1.5 mL of THF. To this suspension 1-bromo-3-butene (0.0365 g, 0.27 mmol) was added and the suspension was sonicated until all of the magnesium dissolved. The gluconolactone 53 (0.1416 g, 0.27 mmol) in 0.5 mL of THF was added dropwise to the solution. The reaction was quenched with 1 mL of 2N HCl and extracted three times with 10 mL of ether. The ether extracts were combined, dried and concentrated. The crude product was purified by chromatography using 3:1 hexane:ethyl acetate to afford 0.1188 g (75%) of 56 as a colorless oil. IR (film) 3440, 3020, 2960, 1495, 1450, 1360, 1088 cm^{-1}.

5,9-Anhydro-1,3,4-trideoxy-1-iodo-6,7,8,10-tetrakis-o-(phenylmethyl)-D-gluco-5-deculo-5,2-furanose (55)

See the general procedure for alkoxy radical cyclizations. The crude product was purified by chromatography using 5:1 hexane:ethyl acetate to afford 0.0579 g (40%) of 55 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.9 (m, 2 H), 2.1 (m, 2 H), 3.7 (m, 3 H), 4.0 (m, 2 H), 4.2-5.0 (m, 12 H), 7.40 (m, 20 H); IR (film) 3030, 2960, 2930, 1710, 1450, 1360, 1080, 910, 730 cm^{-1}. High

resolution mass spectrum m/e for $C_{38}H_{41}O_6I$ requires 720.19480, determined 720.19645.

5-Hydroxypentanoic acid methyl ester (57)

Magnesium (2.91 g, 120 mmol) was dissolved in 100 mL of methanol. Valerolactone (10.0 g, 100 mmol) was added and the solution was stirred at room temperature overnight. Acetic acid (14.4 g, 240 mmol) was added and the solution concentrated to remove the methanol and acetic acid. Then 100 mL of ethyl acetate was added and the reaction was filtered to remove the magnesium acetate. The ethyl acetate was removed to afford 12.26 g (93%) of 57 as a colorless oil which was used without further purification. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 2 H), 1.75 (m, 2 H), 2.35 (m, 2 H), 2.45 (bs, 1 H), 3.65 (m, 5 H); IR (film) 3440, 2970, 1730, 1435, 1200, 1160 cm^{-1}.

5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]pentanoic acid methyl ester (58)

Compound 57 (6.00 g, 45.45 mmol) was dissolved in 250 mL of methylene chloride. Tert-butyldimethylsilyl chloride (7.52 g, 50.0 mmol) and imidazole (6.80 g, 100 mmol) were added and the solution was stirred overnight. The methylene chloride was then washed three times with 50 mL of 2N HCl and twice with saturated sodium chloride, dried and concentrated to afford a quantitative yield of 58. Compound 58 was used without further purification. 300 MHz ^{1}H NMR

(CDCl$_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.55 (m, 2 H), 1.60 (m, 2 H), 2.35 (m, 2 H), 3.62 (m, 2 H), 3.69 (s, 3 H); IR (film) 2972, 2962, 2925, 1740, 1250, 1090 cm^{-1}.

2-Acetyl-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]pentanoic acid methyl ester (59)

Diisopropylamine (0.58 g, 5.76 mmol) was dissolved in 25 mL of THF and cooled to 0°C. n-Butyllithium (5.2 mmol) was added dropwise to the solution and the resulting solution was stirred for 15 minutes at 0°C. The solution was cooled to -78°C and ester 58 (1.18 g, 4.80 mmol) was added dropwise as a solution in 5 mL of THF. Thirty minutes after the addition of the ester, acetyl cyanide (0.36 g, 5.28 mmol) was added all at once and the solution was warmed to 0°C. After 1 1/2 hours at 0°C the reaction was quenched with acetic acid and then it was poured into 100 mL of ether. The ether was washed twice with 20 mL of saturated sodium chloride dried and concentrated. The crude product was purified by chromatography to afford 1.07 g (77%) of 59 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.55 (m, 2 H), 1.70 (m, 2 H), 2.25 (s, 3 H), 3.65 (m, 3 H), 3.70 (s, 3 H); IR (film) 2960, 2930, 1740, 1430, 1260, 1100, 830 cm^{-1}.

5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-[1-(methoxymethoxy)ethylidene]pentanoic acid methyl ester (60)

A 50% dispension of sodium hydride in mineral oil (0.35 g, 7.29 mmol) was washed twice with dry hexane to remove the mineral oil. Dimethylformamide (10 mL) was added, followed by the keto ester 59 (0.70 g, 2.43 mmol) in 1 mL of THF. Chloromethyl methyl ether (0.39 g, 4.86 mmol) was added and the solution was stirred at room temperature for three hours. The reaction was quenched with acetic acid and water (10 mL) and extracted three times with 20 mL of ether. The ether extracts were combined, dried and concentrated to afford the crude product. The product was purified by chromatography using 5:1 hexane:ethyl acetate to afford 0.55 g (81%) of 60 as a colorless oil which is a 1:1 mixture of E and Z isomers. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.05 (m, 6 H), 0.90 (m, 9 H), 1.5 (m, 2 H), 2.3 (m, 5 H), 3.4-3.7 (m, 5 H), 4.05-4.15 (m, 3 H), 4.8-5.1 (m, 2 H); IR (film) 2960, 1740, 1710, 1410, 1250, 1100, 830 cm^{-1}.

5-Hydroxy-2-[1-(methoxymethoxy)ethylidene]pentanoic acid methyl ester (61)

Compound 60 (0.55 g, 1.66 mmol) was dissolved in 10 mL of THF. Tetra-n-butylammonium fluoride (1.82 mmol) was added dropwise and the solution stirred at room temperature for 12 hours. The reaction was poured into 30 mL of ether and washed with 10 mL of water. The ether layer was dried

to afford the crude product. The crude product was purified by chromatography using 1:1 hexane:ethyl acetate to afford 0.0337 g (9%) of $\underline{61}$ as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.7 (m, 2 H), 2.40 (m, 5 H), 3.4 (s, 3 H), 3.5-3.8 (m, 5 H), 5.1 (s, 2 H); IR (film) 3440, 2970, 1700, 1620, 1432, 1270, 1150, 995 cm^{-1}.

2-Acetyltetrahydro-2-furancarboxylic acid methyl ester ($\underline{62}$)

See the general procedure for alkoxy radical cyclizations. The crude product was purified by chromatography using 5:1 hexane:ethyl acetate to afford $\underline{62}$ as a colorless oil in 45% yield. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.75 (m, 2 H), 2.15 (s, 3 H), 2.22 (m, 2 H), 3.60 (s, 3 H), 3.90 (m, 2 H). This compound decomposed before a mass spectrum could be obtained and attempts to duplicate the series of reactions failed because of the difficulty in converting $\underline{60}$ or derivatives of $\underline{60}$ into the alcohol $\underline{61}$ as discussed in the Results and Discussion section.

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PART III. A NOVEL APPROACH TO THE SYNTHESIS

OF THE IRIDOID, 9-HYDROXYSEMPEROSIDE

HISTORICAL

Iridoids represent a large and still expanding group of cyclopenta[c]pyran monoterpenoids. They are found as natural constituents in a large number of plant families, usually, but not invariably as glucosides.[1] The name iridoid was derived because of the similarity of these compounds to one of the simplest members, iridodial 1.[2] Although the name iridoid is generally accepted, these compounds have also been referred to as pseudoindicans, due to the blue coloration that some of them develop upon hydrolysis. They have also been referred to as aucubin glucosides.


1a   1b
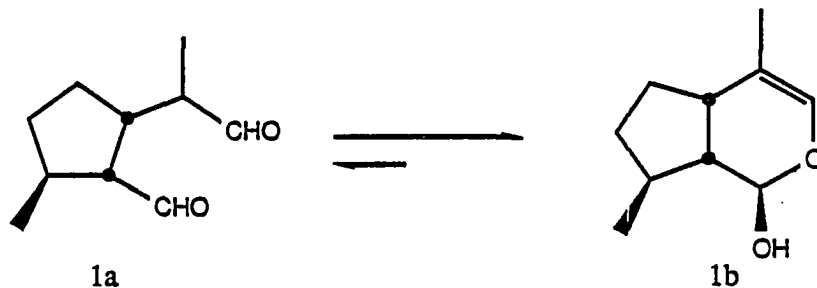
The broad diversity of biological activity exhibited by the iridoids has generated much interest in methods for their synthesis. Various plants containing iridoids have been used in a variety of folk medicines as a bitter tonic, an expectorant, a purgative, and as a treatment for certain skin disorders.[3] Among the isolated iridoids, demonstrated biological activities include antibiotic (genepic acid,

genepinic acid, plumericin fulvoplumierin, udoteatrial),
antifungal (plumericin, fulvoplumierin), hypotensive
(oleuropein), analgesic (herpagoside), diuretic
(catalposide), antipsychotic (gentianine), purgative
(geneposide), tumor inhibitory (allamandin, plumericin,
allamicin, pentstemide), and antiviral properties (elenolic
acid).[4] These terpenoids are also important as defensive
secretions for some species of ants,[5] an attractant for
certain beetles,[6] and a plant defensive mechanism as an
insect antifeedent.[7] Nepetalactone, found in catnip, is a
potent attractant for cats.[8] Some of the compounds are
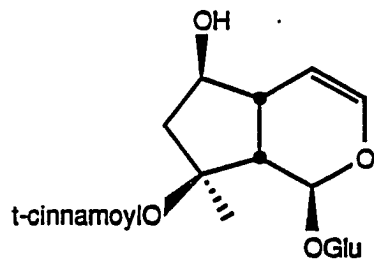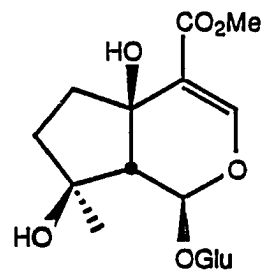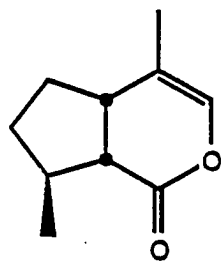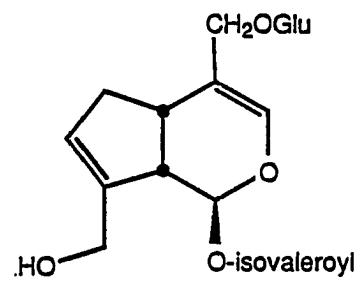shown below as representatives of the iridoids.
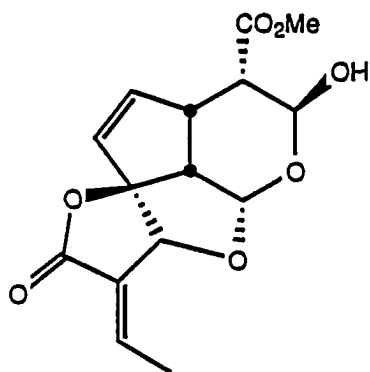
Allamandin
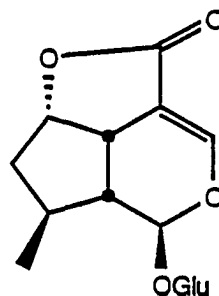
Brasoside

Harpagoside
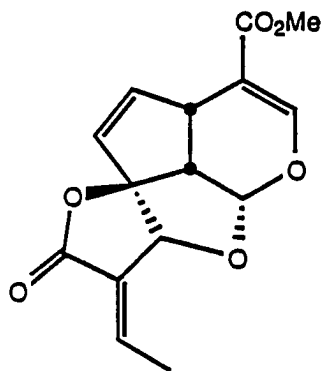

Ipolamiide

Nepetalactone

Pentstemide

Plumericin

Syringenone

p-HO-BenzoylO

HO

OGlu

Catapolside

O

O

CO₂Me

Fulvoplumierin

HOOC

OH

O

Genepic Acid

CO₂Me

O

HO

OGlu
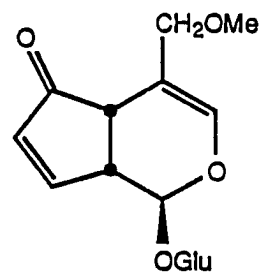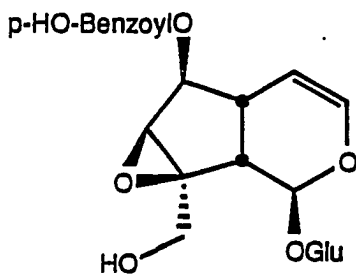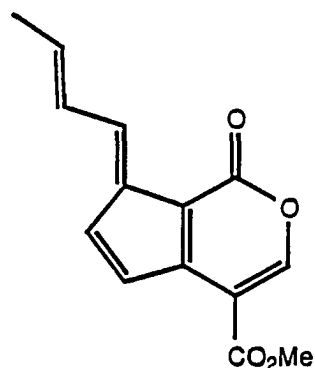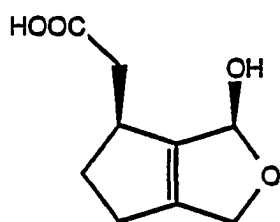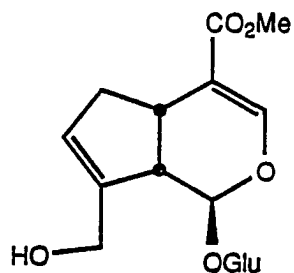
Geniposide

Synthetic Approaches

The cyclopenta[c]pyran ring system (iridane skeleton) of the iridoids can be synthesized by several methods.[9] The most important of these are a) the double cleavage and cyclization of bicyclononadiene derivatives 2, b) the cleavage and cyclization of bicyclooctene derivatives 3, c) the intramolecular hetero Diels-Alder reaction of compounds like 4, d) the intermolecular hetero Diels-Alder reaction of cyclopentenecarbaldehydes 5 and enol ethers 6 to provide 7, and subsequent isomerization of the double bond, and e) the

photochemical cycloaddition of a cyclopentene $\underset{\sim}{8}$ with a
tricarbonyl compound $\underset{\sim}{9}$ to provide the cyclobutane $\underset{\sim\sim}{10}$,
followed by subsequent ring opening to the dihydropyran $\underset{\sim\sim}{11}$.
The syntheses of the iridoids before 1983 have been reviewed
by Tietze[10] and will not be presented here.
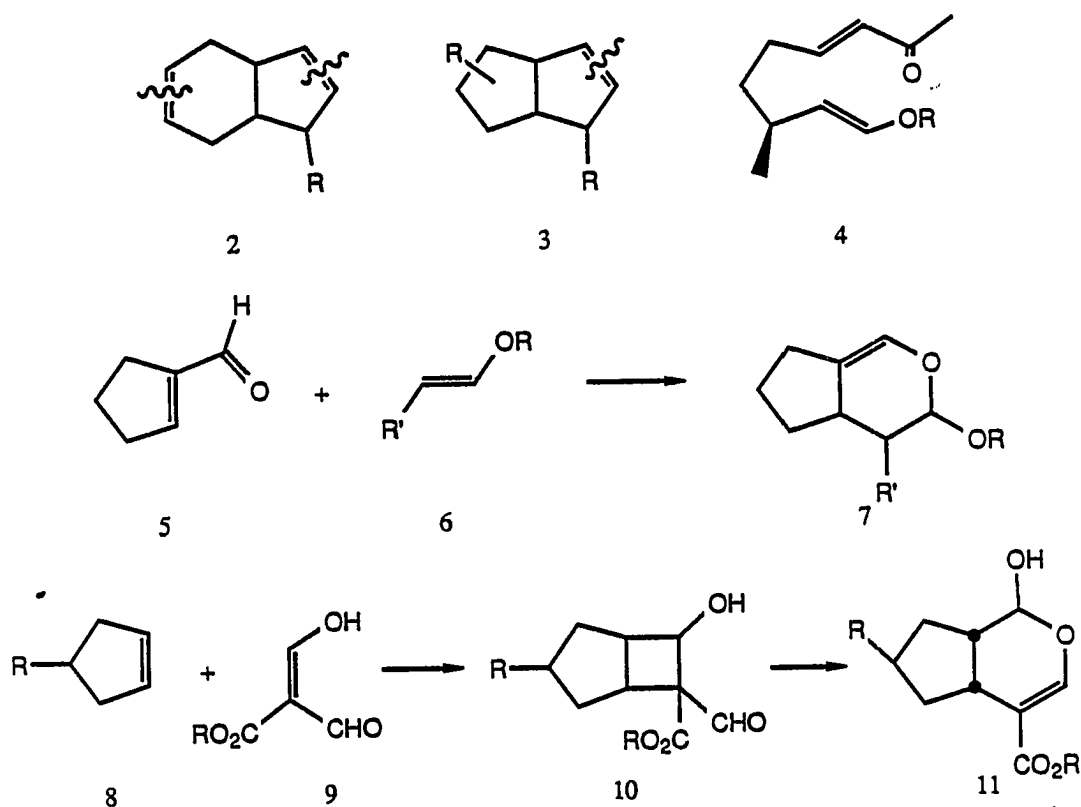
The most popular strategy for the synthesis of the
iridoids has been by the cleavage of the bicyclooctene
derivative $\underset{\sim}{3}$. Riterskamp et al. have used this chemistry

for the synthesis of (+)-iridodial $\underline{1}$.[11] They synthesized

the tricyclic compound $\underline{12}$. Compound $\underline{12}$ was converted into

the bicyclic compound $\underline{13}$. Compound $\underline{13}$ was converted into

the target molecule $\underline{1}$ by formation of a diol with subsequent

cleavage. Wender and Dreyer have used a similar strategy

for the total synthesis of isoiridomyrmecin $\underline{14}$.[12]
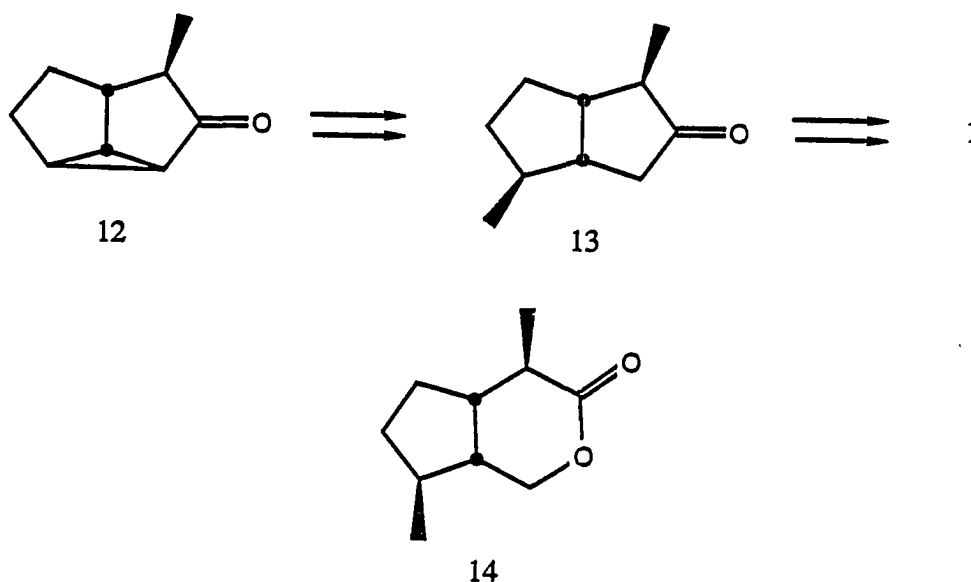
Whitesell et al. have also attempted to use this

strategy for the synthesis of xylomollin $\underline{15}$.[13] They began

with the bicyclooctanone $\underline{16}$ which was converted to the

dialdehyde $\underline{17}$. However, compound $\underline{17}$ could not be converted

into the target molecule $\underline{15}$.

16   17   15
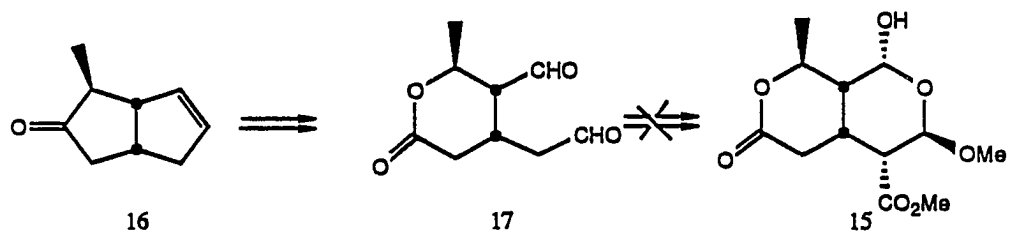
Trost et al. have reported the total synthesis of plumericin, allamcin, and allamandin also from a bicyclooctene.[14] Their synthesis began with the bicyclooctenone 18, which they converted into the

18   19   20

20 ⟹

21
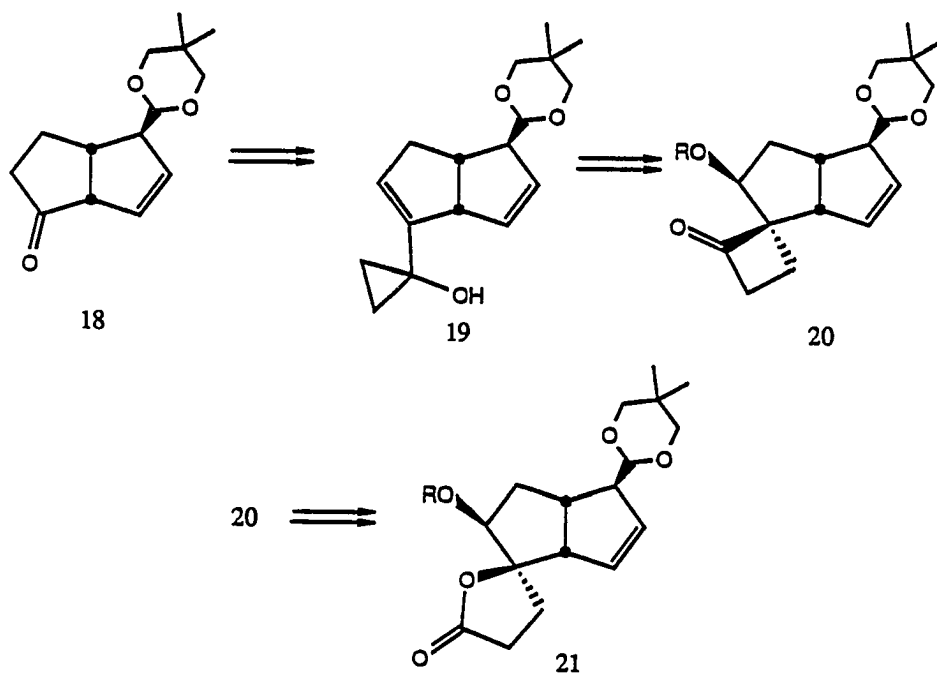
cyclopropanol 19. Ring expansion of 18 resulted in the formation of the cyclobutanone 20. Baeyer-Villiger oxidation of the cyclobutanone led to the spirolactone 21. Compound 21 could be used for the synthesis of all three natural products.

The major disadvantage of the photoannulation strategy for the synthesis of iridoids (method e) is that poor regioselectivity is obtained when unsymmetrical olefins are used. Chaudhuri et al. have overcome this problem by using the allylsilane 22 and the tricarbonyl compound 23.[15] The reaction proceeded regioselectively and the resulting silane 24 could be transformed into intermediates that other groups had used in the total synthesis of iridoids.
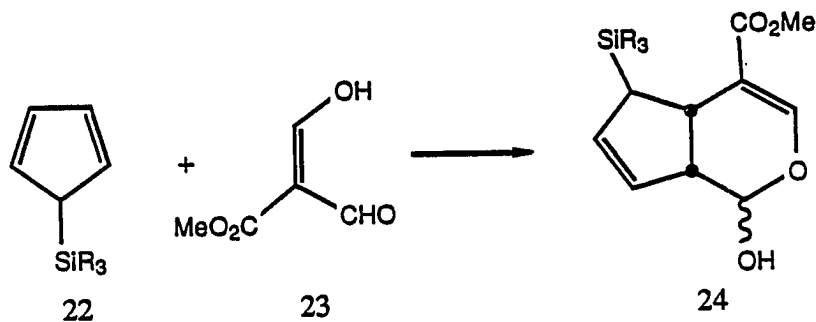
A novel strategy for the synthesis of iridoids has been reported by Callant et al. for the total synthesis of loganin 30.[16] Their strategy involved the fragmentation of the norbornane derivative 26, which is readily available by Diels-Alder chemistry. Thus, the norbornane 26 was

transformed into the tricyclic compound 27. Compound 27 was

transformed in a number of steps to the lactone 28 which was

opened to 29. Compound 29 had previously been transformed

into loganin 30.

26   27   28

28

29   ✦   30
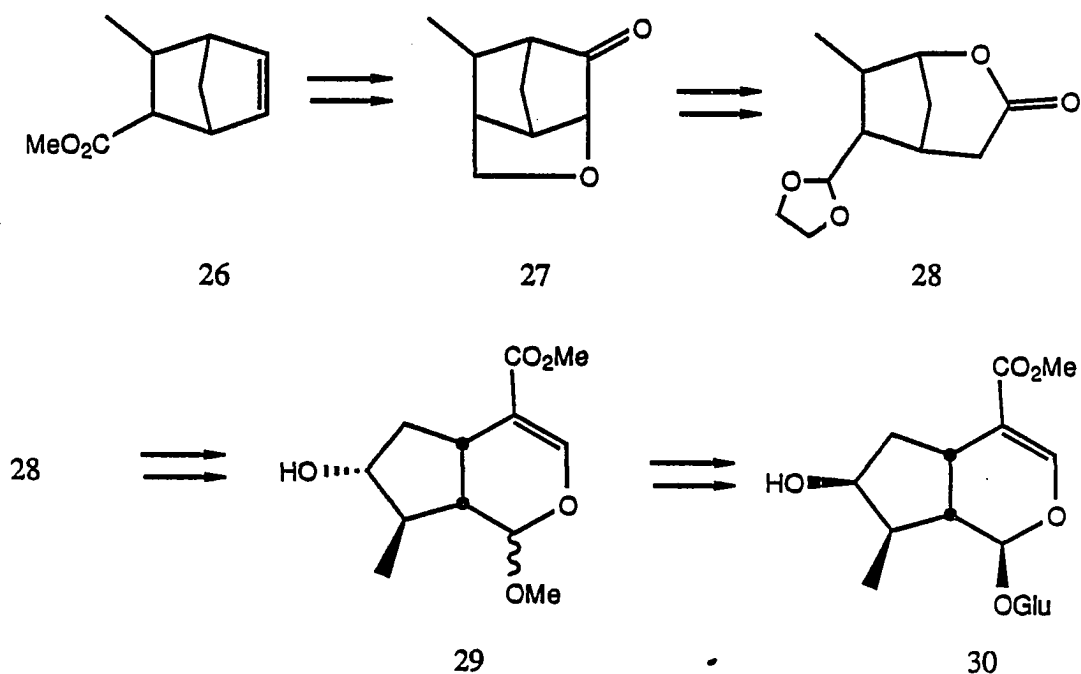
RESULTS AND DISCUSSION

The iridoids, with approximately 300 known naturally occurring compounds,[17] represent a class of highly oxygenated monoterpenoids, characterized by a functionalized cyclopentane ring cis-fused to a dihydropyran (31). However, very few of the iridoids contain a tricyclic structure where the cyclopentane and dihydropyran are linked by a lactone (32). We became interested in developing a general strategy that could be used for the synthesis of these rare iridoids. The molecule we chose as our synthetic target was 9-hydroxysemperoside 33, which was recently isolated from the Gelsemium sempervirens.[18]

31   32   33a R=H
                            b R=Glu
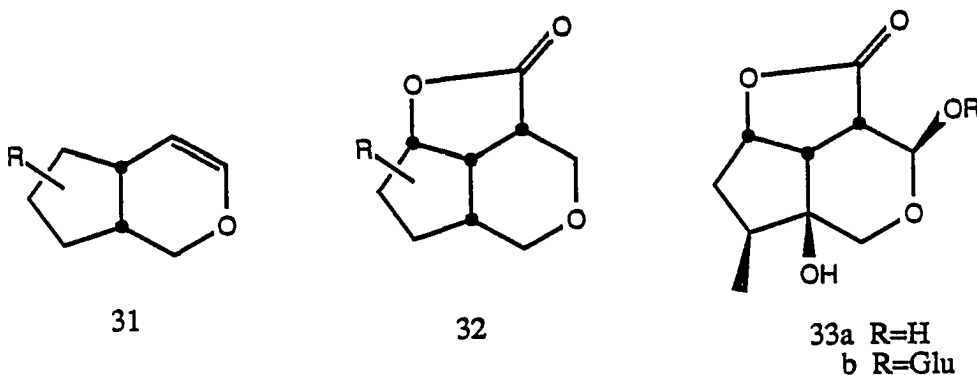
General Strategy

As discussed in the Historical section, there have been five general strategies developed for the synthesis of the iridoids, the most popular being the cleavage of a

bicyclo[3.3.0]octene for the formation of the dihydropyran.
However, these strategies seemed unfeasible for a convergent
synthesis of 33 due to its unique structure. We decided
that the best approach for the synthesis of 33 would be to
form the appropriately substituted oxabicyclooctene 34 and
append the tetrahydropyran ring last. The general strategy
we selected is shown below.

33a R=H   34   35
  b R=Glu
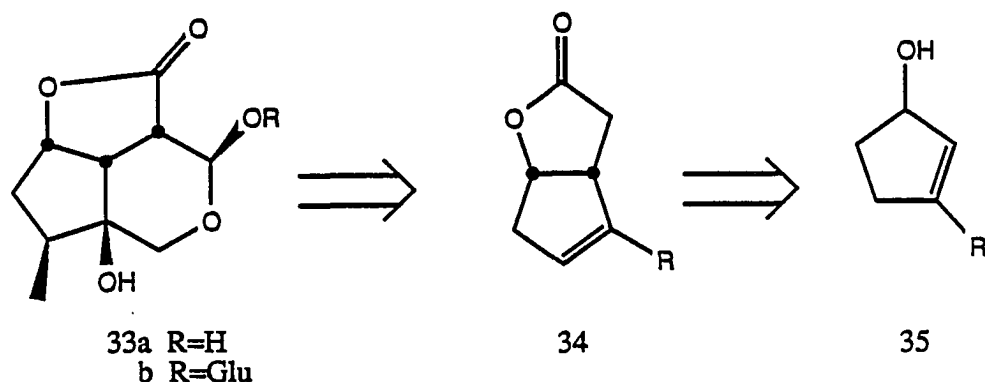
Corey and Ravindranathan have synthesized a molecule 38
similar to 34 in convergent fashion.[19] Their synthesis
began with 1,3-cyclohexadiene, which they reacted with
dichloroketene to obtain 36. This compound was
dehalogenated using zinc and the lactone 37 was formed using
Baeyer-Villiger conditions. The lactone 37 was oxidized
isomerized to the cyclopentane carboxaldehyde 38 using
thallium(III) nitrate. Corey and Ravindrananthan used this
compound for the synthesis of 11-deoxyprostaglandins. We
tried to use 38 for the synthesis of 33, but were forced to

abandon this approach when we were unsuccessful in converting 38 into the unsaturated aldehyde 39.

36

37

37 $\xrightarrow{\text{Tl(NO}_2)_3}$ 38 $\xrightarrow{\text{X}}$ 39
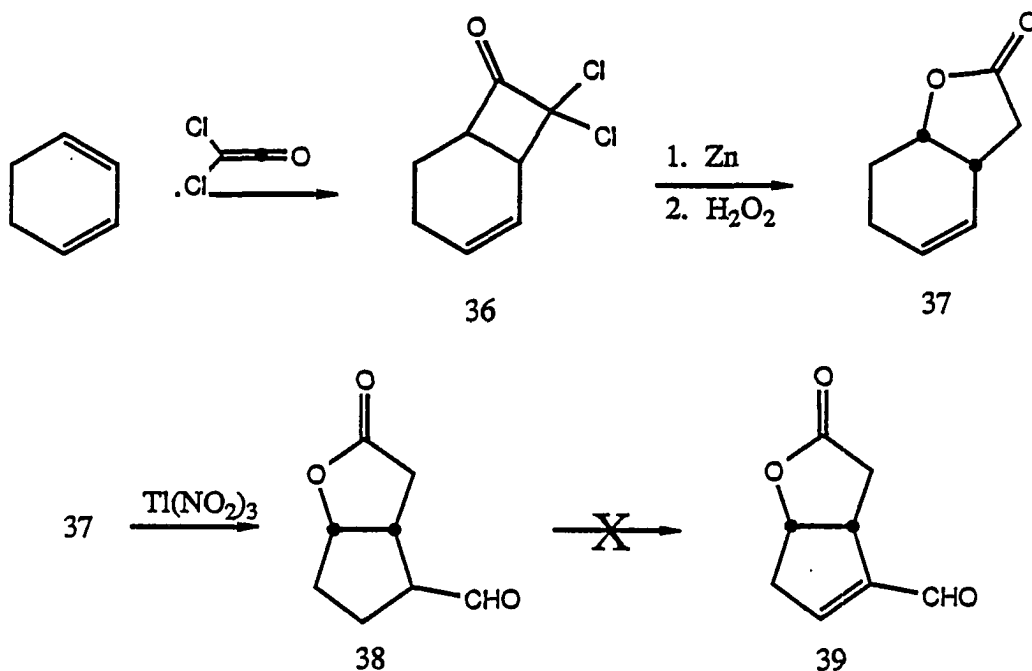
Our next strategy, for the synthesis of 33, involved an intramolecular radical addition to an appropriately substituted cyclopentene 42. Compound 42 was prepared from cyclohexenol 40. Esterification of the cyclohexenol produced 41. Ozonolysis of 41 followed by in situ aldol condensation of the resulting dialdehyde produced 42. Treatment of 42 with a catalytic amount of hexabutyltin failed to produce the desired halide 43.[20]
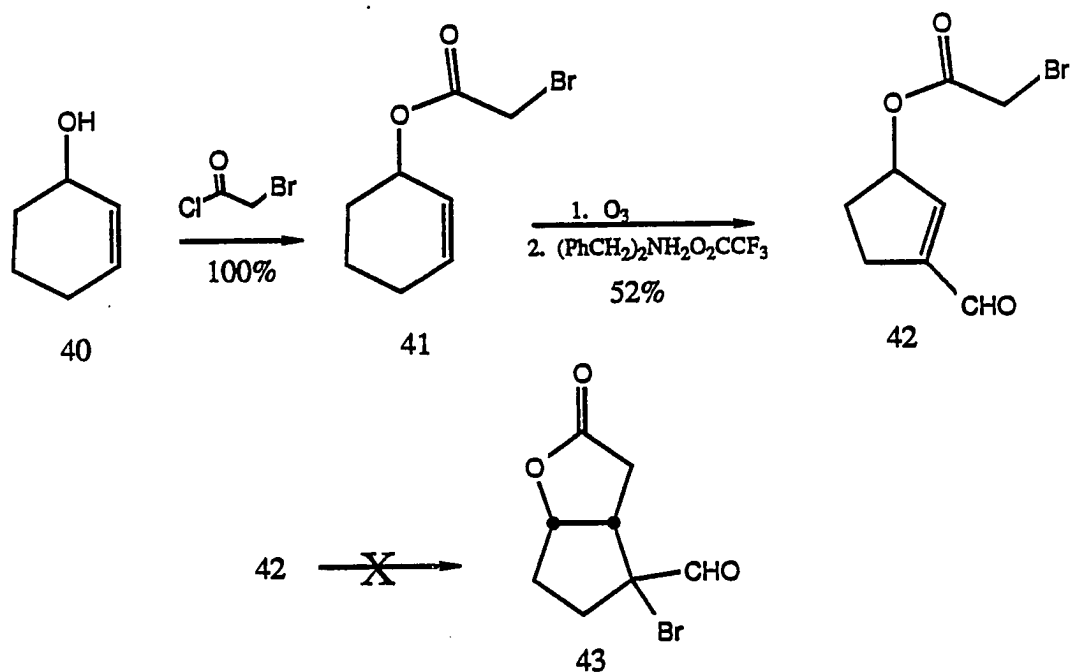
We also attempted this reaction using the iodide 47. The iodide was synthesized from 2-cyclohexen-1-ol acetate ester 44. Ozonolysis of 44 followed by in situ aldol condensation produced the aldehyde 45, which was converted to the dimethyl acetal 46. The iodide 47 was prepared using conditions reported by Rathke and Lindert.[21] This compound also failed to cyclize to the desired intermediate using hexabutylditin. Recently, Jolly and Livinghouse have reported similar cyclizations in complex systems using hexabutylditin in the presence of a large excess of ethyl

iodide.[22] These conditions were not used here as they were unknown at the time this work was under investigation.
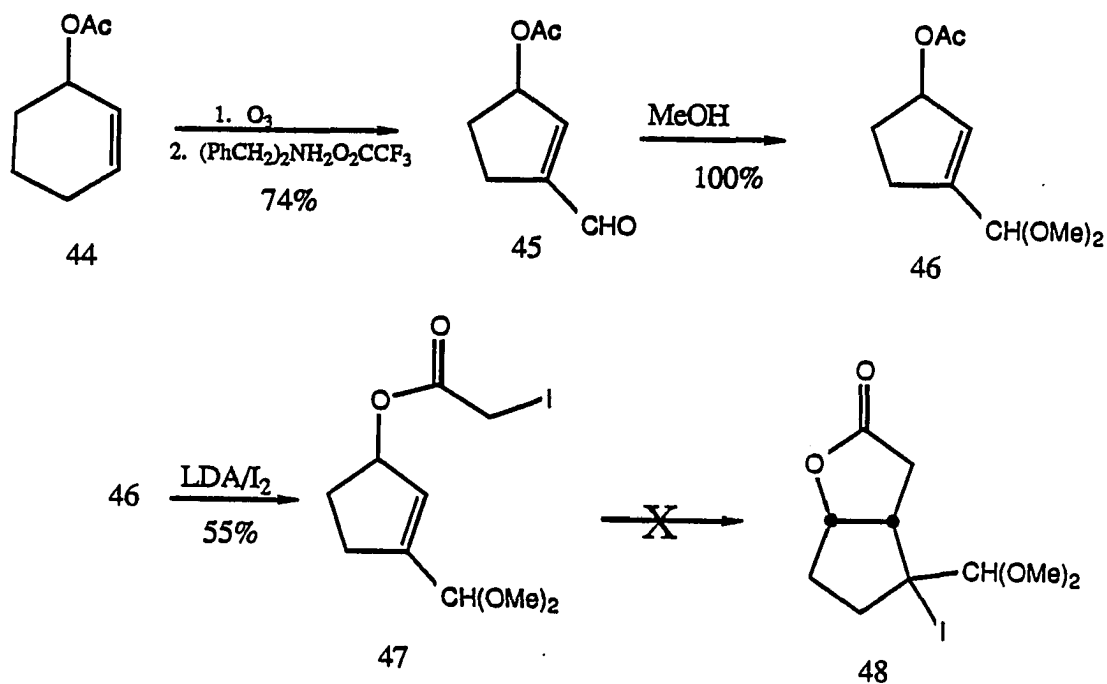
In a last attempt to use a radical cyclization for the formation of a lactone, we attempted to cyclize 49 to the lactone 50 using manganese(III) acetate. However, this reaction also failed to produce the desired product. The formate 49 was readily prepared from the acetate 46.
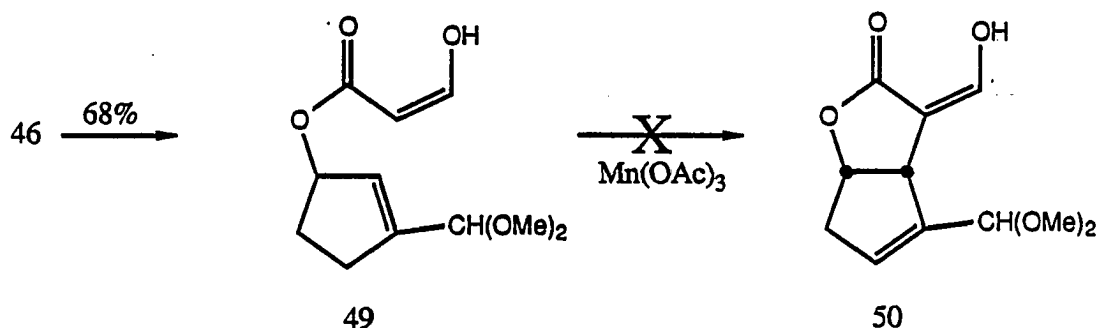
Finally, we turned our attention to a recently reported result by Fugami et al.[23] They have shown that palladium(II) acetate promotes intermolecular cycloalkenylation reaction between allylic alcohols and vinyl ethers to give tetrahydrofuran derivatives in a single step. For example, treatment of 51 with 52 in the presence of palladium acetate provides the tetrahydrofuran 53. Larock and Stinn have also extended this reaction by employing cyclic allylic alcohols.[24]
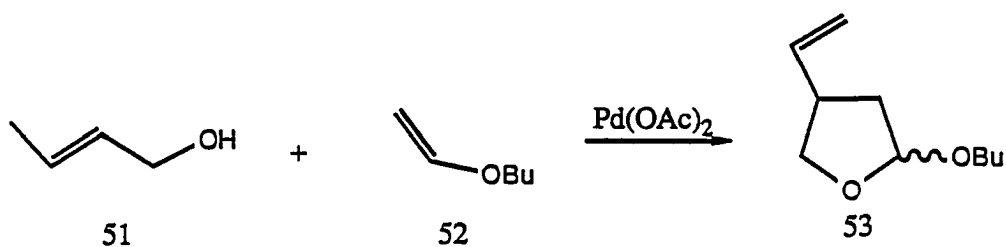
We prepared the cyclic allylic alcohol 56 by lithium aluminum hydride reduction of 46. Reaction of 56 with ethyl

vinyl ether in the presence of palladium acetate provided
the cyclic acetal 57 as a 1:1 mixture of diastereomers.
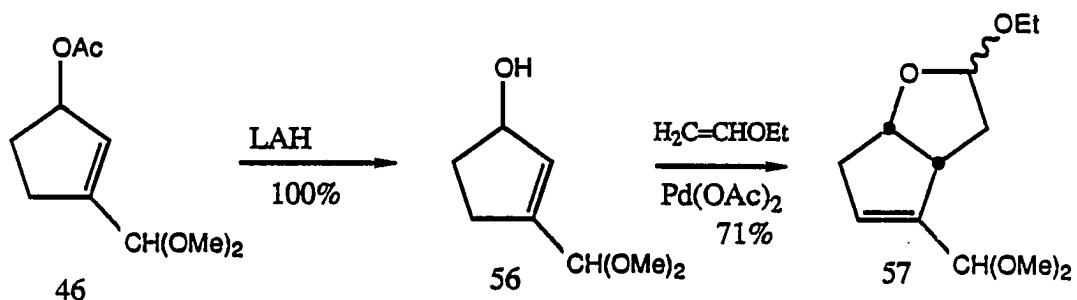
The next step in the synthetic sequence required the
introduction of a methyl group at C-7 in compound 57. It
has been previously shown that allylic acetals react with
Grignard reagents,[25] organoaluminates,[26] or organocuprates[27]
to form vinyl ethers. However, none of these conditions
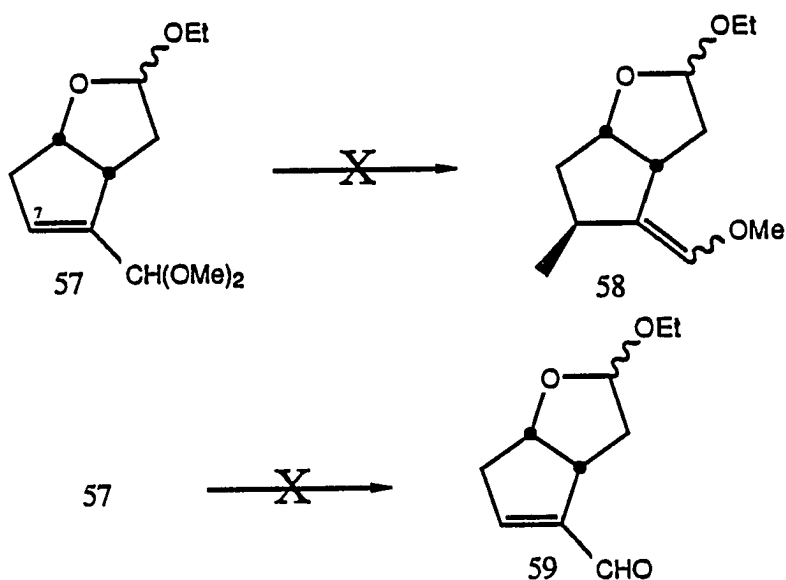
worked for the transformation of $\underset{\sim\sim}{57}$ into the vinyl ether $\underset{\sim\sim}{58}$. Attempts to selectively hydrolyze the dimethyl acetal in $\underset{\sim\sim}{57}$ failed to produce the unsaturated aldehyde $\underset{\sim\sim}{59}$.

We went back to compound $\underset{\sim\sim}{45}$ and attempted to form the cyclic allylic alcohol $\underset{\sim\sim}{60}$ by hydrolysis of the acetate under mild conditions using potassium carbonate in methanol,[28] or potassium cyanide in ethanol.[29] However, this transformation also was difficult. Therefore, we were
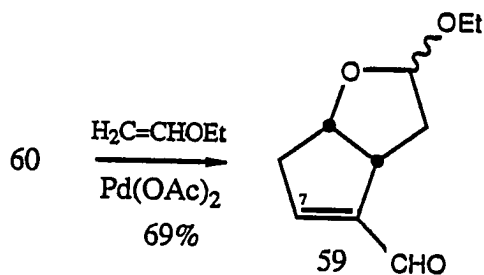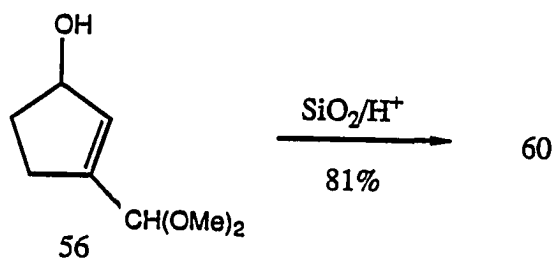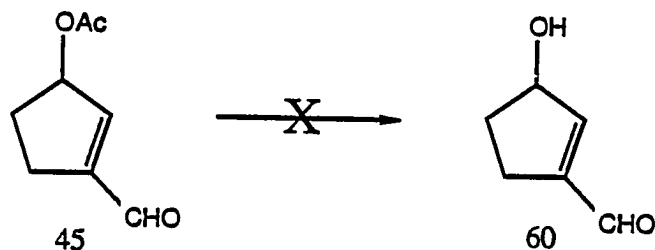
forced to use compound 46 and remove the acetate as previously described to obtain 56. Hydrolysis of the dimethyl acetal in 56 produced the desired unsaturated aldehyde 60.[30] Compound 60 reacted smoothly with ethyl vinyl ether in the presence of palladium acetate to form 59 as a 1:1 mixture of diastereomers.

With 59 in hand, our next step was the introduction of the methyl group at C-7. This was accomplished by reacting the aldehyde with lithium dimethyl cuprate in the presence of trimethylsilyl chloride to provide the enol silyl ether 61.[31] Compound 61 reacted with osmium tetroxide to produce the hydroxy aldehyde 62.[32] The
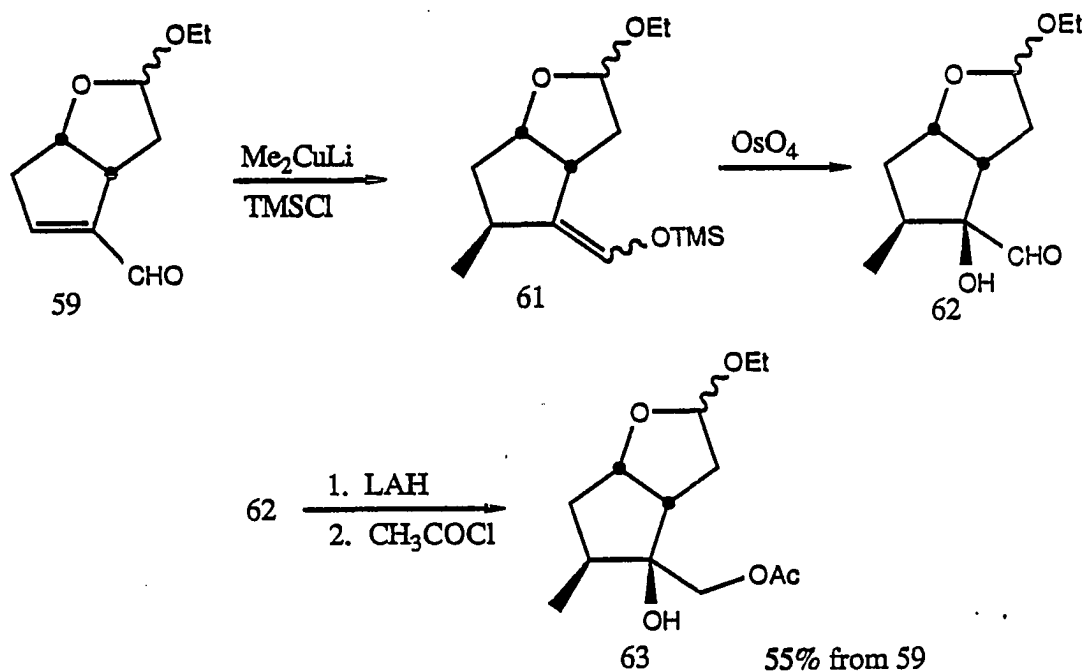
hydroxyaldehyde 62 was reduced with lithium aluminum hydride
and protected using acetyl chloride to provide the acetal
63. The acetal 63 was converted into the lactol 64 by
treatment with dilute acid in acetonitrile. Subsequent
oxidation with Jones reagent provided the lactone 65.
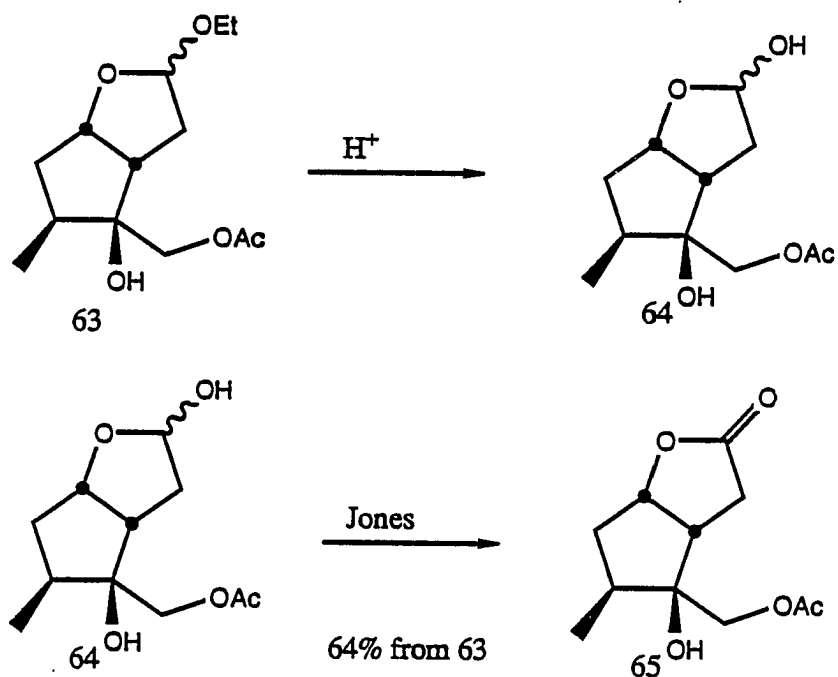
The conversion of the lactone 65 into the deglucoside of
9-hydroxysemperoside 33a proceeded smoothly. Treatment of
the lactone 65 with potassium carbonate in methanol provided
the diol 66. Treatment of the diol 66 with sodium hydride
and ethyl formate followed by acidification with dilute
hydrochloric acid provided 33a.

65 $\xrightarrow[\text{67\%}]{\text{K}_2\text{CO}_3/\text{MeOH}}$ 66

66 $\xrightarrow[\substack{\text{2. aq HCl} \\ \text{35\%}}]{\text{1. NaH/EtO}_2\text{CH}}$ 33a R=H
b R=Glu
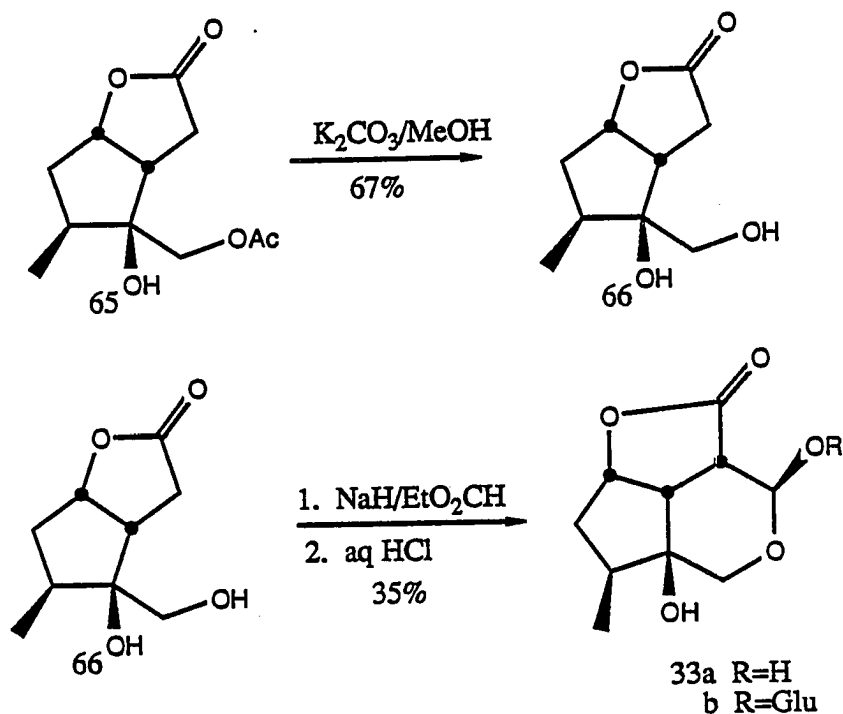
The methodology presented here should prove to be useful for the synthesis of iridoids containing the lactone ring. For example, one could employ the hydrogenation of the enol silyl ether 61 to produce the alcohol 67. This compound should be easily converted into semperoside 68a[18] by the same series of reactions. This chemistry is also being applied to the synthesis of the ginkgolides which were discussed in Part II of this manuscript.

61   67   68a R=H
                                           b R=Glu

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under a nitrogen atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. High field proton nuclear magnetic resonance spectra (300 MHz) were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023

mass spectrometer. Silica gel used for flash chromatography was 230-400 mesh (Kieselgel 60) purchased from EM Science.

2-Cyclohexen-1-ol Bromoacetate Ester (41)

Cyclohexenol (5.00 g, 52.08 mmol) was dissolved in 30 mL of CH_2Cl_2 and the resulting solution was cooled to 0°C. Pyridine (5.35 g, 67.70 mmol) was added followed by the dropwise addition of bromoacetyl chloride (9.84 g, 62.25 mmol). The solution was stirred for one hour and quenched by adding 10 mL of water. The CH_2Cl_2 was washed three times with 10 mL of saturated copper sulfate to remove the excess pyridine. The methylene chloride was dried to afford 9.12 g (81%) of 41 as a colorless oil. 300 MHz ^1H NMR ($CDCl_3$) δ 1.6-2.2 (m, 6 H), 4.08 (s, 2 H), 5.32 (m, 1 H), 5.7 (m, 1 H), 6.0 (m, 1H).

3-Hydroxy-1-cyclopentene-1-carboxaldehyde Bromoacetate Ester (42)

Compound 41 (9.12 g, 41.60 mmol) was dissolved in 100 mL of CH_2Cl_2. This solution was cooled to -78°C and O_3 was bubbled into the solution until the solution turned blue. Nitrogen was passed through the solution to remove the excess O_3, then Ph_3P (10.89 g, 41.60 mmol) was added and the solution was allowed to warm to 0°C. The salt of dibenzylamine and trifluoracetic acid (1.94 g, 6.24 mmol) was added and the solution was stirred for 24 hours. The reaction was then poured into 200 mL of hexane. The hexane

was washed twice with 50 mL of water then dried. The crude product was purified· by chromatography using 3:1 hexane: ethyl acetate to afford 5.00 g (52%) of $\underset{\sim}{42}$ as a pale yellow oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.95-2.05 (m, 1 H), 2.2-2.4 (m, 2 H), 2.6-2.8 (m, 1 H), 4.05 (s, 2 H), 5.90 (m, 1 H), 6.75 (bs, 1 H), 9.9 (·s, 1 H).

3-Hydroxy-1-cyclopentene-1-carboxaldehyde Acetate Ester ($\underset{\sim}{45}$)

See the procedure for the synthesis of $\underset{\sim}{42}$. The crude product was purified by chromatography using 3:1 hexane:ethyl acetate to afford 74% of $\underset{\sim}{45}$ as a pale yellow oil which is unstable. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.9-2.0 (m, 1 H), 2.1 (s, 3 H) 2.4-2.5 (m, 2 H), 2.6-2.8 (m, 1 H), 5.8 (m, 1 H) 6.78 (m, 1 H), 9.85 (s, 1 H). IR (film) 2990, 2970, 1735, 1680, 1370, 1230 cm^{-1}.

1-(Dimethoxymethyl)-3-hydroxy-1-cyclopentene Acetate Ester ($\underset{\sim}{46}$)

Compound $\underset{\sim}{45}$ (2.00 g, 12.98 mmol) was dissolved in 6 mL of methanol. Trimethyl orthoformate (2.06 g, 19.48 mmol) and ammonium nitrate (0.05 g, 0.65 mmol) were added and the solution stirred overnight. To this solution 30 mL of hexane was added followed by 10 mL of saturated sodium bicarbonate. The water layer was back extracted three times with 10 mL of hexane. The hexane extracts were combined and dried to afford $\underset{\sim}{46}$ in quantitative yield as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.8-1.95 (m, 1 H), 2.02 (s, 3 H),

2.25-2.4 (m, 2 H), 2.45-2.6 (m, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 4.88 (bs, 1 H), 5.68 (m, 1 H), 5.88 (m, 1 H); ^{13}C NMR 21.08, 29.72, 29.91, 79.79, 100.88, 127.44, 147.50, 170.63 ppm; IR (film) 2970, 2910, 1730, 1450, 1370, 1240, 1050 cm^{-1}. Low resolution mass spectrum m/e: 43, 75, 95, 101, 109, 127, 141, 169, 199.

<div align="center">

1-(Dimethoxymethyl)-3-hydroxy-1-cyclopentene
Iodoacetate Ester (47)

</div>

Diisopropylamine (0.19 g, 1.93 mmol) was dissolved in 5 mL of THF and the solution cooled to 0°C. To the stirred solution n-butyllithium (0.74 mL, 2.50 molar, 1.84 mmol) was added dropwise. The solution was cooled to -78°C and compound 46 (0.35 g, 1.75 mmol) in 1 mL of THF was added dropwise. Thirty minutes after complete addition, the solution was transferred to a solution of iodine (0.58 g, 2.28 mmol) in 3 mL of THF which was also at -78°C. The resulting solution was warmed to room temperature. After one hour the reaction was poured into 30 mL of ether. The ether was washed with 10 mL portions of 10% sodium bisulfite solution to remove the excess iodine and then dried. The product was purified by chromatography using 3:1 hexane: ethyl acetate to afford 0.31 g (55%) of 47 as a colorless oil. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.9-2.0 (m, 1 H), 2.3-2.4 (m, 2 H), 2.45-2.6 (m, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 3.62

(s, 2 H), 4.9 (bs, 1 H), 5.7 (m, 1 H), 5.95 (m, 1 H); IR
(film) 2965, 1720, 1258, 1050, 732 cm^{-1}.

<div align="center">1-(Dimethoxymethyl)-3-hydroxy-1-cyclopentene
Formylacetate Ester (49)</div>

Diisopropylamine (0.15 g, 1.5 mmol) was dissolved in 3
mL of THF and the solution cooled to 0°C. To the stirred
solution was added n-butyllithium (0.55 mL, 2.50 molar, 1.38
mmol) dropwise. The solution was cooled to -78°C and
compound 46 (0.25 g, 1.25 mmol) in 1 mL of THF was added
dropwise. Thirty minutes after complete addition, ethyl
formate (0.11 g, 1.5 mmol) was added and the solution was
allowed to warm to 0°C. The solution was poured into 30 mL
of ether and washed twice with 5 mL of water. The ether was
dried to afford 0.19 g (68%) of the formate which was used
without purification. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.9 (m, 1
H), 2.2-2.4 (m, 2 H), 2.4-2.5 (m, 1 H), 3.28-3.32 (m, 6 H),
4.45 (m, 1 H), 4.90 (m, 1 H), 5.8-6.0 (m, 2 H).

<div align="center">1-(Dimethoxymethyl)-2-hydroxy-1-cyclopentene (56)</div>

Lithium aluminum hydride (0.20 g, 5.0 mmol) was
suspended in 20 mL of ether. Compound 46 (1.00 g, 5.00
mmol) was added dropwise to the stirred solution. After
three hours saturated sodium sulfate was added dropwise to
the solution until the color turned from gray to white. The
solution was filtered and the solvent removed to afford a
quantitative yield of 56 as a colorless oil. 300 MHz ^{1}H NMR

(CDCl$_3$) δ 1.7-1.8 (m, 1 H), 1.85-1.95 (bs, 1 H), 2.2-2.4 (m, 2 H) 2.45-2.55 (m, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 4.85-4.95 (bs, 2 H), 5.9 (bs, 1 H); IR (film) 3400, 2965, 2910, 1450, 1150, 1050 cm^{-1}. High resolution mass spectrum m/e for C$_8$H$_{14}$O$_3$ requires 158.09430, determined 158.09406.

6-(Dimethoxymethyl)-3-ethoxy-2-oxabicyclo[3.3.0]oct-6-ene (57)

Compound 56 (0.50 g, 3.17 mmol) was dissolved in 7 mL of CH$_3$CN. Ethyl vinyl ether (3 mL, 31 mmol), palladium(II) acetate (0.29 g, 1.27 mmol), and copper(II) acetate (1.44 g, 7.93 mmol) were added and the solution stirred at room temperature for 24 hours. The solution was diluted with 60 mL hexane and 0.6 mL of pyridine was added. The solution was stirred for 30 additional minutes and then filtered to remove the copper and palladium salts. The filtrate was concentrated and purified by chromatography using 3:1 hexane:ethyl acetate to afford 0.51 g (71%) of 57 as a pale yellow oil, which is a 1:1 mixture of diastereomers. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.05-1.25 (m, 3 H), 1.85-2.7 (m, 5 H), 3.2-3.4 (m, 8 H), 4.7-4.9 (m, 2 H), 5.1-5.2 (m, 1 H), 5.6-5.7 (m, 1 H); IR (film) 2960, 2910, 1440, 1095, 1045, 730 cm^{-1}. High resolution mass spectrum m/e for C$_{10}$H$_{14}$O$_3$ (M$^+$-46) requires 182.09430, determined 182.09424.

3-Hydroxy-1-cyclopentene-1-carboxaldehyde (60)

Compound 56 (2.00 g, 12.65 mmol) was dissolved in 50 mL of methylene chloride. Silica gel (6 g, silica gel 60, Merck, for column chromatography, 70-230 mesh) and a 10% aqueous solution of oxalic acid (0.60 g) were added and the resulting solution stirred for 12 hours. The solution was filtered and concentrated to afford 1.20 g (81%) of 60 as a colorless oil which was used without purification. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.7-1.9 (m, 1 H), 2.15 (bs, 1 H), 2.35-2.5 (m, 2 H), 2.6-2.75 (m, 1 H), 5.05-5.15 (bs, 1 H), 6.8 (m, 1 H), 9.85 (s, 1 H); ^{13}C NMR δ 26.78, 33.05, 95.92, 147.52, 151.21, 190.34; IR (film) 3460, 2980, 2940, 1690, 1250, 1165, 1050, 800 cm^{-1}. High resolution mass spectrum m/e for $C_6H_8O_2$ requires 112.05243, determined 112.05229.

3-Ethoxy-2-oxabicyclo[3.3.0]oct-6-ene-6-carboxaldehyde (59)

See the procedure for the preparation of 57. The crude product was purified by chromatography using 3:1 hexane: ethyl acetate to afford 68% of 59 as a pale yellow oil which is a 1:1 mixture of diastereomers. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.05-1.22 (m, 3 H), 1.8-1.95 (m, 1 H), 2.05-2.2 (m, 2 H), 2.6-3.0 (m, 2 H), 3.3-3.7 (m, 2 H), 4.7-4.9 (m, 1 H), 5.1 (m, 1 H), 6.7 (m, 1 H), 9.78 (2s, 1 H); IR (film) 2960, 1678, 1045, cm^{-1}. High resolution mass spectrum m/e for $C_{10}H_{14}O_3$ requires 182.09430, determined 182.09440.

3-Ethoxy-7-methyl-6-trimethylsilyloxymethenyl-2-oxabicyclo[3.3.0]octane (61)

Copper(I) bromide dimethylsulfide (0.34 g, 1.65 mmol) was placed in 3 ml of THF and the solution cooled to -10°C. Methyl lithium (3.26 mmol) was added dropwise to the stirring solution (note that the solution turns bright yellow then returns to colorless). The resulting solution was cooled to -78°C.

The aldehyde 59 (0.20 g, 1.10 mmol) was dissolved in 3 mL of THF and cooled to -78°C. The trimethylsilyl chloride (0.39 g, 4.29 mmol) was added. This solution was transferred to the previous solution via cannula. The resulting solution was warmed to -40°C and stirred for eight hours. It was then poured into 30 mL of hexane and the hexane was washed twice with 10 mL of saturated ammonium chloride. The hexane layer was dried to afford the crude product 61 in quantitative yield as a mixture of four diastereomers which were used without purification. 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.0-1.25 (m, 6 H), 1.7-2.65 (m, 6 H), 3.3-3.7 (m, 2 H), 4.5-4.65 (m, 1 H), 5.05-5.2 (m, 1 H), 5.9-6.1 (m, 1 H).

3-Ethoxy-6-hydroxy-7-methyl-2-oxabicyclo[3.3.0]octane-6-carboxaldehyde (62)

Osmium tetroxide (0.017 g, 0.067 mmol) and N-methyl-morpholine-N-oxide (0.51 g, 3.76 mmol) were dissolved in 18 mL of acetone which contained 8 mL of water. Compound 61

(0.93 g, 3.42 mmol) was added as a solution in 6 mL of acetone and the resulting solution stirred for 12 hours. Sodium hydrosulfite (0.70 g) and fluorisil (2.70 g) were added and the solution stirred for an additional 30 minutes. The solution was filtered and the acetone was removed. The remaining solvent was saturated with sodium sulfate and extracted four times with 20 mL of ether. The ether was dried and concentrated to afford 62 in quantitative yield which was not purified. 300 MHz ^{1}H NMR (CDCl$_3$) δ 0.80-1.25 (m, 6 H), 1.65-3.0 (m, 7 H), 3.3-3.8 (m, 2 H), 4.7-4.85 (m, 1 H), 5.1 (m, 1 H), 9.8-10.0 (3s, 1 H); IR (film) 3440, 2980, 1710, 1630, 1110 cm^{-1}.

<div align="center">

6-Acetoxymethyl-3-ethoxy-6-hydroxy-7-methyl-2-
oxabicyclo[3.3.0]octane (63)

</div>

Lithium aluminum hydride (0.12 g, 5.0 mmol) was suspended in 10 mL of ether. Compound 62 (0.66 g, 3.05 mmol) was added dropwise to the stirring solution. After three hours saturated sodium sulfate was added dropwise to the solution until the color turned from gray to white. The solution was filtered to afford a quantitative yield of the diol. This diol (0.45 g, 2.06 mmol) was dissolved in 25 mL of methylene chloride and acetyl chloride (0.36 g, 4.54 mmol) and pyridine (0.43 g, 5.44 mmol) were added. The resulting solution was stirred for four hours. The solution was washed twice with 10 mL of 10% aqueous sodium

bicarbonate, followed by 10 mL of saturated $CuSO_4$ and dried. The product was purified by chromatography using 1:1 hexane: ethyl acetate to afford 0.53 g (55%) of 63 as a colorless oil (note this is a 55% overall yield from 59). 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.89-0.98 (m, 3 H), 1.2-1.4 (m, 3 H), 1.6-2.9 (m, 10 H), 3.3-3.7 (m, 2 H), 3.95-4.35 (m, 2 H), 4.6-4.7 (m, 1 H), 4.98-5.13 (m, 1 H); IR (film) 3490, 2980, 1740, 1235 cm^{-1}. High resolution mass spectrum m/e for $C_{13}H_{21}O_5$ (M^+-1) requires 257.13890, determined 257.13879.

<div align="center">

6-Acetoxymethyl-6-hydroxy-7-methyl-2-
oxabicyclo[3.3.0]octan-3-one (64)

</div>

Compound 63 (0.10 g, 0.30 mmol) was dissolved in 2 mL of CH_3CN. Hydrochloric acid (1 mL of 0.03 N) was added until the starting material no longer was detectable by thin layer chromatography. Ether (15 mL) was added and the solution dried with sodium sulfate which contained a trace of sodium bicarbonate to neutralize the acid. The crude product (0.09 g, 0.30 mmol) was dissolved in 3 mL of acetone and the solution cooled to 0°C. Jones reagent (0.52 mmol, 0.20 mL) was added and the solution was stirred for 15 minutes. Isopropanol was added to quench the excess Jone's reagent followed by 10 mL of ether. The solution was filtered and the filtrate washed twice with saturated sodium sulfate. The crude product was purified by chromatography using 8:1 ether:acetone to afford 0.043 g (64%) of 64 as a white

solid. M.P. 131-132°C; 300 MHz ^{1}H NMR (CDCl$_3$) δ 1.02 (d, 3 H, J = 5.4 Hz), 1.9-2.1 (m, 4 H), 2.1 (s, 3 H), 2.3-2.45 (m, 1 H), 2.6-2.8 (m, 1 H), 2.9-3.05 (m, 1 H), 3.99-4.29 (ABq, 2 H, J = 6.9 Hz), 5.05 (m, 1 H); ^{13}C NMR δ 11.85, 20.71, 30.85, 36.78, 38.58, 48.17, 67.16, 81.85, 83.64, 170.93, 176.67; IR (film) 3490, 2980, 1765, 1740, 1370, 1230 cm^{-1}. High resolution mass spectrum m/e for C$_{11}$H$_{16}$O$_5$ requires 228.09978, determined 228.09928.

6-Hydroxymethyl-6-hydroxy-7-methyl-2-oxabicyclo[3.3.0]octan-3-one (66)

Compound 65 (0.09 g, 0.39 mmol) was dissolved in 1 mL of methanol. Potassium carbonate (0.01 g, 0.08 mmol) was added and the solution stirred for three hours. Ethyl acetate (5 mL) was added and the resulting solution filtered. The solvent was removed to afford 0.05 g (66%) of 66 which was used without purification. 300 MHz ^{1}H NMR δ 0.98 (d, 3 H, J = 5.5 Hz), 1.8-2.5 (m, 6 H), 2.7-2.9 (m, 1 H), 2.9-3.0 (m, 1 H), 3.5-3.8 (ABq, 2 H, J = 11 Hz), 5.1 (m, 1 H); IR (film) 3470, 2980, 1760, 1180, 1020, cm^{-1}. High resolution mass spectrum m/e for C$_9$H$_{14}$O$_4$ requires 186.08921, determined 186.08951.

9-Hydroxysemperoside (33a)

Compound 66 (0.035 g, 0.113 mmol) was dissolved in 1 mL of ether. Sodium hydride (0.015 g, 0.37 mmol) and ethyl formate (0.027 g, 0.37 mmol) were added and the solution was

refluxed for three hours. The solution was acidified with 0.5 N hydrochloric acid and stirred for one hour. The reaction was poured into 10 mL of ether and the water layer was removed. The product was purified by chromatography using 1:2 hexane:ethyl acetate to afford 0.008 g (35%) of 33a as a white solid. 300 MHz ^{1}H NMR (CDCl$_3$) 1.008 (d, 3 H, J = 6.3 Hz), 1.75-2.20 (m, 4 H), 2.65 (bs, 1 H), 2.99 (s, 2 H), 3.51 and 3.97 (ABq, 2 H, J = 11.7 Hz), 5.03 (m, 1 HO, 5.58 (s, 1 H).

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OVERALL SUMMARY

Part I of this manuscript shows that E-1-benzoyloxy-2-nitroethene can be used as a cis-1,2-aminoalcohol equivalent as well as a nitroacetylene equivalent. Many important natural products contain a 1,2-aminoalcohol moiety.

Part II demonstrates the use of alkoxy radicals for the intramolecular cyclization of cyclic hemiketals with alkenes to form bicyclic ketals. Many important natural products such as the ginkgolides contain the bicyclic ketal moiety. Research is in progress on the application of this methodology to the total synthesis of these biologically important natural products.

The total synthesis of 9-hydroxysemperoside is shown in the last part of this manuscript. The synthesis is short and demonstrates the synthetic utility of some new, unique reactions.

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