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The studies and development of synthetic methods for the synthesis of bioactive natural occurring products

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Iowa State University

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The studies and development of synthetic methods for the synthesis of bioactive naturally occurring products

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Iowa State University, 1993

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The studies and development of synthetic methods for the

synthesis of bioactive natural occurring products

by

Yusheng Wu

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For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1993

DEDICATION

To my parents

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1

GENERAL INTRODUCTION

The various life forms on the earth are composed of thousands of naturally occurring organic compounds. The major goal of science in this century has been to explore the secrets of the formation of all living things and to define a fundamental language of that life at the molecular level. So the synthesis of organic compounds with unique functionalities has become one of the most important area of science.

Synthetic compounds have influenced our daily lives from medicines to perfumes. The field of synthetic organic chemistry will be important for the future of our lives, not only with regard to the health, material and economic needs of our society, but also for the attainment of an understanding of matter, chemical change and life forms at the highest level.

For the past three decades, organic synthesis has been one of the most rapidly developing area of chemistry. New synthetic reagents, reactions and theories are discovered every day. This dissertation has been written for the study and development of synthetic methodologies toward the synthesis of naturally occurring organic compounds. The first part of this dissertation contains a new methodology for the synthesis of angularly fused ring compounds which have often been found to be bioactive. The synthesis of 3-deoxyrabelomycin was achieved by using this methodology. The second part includes some fundamental aspects of photochemical hydrogen atom abstraction reactions. The third part gives the formal total synthesis of podophyllotoxin, which has anti-cancer activity, by utilizing a tandem photoenolization/Diels-Alder reaction. The fourth part contains a new method for the formation of

seven-membered oxocyclic compounds which are common subunits in marine natural products via photochemically induced radical ring opening and closing. The mechanism and effects of the substituents on the ring opening are also discussed. The fifth part demonstrates a new discovery of an intramolecular hydrogen atom abstraction reaction. This method has the potential to be used as an approach to the eight-membered ring marine natural products. The effects of molecular geometry and temperature on the yield of the reaction are also discussed.

This dissertation is organized so that each part represents a publishable or published article. The numbering system adopted for the compounds, schemes and references is independent in each part.

PAPER I

THE SYNTHESIS OF ANGULARLY FUSED AROMATIC RING COMPOUNDS.
THE SYNTHESIS OF 3-DEOXYRABELOMYCIN

INTRODUCTION

The anthracyclines (linearly-fused aromatic compounds) were first encountered by chemists about a half century ago and the earliest efforts at structural characterization appeared in the literature in the 1950's. It has been only within the past fifteen years that anthracyclines have captured the attention of the synthetic community. The principle events which have spawned such enormous interest in anthracycline synthesis were the discovery of adriamycin (**Figure 1**) and the recognition of its broad efficiency in the treatment of human cancers. Later studies also showed that some other anthracycline compounds, such as daunomycinones, have the same anti-cancer activities (**Figure 2**).
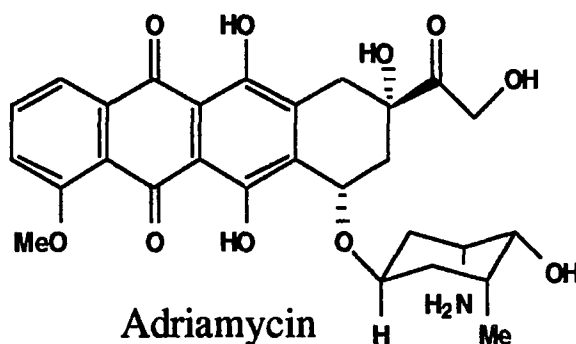
Adriamycin

Figure 1

Since adriamycin has been used as an anti-cancer drug, the total synthesis of anthracyclines has been intensively studied in the last 15 years for the development of new drugs for the treatment of cancers.

Recently, natural products researchers have determined the structures tetracyclic aromatic compouns such as rabelomycin (**1**), ochromycinone (**2**)

and AC5Y (3) which are angularly fused. Quinones (1) and (2) exhibit significantof activity. Among a growing number of synthetic approaches to 1, 2 and 3, only two total syntheses of 2 have been recorded (Figure 3).
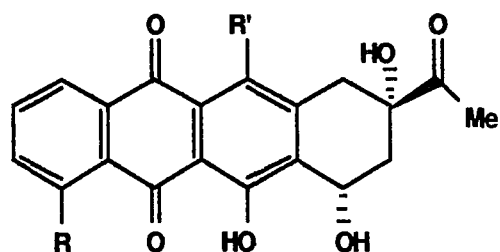
R=H,	R'=OH.	4-Methoxydaunomycinone
R=OMe,	R'=OH.	Daunomycinone
R=OMe,	R'=H.	11-Deoxydaunomycinone
R=OH,	R'=H.	11-Deoxycarminomycinone

Figure 2

1. R=R'=OH
2. R=R'=H

3
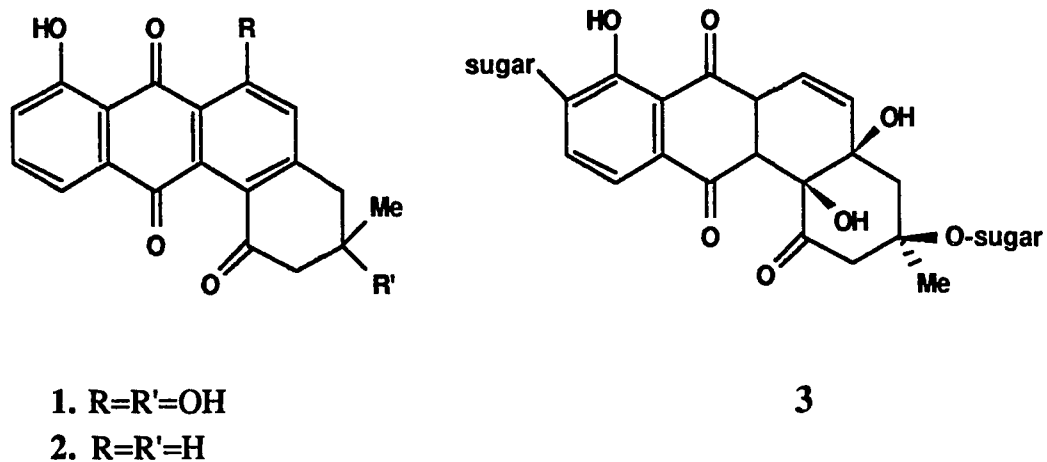
Figure 3

In the first synthesis of ochromycinone, Snieckus and coworkers assembled the angularly-fused tetracyclic ring system by means of their elegant direct ortho metallation protocol.[4] According to his synthesis, the preparation of the requisite 3-methyl-1-tetralol (6)[5] was initiated by the Michael addition of ethyl crotonate with the lithiated species of the dithione 4, followed by hydrogenolysis to give the ester 5. Sequential Friedel-Crafts cyclization and

Snieck:

Ochromycinone
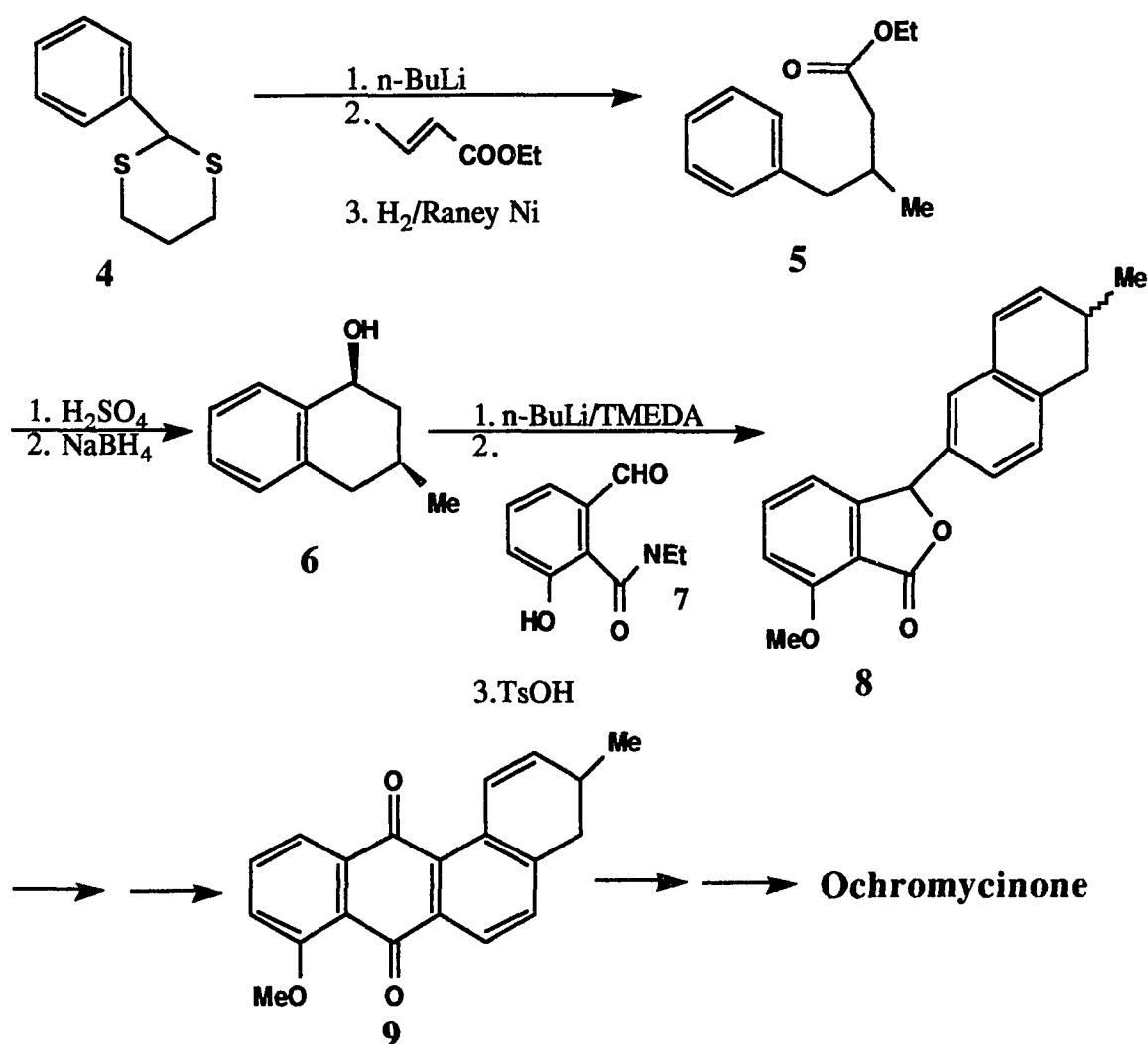
hydride reduction afforded predominantly the *cis-* isomer **6**. The pure *cis-*isomer **6** was metallated and the resulting dilithiated species was coupled with the amide aldehyde **7**, which had been derived from the reaction of lithiated N,N-diethyl-o-anisamide with DMF. The intermediate amide alcohol was not isolated, but subjected to reaction with TsOH in refluxing toluene, to give in good yield the phthalide olefin **8** as a diastereomeric mixture. Zinc hydrogenolysis of **8** in basic solution furnished the benzoic acid which upon TFAA-mediated Friedel-Crafts cyclization in CH_2Cl_2 followed by base-catalyzed aerial oxidation in MeOH, provided the dihydrobenz[a]anthraquinone **9**. Further transformations gave him the final product, ochromycinone.

A second approach to quinone **2** by Guingant[6] featured a Diels-Alder reaction of juglone.[7] In his synthesis, ochromycinone was made via a key [4+2] reaction between the easily prepared juglone **10** and the diene **11**.

Guingant:

$$10 \quad\quad 11 \xrightarrow[CH_2Cl_2]{B(OAc)_3} \quad\quad 2$$
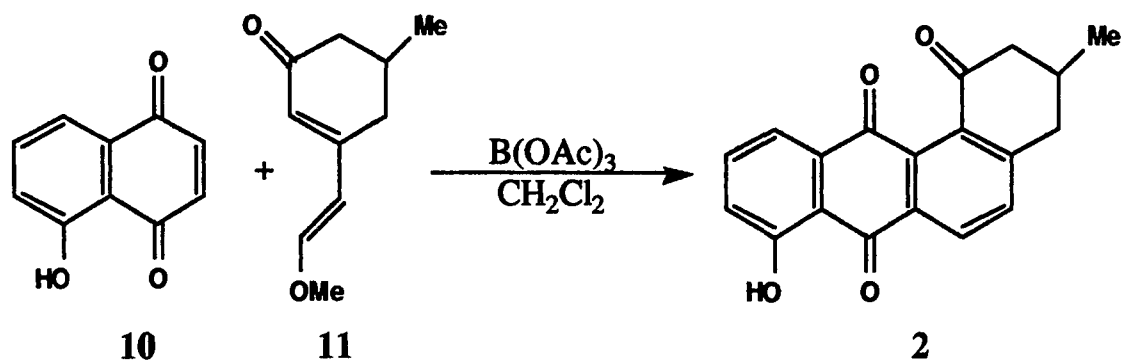
In our pathway, the angularly-fused ring system was assembled by a strategy which is dramatically different from the previously reported pathways. Moreover, our strategy is applicable to the synthesis of **1**, **2** and **3**.

RESULTS AND DISCUSSION

Our synthetic plan is shown in **Scheme I**. The construction of the angularly fused network is readily accomplished by the reaction of the enol silyl ether of a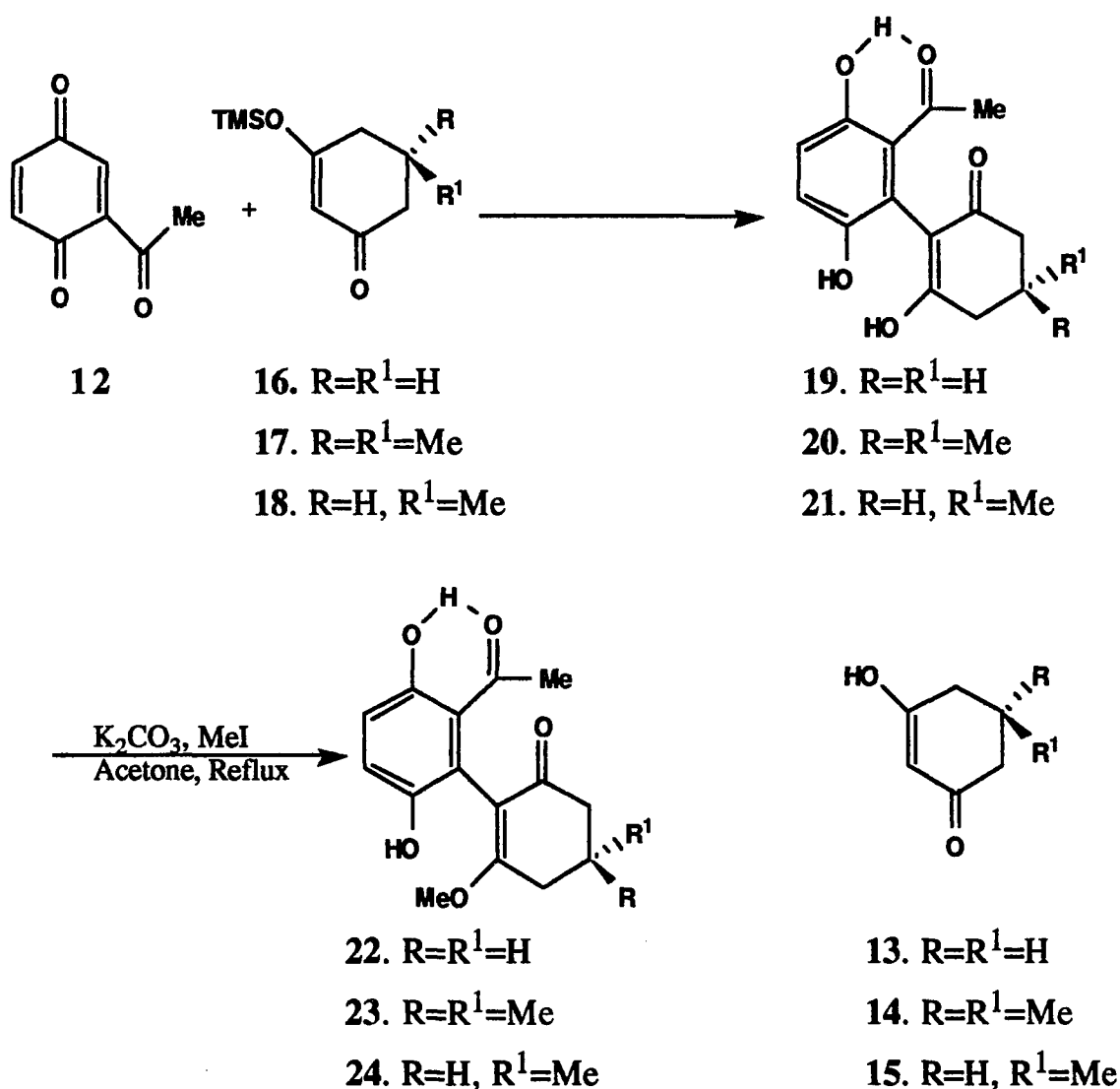 cyclohexane-1,3-dione with either acetylbenzoquinone or 2-acetyl-1,4-naphthoquinone, followed by based-mediated cyclization. The conjugate addition of synthetically useful nucleophiles to electron-deficient quinones was initially studied by Eugster and Fumagali who demonstrated that both dicarbonyl compounds and furans could be employed.[8] Recently, we and others have shown that enol silyl ethers, allylic silanes and electron-rich dienes also react with electron-deficient quinones in good yields[9].

Since cyclohexanediones **13**, **14** and **15** are almost completely enolic in anhydrous solvents,[10] we initially studied the reaction of diketone **13** with acetylbenzoquinone. Although a trace of the desired adduct was formed, the major product seemed to be derived from intermolecular O-alkylation. In order to block this undesired reaction, we prepared the trimethylsilyl enol ether **16**. Acetylbenzoquinone **12** reacted with **16** to provided diketone **19**, which was insoluble in most organic solvents and was absorbed very strongly on silica gel. Both adduct **19** and its gem-dimethyl analog have been reported by Eugster. Treatment of **19** with methyl iodide and potassium carbonate in boiling acetone afforded ether **22** in 56% overall yield. The reaction of the enol silyl ethers of **17** and **18** with acetylbenzoquinone followed by O-methylation furnished ethers **23** and **24** in 68% and 83% overall yield, respectively. Related additions of dicarbonyl compounds to quinone monoketals have been achieved by both Parker and by Duthaler.[11]

Cyclization of compounds similar to ketones **19** and **22** had considerable literature precedent. For example, the synthesis of naphthalene **26** from diketone **25** was accomplished in high yield at ambient temperature[12]. The aldol cyclization of **22** was not readily affected.

Scheme I

12	**16.** R=R^1=H	**19.** R=R^1=H
	17. R=R^1=Me	**20.** R=R^1=Me
	18. R=H, R^1=Me	**21.** R=H, R^1=Me

K$_2$CO$_3$, MeI
Acetone, Reflux

22. R=R^1=H   **13.** R=R^1=H
23. R=R^1=Me   **14.** R=R^1=Me
24. R=H, R^1=Me   **15.** R=H, R^1=Me

Heating compound **22** and excess t-BuOH in DMF in a sealed tube at 100 °C afforded hydroquinone **27** in 32% yield. Optimized conditions for the cyclization of compounds **23** and **24** involved reaction of the ketones with an excess of NaOH in MeOH in a sealed tube at 120 °C. Compounds **28** and **29** were generated in 53% and 60% yields, respectively (**Scheme II**). Although

Tan:

KOH
96%

25   **26**

Scheme II

Base

22. R=R^1=H   **27.** R=R^1=H

23. R=R^1=Me   **28.** R=R^1=Me

24. R=H, R^1=Me   **29.** R=H, R^1=Me
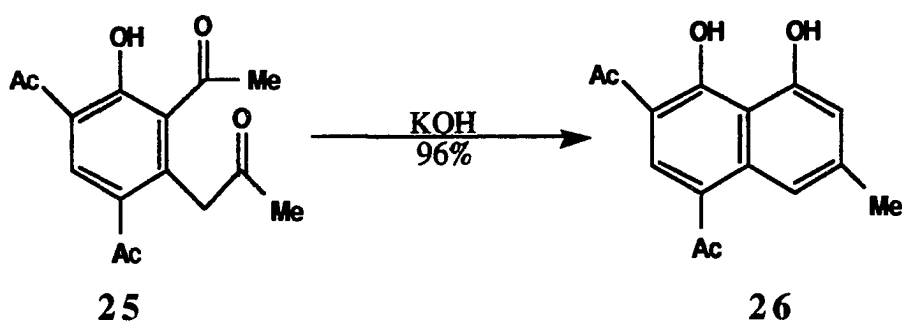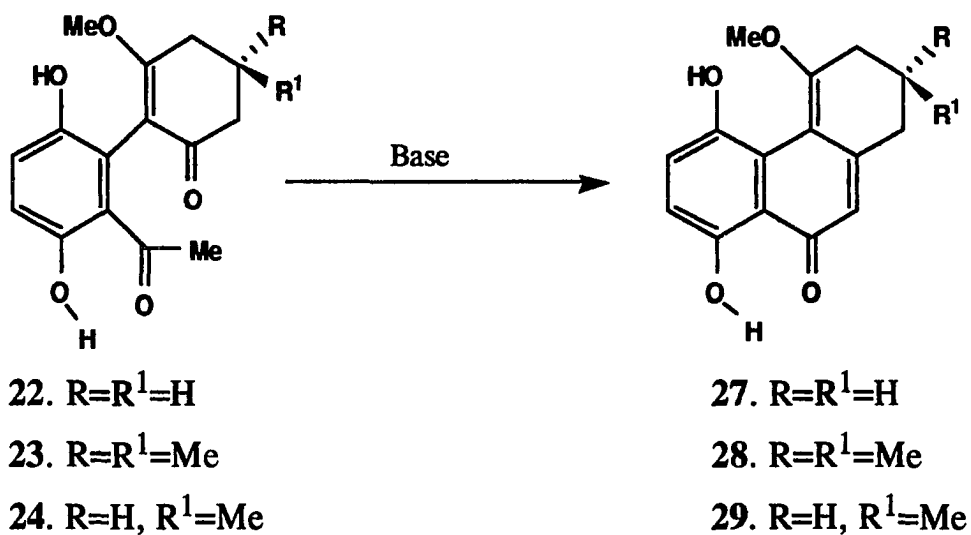
we had expected to isolate a naphthoquinone, the functionality in **28** should be even more useful for eventual conversion to **3**.

The reaction of diketone **15** with 2-acetyl-1,4-naphthoquinone **30** at subambient temperature, followed by methylation, afforded a 52% yield of compound **31**. Attempted cyclization of **31** with NaOH in MeOH at reaction temperatures ranging from 25 ^{0}C to 120 ^{0}C afforded recovered starting material **31** at low temperature and largely decomposition products at higher temperatures. The reaction of **30** in DMF with t-BuOH at 100^0 C provided anthraquinone **34** in 16% yie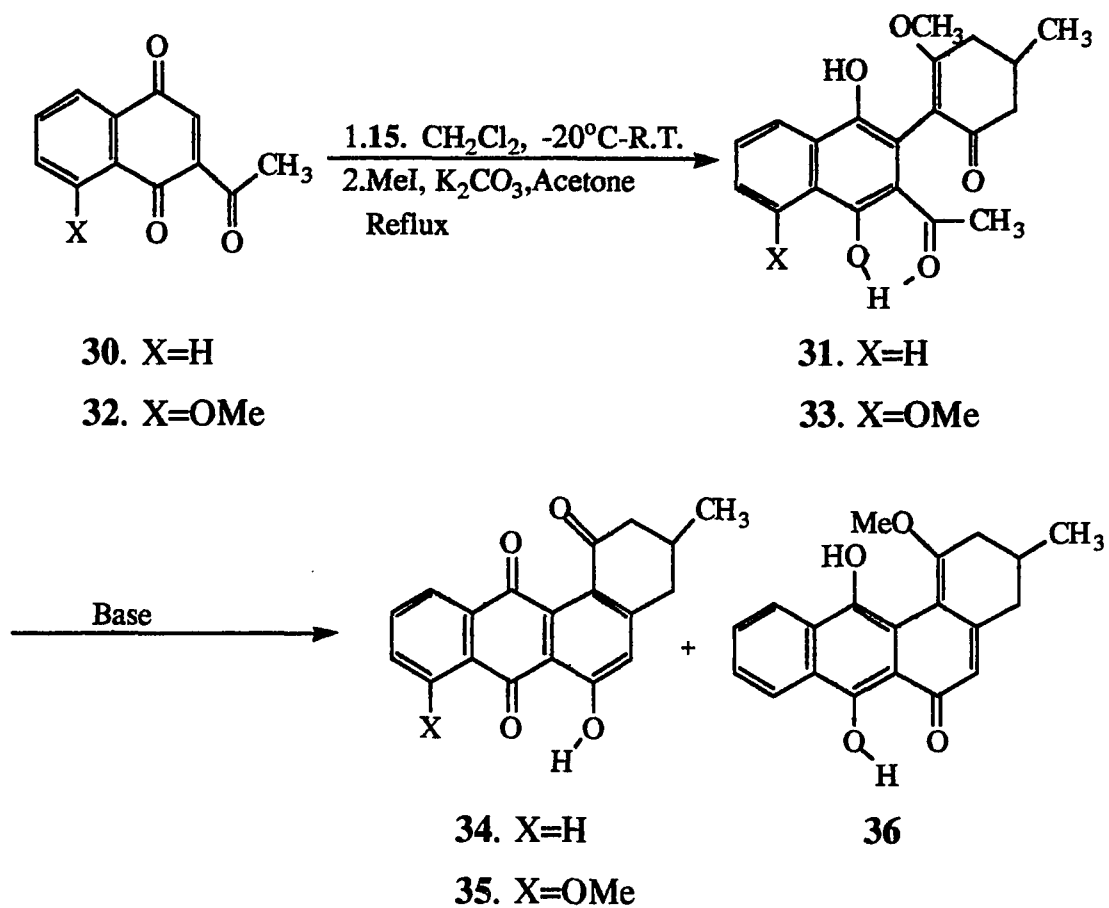ld and naphthalene **36** in 1% yield. Naphthoquinone **32** could be prepared from 7-methoxy-3-cyanophthalide and methyl vinyl ketone in 70% yield.[13] The reaction of **32** with diketone **15**, followed by methylation gave compound **33** in 64% overall yield. The reaction of **33** with NaOH in MeOH at 140 ^{0}C for 14 hours provided anthraquinone **35** in 27% isolated yield (**Scheme III**).

Anthraquinone **35** contains the entire skeleton of **1**. Conversion into 3-deoxyrabelomycin **37** requires the deprotection of the phenol at C-8. In contrast with our successful results with the anthracyclines[14], attempted demethylation of **35** using boron trichloride in methylene chloride led to recovered starting material. Demethylation had been previously achieved using aluminum chloride.[15] Reaction of **35** with AlCl$_3$ at 25 ^{0}C afforded a 58% yield of 3-deoxyrabelomycin (**37**).

The direct preparation of **37** from naphthoquinone **32** illustrates the potential of our methodology. Anthraquinone **37** is available in four steps in approximately 30% overall yield. Additionally, naphthalene **29** represents an attractive precursor to compound **3** (**Scheme IV**).

Scheme III
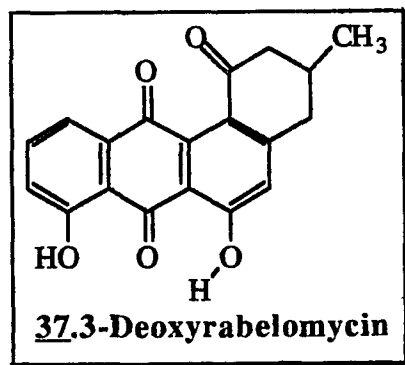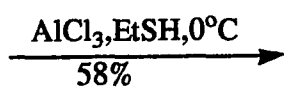
30. X=H

32. X=OMe

1.15. CH₂Cl₂, -20°C-R.T.
2.MeI, K₂CO₃,Acetone
Reflux

31. X=H

33. X=OMe

Base

34. X=H

35. X=OMe

+

36

Scheme IV

35 $\xrightarrow[\text{58\%}]{\text{AlCl}_3,\text{EtSH},0^\circ\text{C}}$

37.3-Deoxyrabelomycin

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all the reactions were conducted under an argon atmosphere. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 1320 spectrophotometer. Nuclear Magnetic Resonance (NMR) spectra were determined on a 300 MHz Nicolet Magnetic Corporation NMC-1280 spectrometer. All chemical shifts were reported relative to tetramethylsilane as an internal standard. Coupling constants were reported in Hz. Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, ABq=ABquartet. Carbon-13 NMR spectra were determined on a Nicolet NMc-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. H:EA referred to hexane/ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR spectrocopic analysis and /or elemental analyses.

2-Acetyl-3-(3-methoxycyclohex-2-en-1-on-2-yl-2)-1,4-dihydrobenzoquinone (22):

To 2.24 grams (20.0 mmol) of 1,3-cyclohexanedione (13) in 50 mL of acetonitrile, bis(trimethylsilyl)acetamide (BTSA) (4.07 g, 20.0 mmol) was added dropwise at room temperatures. The mixture was allowed to stir at room temperatures for about two hours. The solvent was evaporated in vacuo and the residue (crude compound 16) was used for the next step without further purification.

The enol silyl ether 16 was dissolved in 80 mL of CH_2Cl_2 and the solution was cooled to -20 °C. Acetylquinone 12 (3.0 g, 20.0 mmol) in 20 mL of CH_2Cl_2 was added to the solution dropwise. The mixture was then allowed to warm to room temperatures and stirred for another four hours. The solvent was evaporated and the residue was used for the next step without further purification.

The residue (crude compound 19) was dissolved in 150 mL of acetone and MeI (11.36 g, 80.0 mmol) and $K_2CO_3 \cdot 3/2H_2O$ (33.0 g, 200.0 mmol) were added. The mixture was then boiled overnight and cooled to room temperatures and poured into about 200 mL of ether. The ether solution was washed with water and with brine and dried over $MgSO_4$. The solution was then filtered, evaporated and separated by sgc (H:EA=3:1) to give 3.06 grams of pale yellow solid compound 22 (56.3% overall yield for three steps from compound 13).

Compound 22: ^1H NMR (CDCl$_3$) δ (ppm) 7.43 (d, J=9.0 Hz, 1 H) , 6.94 (d, J=9.0 Hz, 1 H), 3.82 (s, 3 H), 3.03 (ABq, J$_1$=6.0 Hz, J$_2$=6.3 Hz, 2 H), 2.67 (s, 3 H), 2.59 (ABq, J$_1$=6.3 Hz, J$_2$=6.6 Hz, 2 H), 2.26 (m, 2 H); IR (film)

2943, 1709, 1674, 1593, 1429, 1258, 1090 cm^{-1}; CI-MS (NH$_3$) for C$_{15}$H$_{16}$O$_4$ 261 (M+1); TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.26.

2-Acetyl-3-(3-methoxy-5,5-dimethylcyclohex-2-en-1-on-2-yl)-1,4-dihydrobenzoquinone (23): n-BuLi (14.0 mmol, 2.52M, 5.55 mL) was added to 2.12 mL (16.8 mmol) of purified diisopropylamine in 100 mL of THF solution at 0 °C. The mixture was allowed to stir at 0 °C for at least 0.5 hour before being cooled to -78 °C. 5,5-Dimethyl-1,3-cyclohexanedione (**14**) (1.96 g, 14.0 mmol) in 20 mL of THF was then added dropwise to LDA solution. The mixture was stirred at -78 °C for about 2 hours and 1.80 mL (16.8 mmol) of TMSCl was added slowly. The mixture was allowed to warm to room temperatures and was poured into about 150 mL of pentane. The salt was filtered out and the solvent was evaporated. The residue (crude compound **17**) was used for the next step without further purification.

The enol silyl ether **17** was dissolved in 60 mL of CH$_2$Cl$_2$ and the solution was cooled to -20 °C. Acetylquinone **12** (2.10 g, 14.0 mmol) in 20 mL of CH$_2$Cl$_2$ was added to the solution dropwise. The mixture was then allowed to warm to room temperature and stirred for another four hours. The solvent was evaporated and the residue was used for the next step without further purification.

The residue (crude compound **20**) was dissolved in 100 mL of acetone and 19.88 grams (140.0 mmol) of MeI and 23.13 grams (140.0 mmol) of K$_2$CO$_3$.3/2H2O were added. The mixture was then boiled overnight and cooled to room temperature and poured into about 200 mL of ether. The ether solution was washed with water and with brine and dried over MgSO$_4$. The

solution was then filtered, evaporated and separated by sgc (H:EA=3:1) to give 2.87 grams of pale yellow solid compound **23** (67.5% overall yield for three steps from compound **15**).

Compound **23**: ^{1}H NMR δ (ppm) 7.38 (d, 1 H), 6.87 (d, 1 H), 3.82 (s, 3 H), 2.85 (s, 2 H), 2.63 (s, 3 H), 2.42 (s, 2 H), 1.15 (s, 6 H); IR (film) 2959, 1709, 1674, 1254, 1090 cm^{-1}; CI-MS (NH$_3$) m/z for C$_{17}$H$_{20}$O$_4$ 289 (M+1); TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.46.

2-Acetyl-3-(3-methoxy-5-methyl-1,2-cyclohexenon-2-yl)-1,4-dihydrobenzoquinone (24):

n-BuLi (7.93 mmol, 2.52M, 3.20 mL) was added to 1.20 mL (9.51 mmol) of purified diisopropylamine in 50 mL of THF solution at 0 $^{\circ}$C. The mixture was allowed to stir at 0 $^{\circ}$C for at least 0.5 hour before cooled to -78 $^{\circ}$C. 5-Methyl-1,3-cyclohexanedione (**15**) in 10 mL of THF was then added to LDA solution dropwise. The mixture was stirred at -78 $^{\circ}$C for about 2 hours and 1.20 mL (9.51 mmol) of TMSCl was added slowly. The mixture was allowed to warm to room temperature and was poured into about 200 mL of pentane. The salt was filtered out and the solvent was evaporated. The residue (crude compound **18**) was used for the next step without further purification.

The enol silyl ether **18** was dissolved in 60 mL of CH$_2$Cl$_2$ and the solution was cooled to -20 $^{\circ}$C. Acetylquinone **12** (1.20 g, 7.93 mmol) in 10 mL of CH$_2$Cl$_2$ was added to the solution dropwise. The mixture was then allowed to warm to room temperature and stirred for another four hours. The solvent was evaporated and the residue was used for the next step without further purification.

The residue (crude compound **21**) was dissolved in 100 mL of acetone and 11.26 grams (79.3 mmol) of MeI and 13.10 grams (79.3 mmol) of $K_2CO_3 \cdot 3/2H2O$ were added. The mixture was then boiled overnight and cooled to room temperature and was poured into about 100 mL of ether. The ether solution was washed with water and with brine and dried over $MgSO_4$. The solution was then filtered, evaporated and separated by sgc (H:EA=3:1) to give 1.78 grams of pale yellow solid compound **24** (82.5% overall yield for three steps from compound **15**).

Compound **24**: ^1H NMR ($CDCl_3$) δ (ppm) 7.40 (d, J=9.0 Hz, 1 H), 6.92 (d, J=9.0 Hz, 1 H), 3.85 (s, 3 H), 3.15 (ABq, 1 H), 2.59 (m, 3 H), 2.65 (s, 3 H), 2.31 (ABq, 1 H), 1.21 (d, J=6.3 Hz, 3 H); IR (film) 2955, 2872, 2837, 1711, 1672, 1582, 1258 cm^{-1}; CI-MS (NH_3) m/z for $C_{16}H_{18}O_5$ 290 (M); TLC (Et_2O:Hexane:EtOH=20:10:1) Rf=0.34.

1,4-Dihydroxy-5-methoxy-10-oxo-7,8,9-trihydrophenanthrene (27): Compound **22** (0.200 g, 0.729 mmol) was dissolved in about 2.0 mL of DMF to which 0.410 grams (3.64 mmol) of t-BuOK was added. The mixture was stirred at 100^0C in a sealed tube for 24 hours. The solution was cooled to room temperature, and was poured into 10 mL of ice water and neutralized by 2N HCl to pH=6. Then the aqueous solution was extracted by ether for three times. The combined organic layer was washed with brine and dried over $MgSO_4$ The solvent was evaporated and the residue was separated by sgc (H:EA=6:1) to afford 0.060 g of red solid compound **27** in 32.1% yield.

Compound **27**: ^1H NMR ($CDCl_3$) δ (ppm) 10.91 (s, 1 H), 10.17 (s, 1 H), 7.21 (d, J=8.7 Hz, 1 H), 7.00 (d, J=8.7 Hz, 1 H), 6,74 (s, 1 H), 4.11 (s, 3

H), 3.10 (t, 2 H), 2.87 (t, 2 H), 2.13 (m, 2 H); IR (film) 3280, 2960, 2920, 1709, 1620, 1360, 1220 cm^{-1}; HRMS: m/z for $C_{15}H_{14}O_4$ Calcd 258.08921 measured 258.08884; TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.49.

1,4-Dihydroxy-7,7-dimethyl-5-methoxy-10-oxo-7,8-dihydrophenanthrene (28): Compound 23 (0.140 g, 0.460 mmol) was dissolved in about 10.0 mL of MeOH to which 0.092 grams (2.30 mmol) of NaOH was added. The mixture was stirred at 120 °C in a sealed tube overnight. The solution was cooled to room temperature, poured to 10 mL of ice water and neutralized by 2N HCl to pH=6. Then the aqueous solution was extracted by ether for three times. The combined organic layer was washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was separated by sgc (H:EA=6:1) to afford 0.070 g of red solid compound 28 in 53.0% yield.

Compound 28: ^{1}H NMR δ (ppm) 10.89 (s, 1 H), 10.59 (s, 1 H), 7.13 (d, J=8.4 Hz, 1 H), 6.93 (d, J=8.7 Hz, 1 H), 6.64 (s, 1 H), 4.06 (s, 1 H), 2.95 (s, 2 H), 2.70 (s, 2 H), 1.12 (s, 6 H); IR (film) 3267, 2957, 1637, 1614, 1514, 1431, 1263, 1153 cm^{-1}; HRMS: m/z for $C_{17}H_{18}O_4$ Calcd 286.12051, measured 286.11978; TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.52.

1,4-Dihydroxy-5-methoxy-7-methyl-10-oxo-7,9-dihydrophenanthrene (29): Compound 24 (0.200 g, 0.609 mmol) was dissolved in about 10 mL of MeOH to which 0.140 grams (3.45 mmol) of NaOH was added. The mixture was stirred at 120 °C in a sealed tube for 20 hours. The solution was cooled to room temperature, poured to 10 mL of ice

water and neutralized by 2N HCl to pH=6. Then the aqueous solution was extracted by ether three times. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was separated by sgc (H:EA=6:1) to afford 0.120 g of red solid compound **29** in 60.0% yield.

Compound **29**: ^{1}H NMR ($CDCl_3$) δ (ppm) 10.87 (s, 1 H), 10.30 (s, 1 H), 7.15 (d, 1 H), 6.95 (d, 1 H), 6.67 (s, 1 H), 2.90 (m, 3 H), 2,43 (m, 2 H), 1.16 (d, J=6.6 Hz, 3 H); IR (film) 3281, 2953, 2841, 1638, 1514, 1431, 1265, 1232 cm^{-1}; HRMS: m/z for $C_{16}H_{16}O_4$ Calcd 272.10432, measured 272.10486; TLC (Et_2O:Hexane:EtOH=20:10:1) Rf=0.35.

3-Acetyl-2-(3-methoxy-5-methylcyclohex-2-en-1-on-2-yl) - 1,4-dihydronaphthoquinone (31): 2-Acetylnaphthoquinone (**30**) (0.200 g, 1.00 mmol) was dissolved in 30.0 mL of CH_2Cl_2 and the solution was cooled to -20 $^{\circ}$C. The dione **15** in 5.0 mL of CH_2Cl_2 was then added to the solution dropwise. The mixture was allowed to warm to room temperature and stirred overnight at room temperature. The solvent was evaporated and the residue was used for the next step without further purification.

The residue was dissolved in 100 mL of acetone to which 1.414 grams (10.0 mmol) of MeI and 1.652 grams (10.0 mmol) of K_2CO_3.3/2H2O had been added. The mixture was then allowed to reflux overnight before cooled to room temperature and poured into 200 mL of ether. The ether solution was washed with water three times and with brine and dried over $MgSO_4$. Then the dry reagent was filtered out and the solvent was evaporated in vacuo. The

residue was separated by sgc (H:EA=4:1) to produce 0.1443 grams of solid compound **31** in 52.2% overall yield from compound **30**.

Compound **31**: ^{1}H NMR (CDCl$_3$) δ (ppm) 8.22 (m, 2 H), 7.83 (m, 2 H), 3.96 (s, 3 H), 3.21 (ABq, J$_1$=6.9 Hz, J$_2$=17.1 Hz, 1 H), 2.68 (m, 3 H), 2.73 (s, 3 H), 2.38 (ABq, J$_1$=6.0 Hz, J$_2$=17.1 Hz, 1 H), 1.27 (d, J=6.3 Hz, 3 H); IR (film) 2959, 1709, 1695, 1456, 1396, 1275, 1153 cm^{-1}; CI-MS (NH$_3$) m/z for C$_{20}$H$_{20}$O$_5$ 340 (M); TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.50.

3-Acetyl-2-(3-methoxy-5-methylcyclohex-2-en-1-on-2-yl)-5-methoxy-1,4-dihydronaphthoquinone (33):   3-Acetyl-5-methoxy-1,4-dihydronaphthoquinone (0.163, 0.703 mmol), Ag$_2$O (0.410 g, 1.76 mmol) and MgSO$_4$ (0.210 g, 1.76 mmol) were added to 25.0 mL of PhH. The mixture was stirred for six hours at room temperature and filtered. The solvent was evaporated in vacuo and the residue (crude compound **32**) was used for the next step without further purification.

The crude compound **32** was dissolved in 10.0 mL of CH$_2$Cl$_2$ and 0.0976 g (0.773 mmol) of the dione compound **15** was then added to the solution at room temperature. The mixture was allowed to stir at room temperature overnight and the solvent was evaporated in vacuo and the residue was used for the next step without further purification.

The residue was dissolved in 80.0 mL of acetone to which 0.440 mL (7.03 mmol) of MeI and 1.16 grams (7.03 mmol) of K$_2$CO$_3$.3/2H2O were then added. The mixture was allowed to reflux overnight, cooled to room temperature and poured into 100.0 mL of ethyl ether. the solution was then washed with water twice and with brine and dried over MgSO$_4$. The dry

reagent was filtered out and the solvent was evaporated in vacuo and the residue was separated by sgc (H:EA=3:1) to afford 0.167 g of solid compound 33 in 64.0% yield.

Compound 33: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.87 (d, J=8.1 Hz, 1 H), 7.54 (ABq, J$_1$=7.8 Hz, J$_2$=8.1 Hz, 1 H), 6.97 (d, J=7.8 Hz, 1 H), 4.05 (s, 3 H), 3.83 (s, 3 H), 3.23 (ABq, J$_1$=4.8 Hz, J$_2$=17.4 Hz, 1 H), 2.80 (ABq, J$_1$=9.6 Hz, J$_2$=17.4 Hz, 1 H), 2.73 (s, 3 H), 2.67 (ABq, J$_1$=3.9 Hz, J$_2$=16.2 Hz, 1 H), 2.58 (m, 1 H), 2.37 (ABq, J$_1$=11.1 Hz, J$_2$=15.9 Hz, 1 H), 1.26 (d, J=6.3 Hz, 3 H); IR (film) 3020, 2920, 1710, 1680, 1580, 1400, 1040 cm^{-1}; TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.50.

6-Hydroxy-3-methyl-1-oxo-2,3,4-trihydrobenz[a]anthrancen-7,12-dione (34) and 7,12-dihydroxy-1-methoxy-3-methyl-6-oxo-2,3,4-trihydrobenz[a]anthrancene (36): Compound 31 (0.290 g, 0.853 mmol) was dissolved in about 10.0 mL of DMF to which 0.485 grams (4.32 mmol)of t-BuOK was then added. The mixture was stirred at 100 $^{\circ}$C in a sealed tube for 24 hours. The solution was cooled to room temperature and poured into 10 mL of ice water and neutralized by 2N HCl to pH=6. Then the aqueous solution was extracted by ether for three times. The combined organic layer was washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was separated by sgc (H:EA=6:1) to afford 0.0035 g of solid compound 34 in 1.3% yield and 0.0431 g of compound 36 in 16.0% yield, respectively.

Compound 34: ^{1}H NMR (CDCl$_3$) δ (ppm) 8.24 (m, 1 H), 7.79 (m, 1 H), 7.00 (s, 1 H), 2.95 (m, 1 H), 2.51 (m, 3 H), 1.19 (d, J=6.0 Hz, 3 H); IR

(film) 3271, 3065, 2955, 2924, 1661, 1639, 1595, 1273, 1070 cm-1; CI-MS (NH$_3$) m/z for C$_{19}$H$_{14}$O$_4$ 307 (M+1); TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.64.

Compound **36**: ^{1}H NMR (CDCl$_3$) δ (ppm) 12.11 (s, 1 H), 11.50 (s, 1 H), 8.69 (m, 1 H), 8.08 (m, 1 H), 7.59 (m, 2 H), 6.61 (s, 1 H), 4.08 (s, 3 H), 2.93 (m, 3 H), 2.43 (m, 2 H), 1.20 (d, J=6.0 Hz, 3 H); IR (film) 3071, 2957, 2926, 1699, 1676, 1639, 1456, 1366, 1290 cm^{-1}; CI-MS(NH$_3$) m/z for C$_{20}$H$_{18}$H$_4$ 323 (M+1); TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.65.

6-Hydroxy-8-methoxy-3-methyl-1-oxo-2,4-dihydrobenz[a]anthrancen-7,12-dione (35): Compound **33** (0.167 g, 0.450 mmol) was dissolved in about 5.0 mL of MeOH to which 0.180 grams (4.50 mmol) of NaOH was added. The mixture was stirred at 140 °C in a sealed tube for 14 hours. The solution was cooled to room temperature, poured into 5.0 mL of ice water and neutralized by 2N HCl to pH=6. Then the aqueous solution was extracted by ether for three times. The combined organic layer was washed with brine and dried over MgSO$_4$. The solvent was evaporated in vacuo and the residue was separated by sgc (H:EA=6:1) to generate 0.0406 g of compound **35** in 26.8% yield.

Compound **35**: ^{1}H NMR (CDCl$_3$) δ (ppm) 13.05 (s, 1 H), 7.74 (m, 2 H), 7.32 (m, 1 H), 6.96 (s, 1 H), 4.06 (s, 3 H), 2.91 (m, 2 H), 2.49 (m, 3 H), 1.18 (d, J=6.3 Hz, 3 H); IR (film) 2930, 1695, 1674, 1637, 1474, 1456, 1265, 1221 cm^{-1}; HRMS for C$_{20}$H$_{16}$O$_5$ Calcd. 336.09977, measured 336.09887; TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.45.

3-Deoxyrabelomycin (37): To a solution of AlCl$_3$ (0.0430 g, 0.320 mmol) in 1.50 mL of EtSH at 0^{0}C, 0.0107 grams (0.0318 mmol) of **35** was added. The mixture was allowed to stir at 0^{0}C for about 2.5 hours, poured into 5.0 mL of ice water and the aqueous layer was extracted by ethyl ether three times. The combined ether solution was then washed by brine and dried over MgSO$_4$. The solvent was evaporated in vacuo and the residue was separated by sgc (H:EA=2:1) to give 0.0032 g of compound **37** in 33.1%.

Compound **37:** ^{1}H NMR (CDCl$_3$) δ (ppm) 12.30 (s, 1 H), 11.70 (s, 1 H), 7.67 (m, 2 H), 7.27 (s, 1 H), 7.00 (s, 1 H), 3.04-2.40 (m, 5 H), 1.18 (d, J=6.0 Hz, 3 H); IR (film) 3260, 1690 cm^{-1}; HRMS m/z for C$_{19}$H$_{14}$O$_5$ Calcd. 322.08391, measured 322.08412; TLC (Et$_2$O:Hexane:EtOH=20:10:1) Rf=0.21.

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PAPER II.

PHOTOCHEMICAL HYDROGEN ATOM ABSTRACTION

INTRODUCTION

In much of synthetic chemistry, chemical reactions are initiated by the application of thermal energy to the reaction. We understand this in terms of the need to overcome some energy barrier to the formation of products. In order to increase the efficiency of the reaction, we can supply thermal energy by raising the temperature (heating mantle, water or oil bath, oven, etc.) thereby increasing the average internal (translational, rotational and vibrational) energy of the molecules. Collisions between molecules with internal energies in excess of the barrier succeed in forming the reaction products. Obviously, the thermal route is the one most adopted in synthetic organic chemistry, but there are many instances where this route is unsatisfactory.

Photochemistry, however, offers possibilities of initial chemical processes that appear to have no analog in the thermal chemistry. The introduction of electromagnetic radiation into the scheme effectively " changes the rules " and opens up a whole new set of possibilities. It offers a chance to access reactions that can not be approached by the thermal conditions.

In this extremely broad field, the photochemical reactions of ketones and aldehydes are the most interesting and studied reactions due to their photochemical reactivity. The polarization of the C=O group in the ground state, which accounts for the facile nucleophilic attack at the carbonyl carbon, is replaced in the excited state by an unpaired electron in both a π^* antibonding orbital and in a p-type orbital on oxygen. The net result is that the oxygen, as well as its n orbital, is now electron-deficient, while the carbon atom becomes

somewhat electron-rich and hence can exhibit marked nucleophilic behavior. In the (n, π^*) triplet state, any zwitterionic nature of the carbonyl group is destabilized since the electrons, having parallel spins, are as far removed from one another as possible. Thus, n, π^* triplet carbonyl chromophores have chemical and physical characteristics of a biradical and in particular have appreciable similarities to alkoxy radicals (RO•) with respect to α-cleavage reactions, their hydrogen abstraction abilities, and reaction with carbon-carbon multiple bonds.

The energy difference between the singlet and triplet (n, π^*) state of aliphatic ketones is smaller than that of ethenes, but intersystem crossing (I.S.C) in some cases is still sufficiently slow to allow chemical reaction of the (n, π^*) singlet to occur. However, since the energy and electron distribution in the two states are similar, the same type of processes, although probably occurring at different rates, are to be expected and reaction may occur from the singlet or triplet states or from a mixture of the two. In conjugated systems, such as aryl ketones and enones, the (n, π^*) and (π, π^*) excited singlet states are lower in energy and hence the associated absorptions are at longer wavelengths compared to those in the isolated chromophores. Furthermore, the rate coefficients for intersystem crossing are increased appreciably by conjugation and the quantum yield of this process for aryl aldehydes and ketones and for enones is unity or very close to unity.

Concerning with the triplet (n, π^*) and (π, π^*) states of such carbonyl compounds, which of the two is the lower energy state depends on the nature and position of substituents on the aryl group or C=C double bond of the conjugated carbonyl compound and on solvent characteristics.

In the $(\pi-\pi^*)$ transition, the electron density at the carbonyl group is increased. Thus, electron donor substituents which are in conjugation with the carbonyl group reinforce this effect, stabilizing this triplet and destabilizing the (n, π^*) triplet state. Conversely, since there is a movement of electron density away from the oxygen in a $(n-\pi^*)$ transition, this state becomes stabilized relative to the (π, π^*) triplet by the presence of substituents which are inductively electron accepting.

Increasing the solvent polarity causes a hypo chromic shift (i.e. to shorter wavelength) of (n, π^*) absorption and a bathochromic shift (i.e. to longer wavelengths) of (π, π^*) absorptions. The overall effect is that polar solvents stabilize the (π, π^*) triplet relative to the (n, π^*) triplet and this can lead to an inversion of these states.

An excited carbonyl group can undergo a number of competitive reactions. Hydrogen atom abstraction by photoexcited carbonyl compounds has played a central role in the development of a general picture of how photochemical reactions occur. Intermolecular and intramolecular versions of this process are very valuable process for the obtention of polycyclic molecules which are common framework in natural products. It is now accepted that hydrogen abstraction in nonpolar solvents from (n, π^*) triplet state may be delivered intermolecularly by a suitable donor molecule, or it may be abstracted intramolecularly from a CH unit which is spatially close to the excited carbonyl group.
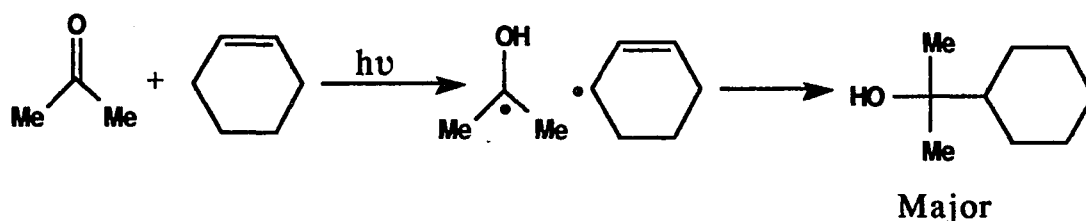
INTERMOLECULAR HYDROGEN ABSTRACTION

The (n, π^*) excited state of ketones and aldehydes can abstract a hydrogen atom intermolecularly from a suitable donor molecule (**Scheme I**). Since aliphatic ketones and aldehydes undergo intersystem crossing more slowly than the corresponding aromatic compounds, the hydrogen abstraction may occur from singlet and triplet states for the aliphatic compounds, whereas the process arises solely from the triplet excited state in the aromatic series.

Scheme I:

Carbonyl compounds which have a (n, π^*) triplet state as the lowest exited state abstract hydrogen from donor molecules efficiently. However, when the (π, π^*) triplet state is the lowest excited state, then photoreduction does not occur or has a very low efficiency. This inefficiency is a result of the relatively high electron density on the oxygen atom in the (π, π^*) state. By comparison, the radical-like structure of the (n, π^*) triplet state is much more able to abstract

hydrogen from donor molecules. The primary products from hydrogen

abstraction by a carbonyl compound are ketyl radical ($R_2\overset{\bullet}{C}$-OH) and the

radical of the hydrogen donor molecule. Ketyl radicals may dimerize to give

pinacols, they may undergo further hydrogen abstraction from the donor

molecule yielding secondary alcohols, or they may combine with the donor

radicals yielding adducts. The preferred final products depends upon the

relative rates of these secondary processes and varies appreciably from system

to system (**Scheme II** and **Scheme III**).

Irradiation of acetone in cyclohexene yields mainly the addition product

by radical combination whereas the major products from the anthrone ethyl

ether system arisen by disproportionation of the ketyl and substrate radicals.

In most systems dimerization of the ketyl radical is a minor process, but,

benzophenone gives high yields of the pinacol and acetone from the irradiation

of its propane-2-ol solution (**Scheme IV**) .

As we know, solvent and substitution can influence the nature of the

lowest excited state of unsaturated carbonyl compounds [i.e., $^3(n, \pi^*)$ or

$^3(\pi, \pi^*)$]. Hence, since the photoreduction arises from the $^3(n, \pi^*)$ state, the

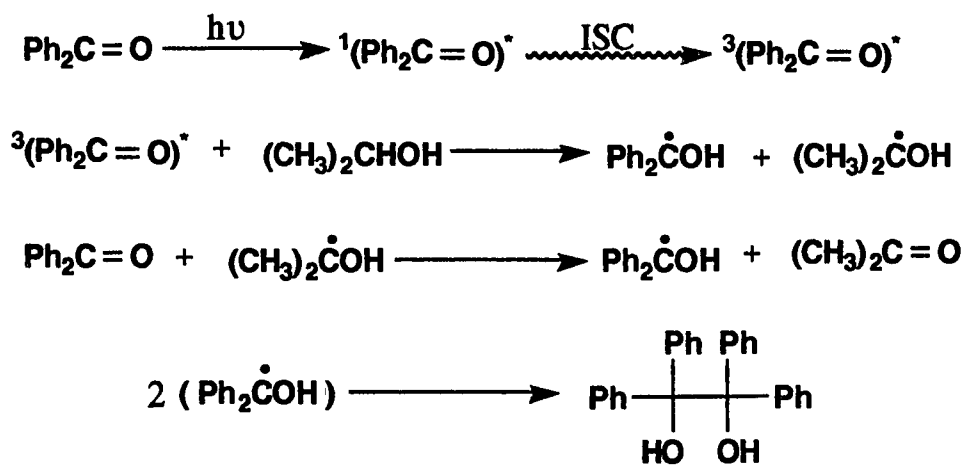efficiency of the process can be markedly affected by a change in solution

Scheme II:

Major

Scheme III:

Scheme IV:

$$Ph_2C = O \xrightarrow{h\upsilon} {}^1(Ph_2C = O)^* \xrightarrow{ISC} {}^3(Ph_2C = O)^*$$

$${}^3(Ph_2C = O)^* + (CH_3)_2CHOH \longrightarrow Ph_2\overset{\bullet}{C}OH + (CH_3)_2\overset{\bullet}{C}OH$$

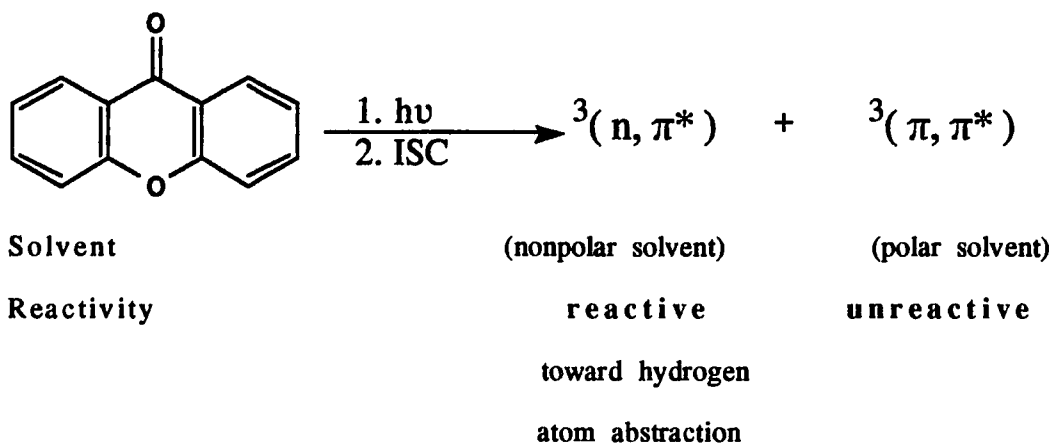$$Ph_2C = O + (CH_3)_2\overset{\bullet}{C}OH \longrightarrow Ph_2\overset{\bullet}{C}OH + (CH_3)_2C = O$$
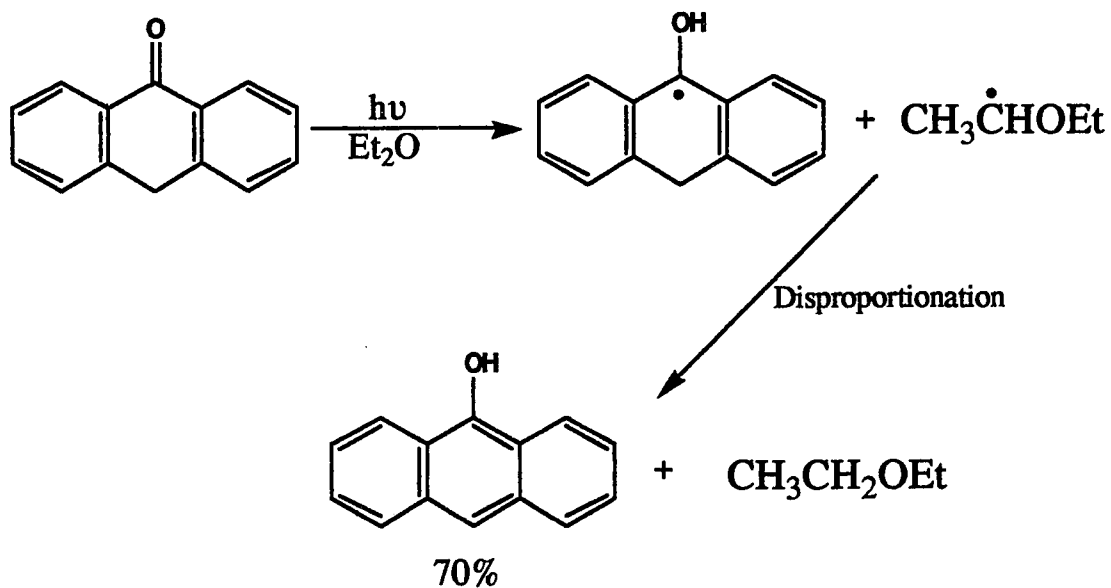
polarity and by the nature and position of substituents on the compounds.

Scaiano found that the abilities of hydrogen abstraction of xanthon was largely depended on the solvent polarization (**Scheme V**).[1]

However, all types of aryl ketones, whether they have low lying (n, π^*) or (π, π^*), charge transfer can effectively reduce those ketones to give photoadducts in nonpolar solvents in the presence of compounds with low ionization potentials (i.e., electron donors). In particular, the reactions of

Scheme V:

$$\xrightarrow[\text{2. ISC}]{\text{1. h}\upsilon} \quad {}^3(\text{n}, \pi^*) \quad + \quad {}^3(\pi, \pi^*)$$

Solvent	(nonpolar solvent)	(polar solvent)
Reactivity	reactive toward hydrogen atom abstraction	unreactive

ketones or aldehydes in the presence of amines have attracted considerable attention. These processes are fundamentally different from the direct hydrogen abstraction (**Scheme VI**)[1]. The intermediate formation of ketyl radicals from irradiation of amine-ketone systems has been confirmed by ESR studies. The mechanism and reactions of such processes have been studied intensively by many chemists. For example, the triplets of fluorenone (π, π^*) and 4-aminobenzophenone (charge transfer) were quenched by triethylamine
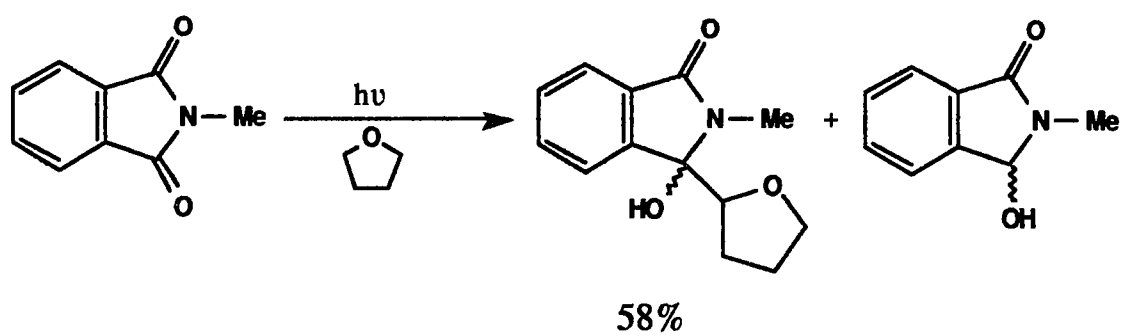
(**Scheme VII**) respectively. The solvents also played an important role in
these processes. In the case of fluorenone, the addition of small concentrations
of acetonitrile to the irradiated solution increases the quantum yield of reaction
consistent with the charge-transfer mechanism. In a neat polar solvent,
however, the efficiency falls by almost 40%. This lowering of the photo-
reduction efficiency is, therefore, rationalized in terms of the rate coefficient
for intersystem crossing being smaller in polar solvents than nonpolar solvents.
But, the polar solvents can stabilize the unreactive charge-transfer states of the
ketones and increase ionic radical lifetime which will increase the quantum
yield of the reaction. Another important effect is that the quenching

Scheme VI:

$$\begin{array}{c} R \\ R \end{array}\!\!\!\!>\!\!=\!\!O \xrightarrow{\ h\upsilon\ } {}^{3}\!\left(\begin{array}{c} R \\ R \end{array}\!\!\!\!>\!\!=\!\!O\right)^{*} + R^{1}CH_{2}NR_{2}^{2}$$

Charge transfer

$$(\ R_{2}\overset{\bullet}{C}\text{-}\overset{-}{O} \quad R^{1}CH_{2}\overset{+\,\bullet}{N}R_{2}^{2}\ )$$

H^{+} transfer

$$R_{2}\overset{\bullet}{C}\text{-}OH \quad + \quad R^{1}\overset{\bullet}{C}HNR_{2}^{2} \qquad\qquad \text{Starting Materials}$$

Products

Scheme VII:

Fluorenone Pinacol

efficiencies of the amines will follow the same order as their ease of oxidation (i.e., tertiary > secondary > primary).

The carbonyl group of a cyclic imide also undergoes intermolecular hydrogen abstraction (**Scheme VIII**)[2]

Scheme VIII:

58%
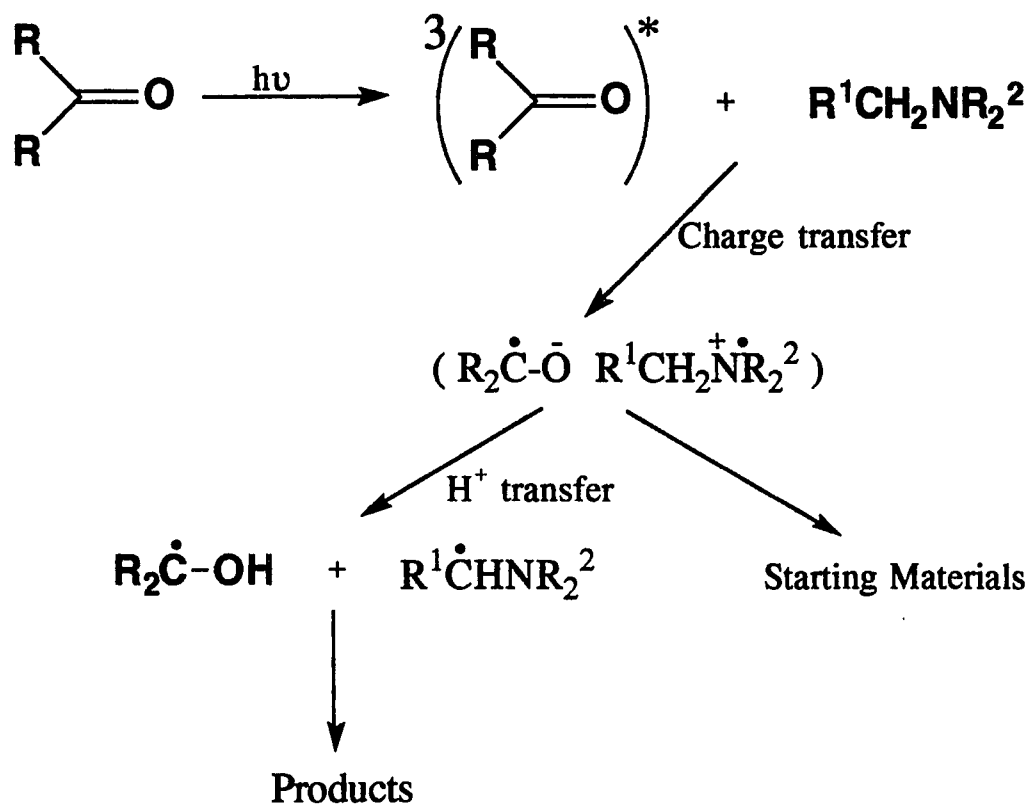
INTRAMOLECULAR HYDROGEN ABSTRACTION

Ketones, aldehydes, esters and cyclic imides, in which the molecular structure allows a close approach between the exited carbonyl group and hydrogen attached to a sp^3 hybridized carbon within the same molecule, undergo intramolecular hydrogen abstraction. Previously, people reported that this process was favored from the γ-carbon atom, since, in this 1,5-hydrogen shift, the two reacting centers could make a close approach in a stain-free chain-like transition state (**Scheme IX**). Intramolecular hydrogen abstraction

Scheme IX:
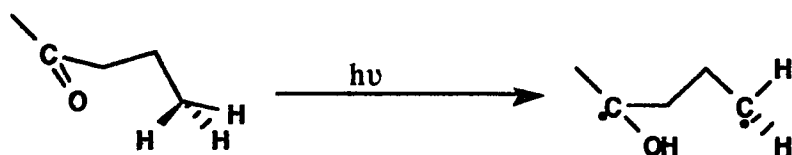
would only occur.from other positions when there were no hydrogens at the γ-position and the molecular conformation allows the other site to come into close proximity to the exited carbonyl group. However, we recently found that intramolecular 1,9-hydrogen atom abstraction (**Scheme X**) was more favored than 1,5-hydrogen abstraction[3] which has significantly extended the scope of such intramolecular hydrogen abstraction.

1,5-Hydrogen atom abstraction The γ-hydrogen atom abstraction may reasonably be considered to yield a 1,4-biradical and certainly the observed products from the process can be conveniently rationalized in terms

of such species[4] (**Scheme XI**). The triplet reactions of aryl ketones have been the most widely studied. The corresponding singlet reaction is less well understood because of short biradical lifetimes and radiationless decay.[5]

Scheme X:

49%
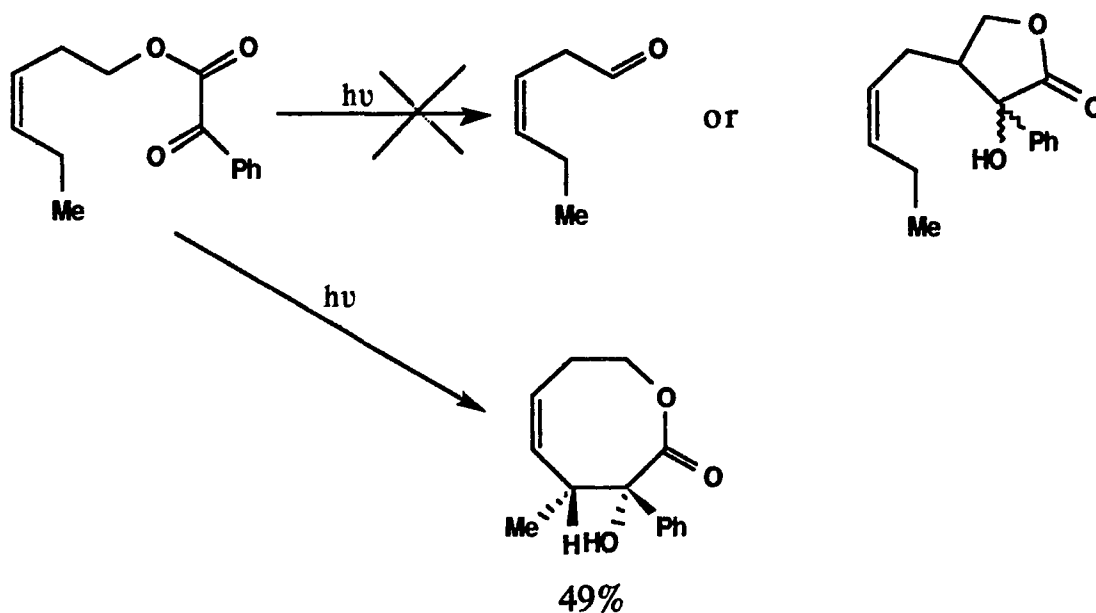
The triplet generated biradical cleavage, cyclization and disproportionation back to starting ketones occur in proportions that vary widely with structure. Added Lewis bases solvate the hydroxy group of the biradical and suppress its reversion to ketones. The most interesting questions related to this Norish type II reaction in the past decade involved the following efforts:

a. The orientational requirements for γ-hydrogen abstraction.

b. The behavior of 1,4-biradicals, particularly how their lifetime depended on structure.

c. How the reaction is affected by the environment.

a. Orientational requirements: Simple straight chain ketones normally have their largest α-substituted eclipsing the carbonyl[6]. The most populated conformer thus is in a geometry very close to that required for the reaction, requiring only rotation around the β-C-γ-C bond. The ketones can attain chair or twist-chair transition state geometry quite easily. Although a linear O-H-C arrangement ($\theta=180^0$) presumably is preferred, it is well

Scheme XI:
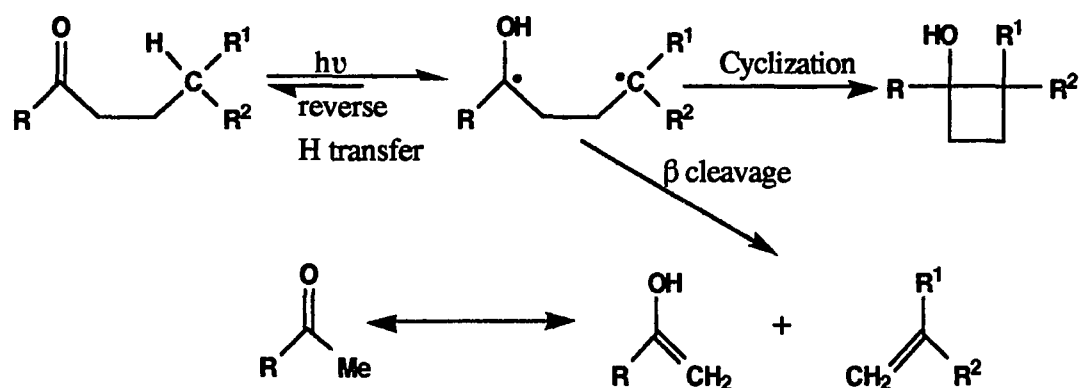
established that hydrogen atom abstraction occurs at values of θ closer to 90^0 (**Scheme XII**)[7].

b. Radical lifetime and reactions: The biradical's existence was first established by trapping studies with thiols[8] and racemization of ketones with an asymmetric γ carbon.[9] The factors that affect partitioning of the 1,4-biradical among cleavage, disproportionation and cyclization have been reviewed[10]. Cleavage appears driven by the stereoelectronic necessity for

overlap of the breaking bond with both singly occupied p orbitals.[11] Anything that prevents such molecular alignment retards or suppresses cleavage. α-Substitution by alkyl groups[12], fluorine[13] and rings[14] all enhance cyclization. α-Diketones do not undergo any cleavage[15], most likely because resonance holds the would-be breaking bond perpendicular to the hydroxyradical site[16]. It is still an open question what affects cyclization and disproportion. Hydrogen bonding to Lewis bases dramatically inhibits the latter and changes the stereoselectivity of the former. The diastereoselectivity also was displayed in the cyclization.

Scheme XII:
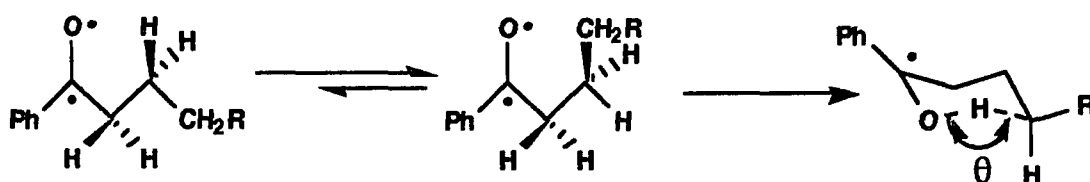
Turro reported that two different types of selectivity arose as demonstrated by valerophenone and α-methylbutyrophenone both of which formed 1-phenyl-2-methylcyclobutanol, but the former gave a 3.5:1 Z/E ratio, while the latter gave only the Z isomer[11b]. He explained that the methyl and phenyl groups assumed anti orientations in the biradical before it cyclize α-methylbutyrophenone. In valerophenone, nonbonded interactions between methyl and phenyl were developed only as the two ends of the biradical began to bond and obviously produced an energy differential that was very small. As a general rule, Wagner pointed out that pre-existing conformational

preferences could be much larger than those developed only during cyclization.[17] When the nonbonded interactions are responsible for diastereoselectivity, it is not easy to predict which mode will prevail.

Wagner also studied the Norish type II reaction of α-allylbutyrophenone to form 4% 2-phenyl-2-norbornanol and concluded that the biradical has a submicrosecond lifetime (**Scheme XIII**).[18]

In 1977 Scaiano and Small reported the first flash spectroscopic detection of the 1,4-biradical intermediate from γ-methylvalerophenone which had a 30 ns lifetime in benzene. Later, Scaiano summarized his several other experiments regarding biradical lifetime.[19] The biradicals were not very sensitive to the substitution at the γ-carbon or on the benzene ring of the ketones, and had lifetime values in the 25-50 nsec range in hydrocarbons and 75-160 nsec in alcohols. Lifetimes were shortened by bimolecular interaction with species such as oxygen and nitroxides (**Scheme XIV**).

The two ends of the biradical have the same characteristics, but different radical reactivity. Simple alkyl radical sites abstract hydrogen from several compounds besides stannanes, including thiols.[8] The hydroxy end of the biradical is especially prone to oxidation.[20]

Scheme XIII:
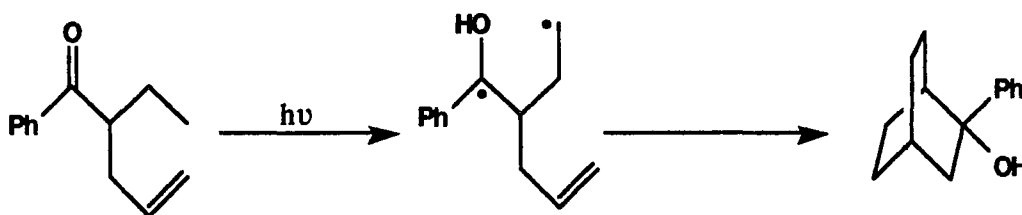
The cyclization, disproportionation and cleavage of the formed biradical by Norish type II reactions were rationalized by the reactive positions of the two radical orbitals (**Scheme XV**).

In 1984 Caldwell reported that cis-1-benzoyl-2-benzhydrylcyclohexane and γ,γ-diphenylbutylphenone produced 1,4-biradicals with very similar lifetimes.[21] The ring in the former compound constrains the biradical to a gauche conformation, whereas the biradical from the latter presumably exists mostly in the stretched *anti-* conformation. The former gave predominantly cyclized product and the latter gave mainly cleavage products (**Scheme XVI**).

Scheme XIV:

Scheme XV:

Cyclization and disproportionation   Cleavage

cisoid   gauche   anti

Scheme XVI:

gauche
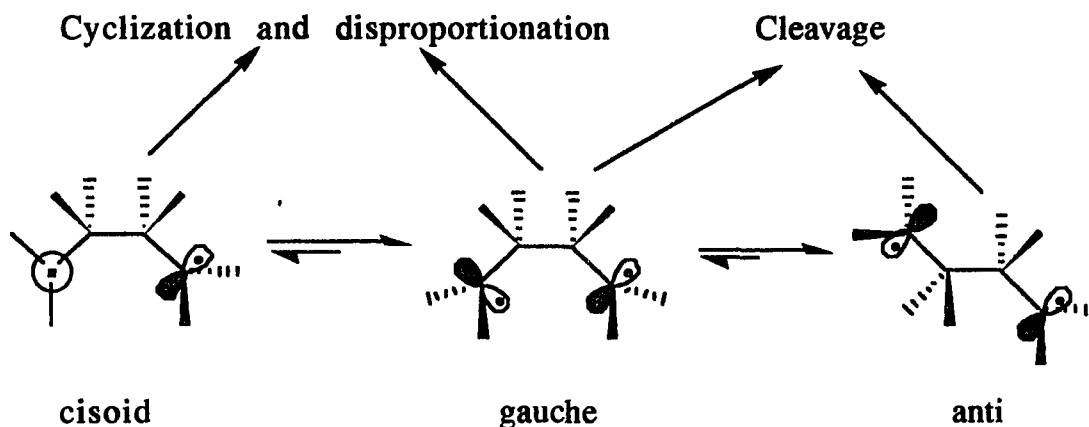
anti
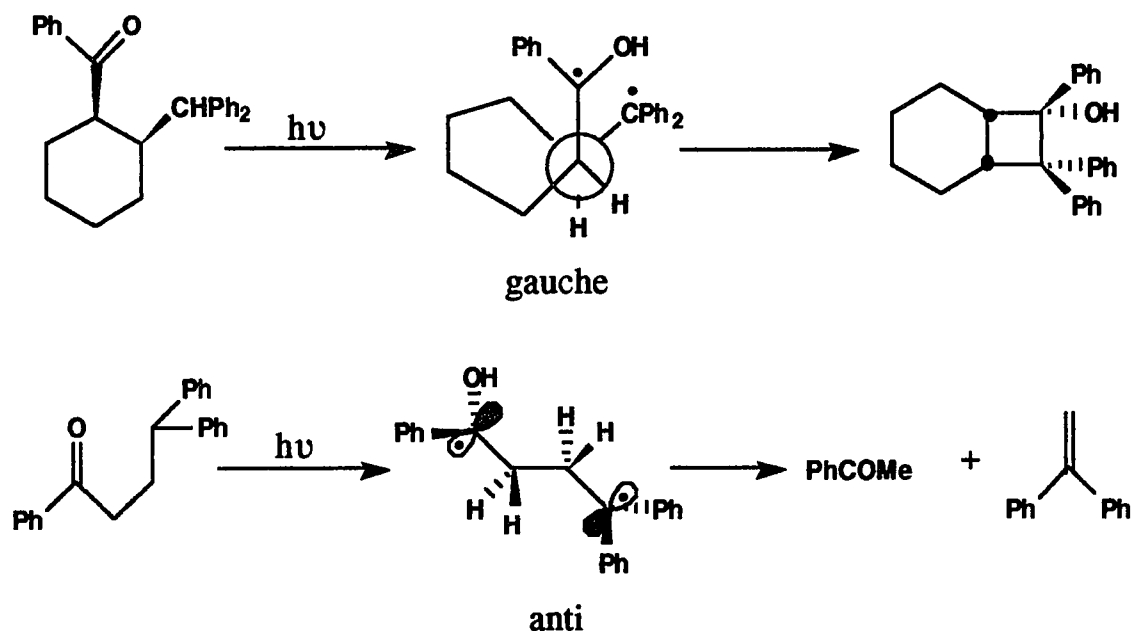
C. Environmental effects: Solvent have a very strong effect on quantum yields, product ratios and stereochemistry of the formed cyclobutanol. Several labs have found that high quantum yields and product ratios in fairly polar environment and suggested in aqueous surfactant solution for ketone irradiation. It is well accepted that the polar end of the ketones and particularly the biradicals reside mostly near the micelle-solvent interface which has Lewis base character. Although micelles produce negligible effects on triplet rate constants, they can improve type II/type I ratios by their " super-cage " effect that enhances the recoupling of radical pairs.[22]

The benzoin ethers were a mechanistic puzzle for years, since they were first reported to produce only α-cleavage to radicals and no type II cleavage or cyclization in solution (**Scheme XVII**).[23] But later DeMayo reported that

~15% type II reaction did compete with radical cleavage when benzoin ethers absorbed on silica gel were irradiated.[24] He pointed out that the silica must force the ketone into a more reactive geometry than found in solution. It also made α-cleavage mostly reversible because of poor translational mobility on the silica surface. Also the use of methanol as solvent provided 5-10% type II reaction. These results explained the normal lack of γ-hydrogen abstraction, since the carbonyl and alkoxy dipoles presumably prefer to oppose each other except in polar media.

Turro looked at the effects of several zeolites on the photochemistry of α,α-dimethylvalerophenone, which underwent competitive type I and type II reaction in solution. Depending on the cavity size of the zeolite, the product ratio (both type I/type II and type II cleavage/cyclization) could either increase or decrease. When mainly type I cleavage was observed, the cavities were too small to allow the conformational changes required for type II reaction.

Scheme XVII:
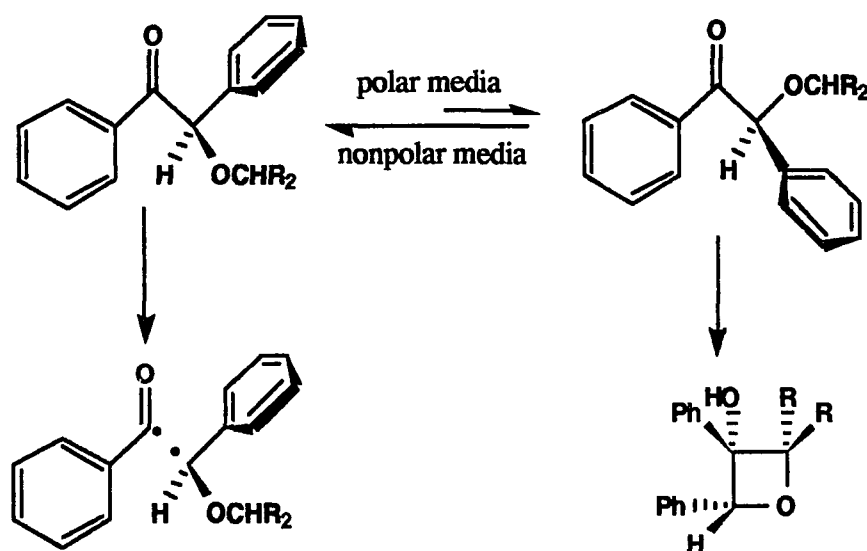
In general, we can see that intramolecular hydrogen abstraction is very complex and the relative ratios of products are largely dependent on various effects. Careful consideration should be made when a photochemical reaction is going to be used in the synthesis of natural products. Actually, 1,5- hydrogen atom abstraction has been extensively studied and developed and used in synthetic organic chemistry.

γ-Hydrogen abstraction from an ortho-alkyl group is identical to the deconjugation reaction and provides one of the simplest forms of photochromism. The transient enols are highly reactive in the Diels-Alder reaction, having been trapped with a variety of dienophiles (Scheme XVIII). Such reactions have been very useful in the synthesis of natural products. There are several synthetic routes to natural products utilizing this strategy in our group[25] (Scheme XIX).

1,6-Hydrogen atom abstraction: It was a common belief that excited ketones abstract only γ-hydrogens if any are present. But, abstraction of remote hydrogen atom will be feasible when there is no γ-hydrogen atom available. This occurs when special conformational effects and particular geometries guide the reactivity. The remote abstraction of hydrogen (other than γ-) by a carbonyl group is also possible only when the site is activated by some group (alkoxy, phenyl, vinyl, etc.). Recently Sengupta studied the mechanism of the hydrogen abstraction process by photo-excited ketones and reported that the activation barriers for such processes decreased in the order of primary > secondary > tertiary alkyl.[26] This means that a hydrogen attached to the tertiary carbon is most likely to be abstracted by the excited carbonyl group if the geometry requirement is reached. Previously reported remote

Scheme XVIII:
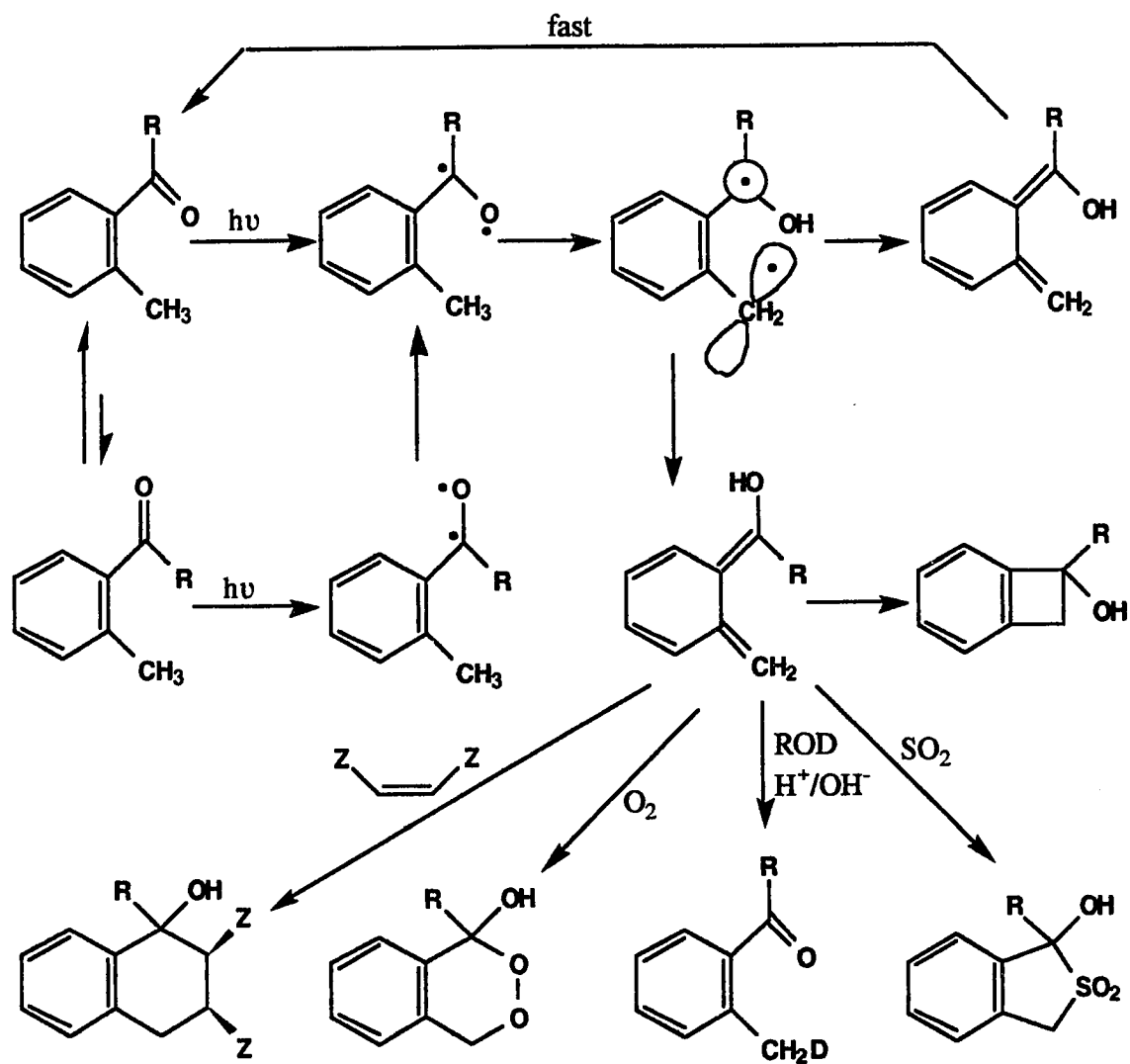
hydrogen atom abstractions includes 1,6-, 1,7-, 1,8- and very remote hydrogen abstractions which are normally involved in electron transfer processes between the excited carbonyl and the remote hetero atoms. Most recently we discovered a 1,9-hydrogen atom abstraction (**Scheme X**)[3] which was faster than 1,5-hydrogen atom abstraction in which the γ-hydrogen was also activated by a carboxylate group.

There are some examples dealing with the photocyclization of various o-alkoxyphenyl ketones.[27] O'Connel reported the cyclization of one o-tert-butyl-phenyl ketone.[28] Pappas conducted a thorough study of o-alkoxyphenyl pyruvate esters[29] and Schultz reported a unique example in the photocyclization of 1-benzoyl-8-benzylnaphthalene.[30] Wagner reported that glycosides made from 4-hydroxy-2-butanone underwent photocyclization at the anomeric carbon.(**Scheme XX**).[31] Some examples were also provided in our group in the synthesis of natural products utilizing this strategy [32]

Remote hydrogen atom abstractions: Similar as δ-hydrogen abstraction, the ε- and ξ-hydrogen atom abstraction reactions are also existed. When the ε- or ξ-hydrogen is activated, the excited carbonyl will abstract hydrogen from the ε- or ξ- position in the absence of a γ-hydrogen. Several examples are available for 1,7- and 1,8-hydrogen atom abstractions.[32] Hydrogen abstractions from very remote sites have been observed in only a few cases and most of such cases involved in electron transfer process except for a couple of examples [32]
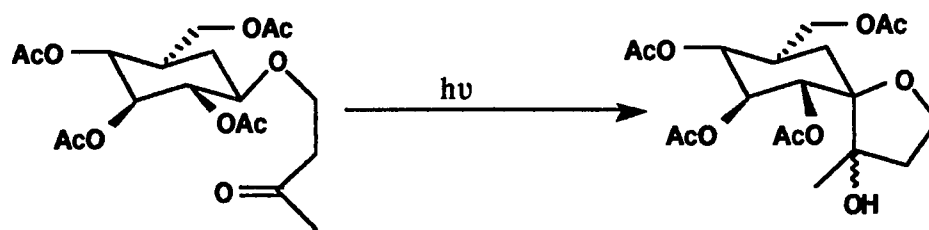
As part of our research, we explored the photoenolization strategy for the synthesis of podophyllotoxin, the photochemical 1,5-hydrogen atom

abstraction followed by radical-induced ring opening and in closing, the 1,9-hydrogen atom abstraction.

Scheme XIX:
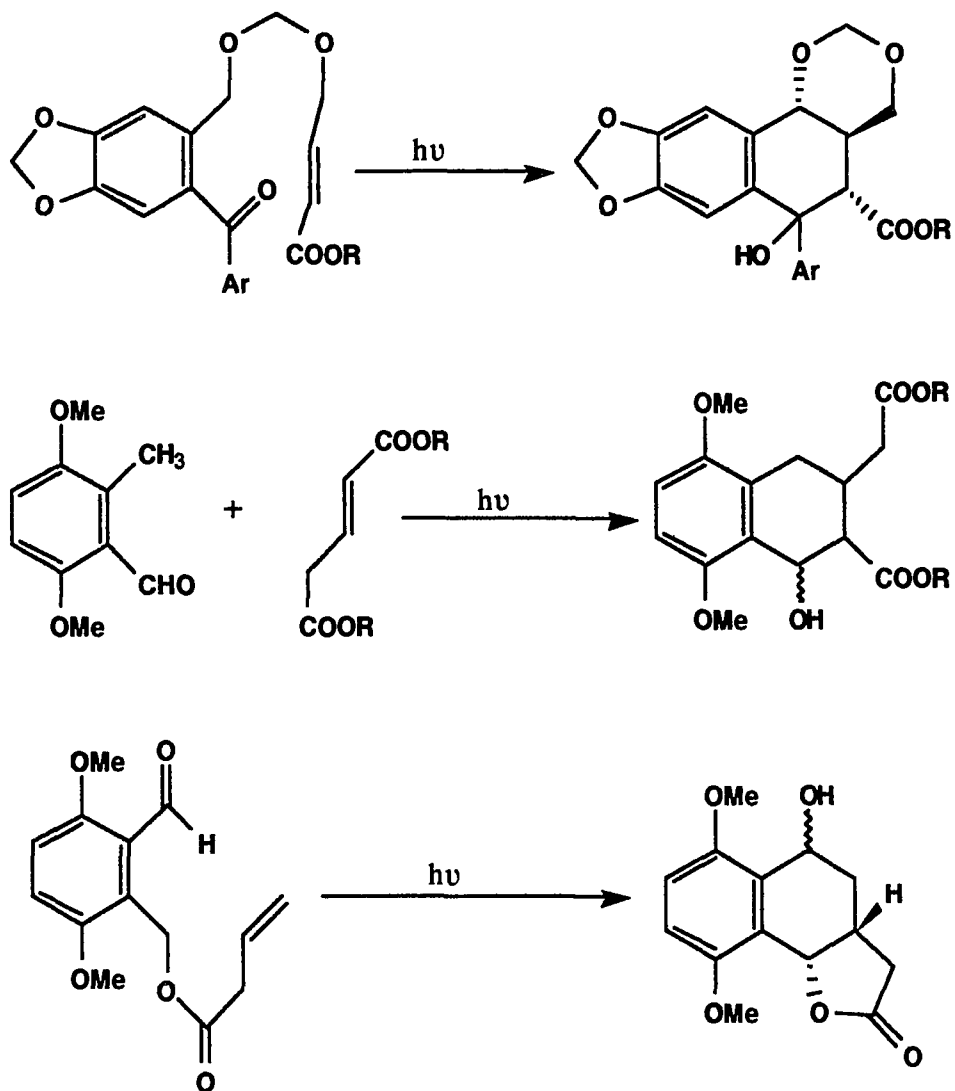
Scheme XX:

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PAPER III

A FORMAL TOTAL SYNTHESIS OF RACEMIC
PODOPHYLLOTOXIN

INTRODUCTION

In the early 1970's several derivatives of podophyllotoxin **1**, the active principle isolated from podophyllin[1], began to show great promise as cancer

1

4
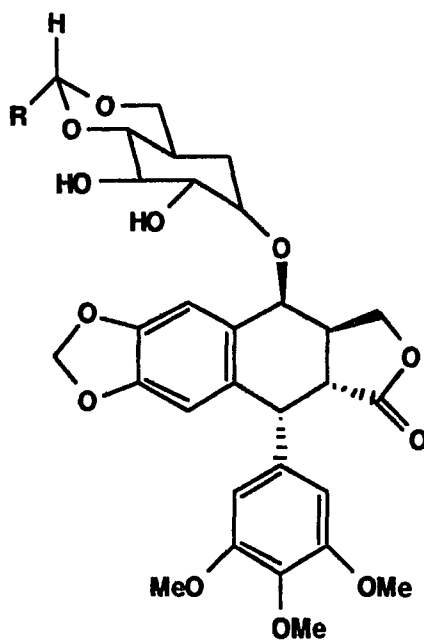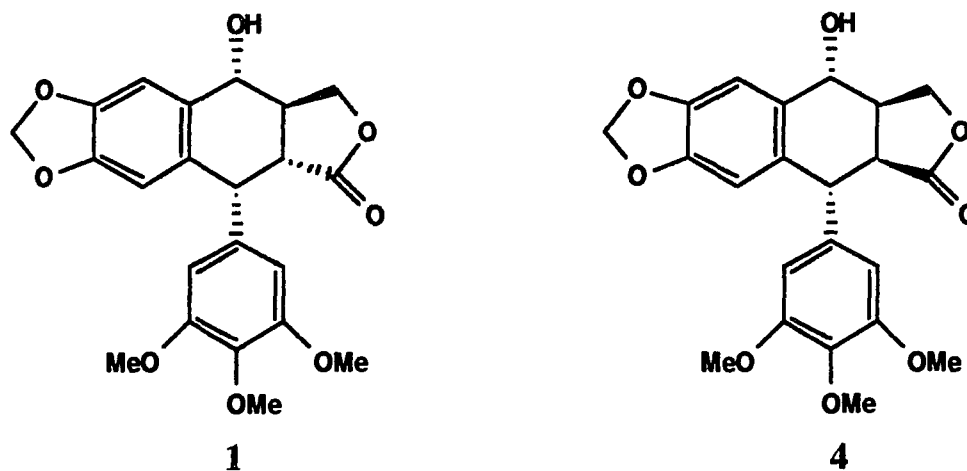

2. R=2-thienyl;   VM-26

3. R=Me;   VP-16-213

chemotherapeutic agents.[2] The result of extensive phase I clinical testing produced two drugs, designated VM-26 (for 4'-demethyl-1-O-[4,6-O-(2-thienyl)-β-D-glucopyroanosyl]epipodophyllotoxin, NSC-122819) (2) and VP-16-213 (for 4'-demethyl-1-O-[4,6-O-(ethylidene)-β-D-glucopyranosyl]epipodophyllotoxin, NSC-141540) (3), which showed acceptable toxicity levels[3] and useful therapeutic benefit against Hodgkin's disease[4]. Further testing has shown these compounds to be effective in cancer chemotherapy, either alone or in combination with other antineoplastic agents.

Synthetic organic chemists have been attracted to podophyllotoxin for the stereochemical challenge represented by its four contiguous chiral centers, rigid trans lactone and axially locked 1-aryl substituent. The problem is accentuated by facile epimerisation at C-2 to the more stable, flexible cis-lactone picropodophyllin 4, with even the slightest trace of base. The 1-axial-2,3-trans stereochemistry is essential[5a, 6] for antimitotic activity, and this fact became another powerful spur for synthetic activity in this area.

A number of total syntheses of 1 and its isomers have been recorded.[8] Many researchers have utilized Friedel-Crafts or cycloaddition strategies. Most closely related to the research described herein are total syntheses of Durst[9] and synthetic approach by Charlton,[10] Jung,[11] and Saa.[81] Durst's synthesis featured an intramolecular cycloaddition of the carbamate of a benzoyl-cyclobutenol to efficiently construct the carbon atom framework. In his synthesis, the thermolysis of compound 5 in MeCN at 90 °C for 5 hours produced a 5:1 mixture of trans and cis acids 7 and 8. Compound 7 was subjected to a three step transformation to afford podophyllotoxin 1 (Scheme I). Charlton utilized an intermolecular photoenolization followed by an

intermolecular Diels-Alder reaction, as a key step in his clever asymmetric synthesis of an analog of podophyllotoxin 1 (**Scheme II**). Jung envisioned an intramolecular Diels-Alder reaction of an acylated benzocyclobutenol as the key step in his synthetic plan (**Scheme III**). Unfortunately, his innovative plan was thwarted by the failure to produce key intermediate 10.
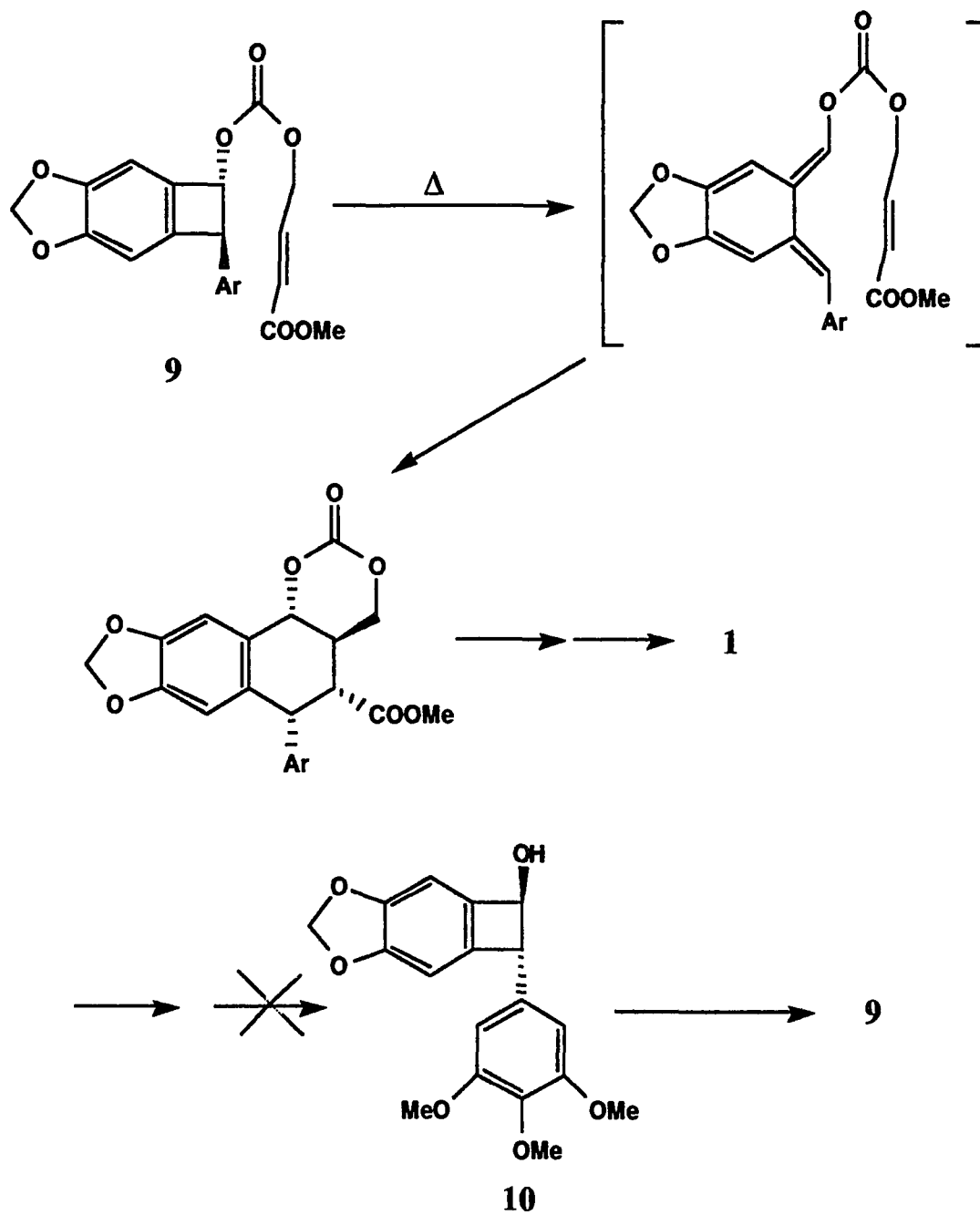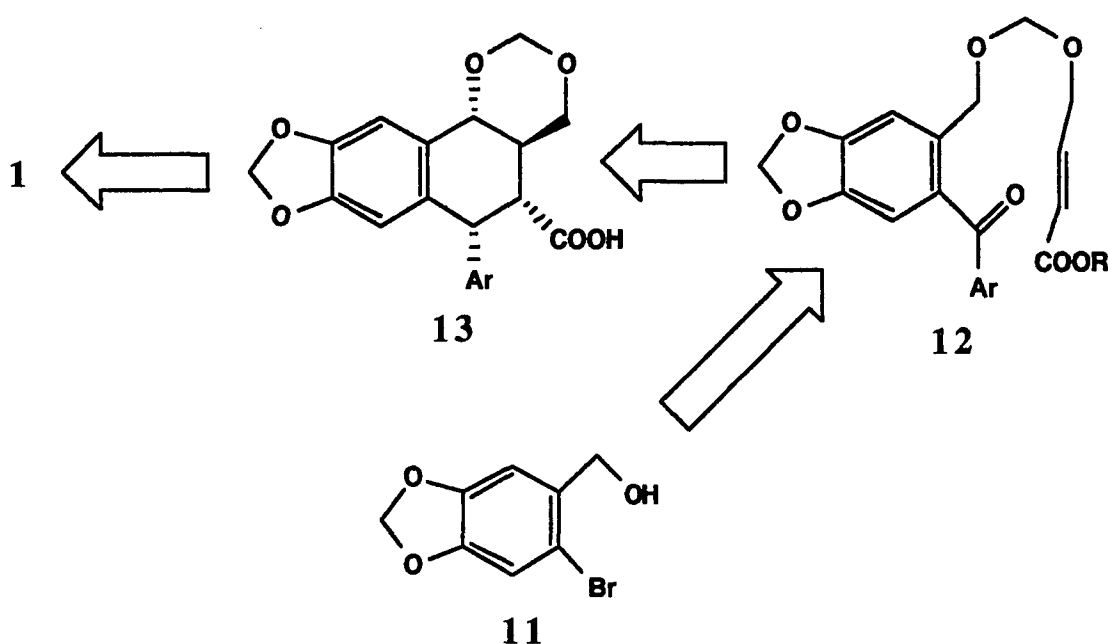
Scheme I:
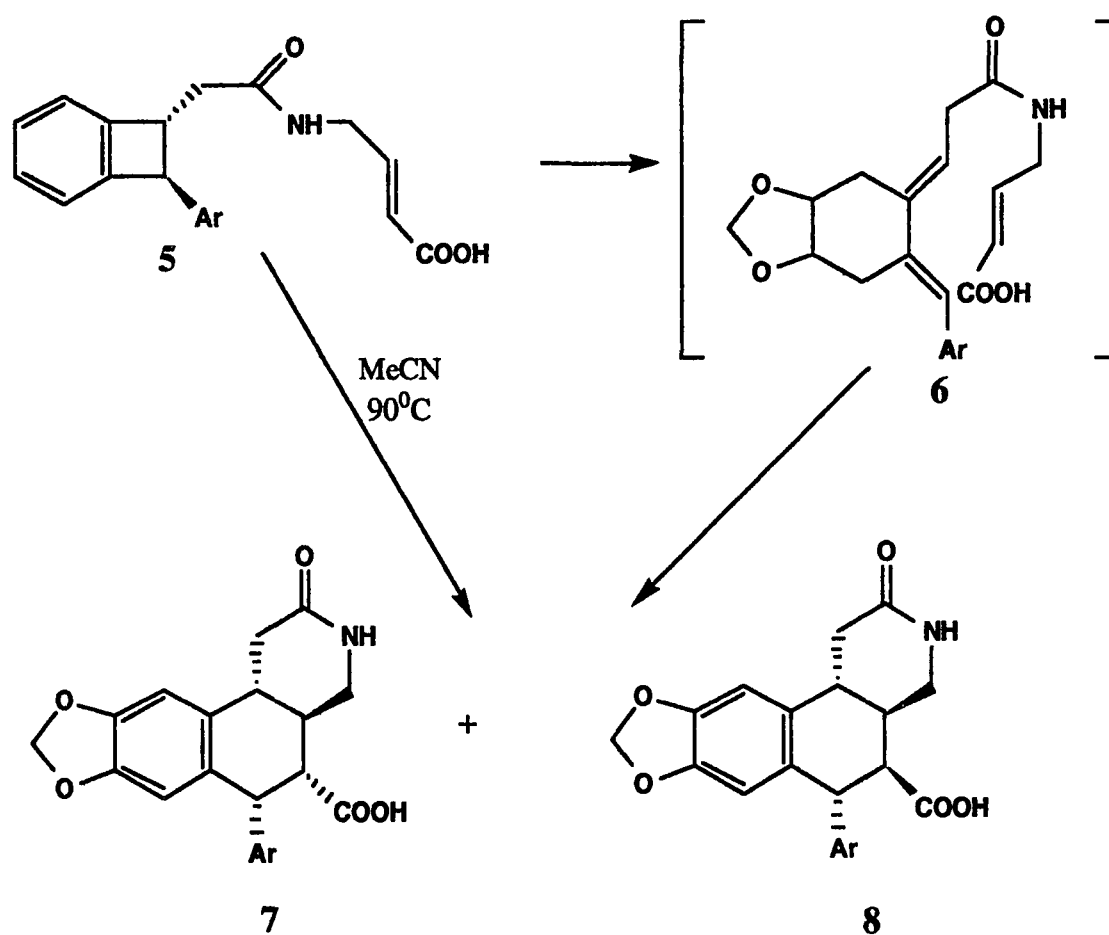
Scheme II:
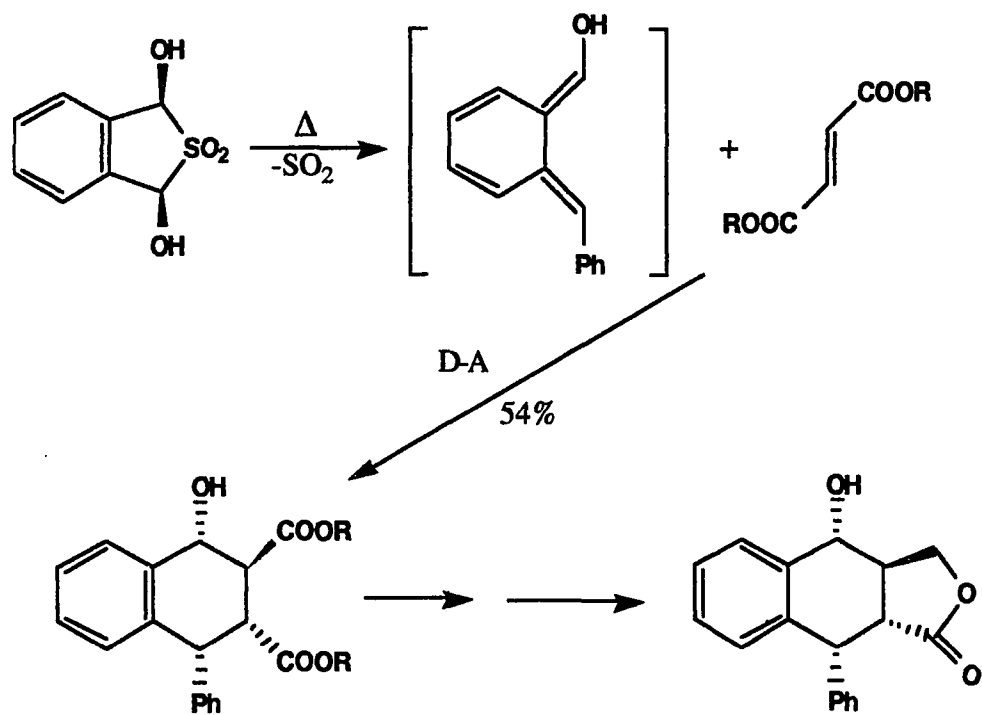
Scheme III: (A proposed route to **1** by Jung)

RESULTS AND DISCUSSION

In the context of our research involving intramolecular hydrogen atom abstraction reactions, we explored the strategy depicted below and report herein a formal total synthesis of racemic podophyllotoxin.

Retrosynthetic Analysis:

The photoenolization reaction depicted above proceeds by the abstraction of a benzylic hydrogen atom by the excited state of the diaryl ketone.[12] The ketone also contains a benzylic ether. Since there was also ample precedent for the photochemically induced fragmentation of a benzylic substituent (particularly if the excited state has $\pi-\pi^*$ character), the success of this key step was uncertain.[13] The key step could be readily examined.

The synthesis of the model precursor **16** was first proposed from commercially available piperonyl alcohol **14** for which this was the shortest route (two steps from **14**) (**Scheme IV**). The electrophilic substitution, which was produced from the coupling of **14** and allyl chloromethyl ether in 47% yield by benzoyl chloride would give the desired precursor **16**. But, unfortunately, we were unable to obtain the desired product **16**, even with modifications of Lewis acids. We next started from compound **11** which could be synthesized in two steps from piperonal to generate the photo precursor **16**. Our proposed reactions are shown in **Scheme V**. The metallation of compound **11** which by n-BuLi gave the aryl lithium which was quenched with benzaldehyde to afford the proposed diol **17**. The primary hydroxyl group
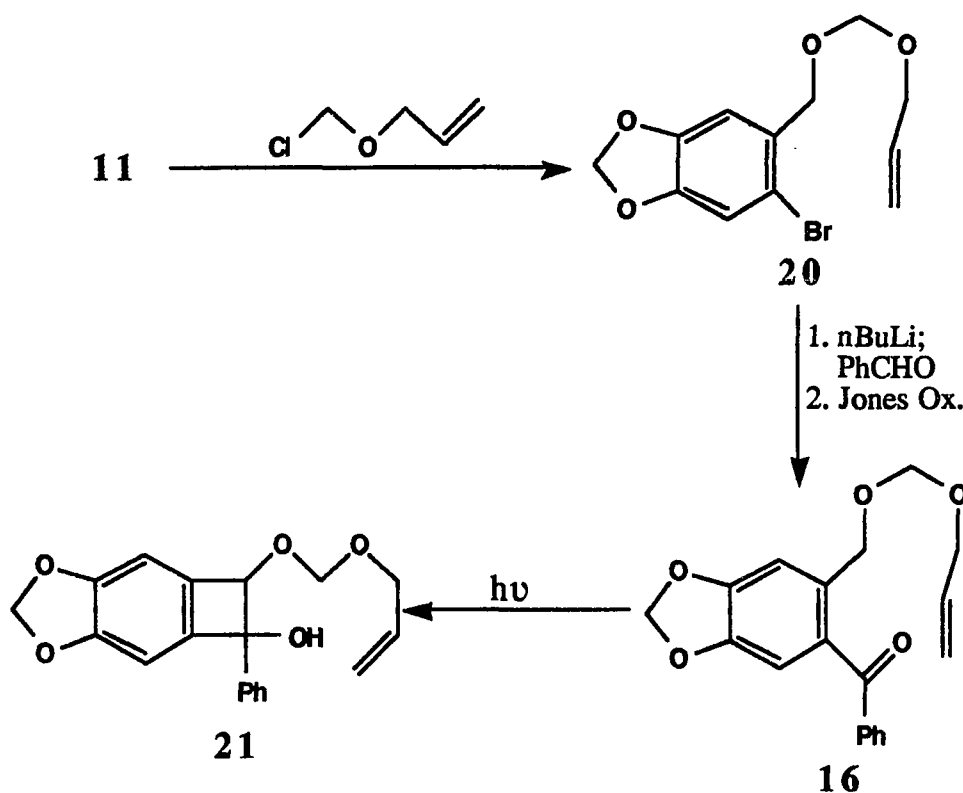
Scheme IV:
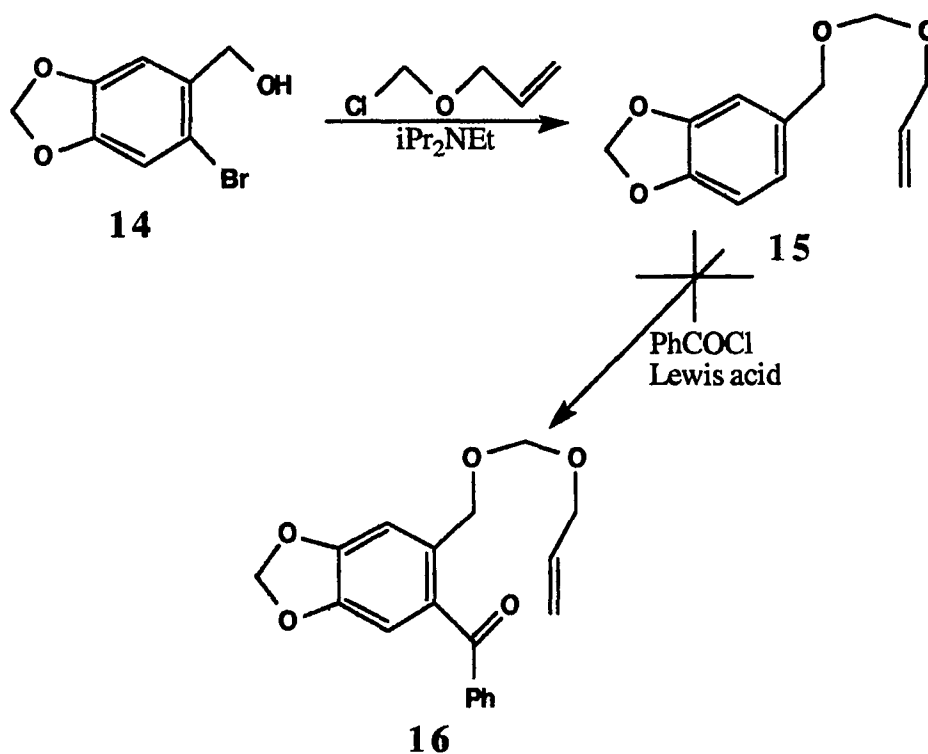
Scheme V:
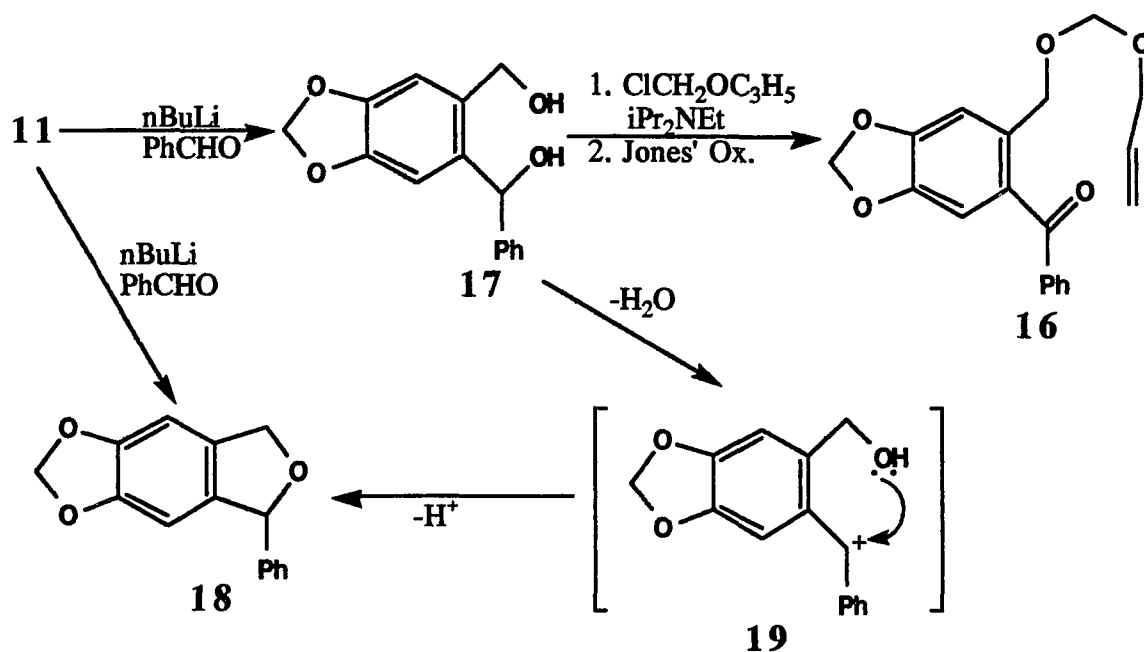
would be more reactive than the secondary hydroxyl group toward the coupling with allyl chloromethyl ether to give mono-coupled alcohol which could be oxidized by Jones' oxidation to generate ketone **16**. However, we didn't get the desired diol **17**; rather, we obtained ester **18** in the first step. The formation of **18** indicated that the protection of the hydroxy group at beginning was essential. So, we started with **20** which was metallated with n-BuLi (**Scheme VI**). The resulting aryl lithium was quenched with benzaldehyde to generate the alcohol which was oxidized by Jones' oxidation to afford the desired ketone **16** in 20% overall yield from **11**.

Irradiation of ketone **16** with a medium pressure Hanovia lamp with a Pyrex filter provided the unstable benzocyclobutenol **21** as a mixture of diastereomers, a clear indication that the photoenolization reaction would

predominate over fragmentation. Although the photoenolization reaction was not followed by an intramolecular Diels-Alder reaction, we knew that the likelihood of a tandem photoenolization reaction/Diels-Alder reaction would be much better with the α, β-unsaturated ester.

Scheme VI:

We prepared the α,β-unsaturated ester **22** from compound **16** in 49% yield by the oxidative cleavage of the double bond, followed by a Wittig reaction on the newly formed aldehyde (**Scheme VII**). Irradiation of the ketone **22** impressively gave the single stereoisomer **23** in 100% yield. The

formation of **23** told us the α, β-unsaturated ester did help the Diels-Alder reaction occur. The C-1, C-2, and C-3 stereochemistry was identified by ^{1}H NMR decoupling experiments and the coupling constants of each proton. Since we successfully synthesized the model compound **23** which had all the required framework and stereochemistry for podophyllotoxin (**1**), we started our synthetic approach to **1**.

Ketone **12** was prepared as shown in **Scheme VIII**. The acetal **20** was metallated and the resulting aryl lithium was reacted with 3,4,5-trimethoxybenzaldehyde (**24**). The resulting alcohol was immediately oxidized with Jones reagent to produce ketone **25** in 58% yield from **20**. Oxidation of the allyl group followed by a Wittig reaction on the newly formed aldehyde, generated ketone **12a** in 41% yield. Irradiation of **12a** using the conditions described previously afforded hydroxy ester **27a** in 60% yield. We did not isolate any benzocyclobutene-containing products. ^{1}H NMR decoupling experiments indicated that the substituents at C-1, C-2 and C-3 were equatorial. Assuming the currently accepted stereochemical outcome of the

Scheme VII:
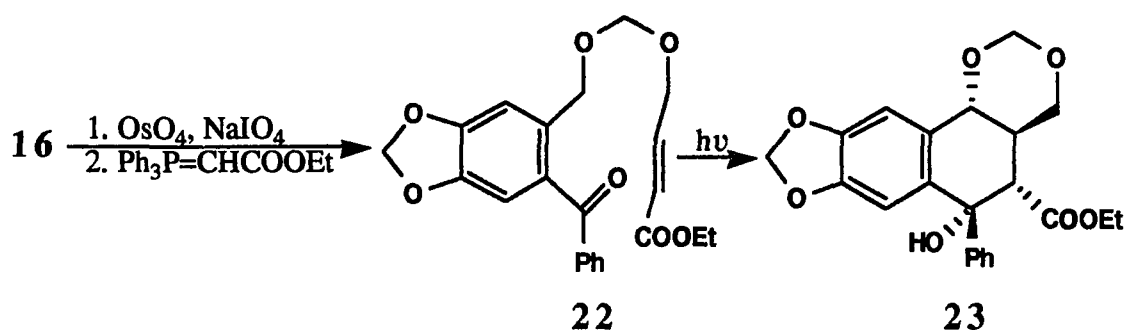
photoenolization reaction and assuming a concerted cycloaddition, the tertiary alcohol should be syn to the ester group.

The conversion of **27a** to **1** required removal of the hydroxyl group and the hydrolysis of the ester and acetal groups. We initially studied the reductive cleavage of the tertiary alcohol using Raney nickel. While this reagent had been used by Rodrigo to cleave a closely related ether,[15] when **27a** was subjected to the Rodrigo conditions, it was recovered in high yield. An attempted ionic hydrogenation using triethylsilane and BF_3-Et_2O gave the dihydronaphthalene

Scheme VIII:

a: R=Et, b: R=t-Bu
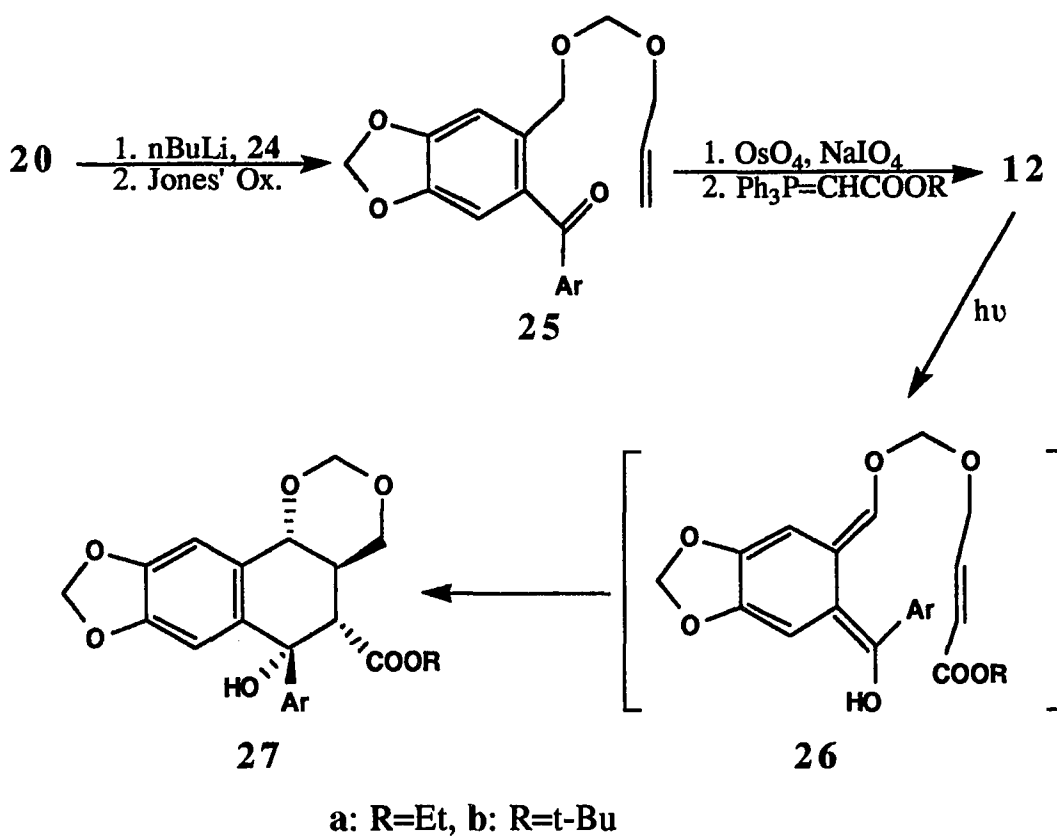
28a in 90% yield (**Scheme IX**). These conditions afforded the best yield of 28a, in part because the reductive conditions suppressed the undesired oxidation to the naphthalene nucleus. Catalytic hydrogenation of **28a** furnished ester **29a** in 100% yield.
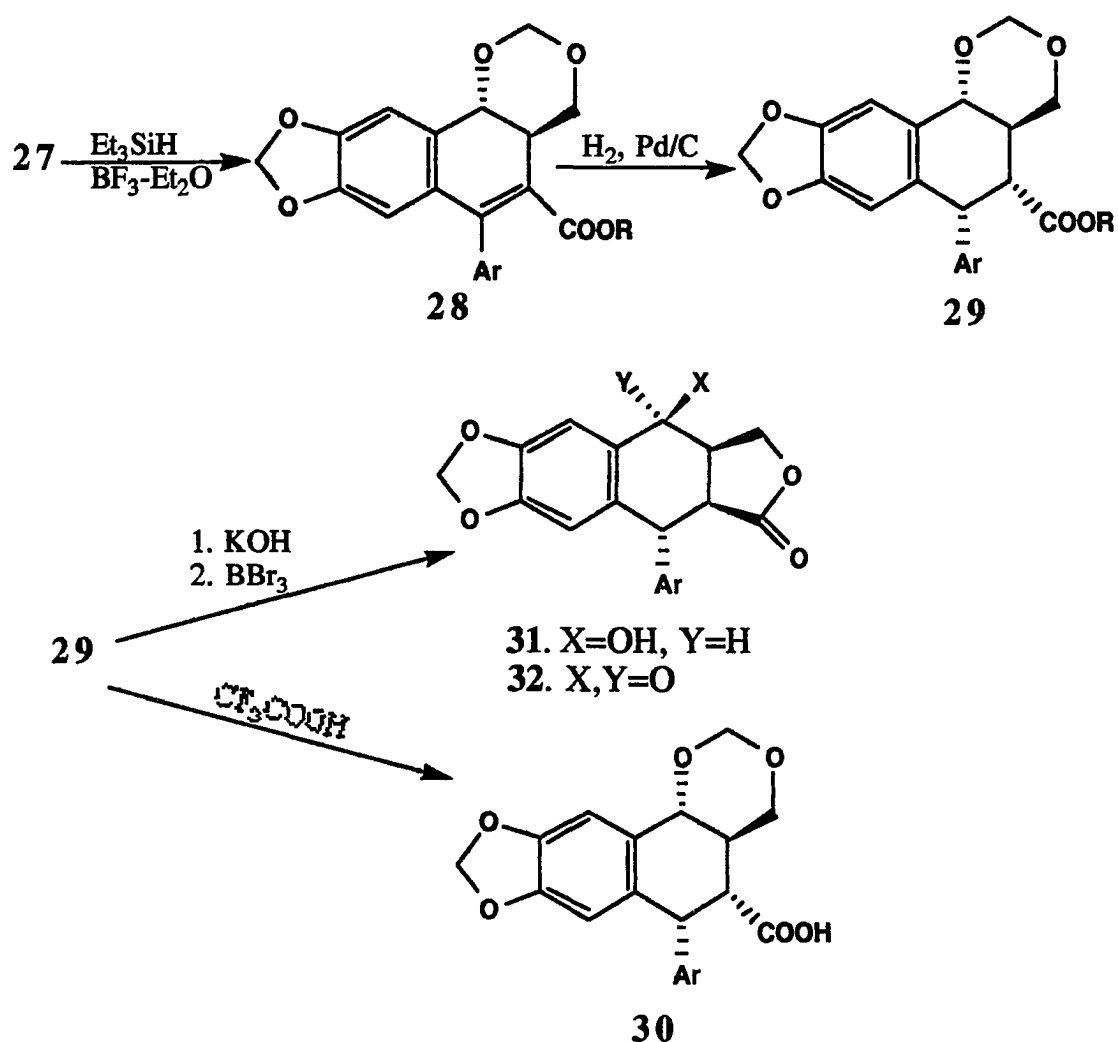
In order to ascertain the stereoselectivity of the hydrogenation reaction, we attempted the iridium-based directed hydrogenation procedures developed by Stork[16] and by Crabtree[17]; however, **28a** did not react under these conditions. The stereochemistry of **29a**, initially assigned on the basis of ^{1}H NMR spectral analysis, was later supported by an x-ray determination of acid **30**.

Base-mediated hydrolysis of **29a** afforded an acid which was treated with BBr_3 to form lactone **31**. The structure of **31** was determined by x-ray spectroscopy. It showed that the product of the two step sequence was the undesired cis-lactone. Lactone **31** could be converted into keto lactone **32** using the PCC oxidation. Since compound **32** has been converted into **1** by Meyers[8i], the synthesis of **32** thus constitutes a formal total synthesis of **1**. Our 300 MHz NMR spectrum of **32** was identical to that reported by Meyers[8i].

We suspected that epimerization of the ester moiety had occurred during the hydrolysis of **29a**. Therefore, we prepared tert-butyl ester **12b** from **25** in 59% yield (**Scheme IX**). Irradiation of **12b** afforded hydroxyl ester **27b** in 51% yield. Using the same conditions that we had employed for the ethyl ester series, we converted **27b** into **29b** in 72% yield. Acid-mediated hydrolysis of **29b** produced acid **30** in 89% yield whose structure was confirmed by x-ray spectroscopy.

We have demonstrated that a tandem photoenolization/Diels-Alder sequence is capable of rapidly constructing the tetrahydronaphthalene subunit of **1**. The deoxygenation of the resulting tertiary alcohol was accomplished with excellent stereoselectivity. The preparation of **32** constitutes a formal total synthesis of **1**, since Myers has converted **32** into **1** by an efficient four step sequence.[8i]

Scheme IX:

27 $\xrightarrow[\text{BF}_3\text{-Et}_2\text{O}]{\text{Et}_3\text{SiH}}$ **28** $\xrightarrow{\text{H}_2,\ \text{Pd/C}}$ **29**

31. X=OH, Y=H
32. X,Y=O

29 $\xrightarrow[\text{2. BBr}_3]{\text{1. KOH}}$

30

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 1320 spectrophotometer. Nuclear Magnetic Resonance (NMR) spectra were determined on a 300 MHz Nicolet Magnetic Corporation NMC-1280 spectrometer. All chemical shifts are reported relative to tetramethylsilane as internal standard. Coupling constants were reported in Hz. Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, ABq=ABquartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. H:EA refers to hexane/ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR spectral analysis and or elemental analyses.

5-Bromo-6-(2,4-dioxa-6-heptenyl)-1,3-benzodioxole (20): To alcohol **11** (1.50 g, 6.54 mmol) in 60 mL of CH_2Cl_2, was added diisopropylethylamine (1.12 g, 13.0 mmol) and chloromethyl allyl ether (1.05 g, 9.84 mmol). The mixture was stirred at r.t. for 10 h. The solution was washed with H_2O and dried over Na_2SO_4. The solvent was removed in vacuo. The residue was separated by sgc (H:EA = 6:1) to give a 71% yield of **20**.

Compound **20**: ^1H NMR ($CDCl_3$) δ (ppm) 6.99 (s, 1 H) , 5.95 (s, 1 H), 6.03-5.87 (m, 3 H), 5.35-5.18 (m, 2 H), 4.80 (s, 2 H), 4.58 (s, 2 H), 4.12 (m, 2 H); IR (film) 3080, 1502, 1479 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ (ppm) 147.49, 147.11, 134.09, 130.32, 118.88, 112.38, 108.18, 101.52, 88.89, 80.84, 68.69, 68.01; TLC (Et_2O:Hexane:EtOH= 20:10:1) R_f = 0.74.

5-Benzoyl-6-(2,4-dioxa-6-heptenyl)-1,3-benzodioxole (16): To **20** (0.46 g, 1.53 mmol) in 10 mL of THF under argon was added n-BuLi (0.74 mL, 1.84 mmol, 2.50 M in hexane) dropwise with stirring. The solution was warmed to r.t. for 0.5 h and was cooled to -78 °C. Benzaldehyde (0.24 mL, 2.30 mmol) was added to the solution dropwise at -78 °C. The solution was then stirred at -78 °C for 2 h, quenched with H_2O at -78 °C and warmed to r.t. The solution was poured into 100 mL of Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was separated by sgc (H:EA = 6:1) to give the alcohol (0.20 g, 40% yield).

The above alcohol (0.072 g, 0.220 mmol) was dissolved in 10 mL of acetone/ether (v/v = 1/10). Jones reagent (0.14 mL, 1.10 mmol) was added dropwise at 0 °C with stirring. The mixture was stirred at 0 °C for 0.5 h and then was washed with brine until the brine washings were clear. The solution

was dried over Na_2SO_4. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 6:1) to afford a 71% yield of compound **16**.

Compound **16**: ^1H NMR (C_6D_6) δ (ppm) 8.20 (s, 1 H), 8.17 (d, J = 1.5 Hz, 1 H), 7.57-7.40 (m, 5 H), 6.13 (m, 1 H), 5.68 (s, 2 H), 5.80-5.52 (m, 1 H), 5.40-5.35 (m, 1 H), 5.23 (s, 2 H), 4.91 (s, 2 H), 4.26 (m, 2 H); IR (film) 2980 1659, 1612 cm^{-1}; TLC (H:EA = 6:1) R_f = 0.25.

Ethyl 4-[(5-(benzoyl)-1,3-benzodioxol-6-yl)methoxymethoxy]-2-butenoate (22): To **16** (0.100 g, 0.307 mmol) in 15 mL of 1,4-dioxane/H$_2$O (v/v = 1/1) was added NaIO$_4$ (0.079 g, 0.368 mmol) and OsO$_4$ (0.0050 g, 0.0197 mmol). The mixture was stirred at r.t. for 6 h and was poured into 100 mL of Et$_2$O. The organic layer was washed with brine and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was not purified, but was used directly for the next step.

The residue from the above procedure was dissolved in 20 mL of CH2Cl2. Ethyl triphenylphosphoranylideneacetate (0.107 g, 0.307 mmol) was added and the mixture was stirred at r.t. for 12 h. The solvent was removed and the residue was purified by sgc (H:EA = 6:1) to give **22** in 49% yield along with some cis -product (trans:cis = 4.3:1).

Compound **22**: ^1H NMR (C_6D_6) δ (ppm) 7.76 (m, 2 H), 7.04 (m, 5 H), 6.85 (dt, J$_1$=15.9 Hz, J$_2$=4.2 Hz, 1 H), 6.12 (dt, J$_1$=15.6 Hz, J$_2$=2.1 Hz, 1 H), 5.25 (s, 2 H), 4.71 (s, 2 H), 4.32 (s, 2 H), 4.00 (q, J=7.2 Hz, 2 H). 3.68 (m, 2 H), 0.955 (t, J=7.2 Hz, 3 H); CI-MS (NH$_3$) m/z for $C_{22}H_{22}O_7$ 399 (M+1); TLC (H:EA=4:1) Rf=0.20.

Ethyl (4aα,5α,6β,11bα)-4a,5,6,11b-tetrahydro-6-hydroxy-6-phenyl- 4*H*-[1,3]benzodioxolo[5,6-h]-1,3-benzodioxin-5-carboxylate (23): Compound 22 (0.355 g, 0.891 mmol) in 50 mL of benzene was degassed with argon for 10 min. and then was irradiated for 4 h. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 6:1) to afford 23 in 100% yield.

Compound 23: ^{1}H NMR (C_6D_6) δ (ppm) 7.38 (m, 2 H), 7.26 (s 1 H), 7.08 (m, 3 H), 6.59 (s, 1 H), 5.19 (d, J=6.0 Hz, 1 H), 5.14 (m, 2 H), 4.79 (s, 1 H), 4.58 (d, J=6.0 Hz, 1 H), 4.15 (d, J=9.9 Hz, 1 H), 4.06 (ABq, J_1=10.8 Hz, J_2=4.2 Hz, 1 H), 3.56 (q, 2 H), 3.28 (t, J=10.8 Hz 1 H), 3.06 (m, 1 H), 2.84 (d, J=12.0 Hz, 1 H), 0.97 (t, J=7.2 Hz, 3 H); CI-MS (NH_3) m/z for $C_{22}H_{22}O_7$ 399 (M+1); TLC (H:EA=4:1) Rf=0.44.

5-(3,4,5-Trimethoxybenzoyl)-6-(2,4-dioxa-6-heptenyl)-1,3-benzodioxole (25): To 20 (9.76 g, 32.4 mmol) in 150 mL of THF at -78 °C under argon was added n-BuLi (16.8 mL, 38.9 mmol, 2.32 M in hexane) dropwise with stirring. The mixture was warmed to 0 °C for 0.5 h and was cooled to -78 °C. Aldehyde 24 (9.54 g, 48.6 mmol) in 30 mL of THF was added to the above solution. The mixture was stirred at -78 °C for 2 h and was warmed to 0 °C. Water was added to quench the reaction. The solution was poured into 300 mL of Et_2O which was washed with brine and was dried over Na_2SO_4. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 3:1) to afford 8.45 g of the alcohol.

The above alcohol (8.45 g, 20.2 mmol) was dissolved in 100 mL of acetone. Jones reagent (12.6 mL, 101 mmol) was added dropwise with stirring

at 0 °C. After 0.5 h, the mixture was poured into 300 mL of Et_2O and was washed with brine until the brine washings were colorless. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 4:1) to afford 58% yield of 25.

Compound 25: ^1H NMR ($CDCl_3$) δ (ppm) 7.07 (s, 1 H), 7.02 (s, 2 H), 6.86 (s, 1 H), 6.02 (s, 2 H), 5.82 (m, 1 H), 5.20 (d, J = 15.6 Hz, 1 H), 5.12 (d, J = 10.2 Hz, 1 H), 4.65 (s, 2 H), 4.61 (s, 2 H), 3.98 (d, J = 5.70 Hz, 2 H), 3.91 (s, 3 H), 3.83 (s, 6 H); IR (film) 2941, 2839, 1659 cm^{-1}; HRMS: m/z for $C_{22}H_{24}O_8$ Calcd. 416.14712, measured 416.14701; TLC (H:EA = 4:1) R_f=0.20.

Ethyl 4-[(5-(3,4,5-trimethoxybenzoyl)-1,3-benzodioxol-6-yl)methoxymethoxy]-2-butenoate (12a):

To 25 (0.523 g, 1.26 mmol) in 30 mL of acetone/H_2O (v/v = 1/1) was added $NaIO_4$ (0.593 g, 2.77 mmol) and OsO_4 (0.0064 g, 0.0252 mmol). The mixture was stirred at r.t. for 16 h and was poured into 100 mL of Et_2O. The organic layer was washed with brine and was dried over Na_2SO_4. The solvent was removed in vacuo and the residue was not purified but was used directly for the next step.

The residue from the above procedure was dissolved in 30 mL of CH_2Cl_2. Ethyl triphenylphosphoranylideneacetate (0.482 g, 1.38 mmol) was added and the mixture was stirred at r.t. for 12 h. The solvent was removed and the residue was purified by sgc (H:EA = 4:1) to give 12a in 41% yield along with some cis -product (trans:cis = 4.3:1).

Compound 12a: ^1H NMR (C_6D_6) δ (ppm) 7.22 (s, 2 H), 7.07 (s, 1 H), 6.92 (s, 1 H), 6.90-6.82 (m, 1 H), 6.17-6.10 (m, 1 H), 5.28 (s, 2 H), 4.77 (s, 2

H), 4.40 (s, 2 H), 3.99 (q, J = 7.2 Hz, 2 H), 3.80 (s, 3 H), 3.74 (q, J = 2.1 Hz, 2

H), 3.29 (s, 6 H), 0.95 (t, J = 7.2 Hz, 3 H); IR (film) 2941, 2905, 1718, 1659

cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 185.23, 165.96, 152.75, 149.45, 148.52, 143.00,

133.08, 192.72, 191.19, 121.18, 108.30, 107.49, 101.65, 84.48, 87.18, 85.87,

80.80, 80.22, 58.19, 14.11; TLC (Et_2O:Hexane:EtOH = 20:10:1) R_f = 0.55.

Ethyl (4aα,5α,6β,11bα)-4a,5,6,11b-tetrahydro-6-hydroxy-6-
(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-h]-1,3-
benzodioxin-5-carboxylate (27a): Compound 12a (0.695 g, 1.42 mmol)
in 50 mL of benzene was degassed with argon for 10 min. and then was
irradiated for 4 h. The solvent was removed in vacuo and the residue was
separated by sgc (H:EA = 4:1) to afford 27a in 60% yield.

Compound 27a: ^1H NMR ($CDCl_3$) δ (ppm) 6.99 (s, 1 H), 6.53 (s, 2
H), 6.36 (s, 1 H), 5.90 (dd, J = 1.2 Hz, 9.6 Hz, 2 H), 5.30 (d, J = 6.0 Hz, 1 H),
4.98 (s, 1 H), 4.97 (d, J = 6.9 Hz, 1 H), 4.56 (d, J = 8.7 Hz, 1 H), 4.02 (q, J =
7.2 Hz, 2 H), 3.84 (s, 3 H), 3.81 (s, 6 H), 3.65 (t, J = 10.5 Hz, 1 H), 2.66 (m, 2
H), 1.05 (t, J = 7.2 Hz, 3 H); IR (film) 3520, 2941, 1730 cm^{-1}; CI-MS (NH_3)
m/z for $C_{25}H_{28}O_{10}$ 488 (M) ;TLC (Et_2O:Hexane:EtOH = 20:10:1) R_f = 0.38.
M.p. 195-196 °C.

Ethyl (4aα,11bα)-4a,11b-dihydro-6-(3,4,5-trimethoxyphenyl)-
4*H*-1,3-benzodioxolo[5,6-h]-1,3-benzodioxin-5-carboxylate (28a):
To 27a (0.147 g, 0.301 mmol) in 30 mL of CH_2Cl_2 at -78 °C under argon
was added Et_3SiH (0.072 mL, 0.451 mmol) in one portion followed by
BF_3•OEt_2 (0.041 mL, 0.331 mmol) dropwise. The mixture was stirred at -78

°C and was allowed to warm to r.t. overnight. Dilute $NaHCO_3$ (15 mL) was added and the solution was washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo to give **28a** in 90% yield.

Compound **28a**: ^1H NMR ($CDCl_3$) δ 7.09 (s, 1 H), 6.38 (s, 2 H), 6.36 (s, 1 H), 5.95 (s, 2 H), 5.30 (d, J = 6.3 Hz, 1 H), 4.87 (d, J = 6.3 Hz, 1 H), 4.63 (d, J = 13.8 Hz, 1 H), 4.52 (dd, J = 4.8 Hz, 11.1 Hz, 1 H), 3.92 (q, J = 6.9 Hz, 2 H), 3.88 (s, 3 H), 3.81 (s, 6 H), 3.66 (t, J = 11.1 Hz, 1 H), 3.08 (m, 1 H), 0.90 (t, J = 7.2 Hz, 3 H); IR (film) 2924, 2853, 1703, 1583 cm^{-1}; TLC (Et_2O:Hexane:EtOH=20:10:1) R_f = 0.50. M.p. 95-96.5 °C.

Ethyl (4aα,5α,6β,11bα)-4a,5,6,11b-tetrahydro-6-(3,4,5-trimethoxyphenyl)-4*H*-1,3-benzodioxolo[5,6-h]-1,3-benzodioxin-5-carboxylate (29a): Ester **28a** (0.106 g, 0.226 mmol) in 30 mL of EtOH/THF (v/v = 1/1) was hydrogenated under 1 atm of H_2 with Pd/C (0.030 g) for 5 days. The mixture was purified via sgc using CH_2Cl_2 to afford a 100% yield of **29a**.

Compound **29a**: ^1H NMR (C_6D_6) δ (ppm) 7.01 (s, 1 H), 6.35 (s, 1 H), 6.20 (s, 2 H), 5.92 (dd, J = 1.2 Hz, 1.2 Hz, 2 H), 5.30 (d, J = 6.0 Hz, 1 H), 4.93 (d, J = 6.0 Hz, 1 H), 4.42-4.33 (m, 3 H), 3.92-3.81 (m, 2 H), 3.80 (s, 3 H), 3.76 (s, 6 H), 3.43 (t, J = 10.5 Hz, 1 H), 2.91 (m, 1 H), 2.57 (m, 1 H), 1.05 (t, J = 7.2 Hz, 3 H); IR (film) 3055, 2930, 2856, 1713 cm^{-1}; CI-MS (NH_3) m/z for $C_{25}H_{28}O_9$ 472 (M), 473 (M+1); TLC (Et_2O:Hexane:EtOH = 20:10:1) R_f = 0.46. M.P. 165-166 °C.

(5α,5aα,8aβ, 9α)-5,5a,8a,9-Tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)-furo[3',4':6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5aH)-one (31): Compound **29a** (0.250 g, 0.530 mmol) and 20 mL of 0.1M NaOH dioxane/H_2O (v/v = 1/1) were heated at reflux for 6 h and cooled to rt. Cold 2N HCl was added to the solution to adjust the pH to 3.0. The solution was extracted with Et_2O, dried over Na_2SO_4 and the solvent was removed in vacuo to afford 0.111 g of crude acid which was not purified but was used directly for the next step.

To the crude acid (0.032 g, 0.072 mmol) in 15 mL of CH_2Cl_2 was added BBr_3 (0.233 mL of a 1 M solution in CH_2Cl_2, 0.233 mmol) dropwise at -78 °C under argon. The mixture was stirred for 5 h and was quenched with $NaHCO_3$ at -78 °C. The solution was warmed to r.t., was poured into 30 mL of CH_2Cl_2, was washed with brine, and dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was separated by sgc (Et_2O:Hexane:EtOH = 20:10:1) to afford **31** (18% yield of **31** from **29a**).

Compound **31**: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.00 (s, 1 H), 6.60 (s, 1 H), 6.36 (s, 2 H), 5.97 (dd, J = 1.2 Hz, 1.2 Hz, 2 H), 4.83 (d, J = 5.1 Hz, 1 H), 4.45 (d, J = 3.0 Hz, 1 H), 4.37 (d, J = 5.4 Hz, 1 H), 4.35 (d, J = 2.1 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 6 H), 3.44 (dd, J = 3.6 Hz, 10.8 Hz, 1 H), 3.17 (m, 1 H); IR (CH_2Cl_2) 2940, 1700, 1580 cm^{-1}; HRMS: m/z for $C_{22}H_{22}O_8$ Calcd. 414.13147, measured 414.13138; TLC (Et_2O:Hexane:EtOH = 20:10:1) R_f = 0.20. M.p. 184-185.2 °C.

(5α,5aα,8aβ)-5,5a,8a,9-Tetrahydro-5-(3,4,5-trimethoxyphenyl)furo[3', 4':6, 7]naphtho[2, 3-*d*]-1, 3-dioxole-

6(5aH),9-(8a*H*)-dione (32): To a suspension of PCC (0.020 g, 0.23 mmol) and celite (0.010 g) in 0.5 mL of CH_2Cl_2 at -10^0C was added dropwise a solution of **31** (0.0056 g, 0.14 mmol) in 0.5 mL of CH_2Cl_2. The suspension was allowed to slowly warm to room temperature over 20 hours. The suspension was directly purified by sgc using 20:10:1=Et_2O:Hexane:EtOH to afford 0.0040 g (72%) of compound **32** as a white solid.

Compound **32**: ^1H NMR ($CDCl_3$) δ (ppm) 7.50 (s, 1 H), 6.69 (s,1 H), 6.23 (s, 1 H), 6.05 (d, J=2.4 Hz, 2 H), 4.77 (d, J=9.3 Hz, 1 H), 4.69 (s, 1 H), 4.35 (m, 1 H), 3.80 (s, 3 H), 3.75 (s, 6 H), 3.31 (s, 1 H), 3.30 (d, J=1.5 Hz, 1 H); IR (film) 2916, 1768, 1665, 1478 cm-1; HRMS m/z for $C_{22}H_{20}O_8$ Calcd. 412.1158, found 412.1160; TLC (Et_2O:Hexane:EtOH 20:10:1) Rf=0.27; mp 94– 95 ^0C.

tert-Butyl (E)-4-[[[5-(3,4,5-trimethoxybenzoyl)-1,3-benzodioxol-6-yl]methoxy]methoxy]-2-butenoate (12b): To **25** (0.734 g, 1.76 mmol) in 40 mL of acetone/H_2O (v/v = 1/1) was added $NaIO_4$ (0.830 g, 3.88 mmol) and OsO_4 (0.00895 g, 0.0352 mmol). The mixture was stirred at r.t. for 16 h and then extracted by Et_2O and dried over Na_2SO_4. The solvent was removed in vacuo and the residue was used for the next step.

The above residue was dissolved in 25 mL of CH_2Cl_2. tert-Butyl triphenylphosphoranylideneacetate (0.73 g, 1.94 mmol) was added and the mixture was stirred at r.t. for 12 h. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 4:1) to afford a 59% yield of compound **12b** containing a small amount of *cis*-product.

Compound 12b: ^{1}H NMR (C_6D_6) δ (ppm) 7.21 (s, 2 H), 7.05 (s, 1 H), 6.91 (s, 1 H), 6.82 (m, 1 H), 6.10 (m, 1 H), 5.27 (s, 2 H), 4.77 (s, 2 H), 4.39 (s, 2 H), 3.80 (s, 3 H), 3.74 (m, 2 H), 3.28 (s, 6 H), 1.38 (s, 9 H); IR (film) 3057, 2973, 2939, 1711, 1659 cm^{-1}; HRMS: m/z for $C_{27}H_{32}O_{10}$ Calcd. 516.19955, measured 516.19896; TLC (Et_2O:Hexane:EtOH = 20:10:1) R_f = 0.67.

tert-Butyl (4aα,5α,6β,11bα)-4a,5,6,11b-tetrahydro-6-hydroxy-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (27b): Compound 12b (1.02 g, 1.98 mmol) in 200 mL of benzene was degassed for 10 min. and then was irradiated for 9 h. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 4:1) to afford a 51% yield of compound 27b.

Compound 27b: ^{1}H NMR ($CDCl_3$) δ (ppm) 6.99 (s, 1 H), 6.55 (s, 2 H), 6.38 (s, 1 H), 5.91 (d, J = 1.2 Hz, 1 H), 5.88 (d, J = 1.2 Hz, 1 H), 5.31 (d, J = 6.3 Hz, 1 H), 5.18 (s, 1 H), 4.97 (d, J = 6.3 Hz, 1 H), 4.56 (d, J = 9.0 Hz, 1 H), 4.05 (dd, J =10.8 Hz, 3.6 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 6 H), 3.65 (t, J = 10.2 Hz, 1 H), 2.94-2.82 (m, 2 H), 1.25 (s, 9 H); IR (film) 3385, 1695 cm^{-1}; HRMS: m/z for $C_{27}H_{32}O_{10}$ Calcd. 516.19955, measured 516.19915; Anal. Calcd: C, 62.78; H, 6.24. Found: C, 63.37; H, 6.61. TLC (Et_2O:Hexane:EtOH = 20:10:1) R_f = 0.65. M.p. 209-210.5 °C.

tert-Butyl (4aα,11bα)-4a,11b-dihydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]-benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (28b). To 27b (0.356 g, 0.688 mmol) in 150 mL of CH_2Cl_2

under argon was added Et$_3$SiH (0.16 mL, 1.03 mmol) in one portion followed by BF$_3$·Et$_2$O (0.093 mL, 0.76 mmol) dropwise at -78 °C. The mixture was then stirred for 1.5 h and quenched with 20 mL of H$_2$O at -78 °C. The solution was allowed to slowly warm to r.t., washed with brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the residue was separated by sgc (H:EA = 4:1) to afford **28b** in 75% yield.

Compound **28b**: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.08 (s, 1 H), 6.44 (s, 1 H), 6.33 (d, J = 4.8 Hz, 2 H), 5.95 (s, 2 H), 5.31 (d, J = 6.0 Hz, 1 H), 4.89 (d, J = 6.3 Hz, 1 H), 4.65 (d, J = 13.8 Hz, 1 H), 4.55 (dd, J = 10.8 Hz, 4.8 Hz, 1 H), 3.89 (s, 3 H), 3.80 (s, 6 H), 3.69 (t, J = 10.8 Hz, 1 H), 3.07 (m, 1 H), 1.19 (s, 9 H); IR (film) 2924, 2853, 1699 cm^{-1}; HRMS: m/z for C$_{27}$H$_{30}$O$_9$ Calcd. 498.18898, measured 498.18762; TLC (Et$_2$O:Hexane:EtOH = 20:10:1) R$_f$ = 0.67. M.p. 186-187 °C.

tert-Butyl (4aα,5α,6β,11bα)-4a,5,6,11b-tetrahydro-6-(3,4,5-trimethoxyphenyl)-4H-[1,3]-benzodioxolo[5,6-h]-1,3-benzodioxin-5-carboxylate (29b): Compound **28b** (0.103 g, 0.21 mmol) in 100 mL of EtOH/THF (v/v = 1/1) was hydrogenated at 1 atm of H$_2$ with Pd/C (0.030 g) for 4 days. The solution was then purified by sgc (CH$_2$Cl$_2$) to afford a 91% yield of compound **29b**.

Compound **29b**: ^{1}H NMR (CDCl$_3$) δ 6.99 (s, 1 H), 6.34 (s, 1 H), 6.28 (s, 2 H), 5.90 (s, 2 H), 5.31 (d, J = 6.3 Hz, 1 H), 4.94 (d, J = 6.0 Hz, 1 H), 4.41 (dd, J = 3.9 Hz, 10.8 Hz, 1 H), 4.33 (s, 1 H), 4.31 (s, 1 H), 3.80 (s, 3 H), 3.77 (s, 6 H), 3.46 (t, J = 10.8 Hz, 1 H), 3.79 (dd, J = 6.9 Hz, 12.3 Hz, 1 H), 2.55 (m, 1 H), 1.18 (s, 9 H); IR (film) 2939, 2837, 1695 cm^{-1}; HRMS: m/z for

$C_{27}H_{32}O_9$ Calcd. 500.20463, measured 500.20410; CMR (CDCl₃) δ (ppm) 171.63, 152.34, 147.33, 146.92, 141.00, 136.66, 132.89, 128.61, 108.66, 103.65, 100.34, 93.90, 82.41, 78.95, 76.59, 75.43, 68.56, 60.46, 55.88, 52.59, 36.37, 27.42; TLC (H:EA = 3:1) R_f = 0.45. M.p. 158.2-159 °C.

(4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-(3,4,5-trimethoxyphenyl)-4H-[1,3]-benzodioxolo[5,6-h   ]-1,3-benzodioxin-5-carboxylic acid (30). To **29b** (0.0933 g, 0.187 mmol) was added 15 mL of 0.5M CF₃COOH in CH_2Cl_2. The mixture was stirred for 30 h and the solvent was removed in vacuo. The residue was separated by sgc (H:EA = 2:1) to give a 89% yield of **30**.

Compound **30**: ¹H NMR (CDCl₃) δ (ppm) 7.01 (s, 1 H), 6.35 (s, 1 H), 6.23 (s, 2 H), 5.92 (dd, J = 1.0 Hz, 1.0 Hz, 2 H), 5.29 (d, J = 6.0 Hz, 1 H), 4.93 (d, J = 6.0 Hz, 1 H), 4.44-4.34 (m, 3 H), 3.79 (s, 3 H), 3.72 (s, 6 H), 3.42 (t, J = 10.5 Hz, 1 H), 2.91 (dd, J = 12.3 Hz, 6.6 Hz, 1 H), 2.52 (m, 1 H); IR (film) 3395, 2930, 1707 cm⁻¹; m/z for $C_{23}H_{24}O_9$ Calcd. 444.14203, measured 444.14482; TLC (Et₂O:Hexane:EtOH = 20:10:1) R_f = 0.36.

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PAPER IV

# PHOTOCHEMICALLY INDUCED
RADICAL RING OPENING AND CLOSING

INTRODUCTION

Development of methods for the synthesis of carbocyclic molecules containing fused seven membered rings is currently an area of active investigation. Such carbon skeletons form the basic structures of many biologically active natural products.[1]

The use of radical reactions in organic synthesis is now well-established.[2] Current topics of research in radical chemistry include the development of nonreductive radical cyclization reaction,[3] the study of acyclic stereochemical control in radical reactions,[4] and the development of new methods for the generation of radicals.[5]

Radical-prompted ring-closure is being investigated extensively[6] as a method for the construction of synthetic intermediates. However, the synthetic applications of radical-induced ring-opening have received much less attention. In contrast, the physical organic chemistry of radical-opening is well-studied.Most of the reported measurements[7] involve small rings, especially the cyclopropylcarbinyl system, because the opening of large rings, at least in the absence of substituents that stabilize the product radical, does not usually occur at an adequate rate.[7,8] The ring-opening of cyclopropanes has been systematically studied. The rate constant for such systems (**Scheme I**) are known over a range of temperature.[9,10] The kinetic date are also available for those cases in which substituents such as methyl[10], ethoxycarbonyl,[10] and phenyl[11] are attached to the basic skeleton. For the parent system, the rate constant[9,10] for ring-opening is about 10^8 s^{-1} at 25^{0}C and the value for the reverse process is about 10^4 s^{-1}. However, the nature of the substitution pattern

can affect the absolute values and their relative magnitude. Beckwith studied the kinetics for ring opening of substituted cyclopropylmethyl radicals and found the rate constant of ring opening was dramatically affected by the substituents on the cyclopropyl ring (**Scheme II**)[10c]. So far there are only a very few reported examples utilizing this ring opening strategy in the synthesis of natural products. The spirocyclizations of this type shown in **Scheme III** may be the first attempts to evaluate and generalize the synthetic

Scheme I:

(25^0C)
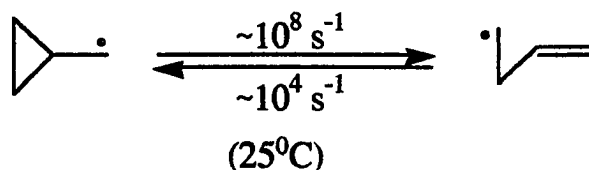
Scheme II:
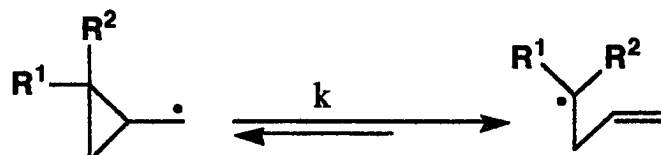
R^1,	R^2	k	temperature, ^0C
H	H	1.75×10^8	60
Me	Me	2.2×10^9	60
Me	H	1.0×10^9	60
H	COOEt	$>5 \times 10^{10}$	60

potential of such reactions.[12] In 1991 Clive gave a general method for attaching alkyl and substituted alkyl groups to an existing cyclic structure by ring-opening of cyclopropyl carbinols.[13] He found the reactions can be often carried out with predictable stereo- and regiochemical control (**Scheme IV**). Recently Robins reported the synthesis of a Uridine analog by the radical-induced ring opening reaction (**Scheme V**).[14]

Scheme III:
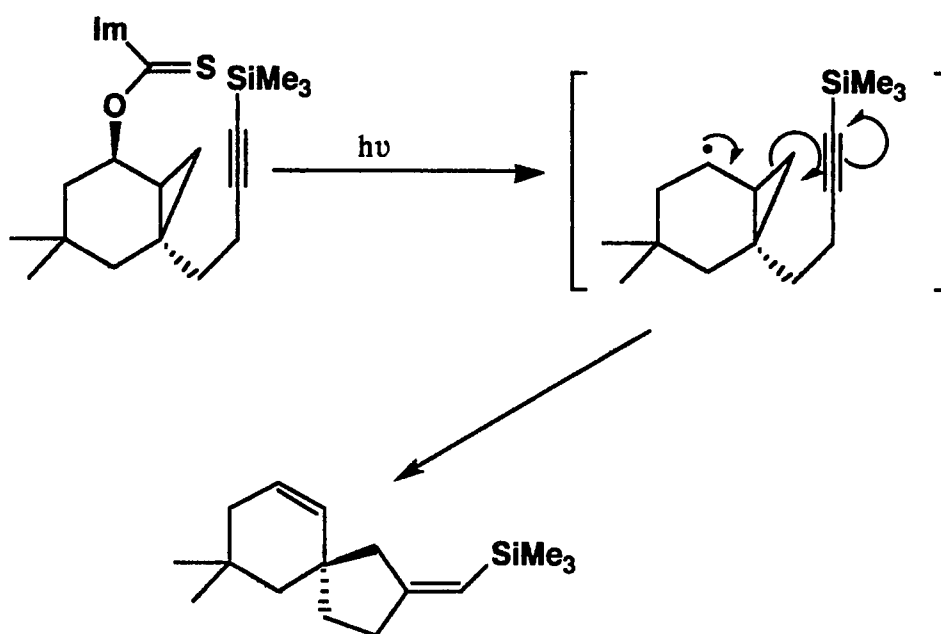
Notably, the most widely used method for generating radicals is the reaction of halides, selenides or sulfides with tri-n-butylstannyl radicals. However, the expense, toxicity and operational difficulties associated with the organotin reagents have prompted the evaluation of alternate methods. Photochemistry has long been used to generate biradical intermediates. But,

few of these reactive biradicals are useful in the generation of new radicals. The exceptions include the biradicals derived from benzophenones and certain quinones, which undergo efficient intermolecular hydrogen abstraction reactions.[15] The trapping of 1,4-biradicals (whose short lifetimes necessitate intramolecular traps) to generate new biradicals which can cyclize is almost unknown. In a classic experiment, Wagner and coworkers irradiated 2-allylpropiophenone and isolated only 4% of 2-phenyl-2-norbornanol (Scheme VI).[16] However, no example of radical induced ring-opening by photochemical processes has ever been reported.
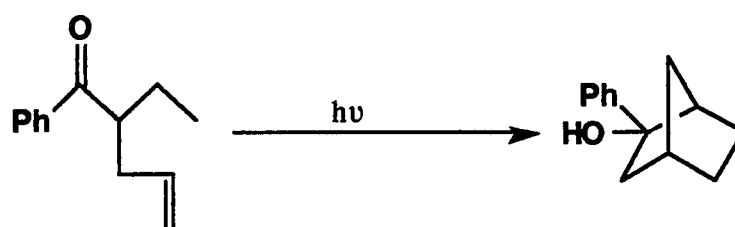
**Scheme IV:**

Scheme V:

65%   25%
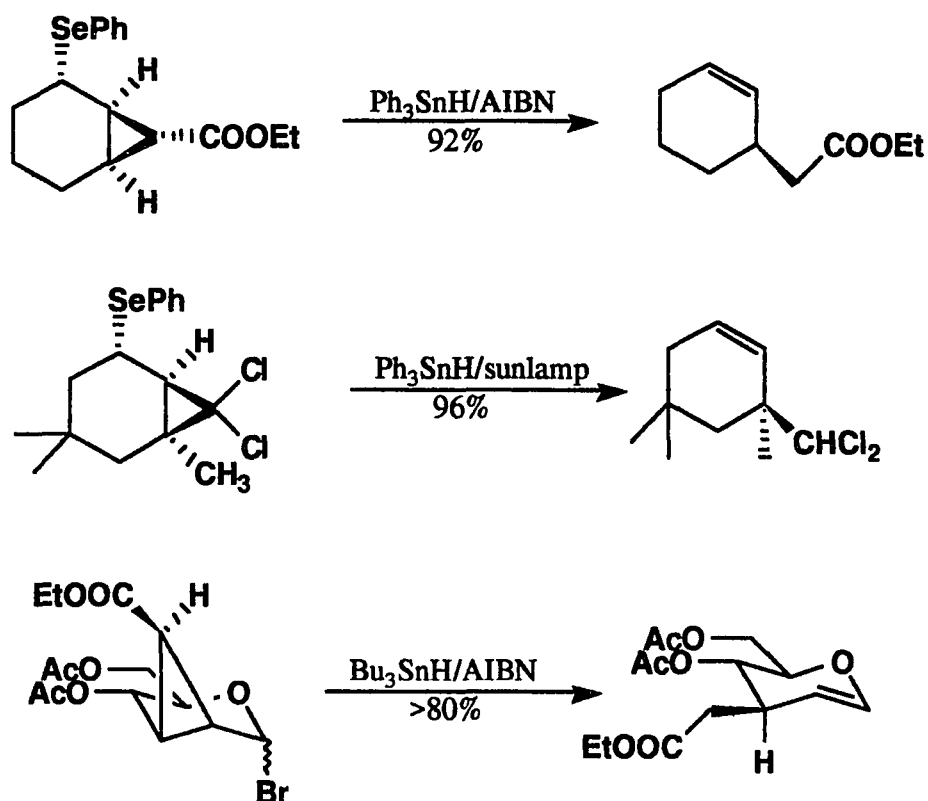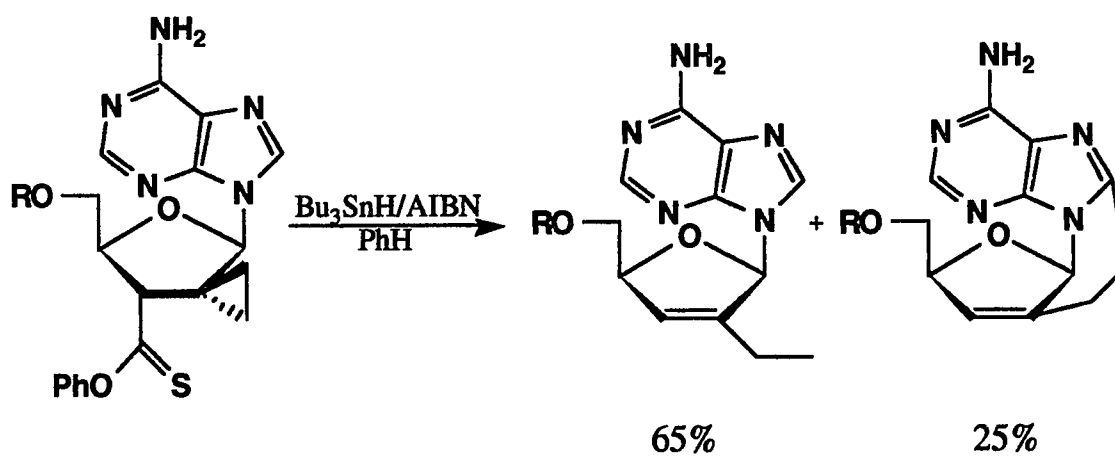
Scheme VI:

RESULTS AND DISCUSSION

In the context of developing new radical cyclization methods for the construction of synthetically useful intermediates, we examined the interception of the biradicals produced by the photolysis of an α-keto ester. The photolysis of α-keto esters has been well studied and has been employed in a mild procedure for the oxidation of alcohols by Binkley.[17] We initially examined the interception of the 1,4-biradicals derived from the photolysis of α-keto esters with an alkene. Acylation of 5-hexene-1-ol with benzoylformic acid using DCC and DMAP, followed by irradiation, afforded a good yield of 5-hexenal (**Scheme VII**).

We did not isolate any products resulting from the intramolecular trapping of the biradical by the alkene.

We next examined the unsubstituted cyclopropyl carbinyl radical

Scheme VII:
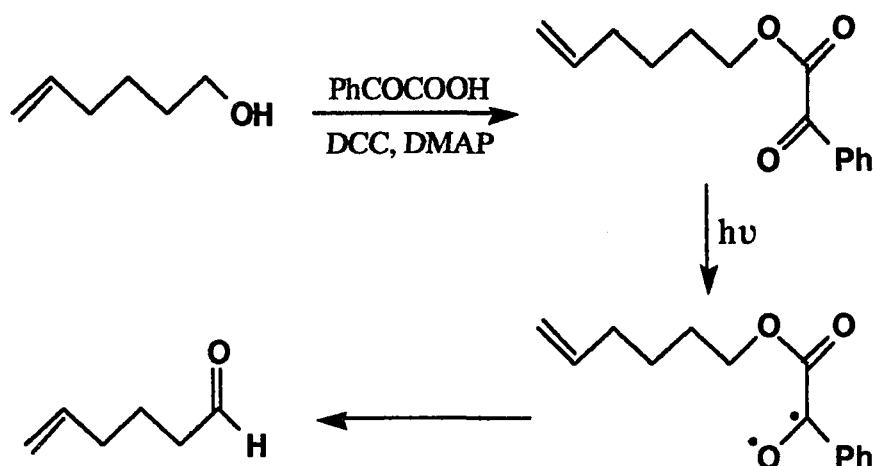
rearrangement as a way to intercept the biradical. Compound 2 was synthesized from cyclohexanone by the method of Murai.[18] The keto ester 3a was then produced in 100% yield from 2 by deprotection of the trimethylsilyl group with n-Bu$_4$NF in THF and followed by esterification with benzoylformic acid. Irradiation of compound 3a provided only compound 7a in quantitative yield without any trace of product resulting from cleavage of the cyclopropane (Scheme VIII). We understand that the yields of products will depend on the relative value of the rate constants. The results told us the value of K$_3$ is much bigger than the ring-opening rate constant-K$_2$ which is ~10^8 s^{-1} at room temperature. Previously, people reported that the substituents on the cyclopropyl ring will dramatically affect the value of the rate constant for ring-opening. Newcomb has demonstrated that phenyl substitution on the cyclopropane increases the rate of the cyclopropyl carbinyl opening by a factor
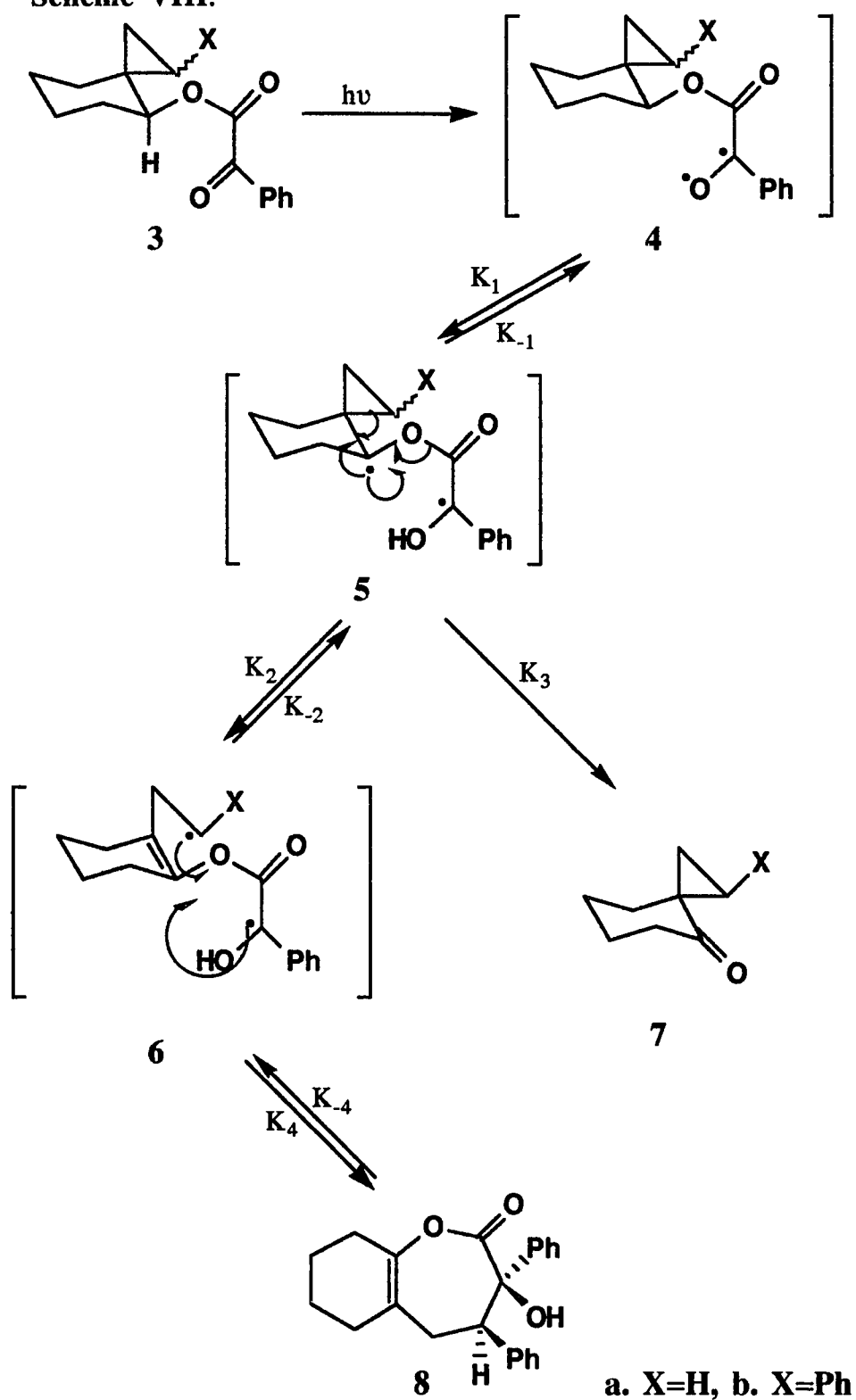

OSiMe$_3$

H

2
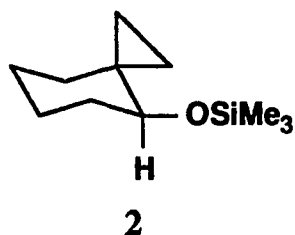
of 100. The keto ester 3b was therefore synthesized from compound 9 (Scheme IX). Irradiation of 3b afforded a 30% yield of the seven-membered ring lactone 8 and a 38% yield of the ketone 7b. Since the ratio of 8 to 7b is about 1.0:1.3, the values of K$_2$ and K$_3$ should be roughly same. The trans relationship of the two phenyl groups in 8 was identified by X-ray structure determination. The pyruvate ester 10 was produced from compound 7b and subjected to the same photochemical conditions. The ring-opening compound
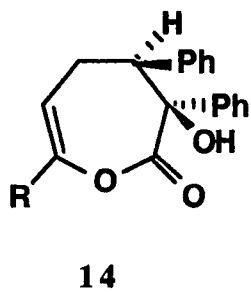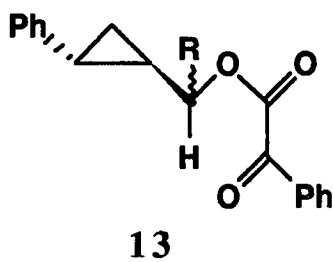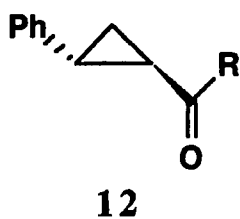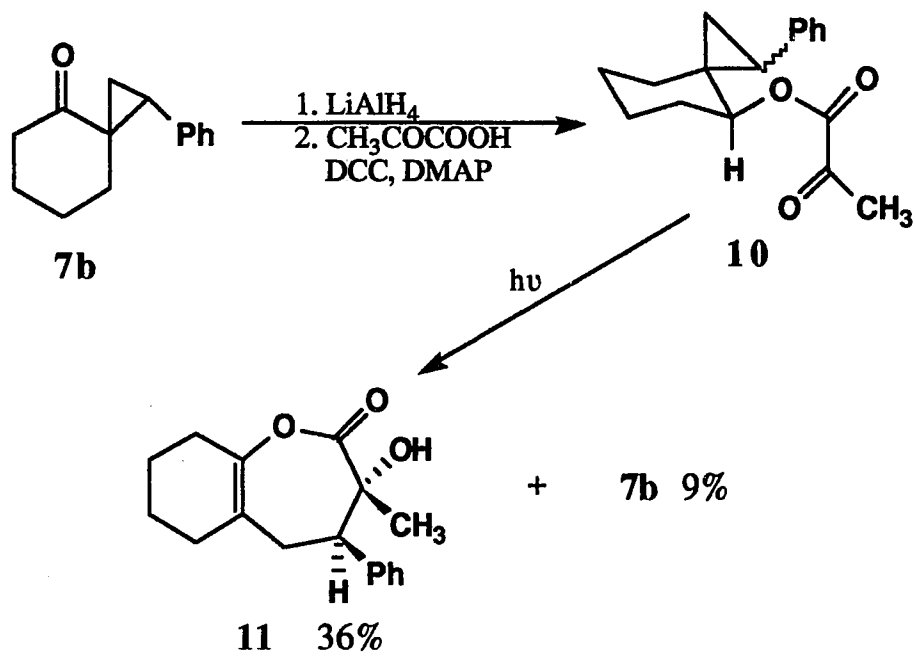
11 in 36% yield and the elimination product **7b** in 9% yield were produced. The acyclic compounds was also synthesized for photochemical elimination. The α-keto ester **13** was produced from **12** by $LiAlH_4$ reduction and esterification with benzoylformic acid using DCC and DMAP. Irradiation of **13a** provided a trace amount of aldehyde **12a** and a 25% yield of lactone **14a**. Compound **13b** was subjected to the same photochemical conditions as **13a** and afforded a mixture of **12b** and the cyclization product **14b** in a 1:1 ratio based on proton NMR spectroscopy. Since **12b** and **14b** had the same Rf value in TLC, the pure **14b** could not be provided by silica gel chromatography. We treated the mixture with 1N NaOH to effect hydrolysis of the lactone and methylated the acid with CH_2N_2 (**Scheme X**). Compound **15** was thereby produced and separated in 16% overall yield (three steps from **13b**) and the ketone **12b** was also separated in 19% overall yield. The formation of **15** proved the cyclization product was **14b** (**Scheme X**). Lactone **14b** was a labile compound, both to column chromatography and, to a lesser extent, to the irradiation conditions.

The results presented herein demonstrate the potential of using photochemically generated 1,4-biradicals for ring formation. The synthetic applications of this strategy remain to be determined and the yield of ring formation needs to be somewhat increased by choosing different functional groups on the cyclopropyl ring.

Scheme VIII:

a. X=H, b. X=Ph

Scheme IX:

7b

1. LiAlH₄
2. CH₃COCOOH
   DCC, DMAP

Ph

O

CH₃

10

hυ

O

OH

CH₃

Ph

H

11   36%

+   7b 9%

Ph

R

O

12

Ph

R

O

O

H

O

Ph

13

H

Ph

Ph

OH

R

O

O

14

a. R=H, b. R=CH₃

Scheme X:

12b + 14b $\xrightarrow[\text{2. CH}_2\text{N}_2]{\text{1. 1N NaOH}}$ 12b +

19%   15 16%

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 1320 spectrophotometer. Nuclear Magnetic Resonance (NMR) spectra were determined on a 300 MHz Nicolet Magnetic Corporation NMC-1280 spectrometer. All chemical shifts were reported relative to tetramethylsilane as internal standard. Coupling constants were reported in Hz. Abbreviations: s=singlet, d=doublet, t=triplet, m=multiplet, ABq=ABquartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. H:EA refers to hexane/ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR spectroscopic analysis and /or elemental analyses.

General procedure for esterification: To the alcohol and benzoylformic acid and 4-N,N'-dimethylaminopyridine (molar ratio: 1.0:1.1:0.1) in a round bottom flask , dry CH_2Cl_2 was added to make about a 0.1 M solution. The mixture was then cooled to 0^0C and 1,3-dicyclohexylcarbodiimide (DCC) in dry CH_2Cl_2 was added dropwise to the mixture. A white precipitate formed instantly. The mixture was allowed to warm to room temperature and stirred overnight. The precipitate was filtered by a short flash silica gel column and the solvent was evaporated in vacuo. The residue was separated by sgc.

General procedure for the irradiation of the ketoesters: The keto ester was dissolved in dry benzene (0.01-0.05 M) in a pyrex tube and the solution was degassed by argon for at least 10 minutes. The solution was then irradiated by a Rayonet photochemical reactor (wavelength=350 nm) for about 10 hours. The solvent was then evaporated in vacuo and the residue was separated by sgc.

1-Benzoylcarboxyl-spiro[5,2]cyclooctane (3a): To 4.480 grams (22.6 mmol) of the silyl ether 2, 34 mL of 1.0 M of n-Bu_4NF in THF was added. The mixture was allowed to stir for 0.5 hours at room temperature and poured into 200 mL of ethyl ether. The solution was then washed with water and with brine and dried over $MgSO_4$. The solution was filtered and evaporated in vacuo. The residue was separated by sgc (H:EA=10:1) to afford 2.85 grams (22.6 mmol) of the alcohol (100% yield).

The alcohol (0.601 g, 4.77 mmol) was esterified by benzoylformic acid to give 0.7065 g (2.74 mmol) of the keto ester 3a (57%) yield after separation by sgc (H:EA=15:1). (See general procedure for esterification)

Compound 3a: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.99 (m, 2 H), 7.66 (m, 1 H), 7.52 (m, 2 H), 4.70 (t, J=3.6, 1 H), 2.00-1.40 (m, 8 H), 0.92 (m, 1 H), 0.69 (m, 1 H), 0.50 (m, 1 H), 0.39 (m,1 H); ^{13}C NMR (CDCl$_3$) δ 186.70, 168.80, 134.59, 132.39, 129.65, 128.72, 79.57, 53.34, 31.38, 29.92, 24.38, 21.51, 20.89, 11.06; CI-MS (NH$_3$) m/z for C$_{16}$H$_{18}$O$_3$ 259 (M+1), 276 (M+18); TLC (H:EA=4:1) Rf=0.77.

Spiro[5,2]cyclooctanone-1 (7a): The keto ester 3a (0.7065 g, 2.74 mmol) was irradiated to give a 100% yield of 7a after separation by sgc (H:EA=10:1). (See general procedure for the irradiation of the keto ester) Compound 7a was same as literature report[18].

1-Benzoylcarboxyl-7-phenylspiro[5,2]cyclooctane (3b): NaH (60%, 0.502 g, 12.55 mmol) was placed in a three necked flask and washed three times with dry hexane. The flask was immediately fitted with a stirrer, a reflux condenser and a septum. The system was evacuated until the last traces of petroleum were removed from the NaH. The vacuum was then taken off and 2.761 grams (12.55 mmol) of trimethyloxosulfonium iodide was introduced through one of the side arms of the flask. The system was placed under argon. DMSO (20 mL) was introduced slowly via syringe. The stirrer started and a vigorous evolution of hydrogen occurred, which ceased after 15-20 minutes, to give a milky-white reaction mixture. The reaction mixture was cooled in a cold

water bath and a solution of 2.125 grams (11.41 mmol) of 2-phenylmethlenecyclohexanone in 10.0 mL of DMSO was added rapidly with stirring. After 5 minutes, the water bath was removed and stirring was continued for 18 hours. The solution was then poured into ice water and the aqueous solution was extracted by ethyl ether and the combined organic solution was washed with water and with brine and dried over $MgSO_4$. The solution was filtered and evaporated. The residue was separated by sgc (H:EA=50:1) to afford 0.7908 g (3.954 mmol) of compound 7b in 35% yield.

To 0.7908 g (3.954 mmol) of 7b in 60.0 mL of ethyl ether, 0.0900 g (2.37 mmol) of LAH was added. The mixture was boiled for 6 hours and cooled to room temperature and poured into ice water. The aqueous solution was extracted by ethyl ether and the combined organic solution was washed with water and with brine and dried over MgSO4. The solution was filtered and evaporated in vacuo. The residue was separated by sgc (H:EA=10:1) to afford 0.547 g (2.74 mmol) of the alcohol as a mixture of diastereomers (ratio ~1:1)

7-Phenylspiro[5,2]cyclooctan-1-ol: (higher Rf) ^1H NMR δ (ppm) 7.23 (m, 5 H), 3.38 (m, 1 H), 2.16 (m, 1 H), 1.78 (m, 3 H), 1.30 (m, 6 H), 0.86 (m, 3 H); IR (film) 3395, 2932, 2856, 1499, 1447, 1070 cm^{-1}; CI-MS (NH$_3$) for C$_{14}$H$_{18}$O 202 (M), 203 (M+1), 220 (M+18); TLC (H:EA=4:1) Rf=0.25.

(lower Rf): ^1H NMR δ (ppm) 7.22 (m, 5 H), 3.42 (broad, 1 H), 2.14 (m, 1 H), 1.80 (m, 1 H), 1.68 (m, 2 H), 1.43 (m, 3 H), 1.25 (m, 1 H), 1.16 (m, 1 H), 0.92 (m, 2 H), 0.83 (m, 1 H); IR (film) 3391, 2934, 2856, 1499, 1458,

1074 cm^{-1}; CI-MS (NH$_3$) for C$_{14}$H$_{18}$O 202 (M), 203 (M+1); TLC (H:EA=4:1) Rf=0.23.

The alcohol (0.186 g, 0.921 mmol) (higher Rf) was esterified by benzoylformic acid to give 0.2153 g (0.645 mmol) of the keto ester 3b in 70% yield after separation by sgc (H:EA=15:1). (See general procedure for esterification)

Compound 3b: ^{1}H NMR δ (ppm) 8.04 (m, 2 H), 7.67 (m, 1 H), 7.53 (m, 2 H), 7.42-7.13 (m, 5 H), 4.83 (m, 1 H), 2.36 (m,1 H), 2.08-1.82 (m, 3 H), 1.67-1.30 (m, 4 H), 1.04-0.66 (m, 3 H); IR (film) 3060, 2937, 1730, 1690, 1202 cm^{-1}; CI-MS (NH$_3$) m/z for C$_{22}$H$_{22}$O$_3$ 352 (M+18); TLC (H:EA=4:1) Rf=0.42.

7-Phenylspiro[5,2]cyclooctanone (7b): The keto ester 3b (0.0700 g, 0.210) was irradiated to give 0.0208 g (0.0623 mmol) of 7b in 30% yield and 0.0143 g (0.0715 mmol) of 8b in 34% yield after separation by sgc (H:EA=20:1). (See general procedure for the irradiation of the keto ester)

Compound 7b: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.27 (m, 5 H), 2.68 (ABq, J$_1$=9.0 Hz, J$_2$=7.2 Hz, 1 H), 2.47 (m, 2 H), 1.95-1.30 (m, 7 H), 1.11 (ABq, J$_1$=6.9 Hz, J2=4.2 Hz, 1 H); ^{13}C NMR (CDCl$_3$) δ 210.61, 136.53, 129.04, 128.00, 126.57, 39.66, 35.20, 34.24, 28.02, 24.02, 23.10, 19.37; IR (film) 2939, 2862, 1690, 1450, 1130 cm^{-1}; CI-MS (NH$_3$) m/z for C$_{14}$H$_{16}$O 201 (M+1), 218 (M+18); TLC (H:EA=3:1) Rf=0.36.

3-Hydroxy-3,4-diphenylcyclohex[f]heptene-6-lactone (8):
Compound 8: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.41-7.26 (m, 10 H), 4.46

(ABq, J_1=11.7 Hz, J_2=6.9 Hz, 1 H), 3.38 (s, 1 H), 2.95 (ABq, J_1=14.7 Hz,

J_2=12.3 Hz, 1 H), 2.10 (ABq, J_1=15.0 Hz, J_2=6.9 Hz, 1 H), 1.93 (m, 3 H), 1.38

(m, 2 H), 1.20 (m, 2 H), 1.01 (m, 2 H); IR (film) 3506, 2935, 1732, 1497,

1175 cm^{-1}; HRMS m/z for $C_{22}H_{22}O_3$ Calcd. 334.15689, measured

334.15706; TLC (H:EA=3:1) Rf=0.24; M.p. 122.5-124.0°C.

1-Benzoylcarboxyl-7-phenylspiro[5,2]cycloheptane (10): 7-

Phenylspiro[5,2]cyclooctan-1-ol (0.179 g, 0.886 mmol) (higher Rf) was

esterified by benzoylformic acid to give 0.091 g (0.350 mmol) of the keto ester

10 in 40% yield after separation by sgc (H:EA=60:1). (See general procedure

for esterification)

Compound 10: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.28-7.10 (m, 5 H), 4.62 (t,

J=3.0 Hz, 1 H), 2.53 (s, 3 H), 2.28-1.15 (m, 8 H), 0.81 (m, 3 H); IR (film)

3026, 2934, 2858, 1718, 1651, 1140 cm^{-1}; HRMS m/z for $C_{17}H_{20}O_3$ Calcd.

272.14124, measured 272.14080; TLC (H:EA=6:1) Rf=0.53.

3-Hydroxy-3-methyl-4-phenyl-cyclohex[f]heptene-6-lacone

(11): The keto ester 10 (0.0751 g, 0.276 mmol) was irradiated to give 0.0250

g (0.0919 mmol) of 11 in 36% yield and 0.0053 g (0.0715 mmol) of 7b in 9%

yield after separation by sgc (H:EA=15:1). (See general procedure for the

irradiation of the keto ester)

Compound 11: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.30 (m, 3 H), 7.18 (m, 2

H), 3.38 (ABq, J_1=11.1 Hz, J_2=5.7 Hz, 1 H), 3.17 (s, 1 H), 2.77 (m, 1 H), 2.16

(m, 5 H), 1.75 (m, 4 H), 1.65 (s, 3 H); IR (film) 3413, 2937, 2862, 1732,

1452, 1150 cm^{-1}; CI-MS (NH3) m/z for $C_{17}H_{20}O_3$ 290 (M+18); TLC (H:EA=4:1) Rf=0.43.

trans-2'-Phenylcyclopropionylmethyl benzoyl formate (13a): To 3.080 grams (21.10 mmol) of 12a in 200 mL of THF, 0.480 g (12.7 mmol) of LAH was added at room temperature. The mixture was allowed to reflux overnight and cooled to room temperature and poured into ice water. The aqueous solution was extracted by ethyl ether and the combined organic solution was washed with water and with brine and dried over $MgSO_4$. The solution was then filtered and evaporated in vacuo. The residue was separated by sgc (H:EA=10:1) to afford 1.5224 grams (10.29 mmol) of the alcohol.

The alcohol (1.210 g, 8.17 mmol) was esterified by benzoylformic acid to give 1.948 grams (6.96 mmol) of the keto ester 13a in 85% yield after separation by sgc (H:EA=70:1). (See general procedure for esterification)

Compound 13a: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.95 (m, 2 H), 7.58 (m, 1 H), 7.38 (m, 2 H), 7.18 (m, 3 H), 7.05 (m, 2 H), 4.35 (m, 2 H), 2.00 (m, 1 H), 1.59 (m, 1 H), 1.06 (m, 2 H); IR (film) 3028, 2955, 1738, 1960, 1452, 1200 cm^{-1}; HRMS m/z for $C_{18}H_{16}O_3$ Calcd. 280.10994, measured 280.10948; TLC (H:EA=3:1) Rf=0.66.

3-Hydroxy-3,4-diphenylcycloheptene-6-lactone (14a): The keto ester 13a (0.560 g, 2.00 mmol) was irradiated to give 0.0946 g (0.338 mmol) of 14a in 25% yield (0.184 g of starting material was returned after separation by sgc) (H:EA=15:1). (See general procedure for the irradiation of the keto ester).

Compound **14a** ^{1}H NMR (CDCl$_3$) δ (ppm) 7.50-7.13 (m, 10 H), 6.25 (m, 1 H), 5.05 (m, 1 H), 4.02 (s, 1 H), 2.60 (m, 1 H), 2.51 (m, 1 H), 1.97 (m, 1 H); IR (film) 3450, 3020, 1732, 1597, 1202, 1177 cm^{-1}; HRMS m/z for C$_{18}$H$_{16}$O$_3$ Calcd. 280.10994, measured 280.10972; TLC (H:EA=6:1) Rf=0.33.

1-(2'-trans-Phenylcyclopropyl)ethyl benzoyl formate (13b):
To 0.552 g (3.45 mmol) of **12b** in 40 mL of THF, 0.0790 g (2.07 mmol) of LAH was added at room temperature. The mixture was then boiled overnight and cooled to room temperature and poured into ice water. The aqueous solution was extracted by ethyl ether and the combined organic solution was washed with water and with brine and dried over MgSO$_4$. The solution was filtered and evaporated in vacuo. The residue was separated by sgc (H:EA=10:1) to afford 0.322 g (higher Rf) and 0.186 g (lower Rf) of two diastereomers of the alcohol in 91% total yield.

The alcohol (0.302 g, 1.86 mmol) (higher Rf) was esterified by benzoylformic acid to give 0.434 g (1.48 mmol) of the keto ester **13a** in 79% yield after separation by sgc (H:EA=70:1). (See general procedure for esterification)

Compound **13b**: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.89 (m, 2 H), 7.57 (m, 1 H), 7.95-7.14 (m, 5 H), 7.08 (m, 2 H), 4.86 (m, 1 H), 2.21 (m, 1 H), 1.51 (d, J=6.6 Hz, 3 H), 1.45 (m, 1 H), 1.06 (m, 2 H); ^{13}C NMR (CDCl$_3$) δ (ppm) 188.82, 164.01, 141.48, 134.70, 132.26, 129.81, 128.74, 128.34, 125.85, 125.48, 77.30, 28.02, 22.60, 19.64, 13.29; IR (film) 3061, 2979, 1733, 1689, 1202 cm^{-1}; HRMS m/z for C$_{19}$H$_{18}$O$_3$ Calcd. 294.12559, measured 294.12554; TLC (H:EA=3:1) Rf=0.66.

Methyl 2,3-diphenyl-6-oxoheptanoate (15): The keto ester **13b** (0.322 g, 1.095 mmol) was irradiated to give a mixture of **12b** and two diastereomers of **14b** with exact by the same Rf value. (See general procedure for irradiation of the keto ester)

The residue (the mixture) was treated overnight with 10 mL of 1N NaOH and acidified to pH~6.0. The aqueous solution was extracted by ethyl ether and the combined organic solution was washed with water and with brine and dried over $MgSO_4$. The solution was filtered and evaporated in vacuo. The residue was not purified and treated with diazomethane of ethyl ether solution until no gas generated. The solvent was evaporated in vacuo and the residue was separated by sgc (H:EA=6:1) to afford 0.0580 g (0.178 mmol) of **15** in 16% overall yield from **13b** and 0.0330 g (0.206 mmol) of **12b** in 19% yield after separation by sgc (H:EA=10:1).

Compound **15**: ^1H NMR ($CDCl_3$) δ (ppm) 7.82 (m, 2 H), 7.36 (m, 8 H), 3.83 (s, 1 H), 3.59 (ABq, J_1=13.2 Hz, J_2=3.9 Hz, 1 H), 3.51 (s, 3 H), 2.07 (m, 3 H), 1.88 (m, 3 H), 1.88 (s, 3 H), 1.71 (m, 1 H); IR (film) 3497, 3059, 2952, 1729, 1714, 1246 cm^{-1}; CI-MS (NH_3) m/z for $C_{20}H_{22}O_4$ 326 (M), 344 (M+18); TLC (H:EA=6:1) Rf=0.32.

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PAPER V

1,9-HYDROGEN ABSTRACTION
PHOTOCHEMICAL STRATEGIES FOR RADICAL CYCLIZATION

INTRODUCTION

A few cases of hydrogen atom abstractions from remote sites have been observed a few cases over the past two decades, ranging from ϵ- hydrogen abstraction in cyclodecanone[1] to the cyclization of benzophenones with long alkyl tails attached in the para position.[2] More often the very remote hydrogen abstractions are involved in electron transfer between the exited carbonyl and remote hetero atoms. An example was the irradiation of phthalimides with N substituents having a terminal methylthio group resulted in the formation of macrocyclic systems (ring sizes C_{16-17}) (**Scheme I**). Such reactions were thought to arise from a photoinduced electron transfer from the methylthio group to the imide unit.
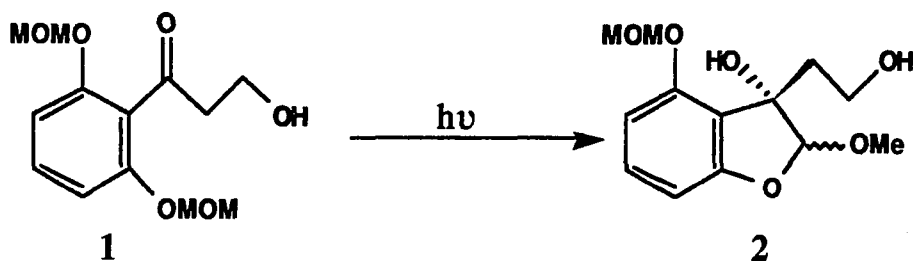
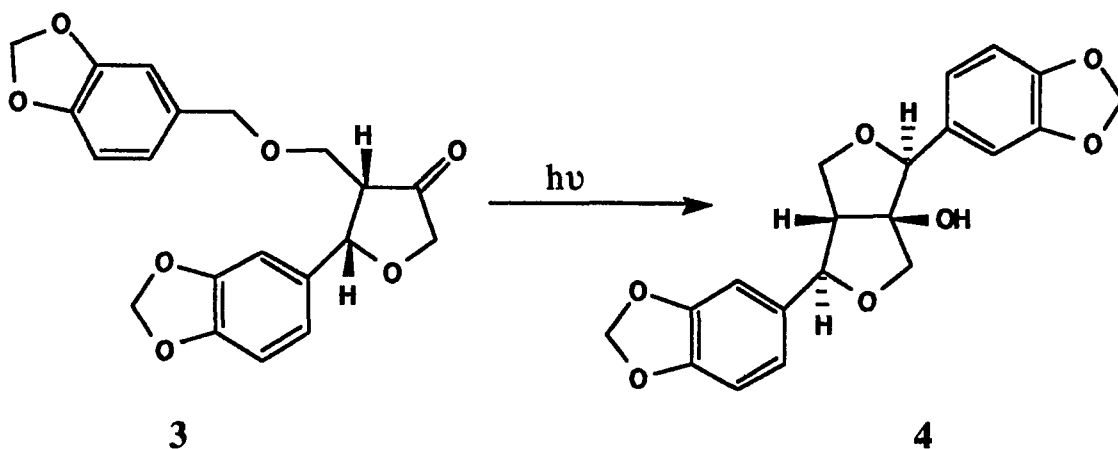**Scheme I:**

48% for m=10, n=1;
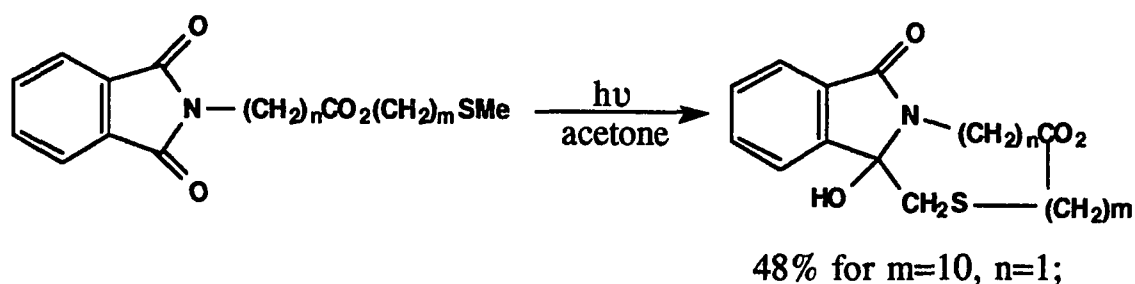
Previously, people recognized that remote hydrogen abstraction could not compete with γ- hydrogen abstraction. Only when there was no γ-hydrogen available was abstraction of hydrogens from the remote sites feasible. Some examples have been reported for 1,6- (δ-), 1,7- (ϵ-), 1,8- (ξ-) and a very remote hydrogen atom abstraction. This kind of hydrogen

abstraction strategy was very useful in the synthesis of naturally occurring products which could make 5-, 6-, 7- and macrocyclic rings. Several δ-hydrogen abstractions by cyclopentanone units were key steps in the synthesis of dodecahedrane,[3] while the same strategy was pursued in the synthesis of punctain.[4] Another example was the construction of the aflatoxin skeleton[5] (Scheme II), which was based on the δ- hydrogen abstraction in compound 1 leading to benz-furanol 2. A similar strategy was presented in the synthesis of paulownin which involved the conversion of furan-3-one 3 to furan-3-ol 4[6] (Scheme III).
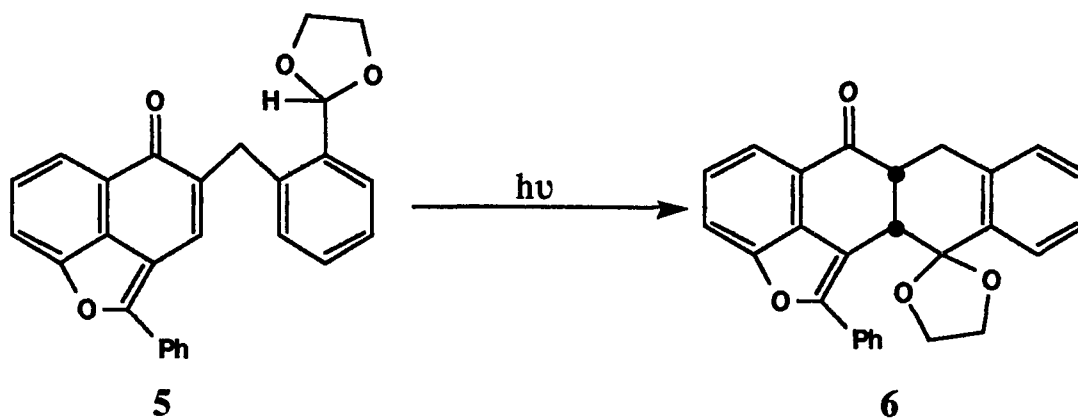
Scheme II:

Scheme III:

Probably the most studied remote hydrogen abstraction is the ε-
hydrogen abstraction. The first example of ε- hydrogen abstraction was
reported by Barton,[7] which involved a β- aryl ketone (**Scheme IV**).
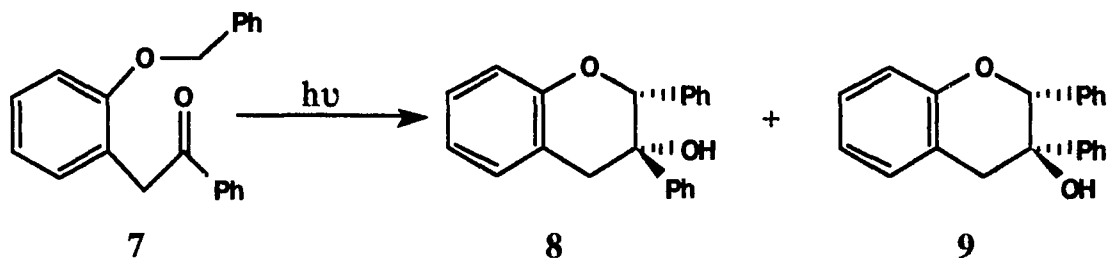
Another example of ε- hydrogen abstraction was reported by Wagner[8]
(**Scheme V**). The photocyclization of acetophenone **7** proceeded in a quantum
yield.

An example of ξ-hydrogen abstraction was given by Carless who
reported several ξ-hydrogen abstractions by exited β-(O-
alkylphenoxy)propiophenones[9] (**Scheme VI**). Cyclization of the 1,7-biradicals

Scheme IV:

Scheme V:

showed little diastereoselectivity. No allylic rearrangements occurred

Another ξ-hydrogen abstraction was reported by Adam[10], in which a site specific ξ-hydrogen abstraction by a gibberellin oxo ester produced the corresponding lactone (**Scheme VII**). The authors found that the hydrogen abstracted lay only 2.5 Å from the carbonyl oxygen.

The very remote hydrogen abstraction from the long alkyl tails of n-alkyl p-benzoyl benzoate ester[1] led to the concept of biomimetic reactions, in this case the oxidation of an otherwise inactivated methylene group.[11] Breslow

Scheme VI:

1 0

R=allyl, phenyl

**1 1**

2

1 2

1 (ratio)

Scheme VII:

13

14

had shown that considerable site selectivity occurred in intramolecular

hydrogen abstraction from steroids[12]. Oxidation of long chain alkyl groups

could be done with better site selectivity than in the original esters. Myristate

ester attached to p-benzoylbenzoic acid via catechol or 1,2-cyclohexanediol

underwent hydrogen atom abstraction and cyclization in a 85% at carbons 7-

10[13] (Scheme VIII).

In contrast to the normal remote intramolecular hydrogen abstractions,

remote electron transfer has been observed for a few cases of ketones and a

Scheme VIII:

CH₃(CH₂)₁₂ structure 15 reacting under $h\upsilon$, $x=2-6$ to give structure 16

15   **16**
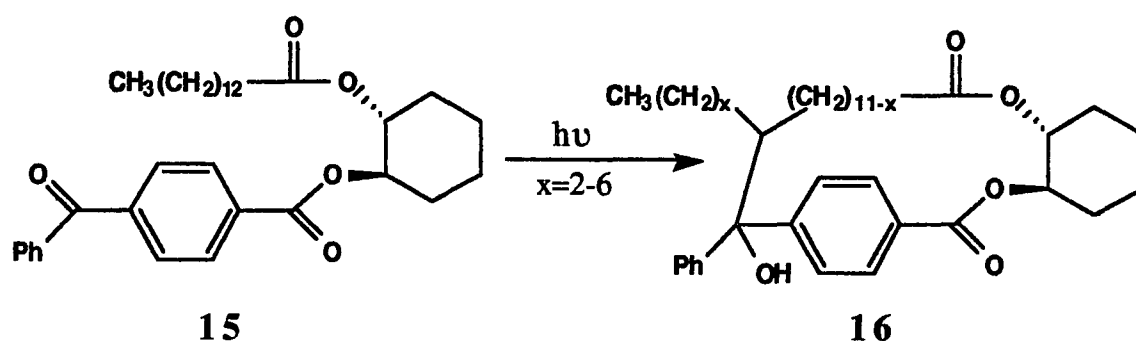
wide variety of imides. The amino and thio ketones and imides could have this

kind of process set up ring size from 4-20. Hasegawa reported that ω-

dialkylaminoalkyl esters of benzoylacetic acid photocyclized in respectable

yields[14] (Scheme IX). The electron transfer induced intramolecular hydrogen

atom abstractions might be the only reported reactions which could compete
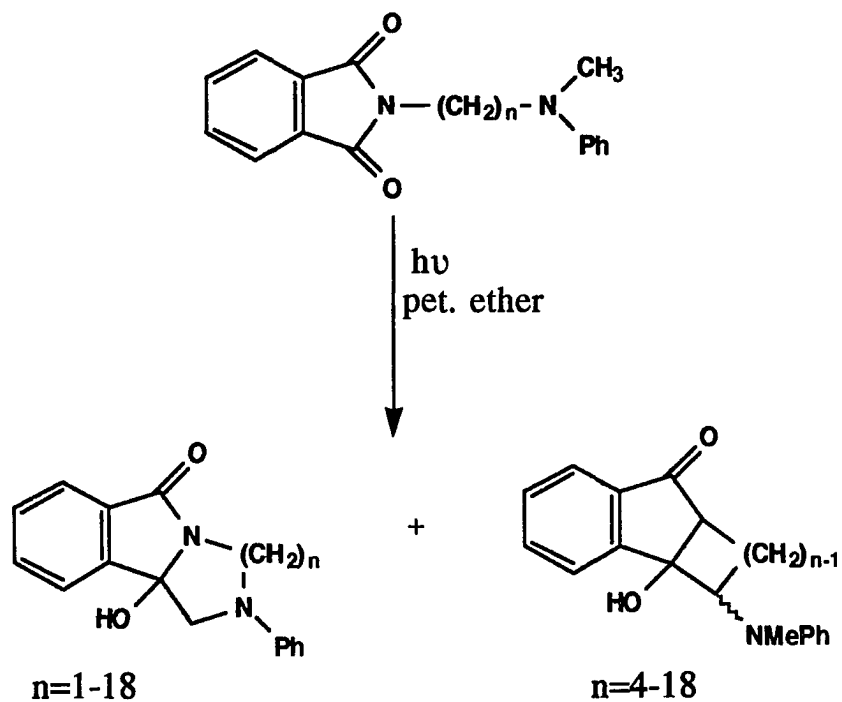
with the normal γ-hydrogen abstraction.

Starting with the remote electron transfer reaction in 1973,[15] Kanaoka

provided many examples of this kind of hydrogen abstraction.[16] He found that the remote hydrogen transfers in aminophalimides were very efficient (Scheme X)[17].

Scheme IX:

R'=H, Me
R=H, Ph   n=2-4   25-63%   7-0%

Scheme X:

hυ
pet. ether
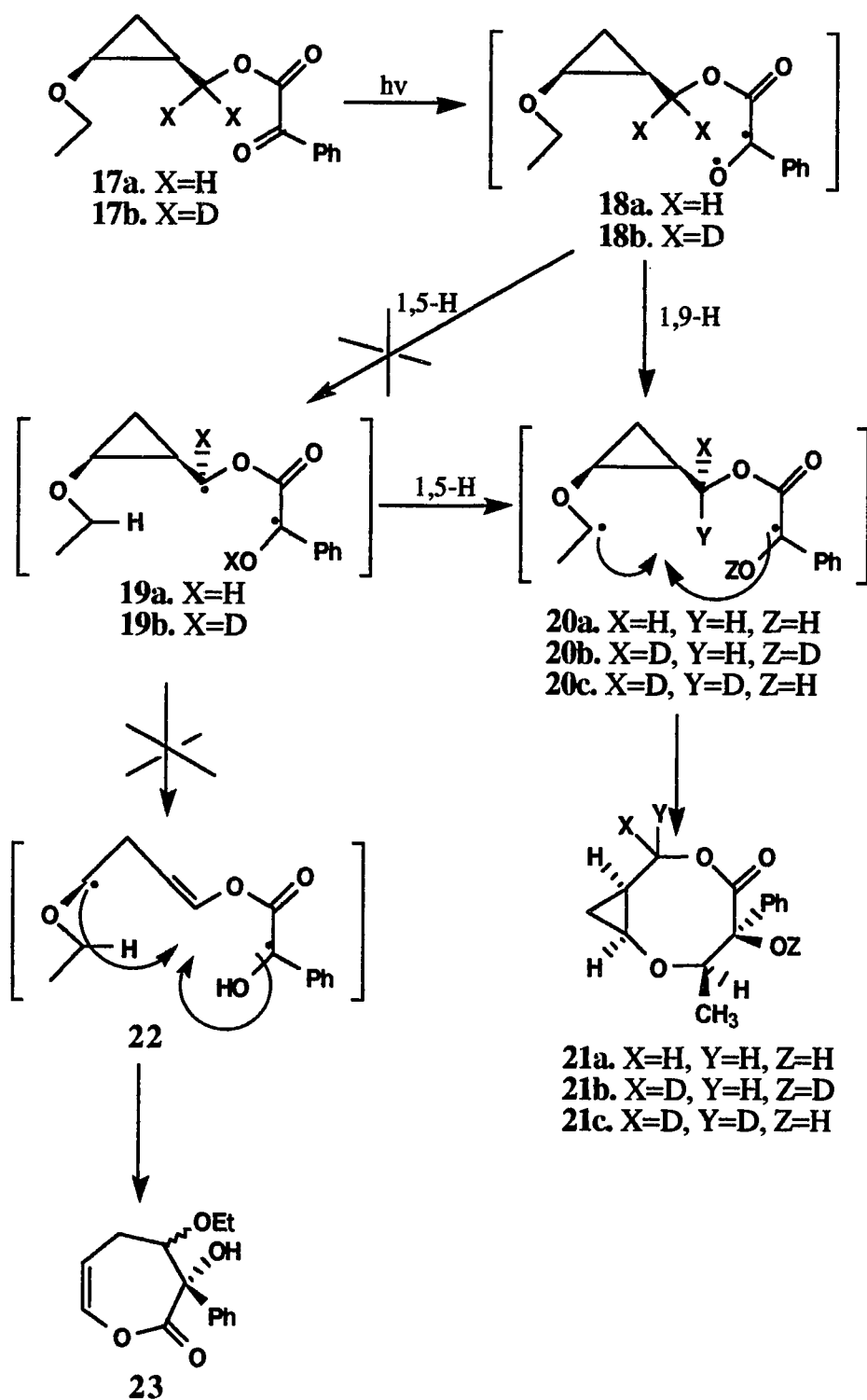
n=1-18   +   n=4-18
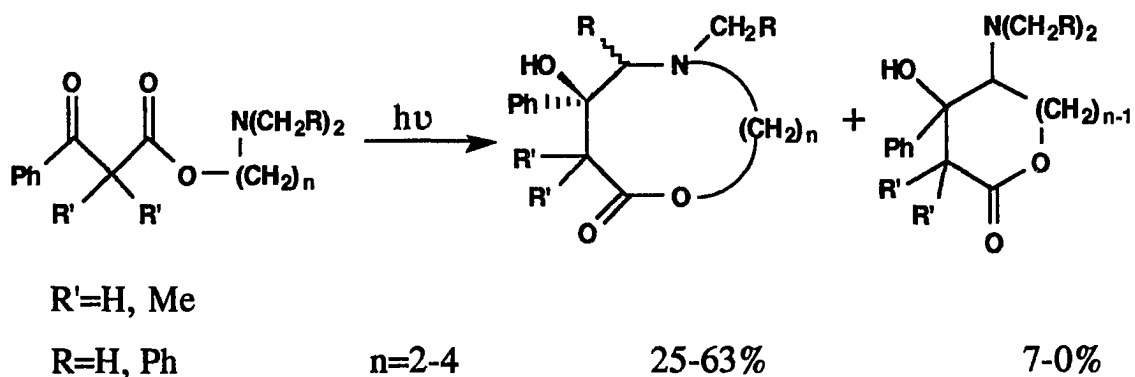
RESULTS AND DISCUSSION

In order to extend the scope of the cyclopropyl carbinyl opening, ester **17a** was prepared by reduction of the known cyclopropyl ester with LAH in ether at 0°C followed by esterification with benzoylformic acid. The expected product from the irradiation of **17a** was **23** via a intermediate **19a** (**Scheme XI**). But, surprisingly, irradiation of **17a** afforded only the eight-membered ring compound **21a** in 51% yield without any ring opening compound. Since the direct 1,9-hydrogen transfer (**18a-20a-21a**) was very unusual, (all of the long range hydrogen atom abstractions could not compete with Norish type II reaction except amino ketones and imides, or sulfide imides which underwent an electron transfer process)[18], we thought lactone **21a** might have been formed from the 1,4-biradical (shown in **Scheme XI**) by a double 1,5-hydrogen transfer followed by cyclization. In order to differentiate between the two mechanisms, deuterated ester **17b** was prepared by the same procedure for **17a**, except using lithium aluminum deuterium (LAD) as the reducing agent, instead of LAH, and subjected to photolysis conditions. *Lactone 21c was isolated in 62% yield, demonstrating that in this case a 1,9-hydrogen abstraction reaction had indeed occurred.* The proton NMR spectrum of the product from the photolysis of **17b** before purification showed no trace of product derived from the 1,5- hydrogen atom abstraction, followed by a 1,5-hydrogen transfer and cyclization. The stereochemistry of **21a** was characterized by 2D Coesy and Noesy. This remarkable selectivity may reflect photoreaction via the favored syn rotamer of the ester. The 1,5-hydrogen abstraction must occur from the anti rotamer.[19]

Several systems have been evaluated to identify structural features

Scheme XI:

17a. X=H
17b. X=D

18a. X=H
18b. X=D

1,5-H

1,9-H

19a. X=H
19b. X=D

1,5-H

20a. X=H, Y=H, Z=H
20b. X=D, Y=H, Z=D
20c. X=D, Y=D, Z=H

22

21a. X=H, Y=H, Z=H
21b. X=D, Y=H, Z=D
21c. X=D, Y=D, Z=H

23

necessary for the formation of eight-membered ring lactones. The production of aldehyde **25** from keto ester **24** was synthesized from 1,3-propanediol without the formation of eight-membered ring compound, indicated that some degree of conformational rigidity was required. The aromatic keto esters **26** [prepared from 2-(o- methylphenyl)-ethanol] and **27** [synthesized from o-bromotoluene] provided eight-membered ring compounds **28** and **29** in 41% and 74% yields, respectively. Lactone **29** was a single stereoisomer as evidenced by proton NMR and TLC. The photo precursor **32** was prepared from 2-ethoxylcarbonylcyclohexanone (**30**). Compound **30** was protected by 1,3-propanediol to give the ketal in 93% yield, which was reduced by LAH to afford the alcohol **31** (Scheme XIII).

Scheme XII:

hv

PhCH₂OCH₂CH₂CHO

24

25. 56%

hυ

26. X=H
27. X=Me

28. X=H. 41%
29. X=Me. 74%
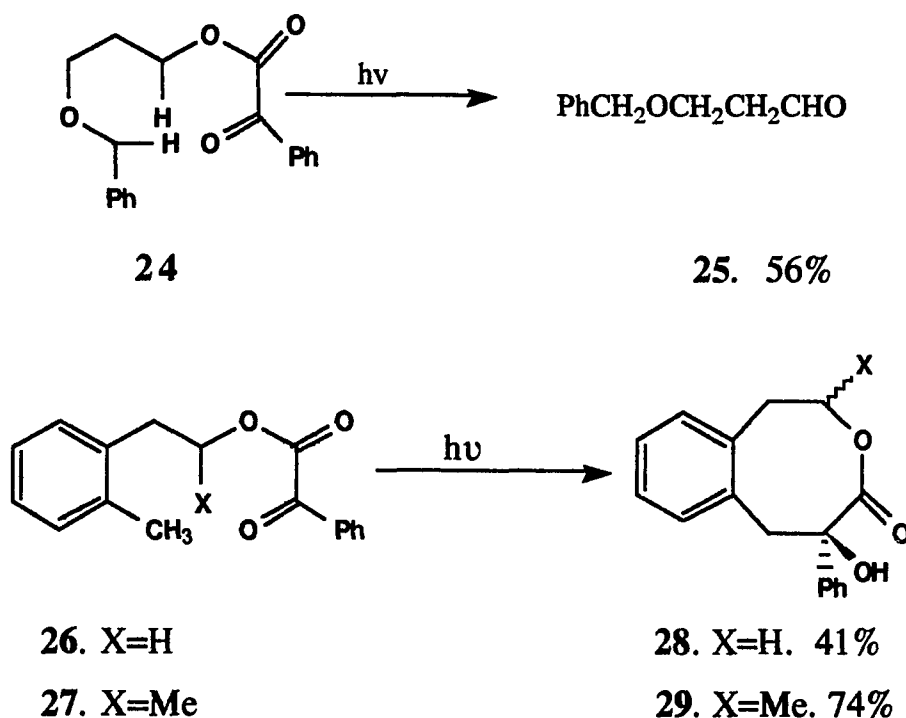
in 24% yield. Alcohol **31** was then esterificated by benzoylformic acid using DCC and DMAP to give the precursor **32**. The irradiation of ketal **32** also produced the expected product **33** in 22% yield (**Scheme XIII**). Lactone **33** was a mixture of stereoisomers at the newly-generated stereogenic center α to the carbonyl.

Scheme XIII:

34   **35**   **36**
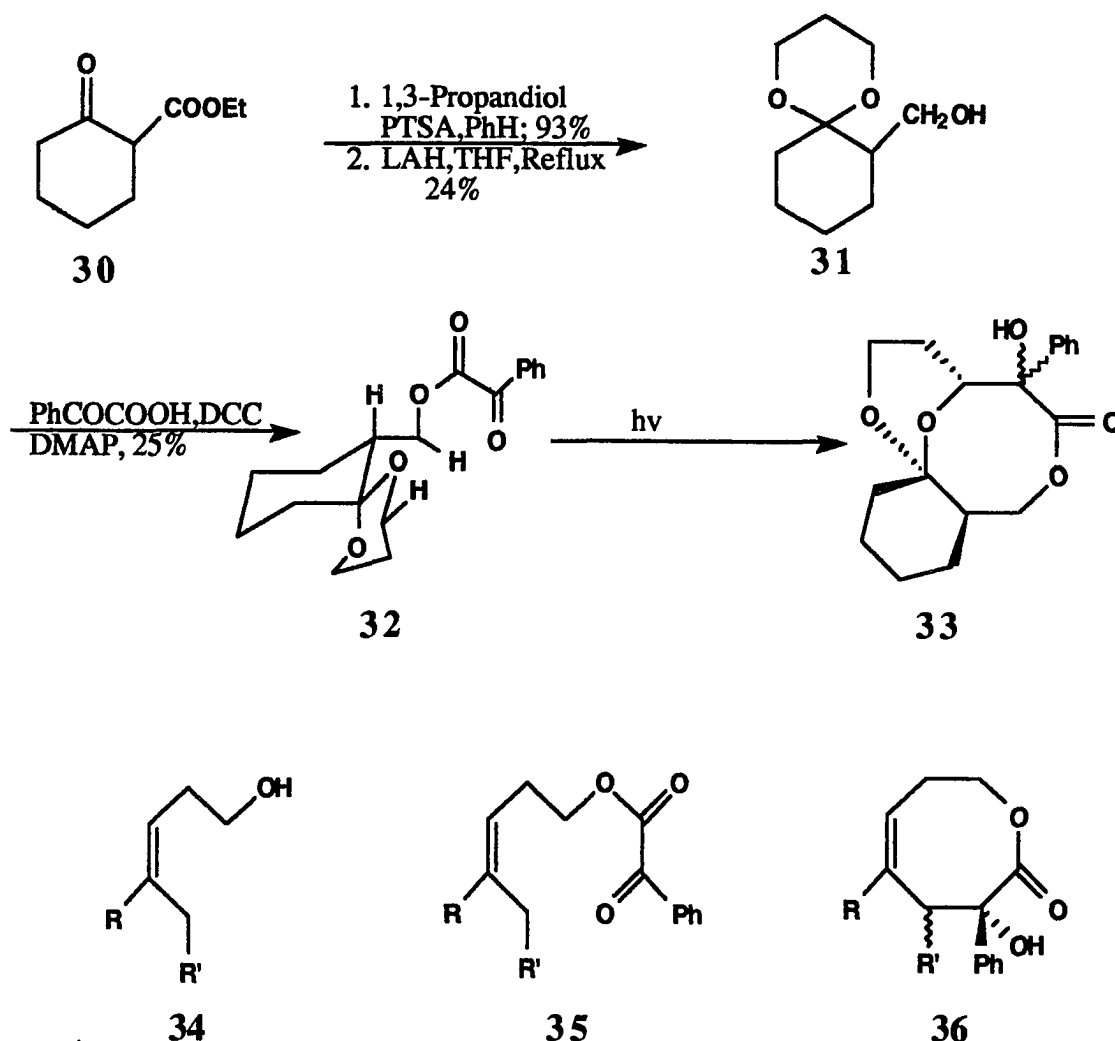
a. R=H, R'=Me;   b. R=Me, R'=H.

Keto ester **35a** was synthesized by the esterification of commercially available alcohol **34a** with benzoylformic acid using DCC and DMAP. Irradiation of **35a** gave a mixture of diastereomers of cyclized product **36a** in 49% yield (diastereomer ratio=1.0:1.8). The cyclization of **35a** to an eight-membered ring lactone, rather than a six-membered ring lactone, was unexpected. A 1,9-hydrogen atom abstraction via the syn rotamer of the ester, followed by rapid closure of the proximate biradical nicely rationalizes this result. Keto ester **35b** produced from **34b** also cyclized to hydroxy lactone **36b** under the same conditions in 31% yield.

To get better evidence for the formation of eight-membered rings, keto ester **40** was made in 3 steps from **37** (Scheme XIV) and subjected to photolysis. An eight-membered ring compound **41** was produced and identified by X-ray analysis.

Since some pyruvate compounds were reported to be oxidized via 1,4-biradicals[20], compound **42** was made from pyruvic acid and cis-3-hexen-1-ol and was irradiated. Compound **43** was therefore produced in 55% yield as a single diastereomer.
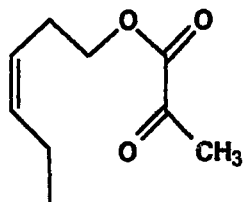
We also examined the effects of temperature on the yield of product formation. We carried out the irradiation of the keto ester **35a** at 0 °C. The yield of the eight-membered ring compound **36a** was dramatically increased to 61% yield. The reaction was then carried out at 80 °C in a sealed tube and the yield of **36a** was decreased to 27% yield. This phenomenon is related to the observation by Gellman that certain dipeptides have conformations with 10-membered hydrogen-bonded rings[19].
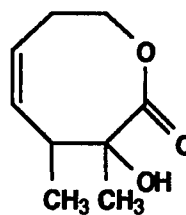
Scheme XIV:
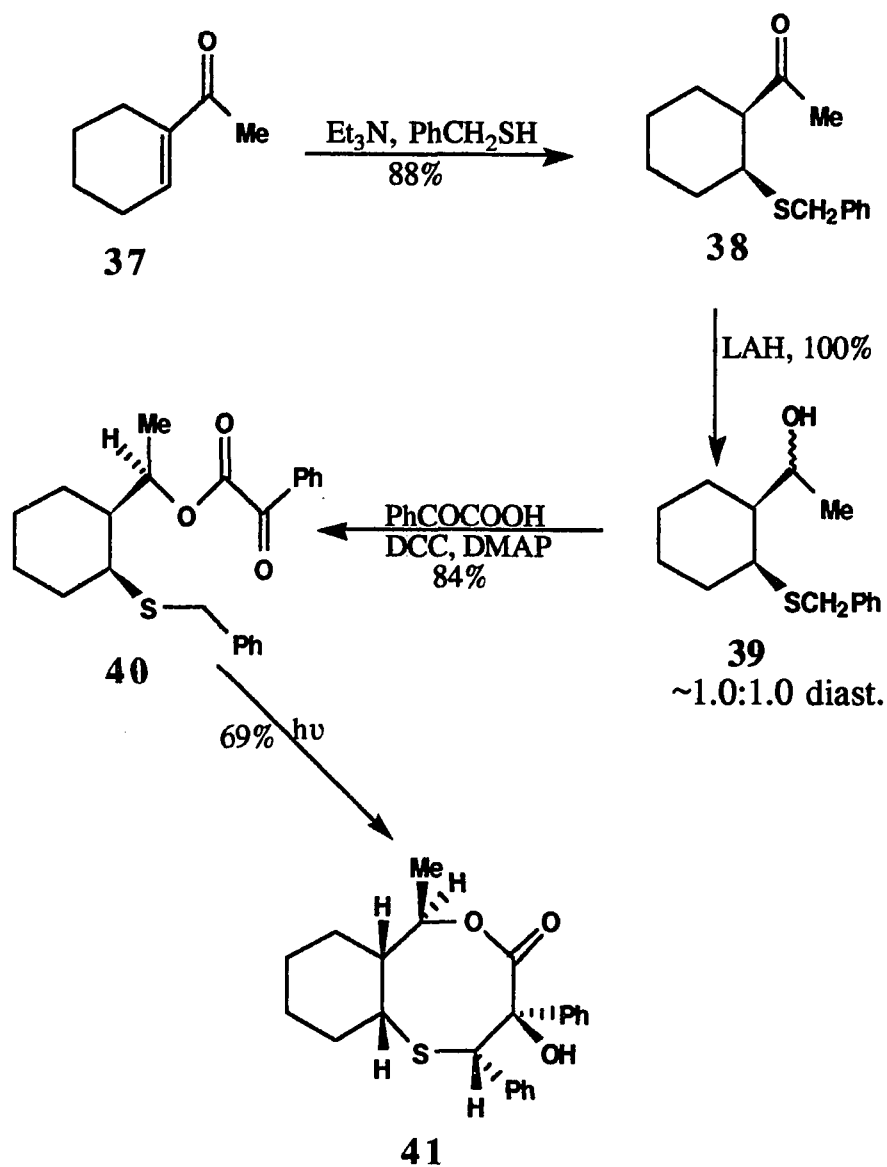
The results presented herein demonstrate the scope of this photochemical hydrogen atom abstraction. A new method for the formation of eight-membered rings was found by 1,9-hydrogen atom abstraction. Since eight-membered oxocyclic rings are common subunits in certain families of marine

natural products, this methodology may be useful for the synthesis of those natural products.

42   43

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reaction were conducted under an argon atmosphere. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 1320 spectrophotometer. Nuclear Magnetic Resonance (NMR) spectra were determined on a 300 MHz Nicolet Magnetic Corporation NMC-1280 spectrometer. All chemical shifts were reported relative to tetramethylsilane as an internal standard. Coupling constants were reported in Hz. Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, ABq=ABquartet. Carbon-13 NMR spectra were determined on a Nicolet NMc-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. H:EA refers to hexane/ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR spectrocopic analysis and /or elemental analyses

General procedure for esterification: To the alcohol and benzoylformic acid and 4-N,N'-dimethylaminopyridine (molar ratio: 1.0:1.1:0.1) in a round bottom flask , dry CH_2Cl_2 was added to make about a 0.1 M solution. The mixture was then cooled to 0^0C and 1,3-dicyclohexylcarbodiimide (DCC) in dry CH_2Cl_2 was added dropwise to the mixture. A white precipitate formed instantly. The mixture was allowed to warm to room temperature and stirred overnight. The precipitate was filtered through a short flash silica gel column and the solvent was evaporated in vacuo. The residue was separated by sgc.

General procedure for the irradiation of the ketoesters: The ketoester was dissolved in dry benzene (0.01-0.05 M) in a pyrex tube and the solution was degassed by argon for at least 10 minutes. And the solution was irradiated by a Rayonet photochemical reactor (wavelength=350 nm) for about 10 hours. The solvent was then evaporated in vacuo and the residue was separated by sgc.

2'-Ethoxylcyclopropylmethyl benzoylformate (17a): To 0.425 g (3.01 mmol) of ethyl 2'-cis-ethoxycyclopropylcarboxylate in 15.0 mL of THF, 0.0685 g of lithium aluminum hydride was added. The mixture was boiled while stirring overnight and then cooled to room temperature. The solution was poured into ice water and extracted by ethyl ether. The combined organic solvents were washed with water and with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a 100% yield of 2'-cis-ethoxycyclopropylmethanol.

The alcohol (0.0940 g, 0.273) was esterified by benzoylformic acid to give 0.1210 g (0.488 mmol) of compound **17a** in 64% yield.(See general procedure for esterification). Compound **17a** was separated by H:EA=20:1.

Compound **17a**: ^{1}H NMR δ (ppm) 8.02 (m, 2 H), 7.66 (m, 1 H), 7.51 (m, 2 H), 4.57 (ABq, J_1=11.4 Hz, J_2=6.9 Hz, 1 H), 4.43 (ABq, J_1=11.4 Hz, J_2=8.4 Hz, 1 H), 3.56 (q, J=6.9 Hz, 2 H), 3.42 (m, 1 H), 1.31 (m, 1 H), 1.20 (t, J=6.9 Hz, 3 H), 0.86 (m, 1 H), 0.62 (m, 1 H); IR (film) 2975, 1735, 1688, 1297, 1198 cm^{-1}; TLC (H:EA=3:1) Rf=0.46.

4-Hydroxy-3-methyl-4-phenyl-2,5-dioxo-bicyclo[6.1.0]nonan-5-one (21a): The keto ester **17a** (0.101 g, 0.385 mmol) was irradiated to give 0.0511 g (0.206 mmol) of **21a** in 51% yield after separation by sgc (H:EA=20:1).

Compound **21a**: ^{1}H NMR δ (ppm) 7.74 (m, 2 H), 7.32 (m, 3 H), 4.94 (ABq, J_1=11.7 Hz, J_2=6.6 Hz, 1 H), 4.24 (ABq, J_1=11.7 Hz, J_2=5.4 Hz, 1 H), 4.11 (s, 1 H), 3.83 (q, J=6.6 Hz, 1 H), 3.44 (m, 1 H), 1.25 (d, J=6.6 Hz, 3 H), 1.08 (m, 1 H), 0.89 (m, 1 H); IR (film) 3497, 2983, 1728, 1237 cm^{-1}; HRMS m/z for $C_{14}H_{16}O_4$, Calcd. 248.10486, measured 248.10527. TLC (H:EA=3:1) Rf=0.36.

2'-Ethoxycyclopropyldideuteriomethyl benzoylformate (17b): To 0.536 g (3.39 mmol) of ethyl 2'-cis-ethoxycyclopropylcarboxylate in 40.0 mL of THF, 0.0860 g (2.04 mmol) of lithium aluminum deuterium was added. The mixture was boiled overnight at stirring and cooled to room temperature. The solution was poured into ice water and extracted by ethyl ether. The

combined organic solvents was washed with water and with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a 100% yield of 2'-cis-ethoxycyclopropyldideuteriomethanol.

The alcohol (0.256 g, 2.17 mmol) was esterified by benzoylformic acid to give 0.2571 g (1.03 mmol) of compound 17b in 47% yield.(See general procedure for esterification). Compound 17b was separated by H:EA=20:1.

Compound 17b: ^1H NMR δ (ppm) 8.02 (m, 2 H), 7.66 (m, 1 H), 7.51 (m, 2 H), 3.56 (q, J=7.2 Hz, 2 H), 3.42 (m, 1 H), 1.31 (m, 1 H), 1.20 (t, J=7.2 Hz, 3 H), 0.86 (m, 1 H), 0.62 (m, 1 H); IR (film) 2976, 1732, 1688, 1207 cm^{-1}; CI-MS m/z for $C_{14}D_2H_{14}O_4$ 268 (M+18); TLC (H:EA=3:1) Rf=0.46.

7,7-Dideuterio-4-hydroxy-3-methyl-4-phenyl-2,5-dioxo-bicyclo[6,1,0]nonan-5-one (21c): Compound 17b (0.060 g, 0.240 mmol) was irradiated to give 0.0375 g (0.150 mmol) of 21c in 63% yield after separation by sgc (H:EA=20:1).

Compound 21c: ^1H NMR ($CDCl_3$) δ (ppm) 7.74 (m, 2 H), 7.32 (m, 3 H), 4.11 (s, 1 H), 3.83 (q, J=6.9 Hz, 1 H), 3.42 (m, 1 H), 1.25 (d, J=6.9 Hz, 3 H), 1.08 (m, 1 H), 0.89 (m, 1 H); IR (film) 3330, 2982, 1733, 1693, 1247 cm^{-1}; CI-MS (NH_3) m/z for $C_{14}D_2H_{14}O_4$ 268 (M+18); TLC (H:EA=3:1) Rf=0.36.

3'-Benzoxylpropyl benzoylformate (24): 3-Benzoxyl propyl alcohol (2.400 g, 14.4 mmol) was esterified by benzoylformic acid to give 2.808 grams (9.42 mmol) of compound 24 in 65% yield.(See general procedure for esterification). 24 was separated by H:EA=20:1.

Compound 24: ^{1}H NMR δ (ppm) 7.98 (m, 2 H) 7.64 (m, 1 H), 7.46 (m, 2 H), 7.28 (m, 5 H), 4.51 (m, 4 H), 3.60 (t, J=6.0 Hz, 2 H), 2.08 (m, 2 H); IR (film) 2959, 2860, 1736, 1688, 1198 cm^{-1}; TLC (H:EA=3:1) Rf=0.58.

3-Benzoxylpropionadehyde (25): The keto ester **24** (0.447 g, 1.50 mmol) was irradiated to give **25** in ~100% yield after separation by sgc (H:EA=20:1).

Compound 25: ^{1}H NMR (CDCl$_3$) δ (ppm) 9.79 (t, 1 H), 7.31 (m, 5 H), 4.53 (s, 2 H), 3.81 (t, J=6.0 Hz, 2H), 2.69 (m, 2 H); HRMS m/z for C$_{10}$H$_{12}$O$_2$ Calcd. 164.08373, measured 164.08401; TLC (H:EA=3:1) Rf=0.54.

2-(2'-Methylphenyl)ethyl benzoylformate (26): o-Methylphenylethanol (0.903 g, 6.64 mmol) was esterified by benzoylformic acid to give 1.705 grams (6.36 mmol) of compound **26** in 97% yield.(See general procedure for esterification). Compound **26** was separated by H:EA=70:1.

Compound 26: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.89 (m, 2 H), 7.64 (m, 1 H), 7.47 (m, 2 H), 7.17 (m, 4 H), 4.58 (t, J=7.2 Hz, 2 H), 3.10 (t, J=7.2 Hz, 2 H), 2.36 (s, 3 H); IR (film) 2959, 1737, 1688, 1196 cm^{-1}; HRMS m/z for C$_{17}$H$_{16}$O$_3$ Calcd. 268.10994, measured 268.10971; TLC (H:EA=6:1) Rf=0.43.

3-Hydroxy-3-phenyl-benz[e]cyclooctanelactone (28): The keto ester **26** (0.574 g, 2.14 mmol) was irradiated to give 0.1928 g of **28** in 41% yield after separation by sgc (H:EA=70:1).

Compound 28: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.73 (d, J=7.5 Hz, 2 H),

7.44-7.14 (m, 7 H), 4.73 (ABq, J$_1$=11.1 Hz, J$_2$=12.0 Hz, 1 H), 4.32 (d, J=10.5

Hz, 1 H), 4.32 (d, J=12.9 Hz, 1 H), 3.48 (s, 1 H), 3.38 (m, 1 H), 3.07 (d,

J=12.9 Hz, 1 H), 2.70 (d, J=14.7 Hz, 1 H); IR (film) 3529, 3053, 2985, 1742,

1264 cm^{-1}; HRMS m/z for C$_{17}$H$_{16}$O$_3$ Calcd. 268.10994, measured

268.10957; TLC (H:EA=6:1) Rf=0.32.

1-Methyl-2-(2'-methylphenyl)ethyl benzoylformate (27): o-

Bromotoluene (1.950 g, 11.40 mmol) was dissolved in 100 mL of THF and

cooled to -78 °C before 5.60 mL of 2.04 M of n-BuLi (11.40 mmol) was added

dropwise. The mixture was allowed to stir for two hours and then 0.662 g

(11.4 mmol) of propene oxide was added. The mixture was stirred for another

six hours at -78 °C and warmed up to room temperature and quenched by

water. The aqueous layer was extracted by ethyl ether. The organic layer was

combined together and washed with water and with brine and dried over

MgSO$_4$. The solvent was evaporated in vacuo and the residue was separated by

sgc (H:EA=20:1) to afford 0.6435 g (4.28 mmol) of 1-(o-

methylphenyl)propan-2-ol in 70% yield accounting to 0.8866 g starting

material back.

1-(o-Methylphenyl)propan-2-ol: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.13

(s, 4 H), 3.98 (m, 1 H), 2.73 (m, 2 H), 2.31 (s, 3 H), 1.81 (s, 1 H), 1.24 (d,

J=6.3 Hz, 3 H); ^{13}C NMR δ 136.77, 136.50, 130.33, 130.04, 126.45, 125.87,

67.841, 42.87, 22.89, 19.59; IR (film) 3364, 3016, 2966, 2927, 1457, 1113

cm^{-1}; HRMS m/z for C$_{10}$H$_{14}$O Calcd. 150.10447, measured 150.10419. TLC

(H:EA=3:1) Rf=0.47.

1-o-Methylphenylpropan-2-ol (0.510 g, 3.40 mmol) was esterified by benzoylformic acid to give 0.862 g (3.05 mmol) of compound 27 in 90% yield.(See general procedure for esterification). 27 was separated by H:EA=40:1.

Compound 27: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.69 (m, 2 H), 7.59 (m, 1 H), 7.40 (m, 2 H), 7.15 (m, 4 H), 5.50 (m, 1 H), 3.07 (ABq, J$_1$=14.1 Hz, J$_2$=8.1 Hz, 1 H), 2.90 (ABq, J$_1$=13.8 Hz, J$_2$=6.0 Hz, 1 H), 2.34 (s, 3 H), 1.44 (d, J=6.6 Hz, 3 H); HRMS m/z for C$_{18}$H$_{18}$O$_3$ Calcd. 282.12559, measured 282.12522; TLC (H:EA=6:1) Rf=0.52.

3-Hydroxy-8-methyl-3-phenyl-benz[e]cyclooctanelactone (29):

The keto ester 27 (0.572 g, 2.03) was irradiated to give 0.4265 g (1.51 mmol) of 29 in 74% yield after separation by sgc (H:EA=30:1).

Compound 29: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.67 (d, J=7.5 Hz, 2 H), 7.44-7.13 (m, 7 H), 5.10 (broad, 1 H), 3.70 (m, 1 H), 3.48 (m, 1 H), 3.34 (broad, 1 H), 3.20 (d, J=13.8 Hz, 1 H), 2.61 (m, 1 H), 1.32 (d, J=5.7, 3 H); IR (film) 3513, 3060, 2937, 1745, 1167 cm^{-1}; HRMS m/z for C$_{18}$H$_{18}$O$_3$ Calcd. 282.12559, measured 282.12500; TLC (H:EA=6:1) Rf=0.35.

7-Hydroxymethyl-1,5-dioxaspiro[5,5]hexadecane (31):

Ethyl 2-cyclohexanone carboxylate (3.40 g, 20.0 mmol), 1,3-propanediol (3.81 g, 50.0 mmol) and PTSA-H$_2$O (0.380 g, 2.00 mmol) were dissolved in 300 mL of benzene. The mixture was allowed to reflux for six hours and cooled to room temperature. The benzene solution was washed by 5% NaHCO$_3$ and water and

with brine and dried over $MgSO_4$. The solution was put through a short silica gel column and benzene was evaporated to give 4.265 grams of the ketal.

To 3.617 grams (15.10 mmol) of the ketal was in 150 mL of THF, LAH was added. The mixture was boiled overnight and cooled to room temperature and poured to ice water. The aqueous solution was extracted by ethyl ether. The combined organic solution was washed with water and with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was separated by sgc (H:EA=3:1) to afford 0.820 g (4.40 mmol) of compound **31** in 29% yield.

Compound **31**: ^{1}H NMR ($CDCl_3$) δ (ppm) 4.11 (td, J_1=12.0 Hz, J_2=2.7 Hz, 1 H), 3.97 (td, J_1=12.0 Hz, J_2=2.7 Hz, 1 H), 3.82 (m, 3 H), 3.59 (m, 1 H), 3.38 (ABq, J_1=6.9 Hz, J_2=3.9 Hz, 1 H), 2.73 (m, 1 H), 2.03 (m, 1 H), 1.73-1.12 (m, 9 H); ^{13}C NMR 100.37, 63.18, 58.75, 58.61, 47.08, 27.36, 25.37, 25.04, 24.64, 21.78; IR (film) 3471, 2936, 2862, 1104 cm^{-1}; HRMS m/z for $C_{10}H_{18}O_3$ Calcd. 186.12559, measured 186.12553; TLC (H:EA=3:1) Rf=0.13.

7-Benzoylcarboxylmethyl-1,5-dioxaspiro[5,5]hexadecane (32):
The alcohol **31** (0.820.g, 4.41 mmol) was esterified by benzoylformic acid to give 0.355.g (1.12 mmol) of compound **32** in 25% yield.(See general procedure for esterification). **32** was separated by H:EA=10:1.

Compound **32**: ^{1}H NMR δ (ppm) 8.01 (m, 2 H), 7.65 (m, 1 H), 7.50 (m, 2 H), 4.88 (ABq, J_1=10.8 Hz, J_2=3.9 Hz, 1 H), 4.31 (ABq, J_1=10.8 Hz, J_2=9.0 Hz, 1 H), 4.07 (m, 1 H), 3.92 (m, 1 H), 3.80 (m, 1 H), 2.68 (m, 1 H), 2.02-1.13 (m, 9 H); HRMS m/z for $C_{18}H_{22}O_5$ Calcd. 318.14672, measured 318.14638; TLC (H:EA=3:1) Rf=0.52.

1-Hydroxy-1-phenyl-7,11-dioxo-cyclohexa[e]spiro[5,3,1]undecalactone-2 (33): The keto ester **32** (355.0 mg, 1.12 mmol) was irradiated to give 0.0450 g (0.126 mmol) of **33** in 22% yield accounting to 0.151 g starting material back after separation by sgc (H:EA=3:1).

Compound **33** ^{1}H NMR δ (ppm) 7.15 (m, 5 H), 5.28 (broad, 1 H), 4.67 (m, 1 H), 4.35 (m, 1 H), 4.08 (m, 1 H), 3.89 (m, 1 H), 3.82 (m, 2 H), 2.68 (m, 1 H), 2.08-1.05 (m, 9 H); HRMS m/z for $C_{18}H_{22}H_5$ Calcd. 318.14672, measured 318.14669; TLC (H:EA=3:1) Rf=0.42.

3'-Hexenyl benzoylformate (35a): *cis*-3-Hexen-1-ol (1.00 g, 10.0 mmol) was esterified by benzoylformic acid to give 1.879 g (8.10 mmol) of compound **35a** in 81% yield.(See general procedure for esterification). Compound **35a** was separated by H:EA=70:1.

Compound **35a:** ^{1}H NMR (CDCl$_3$) δ 8.00 (m, 2 H), 7.65 (m, 1 H), 7.50 (m, 2 H), 5.55 (m, 1 H), 5.35 (m, 1 H), 4.37 (t, J=6.9 Hz, 2 H), 2.53 (q, J=6.9 Hz, 2 H), 2.06 (m, 2 H), 0.94 (t, J=7.5 Hz, 3 H); ^{13}C NMR δ 186.13, 163.64, 135.09, 134.69, 129.80, 128.67, 122.72, 65.40, 26.47, 20.48, 13.97; IR (film) 3063, 2966, 2935, 1737, 1690 cm^{-1}; CI-MS (NH$_3$) m/z for $C_{14}H_{16}O_3$ 232 (M); TLC (H:EA=6:1) Rf=0.49.

3-Hydroxy-3-phenyl-5-cyclooctanelactone (36a): The keto ester **35a** (0.6132 g, 2.64 mmol) was irradiated to give 0.1897 g (0.817 mmol) (higher Rf) and 0.1072 g (0.462 mmol) (lower Rf) of **36a** in 31% and 18% yields, respectively , as a mixture of diastereomers after separation by sgc

(H:EA=50:1).

Compound **36a** (higher Rf): ^{1}H NMR (CDCl$_3$) δ (ppm) 7.76 (m, 2 H),

7.35 (m, 3 H), 5.81 (m, 1 H), 5.65 (m, 1 H), 4.69 (m, 1 H), 4.23 (m, 1 H),

3.62 (m, 1 H), 3.57 (s, 1 H), 2.81 (m, 1 H), 2.13 (m,1 H), 0.92 (d, J=6.9 Hz, 3

H); IR (film) 3511, 3016, 2967, 1738, 1118 cm^{-1}; HRMS m/z for C$_{14}$H$_{16}$O$_3$

Calcd. 232.10994, measured 232.10961; TLC (H:EA=6:1) Rf=0.45.

(lower Rf): ^{1}H NMR (CDCl$_3$) δ (ppm) 7.65 (m, 2 H), 7.25 (m, 3 H),

5.78 (m, 1 H), 5.56 (m, 1 H), 4.48 (m, 1 H), 4.08 (m, 1 H), 3.47 (s, 1 H), 2.84

(m, 1 H), 2.65 (m, 1 H), 2.09 (m, 1 H), 0.86 (d, J=6.9 Hz, 3 H); HRMS m/z

for C$_{14}$H$_{16}$O$_3$ Calcd. 232.10994, measured 232.10959; TLC (H:EA=6:1)

Rf=0.29.

4'-Methyl-hex-3'-enyl benzoylformate (35b): 4-Methyl-3-

penten-1-ol (0.2517 g, 2.51 mmol) was esterified by benzoylformic acid to

give 0.390 g (1.68 mmol) of compound **35b** in 67% yield.(See general

procedure for esterification). Compound **35b** was separated by H:EA=20:1.

Compound **35b**: ^{1}H NMR (CDCl$_3$) δ (ppm) 8.00 (m, 2 H), 7.66 (m, 1

H), 7.51 (m, 2 H), 5.15 (m, 1 H), 4.37 (t, J=6.9 Hz, 2 H), 2.47 (q, J=6.9 Hz, 2

H), 1.72 (s, 1 H), 1.63 (s, 1 H); IR (film) 2967, 2930, 1737, 1689, 1199 cm^{-1};

HRMS m/z for C$_{14}$H$_{16}$O$_3$ Calcd. 232.10994, measured 232.10946; TLC

(H:EA=6:1) Rf=0.36.

3-Hydroxy-3-phenyl-cyclooct-5-enelactone (36b): The keto

ester **35b** (0.1021 g, 0.440 mmol) was irradiated to give 0.0222 g (0.0957

mmol) of **36b** in 31% yield after separation by sgc (H:EA=20:1).

Compound **36b**: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.65 (m, 2 H), 7.36 (m, 3 H), 5.64 (t, J=7.8 Hz, 1 H), 4.60 (m, 1 H), 4.14 (m, 1 H), 3.82 (s, 1 H), 3.51 (d, J=12.6 Hz, 1 H), 2.65 (m, 1 H), 2.42 (d, J=12.6 Hz, 1 H), 2.07 (m, 1 H), 1.94 (d, J=0.3 Hz, 3 H); IR (film) 3509, 2961, 2929, 1741, 1189 cm^{-1}; HRMS m/z for C$_{14}$H$_{16}$O$_3$ Calcd. 232.10994, measured 232.10974; TLC (H:EA=6:1) Rf=0.45.

cis-1-Acetyl-2-benzylthiocyclohexane (38): 1-Acetylcyclohexene (1.860 g, 15.0 mmol), benzyl thiol (2.24 g, 18.0 mmol) and triethylamine (1.82 g, 18.0 mmol) were dissolved in 100 mL of methylene chloride. The mixture was allowed to stir for about four days at room temperature and the solvent was evaporated in vacuo. The residue was separated by sgc (H:EA=20:1) to produce 1.579 grams of **38** in 88% yield accounting to 0.9607 g starting material back.

Compound **38**: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.24 (m, 5 H), 3.62 (m, 2 H), 3.21 (m, 1 H), 2.49 (dt, J$_1$=11.4 Hz, J$_2$=3.6 Hz, 1 H), 1.87 (s, 3 H), 1.94-1.10 (m, 8 H); IR (film), 3026, 2929, 2854, 1706 cm^{-1}; HRMS m/z for C$_{15}$H$_{20}$OS Calcd. 248.12349, measured 248.12341; TLC (H:EA=4:1) Rf=0.44.

cis-1-(2'-Benzylthiocyclohexyl)ethanol (39): To 0.496 g (2.00 mmol) of compound **38** in 20 mL of THF, 0.0460 g (1.20 mmol) of LAH was added at 0^{0}C. The mixture was allowed to warm to room temperature and stirred overnight and was poured into ice water. The aqueous solution was extracted by ethyl ether. The combined organic solution was washed with

water and with brine and dried over MgSO$_4$. The solution was filtered and evaporated and the residue was separated by sgc (H:EA=20:1) to afford ~0.500 g (2.00 mmol) of compound **39** in ~100% yield (1:1 ratio of diastereomers).

Compound **39** (diastereomers): (higher Rf): ^{1}H NMR (CDCl$_3$) δ (ppm) 7.28 (m, 5 H), 3.75 (d, J=13.5 Hz, 1 H), 3.61 (d, J=13.5 Hz, 1 H), 3.13 (broad, 1 H), 1.96-1.00 (m, 10 H), 1.08 (d, J=6.3 Hz, 3 H); IR (film) 3433, 3026, 2928, 2953, 1451 cm^{-1}; HRMS m/z for C$_{15}$H$_{22}$OS Calcd. 250.13914, measured 250.13888; TLC (H:EA=3:1) Rf=0.55.

(lower Rf): ^{1}H NMR (CDCl$_3$) δ (ppm) 7.27 (m, 5 H), 3.68 (m, 2 H), 2.86 (broad, 1 H), 2.48 (s, 1 H), 1.84-1.16 (m, 10 H), 1.00 (d, J=6.3 Hz, 3 H); IR (film) 3421, 2912, 2897 cm^{-1}; HRMS m/z for C$_{15}$H$_{22}$OS Calcd. 250.13914, measured 250.13920; TLC (H:EA=3:1) Rf=0.45.

cis-1-(2'-Benzylthiocyclohexyl)ethyl benzoylformate (40):

The alcohol **39** (0.1431 g, 0.572 mmol) (higher Rf) was esterified by benzoylformic acid to give 0.1835 g (0.480 mmol) of compound **40** in 84% yield.(See general procedure for esterification). **40** was separated by sgc (H:EA=20:1).

Compound **40**: ^{1}H NMR (CDCl$_3$) δ (ppm) 8.05 (m, 2 H), 7.85 (m, 1 H), 7.50 (m, 2 H), 7.24 (m, 5 H), 5.35 (m, 1 H), 3.68 (s, 1 H), 3.26 (broad, 1 H), 1.93-1.45 (m, 8 H), 1.41 (d, J=6.3 Hz, 3 H), 1.22 (m, 2 H); IR (film) 2930, 2855, 1732, 1686, 1203 cm^{-1}; HRMS for C$_{23}$H$_{26}$O$_3$S Calcd. 382.16027, measured 382.15936; TLC H:EA=6:1) Rf=0.55.

3,4-Diphenyl-3-hydroxy-8-methyl-5-thio-cyclohexa[cis,f]cyclooctanelactone (41): The keto ester **40** (0.1585 g, 0.415 mmol) was irradiated to give 0.1096 g (0.286 mmol) of **41** in 69% yield after separation by sgc (H:EA=6:1).

Compound **41**: ^{1}H NMR (CDCl$_3$) δ (ppm) 7.39 (m, 2 H), 7.16 (m, 3 H), 7.01 (m, 3 H), 6.74 (m, 2 H), 5.05 (m, 1 H), 4.52 (s, 1 H), 3.51 (broad, 1 H), 2.91 (s, 1 H), 2.06 (m, 2 H), 1.86-1.50 (m, 6 H), 1.46 (d, J=6.9 Hz, 3 H), 1.25 (m, 2 H); IR (film) 3457, 2930, 1725, 1710, 1240 cm^{-1}; HRMS m/z for C$_{23}$H$_{26}$O$_3$S Calcd. 382.16027, measured 382.15989; TLC (H:EA=4:1) Rf=0.31.

cis-3'-Hexenyl pyruvate (42): 3-Hexen-1-ol (1.00 g, 10.0 mmol) was esterified by pyruvic acid to give compound **42** in 48% yield.(See general procedure for esterification). **42** was separated by H:EA=30:1.

Compound **42**: ^{1}H NMR (CDCl$_3$) δ (ppm) 5.54 (m, 1 H), 5.32 (m, 1 H), 4.25 (t, J=7.2 Hz, 2 H), 4.48 (m, 2 H), 2.47 (s, 3 H), 2.06 (m, 2 H), 0.97 (t, J=7.5 Hz, 3 H); ^{13}C NMR (CDCl$_3$) δ 191.63, 160.57, 135.11, 122.56, 65.63, 26.61, 26.35, 20.48, 14.09; IR (film) 3011, 2964, 1733, 1145 cm^{-1}; CI-MS (NH$_3$) m/z for C$_9$H$_{14}$O$_3$ 188 (M+18); TLC (H:EA=3:1) Rf=0.80.

3-Hydroxy-3,4-dimethyl-cyclooct-5-enelactone (43): The keto ester **42** (0.826 g, 4.86 mmol) was irradiated to give **43** in 55% yield after separation by sgc (H:EA=10:1). (See general procedure for irradiation of the keto ester)

Compound **43**: ^{1}H NMR (CDCl$_3$) δ (ppm) 5.69 (m, 1 H), 5.51 (m, 1 H), 4.61 (ABq, J$_1$=11.1 Hz, J$_2$=12.0 Hz, 1 H), 4.30 (m, 1 H), 2.95 (m, 1 H),

2.93 (s, 1 H), 2.64 (m, 1 H), 2.05 (m, 1 H), 1.11 (d, J=6.9 Hz, 3 H); IR (film) 3511, 3010, 2966, 1743, 1112 cm^{-1}; CI-MS (NH$_3$) for C$_9$H$_{14}$O$_3$ 188 (M+18); TLC (H:EA=3:1) Rf=0.66.

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GENERAL CONCLUSION

The construction of the angularly fused network present is readily accomplished by the reaction of the enol silyl ether of a cyclohexane-1,3-dione with acetylquinone compounds followed by based-mediated cyclization. The synthesis of 3-deoxyrabelomycin is therefore completed by this method.

Photochemical hydrogen atom abstraction reactions have been extensively employed in the construction of bioactive naturally occurring products. The formal total synthesis of Podophyllotoxin has been accomplished by utilizing a photoenolization/Diels-Alder reaction which efficiently set up three required stereo centers in one step.

The valuable formation of seven membered ring compounds were proceeded by the Norish type II reaction, followed by radical-induced ring opening and closing. The substituents on cyclopropane play an important role in the ring opening. This method is potentially useful for the synthesis of oxocyclic seven membered rings which are common subunits in certain families of marine natural products.

Hydrogen atom abstraction from remote sites (other than the γ-position) has been observed over the past two decades. Previously, people recognized that the remote hydrogen atom abstraction could not compete with γ-hydrogen atom abstraction except by electron transfer processes. The discovery of 1,9-hydrogen atom abstraction has significantly extended the scope of hydrogen atom abstraction reactions. The convergent formations of oxocyclic eight membered rings by this method provides a new route to such compounds which are often found in marine products.

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