AN ABSTRACT OF THE THESIS OF

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Abstract approved: _____

Carmen Somoza

A new approach towards a total synthesis of paeoniflorigenin is discussed. The approach involves the application of regio- and stereoselective [2+2] photocycloaddition for the preparation of a key intermediate, cyclobutanone **86,** and model studies on diiodosamarium (SmI_2) mediated pinacol coupling of a diketone. Intermolecular [2+2] photocycloaddition of α,β-unsaturated lactam **33** to ketene acetal **34** generated exclusively a head-to-tail and endo cyclobutanone derivative **35.** Singlet oxygen oxidation generated butenolide **76**, which is a precursor for preparation of photosubstrate **78**. Intramolecular [2+2] photocycloaddition using a siloxane as temporary tether, a key step in this synthetic sequence, resulted in tricyclic siloxane intermediate **79**. A stepwise oxidative cleavage of O-Si and C-Si bonds in **79** according to Tamao's procedure afforded cyclobutanol **85**. Swern oxidation of **85** resulted in highly oxygenated cyclobutanone **86**. Overall, a total of eleven steps from the commercial available 3-furaldehyde allowed us to prepare this highly functionalized intermediate **86**. Diiodosamarium (SmI_2) mediated pinacol coupling of diketone **92** formed a diastereomeric mixture of vicinal bis-tertiary diols **93a** and **93b**.

Synthetic Studies Toward a Total Synthesis of Paeoniflorigenin

by

Zhenqiu Hong

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APPROVED:

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Major Professor, representing Chemistry

Redacted for Privacy

Chair of Department of Chemistry

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Zhenqiu Hong, Author

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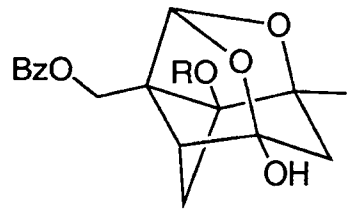
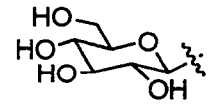
Synthetic Studies Toward a Total Synthesis of Paeoniflorigenin

INTRODUCTION

1. Background

Paeoniflorin **1**, the β-glucoside of paeoniflorigenin **2**, was first isolated from the roots of the Chinese paeony (*Paeonia albiflora Pallas*) by Shibata and coworkers[1] in 1963. Several herbal preparations containing *Paeonia albiflora Pallas* have been used widely in oriental medicine for the treatment of a variety of painful afflictions.



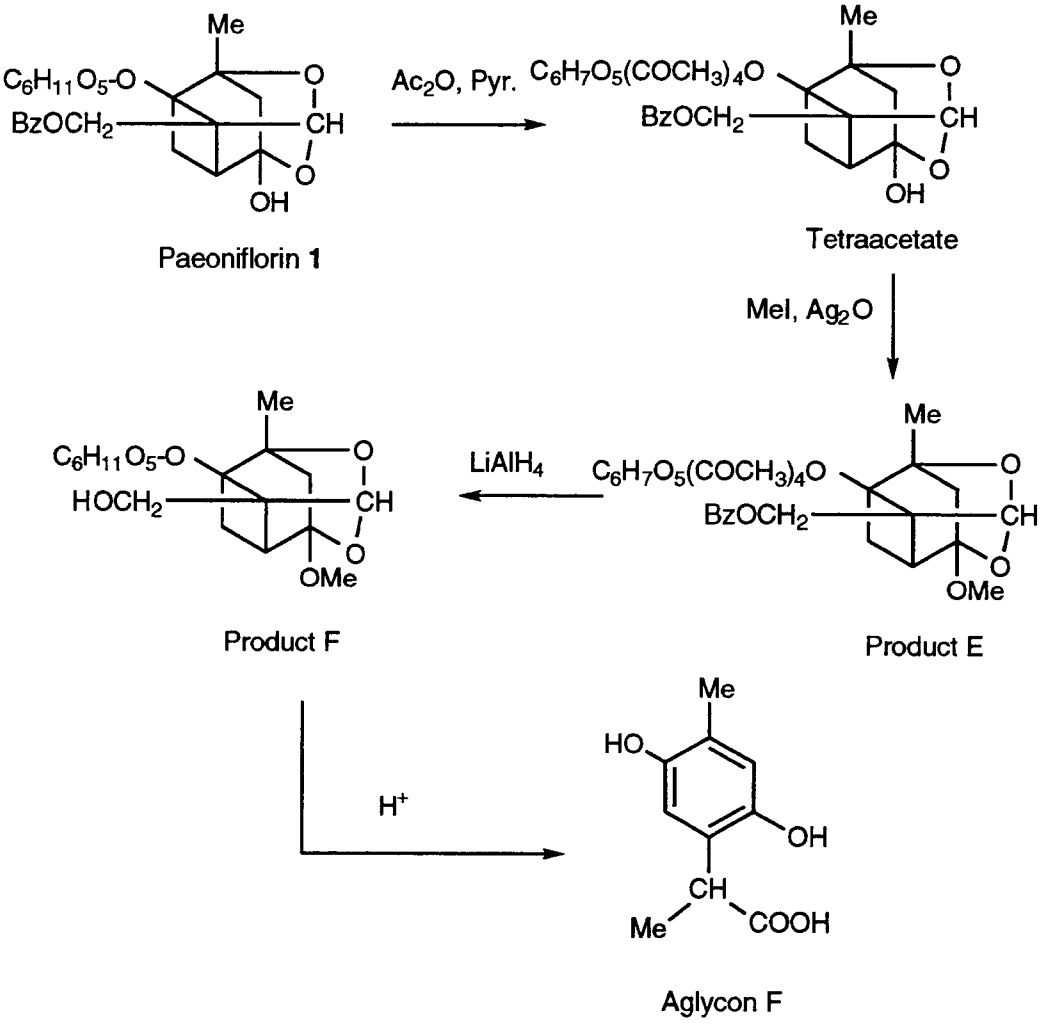
Paeoniflorin 1: R = 

Paeoniflorigenin 2: R = H

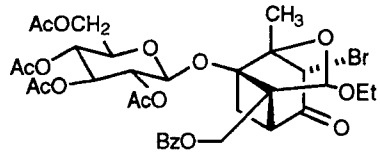
Some interesting biological activities such as antiinflamatory, anticoagulant and sedative have prompted many studies on the pharmacologically active components of those extracts.[2] Among them, paeoniflorin is known to be the main constituent of the paeony root, 2-3% of dry weight, and mostly responsible for its biological activity. Recent studies have

also indicated that paeoniflorin **1** has therapeutic potential in Alzheimer's disease.[3]

Both paeoniflorin and paeoniflorigenin are novel and complex monoterpenoid compounds. The structure and relative stereochemistry of paeoniflorigenin were established by spectroscopic methods and chemical degradation. A series of reactions and spectroscopic analysis of the resulting degradation products led Watanabe and coworkers[4] to establish the structure of paeoniflorin as **1**. Some of those transformations are shown below:



Acetylation of paeoniflorin resulted in tetraacetylation of the D-glucosyl group. Upon treatment with methyl iodide (MeI), an acetal (product E) was formed. Reduction with lithium aluminum hydride furnished a key compound, product F, which retains all ten carbon atoms corresponding to the aglycone moiety of paeoniflorin. Acid hydrolysis of product F triggers a complex rearrangement to give an aromatic derivative. Extensive NMR studies of the degradation products allowed the complex structure of paeoniflorin to be established as shown in **1**. Furthermore, an X-ray analysis of bromo derivative **3a** confirmed that structure and established the absolute stereochemistry as depicted in **1**.[5,6]

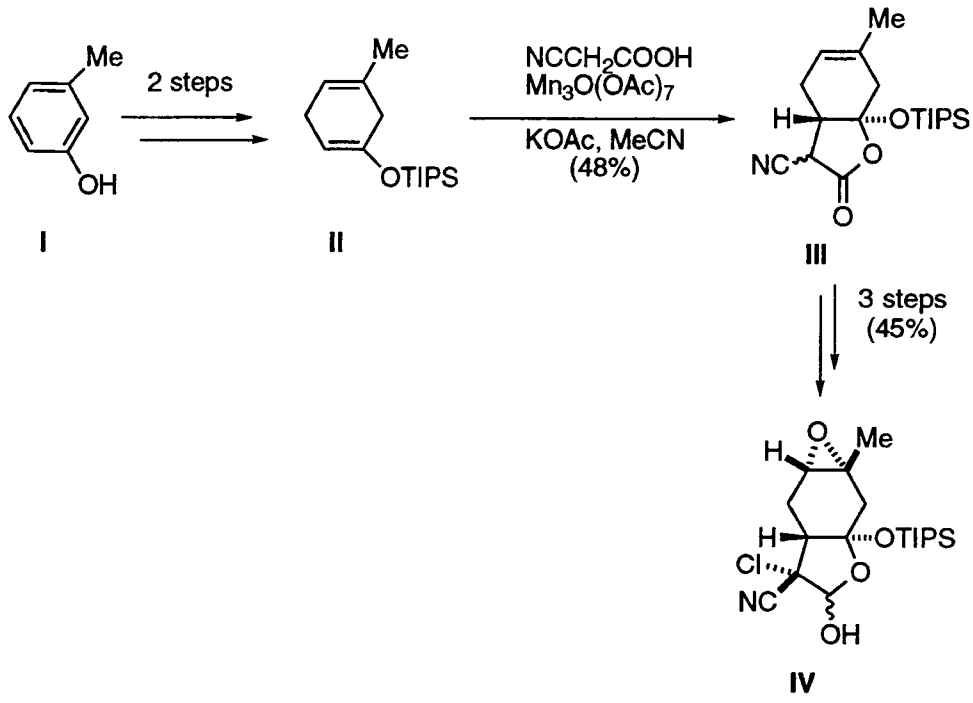


3a

Due to the unique structures of paeoniflorin **1** and paeoniflorigenin **2**, chemical synthesis of these two natural products remains a big challenge to synthetic organic chemists. Both of these molecules have a highly oxygenated cage-like pinane skeleton; they possess four tetrasubstituted carbon centers and a bridged cyclobutane ring fused with two five-membered heterocyclic rings. The first total synthesis of paeoniflorin **1** and paeoniflorigenin **2** was not completed until 1993, almost three decades after their structure determination. Corey and coworkers[7] reported the first total synthesis of the racemic forms of paeoniflorin and paeoniflorigenin. One year later, Hatakeyama, Takano and coworkers[8] reported their total synthesis of the naturally occurring enantiomer of

paeoniflorin. An earlier report of synthetic studies on paeoniflorin was published in 1992 also by Hatakeyama and Takano's group.[9]

Corey's synthesis of (±)-paeoniflorigenin began with *m*-cresol. At a very early stage, all ten carbons of the terpenoid moiety of paeoniflorigenin were incorporated by a Mn (III)-promoted oxidative annulation of the triisopropylsilyl (TIPS) ether of dihydro-*m*-cresol with cyanoacetic acid (**Scheme 1**).

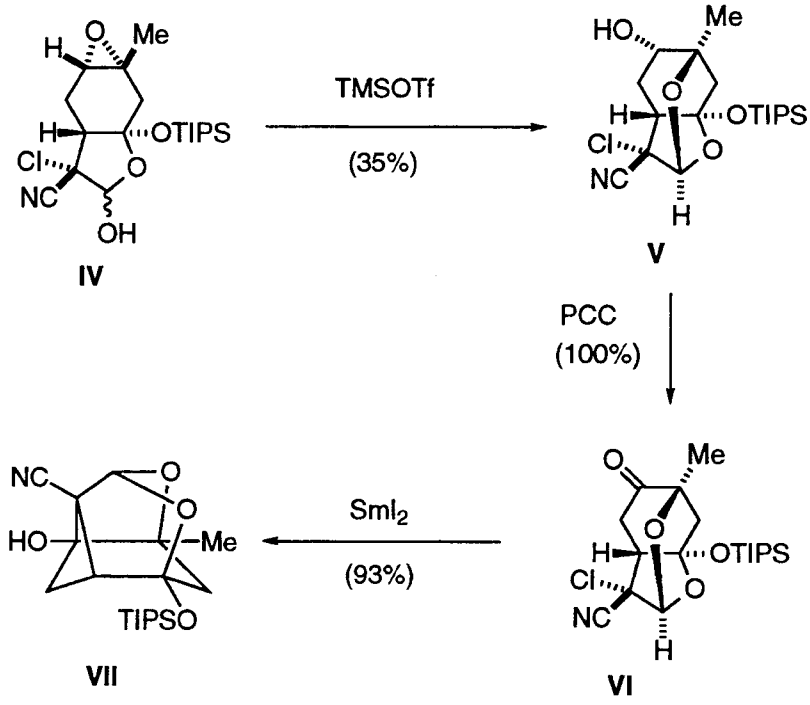


Scheme 1

Stereospecific chlorination of **III** was followed by epoxidation of the double bond and reduction of the lactone to afford a mixture of lactols **IV**.

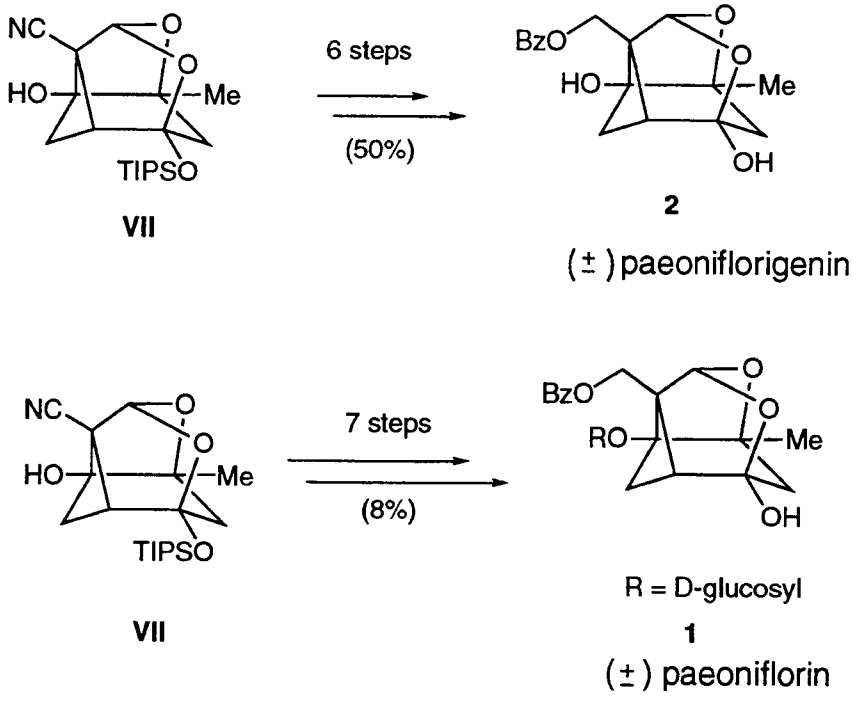
Nucleophilic cyclization of one of the epimers of lactol **IV** in the presence of trimethylsilyl triflate at low temperature furnished the hydroxyl tricyclic ether **V** (**Scheme 2**). After oxidation of the secondary hydroxyl group with pyridinium

chlorochromate (PCC), a SmI_2-induced cyclization of the tricyclic ketone was successfully carried out to give the core structure of paeoniflorigenin. The SmI_2-induced cyclization is believed to occur through an electron transfer to generate a nitrile stabilized radical. Compound **VII** turned out to be base sensitive, undergoing rapid retro aldol cleavage of the strained cyclobutane ring.

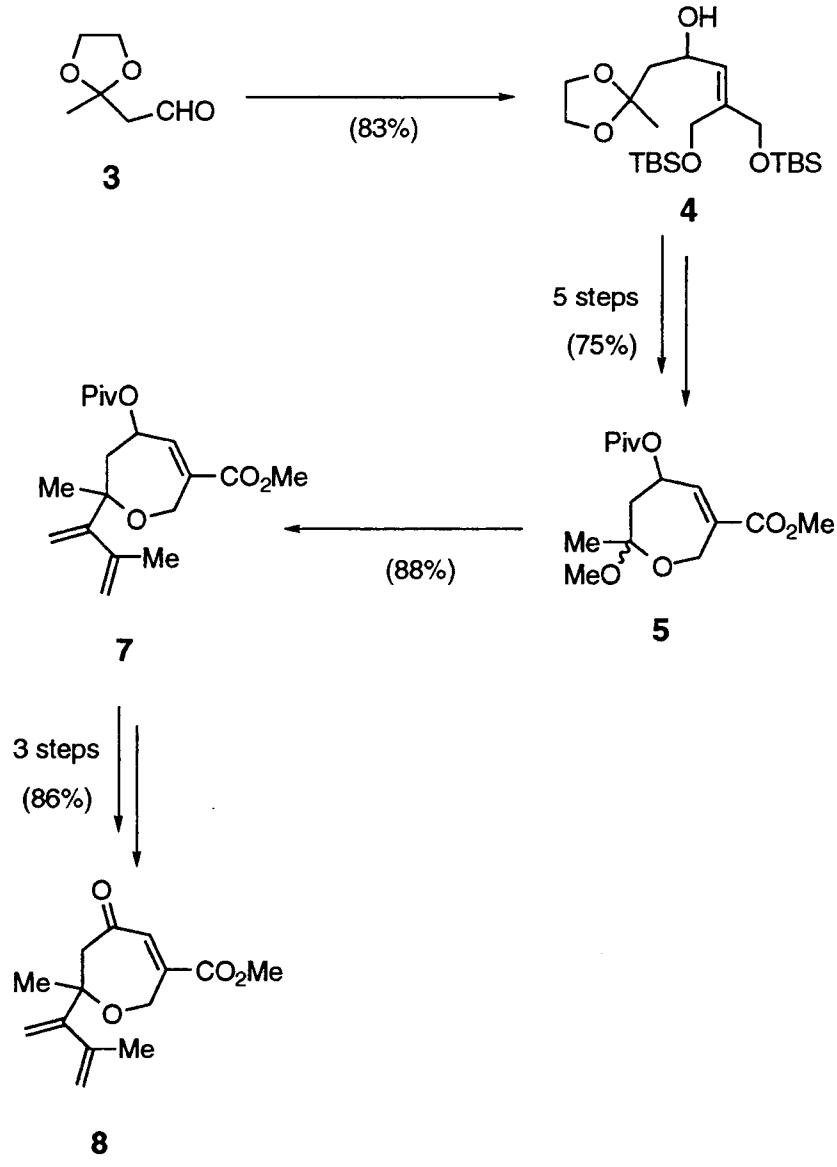


Scheme 2

The last six steps to complete the synthesis of paeoniflorigenin **2** involved: 1) protection of the tertiary hydroxyl group; 2) transformation of the cyano group to hydroxymethyl group; 3) desilylation of the TIPS ether. Another seven steps from **VII** were required to complete the synthesis of paeoniflorin **1**.

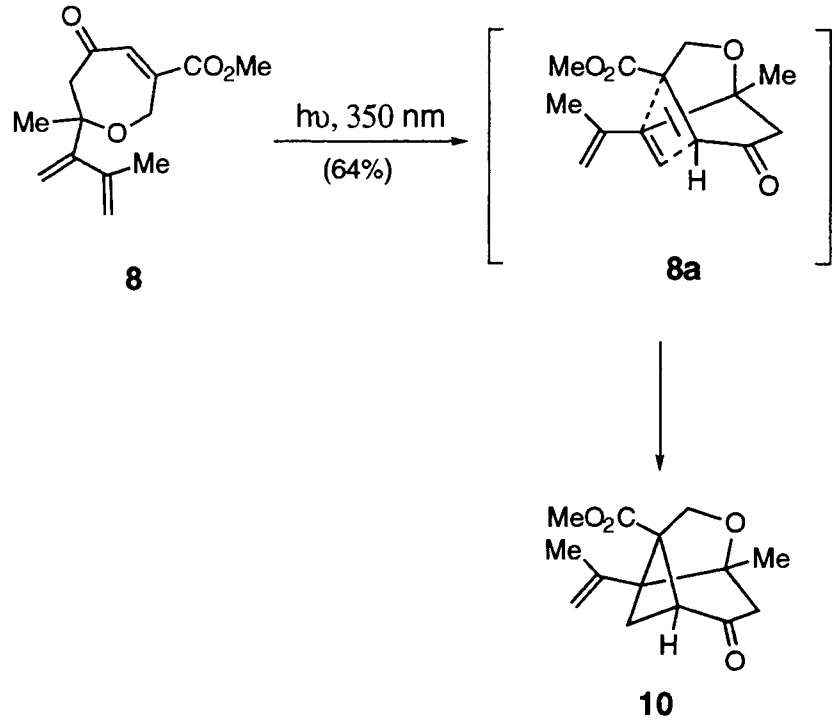


Hatakeyama and Takano's synthesis of (-)-paeoniflorin took advantage of a regioselective intramolecular [2+2] photocycloaddition. From aldehyde **3**, alkenyllithium addition yielded alcohol **4** (**Scheme 3**). Upon sequential pivaloylation, acidic methanolysis, oxidation, and esterification, alcohol **4** was converted to ester **5**. Addition of an allenylmethyl-trimethyl silane to **5** in the presence of a catalytic amount of trimethylsilyl triflate proceeded smoothly to give a diastereomeric mixture of trienes **7**. Photosubstrate enone **8** was obtained by hydrolysis followed by re-esterification and Swern oxidation.



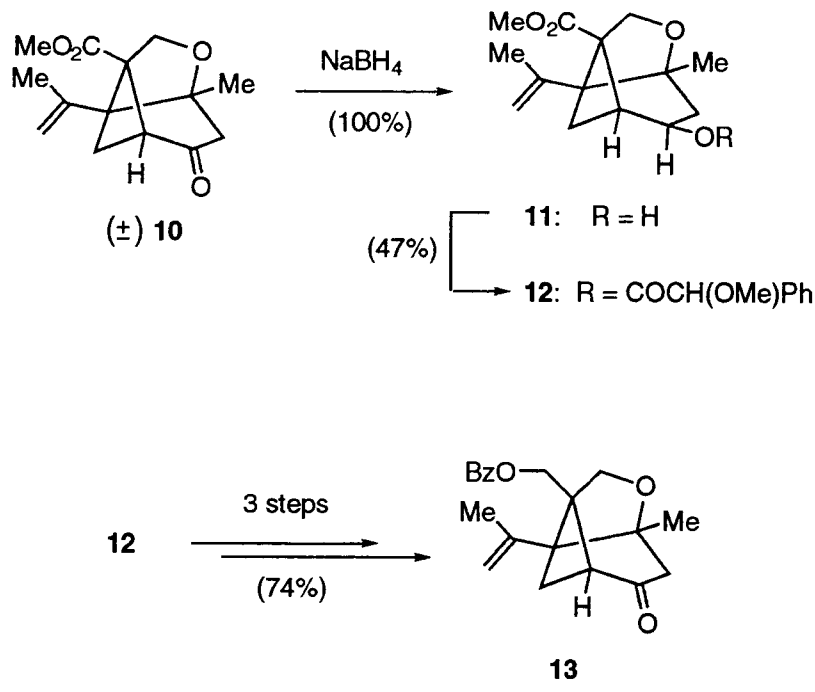
Scheme 3

Hatakeyama and Takano's strategy to construct the oxatricyclo [4.3.0.$0^{3,9}$] nonane **10** relies on the intramolecular [2+2] photocycloaddition of dienyl enone **8** (**Scheme 4**). This reaction was shown to take place with complete regioselectivity to yield tricyclic compound **10**.



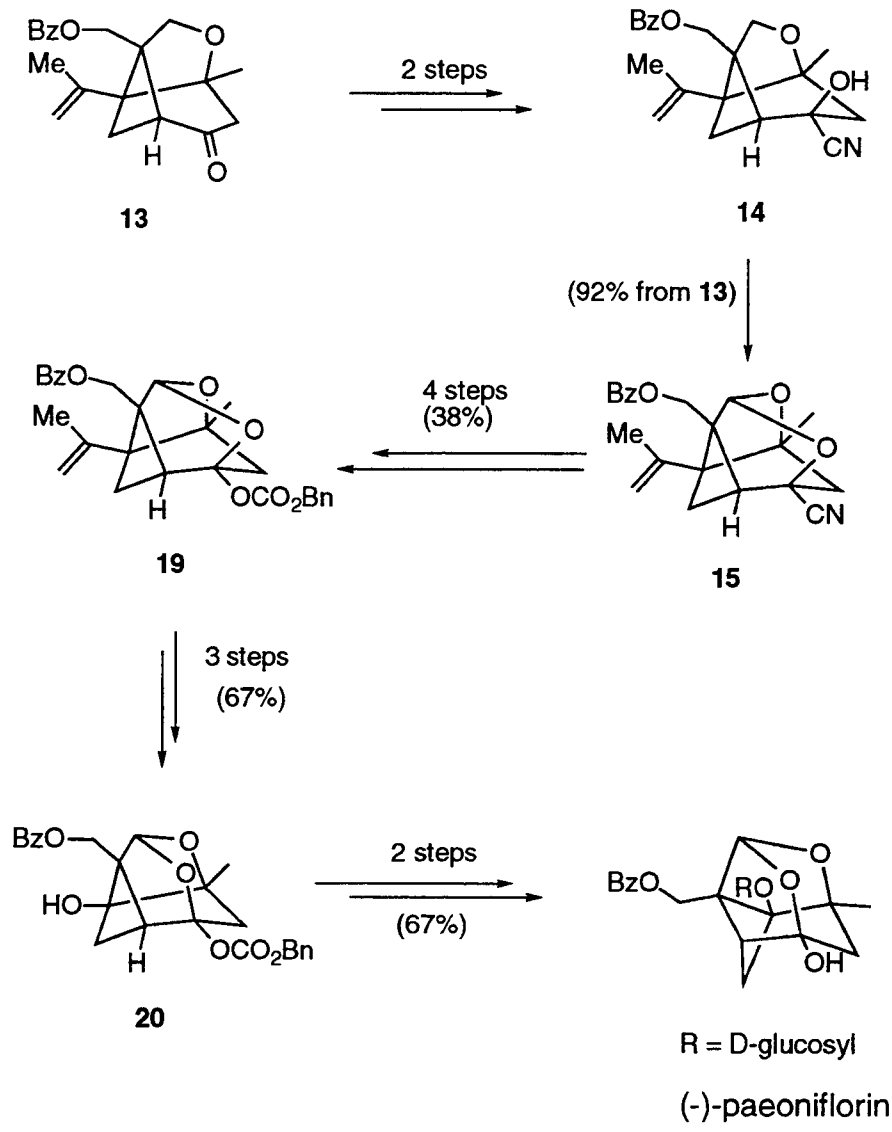
Scheme 4

At this stage, racemic compound **10** was resolved (**Scheme 5**). Stereoselective reduction, followed by esterification of the resulting alcohol **11** with (R)-O-methylmandelic acid, yielded diastereomerically pure mandelate **12** after chromatographic separation. The resolved mandelate **12** was then converted into ketone **13** by sequential reduction, selective benzoylation and Swern oxidation.



Scheme 5

The synthesis of (-)-paeoniflorin from **13** required a rather lengthy sequence including two radical reactions, oxidative degradation of the isopropenyl group and final attachment of a D-glucosyl group (**Scheme 6**). Initially, ketone **13** was converted to cyanohydrin **14**. Irradiation of crude **14** with a tungsten lamp in the presence of phenyliodine (III) diacetate and iodine afforded **15**, a product of radical cyclization. After sequential acid hydrolysis, decarboxylative radical oxygenation and protection, intermediate **19** was obtained. Ozonolysis followed by a Baeyer-Villiger rearrangement and hydrolysis afforded tertiary alcohol **20**, the benzyl carbonate derivative of paeoniflorigenin. The synthesis of the glucoside (-)-paeoniflorin was completed by the introduction of the D-glucosyl group and deprotection.

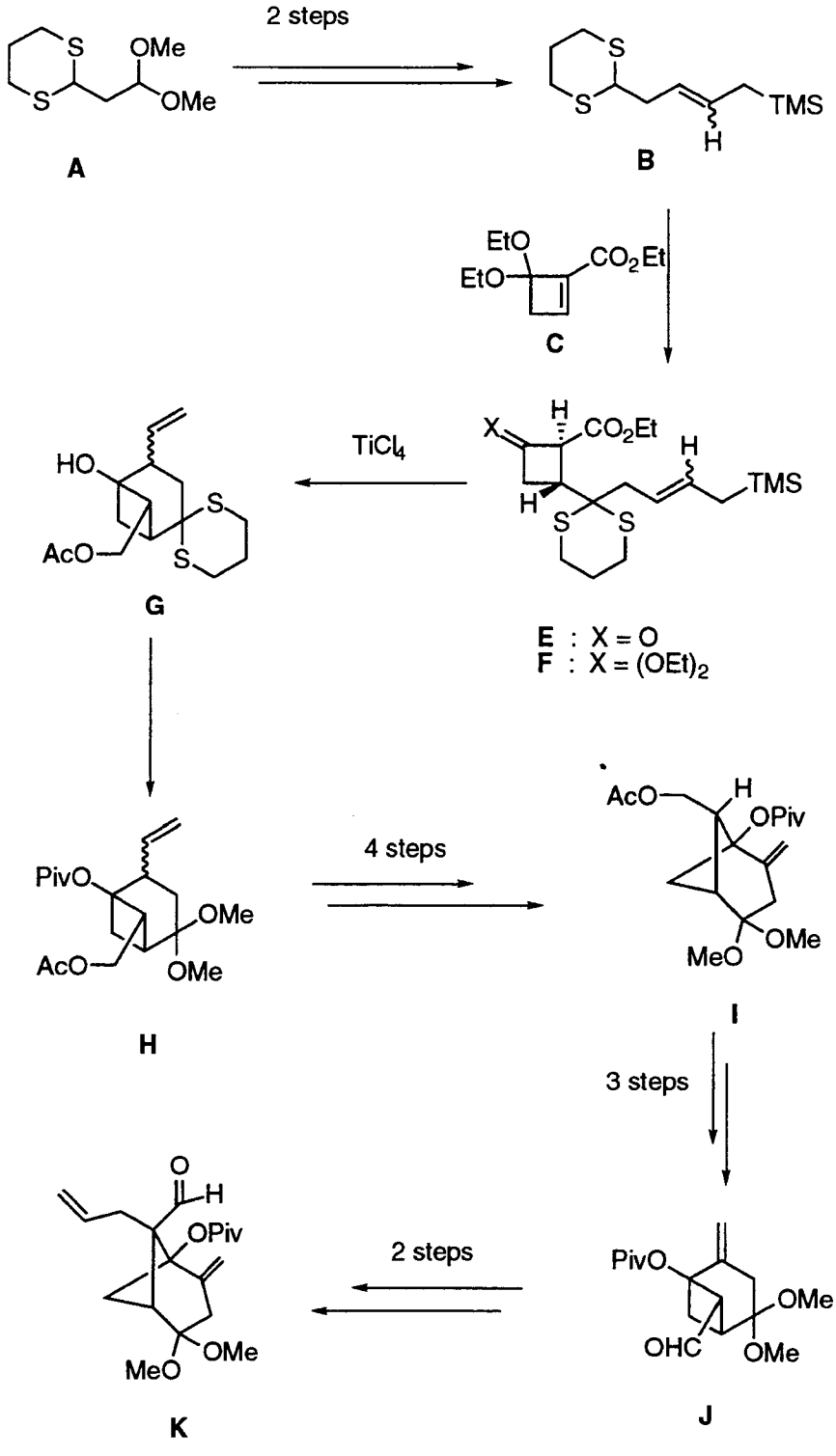


Scheme 6

Comparing these two syntheses, the advantage of Corey's approach is obvious as the synthetic sequence is concise. Total synthesis of these highly oxygenated terpenoids was completed by his group within twenty steps. Hatakeyama and Takano's approach requires 29 steps. This group's strategy

took advantage of the efficiency of a completely regioselective intramolecular [2+2] photocycloaddition to construct the core structure of paeoniflorigenin. Corey's approach is concise enough as to be reasonable in spite of several low yielding steps. It is, however, a racemic synthesis. Hatakeyama and Takano's approach affords the natural enatiomer of paeoniflorin, but requires a resolution midway through the synthetic sequence.

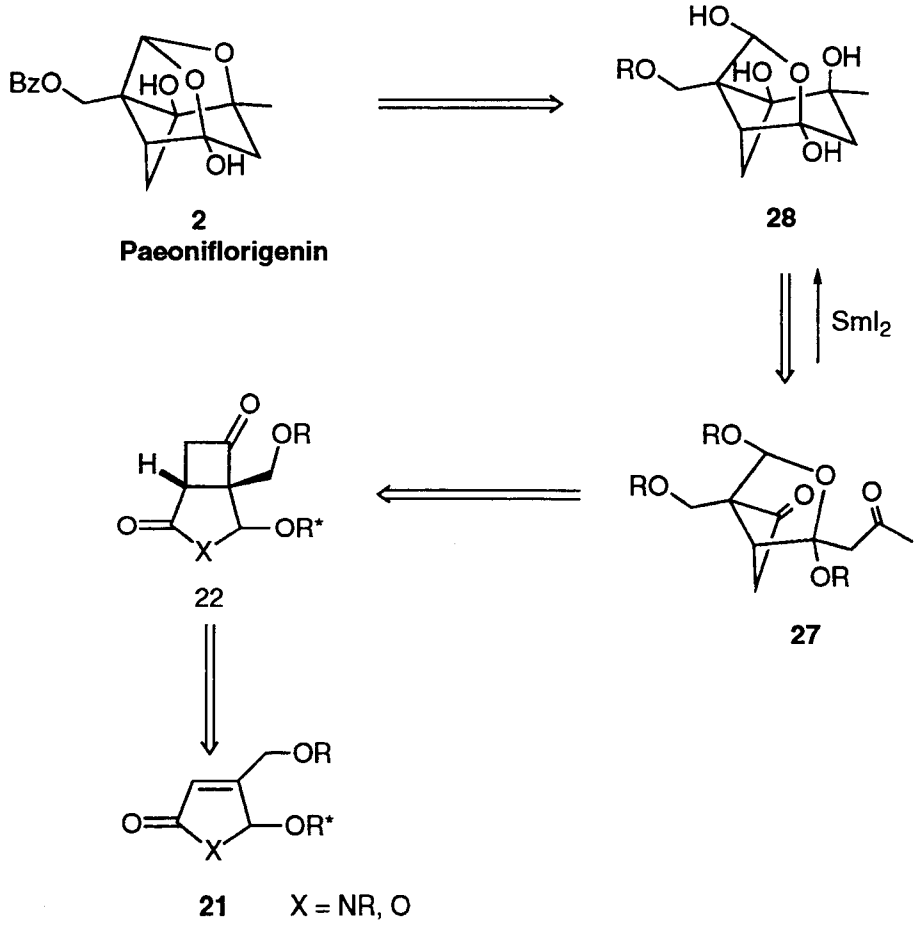
Prior to their reported total synthesis of paeoniflorin, Hatakeyama and Takano's group[9] also reported other synthetic studies toward paeoniflorin. They presented a synthetic route including 17 steps to construct a functionalized pinane skeleton (**Scheme 7**). This approach is quite different from the one discussed in **Scheme 3**, **4** and **5**. The required reagent ω-dithianylmethylallyl silane **B** was prepared in two steps from dithiane **A**. After deprotonation of **B** with *n*-butyllithium, Michael addition of the resulting lithiated dithiane to the α,β-unsaturated ester **C** afforded *trans*-adduct **D**. The crucial intramolecular Hosomi-Sakurai reaction was investigated using substrate **E** and **F**. Upon treatment of **E** and **F** with Ti (VI) chloride, both of the substrates gave 1:1 epimeric mixture of cyclization product **G**. Pivaloylation followed by treatment with N-chlorosuccinimide gave the dimethyl ketal **H**. Conversion of the vinyl group in **H** into the *exo*-methylene group as in compound **I** was done by ozonolysis, reduction, selenylation followed by oxidation-elimination to give **I** as the only product. The aldehyde **J** was obtained by deacetylation followed by reduction of compound **I**. Finally, the target compound **K** was obtained from alkylation of aldehyde **J**.



Scheme 7

2. Our Retrosynthetic Analysis of Paeoniflorigenin

The aim of our synthetic studies on paeoniflorigenin is to explore novel methodologies in order to find efficient methods to construct a highly functionalized compound having many stereocenters. In this context, a regio- and stereoselective photocycloaddition to build a stereo-defined cyclobutanone derivative and an intramolecular reductive coupling of two carbonyl groups to construct a vicinal bis-tertiary diol are of particular interest. Our retrosynthetic plan for a total synthesis of paeoniflorigenin is shown in **Scheme 8**.

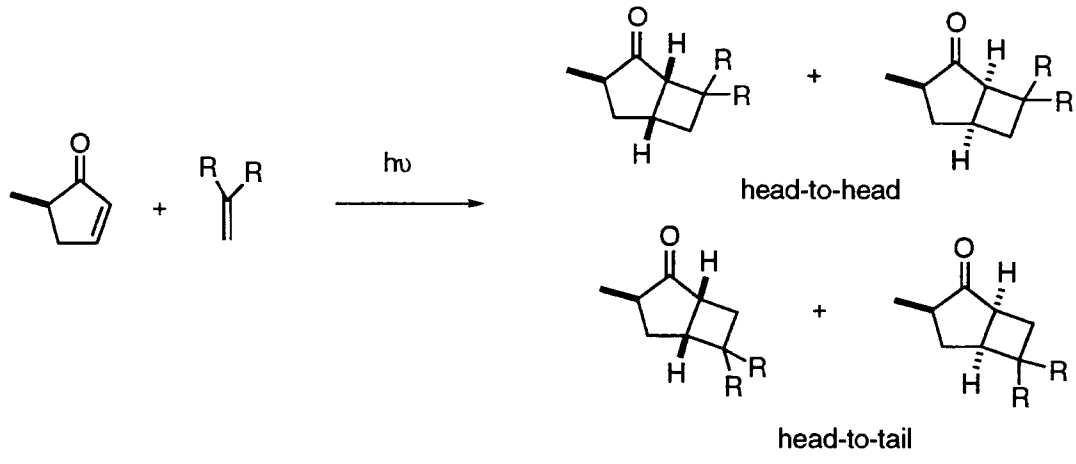


Scheme 8

As shown in **Scheme 8**, the target molecule paeoniflorigenin **2** is expected to derive from acetalization between a hemiacetal and a tertiary hydroxyl group in precursor **28**. These two groups are in close proximity in **28** and will be able to cyclize easily to form an acetal linkage.

Intermediate **28** is expected to be prepared from diketone **27**. The bond between the two vicinal tertiary hydroxyl groups is anticipated to be formed in an intramolecular diiodosamarium (SmI_2) promoted pinacol coupling of two carbonyl groups in **27.** Intermediate ketone **27** is anticipated to derive from cyclobutanone **22** after introduction of an acetonyl group. The *cis*-fused cyclobutanone **22** contains one quaternary stereocenter. The most direct approach to achieve **22** would be a regio- and stereoselective intermolecular [2+2] photocycloaddition between a chiral precursor **21** and a ketene acetal as shown in **Scheme 8**.

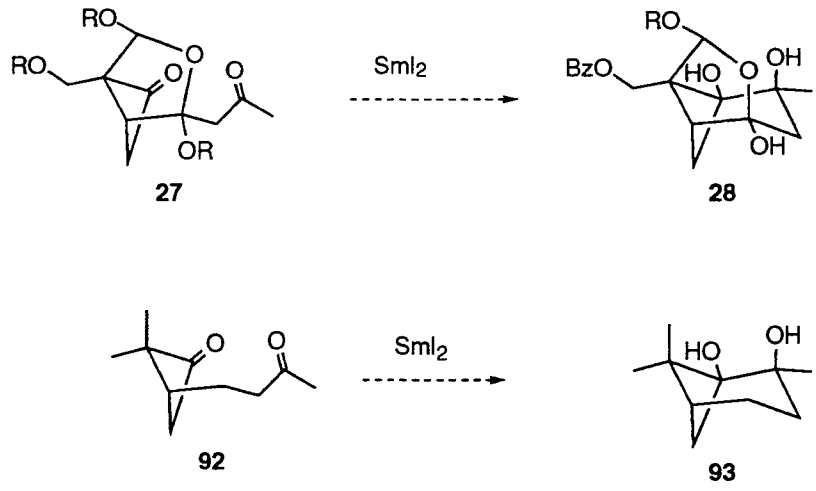
The first key step in our synthetic plan is regio- and stereoselective photocycloaddition of **21** to afford a cyclobutanone intermediate **22**. In general, [2+2] photocycloaddition of cyclic enone or enone-like compounds with olefins can afford up to four *cis*-fused products. Depending on the relative orientation of the olefin and enone, "head-to-head" or "head-to-tail" regioisomers can be formed, each as a mixture of stereoisomers.



In the first key step in the transformation from **21** to **22** in our synthetic plan, it is critical to have a good control of both regio- and stereoselectivity in [2+2] photocycloaddition in order to obtain cyclobutanone derivative **22**. Therefore, regio- and stereochemistry will be one of our focuses in the course of this study.

The second key step in our synthetic plan is the diiodosamarium (SmI_2) mediated intramolecular pinacol coupling of **27** to afford the bicyclo [3.1.1] heptane skeleton of paeoniflorigenin. To investigate the feasibility of this SmI_2 mediated reductive coupling, we will carry out a model study on the intramolecular coupling of a simpler diketone **92** as shown in **Scheme 9**.

This thesis will focus on the studies on both key steps in the synthesis of paeoniflorigenin shown in **Scheme 8.** The first part will discuss the studies on the regio- and stereoselectivity of photocycloaddition of the lactam and butenolide derivatives of **21** with substituted olefins. The second part will address the SmI_2 mediated reductive coupling of model compound **92**.

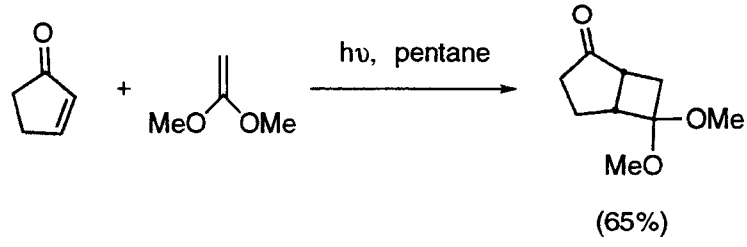


Scheme 9

RESULTS AND DISCUSSION

1. Regio- and Stereoselective [2+2] Photocycloaddition

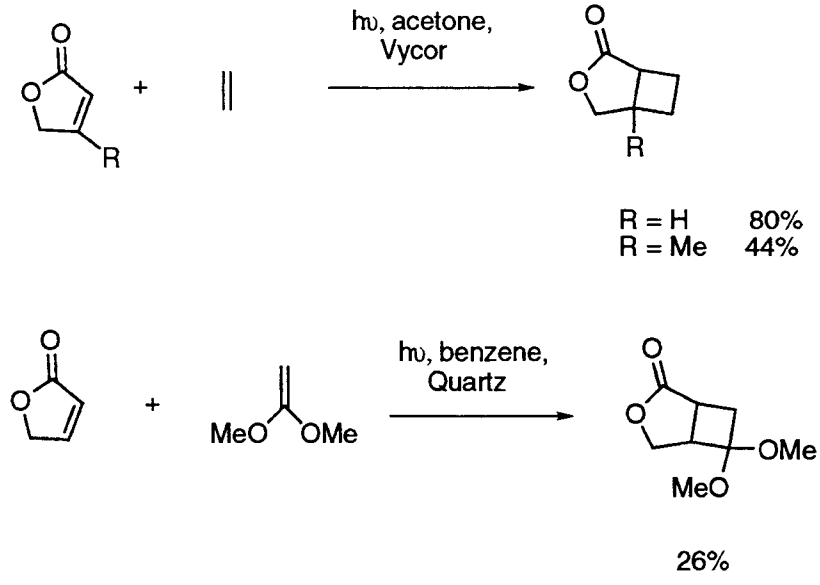
In 1977, Vandewalle and coworkers[10] reported the results of intermolecular photocycloaddition between 2-cyclopentenone and electron-rich alkenes



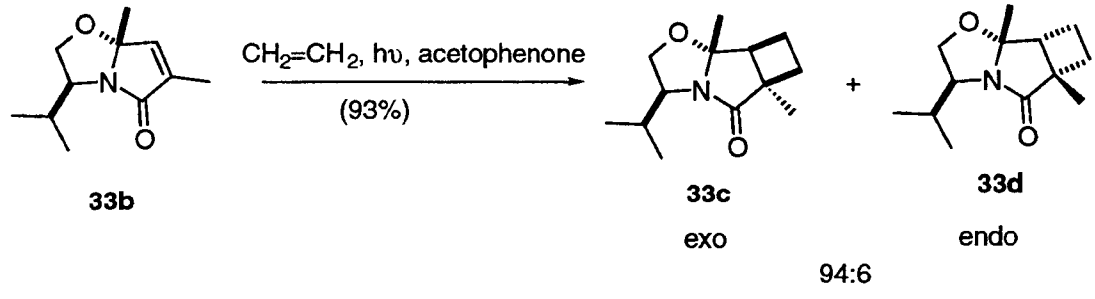
(65%)

The head-to-tail photoproduct was obtained in 65% yield together with less than 1% of its head-to-head regioisomer.

Although cycloalkenones have been extensively employed in [2+2] photocycloadditions, α,β-unsaturated lactones and lactams are far less popular. The λ_{max} corresponding to these chromophores occurs at shorter wavelength and in most cases, their photoreactions are carried out in the presence of appropriate sensitizers. The regiochemical outcome is however similar.[11]



In 1986, Meyers et al[12] reported very good diastereoselectivity in the photocycloaddition of pyrrolone **33b** with the simplest olefin, ethylene (**Scheme 10**).



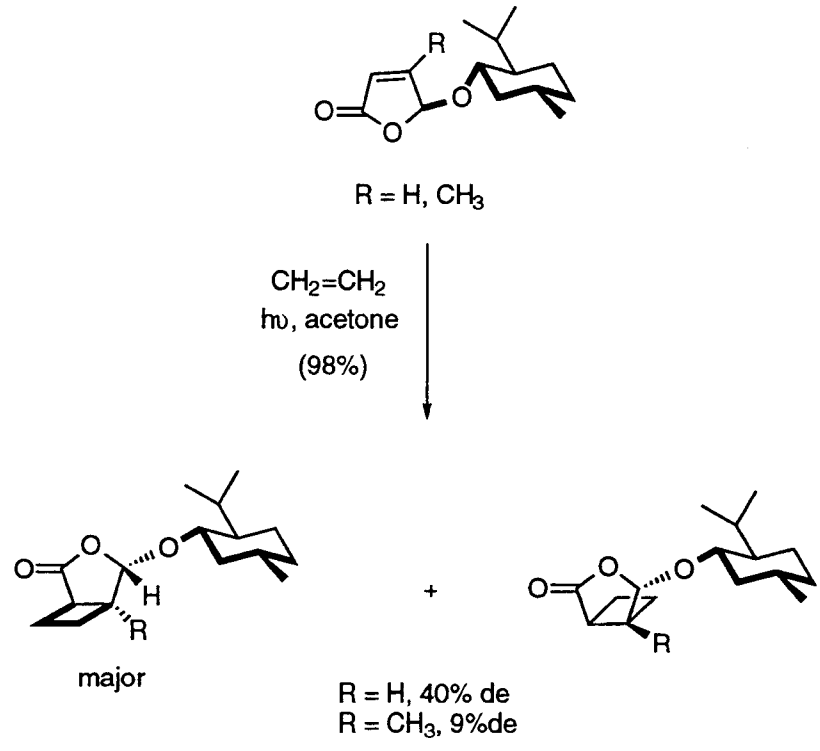
Scheme 10

As already mentioned in the introduction, the establishment of the correct absolute stereochemistry in compound **22** requires the use of a chiral auxiliary in order to control the facial selectivity in the cycloaddition step. The best results

reported so far in the literature concern the use of 2-(5H)-furanones and 2-(5H)-pyrrolones derivatives.

However, no reports on the outcome of this reaction on different lactam derivatives or with substituted alkenes have been published in the literature.

Scharf and coworkers[13,14] have studied the photocycloaddition of furanone derivatives. The diastereoselectivity achieved with the menthol derivative is however moderate at best.

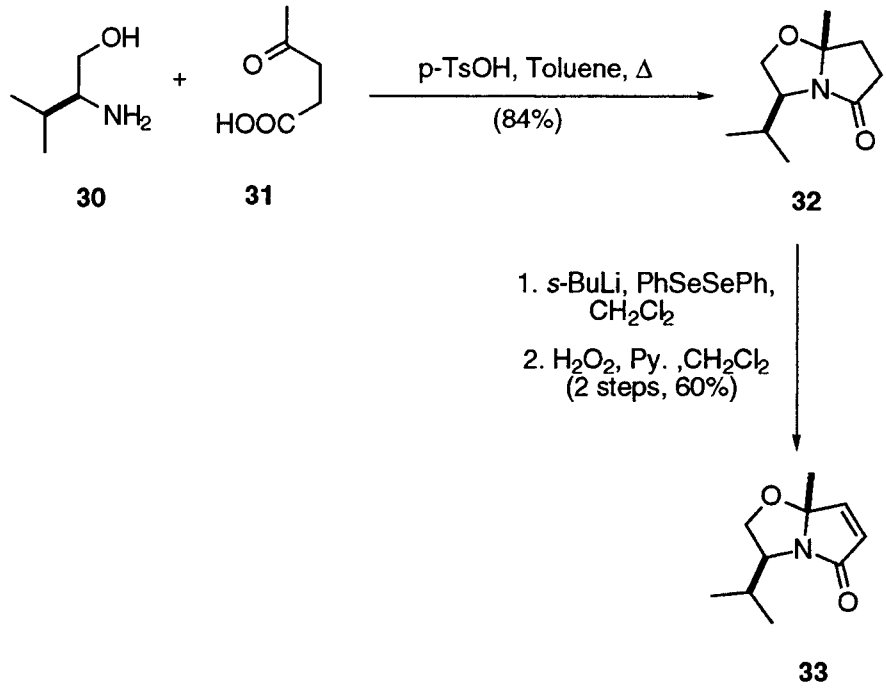


The poor diastereoselectivity obtained in the case of 4-substituted furanones makes this chiral auxiliary less attractive than the valinol derivatives described by Meyers et al.[12]

1.1. Regioselective Intermolecular [2+2] Photocycloaddition of α,β-Unsaturated Lactam

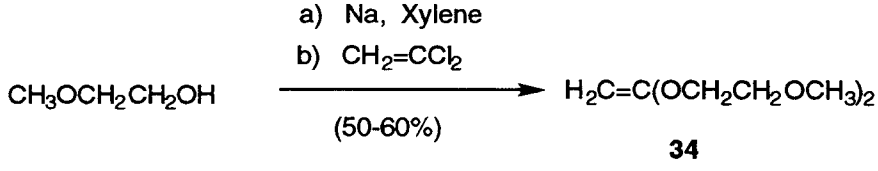
Meyers' studies[12] on asymmetric photocycloaddition of pyrrolone **33b** with ethylene first attracted our attention since good diastereoselectivity was observed (see **Scheme 10**). The chiral auxiliary in **33b** is believed to control the facial selectivity of the photocycloaddition. We would like to take advantage of the known stereochemistry in this photocycloaddition. Therefore, we proposed an intermolecular [2+2] photocycloadditon to obtain a cyclobutanone derivative intermediate **22**, in which the same chiral auxiliary will be used. Since the regiochemistry of the proposed photocycloaddition is still unknown, it will be the first issue to be investigated in this study.

The bicyclic α ,β-unsaturated lactam **33** was prepared from (S)-valinol **30** and levulinic acid **31** according to Meyers' procedure.[12] Azeotropic condensation of **30** and **31** in the presence of a catalytic amount of *p*-toluenesulfonic acid in toluene gave the bicyclic lactam **32**. Addition of a mixture of *s*-butyllithium and diphenyl diselenide followed by the selenyl group oxidative elimination afforded product **33** (**Scheme 11**).



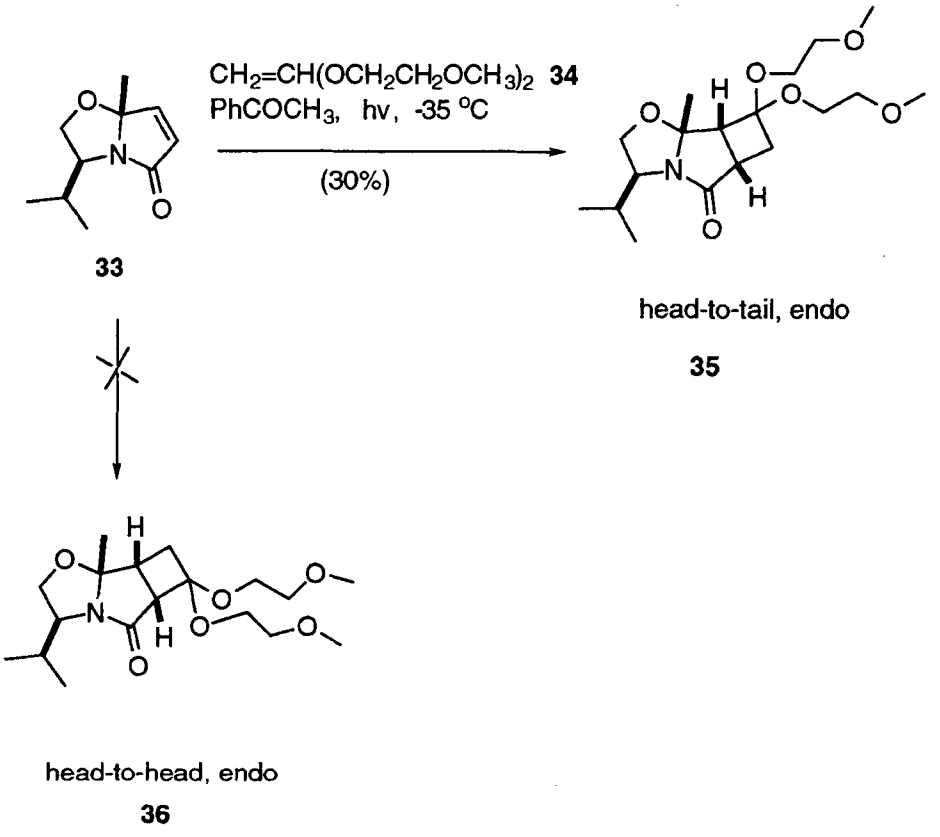
Scheme 11

Ketene bis(2-methoxyethyl) acetal **34** was prepared according to the procedure reported by Kuryla and Hyre[42] as shown below. Pure **34** was obtained by distillation under reduced pressure. It must be stored in a sealed flask which was previously washed with a hot concentrated caustic solution.



With both lactam **33** and ketene acetal **34** in hand, we were ready to try the intermolecular [2+2] photocycloaddition. Irradiation of a solution of **33** in dry

dichloromethane with 10-15 equivalents of ketene bis(2-methoxyethyl) acetal **34** and 10 equivalents of acetophenone as a photosensitizer at -35^{0}C yielded exclusively the head-to-tail photoadduct **35** (**Scheme 12**). The regiochemistry of the addition was determined by COSY and NOE NMR studies, which will be discussed later. The other regioisomer (head-to-head) was not detected.

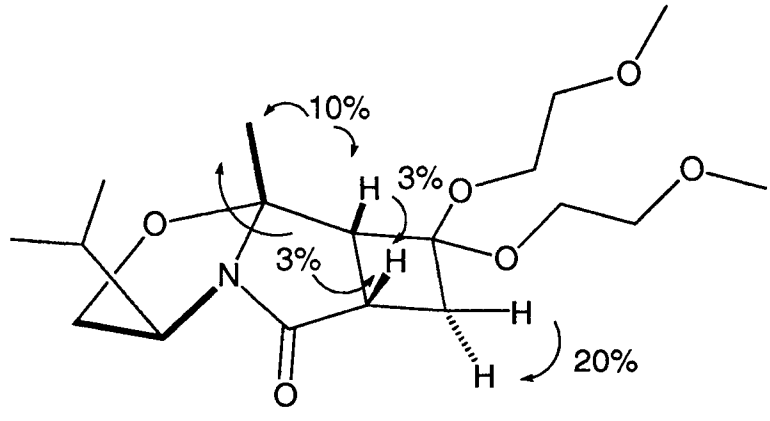


Scheme 12

We have found from our experiments that irradiation of **33** with ketene acetal **34** at temperatures above 0^{0}C only returned substrate **33** together with a large amount of byproducts presumably from polymerization of the ketene

acetal. Low temperature was a crucial factor to ensure [2+2] photocycloaddition to occur.

The regio- and stereochemistry of compound **35** were determined by ^{1}H, ^{13}C, COSY and NOE NMR experiments. The result from NOE studies is shown below (**Fig.1**)

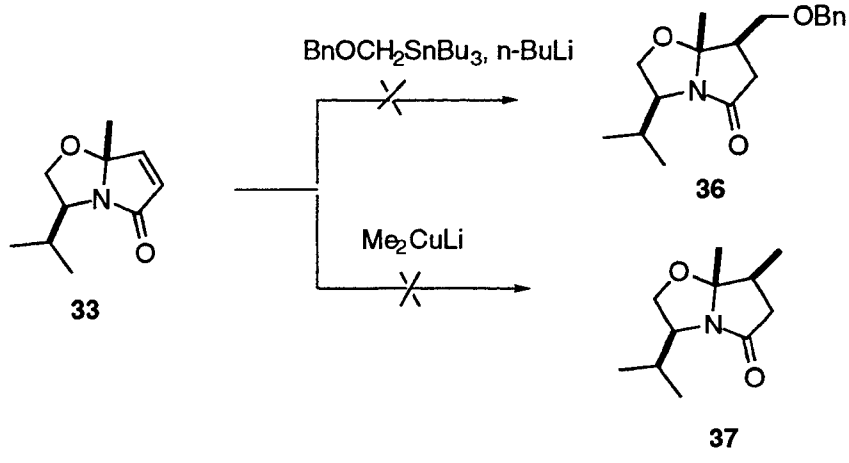


35

Figure 1. NOE studies on stereochemistry of intermolecular [2+2] photoaddition product **35**.

Combined COSY and NOE NMR studies have shown clearly that the regio- and facial selectivity of the [2+2] photocycloaddition favored the head-to-tail and endo addition fashion. Contrary to the stereoselectivity observed by Meyers in **Scheme 10**, photocycloaddition of α,β-unsaturated lactam **33** with ketene acetal **34** favors the endo cycloadduct. The methyl and isopropyl groups in the lactam **33** presumably direct the facial selectivity in the intermolecular [2+2] photocycloaddition of α,β-unsaturated lactam **33** with ketene acetal **34**. The photoadduct **35** is the desired regio- and steroisomer.

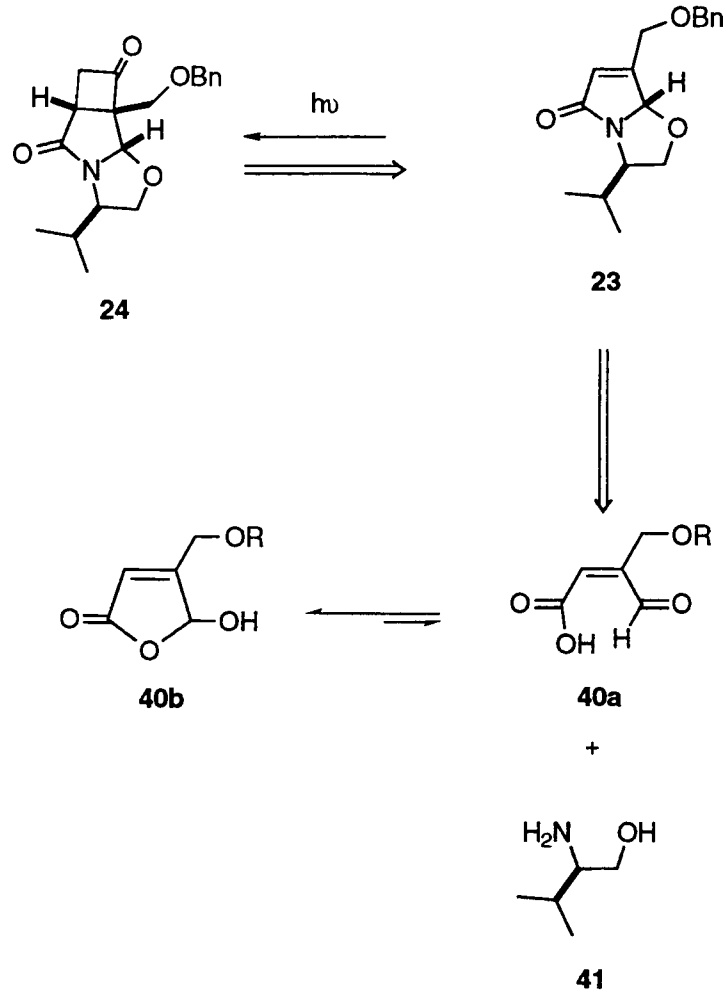
After knowing the regio- and stereoselectivity of intermolecular [2+2] photocycloaddition of α,β-unsaturated lactam **33**, we planed to investigate the regio- and stereoselectivity of photocycloadditon of an analog of **21** with a substituent in the β-position. We intended to prepare the β-substituted analog of **21**, such as either bicyclic compound **36** or **37**, from lactam **33** by use of 1.4-addition (**Scheme 13**). Unfortunately, we did not observe any conjugate addition product when α,β-unsaturated lactam **33** was subjected to benzloxymethyl lithium ($BnOCH_2Li$) reagent[15,16] in the presence of boron trifluoride etherate or chlorotrimethylsilane.[17] Compound **37** was not observed either after addition of dimethyl cuprate in the presence of chlorotrimethylsilane.[18] One explanation could be the hindrance produced by the methyl group in **33** which shielded incoming alkyl anions.



Scheme 13

The failure of the conjugate addition on compound **33** suggests the need for a different approach to photosubstrates of the type **21**. In particular, the

introduction of the chiral auxiliary on aldehyde-acid **40a** becomes more attractive (**Scheme 14**).



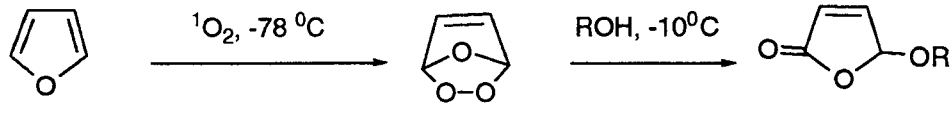
Scheme 14

In analogy to the preparation of **33**, the preparation of compound **23** requires the condensation of (R)-valinol **41** and aldehyde **40a**. Compound **40a** should exist more favorably in the form of five-membered butenolide **40b**. The structure of **40b** is very much similar to the precursor **21** in our retrosynthetic

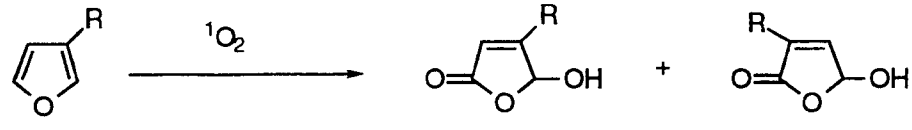
Scheme 8. It only requires the acetalization of the free hemiacetal hydroxyl group in **40b** with a chiral alcohol in order to achieve good stereoselectivity in the photocycloaddition step. It is also similar to the menthyloxyfuranone derivatives studied by Scharf. It became of interest then to study the photocycloaddition of alkoxybutenolides with ketene acetals. The first task then is to find an efficient way to prepare butenolide **21**.

1.2. Intermolecular [2+2] Photocycloaddition of Butenolides

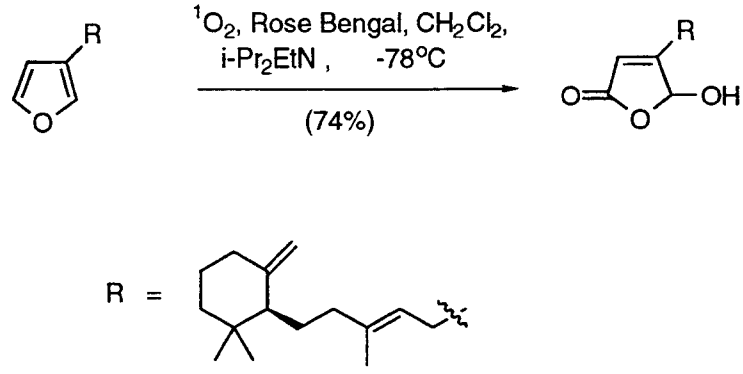
Derivatives of 2-(5H)-furanone are very conveniently prepared through photooxidation of furans.[19,43]



However, under these conditions, 3-substituted furans afford mixtures of regioisomeric butenolides.

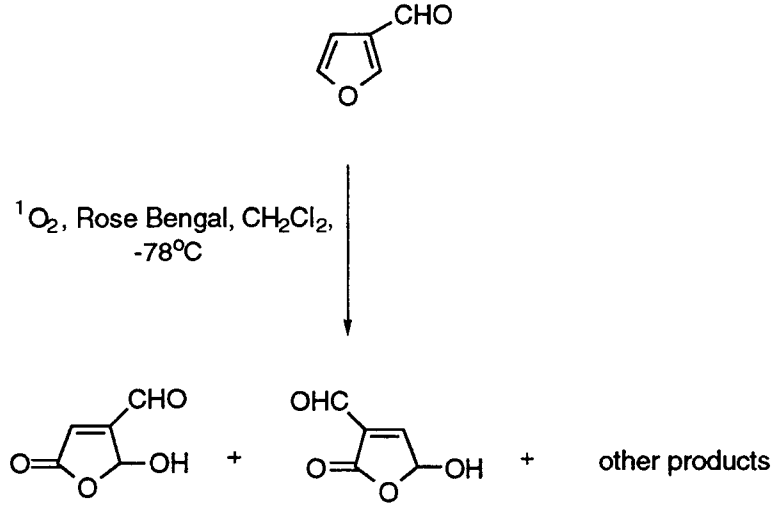


Faulkner et al [20] reported that the addition of a hindered base such as diisopropylethylamine (*i*-Pr$_2$EtN) improves both the yield and regioselectivity of the oxidation.



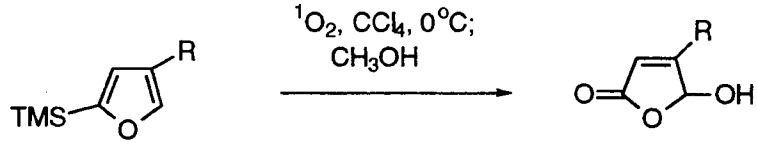
These authors did not detect the formation of the alternative 2-alkyl butenolide regioisomer in any of several related examples.

From our experiments, however, we have found that singlet oxygen oxidation of 3-furaldehyde under the same condition resulted in a mixture of regioisomers and other unidentified byproducts rather than a single regioisomer as shown below (**Scheme 15**). In spite of Faulkner's results, we are not the first to find low regioselectivity in the photooxygenation of furan derivates.[21]

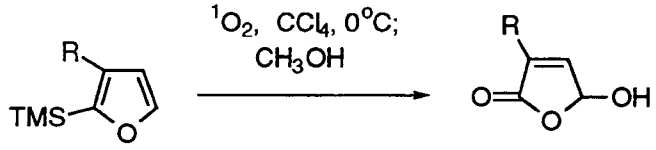


Scheme 15

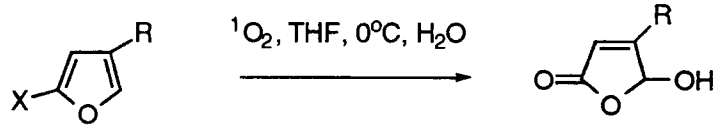
Fortunately, the regioselectivity of this reaction can be controlled through the introduction of a silyl group. Katsumura, Isoe and coworkers[22] reported the photooxidation of a variety of 3-alkylfurans substituted at positions 5 with trimethylsilyl (TMS) group.



The presence of the trimethylsilyl (TMS) group dramatically increases the regioselectivity of the photooxidation. In every case only one regioisomer was observed in yields above 90%.

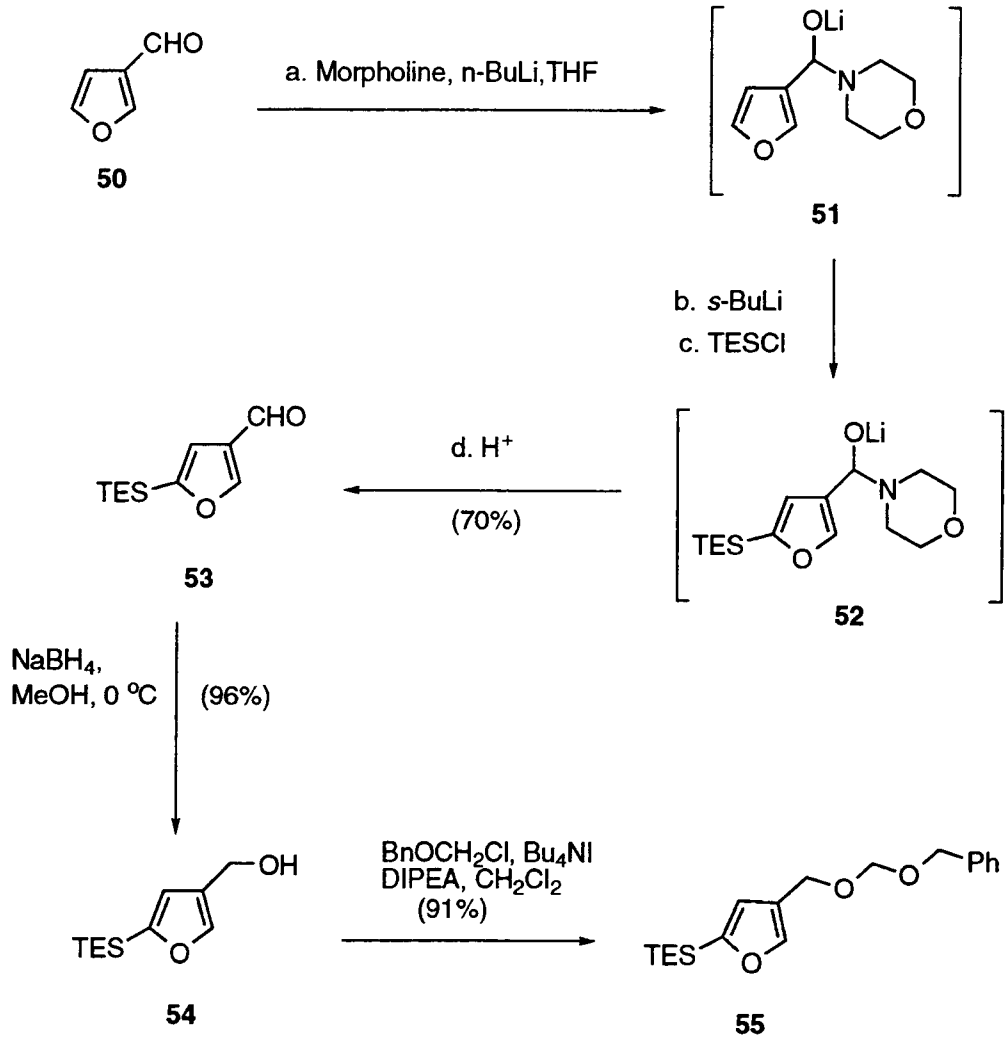


Lee, Garst and coworkers[23] have extended the photooxidation to other trialkylsilyl furans, including triethylsilyl (TES) and t-butyldimethylsilyl (TBS) substituted furan derivatives.



X = TMS, TBS, TES

Our preparation of precursor butenolide **57a** is shown in **Scheme 16a** and **16b**.



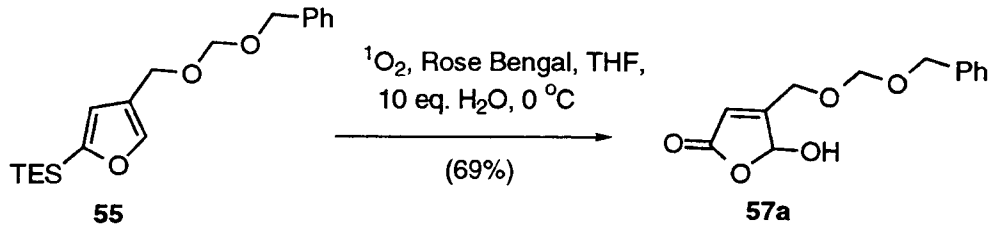
Scheme 16a

5-TES-3-furaldehyde **53** was first prepared according to the procedure reported by Lee, Garst and coworkers[24] (**Scheme 16a**). Addition of 3-furaldehyde into a mixture of morpholine and n-butyllithium in tetrahydrofuran

(THF) resulted in *in situ* protection of the aldehyde **51**. The bulky morpholide directed the second metalation with *s*-BuLi to the remote C-5 position of the furan ring; addition of the electrophile chlorotriethylsilane (TESCl) afforded intermediate **52**. Subsequent mild acidic workup produced 5-TES-3-furaldehyde **53** with only a trace amount of the other regioisomer.[15]

Reduction of **53** with sodium borohydride in methanol proceeded smoothly to yield alcohol **54** that was immediately protected with benzyloxymethyl chloride ($BnOCH_2Cl$) to afford **55**.

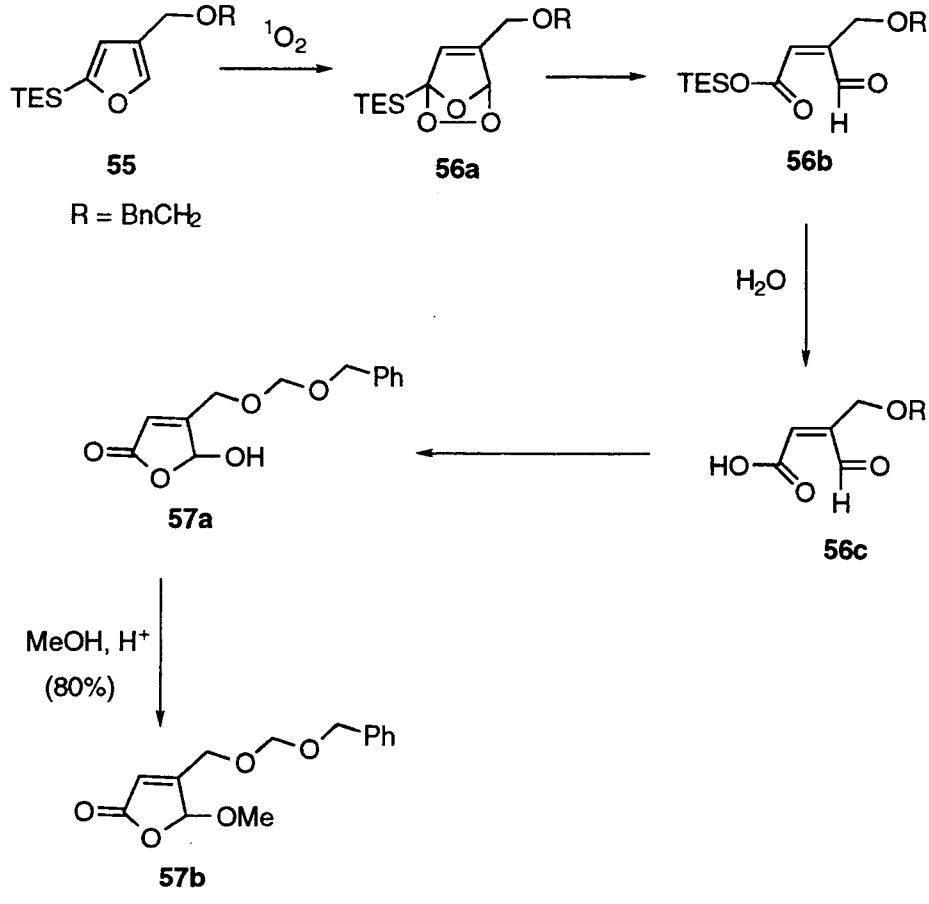
Singlet oxygen oxidation of furan **55** was carried out in the presence of Rose Bengal as photo-sensitizer and an excess amount of water (10-15 equivalents) in THF to yield a single regioisomer **57a** (**Scheme 16b**).[23]



Scheme 16b

The mechanism for the singlet oxygen oxidation of 5-TMS-furan has been postulated by Adam et al[25] to involve an intramolecular trimethylsilyl migration in the endoperoxide intermediate. Regioselective formation of the desired 4-substituted-5-hydroxy-2(5H)-furanone **57a** is controlled by the presence of the triethylchlorosilane (TES) group. Singlet oxygen oxidation of **55** should follow a mechanism similar to that proposed by Adam and coworkers[23,25] as shown in **Scheme 17**. Thus, photooxidation of **55** should give peroxide **56a,** which on

rearrangement gives silyl ester **56b**. In the presence of excess water, the TES ether **56b** undergoes hydrolysis to give carboxylic acid **56c**. Upon intramolecular ring closure of **56c**, the product **57a** is formed (**Scheme 17**).

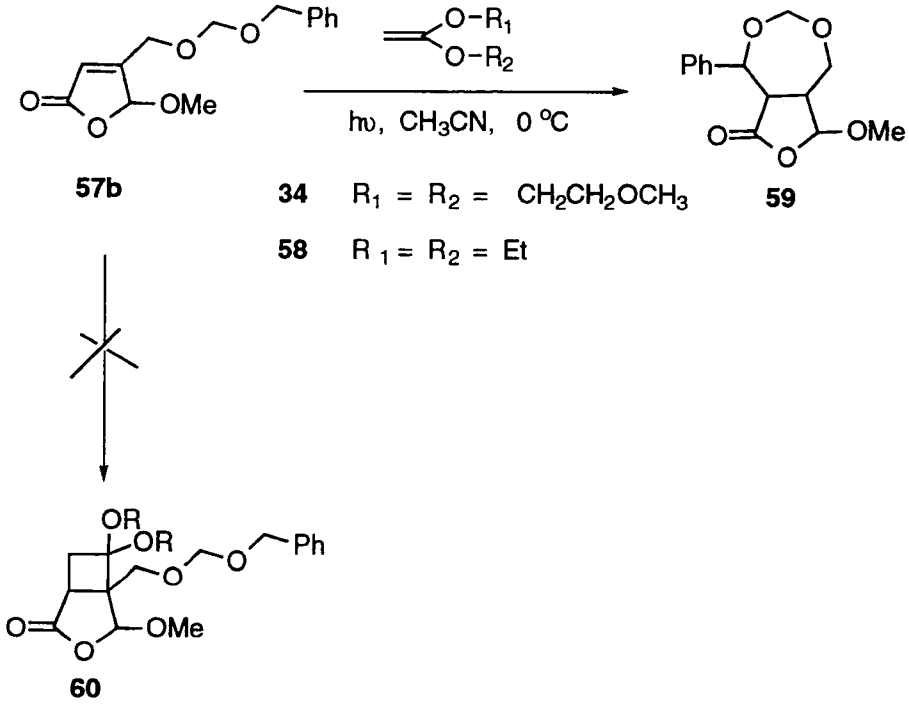


Scheme 17

Protection of the hydroxyl group in **57a** was done by refluxing in methanol in the presence of a catalytic amount of hydrochloric acid to afford photosubstrate **57b**.

The next step in our synthetic plan is the intermolecular [2+2] photocycloaddition of butenolide **57b** with ketene acetals to obtain a

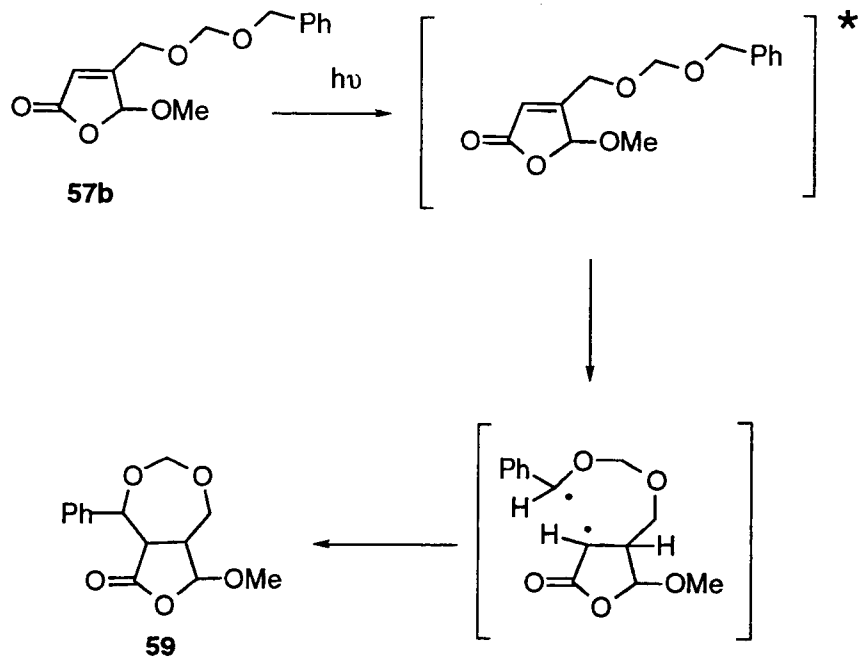
cyclobutanone intermediate. Irradiation of butenolide **57b** with ketene acetal **34** or **58** in dry acetonitrile gave unexpectedly product **59** as a single isomer (**Scheme 18**). We did not observe any of the desired product **60** arising from intermolecular [2+2] photocycloaddition with the ketene acetals. The structure of **59** was confirmed by ^{1}H, ^{13}C and DEPT NMR experiments and mass spectroscopy. Furthermore, irradiation of **57b** in the absence of ketene acetal also provided product **59**.



Scheme 18

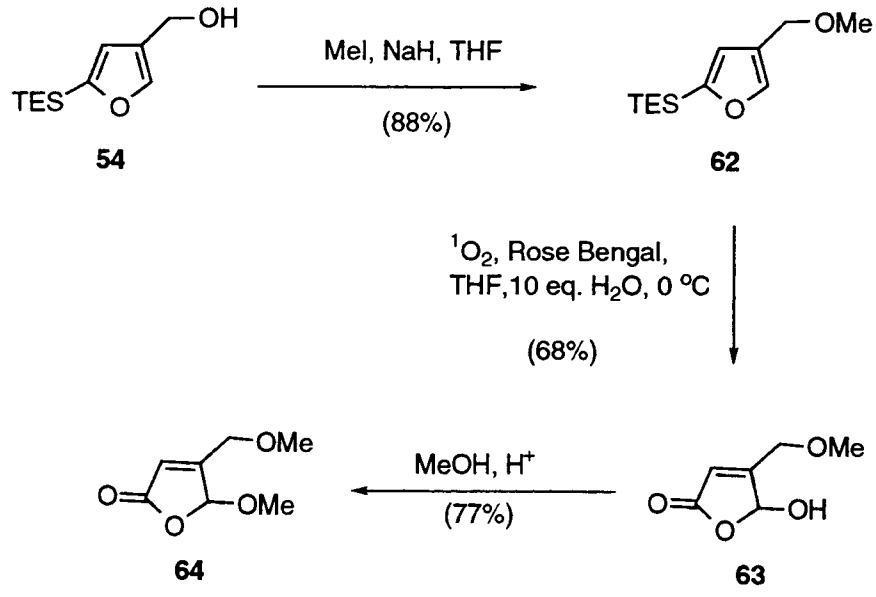
The formation of bicyclic compound **59** can be rationalized as follows. Upon irradiation with uv light, the excited state of chromophore **57b** underwent

hydrogen abstraction to form a biradical intermediate, which on cyclization yielded a single isomer of bicyclic compound **59** (**Scheme 19**).

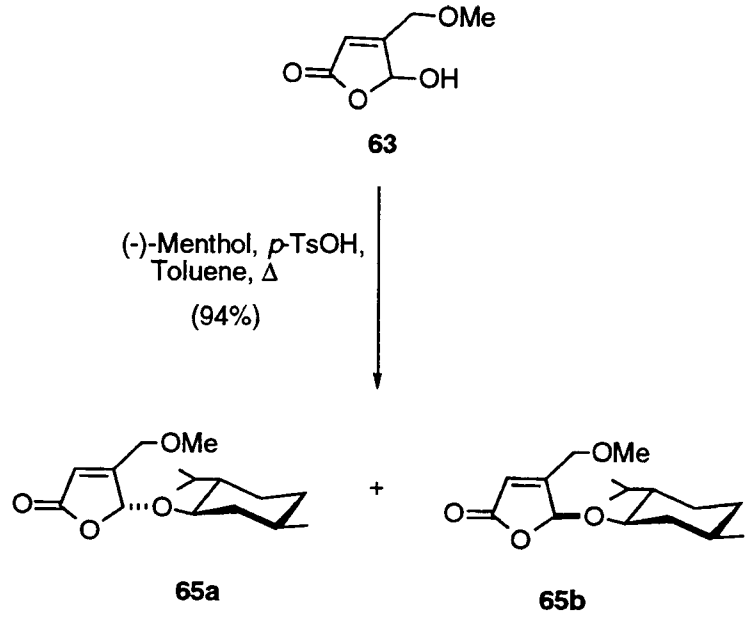


Scheme 19

In order to avoid the formation of product **59** we decided to change the benzyloxymethyl protecting group in **57b** to a simple methyl group. Thus, butenolide **64** was prepared by sequential protection of primary alcohol **54**, singlet oxygen oxidation of **62** and protection of hemiacetal **63** (**Scheme 20**).



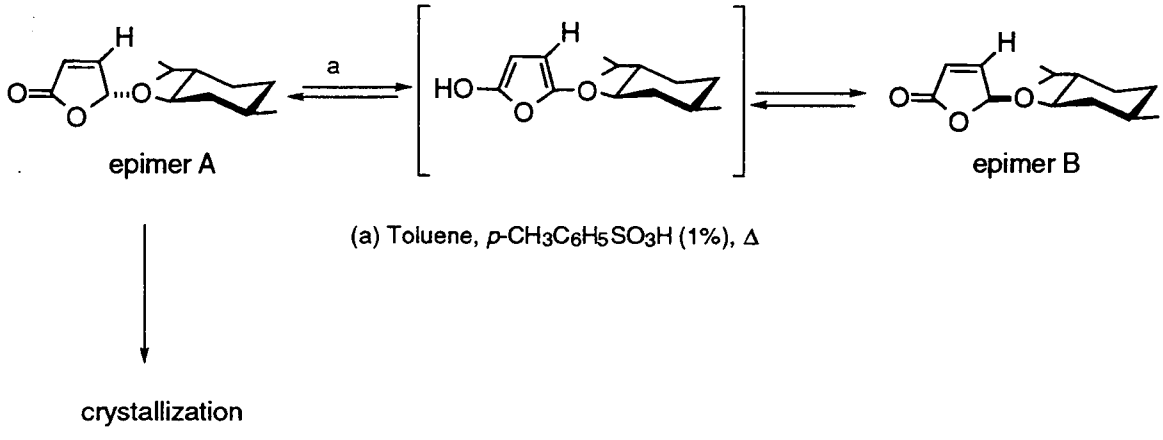
Scheme 20



Scheme 21

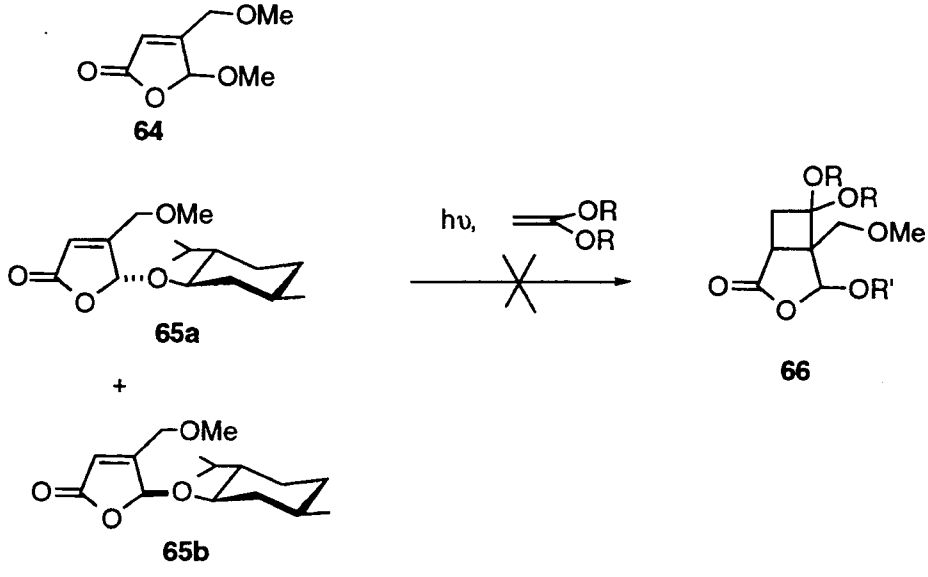
As mentioned before, to achieve stereoselectivity in the intermolecular [2+2] photoadditions, a chiral (l)-menthyl group was incorporated into the molecule **63** to give a mixture of **65a** and **65b** in a ratio of 1:1 as expected[13,14,26,27] (**Scheme 21**).

In contrast to the case of simpler furanones, the diastereomer **65a** and **65b** were not separable on attempted chromatography. Feringa et al[26,27] reported a method to separate a mixture of diastereomers by a "crystallization-induced epimerization" process, which is essentially, continuous removal of one major crystalline isomer from the solution of the mixture upon crystallization. Removal of the major crystalline isomer further induces the epimerization of one isomer to the other. This epimerization is postulated to take place via enolization of either diastereomer to an unstable intermediate as shown below.



Our efforts on the separation of the diastereomers **65a** and **65b** according to the above procedure were not successful. We only observed insignificant epimerization and could not succeed in crystallizing either isomer.

Without separation of **65a** and **65b**, we proceeded to carry out the photoaddition of the mixture with ketene acetals. However, intermolecular [2+2] photocycloadditions carried out by irradiation of **64**, or a mixture of **65a** and **65b** in acetonitrile with 5-10 equivalents of ketene acetal **34** or **58** with or without photosensitizer under different wavelengths (>220 nm, >280 nm and 350 nm) did not afford any of the desired photoadducts **66** (**Scheme 22**). We had difficulty to isolate any compound out of the crude reaction mixtures due to a large amount of byproducts resulting from polymerization of the ketene acetals.

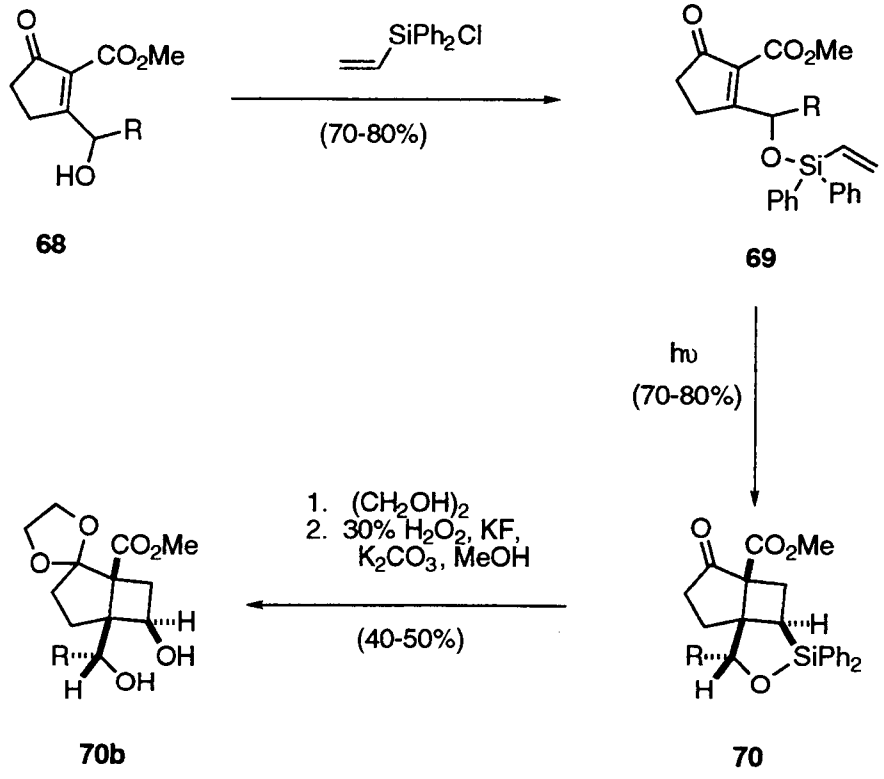


Scheme 22

Regardless of our arduous efforts, we were not able to isolate compound **66**. After recognizing the problem as being typical of intermolecular [2+2] photocycloaddition with photosensitive olefins, we looked for an alternative way to construct cyclobutane ring. Intramolecular [2+2] photocycloaddition came into our plan.

1.3. Intramolecular [2+2] Photocycloadditon

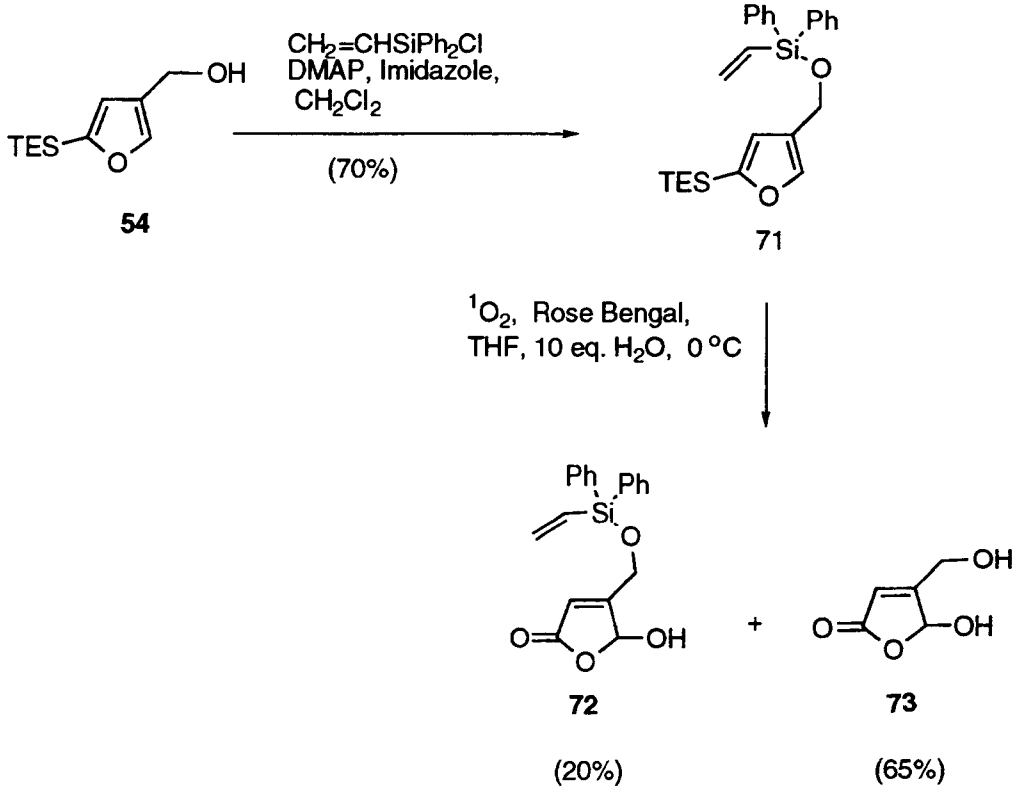
Crimmins[28] reported an efficient method to build cyclobutane rings by the use of siloxanes as temporary tethers in [2+2] photocycloaddition of enone and olefin systems. This example is shown below.



Cyclopentenone **68** was treated with chlorodiphenylvinylsilane to afford photosubstrate **69**. Intramolecular [2+2] photoaddition of **69** gave product **70** with a cyclobutane ring in *cis*-fusion. Protection of the ketone was followed by oxidative cleavage of O-Si and C-Si bonds to afford diol **70b**. One advantage of

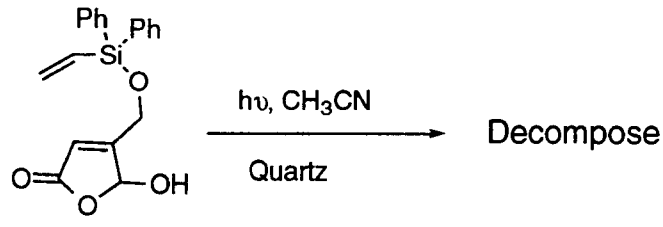
this type of reaction is that it has good regio- and stereoselectivity, and is expected to give less byproducts than intermolecular [2+2] photocycloaddition.

Based on that precedent, we prepared an intermediate incorporating a vinylsilane moiety onto our butenolide chromophore as in compound **72** (**Scheme 23**). Alcohol **54** was treated with chlorodiphenylvinylsilane to afford **71**. Singlet oxygen oxidation under the same conditions used for the preparation of **63** afforded substrate **72** in only 20% yield. The low yield of the singlet oxygen oxidation resulted from cleavage of the silyl ether bond in **71**, which gave a substantial amount of undesired byproduct **73**.



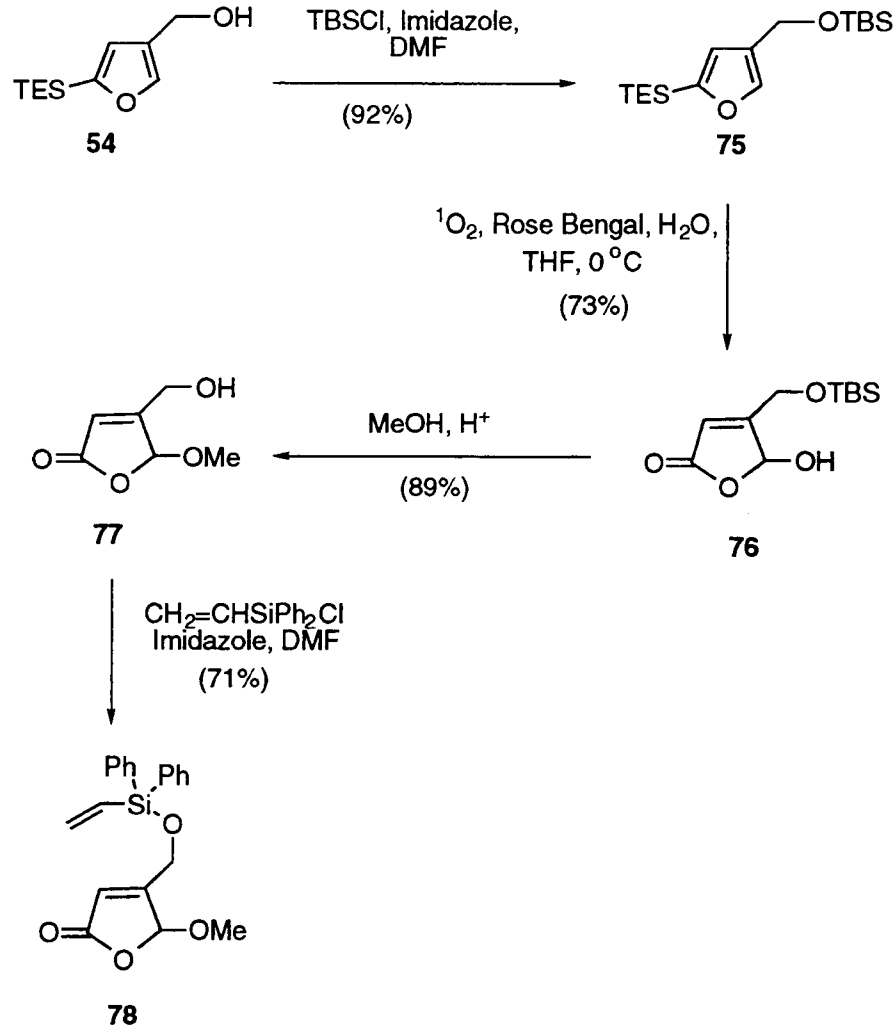
Scheme 23

Direct irradiation of unprotected γ-hydroxybutenolide **72** in acetonitrile led to decomposition of the substrate. We were unable to detect the formation of any cycloadduct under any condition tried.



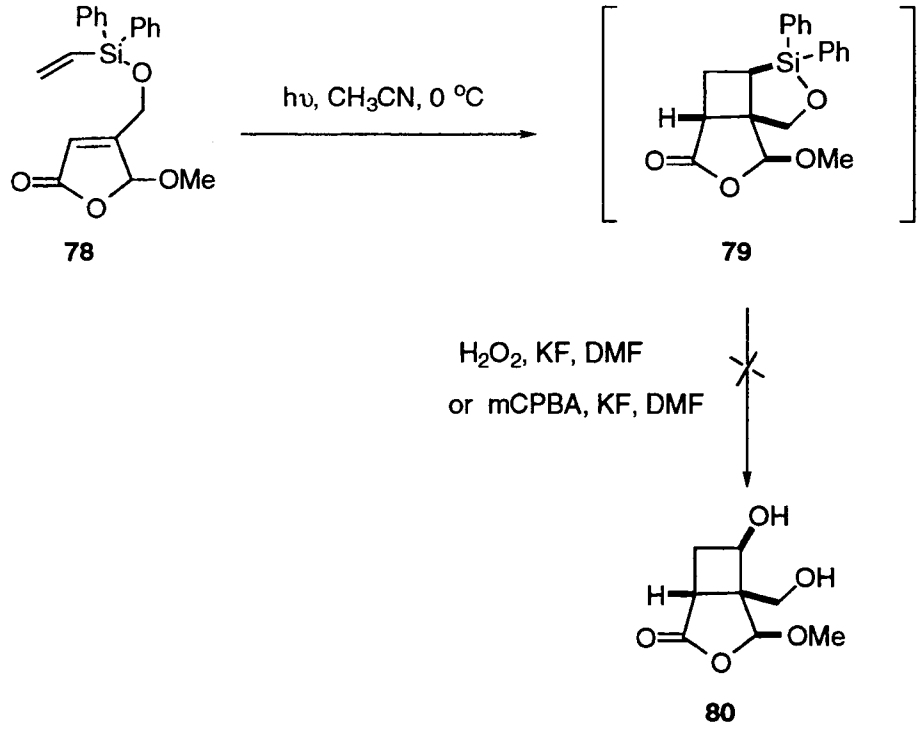
72

Protection of the hydroxyl group seems to be necessary to avoid decomposition. Although the hydroxyl group in **72** could be directly protected, we were more concerned about the low yield in the transformation from **71** to **72** since most of product **72** was converted to diol **73** (see **Scheme 23**). We have found a more efficient way to prepare intermediate **78** (**Scheme 24**). Alcohol **54** was first protected with t-butylchlorodimethylsilane (TBSCl) and imidazole in THF to yield substituted furan **75**. Photooxidation of **75** afforded **76** in good yield. The TBS group was cleaved during the protection of hemiacetal **76** to afford primary alcohol **77**, which on treatment of chlorodiphenylvinylsilane yielded photosubstrate **78**.



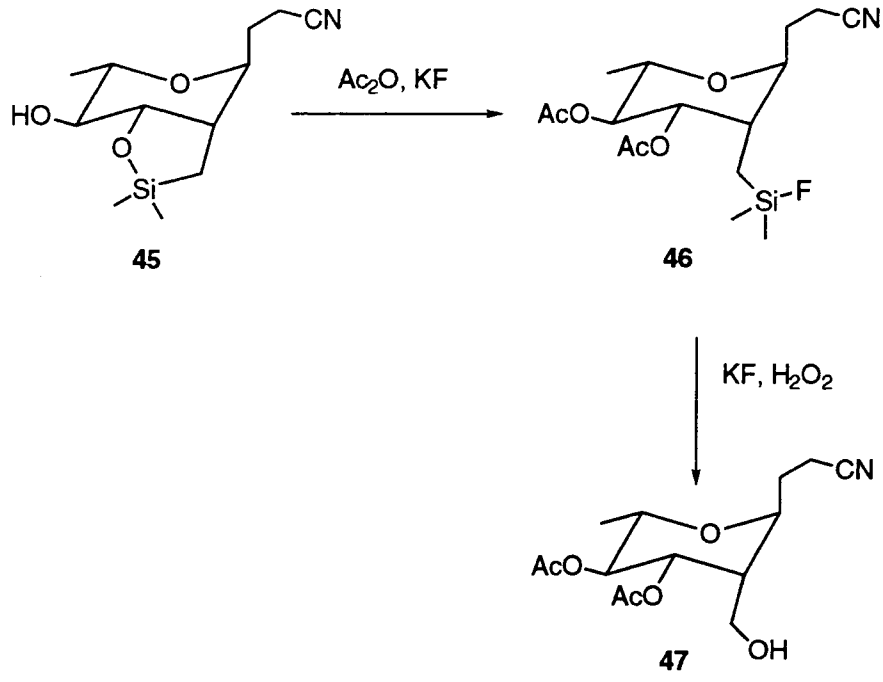
Scheme 24

Irradiation of **78** in acetonitrile afforded a tricylic intermediate **79**, which was extremely unstable. The compound decomposed on standing in $CDCl_3$ solution or on silica gel upon attempted chromatographic separation (**Scheme 25**).



Scheme 25

Without further purification, the crude photoproduct **79** was treated with hydrogen peroxide or *m*-chloroperoxybenzoic acid (mCPBA) and potassium fluoride[29,30] in N,N-dimethylformamide (DMF) to afford diol **80**, which unfortunately could not be separated from byproducts. An alternative way to carry out the C-Si oxidation is through a stepwise cleavage of the crude tricyclic intermediate **79**. *In situ* protection of the resulting alcohol with acetic anhydride is then followed by C-Si oxidation.[31,32] One example of this stepwise cleavage of a cyclic silylether is shown below.[32]

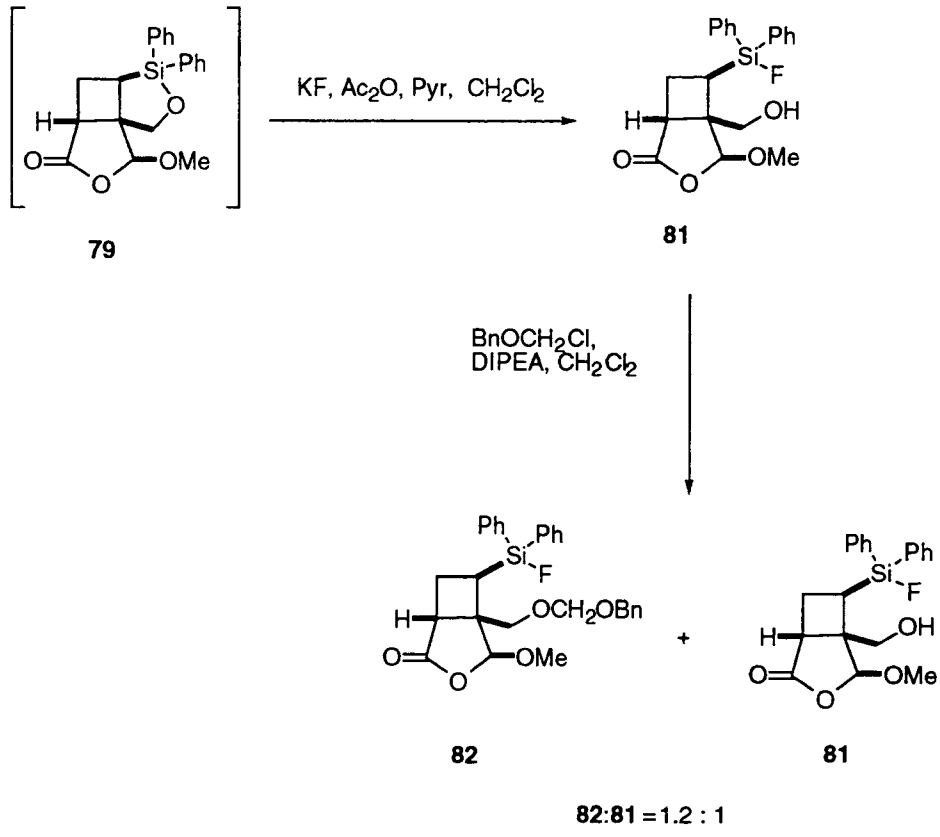


45 46 47

Treatment of siloxane **45** with acetic anhydride (Ac_2O) and potassium fluoride resulted in acetate **46**. Oxidative cleavage of the C-Si bond in **46** afforded alcohol **47**.

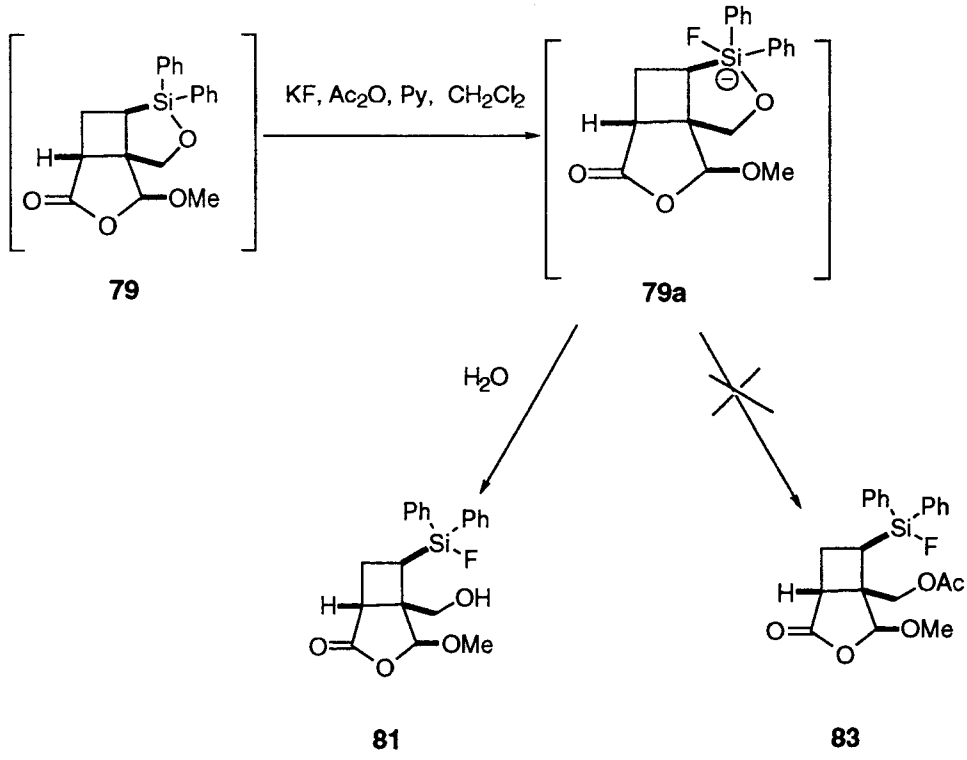
When crude **79** was submitted to a mixture of potassium fluoride and acetic anhydride in the presence of pyridine in dichloromethane according to these conditions, the product **81** was observed, in which the free alcohol was unexpectedly retained (**Scheme 26**).

Protection of alcohol **81** was carried out by treatment with benzyloxymethylchloride ($BnOCH_2Cl$) in the presence of diisopropylethylamine (DIPEA) to give a mixture of **82** and starting material **81** in a ratio 1.2 to 1.



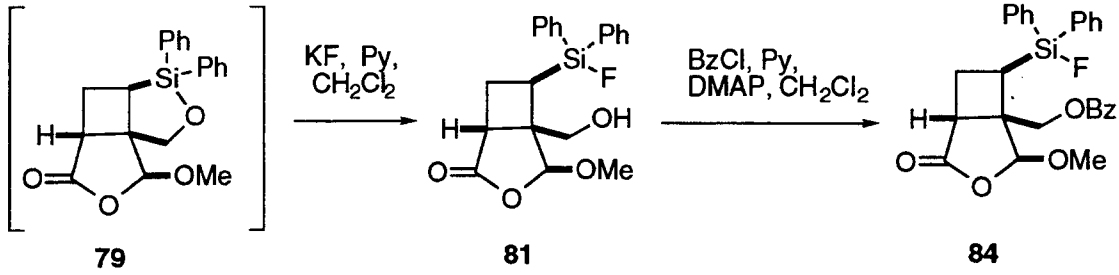
Scheme 26

The failure of *in situ* protection of the free alcohol **81** could be explained by the formation of a penta-valent silicon intermediate **79a** (**Scheme 27**). The anion was presumably formed after treatment of **79** with potassium fluoride (KF). After aqueous workup, the alcohol **81** was formed rather than acetate **83**.



Scheme 27

Since protection of **81** with $BnOCH_2Cl$ hardly goes to completion as shown in **Scheme 26**, we decided to adopt the two step protocol shown in **Scheme 28** for the oxidative cleavage of the O-Si bond. First, treatment of



Scheme 28

crude **79** with KF and pyridine without acetic anhydride gave the same alcohol **81**, which upon benzoylation with benzoyl chloride (BzCl) afforded **84** (**Scheme 28**).

We then were at a position to carry out the oxidative cleavage of the C-Si bond of **84**. Compound **84** was submitted to the conditions reported by Tamao et al.[29,30] Oxidative cleavage of the C-Si bond by *m*-chloroperoxybenzoic acid (mCPBA) and potassium fluoride gave desired alcohol **85**, which could be isolated, purified and fully characterized (**Scheme 29**).

84 **85**

Scheme 29

Again, the relative stereo- and regiochemistry of **85** were confirmed by NOE studies as illustrated below (**Fig. 2**).

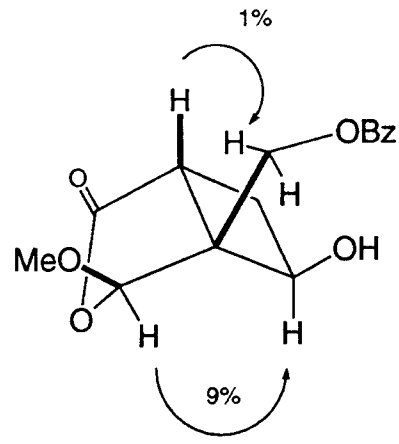
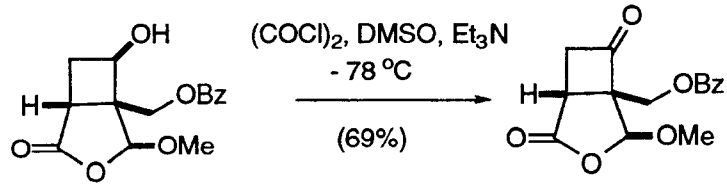


Figure 2. NOE studies on cyclobutanol **85**.

As expected, Swern oxidation[33] of compound **85** afforded the highly functionalized bicyclic cyclobutanone **86** (**Scheme 30**) It is noteworthy that **86**, prepared in eleven steps from 3-furaldehyde, contains a carboxylic acid derivative, aldehyde derivative, primary alcohol derivative and ketone group.

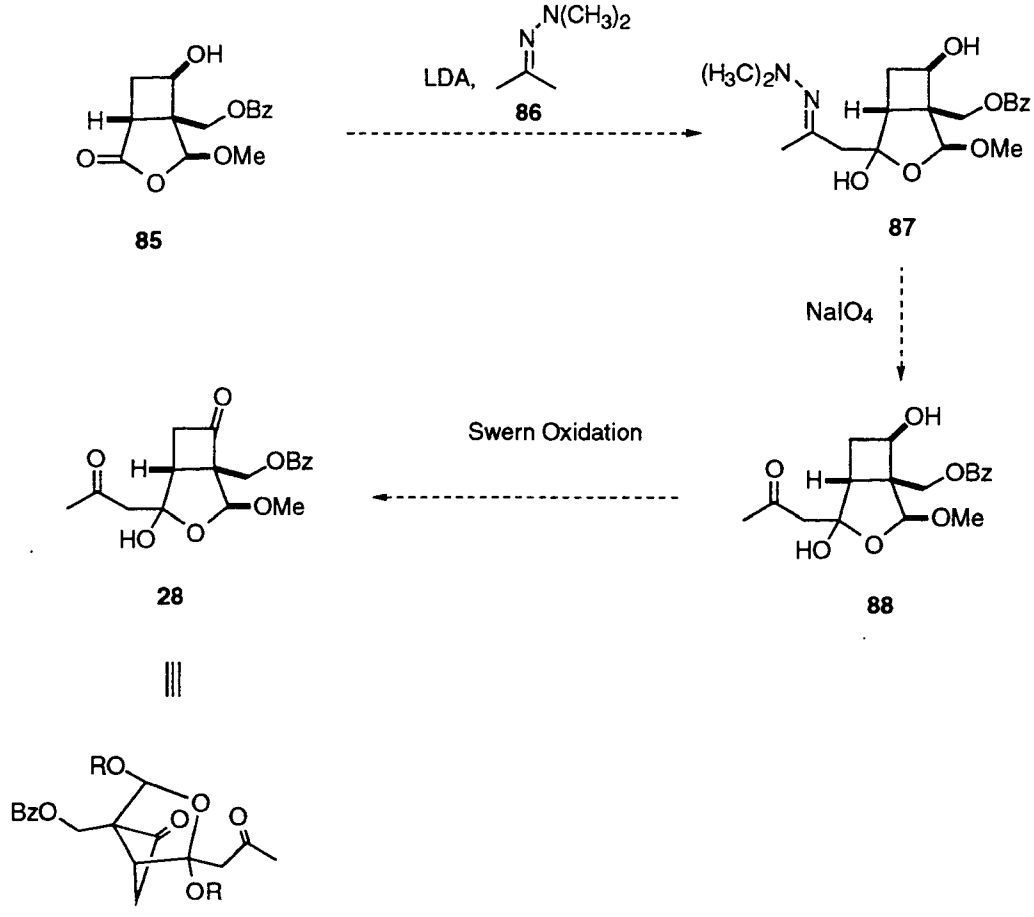


85 **86**

Scheme 30

1.4. Future Work for Total Synthesis of Paeoniflorigenin

Having secured an efficient supply of compound **85**, the next few steps towards a total synthesis of paeoniflorigenin can be proposed .



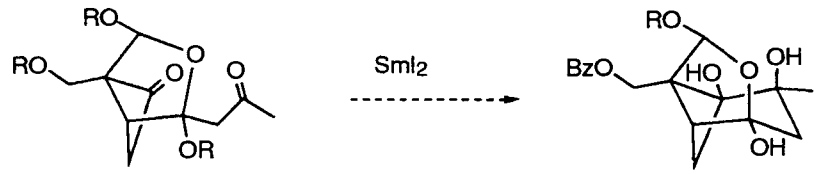
Scheme 31

Another key intermediate **28** is anticipated to be prepared from alcohol **85** (**Scheme 31**). The acetonyl group is expected to be incorporated by nucleophilic attack of acetone dimethylhydrazone followed by oxidative cleavage of the

hydrazone in **87** with sodium periodate. Swern oxidation of **88** is then expected to afford the key intermediate diketone **28**, the required substrate for the SmI_2 promoted intramolecular reductive coupling. Also, further work is necessary to find conditions to transform compound **78** in **Scheme 24** into a single chiral acetal.

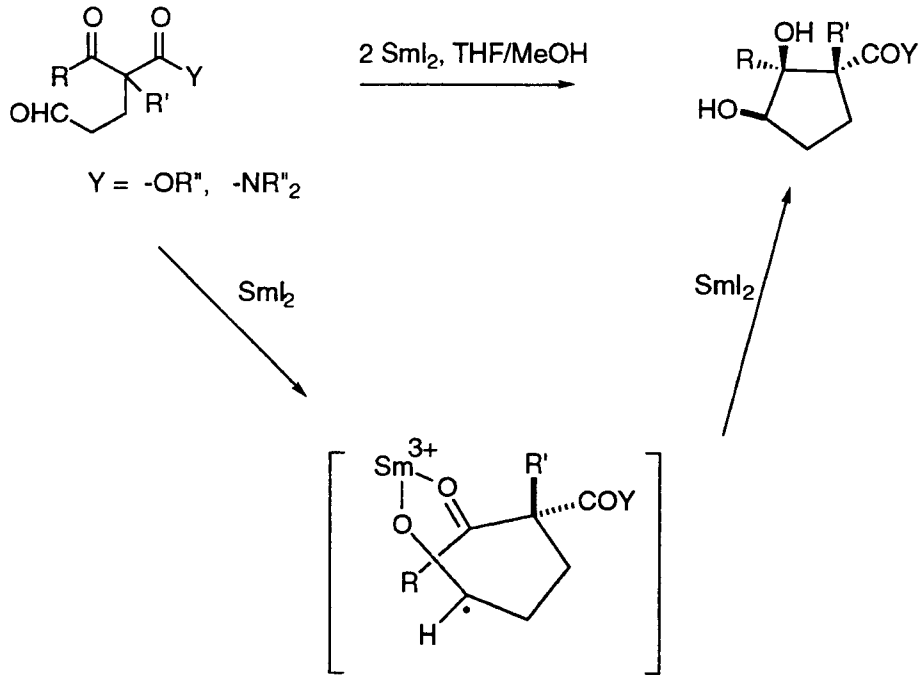
2. Model Studies on SmI_2 Mediated Intramolecular Pinacol Coupling of a Diketone

The second key step in our retrosynthetic scheme is the SmI_2 mediated intramolecular pinacol coupling of a diketone, such as intermediate **27**, for constructing the bis-tertiary diol **28** as shown below.



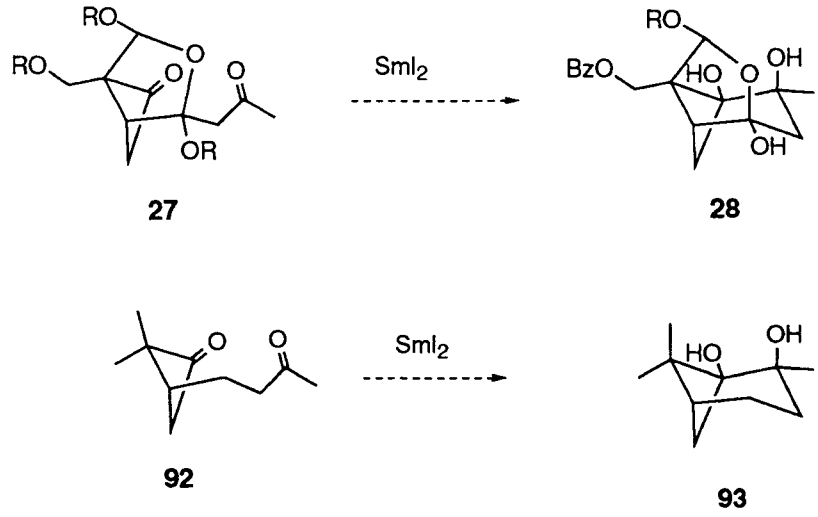
27 **28**

SmI_2 promoted intramolecular pinacol coupling reactions have been described in the literature.[34,35] Molander and coworkers[36] have described stereocontrolled intramolecular reductive coupling of keto aldehyde substrates (**Scheme 32**). Vicinal bis-tertiary diols were the observed products. The yields range from 35 to 82% depending on the type of substrates. The mechanism for the pinacol coupling they proposed involves cyclization after one-electron reduction.[37]



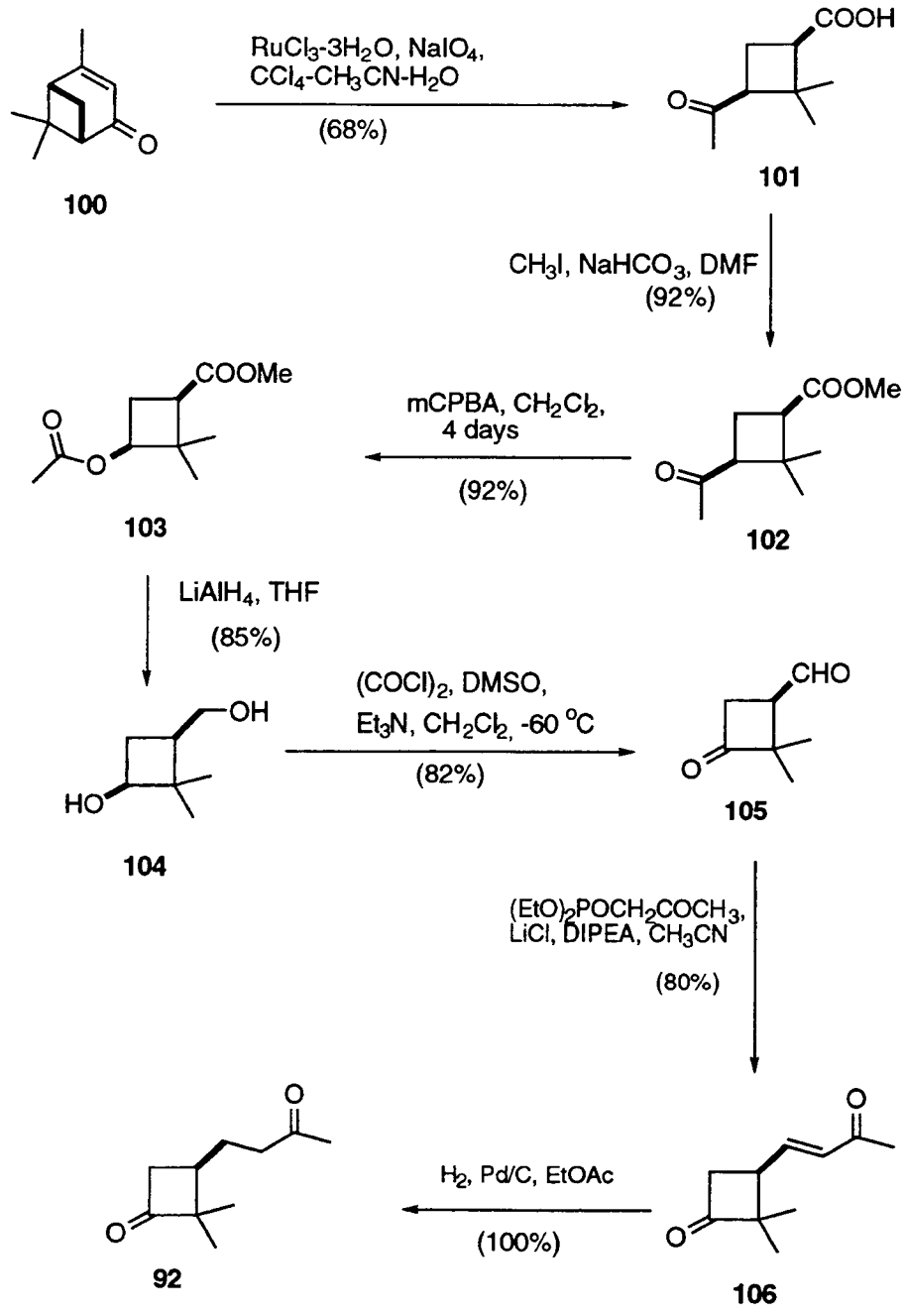
Scheme 32

We felt, it would be very appropriate to conduct synthetic studies on a more accessible model compound which also has a cyclobutanone and a ketone group. To do so, a model compound **92** was prepared in order to study its reductive coupling with SmI_2 (**Scheme 33**).



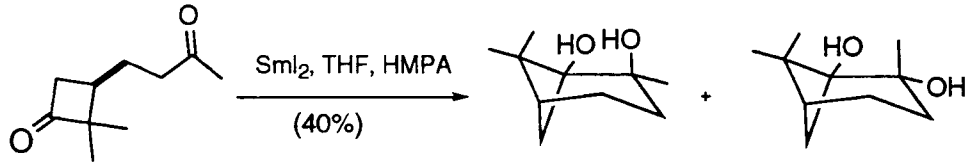
Scheme 33

Model compound **92** was prepared as shown in **Scheme 34**. The first step is an oxidative degradation of (+)-verbenone with $RuCl_3 \cdot 3H_2O$ and sodium metaperiodate in a mixed solvent system consisting of carbon tetrachloride, acetonitrile and water in a 2:1:4 ratio.[38] The resulting pinonoic acid **101** was treated with methyl iodide to yield ester **102** in 92% yield. Subsequent Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid (mCPBA) led to diester **103.**[39] Reduction of diester **103** by lithium aluminum hydride afforded diol **104** and upon Swern oxidation, ketone aldehyde **105** was obtained. The chain extension was carried out by a diastereoselective Horner-Emmons-Wittig protocol to give a single isomer of α, β-unsaturated diketone **106.**[40] The chosen mild conditions ensure a selective condensation of the aldehyde carbonyl to occur while the ketone carbonyl remains intact. Hydrogenation of the α,β-unsaturated diketone **106** proceeded smoothly to yield model compound diketone **92**.


RuCl3-3H2O, NaIO4,
CCl4-CH3CN-H2O
(68%)
COOH
100
101
CH3I, NaHCO3, DMF
(92%)
COOMe
mCPBA, CH2Cl2,
4 days
(92%)
COOMe
103
102
LiAlH4, THF
(85%)
(COCl)2, DMSO,
Et3N, CH2Cl2, -60 °C
(82%)
CHO
OH
HO
104
105
(EtO)2POCH2COCH3,
LiCl, DIPEA, CH3CN
(80%)
H2, Pd/C, EtOAc
(100%)
92
106

Scheme 34

Treatment of diketone **92** with freshly prepared SmI_2 in the presence of hexamethylphosphoramide (HMPA) in THF gave a inseparable diastereomeric mixture of **93a** and **93b** in an approximate ratio of 1:1.



92 **93a** **93b**

This result suggests that a vicinal bis-tertiary diol can be obtained by reductive coupling of a diketone by the use of SmI_2 promoted pinacol coupling.

The most plausible mechanism involved in our model study should also be one-electron process, and be similar to that proposed by Molander et al.[36,37]

One point needed to be addressed from our model studies is that HMPA plays an important role in the SmI_2 mediated pinacol coupling. In agreement with the reports from other research groups[36,41], without HMPA, we only observed an unidentified mixture of products along with remaining substrate.

CONCLUSIONS

Our studies explored regio- and stereoselective inter- and intramolecular [2+2] photocycloaddition protocols to access a stereodefined cyclobutanone intermediate towards the synthesis of paeoniflorigenin.

Intermolecular [2+2] photocycloaddition of a α,β-unsaturated lactam to a ketene acetal afforded exclusively the head-to-tail and endo photoadduct in contrast with the stereoselectivity observed by Meyers. Introduction of an alkoxymethyl side chain moiety into the α,β-unsaturated lactam could not be achieved by conjugate additions. Presumably, the failure of regio- and stereoselective intermolecular [2+2] photocycloaddition of butenolide with ketene acetals is due to preferential formation of polymeric material from photosensitive ketene acetals.

An alternative approach, regio- and stereoselective intramolecular [2+2] photocycloaddition, was found to be a successful route to access the cyclobutanone intermediate. The vinylsilane butenolide photosubstrate for the intramolecular photocycloaddition, was readily prepared in a singlet oxygen oxidation of 5-TES-3-furaldehyde. Intramolecular [2+2] photocycloaddition of vinylsilane butenolide using a siloxane as temporary tether successfully formed the desired tricyclic adduct, which required stepwise cleavages of O-Si and C-Si bonds to yield a key cyclobutanone derivative intermediate. Finally, a total of eleven steps starting from the commercial available 3-furaldehyde provided us with a highly functionalized cyclobutanone intermediate **86**, which contains carboxylic acid derivative, aldehyde derivative, alcohol derivative and a cyclobutanone in a single molecule.

Model studies on SmI_2 mediated pinacol coupling of a simple diketone resulted in a diastereomeric mixture of vicinal bis-tertiary diols, which provides us a basis for further application of this novel methodology to obtain a highly complex bis-tertiary diol intermediate in a later step in the synthesis of paeniflorigenin.

EXPERIMENTAL SECTION

1. 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.

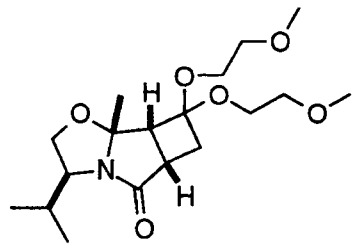
Analytical thin layer chromatography (TLC) was performed using precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a 3-5% solution of phosphomolybodic acid in ethanol, or a 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.

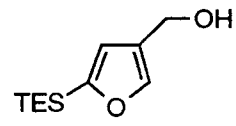
All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^1H NMR spectral data are reported in the order of: chemical shift, number of protons, multiplicity (s=singlet, d=doublet, dd=doublet doublet, t=triplet, q=quartet, m=multiplet and br=broad), 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. Electron impact (EI) mass spectra (HRMS and MS) were obtained using a Varian MAT311 or a Finnegan 4000 spectrometer. Photolysis was carried out in solution using Pyrex or Vycor or Quartz filter with a Hanovia 450W medium-pressure lamp.

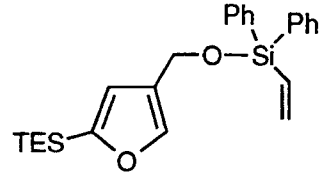
2. Experimental



Cyclobutanone Derivative 35. A solution of α,β–unsaturated lactam **33** (202 mg, 1.1 mmol), acetophenone (660 mg, 5.5 mmol), ketene bis(2-methoxyethyl) acetal **34** (970 mg, 5.5 mmol) in dry dichloromethane (80 mL) was degassed for 30 min in immersion chamber and was irradiated by a 450 Watt mercury lamp through a Pyrex filter at -35°C for 3 h. Removal of the solvent followed by column chromatography on silica gel by 30% ethyl acetate in hexane afforded 120 mg of **35** (30%). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.88 (3H, d, J=6.5 Hz), 0.95 (3H, d, J=6.8Hz), 1.38 (3H, s), 1.62-1.70 (1H, m), 2.30 (1H, dd, J=9.1, 12.3Hz), 2.48 (1H, dd, J=1.1, 11.8Hz), 2.82 (1H, d, J=7.1Hz), 3.04-3.10 (1H, m), 3.32-3.39 (15H, m), 3.90 (1H, dd, J=3.4, 7.4 Hz), 4.33 (1H, d, J=7.3Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 19.8, 28.3, 32.7. 34,9, 37.9, 54.4, 58.4, 58.9, 60.0, 71.4, 71.5, 71.9, 72.6, 97.8, 102.6, 180.8 ppm; IR (neat) 2960, 2932, 2877, 2822, 1705, 1617, 1375, 1172, 1128, 1056, 979 cm^{-1}; MS (CI) m/z 358 (M^++1), 300, 282, 185, 85; HRMS (CI) m/z 358.2230 (M^++1) 342.1917 (M^+-CH_3) (calcd for $C_{18}H_{31}NO_6$+H^+: 358.2240).

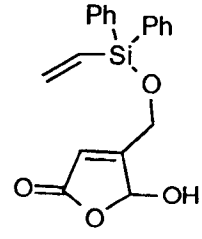


Alcohol 54. To a solution of 5-TES-3-furaldehyde **53** (900 mg, 4.28 mmol) in methanol (18 mL) at 0 °C was added sodium borohydride (93.6 mg, 1.08 mmol). The solution was stirred for 30 min then allowed to warm to room temperature. After TLC indicated the completion of the reaction, the mixture was diluted with ethyl acetate (30 mL) and was quenched by saturated aqueous ammonium chloride (2 mL). The resulting mixture was washed with saturated aqueous sodium bicarbonate and sodium chloride. The organic layer was dried over sodium sulfate anhydrous. After removal of solvent, the residue was purified by chromatography (30% ethyl acetate in hexane) to give 868 mg of pure oil **54** (96%). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.76 (6H, dd, J=8.0, 8.0Hz), 1.00 (9H, t, J=8 Hz), 1.56 (1H, br), 4.57 (2H, s), 6.68 (1H, s), 7.61 (1H, d, J=1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.7, 7.2, 56.6, 120.7, 124.9, 144.2, 159.8 ppm; IR (neat) 3320, 2948, 2905, 2873, 1067, 1014, 722 cm^{-1}; MS (CI) m/z 212 (M^+), 195, 183, HRMS (CI) m/z 212.1232 (calcd for $C_{11}H_{20}O_2Si$: 212.1233).



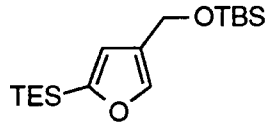
Vinylsilane 71. To a solution of alcohol **54** (1.34g, 7.53mmol), diisopropylethylamine (12.5 mL, 8.63 mmol) and tetrabutylammonium iodide (1.25 g, 3.40 mmol) in methylene chloride (60 mL) was added chlorodiphenyl-

vinylsilane (2 mL, 10 mmol). The mixture was reflux for 5 h until TLC showed all alcohol **54** was consumed. Ethyl acetate (60 mL) was then added after methylene chloride was evaporated. The solution was washed by saturated aqueous sodium bicarbonate and sodium chloride three times, respectively. After separation, the organic layer was collected and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by chromatography (30% ethyl acetate in hexane) to give 2.20 g of pure **71** (69.5%). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.77 (6H, q, J=7.2Hz), 0.98 (9H, t, J=8.0 Hz), 4.72 (2H, s), 5.90 (1H, dd, J=20.2, 3.9 Hz), 6.28 (1H, dd, J=14.9, 3.9 Hz), 6.48 (1H, dd, J=20.2, 14.9 Hz), 6.56 (1H, s), 7.36-7.45 (6H, m), 7.61 (1H, s), 7.61-7.64 (4H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz), δ 3.1, 7.2, 57.6, 120.9, 124.4, 127.7, 129.9, 133.9, 134.9, 137.0, 144.1, 158.9 ppm; IR (neat) 3065, 3059, 3001, 2948, 2910, 2868, 1890, 1816, 1588, 1460, 1428, 1396, 1375, 1237,1110, 1078, 1014, 961, 902, 83,711 cm^{-1}.

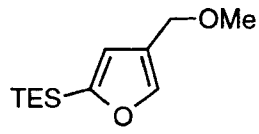


Siloxane 72. A reaction mixture of compound **71** (825 mg, 1.96 mmol), catalytic amount of Rose Bengal (10 mg) in THF (50 mL) and 10 equiv. of water (360 mL) was irradiated by a 500 Watt halogen lamp at 0^{o}C while oxygen was bubbling into the solution. The singlet oxygenation completed within 1 h. After removal of solvent, the residue was purified by chromatography (50% ethyl acetate in hexane) to give 160 mg of pure **72** (20 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.42 (

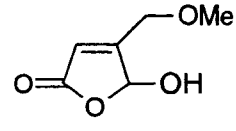
1H, br), 4.52-4.73 (2H, m), 5.95 (1H, dd, J=19.8, 3.9 Hz), 6.02 (1H, s), 6.13 (1H, s), 6.33 (1H, dd, J=14.9, 3.9 Hz), 6.42-6.54 (1H, dd, J=20.1, 14.9 Hz), 7.38-7.61 (10 H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz), δ 59.3, 97.0, 117.7, 128.0 , 130.4, 132.0, 132.7, 134.8, 138.1, 167.8, 170.7 ppm; IR (neat) 3338, 3065, 3005, 2941, 1753, 1658, 1589, 1430, 1405, 1266, 1151, 1116, 1007, 962, 858, 818 cm^{-1}.



Silyl ether 75. A reaction mixture of **54** (212 mg,1 mmol), tert-butyldimethylsilyl chloride (181 mg, 1.2 mmol) and imidazole (170 mg, 2.5 mmol) in N,N-dimethylformamide (2 mL) was stirred at room temperature for 10 h. Upon completion of the protection, the mixture was concentrated, and ethyl acetate (10 mL) was added. The resulting solution was washed by saturated aqueous sodium bicarbonate and sodium chloride, respectively. The organic layer was collected and dried over sodium sulfate anhydrous. After removal of solvent, the residue was purified by chromatography (30% ethyl acetate in hexane) to give 300 mg of pure product **75** (92%). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (6H, s), 0.75 (6H, q, J=7.8 Hz), 0.98 (9H, t, J=7.9Hz), 4.61 (2H, s), 6.59 (1H, s), 7.55 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ -4.9, 3.5, 7.5, 18.6, 26.2, 57.7, 120.9, 125.7, 143.8, 159.2 ppm; IR (neat) 2948, 2932, 2868, 1400, 1412, 1253, 1078, 1009, 833, 770, 722 cm^{-1}.

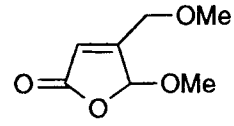


Furan 62. To a 500 mL flask was charged with 600 mg of sodium hydride (60% in mineral oil, 1.5 mmol). After washed by pentane (10 mL) 3 times, the reagent was flashed by argon and 250 mL of dry THF and the starting material alcohol **54** (2.10 g, 10 mmol) was added. The solution was stirred under argon at room temperature for about 2 h until bubbling ceased. The mixture was cooled down to 0 °C and methyl iodide (1.9 mL, 30 mmol) was added and then allowed to warm up to room temperature. Stirring was continued for about 12 h until the reaction went to completion. The reaction was quenched by saturated ammonium chloride (15 mL). The organic layer was collected and the aqueous layer was extracted by diethyl ether (30 mL). The combined organic layer was washed by saturated sodium bicarbonate and brine. After dried over sodium sulfate anhydrous, the organic solvent was evaporated under reduced pressure. Chromatography of the crude by 20% ethyl acetate in hexane afforded 1.573 g of **62** (88%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (6H, dd, J=7.9, 8.1Hz), 0.97 (9H, t, J=8.1Hz), 3.36 (3H, s), 6.65 (1H, s), 7.61 (1H, s) ppm; ^{13}CNMR ($CDCl_3$, 75 MHz) δ 3.0 (3C), 7.1 (3C), 57.7, 65.7, 121.1, 121.7, 144.8, 759.3 ppm.

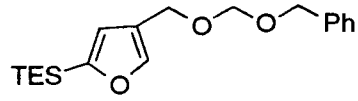


Butenolide 63. A reaction mixture of compound **62** (1.573 g, 6.9 mmol), catalytic amount of Rose Bengal (8 mg) in THF (90 mL) and 10-15 equiv. of water (8 mL) was irradiated by a 500 watt halogen lamp at 0 °C while oxygen

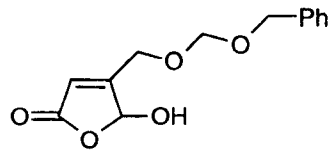
was bubbling into the solution. The singlet oxygenation completed within 1.5 h. After removal of solvent, the residue was purified by chromatography (50% ethyl acetate in hexane) to give 552 mg of pure **63** (55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.45 (3H, s), 4.23-4.36 (2H, m), 4.73 (1H, br), 6.097 (1H, s), 6.098 (1H, d, J=4Hz) ppm; ^{13}CNMR ($CDCl_3$, 75 MHz) δ 59.2, 67.3, 97.1, 118.4, 164.8, 170.2 ppm; IR (neat) 3345, 2935, 1752, 1098, 981 cm $^{-1}$.



Butenolide 64. To a solution of catalytic amount of acetyl chloride (10 μL) in methanol (100 mL) at 0 ^{o}C was added starting material **63** (480 mg, 3.33 mmol). The mixture was warmed up to room temperature then was reflux for 3 h. After the protection was complete, the solvent was removed under reduced pressure and 50 mL of ethyl acetate was added to the residue. The solution was washed by saturated aqueous sodium bicarbonate and brine. After dried over sodium sulfate anhydrous, the organic solvent was evaporated under reduced pressure. Chromatography of the crude by 30% ethyl acetate in hexane afforded 400 mg of pure **64** as yellow oil (77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.44 (3H, s), 3.58 (3H, s), 4.91 (2H, m), 5.71 (1H, s), 6.08-6.09 (1H, m) ppm; ^{13}CNMR ($CDCl_3$, 75 MHz) δ 57.3, 59.5, 67.7, 103.1, 119.2, 169.7, 170.2 ppm; IR (neat) 2925, 2842, 1791, 1752, 1098, 976 cm^{-1}.

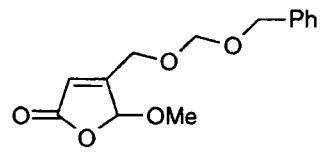


Furan Derivative 55. To a solution of alcohol **54** (220 mg, 1.01 mmol) in dichloromethane (6 mL) containing diisopropylethylamine (2 mL, 1.38 mmol) and tetrabutylammonium iodide (224mg, 0.61 mmol) was added benzyloxy methyl chloride (0.3 mL, 2.02 mmol). The mixture was reflux for 3 h. After cooled down to room temperature, ethyl acetate (6 mL) was added. The mixture was washed by saturated aqueous sodium bicarbonate, sodium sulfite and brine. The organic layer was dried over sodium sulfate anhydrous. Concentrated followed by chromatography (30% ethyl acetate in hexane) afforded 304 mg of pure **55** (90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (6H, dd, J = 8, 8 Hz), 0.99 (9H, t, J=8 Hz), 4.53 (1H, s), 4.64 (1H, s), 4.8 (1H, s), 6.64 (1H, s), 7.31-7.37 (5H, m), 7.62 (1H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.1,(3C), 7.2 (3C), 60.6, 69.4, 93.6, 121.2, 121.4, 127.6 (2C), 127.8 (2C), 128, 137.8, 145.0, 159.5 ppm; IR (neat) 3027, 2950, 2873, 1047, 907, 732 cm^{-1}.

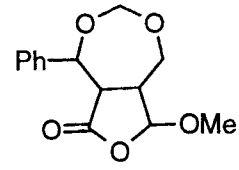


Butenolide 57a. A reaction mixture of compound **55** (2.6 g, 7.82 mmol), catalytic amount of Rose Bengal (10 mg) in THF (100 mL) and 10 equiv. of water (7 mL) was irradiated by a 500 watt halogen lamp at 0 °C while oxygen was bubbling into the solution. The singlet oxygenation completed within 1 h. After removal of solvent, the residue was purified by chromatography (50% ethyl acetate in hexane) to give 1.32 g of pure **57a** (69%). ^{1}H NMR ($CDCl_3$, 300 MHz

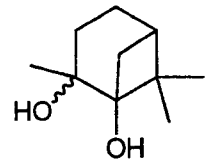
) δ 4.37-4.53 (2H, m), 4.63 (2H, s), 4.83 (2H, s), 5.10 (1H, br), 6.04 (1H, s), 6.06 (1H, s), 7.30-7.39 (5H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.4, 69.9, 94.5, 97.5, 118.2, 127.9 (2C), 128.4 (2C), 137.0, 165.3, 170.8 ppm; IR (neat) 3334, 3010, 2888, 1716, 1056 cm^{-1}.



Butenolid 57b. To a solution of butenolide **57a** (700 mg, 2.8 mmol) in methanol (80 mL) was slowly added acetyl chloride (8 μL). The mixture was heated to reflux for 2 h. After cooled down to room temperature, the evaporation of methanol under reduced pressure was followed by the addition of ethyl acetate (50 mL). The solution was washed by saturated aqueous sodium bicarbonate 3 times (25 mL). The organic solution was dried over sodium sulfate anhydrous. Chromatography of the crude in 30 % ethyl acetate in hexane afforded 592 mg of pure **57b** as yellow oil (80%). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.56 (3H, s), 4.34-4.48 (2H, m), 4.62 (2H, d, J=1 Hz), 4.82 (2H, s), 5.72 (1H, s), 6.09 (1H, s), 7,29-7.38 (5H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.6, 57, 62.3, 69.8, 94.5, 102.7, 118.9, 127.8 (2C), 128.4 (2C), 137.3, 163.2, 169.8 ppm; IR (neat) 3022, 2935, 28886, 1791, 1762, 1459, 1108, 1044, 971, 941, 741 cm^{-1}.

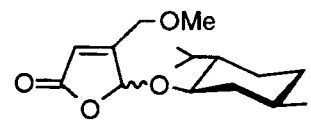


Bycyclic Lactone 59. A solution of **57b** (80 mg, 0.245 mmol) in dry acetonitrile (80 mL) was irradiated by a 450 Watt mercury lamp through Quartz filter at 0 °C for 6 h. After removal of solvent. The crude mixture was separated by column chromatography (30% ethyl acetate in hexane) to yield 24 mg of the bicyclic product **59** (30%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70-2.81 (1H, m), 3.49 (3H, s), 3.51 (1H. s), 4.03-4.18 (2H, m), 4.65 (1H, d, J=6 Hz), 5.11-5.13 (2H, m), 5.26 (1H, d, J=2Hz), 7.28-7.44 (5H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.8, 48.3, 56.7, 68.2, 77.7, 96.3, 108.2, 126.5 (2C), 128.7 (2C), 139.8, 174.1 ppm; IR (neat) 3010, 2949, 2910, 1777, 1044, 1029, 951; MS (CI) m/z 264 (M^+), 235, 217, 203, 185; HRMS (CI) m/z 264.0997 (calcd for $C_{14}H_{16}O_5$: 264.0998).



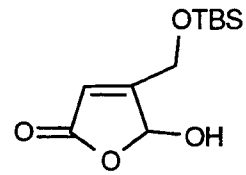
Diol 93a and **93b**. A flame-dried flask under argon at room temperature was charged with samarium (424 mg, 2.83 mmol) and purged with argon for 15 min. Freshly distilled THF (5 mL) and diiodomethane (180 µl, 2.25 mmol) were added with vigorous stirring under argon at room temperature. The mixture was stirred until the dark blue color appeared, then additional THF (12 ml) was added, and stirring was continued for 1 h at room temperature. To this blue mixture at 0°C was added diketone **92** (120 mg, 0.78 mmol) in THF (3 mL) and HMPA (0.64 ml, 3.65 mmol). The resulting mixture was stirred for 2 h and allowed to warm to

room temperature for 3 h. The mixture was exposed to air, stirred until it turned yellow, and diluted with ethyl acetate (10 mL). Saturated aqueous sodium bicarbonate (5 mL) was added into the mixture and continued to stir for 15 min. The resulting mixture was washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted three times with ethyl acetate (20 mL), and the combined organic extracts were dried over sodium sulfate anhydrous. Removal of the solvent followed by chromatography of the residue on silica gel, using 40% ethyl acetate in hexane as eluant, gave 48 mg of **93a** and **93b** (40%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.94-1.25 (5H, m), 1.28-1.52 (11H, m), 1.54-1.61 (1H, m), 2.02-2.05 (1H, m) ppm; ^{13}C NMR ($CDCl_3$, 75MHz) δ 17.2, 23.4, 23.6, 23.7, 24.4, 29.0, 29.1, 37.8, 40.8. 42.1, 44.6, 70.8, 72.5, 76.4 ppm; IR (neat) 3366 (br), 2963, 2933, 1458, 1233 cm^{-1}.

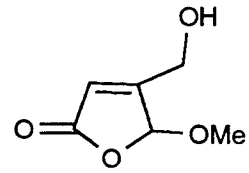


Butenolide 65a and **65b**. A solution of **63** (60 mg, 0.42 mmol), (1R,2S,5R)-(-)-menthol (77mg, 0.49 mmol) and *p*-toluenesulfonic acid (4 mg) in toluene (6 ml) was reflux for 48 h. After removal solvent, 10 ml ethyl acetate was added. The resulting solution was washed by saturated aqueous sodium bicarbonate and brine, respectively. The resulting orgainc layer was dried over sodium sulfate anhydrous. Removal of the solvent followed by chromatography of the residue on silica gel, using 50% ethyl acetate in hexane as eluant, gave 110 mg of a mixture of **65a** and **65b** (94%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.79-0.96 (24H, m), 0.98-1.08 (4H, m), 1.10-1.42 (5H, m), 1.63-1.69 (4H, m), 2.08-2.32 (4H, m), 3.42 (3H, s), 3.43 (3H, s), 3.47-3.59 (1H, m), 3.61-3.68 (1H, m), 4.12-4.31 (4H, m),

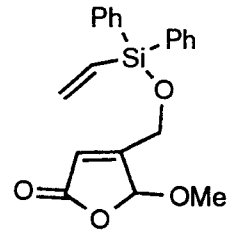
5.82 (1H, s), 5.91(1H, s), 6.03-6.04 (4H, m) ppm; ^{13}C NMR ($CDCl_3$, 75MHz) δ 15.6, 20.7, 20.8, 22.1, 23.1, 25.1, 25.3, 31.3, 31.5, 33.9, 34.0, 40.2, 42.2, 47.6, 47.9, 59.0, 67.2, 79.5, 83.4, 99.5, 103.4, 118.3, 118.5, 163.5, 163.9, 170.2, 179.3 ppm.



Butenolide 76. A reaction mixture of compound **75** (850 mg, 2.60 mmol), catalytic amount of Rose Bengal (5 mg) in THF (50 mL) and 10 equiv. of water (468 mL) was irradiated by a 500 watt halogen lamp at 0 ^0C while oxygen was bubbling into the solution. The singlet oxygenation completed within 1 h. After removal of solvent, the residue was purified by chromatography (50% ethyl acetate in hexane) to give 465 mg of pure **76** as yellow oil (73%). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (6H, s), 0.91 (9H, s) 4.52 (2H, m), 5.18 (1H, br), 6.03 (1H, s), 6.10 (1H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5 (2C), 18.2, 25.7 (3C), 59.1, 97.5, 117.2, 169.4, 171.4 ppm; IR (neat), 3351 (br), 1736, 1465, 1152, 1104 cm $^{-1}$; MS (CI) m/z 245 (M^++1), 117, 87, 85, 75; HRMS (CI) m/z 245.1209 (calcd for $C_{11}H_{20}O_4Si + H^+$: 245.1210).

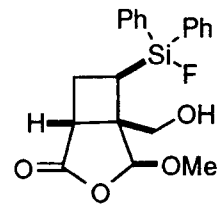


Alcohol 77. A reaction mixture of **76** (432 mg,1.77 mmol) and catalytic amount of acetyl chloride (20 μL) in methanol (20 mL) was reflux for 2 h. After removal of the solvent, ethyl acetate (30 mL) was added. The resulting solution was washed by saturated aqueous sodium bicarbonate and sodium chloride. The organic layer was collected and dried over sodium sulfate anhydrous. After removal of solvent, the residue was purified by chromatography (30% ethyl acetate in hexane) to give 228 mg of pure product **77** (89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (1H, br), 3.55 (3H, s), 4.46 (2H, m), 5.72 (1H, s),6.08 (1H, s) ppm; ^{13}C NMR ($CDCl_3$,100 MHz) δ 57.4, 58.5,103.3, 118.1, 167.1, 170.8 ppm; IR (neat) 3418 (br), 2938, 2841, 2362, 1758, 1655, 1438, 1370, 1204, 1119, 1062, 942 cm^{-1}; MS (CI) m/z 145 (M^{+}+1), 113; HRMS (CI) m/z 145.0501 (calcd for $C_6H_8O_4$ + H^{+}: 145.0501).



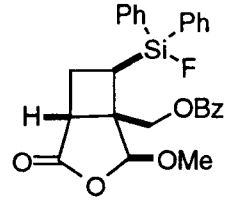
Vinylsilane 78. To a solution of alcohol **77** (350 mg, 2.43 mmol) in dichloromethane (25 mL) was added imidazole (189 mg, 2.92 mmol), DMAP (10 mg) and chlorodiphenylvinylsilane (718 μL, 3.4 mmol). The mixture was stirred at room temperature for 12 h. After filtrate, the clear solution was concentrated

to give a crude mixture which was purified by chromatography (30% ethyl acetate in hexane) to give 430 mg of **78** (70%) and 100 mg of starting material **77** back. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (3H, s), 4.50-4.66 (2H, m), 5,67 (1H, s), 5.95 (1H, dd, J=3.73, 19.92Hz), 6.15 (1H, s), 6.33 (1H, dd, J=3.78, 15.3 Hz), 6.48 (1H, dd, J=14.9, 19.99 Hz), 7.39-7.60 (10H, m) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.7, 59.4, 102.5, 118.4, 128.1, 130.5, 132.3, 132.9, 134.8, 138.0, 165.9, 169.9 ppm; IR (neat) 3047, 3008, 2935, 1791, 1762, 1592, 1430, 1367, 1152, 1117, 1088, 956, 814, 717 cm^{-1}; MS (CI) m/z 353 (M^{+}+1), 335, 325, 275, 209, 149, 133; HRMS (CI) m/z 353.1209 (calcd for $C_{20}H_{20}O_4Si$ + H^{+}: 352.1210).

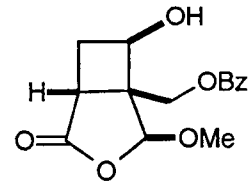


Alcohol 81. A solution of **78** (80 mg, 0.245 mmol) in dry acetonitrile (80 mL) was irradiated by a 450 Watt mercury lamp through Vycor filter at 0 °C for 6 h. After removal of the solvent, the residue was submitted to a solution containing dichloromethane (2 mL), KF (23 mg, 0.24 mmol) and pyridine (24 μL). The resulting mixture was stirred at room temperature for 12 h. The mixture was diluted with dichloromethane (5 mL) and was filtered. The clear solution was condensed and followed by chromatography (30% ethyl acetate in hexane). The separation afforded 15 mg of alcohol **81**, and 20 mg of **78** was recovered. The compound **81** was subjected to next step reaction without any further purification.

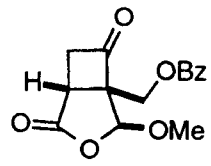
^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21-2.35 (2H, m), 2.60 (1H, t, J=9.3Hz), 3.02 (1H, d, J=7Hz), 3.36 (3H, s), 3.66-3.73 (2H, m), 4.82 (1H, s), 7.29-7.6 (10H, m) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 27.3, 39.0, 52.3, 56.9, 60.3, 109.8, 127.9, 128.0, 130.1, 130.3, 134.4, 134.6 (2C), 134.7 (2C), 137.0, 179.1 ppm; IR (neat) 3553 (br), 3054, 3065, 2937, 1774, 1428, 1115, 700 cm^{-1}; MS (CI) m/z 353 (M+-19), 335, 321, 275; HRMS (CI) m/z 353.1209 (calcd for $C_{20}H_{21}FO_4Si$ - F$^+$: 353.1209).



Bicyclic Lactone 84. To a solution of the previously obtained alcohol **81** (28 mg) in dichloromethane (3 mL) at 0 °C was added DMAP (5 mg), pyridine (33.6 μL) and benzyol chloride (36.4 μL). The mixture was stirred for 1 h at 0 °C and warmed up to room temperature. The mixture was diluted with ethyl acetate (4 mL) after TLC showed that the reaction went to completion. The solution was washed by saturated aqueous sodium bicarbonate and sodium chloride. After removal of solvent, column chromatography of the crude mixture by 20% ethyl acetate in hexane afforded 16 mg of **84**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.18 (1H, dd, J=1, 9Hz), 2.60 (1H, dd, J=7, 15Hz), 2.70 (1H, dd, J=10, 15Hz), 2.86 (1H, d, J=8Hz), 3.30 (3H, s), 4.19 (1H, d, J=11Hz), 4.49 (1H, d, J=11Hz), 5.04 (1H, s), 7.27-7.59 (15H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.7, 26.7, 40.5, 50.6, 53.3, 56.8, 58.1, 61.9, 108.1, 127.7 (2C), 127.8, 128.0, 129.2, 129.6, 129.9, 130.1, 130.2, 132.4, 134.3, 134.6, 136.8 ppm; IR (neat) 3066, 3047, 3008, 2944, 1782, 1718, 1269, 1112, 1068, 961 cm^{-1}.

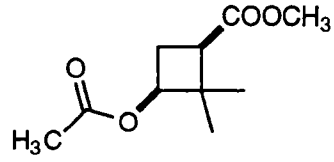


Alcohol 85. To a solution of the previously obtained compound **84** (16 mg) in N,N-dimethylformamide (4 mL) was added mCPBA (45 mg, ca. 50-60%, 0.14 mmol) and KF (18 mg, 0.19 mmol). The mixture was stirred for 12 h at room temperature then was diluted with ethyl acetate (5 mL) and washed by saturated aqueous sodium bicarbonate and sodium chloride. After removal of the solvent, the crude mixture was purified by chromatography (30% ethyl acetate in hexane) to give 6 mg of **85** (yield 21%, 4 steps from **78**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.61-2.65 (1H, m), 2.98 (1H, d, J=10.2Hz), 3.52 (3H, s), 2.48-2.59 (2H, m), 4.44 (1H, dd, J=7.7, 7.8Hz), 4.65 (1H, d, J=11.7Hz), 5.33 (1H, s), 4.99 (1H, d, J=11.5Hz), 7.47 (2H, dd, J=7.5, 7.6Hz), 7,58-7.63 (1H, m) 8.0 (2H, d, J=7.9Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.6, 34.9, 56.4, 56.8, 60.2, 68.9, 106.2, 128.6, 129.5, 133.4, 166.2, 177.6 ppm; IR (neat) 3467 (br), 3066, 2949, 1777, 1718, 1274, 1088, 948 cm^{-1}; MS (CI) m/z 293 (M^+ + 1), 274, 261, 171, 139, 123, 105; HRMS (CI) m/z 293.1025 (calcd for $C_{15}H_{16}O_6$ + H^+: 293.1026).



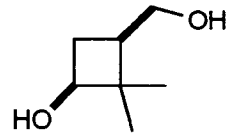
Bicyclic Cyclobutanone 86. To oxallyl chloride (16 mL, 0.18 mmol) in dichloromethane (0.5 mL) at -78 °C was added DMSO (28 mL, 0.37 mmol) in (0.1 mL) dichloromethane (0.1 mL). The reaction mixture was stirred for 2 min

and 0.5 mL of the mixture was removed. To the remaining solution was added the alcohol **86** (3 mg, 0.01 mmol). Stirring was continued for an additional 15 min. Triethylamine (40 mL, 0.29 mmol) was added and reaction mixture was stirred for 5 min and then allowed to warm to room temperature. The mixture was diluted by the addition of ethyl acetate (2 mL) and water (1 mL). The aqueous layer was reextracted by dichloromethane (2 mL). The combined organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. After removal of solvent, the crude mixture was separated through silicon gel packed in a pipette to give 2 mg of pure **86** (69%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.28 (1H, dd, J=3.3, 18.2 Hz) 3.51 (1 H, dd, dd, J=3.3, 10.5 Hz), 3.56 (3H, s), 3.78 (1 H, dd, J=10.47, 18.2 Hz), 4.61 (1H, d, J=12 Hz), 5.46 (1H, d, J=12 Hz), 7.46 (2H, dd, J=7.8, 7.2 Hz), 7.60 (m, 1H), 7.96 (2H, m) ppm; ^{13}C NMR ($CDCl_3$,75 MHz) δ 33.9, 53.3, 57.3, 60.4, 74.4, 102.1, 128.6, 128.9, 129.4, 133.5, 155.6, 175.2, 201.3 ppm; IR (neat) 3069, 2940, 2848, 1794, 1789, 1271, 1111, 945, 704 cm^{-1}; MS (CI) m/z 290 (M^+), 259, 218, 169; HRMS (CI) m/z 290.0970 (calcd for $C_{15}H_{14}O_6$: 290.0970).

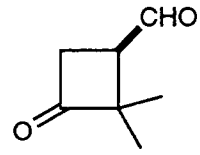


Diester 103. A solution of **102** (2.9 g,15.7 mmol) and m-chloroperoxybenzoic acid (mCPBA) (8.86g ,ca. 50-60%, 26.7 mmol) in dichloromethane (65 mL) was stirred at room temperature for 4 days. The white precipitate was filtered away and the clear solution was washed by saturated aqueous sodium sulfite three times (10 mL). The organic layer was washed by saturated aqueous sodium

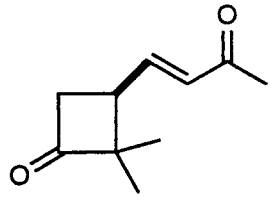
bicarbonate, cold 5% sodium hydroxide and saturated aqueous sodium chloride, then dried over sodium sulfate anhydrous. After concentrated, the crude was purified by chromatography (30% ethyl acetate in hexane) to give 2.9 g of pure **103** as yellow oil (92%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (3H, s), 1.29 (3H, s), 2.04 (3H, s), 2.33 - 2.38 (2H, m), 2.51 (1H, t, 9.0 Hz), 3.69 (3 H, s), 4.69 (1H, t, J=8.16 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 Hz) δ 16.6, 20.6, 28.1, 41.3, 46.1, 51.3, 72.5, 170.5, 172.4 ppm; **IR** (neat) 2951, 1737, 1435, 1364, 1233, 1050 cm $^{-1}$; MS (CI) m/z 201 (M^++1), 141, 115, 109; HRMS (CI) m/z 201.1126 (calcd for $C_{10}H_{16}O_4 + H^+$: 201.11127).



Diol 104. A solution containing ester **103** (2.9 g, 14.5 mmol) in dry THF (30 mL) was added to a slurry of lithium aluminum hydride (4.4 g, 87 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h and then 2 mL of 10% NaOH was added. The resulting mixture was extracted by diethyl ether and the organic solution was washed by saturated aqueous sodium bicarbonate and sodium chloride, and was dried over sodium sulfate anhydrous. After removal of solvent, the residue was purified by chromatography (30% ethyl acetate in hexane) to give 2.7 g of pure product **104** (92 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (3H, s), 1.14 (3H, s), 1.42 - 1.57 (1H, m), 1.69-1.81 (2H, m), 2.32-2.38 (1H, m), 3.62 - 3.67 (2H, m), 3.78 (1H, dd, J=7.6, 15Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.9, 28.6, 31.1, 39.0, 43.2, 63.1, 71.9 ppm; **IR** (neat) 3316 (br), 2959, 2866, 1459, 1132, 1005 cm^{-1}; MS (CI) m/z 131 (M^++ 1), 113, 111, 95; HRMS (CI) m/z 131.1072 (calcd for $C_7H_{14}O_2 + H^+$: 131.1073).

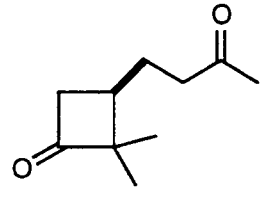


Ketone Aldehyde 105. To a solution of oxally chloride (1.83 mL, 20.9 mmol) in dichloromethane (25 mL) was added DMSO (2.98 mL, 42 mmol). The mixture was stirred for 3 min followed by addition of the diol **104** (1.24 g, 9.5 mmol) in dichloromethane (10 mL). Stirring was continued for 15 min and triethylamine (13.3 mL, 95.3 mmol) was added. The resulting mixture was stirred for 40 min and then allowed to warm up to room temperature and 70 mL of water was added. After separation, the aqueous layer was extracted by dichloromethane (60 mL). The combined organic layer was washed by saturated brine and dried over magnesium sulfate anhydrous. The solvent was removed under reduced pressure. Chromatography of the crude (30% ethyl acetate as eluent) gave 760 mg of pure aldehyde **105** (75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (3H, s), 1.35 (3H, s), 2.93-3.05 (2H, m), 2.93-3.05 (2H, m), 3.56 (1H, dd, J=6.5, 17Hz), 9.86 (1H, d, J=2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 23.5, 42.0, 46.7, 65.1, 200.6, 209.9 ppm. IR (neat) 2964, 2925, 1782, 1714 cm^{-1}. MS (CI) m/z 126 (M^+), 109, 99. HRMS (CI) m/z 126.0681 (calcd for $C_7H_{10}O_2$: 126.0681).



Diketone 106. To a solution of aldehyde **105** (400 mg, 3.17 mmol) in acetonitrile (38 mL) was added lithium chloride (280 mg, 6.98 mmol),

diisopropylethylamine (1.16 mL) and diethyl (2-oxopropyl) phosphonate (0.675 mL, 3.76 mmol). The mixture was stirred for 12 h at room temperature. After the addition of water (30 mL) followed by separation, the aqueous layer was reextracted by diethyl ether (30 mL). The combined organic layer was washed by brine and was dried over sodium sulfate anhydrous. The removal of solvent was followed by column chromatography (50% ethyl acetate in hexane) to yield 420 mg of pure **106** (80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.83 (1H, dd, J+8.2, 1.5 Hz), 6.14 (1H, dd, J=1.0, 15 Hz), 3.32 (1H, dd, J=9.2, 18 Hz), 3.06 (1H, dd, J=7.5, 7.6 Hz), 2.80-2.89 (1H, m). 2.25 (3H, s), 1.22 (3H, s), 1.07 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 22.8, 27.3, 38.9, 47.1, 64.5, 132.3, 145.3, 197.5, 211.6 ppm; **IR** (neat) 3090, 2959, 2925, 1777, 1669, 1620, 1259, 1064, 981 cm^{-1}; MS (CI) m/z 167 (M^++1), 125, 109, 97, 81, 70. HRMS (CI) m/z 167.1072 (calcd for $C_{10}H_{14}O_2 + H^+$: 167.1073).



Diketone 92. A solution of the α,β - unsaturated ketone **106** (100 mg, 0.6 mmol) and palladium on activated carbon (10 mg) in ethyl acetate (2 mL) was stirred under hydrogen for 12 h. After filtrate and removal of solvent, 101 mg of clean product **92** was obtained (100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06(3H, s), 1.14 (3H, s), 1.55-1.68 (1H, m), 1.81-2.08 (2H, m), 2.12 (3H, s), 2.43 (2H, dd, J=1, 8Hz), 2.63 (1H, dd, J=7, 17Hz), 3.05 (1H, dd, J=8.8, 17 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.0, 23.4, 29.9, 35.7, 42.1, 48.1, 60.7, 207.9, 214.2 ppm; IR

(neat) 2954, 1772, 1714, 1362; MS (CI) m/z 169 (M^++1), 115, 126, 113, 99, 85; HRMS (CI) m/z 169.1229 (calcd for $C_{10}H_{16}O_2$ + H^+: 169.1229).

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