AN ABSTRACT OF THE THESIS OF

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Regiochemistry of intramolecular [2+2] photocycloadditions of oxygenated 6-alkenyl-3-alkoxy-2-cyclohexenones is studied. Application of this methodology to construct a key intermediate [3.3.2] bicyclic skeleton of ryanodol is described as well. Irradiation of (3-butenyl)compounds **3**, **11**, **14** and of (4-pentenyl)compound **6** afforded exclusively the linear photoadducts **4**, **12**, **15** and **7** respectively. Irradiation of allyl compound **25** brought the desired crossed photoadduct **26**. The structures of the photoadducts **4**, **7** and **26** were assigned based on spectroscopic analysis and confirmed by subsequent retroaldol cleavage reactions of the corresponding photoproducts. The regiochemistry of linear adduct **15** was deduced by a sequence of transformations. Retroaldol cleavage of the photoadduct **15**, followed by transannular reductive coupling with SmI_2, and hydrolysis of the protecting group provided triol **18**. PDC oxidation of **18** gave [4.2.2] bicyclic triketone **20** and a cyclic hemiketal **21**. Finally, Swern oxidation of **18** confirmed both isomers of photoproduct **15** are linear adducts. Selective retroaldol ring opening of compound **26** resulted in the formation of the

bicyclo[3.3.1]nonane skeleton, amenable through a one carbon ring expansion to establish the core bicyclo[3.3.2]decane system in ryanodol.

Photochemistry of 6-Alkenyl-2-Cyclohexenones. Synthetic Studies towards Precursors of Ryanodol

by

Bingbing Wang

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This thesis is dedicated to my Mother and Father,

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and my Brother

Ziyi Wang

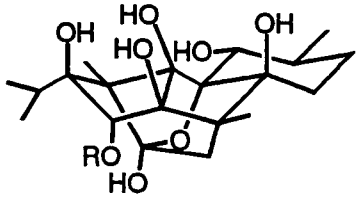
I could not have made it without your unconditional love, confidence and emotional and financial support. No matter where I am, you will be always in my heart and spirit. I love you all deeply.

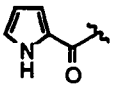
PHOTOCHEMISTRY OF 6-ALKENYL-2-CYCLOHEXENONES. SYNTHETIC STUDIES TOWARDS PRECURSORS OF RYANODOL

INTRODUCTION

I. **Objective**

The botanical insecticide ryania is the ground stemwood of *Ryania speciosa* Vahl.[1] Eleven ryanoids have been obtained from various ryania preparations by a combination of wet chloroform extraction and chromatography.[2,3] The insecticidal activity of ryania extracts was originally attributed to ryanodine (**1**), isolated in 1948 by Folkers and his co-workers.[2]



Ryanodine (**1**) R = 

Ryanodol (**2**) R = H

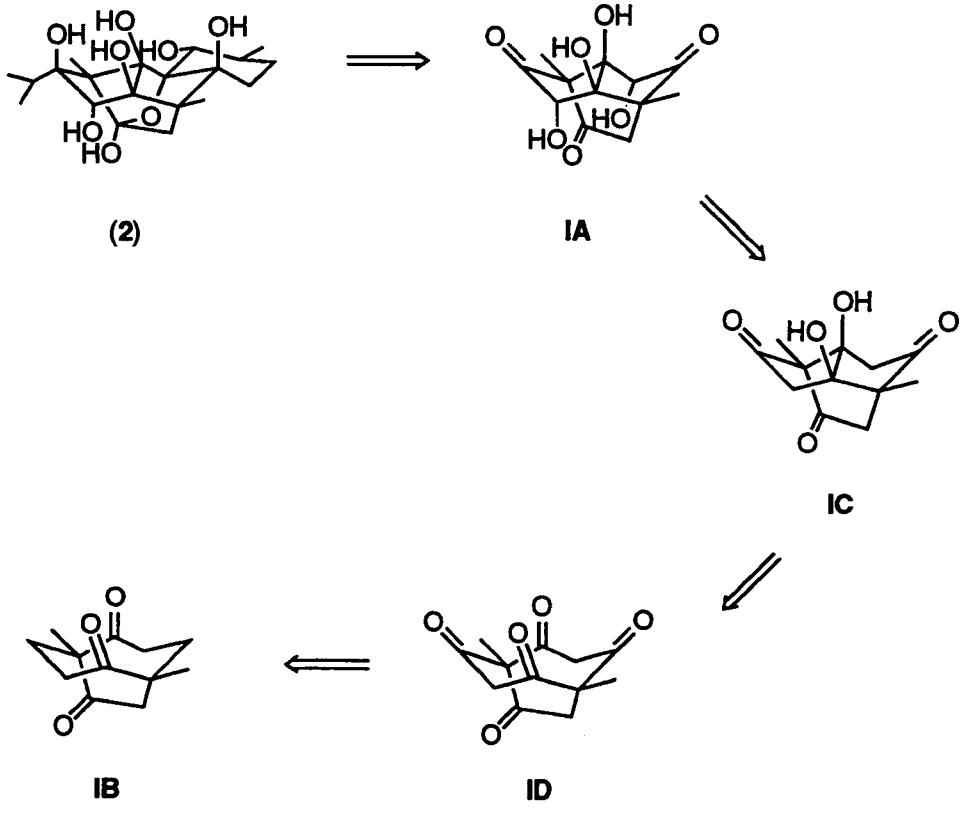
Ryanodine, a neutral plant alkaloid, has been found to possess powerful insecticidal as well as pharmacological actions.[4,5] Studies of the effects of ryanodine on invertebrates and vertebrates revealed powerful actions on the contraction of striated muscle. The mechanistic basis of the actions of this agent on vertebrates skeletal muscle was shown to involve effect on calcium

permeability of the sarcoplasmic reticulum (SR).[6,7] Similar actions were demonstrated for cardiac muscle.[8] Subsequent studies demonstrated that ryanodine is a specific modulator of the SR calcium release channel that can increase, as well as decrease, SR membrane calcium permeability.[9] Ryanodine was tritiated to a high specific activity and demonstrated to be a specific ligand for the triad junction foot protein, commonly referred to as the ryanodine receptor.[10,11,12] This receptor has been cloned from rabbit cardiac muscle SR.[13] Evidence has recently been presented for the presence of ryanodine receptors in brain and other cells, including neutrophils.[14,15]

The structure of ryanodine including its absolute configuration was elucidated several decades ago by Wiesner and his co-workers at the University of New Brunswick by chemical degradation[16,17] and confirmed on the basis of X-ray analysis by Srivastava and Przybylska.[18] From a chemical point of view, ryanodine is the α-pyrrolecarboxylate ester of the complex pentacyclic diterpene ryanodol (**2**). The structure of ryanodol contains eleven contiguous chiral centers and seven hydroxyl groups. The skeletal complexity together with the exceptional biological activity make ryanodol a very attractive and challenging synthetic target.

Deslongchamps's group completed a total synthesis of (+)-ryanodol in 1979. A detailed report on this work has been published in 1990 by the same group.[19] Their 45 step synthesis involved the construction of a key intermediate via a Diels-Alder cycloaddition. Recently, a series of semi-synthetic derivatives of ryanodine have been achieved by Deslongchamp's and Jefferies' groups.[20]

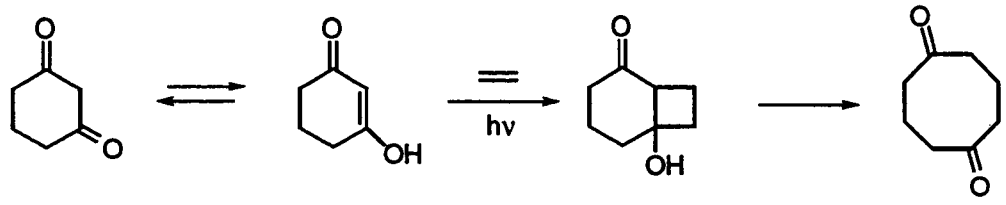
Our synthetic plan shown in **scheme I.1** derives the synthesis of ryanodol from the functionalized tricyclic core system **IA**. It is envisioned that **IA** will be formed from **IC** through a bis-hydroxylation reaction. The *syn* tertiary hydroxyl



scheme I.1

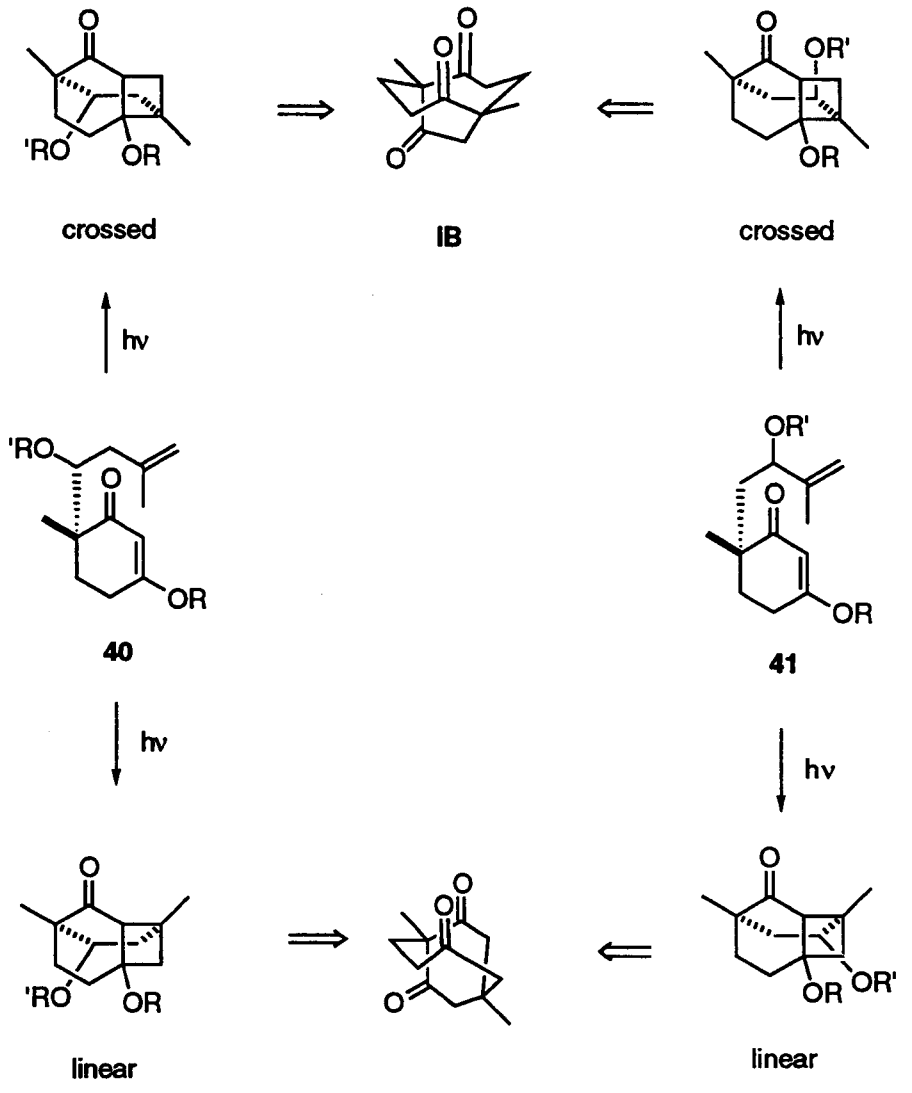
groups in **IC** will derive from the transannular reductive coupling of carbonyl groups in bicyclic pentaketone **ID**. Therefore, we have focused our attention on the construction of the initial bicyclo[3.3.2]decanetrione **IB**.

Our approach to the synthesis of **IB** is influenced by the fact that simple 1,5-cyclooctanedione derivatives are readily available from 1,3-cyclohexanedione by employing the de Mayo type photocycloaddition-cyclobutane fragmentation sequence (**scheme I.2**).[21] The reaction proceeds through the enol tautomer of the 1,3-diketone. Photocycloaddition of an olefin to this enol results in a β-hydroxyketone that normally undergoes retroaldol cleavage to give the product 1,5-cyclooctanedione.



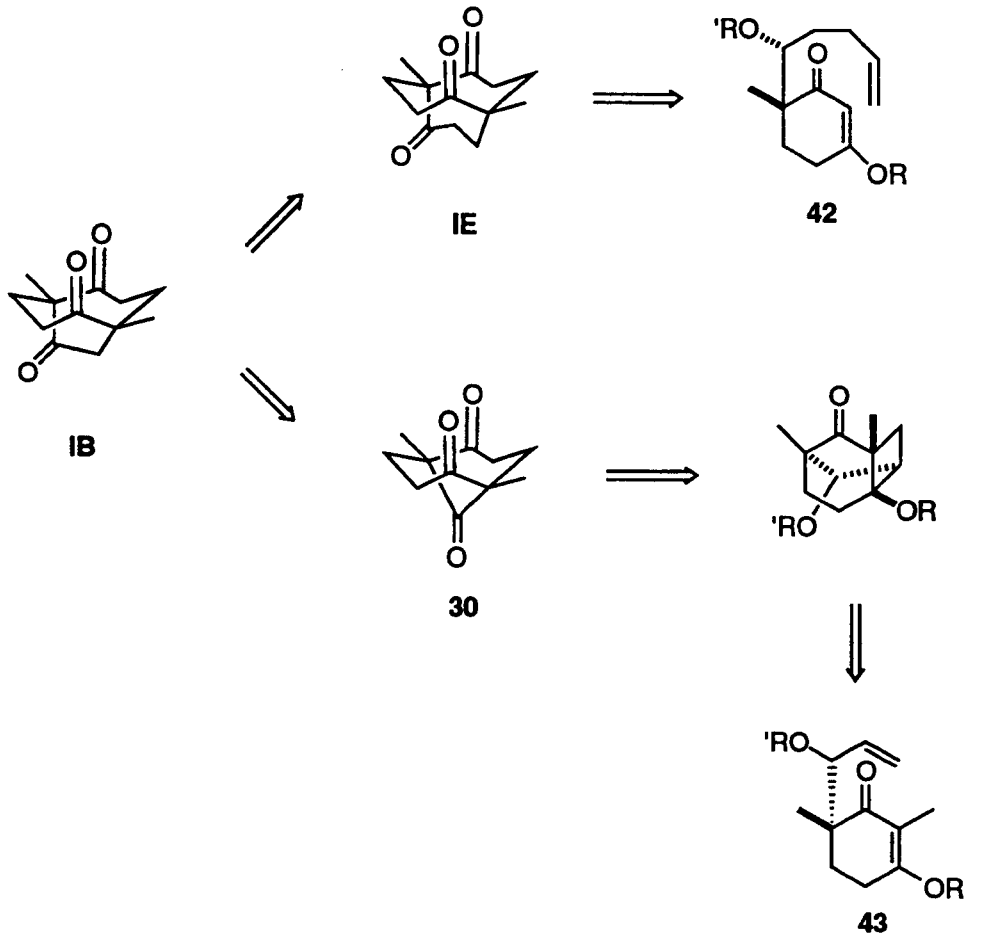
scheme I.2

Two routes are considered to achieve the [3.3.2] bicyclic skeleton of **IB. Scheme I.3** shows a direct route to build up this skeleton through intramolecular [2+2] photocycloaddition of oxygenated 6-(3-butenyl)-cyclohexenone, **40** or **41**, followed by retroaldol cleavage of the β-alkoxycyclobutane ring of the resulting photoproduct. However, in principle two photoadducts, linear and/or crossed, can be generated from each cyclohexenone precursor. Only fragmentation of the crossed photoadduct is capable of affording the required bicyclo[3.3.2]decane derivative **IB**. The linear photoadduct will give a bicyclo[4.2.2]decane derivative instead.



scheme I.3

The second route involves a one-carbon ring contraction (**scheme I.4**) of [3.3.3] bicyclic derivative **IE** or a one-carbon ring expansion of bicyclo[3.3.1]nonane **30** to construct [3.3.2] bicyclic skeleton **IB**. Both **IE** and **30** are derived from intramolecular photocycloaddition reactions of **42** and **43**, followed by retroaldol cleavage of crossed photoadducts.

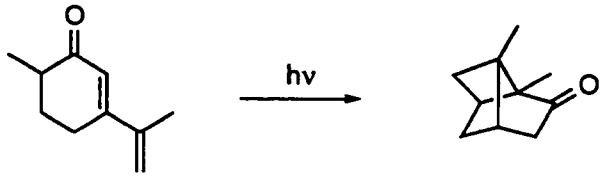


scheme I.4

As shown in **schemes I.3** and **I.4**, the regiochemistry of intramolecular [2+2] photoadditions is a central feature of this plan in order to achieve the key intermediate bicyclo[3.3.2]decane **IB**. The research embodied within this thesis concerns the regiochemistry of intramolecular photocycloadditions of model compounds. Therefore, the following section of this introduction will address mechanistic aspects of enone-olefin [2+2] photocycloadditions as they relate to the regiochemical outcome of these reactions.

II. Intramolecular [2+2] photocycloadditions of enones to olefins. Background

The intramolecular enone-olefin photochemical cycloaddition reaction, the light-induced [2+2] cycloaddition of a ground-state alkene tethered to an excited state enone to form a cyclobutane, was first reported in 1908 by Ciamician and Silber who found that carvone was converted to carvonecamphor on exposure to "Italian sunlight" (**scheme I.5**).[22] In the early 1960s mechanistic and synthetic



scheme I.5

work,[23-26] particularly in the laboratories of Corey,[33] Eaton,[27] and de Mayo,[28] focused on intermolecular [2+2] photoadditions of cyclic enones to olefins.

Following these pioneering studies, intermolecular as well as intramolecular [2+2] photocycloadditions have become part of the standard repertoire of synthetic organic chemistry.[29,30] However, the main impediment for the extensive use of intermolecular photocycloadditions in synthesis remains the relatively low regioselectivity. In this respect, a major attraction of the intramolecular approach is that the tether between the enone and alkene not only becomes a ring in the product, but also can control the regiochemistry and sometimes the stereochemistry of the addition of the alkene to the enone. In recent years this intramolecular reaction has frequently been utilized for the synthesis of complex ring systems and natural products.[31,32,34,35]

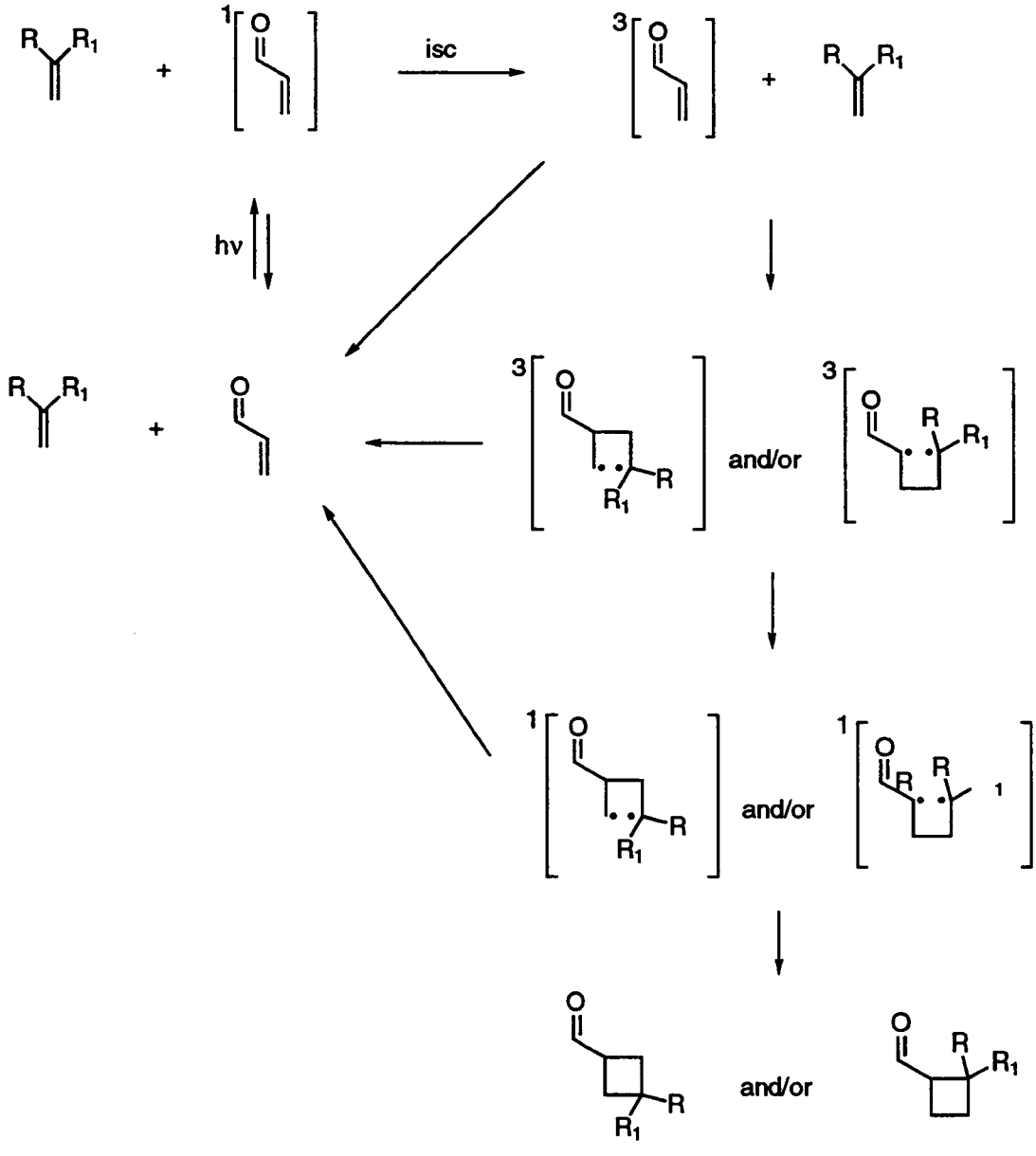
III. Mechanism of [2+2] photoadditions of enones to olefins

A mechanism for [2+2] photoaddition of enones to olefins was proposed initially by Corey on the basis of the regiochemistry of the intermolecular reaction between a conjugated cyclic enone and an alkene.[33] As a consequence of kinetic studies and quenching experiments carried out by the groups of de Mayo, and Caldwell, the original proposal was modified to arrive at the Corey-de Mayo mechanism[28,35] involving the initial n, π^* excitation of the enone to a short-lived singlet state followed by intersystem crossing to a π, π^* long-lived triplet enone, and subsequent complexation with the olefin to form an exciplex. Collapse of the exciplex to a 1,4-biradical followed by spin inversion of the triplet diradical to a singlet state set the ground for ring closure to form the cyclobutane ring.

Recently, significant progress has been made in the mechanistic aspects of [2+2] photocycloaddition reactions. Experimental evidence for the structures of triplet 1,4-biradical intermediates has been obtained by Weedon using H_2Se as a hydrogen atom donor to reduce the biradicals.[36,37] This author found essentially no difference in the reactivity of the α and β carbons of the enone triplet with the ground state alkene. Furthermore, detection and trapping of the triplet 1,4-biradical intermediates performed by Shuster and Caldwell suggest that direct biradical formation without the intermediacy of a triplet exciplex is operative.[36-38,39,40] Currently, there is no experimental support to justify Corey-de Mayo's original proposal that initial interaction of enone excited states and alkene involves formation of an enone-alkene exciplex.

A general working mechanism shown in **scheme I.6** details the course of these reactions and highlights the multiple pathways conducing to the observed

products as well as the competing reversion to ground state that can occur at different stages of the process.



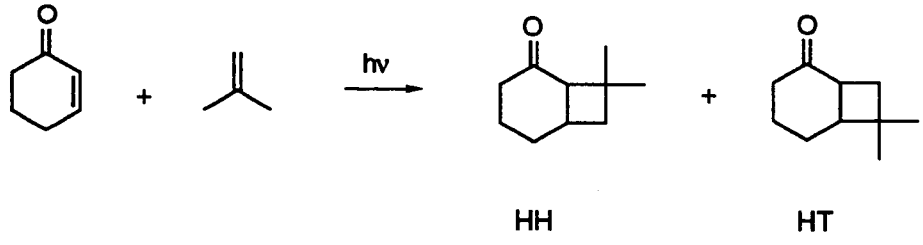
scheme I.6

Although the photochemical behavior of numerous enone-olefin systems has been examined in some detail and many molecules have been synthesized

through photocycloaddition reactions, and plenty of information and technical data has been gathered as well, many details about the reaction mechanism still remain to be elucidated. It is believed that new techniques in laser photolysis and an improved trapping methodology will lead to some future clarification of unanswered questions.[41,42]

IV. Regiochemistry of [2+2] photoadditions of enones to olefins

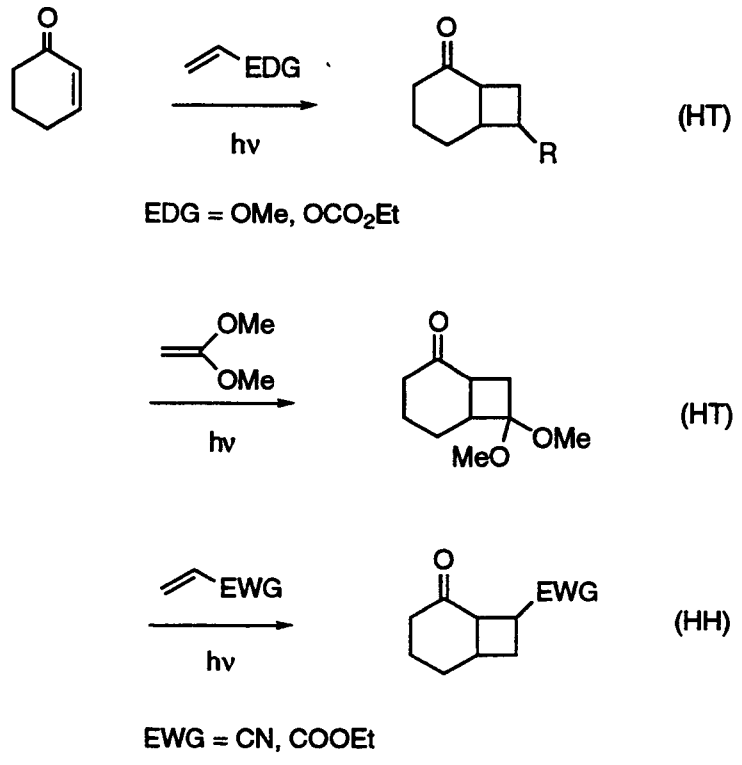
When an unsymmetrical enone and an unsymmetrical alkene undergo an intermolecular [2+2] photocycloaddition, two possible regioisomers, the head-to-head (HH) and head-to-tail (HT) isomers, can result (**scheme I.7**).



scheme I.7

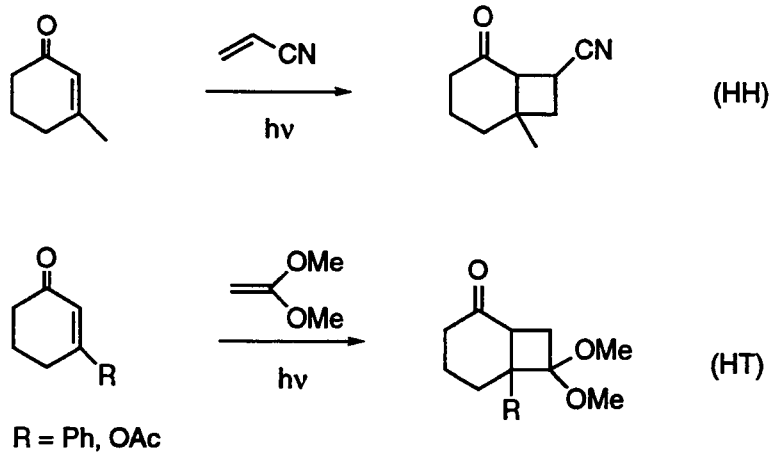
One of the most interesting findings in Corey's pioneering study in 1964 was that the regioselectivity was apparently governed by the electron demand of the substituents on the olefin.[35] Corey and his co-workers reported that in photocycloadditions of 2-cyclohexenone to a variety of unsymmetrical electron-rich alkenes, such as methyl vinyl ether, vinyl acetate and 1,1-dimethoxyethylene, a clear preference for formation of head-to-tail vs head-to-head adducts was observed. In contrast, photoadditions of cyclohexenone to

alkenes containing electron withdrawing groups gave exclusively HH adducts (**scheme I.8**).



scheme I.8

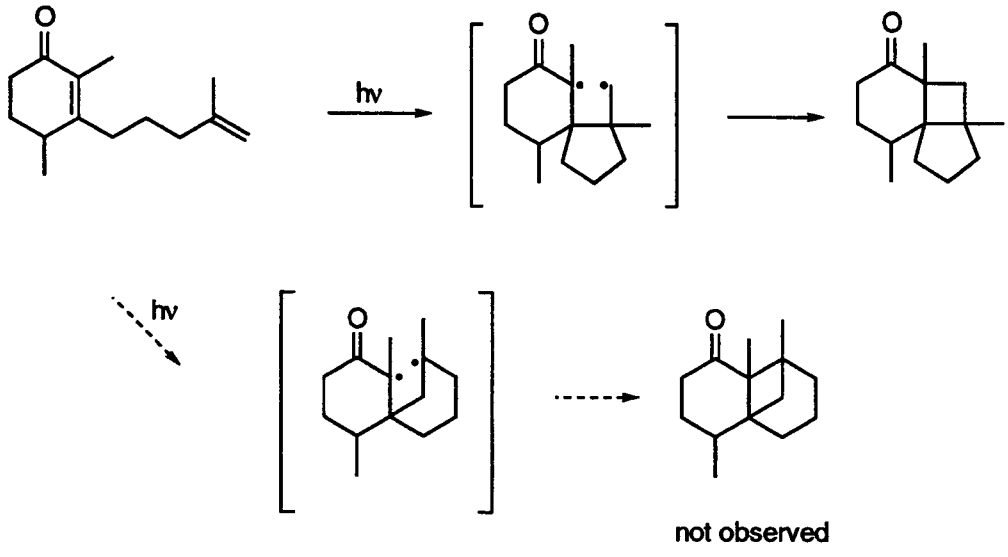
Cantrell later reported that intermolecular photoadditions of β-substituted enones to the same alkenes which were utilized by Corey (**scheme I.7**) produced the same regioisomers.[43]



scheme I.7

However, on the basis of the investigations by Lange,[44] Weedon[45] and Tada,[46] it is now recognized that the regiochemistry of intermolecular photocycloadditions of enone-alkene is more complex than originally envisioned by Corey. They pointed out that the regiochemistry can be easily modified or even outweighed by other features as steric and electronic effects seem to be responsible for the formation of isomeric mixtures.

On the other hand, in respect to the regiochemistry of the intramolecular reaction of conjugated cyclic enones tethered to an alkene, the structure of the products suggest that, in the absence of special constraints, the favored ring system will be that derived from an initial 5-*exo*-*trig* cyclization of the triplet to form a biradical possessing a five-membered ring. This observation, which appears to be responsible for the reaction regioselectivity, has been termed the "rule of five" by Hammond and Srinivasam[47] and further established particularly by Wolff and Agosta (**scheme I.8**).[48-50]



scheme I.8

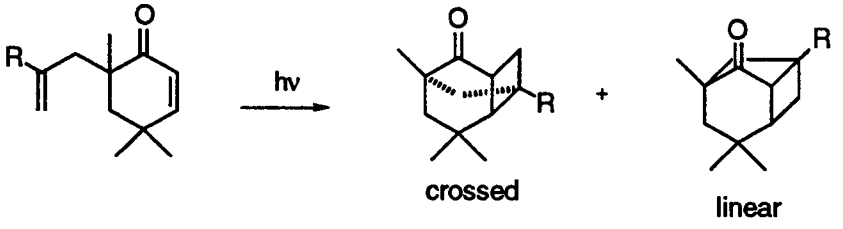
Limitations of this rule have been demonstrated in many cases[32] and no predictive rule has been advanced for situations where no five-membered ring is involved. Therefore, predictions on the regiochemical outcome of enone-olefin photocycloadditions rely mostly on experimental precedents.

IV. Precedents for the regiochemistry of ω-alkenyl-2-cycloalkenones.

Many examples of the formation of cyclobutane derivatives from intramolecular [2+2] photoadditions of 2-, 3-, and 4-alkenyl-2-cyclohexenones have been reported.[29,30,31,32] However, the crossed ring version proposed for the synthesis of ryanodol has not been applied very often.

The photochemistry of 6-allyl-4,4,6-trimethyl-2-cyclohexenones was studied by Margaretha.[51,52] This author found a decrease in the amount of crossed photoadducts with increasing steric demand of the R group on the

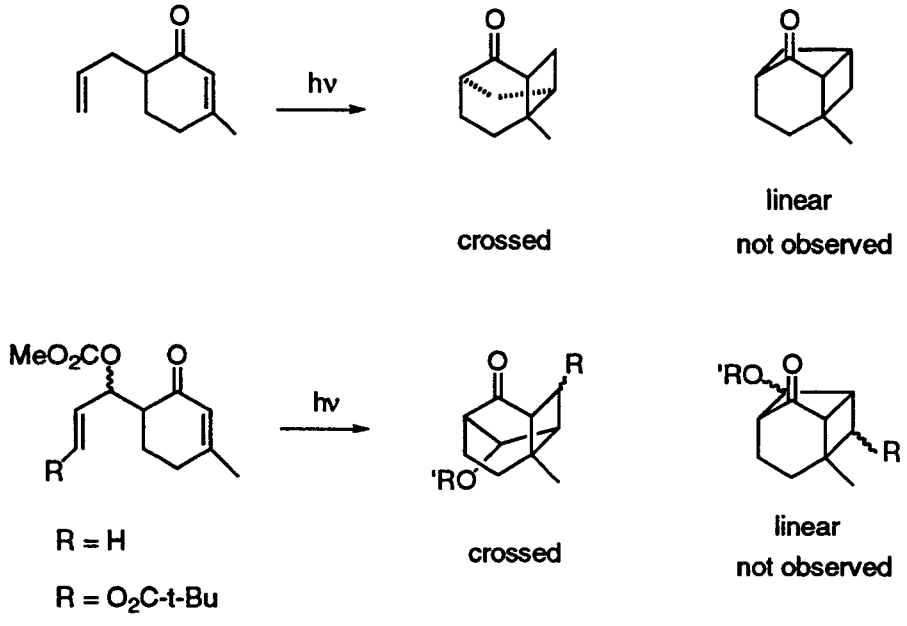
alkene (**scheme I.9**). It is noteworthy that the formation of crossed regioisomers constitutes a violation of the "rule of five".



R = H	100:0
Me	71:29
iPr	58:42

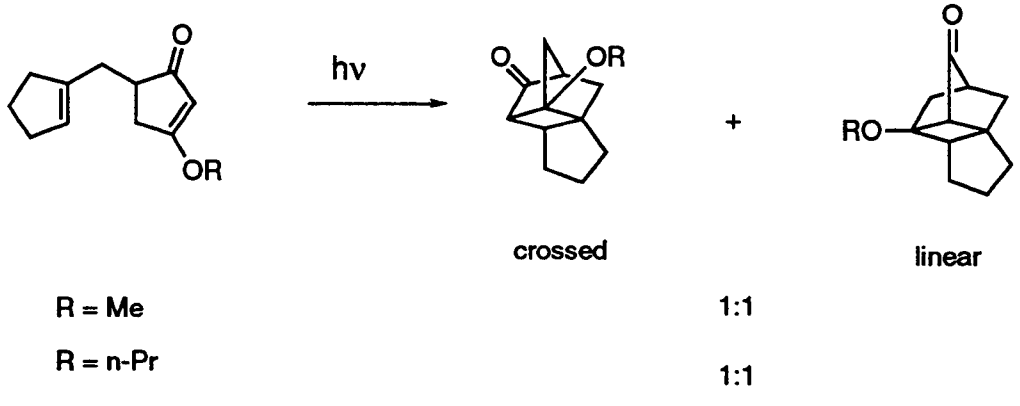
scheme I.9

Martin attempted to override the normal regiochemical preference in the photocycloaddition of 6-allyl-3-methyl-2-cyclohexenone by significantly changing the electronic nature of the olefinic side chain through incorporation of an oxygen substituent. However, this approach failed as only the usual crossed products were obtained (**scheme I.10**),[53] once again in violation of the "rule of five".



scheme I.10

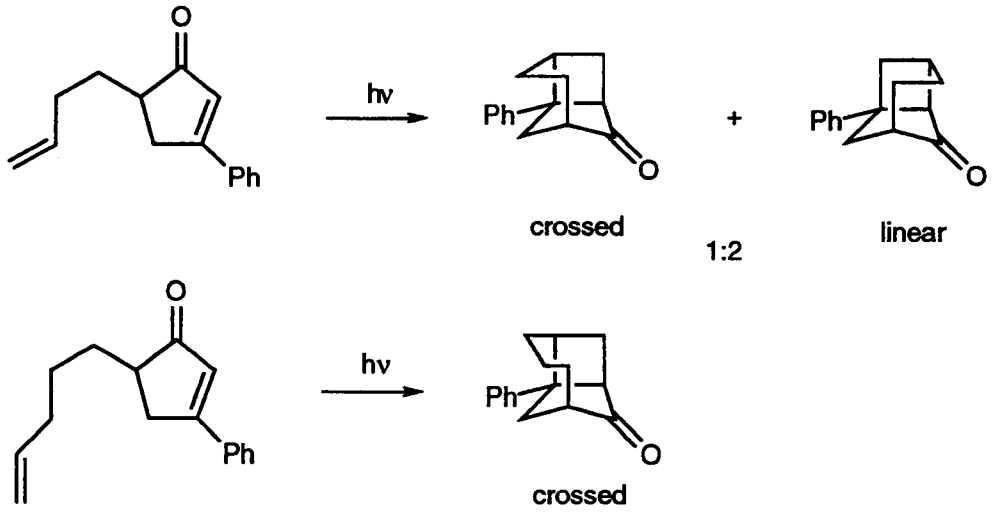
Oppolzer studied the photocycloaddition of 3-alkoxy-5-(1-cyclopentenylmethyl)-2-cyclopentenone derivatives (**Scheme I.11**).[54] This author concluded that steric effects on the β-substituted enone moiety did not influence the regioselectivity in these intramolecular photocycloaddition reactions. Although linear and crossed regioisomers were formed, both would derive from initial formation of a biradical intermediate possessing a five-membered ring.



scheme I.11

Gleiter pointed out that the number of atoms connecting the two alkenes is one of the most important factors in determining regiochemical results of the intramolecular [2+2] photocycloadditions of alkenes.[55,56]

McMurry further explored the influence of the number of atoms connecting the enone and olefin moieties on the regioselectivity of these enone-olefin [2+2] photocycloaddition reactions.[57,58] He found that photolysis of 5-(3-butenyl)-3-phenyl-2-cyclopentenone afforded two products in a 2:1 ratio, the crossed product being minor. In contrast, increasing the length of the tether caused photolysis of 5-(4-pentenyl)-3-phenyl-2-cyclopentenone to provide exclusively the crossed product (**scheme I.12**).

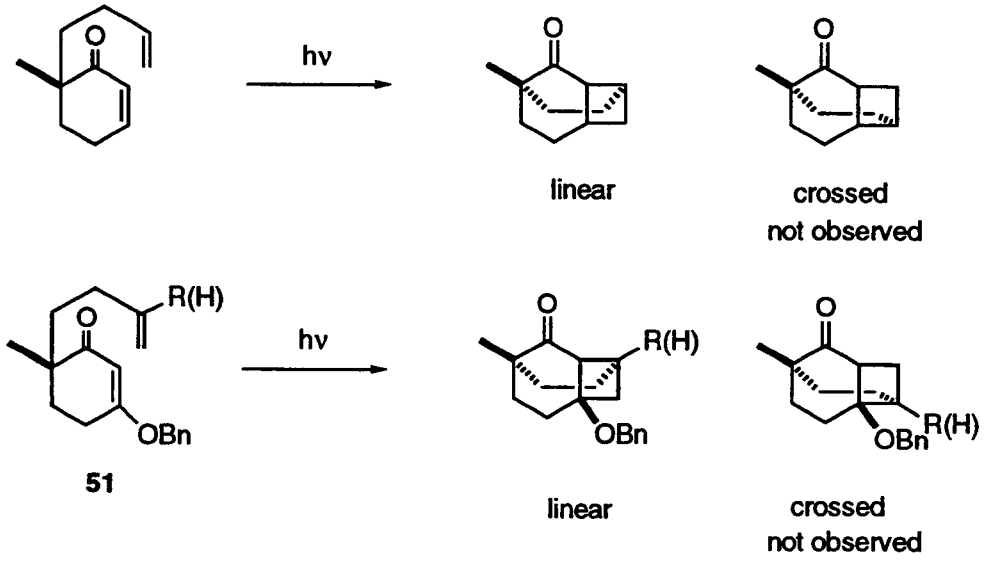


scheme I.11

The investigations above have shown that substitution effects, electronic effects and ring size effects, all influence the regiochemistry of intramolecular photocycloadditions of enone-olefins. However, no general trends with regard to regioselectivity can be listed for each of these effects. A systematic examination of the effect of structures on regiochemistry is then necessary in the

photochemical reactions of the proposed substrates, 6-alkenyl-3-alkoxy-2-cyclohexenones **40**, **41**, **42**, and **43** shown in **schemes I.3** and **I.4**.

In order to evaluate the feasibility of a photochemical approach to **IB**, a number of unconjugated dienones were studied previously in this group.[59] Photocycloaddition of β-alkoxycyclohexenone **51** afforded only the linear product (**scheme I.13**). The structure of this product was established on the basis of extensive spectroscopic analysis together with further chemical transformations. Steric effects due to the introduction of substituents on the olefinic carbons did not affect the regiochemistry.

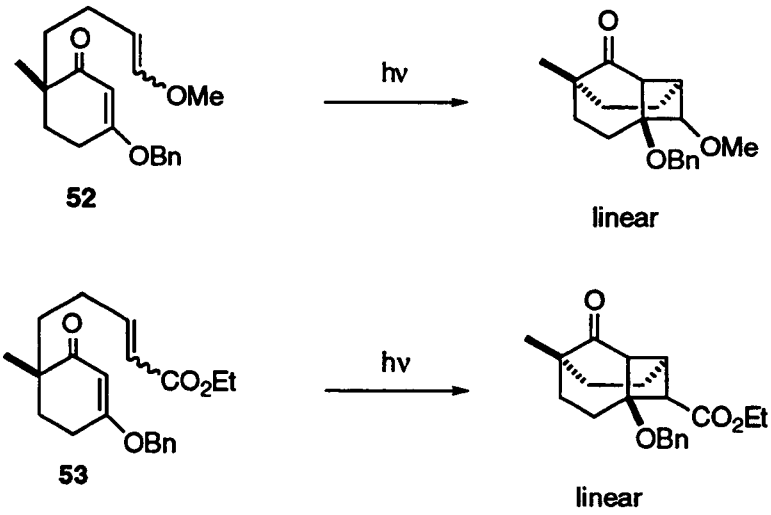


scheme I.13

Based on the preferred orientation observed in the bimolecular photoadditions of cyclic enones to enol ethers and enol esters discussed earlier in **schemes I.8 and I.9**,[35,60] the electronic effect of substituents on the isolated olefin was also explored (**scheme I.14**).[59] As expected, intramolecular

photocycloaddition of **52** in which one of the terminal olefinic hydrogens was replaced with an electron-donating group still led to a linear product.

However, photocycloaddition of **53** containing an electron-withdrawing group on the isolated double bond proceeded in a regiochemical sense opposite to the general trend observed by Corey and Cantrell in the intermolecular processes, i.e., the head-to-head product was not observed. Spectroscopic data showed that only the linear product was formed in the photocycloaddition of **53**.



52 linear

53 linear

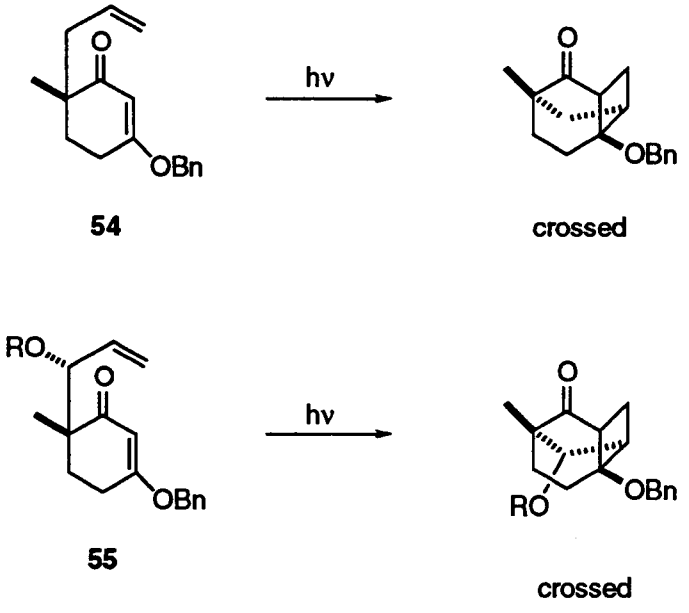
scheme I.14

These observations led to the conclusion that changing the electronic nature of the olefin moiety does not influence the regiochemistry of intramolecular photocycloaddition in these systems.

The intramolecular photoadditions of 6-allyl-3-benzyloxy-2-cyclohexenones were also studied in this group (**scheme I.15**).[59] The basic preference for this type of system was shown in the photolysis of the unsubstituted 6-allyl-3-benzyloxy-2-cyclohexenone **54** affording exclusively the crossed product. The outcome of this photocycloaddition is consistent with

Martin's findings for 6-allyl-3-methyl-2-cyclohexenones[53] and it further demonstrates that the change of the chromophoric system from an enone to a vinylogous ester has little if any effect on regiochemical preference.

Introduction of an oxygen substituent in the tether of **55** did not change the regioselectivity of photoaddition either: the crossed product was once again formed.



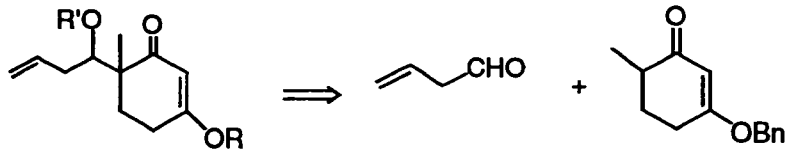
scheme I.15

With these substantial findings, efforts were continued. The main objectives of the work included in this thesis were first to investigate the regiochemistry of intramolecular photocycloadditions of 6-(ω-alkenyl)-3-alkoxy-cyclohexenones and to apply this methodology to the construction of [3.3.2] bicyclic skeleton **IB**.

RESULTS AND DISCUSSION

Section A: Intramolecular [2+2] Photocycloadditions of 6-alkenyl-3-alkoxy-2-cyclohexenones.

The following section describes in detail the effect on the regiochemistry of intramolecular photocycloadditions of 6-alkenyl-2-cyclohexenones of the introduction of an oxygen substituent in the tether connecting the olefin and enone. Molecular models show that the introduction of substituents on the chain connecting the enone to the olefin could in principle affect the approach of both moieties. Based on the mechanistic picture shown in **scheme I.6**, substituents



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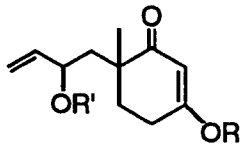
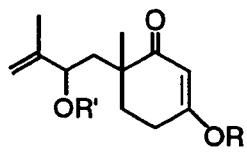
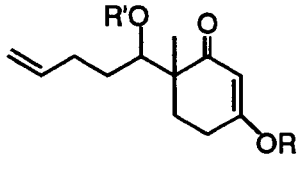


IIb



IIc



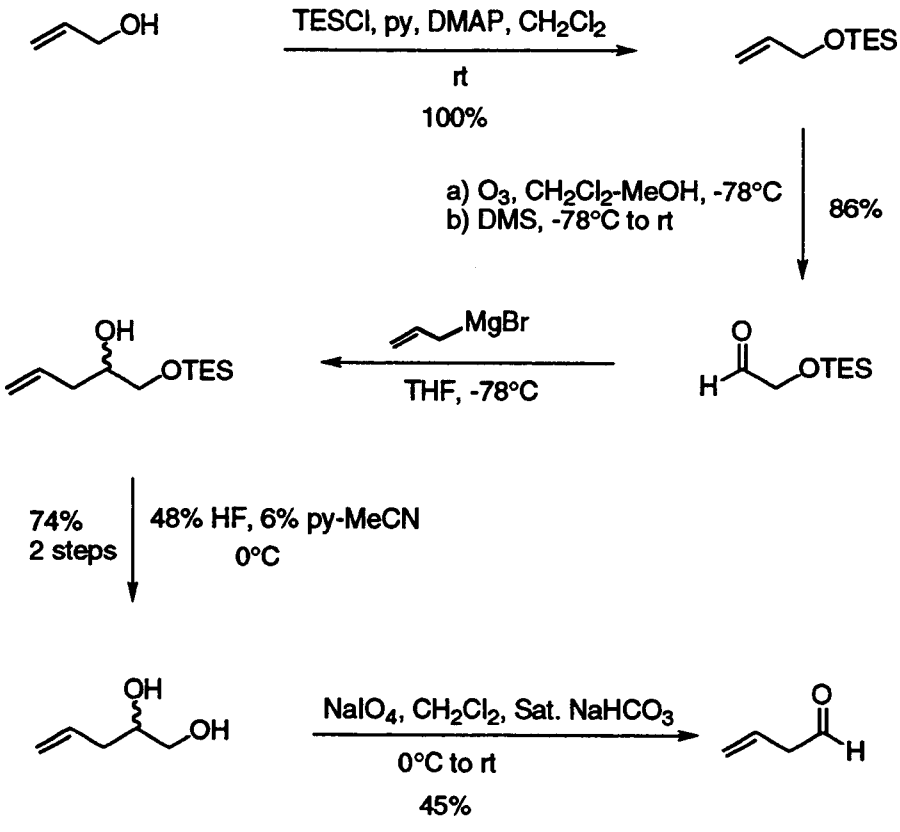
IId

scheme II.1

on the tether can affect the delicate balance between the competing pathways leading the intermediate biradicals towards crossed or linear products or towards reversion to starting material. The choice of alkoxy substituents is dictated by the presence of oxygen functionality on the two carbon bridge in **IB**.

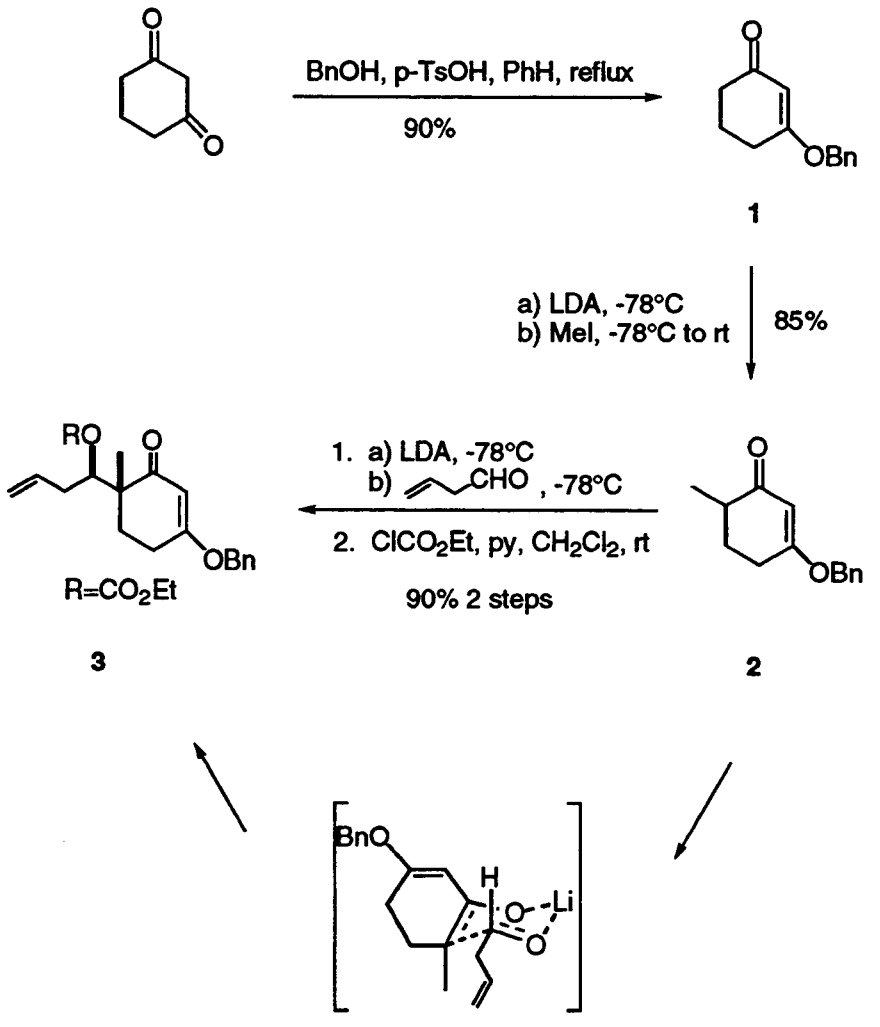
The investigation began with 6-(3-butenyl)-2-cyclohexenone derivatives **IIa**, **IIb**, **IIc** and 6-(4-pentenyl)-cyclohexenone **IId** (**scheme II.1**). Synthesis of the oxygenated derivatives **IIa** and **IId** was achieved by directed aldol reactions.

In our hands, the preparation of 3-buten-1-al, the precursor for the aldol reaction leading to **IIa**, by alcohol oxidation with CrO_3•pyridine complex[61] in methylene chloride was troublesome. Partial isomerization of the resulting aldehyde to the α,β–unsaturated isomer led us to find an alternative pathway, outlined in **scheme II.2**, and began with silylation of allyl alcohol. Ozonolysis of the resulting crude allyl triethylsilyl ether gave the aldehyde which was used without purification. Addition of the aldehyde to an allyl Grignard reagent, followed by removal of the silyl protecting group, afforded the 1,2-diol in pure form after flash chromatography. Oxidative cleavage of the 1,2-diol with sodium periodate[62] gave 3-buten-1-al which was dried over molecular sieves and used in the aldol reaction without further purification.



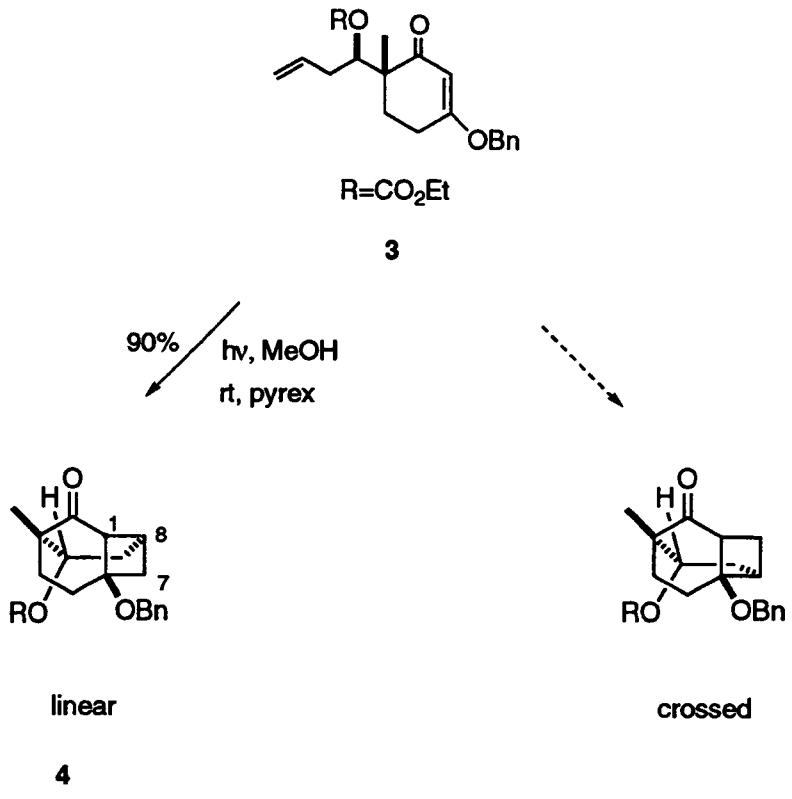
scheme II.2

The requisite substrate **2** for the aldol condensation was prepared by methylation of the vinologous ester **1**.[63] Kinetic deprotonation of **2** with lithium diisopropylamide followed by aldol reaction of the resulting enolate with 3-buten-1-al, and subsequent protection of the resulting secondary alcohol upon treatment with ethyl chloroformate, furnished exclusively the protected aldol product **3** (**scheme II.3**). The stereochemistry of **3** resulted from a chairlike cyclic transition state in which lithium is coordinated to both the enolate oxygen and the carbonyl oxygen.[64]



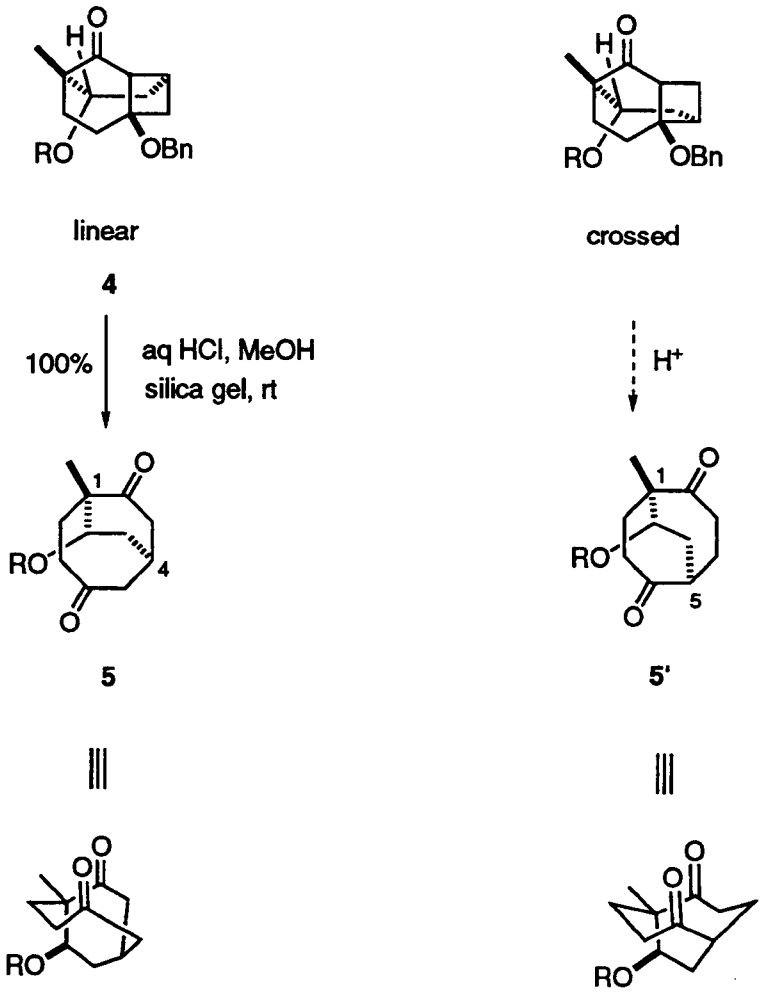
scheme II.3

Irradiation of **3** in methanol through a Pyrex filter afforded a good yield of a single linear photocycloadduct **4** as a stable white crystalline solid (**scheme II.4**). The regiochemistry of **4** was deduced spectroscopically and then verified through comparison of its spectra with those previously studied for the corresponding system without the oxygen substituent on the tether.[59]



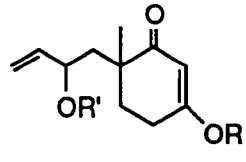
scheme II.4

The structure of **4** was further confirmed by carrying out the retro-aldol ring opening of the β-benzyloxy cyclobutane (**scheme II.5**). In principle, hydrolysis of the crossed photoadduct would give the required bicyclo[3.3.2]decane derivative **5'**. However, only the [4.2.2] derivative **5** was observed after the fragmentation.



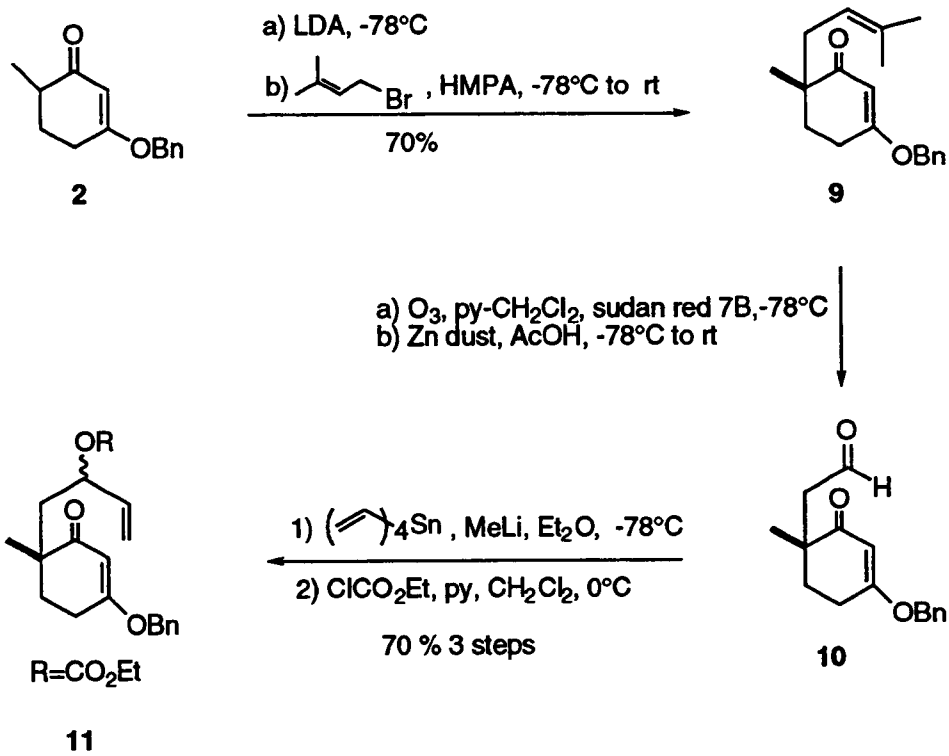
scheme II.5

We next turned our attention to examine the effect on the regiochemistry of intramolecular photocycloaddition of **IIb** of moving the oxygen substituent on the sidechain to the adjacent carbon, which is closer to the olefinic double bond.



IIb

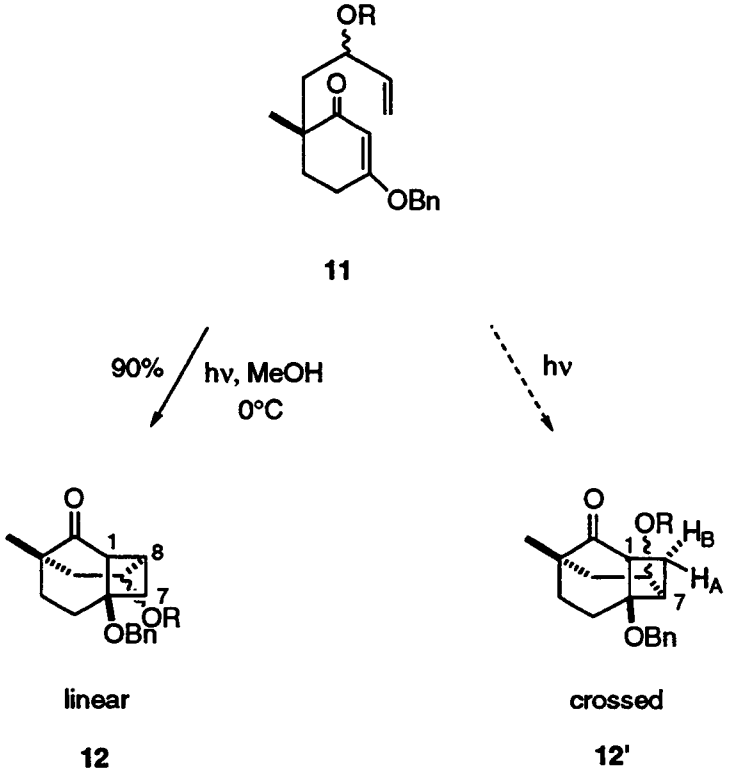
The preparation of the requisite substrate **11** began with **2** (**scheme II.6**). Deprotonation of **2** with lithium diisopropylamide followed by alkylation with 1-bromo-3-methyl-but-2-ene afforded **9**.[65] The double bond of the 3-methyl-2-butenyl moiety was chemoselectively cleaved with ozone in the presence of the vinologous ester.[66] Chemoselective 1, 2-addition of vinyllithium[67] (generated in ether solution by transmetalation of tetravinyltin with methyllithium) to the aldehyde group of **10** and protection of the resulting alcohol with ethyl chloroformate furnished an inseparable 1:1 mixture of diastereomers **11**.



scheme II.6

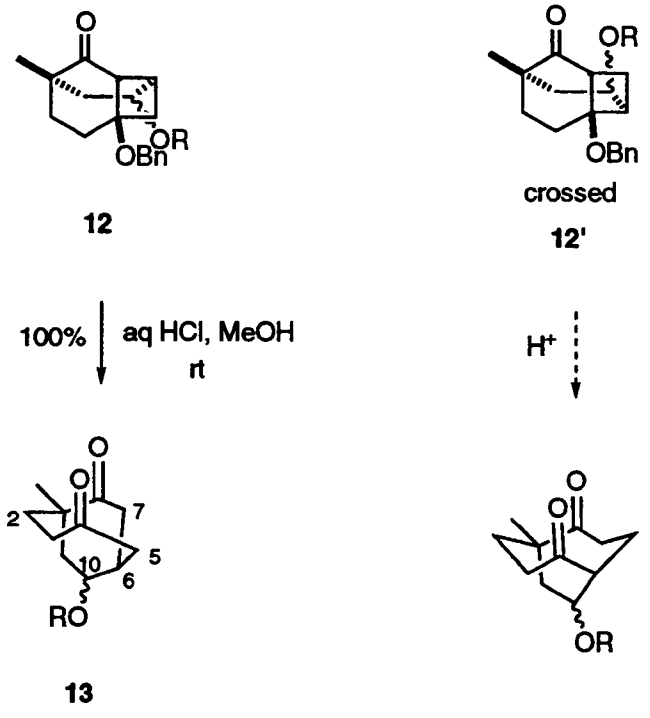
Irradiation of the mixture **11** gave a 3:2 mixture of photoproducts (**scheme II.7**). One isomer was relatively unstable and consequently difficult to handle. Chromatographic purification, for example, led to partial decomposition. Both isomers of photoproduct **12** were assumed to be the linear adducts based on spectroscopic evidence. The proton NMR showed the signal of the hydrogen on

C-1 adjacent to the carbonyl group was a broad doublet (J = 10 Hz) from splitting by the adjacent hydrogen on C-8. The large coupling constant is in agreement with the *cis* relationship of C-1 and C-8 cyclobutyl protons in **12**, so that the angle between the hydrogens on C-1 and C-8 is close to zero. The broadness is due to the long range coupling between H-1 and H-7. However, the other possibility, namely **12'**, could not be completely ruled out as the signal of the hydrogen on C-1 in this case might be a broad doublet too: if the angle between the corresponding hydrogen on C-1 and H_B on C-8 of the cyclobutane ring is close to 90°, the coupling constant will be close to zero and very little if any splitting will occurr between these two protons. Meanwhile, as the hydrogen on C-1 will still be split by the vicinal proton H_A, a large *cis* coupling constant will be observed.



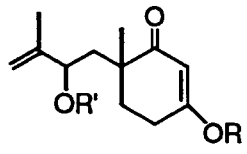
scheme II.7

Strong overlapping of signals in the region from 1.7 to 2.7 ppm on the proton NMR spectrum made a definitive structural confirmation on **12** difficult at this stage. Unfortunately, fragmentation of the alkoxy cyclobutane ring did not help as both isomers of **13** showed strong overlapping of the signals corresponding to their proton NMRs (**scheme II.8**).



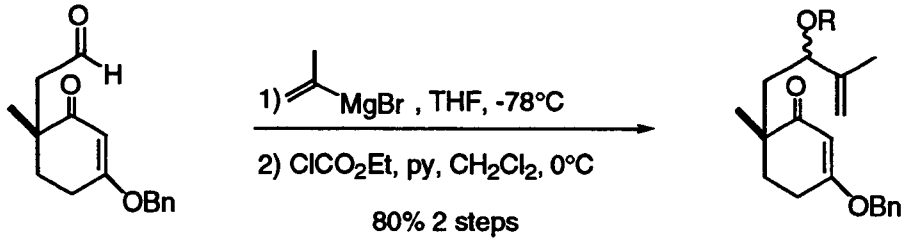
scheme II.8

Introduction of a methyl substituent on C-6 of **13** should simplify the coupling pattern of the hydrogens on C-5 and C-7 by removal of the bridgehead hydrogen. This compound could derive from retroaldol cleavage of the photocycloadduct of **IIc**.



IIc

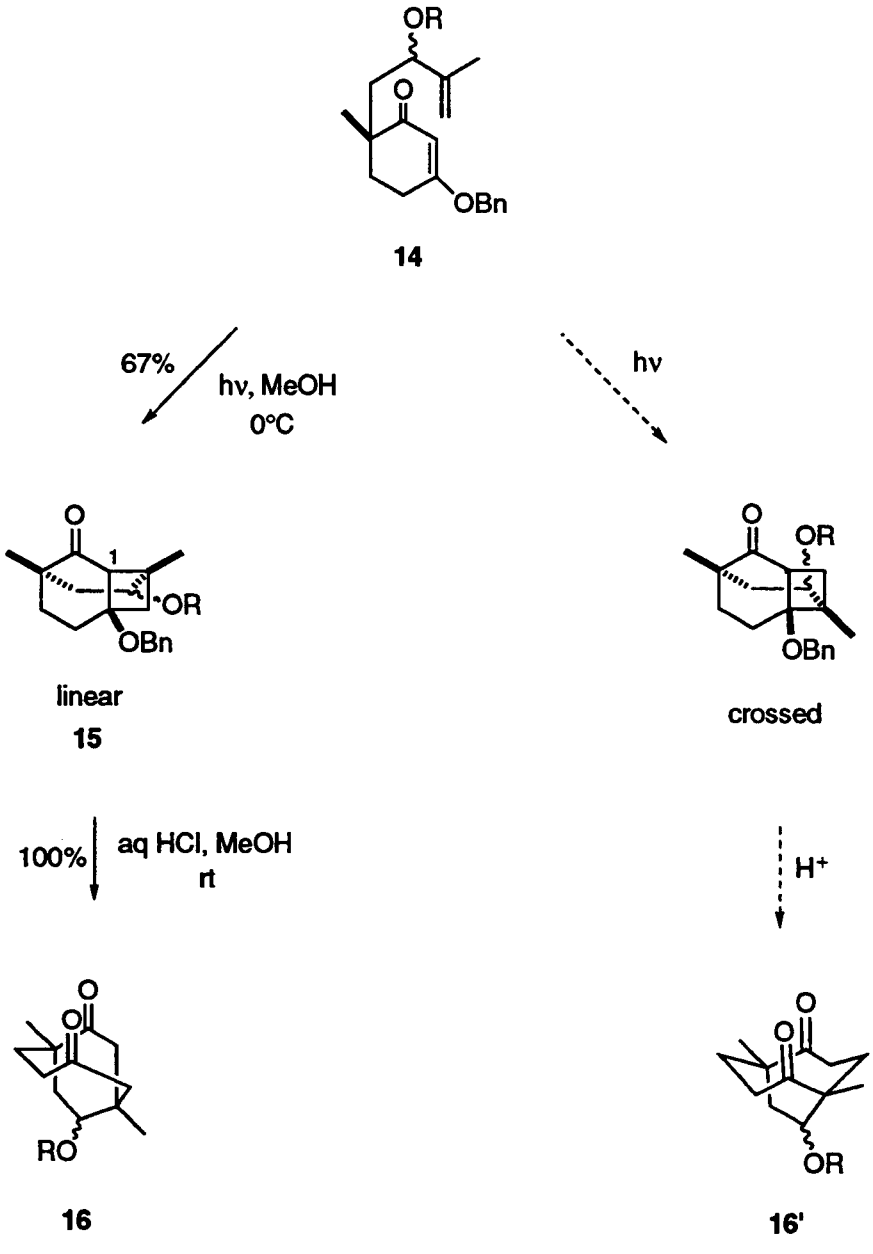
Grignard addition to the preformed aldehyde **10** followed by protection of the resulting alcohol provided an inseparable 1:1 mixture **14** for this study (**scheme II.9**).



10 **14**

scheme II.9

Irradiation of a mixture of **14** yielded a separable 1:1 mixture of unstable photoadducts **15** (**scheme II.10**). Each isomer of the photoadducts **15** was assumed to be linear as ^{1}H NMR showed a singlet at δ = 2.80 ppm or 2.96 ppm which corresponds to H-1. Confirmation of the regiochemistry of each

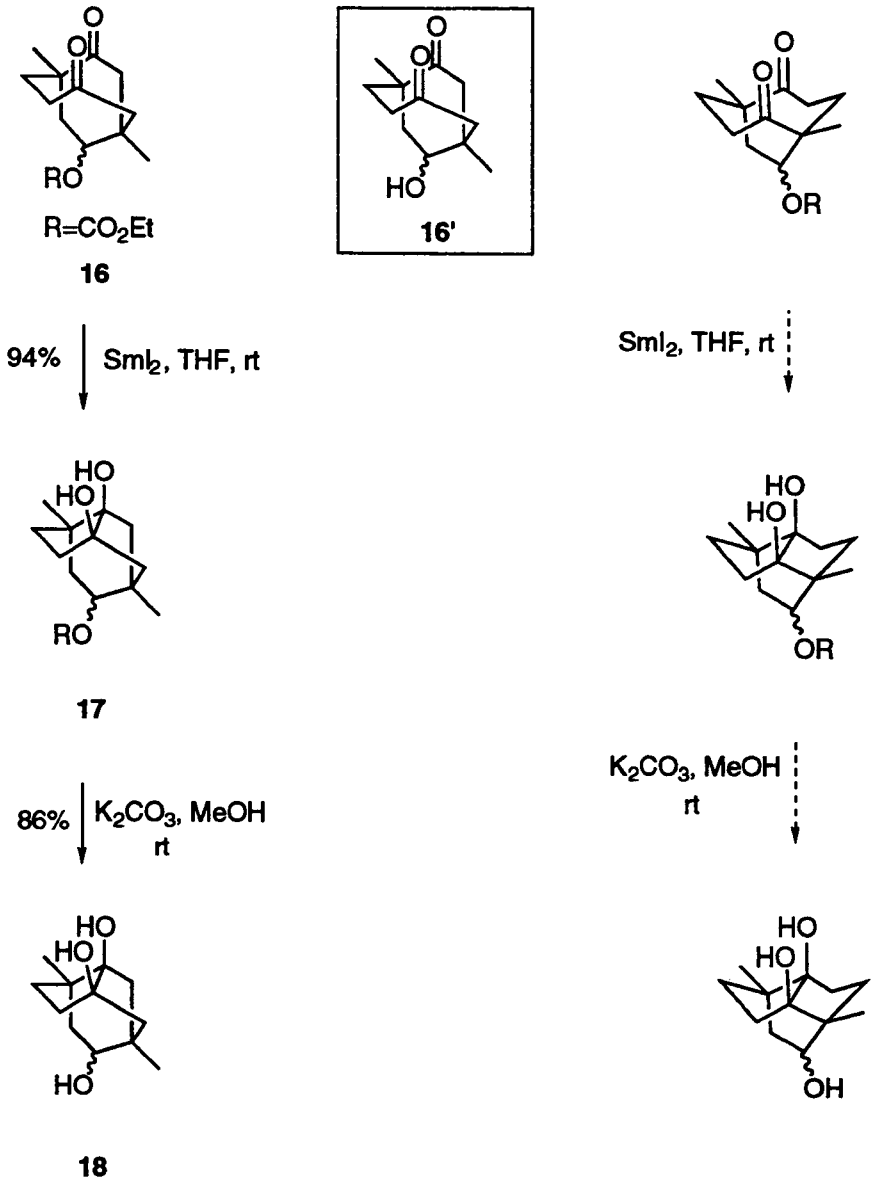


scheme II.10

photoadduct could not be deduced directly from simple ^{1}H and ^{13}C spectra, and even from 2D NMR data due to the complex coupling and strong overlapping of signals. One isomer of the photoadducts **15** was again unstable and decomposed during flash chromatography. It was therefore necessary to subject

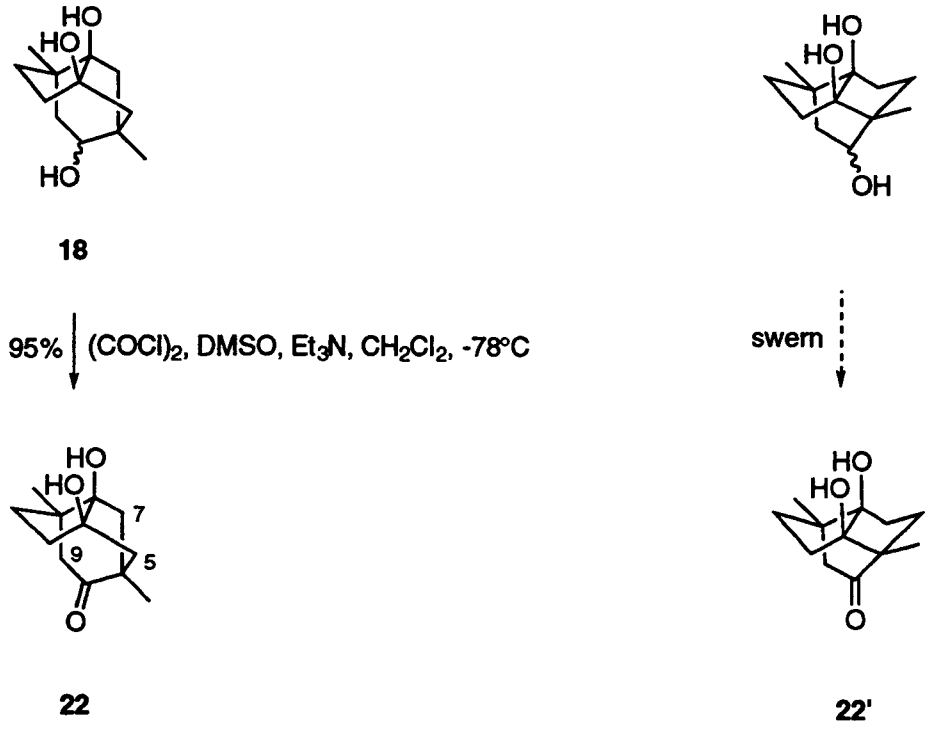
the crude mixture of photoproducts to retro-aldol ring opening conditions. An inseparable mixture **16** resulted.

The strategy for an unambiguous confirmation of the regiochemistry of **15** requires cleavage of the protecting group on the secondary alcohol of compound **16** and oxidation of the resulting alcohol to remove this chiral center. If both photoproducts are indeed epimers at that center, oxidation of the mixture of **16'** should afford just one product. To prevent nucleophilic attack of the free hydroxyl group to the carbonyl groups in **16'** and formation of a hemiacetal, or in its crossed regioisomer, the diketone moiety was protected through a transannular reductive carbonyl coupling to afford an inseparable mixture of *syn* diols **17**. Hydrolysis of the ethyl carbonate group gave again an inseparable mixture of triols **18** (**scheme II.11**).



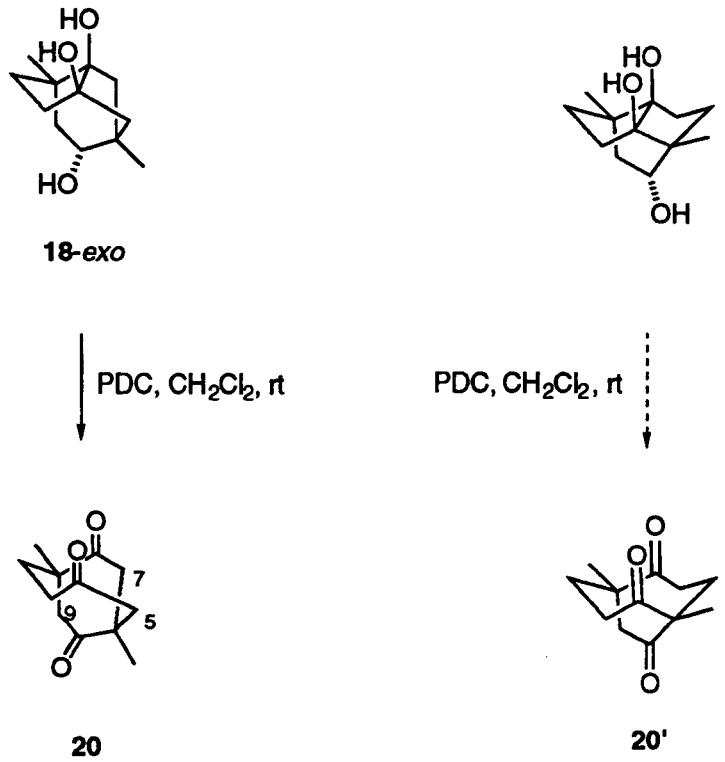
scheme II.11

Swern oxidation of the mixture of **18** turned out a single product **22** (**scheme II.12**).[68] This established that the two photoadducts have the same regiochemisty and differ only on the configuration of the acyloxy group. Three pairs of doublets for the hydrogens at C-5, C-7, and C-8 were observed in the proton NMR of **22**, which allow us to rule out the almost symmetric structure **22'**.



scheme II.12

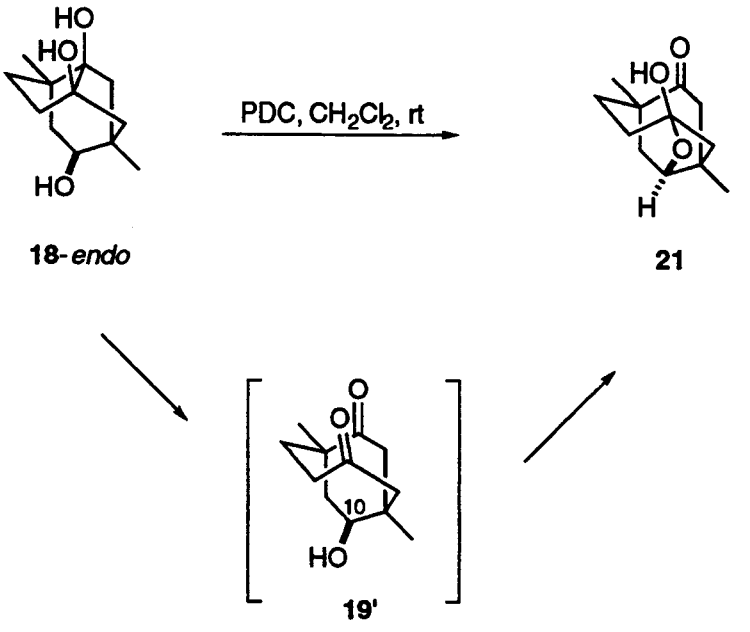
Surprisingly, when the oxidation of **18** was performed with PDC (**scheme II.13**), two products were obtained which had very different polarities. The IR spectum of **20**, the less polar oxidation product, showed no absorption corresponding to hydroxyl groups, only strong carbonyl absorption was observed. The ^{1}H NMR spectrum of **20** clearly showed three pairs of doublets, which were assigned to the three methylene groups on C-5, C-7, and C-9, each of them adjacent to a carbonyl group and a quaternary carbon. The formation of triketone **20** can be rationalized by oxidation of the unhindered *exo*-secondary hydroxyl group in **18** followed by oxidative cleavage of the bis-tertiary alcohol system.[69]



scheme II.13

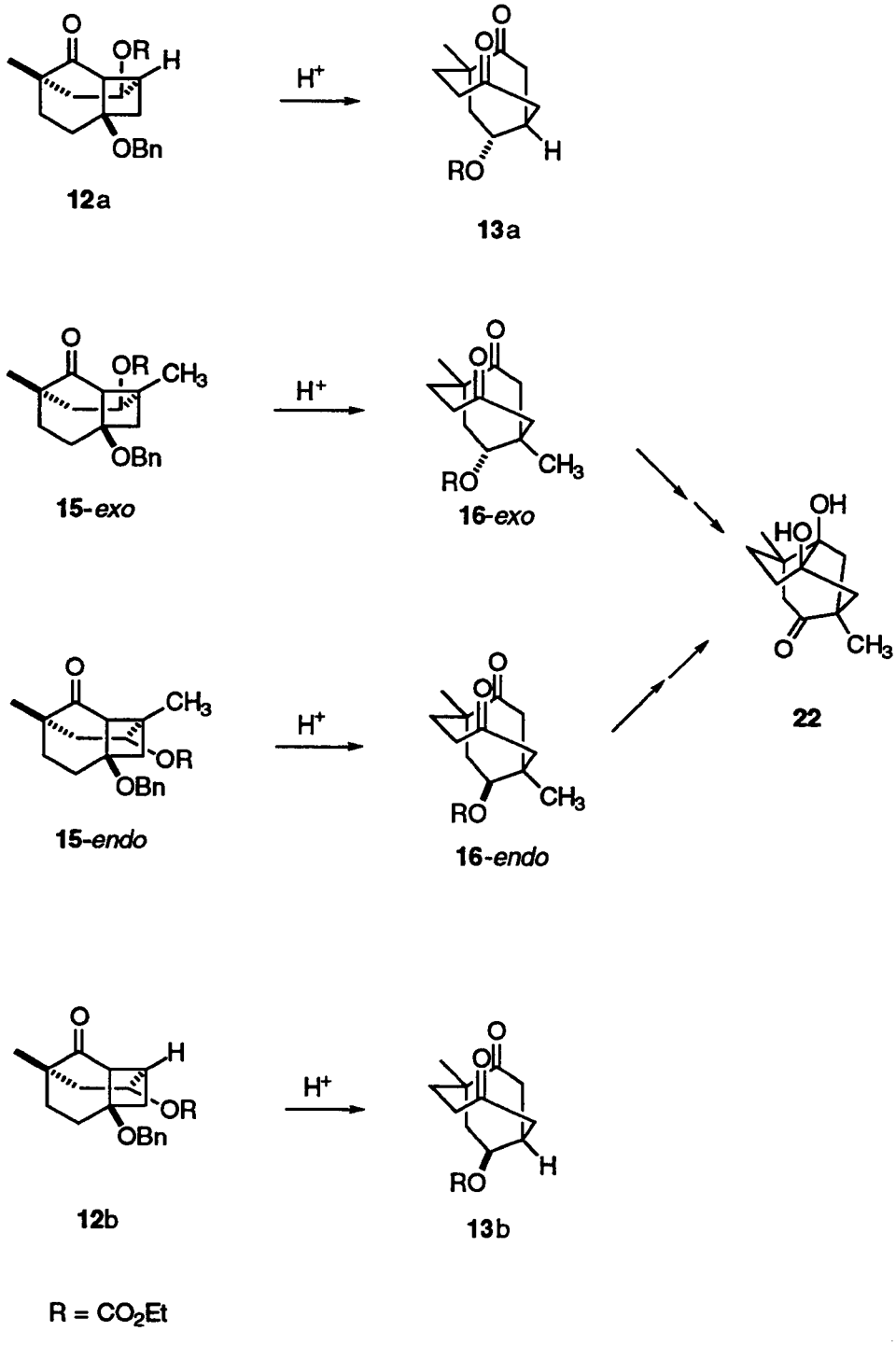
On the other hand, IR showed that the structure of the more polar product from PDC oxidation contains both ketone and hydroxyl functionalities. Its proton NMR showed a downfield triplet signal at δ = 4.37 ppm. ^{13}C NMR showed one carbonyl group, and a singlet at low field (106.9 ppm) characteristic of the carbon of a hemiacetal.

On the basis of spectroscopic analysis, it was concluded that the oxidation of the isomer, **18**-*endo* with PDC affords hemiketal **21** (**scheme II.14**). Steric hindrance in **18**-*endo* presumably slows down the oxidation of the secondary hydroxyl group over the oxidative cleavage. Nucleophilic attack of this hydroxyl group on the carbonyl group at C-10 of **19'** forms an unstrained cyclic hemiketal that effectively protects the hydroxyl group from further oxidation.



scheme II.14

The structural difference between **12** and **15** is only the presence of a methyl group (**scheme II.15**). In retrospect, comparison of the spectral data for


O
OR
H
OBn
12a
H+
O
O
RO
H
13a
O
OR
CH3
OBn
15-exo
H+
O
O
RO
CH3
16-exo
OH
HO
O
CH3
22
O
CH3
OR
OBn
15-endo
H+
O
O
RO
CH3
16-endo
O
H
OR
OBn
12b
H+
O
O
RO
H
13b
R = CO2Et

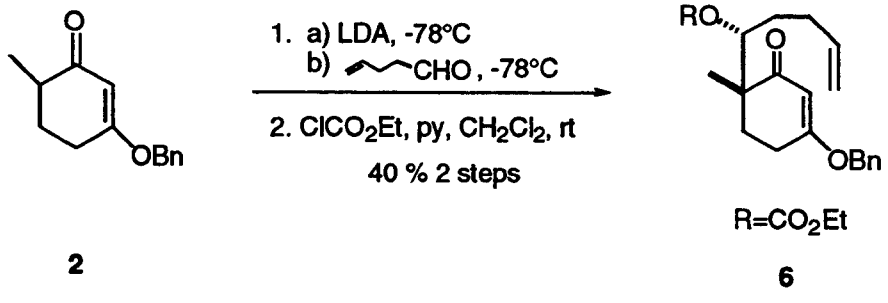
scheme II.15

the most stable isomers of **12** (**12**a) and **15**, and also for their corresponding hydrolysis products **13**a and **16**-*exo* shows that they are completely consistent with the substitution of the bridgehead hydrogen for a methyl group.

The spectral data for the least stable isomer of **12** (**12**b) does not quite match the data for **15**-*endo*. However, the spectral data for the diketones **13**b and **16**-*endo* obtained after their hydrolysis are now consistent with replacement of the bridgehead methyl of **16**-*endo* with a hydrogen atom in **13**b. The regiochemistry of **16**-*endo* and **16**-*exo* was firmly established through their transformation into a unique ketodiol **22**. Therefore, the regiochemistry of the related **13**a and **13**b, and their precursors **12**a and **12**b must also be linear.

The studies discussed so far show that the outcome of the intramolecular photocycloaddition of 3-alkoxy-6-(3-butenyl)-2-cyclohexenones is not affected by the introduction of chiral centers in the chain linking the olefinic moieties.

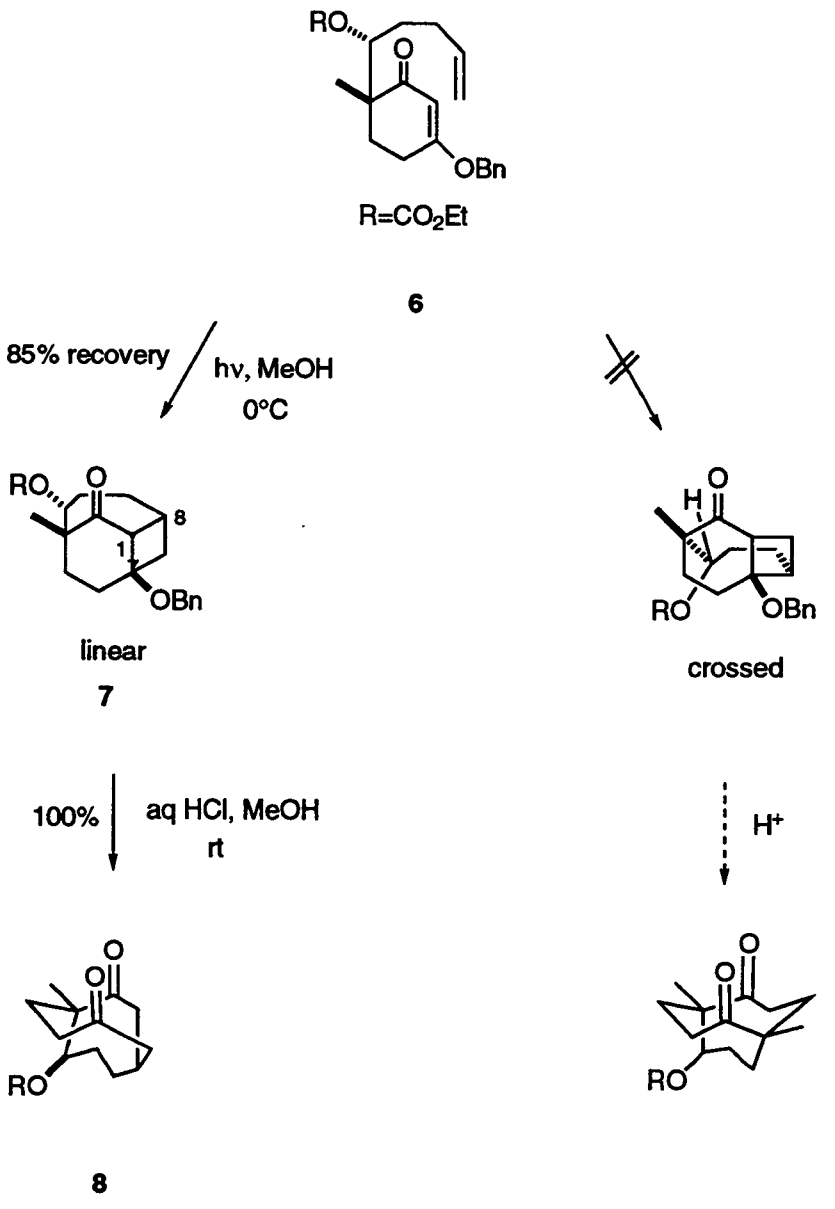
Next, the effect of the length of the tether on the regioselectivity of the photocycloaddition was examined in our systems. The 4-pentenyl derivative **6** for this investigation was again prepared by an aldol reaction of the parent substrate **2** with commercially available 4-penten-1-al, followed by protection of the resulting alcohol (**scheme II.16**).



2 **6**

scheme II.16

Irradiation of **6** furnished photoadduct **7** (**scheme II.17**). This reaction proceeded much more slowly than in the cases of **11** and **14** and as a consequence very low conversion was achieved. ^{1}H NMR showed the signal of the hydrogen on C-1 of **7** was a doublet (J = 12 Hz, 3.32 ppm). The only distinguishing feature between the ^{1}H NMR spectra of **4** shown in **scheme II.4** and **7** is that the coupling constant between the *cis* vicinal hydrogens on C-1 and C-8 increased from 10 Hz to 12 Hz. It is reasonable to conclude that the photocycloaddition of **6** furnished only the linear photoadduct **7**. ^{13}C NMR spectra showed both **4** and **7** had a very similar pattern. Fragmentation of the resulting β-benzyloxy cyclobutane **7** provided [4.3.2] bicyclic derivative **8**, confirming the regiochemistry of **7**.



scheme II.17

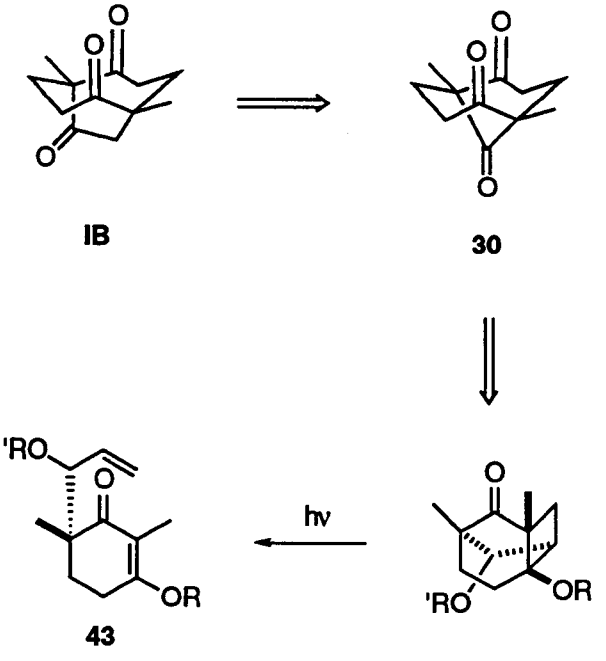
The photocycloaddition of all of the derivatives studied so far produced exclusively linear regioadducts. Moreover, oxygen substituents on the isolated double bond of these systems played no part in controlling the regiochemistry.

Section B: Synthetic studies towards the synthesis of [3.3.2] bicyclic triketone IB.

A reduction in the length of the tether held better promise to afford a change in the regiochemical outcome of the photocycloaddition.

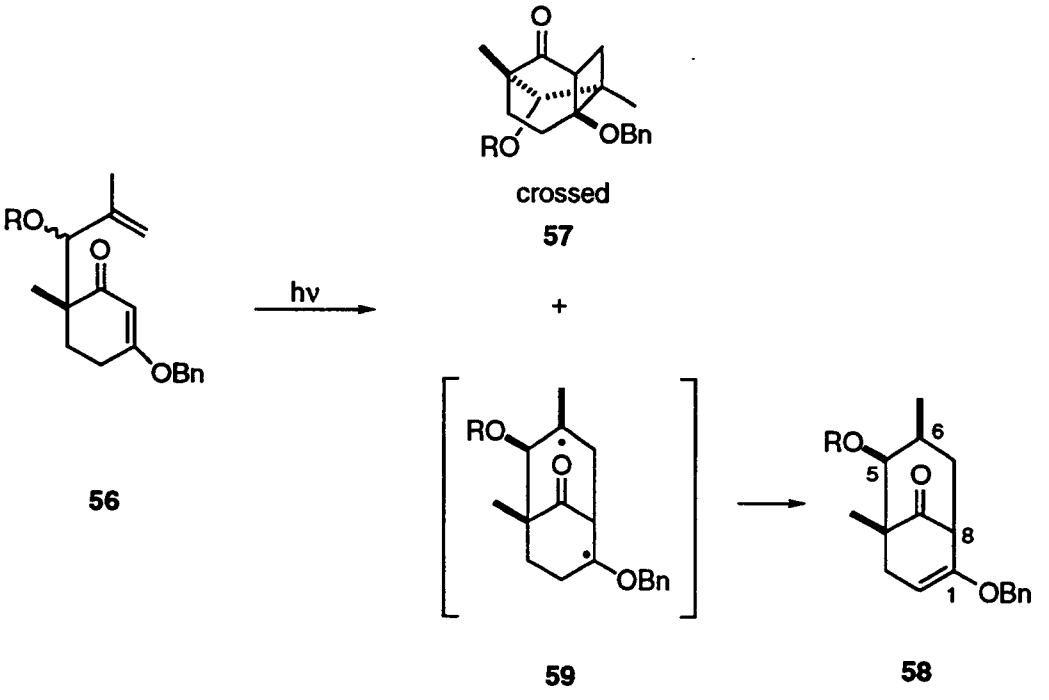
As was mentioned in the introduction (**scheme I.16**), previous studies in this group found that intramolecular photocycloadditions of 3-alkoxy-6-allyl-cyclohexenones **36** and **37** gave crossed photoadducts.

It was decided to extend this approach to find an alternative way to build up the required bicyclo[3.3.2]decane skeleton **IB** through a one carbon ring expansion of a bicyclo[3.3.1]nonane derivative **30** (**scheme II.18**) based on the ring expansion strategy shown in **scheme I.4**.



scheme II.18

However, increasing the substitution on the internal carbon of the allyl group as in compound **56** led to a noteworthy exception (**scheme II.19**).[59] The crossed adduct **57** was obtained along with an isomer **58**, which presumably arose from an intramolecular 1,5-hydrogen abstraction in the intermediate diradical **59**.

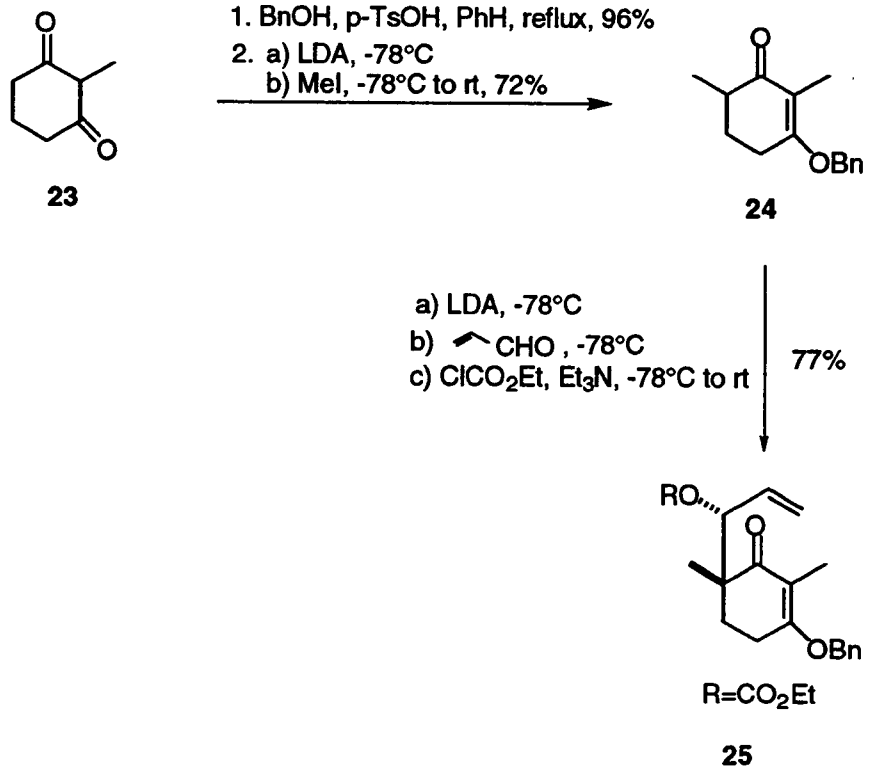


scheme II.19

The structure of **58** is very close to the required [3.3.1] bicyclic skeleton, except that the methyl group at C-6 should be at the bridgehead C-8. The formation of this bicyclic skeleton prompted a search for an alternative pathway which might establish this [3.3.1] nonane skeleton substituted with methyl groups at both bridgehead positions.

The establishment of the [3.3.1] bicyclic compound **30** began with **23** bearing a methyl group at C-2 (**scheme II.20**). The preparation of **25** was once

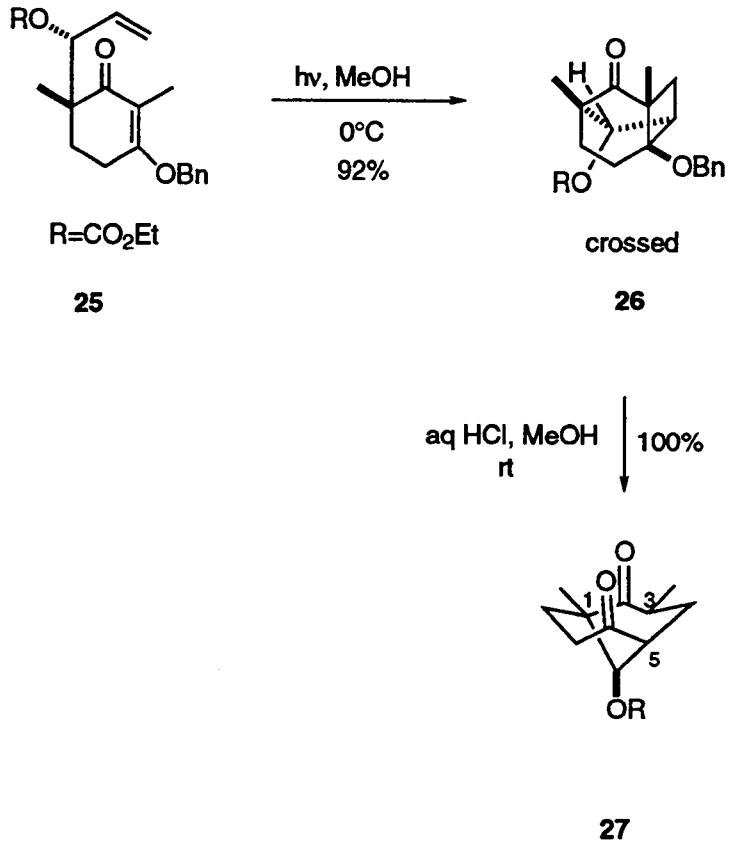
again based on the procedure described for **3** . Only one aldol epimer was formed in this reaction.



scheme II.20

Photoaddition of **25** provided a single product **26**, isolated in 92% yield (**scheme II.21**). The regiochemistry of **26** was determined by comparison of its ^1H NMR spectrum with those of the corresponding [2+2] photoadducts of 6-allyl-cyclohexenones shown in **scheme I.16**, which in turn where established by extensive spectroscopic studies.[59] Retroaldolization upon acidic hydrolysis led to **27**, whose structure was assigned based on 2D NMR data, confirming the regiochemistry of photocycloaddition of **25**.

As discussed in the introduction, the exclusive formation of the crossed adduct in violation of the "rule of five" seems to be typical of photocycloadditions of 6-allyl-2-cyclohexenones.



R=CO_2Et

25

crossed

26

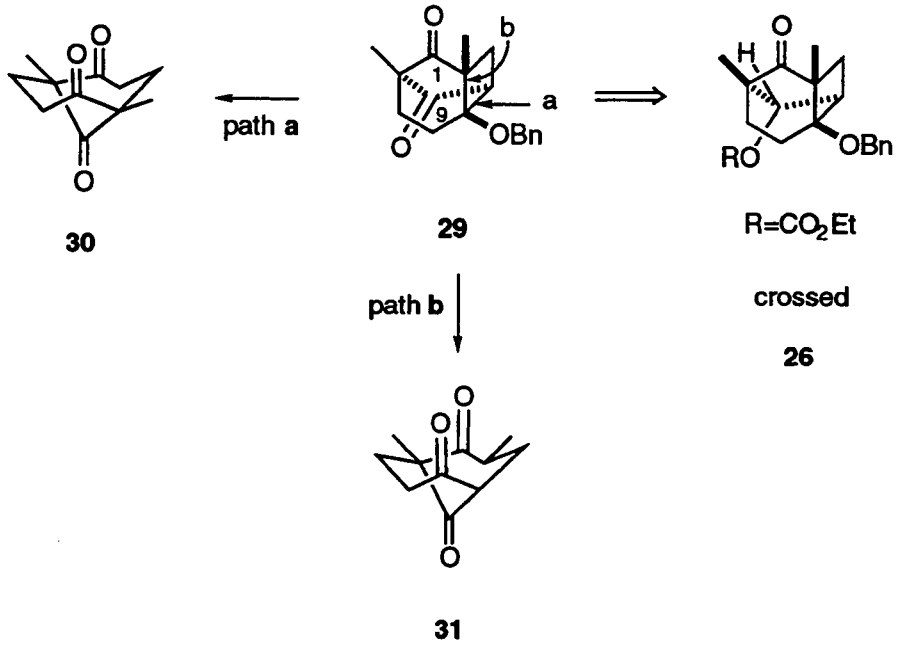
27

scheme II.21

The desired [3.3.1] bicyclic skeleton of **IB** shown in **scheme II.17** requires two methyl groups at the bridgehead positions C-1 and C-5. It is believed that a structure, such as **26**, could be manipulated to secure the selective retroaldol cleavage in the desired fashion (**scheme II.22**). Transformation of this compound into **29** will open two different retroaldol alternatives, path **a** and path **b**, as the benzyloxyl group is now β to both carbonyl groups at C-1 and C-9.

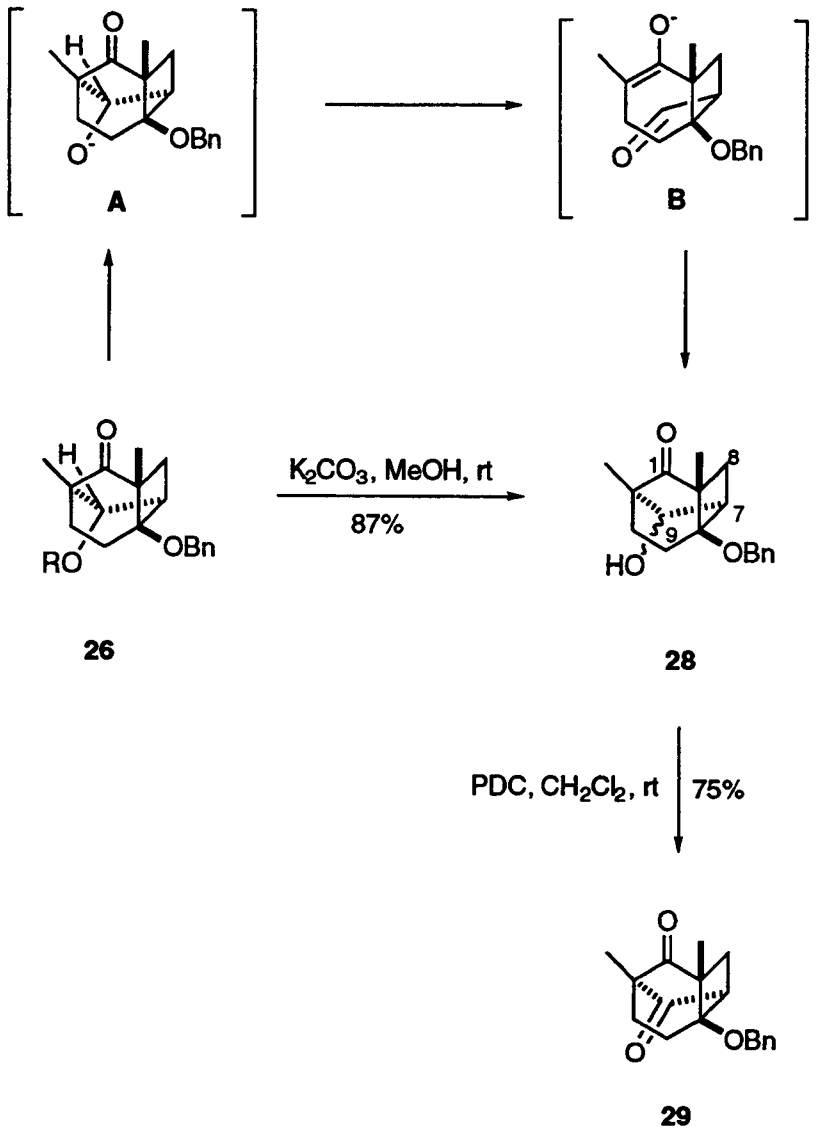
While the cleavage of bond **a** will give the desired [3.3.1] nonane derivative **30**, the cleavage of bond **b** will afford **31**.

The feasibity of such a process was tested beginning with the transformation of **26** into **29**. Base hydrolysis of **26** produced the β-hydroxy



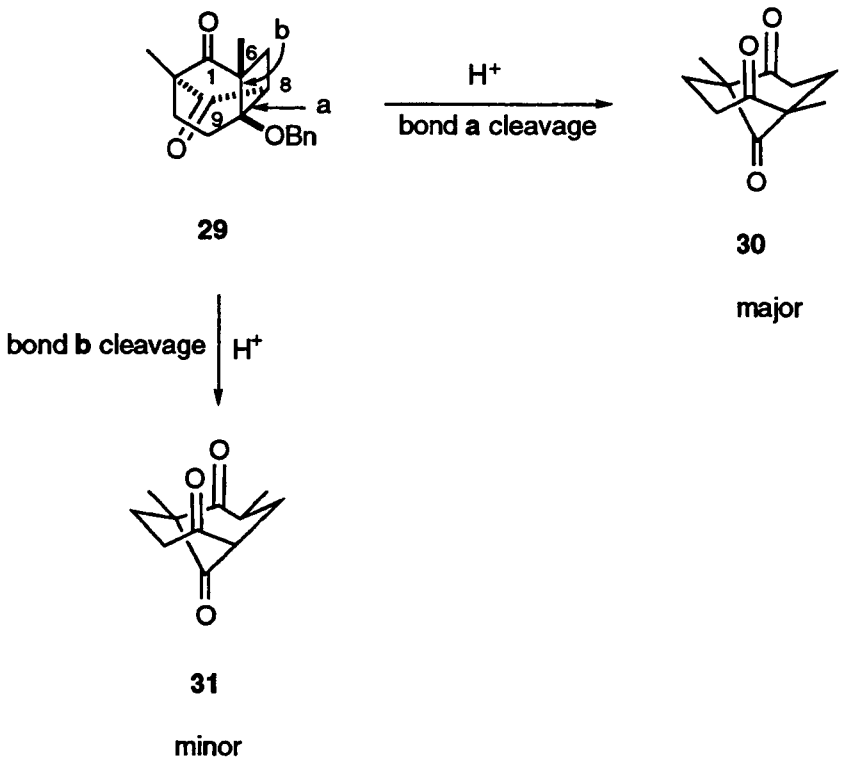
scheme II.22

ketone **28** as a mixture of epimers on C-9. This outcome is clearly the result of retroaldol fission of alkoxide **A** followed by thermodynamically driven reclosure of the derived enolate **B** confirming the epimeric nature of the mixture **28**. Subsequent oxidation of both epimers with PDC provided a single β-benzyloxy diketone **29 (scheme II.23).**



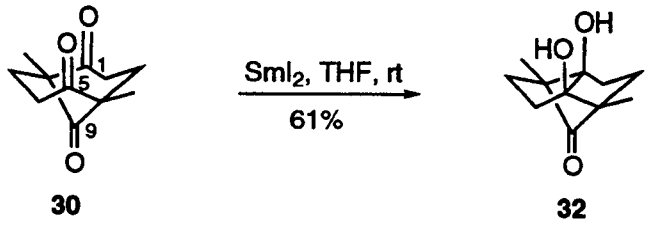
scheme II.23

Retroaldol cleavage of **29** afforded the major symmetric product **30** along with the minor product **31** in about 5:1 ratio. The major product **30** obviously arose from the cleavage of bond **a** in the β-alkoxy ketone **29**, while the minor product **31** was derived from the cleavage of bond **b** (**scheme II.24**). However, this outcome could not be rationalized by consideration of the stability of the corresponding reaction intermediates..



scheme II.24

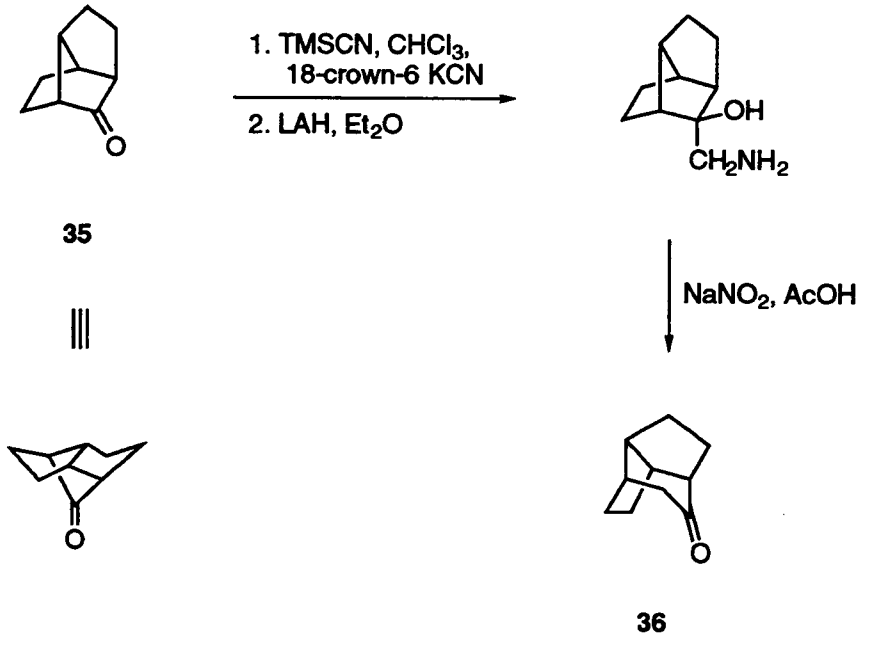
With the promising intermediate **30** in hand, a one carbon ring expansion can be addressed. However, compound **30** presents three carbonyl groups. To ensure the ring expansion occurred at C-9 in **30**, both carbonyl groups at C-1 and C-5 should be protected. This protection was achieved by intramolecular reductive coupling of **30** with SmI_2 affording keto diol **32** as the major product in 61% isolated yield (**scheme II.25**). Reductive coupling between either carbonyls on C-1 and C-9 or carbonyls on C-5 and C-9 was unlikely in this reaction as the resulting strained three-membered ring would be less favored than the five-membered ring.



30 **32**

scheme II.25

Compound **32** now stands ready for a one-carbon ring expansion. This task could be accomplished in a variety of ways. Stern and Nickson have described the ring expansion of a similar carbon skeleton in the transformation of compound **35** into compound **36** (**scheme II.26**).

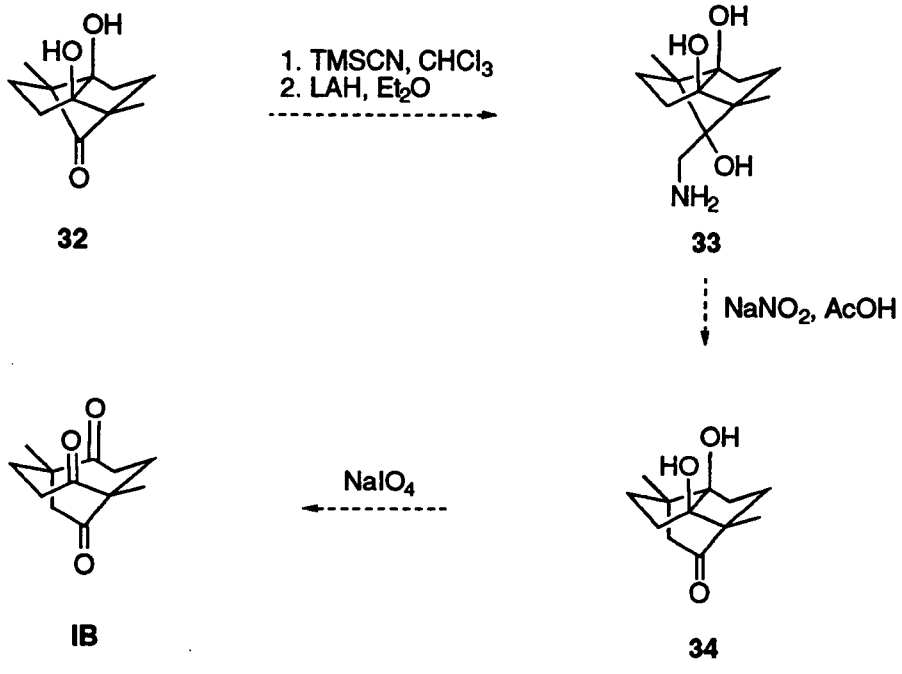


35 **36**

scheme II.26

This route is expected to convert **32** into the amino alcohol **33** by sequential action of trimethylsilyl cyanide and $LiAlH_4$, followed by Tiffeneau-

Demjanov rearrangement of β-hydroxy amine **33** with nitrous acid and oxidative cleavage of the resulting ketodiol **34** with sodium periodate to give the desired [3.3.2] triketone **IB**. (**scheme II.27**).[70]



scheme II.27

It is clear from these results that this intramolecular photocycloaddition methodology could provide an efficient entry towards the core ring system **IB**, which should allow the completion of the synthesis of ryanodol.

CONCLUSIONS

It follows from the above discussion that the photochemical cyclization of 3-alkoxycyclohexenones bearing either 3-butenyl or 4-pentenyl groups on C-6 leads to the exclusive formation of linear adduct. Oxygen substituents on the olefinic sidechain, changes in the electronic nature of the olefin and introduction of substituent groups into the internal carbon of the olefin, all play no role in altering the regioselectivity of intramolecular photocycloadditions of 3-alkoxy-6-butenyl-2-cyclohexenones. On the other hand, intramolecular photocycloadditions of 3-alkoxy-6-allyl-2-cyclohexenones afford crossed photoadducts.

These studies have permitted simple preparations of several different types of bridged 1,5-cyclooctanedione ring systems, such as bicyclic [4.2.2], [4.3.2] and [3.3.1] compounds. The latter could be employed to provide easy access to the intermediate bicyclo[3.3.2]decane skeleton of **IB** in a future synthesis of ryanodol. Consequently, multistep sequences for the synthesis of ryanodol will be shortened, as a good part of its complex polycyclic skeleton can be assembled in a key photochemical reaction. It is likely that these studies will lay the groundwork for future efforts in the total synthesis of ryanodol.

EXPERIMENTAL SECTION

Experimental Section General

Starting materials and reagents were obtained from commercial sources and were generally used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, and dichloromethane were distilled from calcium hydride under argon. The solvents used for routine isolation of products and chromatography were reagent grade, the solvent used for chromatography of the precursors of photolysis were HPLC grade. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Glass syringes and reaction flasks were oven dried prior at 120 °C.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure.

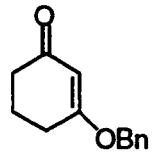
Analytical thin layer chromatography (TLC) was performed using precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a 3-5% solution of phosphomolybodic acid in ethanol, or a 2.5% *p*-anisaldehyde in 88% ethanol, 5% water, 3.5% concentrated sulfuric acid and 1% acetic acid. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM).

Infrared (IR) spectra were recorded with a Nicholet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from

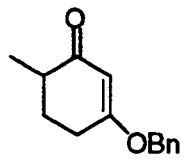
tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order of: chemical shift, number of protons, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad), and coupling constant (*J*) in Hertz (Hz).

Chemical ionization (CI) high and low resolution mass spectroscopy (HRMS and MS) were obtained using a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokarosene was used as a reference. Photolysis was carried out in methanol solution using a Pyrex filter with a Hanovia 450W medium-pressure lamp.

EXPERIMENTAL

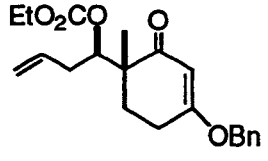


3-Benzyloxy-cyclohex-2-enone (1). A stirred solution of 1, 3-cyclohexadione (10.0 g, 89 mmol), benzyl alcohol (9.2 mL, 89.2 mmol), and *p*-toluenesulfonic acid (0.5 g) in benzene (60 mL) was heated at reflux under argon for 12 h with azeotropic removal of water by Dean-Stark trap. The mixture was allowed to cool to room temperature, diluted with ethyl acetate (60 mL) and washed with saturated sodium bicarbonate (60 mL) and brine (40 mL). The aqueous washings were extracted three times with ethyl acetate (250 mL), and the combined extracts were dried (sodium sulfate). The solvent was evaporated under reduced pressure. The crude product was recrystalized from 30% ethyl acetate in hexane at 0°C to yield 16 g (90%) of **1** as a pale white solid: IR (neat) 3060, 3029, 2942, 2880, 1658, 1601, 1360, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.99 (2H, m), 2.35 (2H, t, J = 6 Hz), 2.46 (2H, t, J = 6 Hz), 4.87 (2H, s), 5.47 (1H, s), 7.31-7.40 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 21.1, 29.0, 36.7, 70.3, 103.3, 127.8 (2C), 128.4, 128.6 (2C), 134.9, 177.4, 199.5; MS (CI) *m/z* 203 (M^++1), 119, 113, 91, 86, 84; HRMS (CI) *m/z* 203.1072 (M^++1) (calcd for $C_{13}H_{15}O_2$: 203.1072).



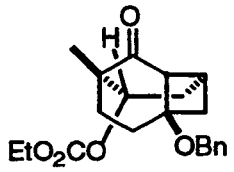
3-Benzyloxy-6-methyl-cyclohex-2-enone (2). To a solution of lithium diisopropylamide (0.33 M, 31 mmol) [prepared from a 1.65 M solution of butyllithium in hexane (19 mL, 31 mmol) and diisopropylamine (4.7 mL, 32.6

mmol) in THF (25 mL) under argon at -15°C.] was added a solution of **1** (5.0 g, 25 mmol) in THF (25 mL) dropwise *via* cannula at -78°C. The mixture was stirred for 30 min at -78°C. Then iodomethane (3.5 mL, 56.22 mmol) was added in one portion at -78°C. The mixture slowly warmed to room temperature over 12 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with saturated sodium bicarbonate (30 mL) and brine (20 mL). The aqueous washings were extracted three times with ethyl acetate (150 mL). The combined extracts were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, gave 4.5 g (85%) of **2** as a pale yellow solid: IR (neat) 3070, 3024, 2932, 2870, 1658, 1612, 1360, 1186 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.14 (3H, d, J = 7 Hz), 1.68-1.75 (1H, m), 2.02-2.08 (1H, m), 2.27-2.32 (1H, m), 2.43-2.57 (2H, m), 4.86 (2H, s), 5.44 (1H, s), 7.31-7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ 15.3, 28.4, 29.2, 40.2, 70.4, 102.7, 127.8 (2C), 128.5, 128.7(2C), 135.1, 176.5, 201.8; MS (CI) *m/z* 217 (M^++1), 127, 108, 91; HRMS (CI) *m/z* 217.1227 (M^++1) (calcd for $C_{14}H_{17}O_2$: 217.1229).



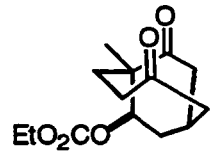
Ethyl carbonate (3). To a solution of lithium diisopropylamide (1.7 mmol) prepared *in situ* (refer to the above procedure) under argon at -78°C was added to a solution of **2** (385 mg, 1.78 mmol) in THF (2 mL). The mixture was stirred for 30 min at -78°C. Then a solution of crude 3-buten-1-al (150 mg) in THF (0.5 mL) predried over activated 4Å molecular sieves was added. The mixture was stirred for 1 h at -78°C, then warmed to -45°C, and stirred for 20 min, next, ethyl chloroformate (1.7 mL, 21 mmol) and triethylamine (0.7 mL, 5 mmol) were added at -45°C. The resulting mixture was allowed to warm up to room temperature

over 12 h. The mixture was diluted with ethyl acetate (30 mL) and washed with saturated sodium bicarbonate (40 mL). The aqueous layer was extracted three times with ethyl acetate (60 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 8% ethyl acetate in benzene as eluant, produced 550 mg (90%) of **3** as a yellow oil: IR (neat) 3070, 2978, 2932, 2875, 1745, 1658, 1607, 1370, 1262, 1196, 995 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.16 (3H, s), 1.25 (3H, t, *J* = 6 Hz), 1.82-1.88 (1H, m), 2.03-2.06 (1H, m), 2.24-2.29 (2H, m), 2.43-2.53 (2H, m), 4.10-4.17 (2H, m), 4.84 (2H, s), 4.97-5.08 (2H, m), 5.28-5.32 (1H, m), 5.36 (1H, s), 5.72-5.78 (1H, m), 7.31-7.37 (5H, m); ^{13}C NMR (CDCl3, 75MHz) δ 14.1, 20.0, 25.5, 26.9, 35.2, 47.1, 63.8, 70.5, 80.5, 102.2, 117.4, 127.7 (2C), 128.5, 128.6 (2C), 133.8, 134.8, 155.0, 175.5, 200.9; MS (CI) *m/z* 359 (M^++1), 269, 179, 128, 91; HRMS (CI) *m/z* 359.1856 (M^++1) (calcd for $C_{21}H_{27}O_5$: 359.1858).

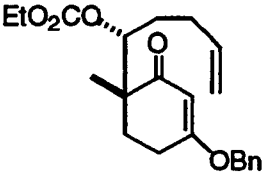


Photolysis of 3 (4). A degassed solution of **3** (46 mg, 0.13 mmol) in dry methanol (60 mL) was irradiated for 2 h at room temperature. Removal of the solvent followed by chromatography of the residue on silica gel, using 8% ethyl acetate in hexane containing 0.5% triethylamine as eluant, gave 42 mg (90%) of **4** as a white solid which was recrystalized from 10% methylene chloride in hexane: IR (neat) 2988, 2936, 2875, 1750, 1715, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.17(3H, s), 1.32 (3H, t, *J* = 7 Hz), 1.69-1.87 (4H, m), 2.01 (1H, d, *J* = 10 Hz), 2.54-2.65 (2H, m), 2.75-2.79 (2H, m), 3.14 (1H, d, *J* = 10 Hz), 4.20 (2H, q, *J* = 7 Hz), 4.39 (2H, s), 4.63 (1H, t, *J* = 9 Hz), 7.28-7.35 (5H, m); ^{13}C NMR

($CDCl_3$, 100MHz) δ 10.5, 17.8, 19.6, 28.6, 30.2, 31.4, 40.6, 50.2, 50.9, 64.2, 64.8, 82.0, 82.2, 127.3 (2C), 127.5, 128.4 (2C), 138.3, 154.5, 212.9; MS (CI) *m/z* 359 (M^++1), 269, 251, 179, 161, 119, 91; HRMS (CI) *m/z* 359.1860 (calcd for $C_{21}H_{27}O_5$: 359.1858).

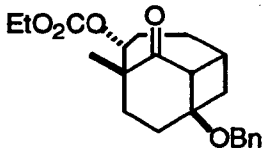


Hydrolysis of 4 (5). A solution of **4** (5 mg) in 1N HCl (0.1 mL) and methanol (1 mL) was stirred for 12 h at room temperature. The mixture was diluted with ethyl acetate (30 mL), and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave **5** (100%) as a white solid: IR (neat) 2925, 2857, 1747, 1717, 1254, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.16 (3H, s), 1.35 (3H, t, *J* = 7 Hz), 1.77-1.90 (1H, m), 2.04-2.18 (2H, m), 2.45-2.68 (6H, m), 2.90-3.10 (2H, m), 4.24 (2H, q, *J* = 7 Hz), 5.03 (1H, t, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.1, 224.5, 24.7, 31.1, 33.1, 39.6, 42.6, 51.2, 52.9, 64.4, 77.3, 154.8, 211.4, 212.1; MS (CI) *m/z* 269 (M^++1), 207, 179; HRMS (CI) *m/z* 269.1388 (M^++1) (calcd for $C_{14}H_{21}O_5$: 269.1389).



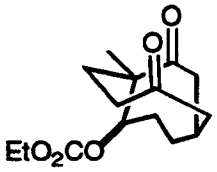
6-(pent-4-enyl)-cyclohex-2-enone (6). To a solution of lithium diisopropylamide (0.57 mmol) prepared *in situ* under argon at -78°C was added a solution of **2** (117 mg, 0.55 mmol) in THF (0.5 mL). The mixture was stirred for 20 min at -78°C

and for 1 h at -45°C. 4-Penten-1-al (0.1 mL, 1 mmol) was added to the mixture at -78°C. The mixture was stirred for 40 min at -78°C and 1 h at -45°C. Ethyl chloroformate (0.6 mL, 7.4 mmol) and triethylamine (0.2 mL, 1.4 mmol) were added at -45°C. The resulting mixture slowly warmed to room temperature for 12 h. This mixture was diluted with ethyl acetate (40 mL) and washed with saturated sodium bicarbonate (30 mL). The aqueous layer was extracted three times with ethyl acetate (50 mL). The combined extracts were dried (sodium sulfate) and the solvent was removed under reduced pressure. The crude residue was columned using 30% ethyl acetate in hexane as eluant to yield 81 mg of **6** (40%) as a colorless oil: IR (neat) 3063, 2976, 2936, 1744, 1651, 1611, 1370, 1256, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.17 (3H, s), 1.31 (3H, t, *J* = 3 Hz), 1.51-1.73 (2H, m), 1.83-1.91 (1H, m), 2.06-2.16 (3H, m), 2.41-2.56 (2H, m), 4.22 (2H, q, *J* = 3 Hz), 4.88 (2H, s), 4.92-5.06 (2H, m), 5.30 (1H, dd, *J* = 2, 10 Hz), 5.43 (1H, s), 5.72-5.86 (1H, m), 7.26-7.43 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.2, 19.8, 25.4, 26.9, 30.0, 30.5, 47.5, 63.9, 70.5, 81.3, 102.3, 115.0, 127.8 (2C), 128.5, 128.7 (2C), 134.8, 137.5, 155.2, 175.5, 201.2; MS (CI) *m/z* 373 (M^++1), 283, 193, 128; HRMS (CI) *m/z* 373.2014 (M^++1) (calcd for $C_{22}H_{29}O_5$: 373.2015).

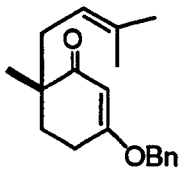


Photolysis of 6 (7). A degassed solution of **6** (55 mg, 0.15 mmol) in dry methanol (60 mL) was irradiated under argon for 1 h in icebath. Removal of the solvent followed by chromatography of the residue on silica gel, using 15% ethyl acetate in hexane as eluant, gave **7** (85% recovery) as a white solid: IR (neat) 2979, 2935, 2847, 1748, 1694, 1259, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.21 (3H, s), 1.33 (3H, t, *J* = 7Hz), 1.53-1.76 (4H, m), 1.97-2.03 (2H, m), 2.17-

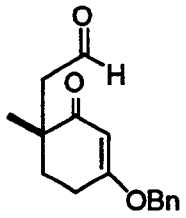
2.25 (1H, m), 2.38-2.58 (3H, m), 2.85-3.05 (1H, m), 3.23 (1H, d, J = 12 Hz), 4.21 (2H, q, J = 7 Hz), 4.42-4.50 (3H, m), 7.27-7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.2, 23.4, 24.5, 24.6, 26.7, 27.2, 29.2, 29.7, 50.7, 55.0, 64.1, 64.5, 77.9, 81.9, 127.2 (2C), 127.4, 128.3 (2C), 138.4, 154.7, 212.7; MS (CI) *m/z* 373 (M^++1), 297, 283, 237, 193, 175, 133, 119, 91; HRMS (CI) *m/z* 373.2014 (M^++1) (calcd for $C_{22}H_{29}O_5$: 373.2015).



Hydrolysis of 7 (8). A solution of **7** (5 mg) in 1N HCl (0.1 mL) and methanol (1 mL) was stirred for 12 h at room temperature. The mixture was diluted with ethyl acetate (30 mL), and washed with saturated sodium bicarbonate (15 mL). The aqueous layer was extracted three times with ethyl acetate (30 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ethyl acetate in hexane as eluant, gave **8** (100%) as a colorless oil: IR (neat) 2981, 2940, 1743, 1689, 1263, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.25 (3H, s), 1.31 (3H, t, J = 7 Hz), 1.61-1.66 (1H, m), 1.96-2.08 (4H, m), 2.35-2.50 (4H, m), 2.60-2.79 (3H, m), 2.94 (1H, dd, J = 1.5, 5.5 Hz), 4.19 (2H, q, J = 7 Hz), 4.91 (1H, d, J = 10 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.1, 25.9, 29.3, 30.8, 32.9, 33, 41.6, 49.5, 51, 54.8, 64.1, 79.8, 188.8, 211, 212; MS (CI) *m/z* 283 (M^++1), 209, 193, 175, 165, 147, 133, 91; HRMS (CI) *m/z* 283.1545 (M^++1) (calcd for $C_{15}H_{23}O_5$: 283.1545).

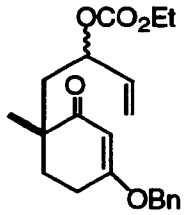


3-Benzyl-6-(3-methylbut-2-enyl)cyclohex-1-enone (9). To solution of LDA (2 mmol) prepared *in situ* under argon at -78°C was added a solution of **2** (0.4 mg, 1.87 mmol) in THF (1.5 mL) dropwise. The mixture was stirred for 30 min at -78°C. 1-Bromo-3-methyl-but-2-ene (0.4 mL, 3.4 mmol) was added in one portion at -78°C and the mixture was slowly warmed to room temperature over 12 h. The mixture was poured into saturated ammonium chloride (15 mL) and extracted three times with ethyl acetate (60 mL). The combined organic layers were washed with brine (15 mL), dried (sodium sulfate) and the solvent evaporated under reduced pressure. The remaining yellow oil was purified by flash chromatography, using 30% ethyl acetate in hexane, gave 369 mg (70%) of **9** as a yellow oil: IR (neat) 3058, 3034, 2963, 2921, 2863, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.08 (3H, s), 1.61 (3H, s), 1.71 (3H, s), 1.61-1.76 (1H, m), 1.90-1.98 (1H, m, *J* = 6 Hz), 2.14-2.31 (2H, m, *J* = 8 Hz), 2.47 (2H, t, *J* = 6 Hz), 4.87 (2H, s), 5.06-5.12 (1H, m) , 5.39 (1H, s), 7.32-7.41 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 17.9, 22.1, 26.0, 31.6, 35.2, 44.0, 70.3, 102, 120.0, 127.8 (2C), 128.4, 128.6 (2C), 134.1, 135.1, 175.3, 191.4, 205.5; MS (CI) *m/z* 285 (M^++1), 206, 192, 178, 86; HRMS (CI) *m/z* 285.1855 (M^++1) (calcd for $C_{19}H_{25}O_2$: 285.1855).



(1-methyl-4-Benzyloxy-2-oxocyclohex-3-enyl)ethanal (10). To a solution of **9** (47 mg, 0.167 mmol) in methylene chloride (3 mL) was added pyridine (24 μL)

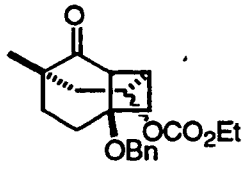
and a trace amount of sudan red 7B. The mixture was cooled to -78°C and ozonized until the red color disappeared. The excess ozone was removed by bubbling argon through the reaction mixture for 10 min. The reaction mixture was poured on zinc dust (115 mg), and acetic acid (0.16 mL) was added. The mixture was warmed to room temperature for 2 h. After filtration through a pad of Celite rinsed with ethyl acetate (15 mL), the solution was diluted with ethyl acetate (30 mL), washed successively with 15% NaOH twice (10 mL), brine (20 mL), and was dried (sodium sulfate). The solvent was evaporated under reduced pressure to give 41 mg of crude **10** as a yellow oil which was used without purification: IR (neat) 3032, 2927, 2867, 2735, 1717, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.25 (3H, s), 1.76-1.79 (1H, m), 2.12-2.20 (1H, m), 2.39-2.48 (2H, m), 2.42-2.48 (2H, m), 2.58-2.78 (2H, m), 4.90 (2H, d, J = 3 Hz), 5.45 (1H, s), 7.26-7.43 (5H, m), 9.78 (1H, t, J = 2 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.4, 25.8, 32.3, 42.6, 51.1, 70.6, 101.5, 127.8 (2C), 128.5, 128.6 (2C), 134.8, 175.6, 201.2, 201.8.



Ethyl Carbonate 11. Methyllithium (0.45 mL, 0.63 mmol, 1.4 M in Et_2O) was added *via* syringe to a stirred solution of tetravinyltin (31 μL, 0.17 mmol) in anhydrous ether (1 mL) under argon at 0°C. The mixture was stirred for 15 min at 0°C, then cooled to -78°C, and cannulaed into the solution of **10** (160 mg, 0.625 mmol) in ether (3 mL) under argon at -78°C. The resulting mixture was stirred for 1 h at -78°C, diluted with ethyl acetate (30 mL), and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (50 mL). The combined organic extracts were dried

(sodium sulfate) to give 142 mg (80%) of crude product as a yellow oil which was used for the next step without purification.

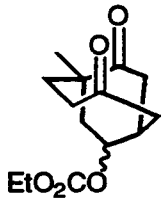
To a solution of above crude product in methylene chloride (5 mL) was added pyridine (0.8 mL) and ethyl chloroformate (0.4 mL, 5 mmol) at 0°C. The mixture was stirred for 2 h at 0°C, diluted with ethyl acetate (25 mL) and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL). The combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 25% ethyl acetate in hexane as eluant, gave 125 mg (70%) of a mixture of two isomers **11** as a yellow oil: IR (neat) 2974, 2922, 2865, 1742, 1652, 1607, 1363, 1254, 1184, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.15 (3H, s), 1.16 (3H, s), 1.26 (3H, t, J = 7 Hz), 1.79-1.86 (2H, m), 1.93-2.04 (2H, m), 2.48-2.53 (2H, m), 4.18 (2H, q, J = 7 Hz), 4.87 (2H, s), 5.13-5.17 (1H, m), 5.25-5.31 (2H, m), 5.37-5.38 (1H, d, J = 5.5 Hz), 5.74-5.86 (1H, m), 7.26-7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.2, 21.9, 23.1, 25.9, 32.0, 40.4, 41.0, 42.5, 42.7, 63.8, 70.4, 75.7, 76.0, 101.5, 101.9, 116.7, 127.7, 127.8, 128.4 (2C), 128.6 (2C), 135.0, 136.6, 136.7, 154.2, 175.0, 175.4, 202.5, 202.8.



Photolysis of 11 (12). A degassed solution of **11** (35 mg, 0.1 mmol) in dry methanol (40 mL) was irradiated under argon for 2.5 h in an icebath. Removal of the solvent followed by chromatography of the residue on silica gel, using 25% ethyl acetate in hexane as eluant, gave 31 mg (90%) of **12** as a colorless oil. One of the isomers was unstable and partially decomposed on silica gel. One isomer: IR (neat) 3064, 2977, 2867, 1739, 1709, 1370, 1265, 1013 cm^{-1}; ^1H

NMR (C_6D_6, 300MHz) δ 0.38 (3H, s), 0.88 (3H, t, *J* = 7 Hz), 1.30-1.32 (1H, m), 1.45 (2H, t, *J* = 7 Hz), 1.51- 1.65 (1H, m), 1.88-1.91 (1H, m), 1.97-2.05 (1H, m), 2.23-2.26 (2H, m), 2.80-2.91 (1H, m), 3.02 (1H, d, *J* = 10 Hz), 3.85 (2H, q, *J* = 7Hz), 4.08 (2H, d, *J* = 4 Hz), 4.74 (1H, q, *J* = 7 Hz), 7.04-7.17 (5H, m); ^{13}C NMR (C_6D_6, 75MHz) δ 13.9, 24.8, 30.2, 30.6, 30.8, 37.8, 42.1, 43.7, 50.8, 63.4, 64.4, 71.4, 81.1, 124.7 (2C), 127.7, 128 (2C), 138.8, 154.4, 212.5; MS (CI) *m/z* 359 (M^++1), 301, 283, 269, 207, 179, 105, 91; HRMS (CI) *m/z* 359.1860 (M^++1) (calcd for $C_{21}H_{27}O_5$: 359.1858).

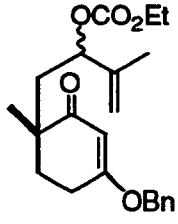
The other isomer: ^1H NMR ($CDCl_3$, 300MHz) δ 1.14 (3H, s), 1.30 (3H, t, *J* = 7 Hz), 1.82-2.16 (4H, m), 2.18-2.27 (2H, m), 2.66-2.75 (2H, m), 2.95-3.19 (1H, m), 3.20-3.22 (1H, d, *J* = 9.6Hz), 4.16 (2H, q, *J* = 7 Hz), 4.40 (2H, s), 4.95-5.0 (1H, s), 7.26-7.39 (5H, m).



Hydrolysis of 12 (13). A solution of each isomer of **12** (5 mg) in 1N HCl (0.1 mL) and methanol (1 mL) was stirred for 12 h at room temperature. The mixture was diluted with ethyl acetate (25 mL), and washed with saturated sodium bicarbonate (15 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave **13** (100%) as a white solid. One isomer: IR (neat) 2922, 1739, 1702, 1258, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.13 (3H, s), 1.33 (3H, t, *J* = 7 Hz), 1.73-1.78 (1H, m), 1.83-1.88 (1H, m), 1.96 (1H, dd, *J* = 7, 15 Hz), 2.34 (1H, dd, *J* = 7, 15 Hz), 2.40-2.49 (2H, m), 2.69 (2H, d, *J* = 4 Hz), 2.76-2.89 (2H, m), 2.96 (1H, dd, *J* = 4, 14 Hz), 4.19-4.26

(2H, m), 5.16-5.13 (1H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.1, 28.4, 33.2, 37.6, 39.2, 41.8, 42.7, 45.4, 46.3, 64.3, 72.4, 154.4, 212.8, 213.5; MS (CI) *m/z* 269 (M^++1), 207, 179; HRMS (CI) *m/z* 269.1388 (M^++1) (calcd for $C_{14}H_{21}O_5$: 269.1389).

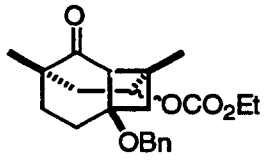
The other isomer: ^1H NMR ($CDCl_3$, 300MHz) δ 1.12 (3H, s), 1.34 (3H, t, *J* = 7 Hz), 1.58-1.61 (1H, m), 1.95-2.05 (2H, m), 2.41-2.70 (6H, m), 2.84-2.90 (2H, m), 4.22 (2H, q, *J* = 7 Hz), 5.41 (1H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 14.2, 28.1, 35.2, 39.0, 39.1, 39.7, 40.3, 42.5, 50.6, 64.3, 75.3, 146.5, 209.0, 210.5.



Ethyl Carbonate 14. To a solution of **10** (56 mg, 0.22 mmol) in THF (1 mL) under argon at -78°C was added pre-cooled isopropenyl magnesium bromide in THF (0.5 M, 0.25 mmol) dropwise. The mixture was stirred for 2.5 h at -78°C, diluted with ethyl acetate (15 mL), and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL). The combined organic extracted was dried (sodium sulfate) to give 60 mg of crude product as a yellow oil which was used for the next step without purification.

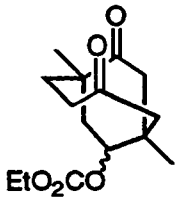
To a solution of above crude product in methylene chloride (3 mL) was added pyridine (0.2 mL) and ethyl chloroformate (0.1 mL, 1.25 mmol) at 0°C. The mixture was stirred for 2 h at 0°C, diluted with ethyl acetate (25 mL) and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL). The combined organic extracted was dried (sodium sulfate). Removal of the solvent followed by chromatography of

the residue on silica gel, using 20% ethyl acetate in hexane as eluant, gave 70 mg (80%) of a mixture of two isomers **14** as a yellow oil: IR (neat) 3030, 2928, 2870, 1747, 1655, 1604, 1730, 1256, 1188, 999 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.15 (3H, s), 1.17 (3H, s), 1.30 (3H, t, *J* = 7 Hz), 1.74 (3H, s), 1.78 (3H, s), 1.79-2.04 (4H, m), 2.42-2.57 (2H, m), 4.17 (2H, q, *J* = 7 Hz), 4.83-4.87 (3H, m), 5.01-5.16 (2H, m), 5.39 (1H, d, *J* = 6.5 Hz), 7.26-7.42 (5H, m);^{13}C NMR ($CDCl_3$, 75MHz) δ 14.2, 18.0, 21.7, 22.6, 26.0, 31.6, 31.9, 39.4, 40.3, 42.6, 42.9, 63.8, 70.5, 78.0, 78.4, 101.6, 102.0, 112.1, 112.4, 127.8, 128.0 (2C), 128.6, 128.7 (2C), 135.0, 144.0, 144.2, 154.2, 154.3, 175.1, 175.6, 202.6, 203.0.



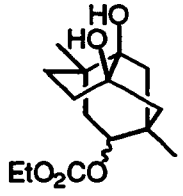
Photolysis of 14 (15). A degassed solution of **14** (27 mg, 0.073 mmol) in dry methanol (70 mL) was irradiated under argon for 2 h in an icebath. Removal of the solvent followed by chromatography of the residue on silica gel, using 20% ethyl acetate in hexane containing 0.5% triethylamine as eluant, gave 10 mg of **15**-*exo* and 8 mg of **15**-*endo* as colorless oils, **15**-*exo* was not very stable and partially decomposed on silica gel: **15**-*exo* IR (neat) 3024, 2957, 2927, 2865, 1740, 1263 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.13 (3H, s), 1.31 (3H, t, *J* = 7 Hz), 1.33 (3H, s), 1.79-1.84 (1H, m), 1.91-2.0 (1H, m), 2.07-2.19 (3H, m), 2.23-2.38 (2H, m), 2.71 (1H, d, *J* = 4 Hz), 2.80 (1H, s), 4.18 (2H, q, *J* = 7 Hz), 4.37 (2H, d, *J* = 1 Hz), 4.56 (1H, dd, *J* = 7, 9 Hz), 7.27-7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.1, 24.8, 28.1, 30.4, 37.8, 38.4, 39.8, 42.8, 42.9, 58.8, 64.1, 64.5, 77.2, 78.4, 127.2 (2C), 127.5, 128.4 (2C), 138.0, 154.6, 214.2; MS (CI) *m/z* 372 (M^+), 311, 283, 265, 221, 193, 175, 123, 91; HRMS (CI) *m/z* 372.1936 (calcd for $C_{22}H_{28}O_5$: 372.1937).

15-*endo* IR (neat) 3026, 2960, 2922, 2867, 1739, 1250 cm^{-1}; ^1H NMR (C_6D_6, 400MHz) δ 0.93 (3H, t, *J* = 7 Hz), 1.01 (3H, s), 1.19 (3H, s), 1.38-1.62 (4H, m), 1.96 (2H, d, *J* = 5 Hz), 2.10 (1H, dd, J = 2, 16 Hz), 2.25 (1H, dd, *J* = 4, 16 Hz), 2.96 (1H, s), 3.94 (2H, q, *J* = 7 Hz), 4.22 (2H, dd, *J* = 11, 27 Hz), 4.76 (1H, t, *J* = 2.7 Hz), 7.14-7.31 (5H, m); ^{13}C NMR (d-Benzene, 75MHz) δ 13.4, 26.2, 26.3, 29.7, 37.8, 39.8, 40.1, 40.5, 45.1, 57, 63.5, 64.3, 77.8, 78, 127.1 (2C), 127.7, 128.2 (2C), 138.8, 154.7, 211.3; MS (CI) *m/z* 372 (M^+), 311, 283, 265, 193, 175, 123, 91; HRMS (CI) *m/z* 372.1936 (calcd for $C_{22}H_{28}O_5$: 372.1937).



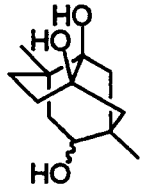
Hydrolysis of 15 (16). A solution of **15**-*exo* (10 mg) or **15**-*endo* (8 mg) in 1N HCl (0.2 mL) and methanol (1.5 mL) was stirred for 12 h at room temperature. The mixture was diluted with ethyl acetate (15 mL), and washed with saturated sodium bicarbonate (10 mL). The aqueous layer was extracted three times with ethyl acetate (25 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave **16** (100%) as a colorless oil: **16**-*exo* IR (neat) 2961, 2927, 1752, 1704, 1261, 999 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.14 (3H, s), 1.34 (3H, t, *J* = 7 Hz), 1.57 (3H, s), 1.70-1.75 (1H, m), 1.87-1.93 (2H, m), 2.20 (1H, d, *J* = 14 Hz), 2.42-2.47 (3H, m), 2.67 (1H, d, *J* = 19 Hz), 2.72-2.80 (1H, m), 2.96 (1H, d, *J* = 14 Hz), 4.23 (2H, q, *J* = 4, 7 Hz), 4.92 (1H, dd, *J* = 7.5, 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.1, 28.2, 30.6, 38.0, 38.8, 38.9, 41.7, 46.5, 50.3, 52.8, 64.3, 77.3, 154.8, 212.1, 213.4; MS (CI) *m/z* 282 (M^+), 221, 193, 177, 149, 133; HRMS (CI) *m/z* 282.1466 (calcd for $C_{15}H_{22}O_5$: 282.1467).

16-*endo* IR (neat) 2964, 2932, 1742, 1694, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.12 (3H, s), 1.15 (3H, s), 1.30 (3H, t, *J* = 7 Hz), 1.71-1.79 (2H, m), 2.02 (1H, dd, *J* = 3, 6.6 Hz), 2.23 (1H, dd, *J* = 5.6, 6.8 Hz), 2.44-2.60 (5H, m), 2.75 (1H, dd, *J* = 1, 9 Hz), 4.18 (2H, q, *J* = 7 Hz), 4.95 (1H, t, *J* = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 14.1, 27.9, 28.3, 38.6, 38.9, 39.4, 40.2, 41.4, 44.4, 47.3, 57.8, 64.2, 154.5, 211.6, 213.9; MS (CI) *m/z* 282 (M^+), 221, 207, 193, 108, 91, 79; HRMS (CI) *m/z* 282.1466 (calcd for $C_{15}H_{22}O_5$: 282.1467).

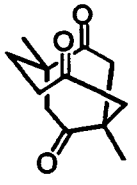


Diol 17. A flame-dried flask under argon at room temperature was charged with samarium (60 mg, 0.40 mmol) and purged with argon for 15 min. Freshly distilled THF (1 mL) and diiodomethane (20 µl, 0.25 mmol) were added with vigorous stirring under argon at room temperature. The mixture was stirred until the dark blue color appeared, then additional THF (1ml) was added, and stirring was continued for 1 h at room temperature. To this blue mixture at 0°C was added the mixture of **16** (28 mg, 0.099 mmol) in THF (0.5 mL). The resulting mixture turned green and was allowed to warm to room temperature for 2 h. The mixture was exposed to air, stirred until it turned yellow, and diluted with ethyl acetate (10 mL). Saturated sodium bicarbonate (5 mL) was added into the mixture and continued to stir for 15 min. The resulting mixture was washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (45 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave 26 mg (94%) of **17** as a colorless oil: IR (neat) 3400 (broad), 2957, 2872, 1742, 1257 cm^{-1}; ^1H

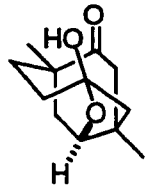
NMR ($CDCl_3$, 300MHz) δ 1.03 (3H, s), 1.10 (3H, s), 1.29-1.37 (5H, m), 1.67-1.86 (6H, m), 2.04-2.11 (2H, m), 2.25 (2H, b), 4.15-4.20 (2H, q, J = 7 Hz), 4.48-4.49 (1H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ 14.3, 22.0, 23.5, 37.2, 37.6, 38.2, 39.7, 41.0, 43.2, 52.8, 63.8, 81.2, 85.4, 86.7, 155.0.



Triol (18). To a solution of **17** (20 mg, 0.07 mmol) in methanol (5 mL) was added potassium carbonate (40 mg, 0.28 mmol) at room temperature, and stirred for 12 h. The mixture was diluted with ethyl acetate (25 mL), and washed with 50% sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ethyl acetate in hexane as eluant, gave 13 mg (86%) of a mixture of **18** as a colorless oil: IR (neat) 3394 (broad), 2951, 2867, 1465, 1286, 1177, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.06 (3H, s), 1.15 (3H, s), 1.22-1.27 (2H, m), 1.54 (1H, dd, J = 2.4, 5.5 Hz), 1.67-1.84 (5H, m), 1.94 (3H, b), 2.03-2.11 (2H, m), 3.50-3.52 (1H, m); ^{13}C NMR ($CDCl_3$, 100MHz) δ 22.5, 23.8, 36.3, 37.7, 38.4, 41.9, 42.9, 43.3, 53.2, 75.6, 85.5, 87.2.



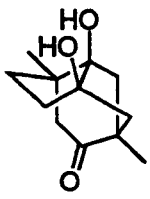
and



Triketone (20) and semiketal (21). To a solution of a mixture of **18** (13 mg, 0.061 mmol) in methylene chloride (1 mL) was added PDC (30 mg, 0.08 mmol) at room temperature. The mixture was stirred for 3 h at room temperature,

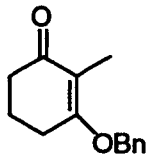
diluted with ether (15 mL) and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ethyl acetate in hexane as eluant, gave 5 mg (42%) of **20** and 4 mg (34%) of **21** as colorless oils: **20** IR (neat) 2967, 2828, 2876, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.18 (3H, s), 1.26 (3H, s), 1.56-1.65 (1H, m), 2.04-2.15 (1H, m), 2.20-2.28 (1H, m), 2.32 (1H, d, *J* = 13 Hz), 2.55-2.69 (2H, m), 2.71 (1H, d, *J* = 17 Hz), 2.80 (1H, d, *J* = 16 Hz), 2.87 (1H, d, *J* = 9.5 Hz), 2.91 (1H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 26, 26.7, 38, 38.4, 44.9, 47.3, 49.2, 49.7, 59.3, 208.3, 211.9, 214.4; MS (CI) *m/z* 209 (M^++1), 191, 181, 163, 151, 139, 121, 109, 97, 83, 69; HRMS (CI) *m/z* 209.1179 (M^++1) (calcd for $C_{12}H_{17}O_3$: 209.1778).

21 IR (neat) 3414 (broad), 2922, 2879, 1764, 1714, 1462, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.11 (3H, s), 1.34 (3H, s), 1.73-1.77 (2H, m), 1.86 (1H, dd, *J* = 2.7, 14.7 Hz), 1.96-1.99 (5H, m), 2.29 (2H, dd, *J* = 15.2, 29.2 Hz), 2.47-2.56 (1H, b), 4.37 (1H, t, *J* = 2.7 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 26.6, 31.0, 36.3, 39.5, 42.3, 43.8, 45, 51, 56.5, 82.4, 106.9, 217.6; MS (CI) *m/z* 211 (M^++1), 193, 175, 165, 151, 133, 89; HRMS (CI) *m/z* 211.1330 (M^++1) (calcd for $C_{12}H_{19}O_3$: 211.1334).



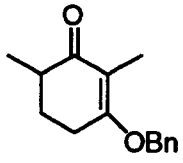
Keto Diol (22). To a solution of oxalyl chloride (5 μl, 0.0566 mmol) in methylene chloride (0.5 mL) under argon at -78°C was added dimethyl sulfoxide (8 μl, 0.113 mmol). The mixture was stirred for 5 min at -78°C. A solution of **18** (10 mg, 0.047 mmol) in methylene chloride (0.5 mL) and dimethyl sulfoxide (0.5 mL) was

added and stirring was continued for 1 h at -78°C. Triethylamine (0.035 mL, 0.25 mmol) was added at -78°C. The resulting mixture was stirred for 1 h at -78°C and allowed to warm to -30°C for 1 h. The mixture was diluted with ethyl acetate (15 mL) at -78°C and washed with saturated sodium bicarbonate (10 mL). The aqueous layer was extracted three times with ethyl acetate (40 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ethyl acetate in hexane as eluant, gave 9 mg (95%) of **22** as a colorless oil: IR (neat) 3397 (broad), 2942, 2858, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.15 (3H, s), 1.18 (3H, s), 1.33-1.38 (1H, m), 1.62 (1H, d, *J* = 12 Hz), 1.67-1.72 (1H, m), 1.77-1.88 (3H, m), 1.98 (1H, d, *J* = 12 Hz), 2.11 (1H, d, *J* = 12 Hz), 2.17 (1H, d, *J* = 17 Hz), 2.39 (1H, d, *J* = 17 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 19.8, 23.2, 37.8, 38.5, 42.3, 43.9, 49.6, 51.4, 53.4, 85, 85.3, 215.9; MS (CI) *m/z* 211 (M^++1), 193, 175, 165, 151, 88; HRMS (CI) *m/z* 211.1334 (M^++1) (calcd for $C_{12}H_{19}O_3$: 211.1334).

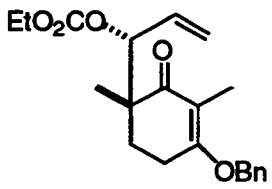


2-methyl-3-Benzoxy-cyclohex-2-enone (23). A stirred solution of 2-methyl-1, 3 -cyclohexadione (10.0 g, 79.3 mmol), benzyl alcohol (8.2 mL, 79.3 mmol), and *p*-toluenesulfonic acid (0.75g) in benzene (60 mL) under argon was heated at reflux for 12 h using a Dean-Stark trap to remove water. The mixture was allowed to cool to room temperature, diluted with ethyl acetate (40 mL) and washed with saturated sodium bicarbonate (40 mL) and brine (30 mL). The aqueous washings were extracted three times with ethyl acetate (150 mL), and the combined extracts were dried (sodium sulfate). The solvent was evaporated under reduced pressure and the crude product was recrystalized from 20% ethyl acetate in hexane at 0°C to yield 16.4 g (96%) of **23** as a pale white solid: IR

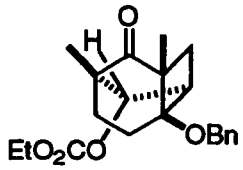
(neat) 2942, 2883, 1614, 1354 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.75 (3H, t, *J* = 1.3 Hz), 1.87-1.92 (2H, m), 2.26-2.31 (2H, m), 2.53 (2H, t, *J* = 4.3 Hz), 5.06 (2H, d, *J* = 1.5 Hz), 7.31-7.37 (5H, m); ^{13}C NMR (CDCl3, 75MHz) δ 7.5, 20.9, 25.5, 36.2, 69.2, 115.6, 127.7 (2C), 128.1, 128.6 (2C), 136.5, 170.9, 198.7; MS (CI) *m/z* 217 (M^++1), 127, 91, 89; HRMS (CI) *m/z* 217.1227 (M^++1) (calcd for $C_{14}H_{17}O_2$: 217.1229).



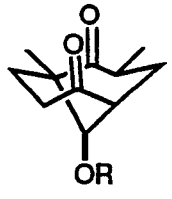
2-methyl-3-Benzoxy-6-methyl-cyclohex-2-enone (24). To a solution of lithium diisopropylamide (2.06 mmol) prepared in situ under argon at -78°C was added a solution of **23** (400 mg, 1.87 mmol) in THF (4 mL) dropwise at -78°C. The mixture was stirred for 30 min at -78°C. Iodomethane (0.23mL, 3.74 mmol) was added in one portion at -78°C and the mixture slowly warmed to room temperature over 12 h. The mixture was diluted with ethyl acetate (30 mL) and washed with saturated sodium bicarbonate (40 mL) and brine (15 mL). The aqueous washings were extracted three times with ethyl acetate (60 mL), and the combined extracts were dried (sodium sulfate). Removal of the solvent was followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, gave 309 mg (72%) of **24** as a pale yellow solid: IR (neat) 2923, 2860, 1614, 1356, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.12 (3H, d, *J* = 6.7 Hz), 1.58-1.70 (1H, m), 1.77 (3H, t, *J* = 1.5 Hz), 2.99-2.06 (1H, m), 2.21-2.29 (1H, m), 2.52-2.62 (2H, m), 5.09 (2H, d, *J* = 2 Hz), 7.31-7.40 (5H, m); ^{13}C NMR (CDCl3, 75MHz) δ 7.8, 15.5, 24.7, 28.8, 39.4, 69, 115, 126.6 (2C), 128, 128.6 (2C), 136.6, 169.7, 201.1; MS (CI) *m/z* 231 (M^++1), 179, 139, 128, 106, 90, 78; HRMS (CI) *m/z* 231.1384 (M^++1) (calcd for $C_{15}H_{19}O_2$: 231.1385).



Ethyl carbonate (25). To a solution of lithium diisopropylamide (1.9 mmol) prepared in situ under argon at -78°C was added a solution of **24** (415 mg, 1.8 mmol) in THF (2 mL). The mixture was stirred for 30 min. The solution of acrolein (0.24 mL, 3.6 mmol) in THF (0.5 mL) predried over calcium sulfate was added. The resulting mixture was stirred for 2 h at -78°C, allowed to warm to -45°C for 1 h. Ethyl chloroformate (1.7 mL, 18 mmol) and triethylamine (0.76 mL, 5.4 mmol) were added successively at -45°C. The resulting mixture slowly warmed to room temperature over 12 h. The mixture was diluted with ethyl acetate (35 mL) and washed with saturated sodium bicarbonate (25 mL). The aqueous layer was extracted three times with ethyl acetate (80 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, produced 497 mg (77%) of **25** as a yellow oil: IR (neat) 3032, 2982, 2933, 2872, 1739, 1612, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.14 (3H, s), 1.30 (3H, t, *J* = 7 Hz), 1.75 (3H, m), 1.77-1.83 (1H, m), 1.97-2.03 (1H, m), 2.52-2.67 (2H, m), 4.18 (2H, q, J = 7 Hz), 5.11 (2H, d, J = 5 Hz), 5.18-5.25 (2H, m), 5.55 (1H, d, J = 5.7 Hz), 5.76-5.85 (1H, m), 7.32-7.40 (5H, m); ^{13}C NMR (CDCl3, 100MHz) δ 7.9, 15.6, 22.2, 26.9, 32.2, 46.4, 64, 69.2, 81.8, 114.6, 117.8, 126.7 (2C), 128.2, 128.7 (2C), 133.1, 136.5, 154.6, 169, 199.9; MS (CI) *m/z* 359 (M^++1), 269, 174, 128, 91; HRMS (CI) *m/z* 359.1857 (M^++1) (calcd for $C_{21}H_{27}O_5$: 359.1858).

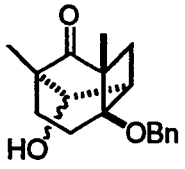


Photolysis of 25 (26). A degassed solution of **25** (130 mg, 0.36 mmol) in dry methanol (60 mL) was irradiated under argon for 1 h 15 min in icebath. Removal of the solvent followed by chromatography of the residue on silica gel, using 25% ethyl acetate in hexane containing 0.5% triethylamine as eluant, gave 121 mg (92%) of **26** as a colorless oil: IR (neat) 2971, 2934, 2861, 1746, 1927, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.17(3H, s), 1.18 (3H, s), 1.33-1.38 (4H, m), 1.48 (1H, d, *J* = 10 Hz), 1.57-1.60 (1H, m), 2.19-2.23 (2H, m), 2.58-2.64 (1H, m), 2.73 (1H, d, *J* = 7.4 Hz), 4.25 (2H, t, *J* = 7 Hz), 4.54 (2H, d, *J* = 3 Hz), 4.81 (1H, s), 7.28-7.35 (5H, m); ^{13}C NMR (CDCl3, 75MHz) δ 10.8, 14.2, 17.3, 21.7, 27.9, 31.9, 40, 47.9, 58, 64.2, 65.6, 81.4, 83.6, 126.8 (2C), 127.3, 128.43 (2C), 138.7, 154.8, 211.1; MS (CI) *m/z* 359 (M^++1), 269, 251, 241, 223, 211, 207, 179, 161, 146, 132, 118, 91; HRMS (CI) *m/z* 359.1860 (M^++1) (calcd for $C_{21}H_{27}O_5$: 359.1858).



Hydrolysis of 26 (27). A solution of **26** (50 mg) in 1N HCl (0.4 mL) and methanol (4 mL) was stirred for 12 h at room temperature. The mixture was diluted with ethyl acetate (25 mL), washed with saturated sodium bicarbonate (15 mL). The aqueous layer was extracted three times with ethyl acetate (35 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, gave **27** (100%) as a colorless oil: IR (neat) 2928,

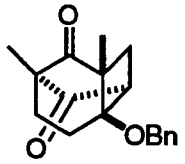
2861, 1752, 1715, 1456, 1253, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.09 (3H, d, *J* = 6 Hz), 1.17 (4H, m), 1.30 (3H, t, *J* = 7 Hz), 2.02-2.22 (4H, m), 2.52-2.75 (2H, m), 3.11-3.16 (1H, m), 4.20 (2H, q, *J* = 7 Hz), 5.35 (1H, d, *J* = 4 Hz); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.8, 14.1, 20.8, 27.9, 30.7, 34.4, 38.2, 47.4, 48.8, 64.6, 78.9, 154.4, 210, 214.8; MS (CI) *m/z* 269 (M^++1), 207, 193, 179, 99; HRMS (CI) *m/z* 269.1388 (M^++1) (calcd for $C_{14}H_{21}O_5$: 269.1389).



Alcohol 28. To a solution of **26** (830 mg, 2.13 mmol) in methanol (25 mL) was added potassium carbonate (500 mg, 5.10 mmol) at room temperature, and stirred for 12 h. The mixture was diluted with ethyl acetate (50mL), and washed with 50% sodium bicarbonate (40 mL). The aqueous layer was extracted three times with ethyl acetate (100 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, gave 577 mg (87%) of a mixture of **28** as a colorless oil: one epimer IR (neat) 3475 (broad), 3036, 2945, 2860, 1706, 1467, 1330, 1068, 748, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.13 (3H, s), 1.16 (3H, m), 1.51-1.68 (3H, m), 1.86 (1H, b), 2.04-2.14 (1H, m), 2.16 (1H, d, *J* = 9.8 Hz), 2.48-2.52 (1H, m), 2.95 (1H, t, *J* = 6.2 Hz), 4.11-4.12 (1H, m), 4.58 (2H, s), 7.26-7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 10.7, 14.1, 15.6, 21.7, 31.2, 32.7, 41.2, 49.0, 58.8, 65.5, 75.5, 84.3, 126.8 (2C), 127.3, 128.3 (2C), 138.8, 214.5.

The other epimer: IR (neat) 3453 (broad), 2975, 2927, 2868, 1710, 1466, 1328, 1105, 1062, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.17 (6H, s), 1.20-1.30 (1H, m), 1.36-1.39 (1H, d, *J* = 10 Hz), 1.50-1.60 (2H, m), 1.92 (1H, b), 2.21 (2H, d, *J* =

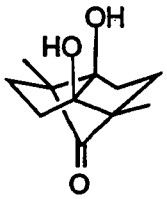
9 Hz), 2.56-2.59 (2H, m), 3.88 (1H, s), 4.57 (2H, s), 7.26-7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 10.9, 17.4, 21.8, 27.0, 32.4, 42.5, 49.3, 58.0, 60.9, 64.5, 84.1, 126.8 (2C), 127.3, 128.3 (2C), 139.1, 213.1.



Ketone 29. To a solution of a mixture of **28** (9 mg, 0.0315 mmol) in methylene chloride (0.5 mL) was added PDC (15 mg, 0.041 mmol) at room temperature. The mixture was stirred for 12 h at room temperature, diluted with ether (15 mL) and washed with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (35 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 35% ethyl acetate in hexane as eluant, gave 7 mg (75%) of **29** a colorless oil: IR (neat) 2996, 2936, 2876, 1738, 1704, 1457, 1330, 1109, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.26 (3H, s), 1.27 (3H, s), 1.70-1.87 (4H, m), 2.12-2.21 (1H, m), 2.70-2.74 (1H, m), 3.35 (1H, d, J = 7Hz), 4.60 (2H, d, J = 8.5 Hz), 7.33-7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 75MHz) δ 10.5, 12.4, 22.9, 30.3, 32.7, 51.2, 58.9, 59.5, 66.1, 88.6, 126.8 (2C), 127.6, 128.4 (2C), 138, 208, 209.

Triketone 30 and 31. A solution of **29** (50 mg) in 1N HCl (0.4 mL) and methanol (4 mL) was stirred for 12 h at room temperature. The mixture was diluted with ethyl acetate (15 mL), washed with 50% sodium bicarbonate (15 mL). The

aqueous layer was extracted three times with ethyl acetate (25 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 30% ethyl acetate in hexane as eluant, gave 21 mg of **30** (61%) as a white solid. **31** was recrystalized from **30** by hexane. Compound **30** IR (neat) 2988, 2937, 2870, 1694, 1442, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.31 (6H, s), 1.69-1.77 (1H, m), 2.07-2.16 (3H, m), 2.56-2.61 (3H, m), 3.60 (1H, s); ^{13}C NMR ($CDCl_3$, 75MHz) δ 16.8 (2C), 30.8 (2C), 37.6 (2C), 62.4 (2C), 205.5, 208.5 (2C); MS (CI) *m/z* 195 (M^++1), 167, 152; HRMS (CI) *m/z* 195.1022 (M^++1) (calcd for $C_{11}H_{15}O_3$: 195.1021). Compund **31** ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.6, 28.6, 288.8, 29.7, 41.1, 41.5, 51.5, 63.3, 210.0, 211.0, 211.5.



Keto Diol 32. A flame-dried flask under argon at room temperature was charged with samarium (288 mg, 1.92 mmol) and purged with argon for 15 min. Freshly distilled THF (3 mL) and diiodomethane (96 μl, 1.20 mmol) were added with vigorous stirring under argon at room temperature. The mixture was stirred until the dark blue color appeared, then additional THF (6 mL) was added, and stirring was continued for 1 h at room temperature. To this blue mixture at 0°C was added **30** (91 mg, 0.467 mmol) in THF (2.5 mL). The resulting mixture turned green and was allowed to warm to room temperature for 2 h. The mixture was exposed to air, stirred until it turned yellow, and diluted with ethyl acetate (10 mL). Saturated sodium bicarbonate (4 mL) was added into the mixture and continued to stir for 15 min. The resulting mixture was washed with saturated sodium bicarbonate (25 mL). The aqueous layer was extracted three times with

ethyl acetate (50 mL), and the combined organic extracts were dried (sodium sulfate). Removal of the solvent followed by chromatography of the residue on silica gel, using 60% ethyl acetate in hexane as eluant, gave 56 mg (61%) of **32** as a white solid: IR (neat) 3407 (broad), 2967, 2939, 2870, 1718, 1301, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.02 (6H, s), 1.23-1.33 (2H, m), 1.63-1.77 (4H, m), 1.93-2.04 (2H, m), 2.07 (2H, b); ^{13}C NMR ($CDCl_3$, 75MHz) δ 8.6 (2C), 25.2 (2C), 29.6 (2C), 59.6 (2C), 88.1 (2C), 213.0.

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