INFORMATION TO USERS

The most advanced technology has been used to photograph and reproduce this manuscript from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book. These are also available as one exposure on a standard 35mm slide or as a 17" x 23" black and white photographic print for an additional charge.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

U·M·I

University Microfilms International
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
313/761-4700 800/521-0600

Order Number 8914806

Approaches to the synthesis of the bicyclic fragment of the kaurane derived diterpenes

Yiannikouros, George Petros, Ph.D.

City University of New York, 1988

Copyright ©1988 by Yiannikouros, George Petros. All rights reserved.

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

Approaches to the synthesis of the bicyclic fragment of the kaurane derived diterpenes

by

GEORGE PETROS YIANNIKOURIS

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of the Doctor of Philosophy, The City University of New York.

1988

© 1988
GEORGE PETROS YIANNIKOUROS
All Rights Reserved

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

22nd August 1988
Date

Chair of Examining Committee

24 August 1988
Date

Executive Officer

Dr. William Berkowitz

Dr. Klaus G. Grohmann

Dr. Neil McKelvie

Supervisory Committee

The City University of New York

ABSTRACT

Appoaches to the synthesis of the bicyclic fragment of the kaurane derived diterpenes

by

George Petros Yiannikouros

Advisor: Professor Vernon Box

Developments in the free radical chemistry through the decades have come with exponential growth, and the application of free radical reactions to carbocyclization has emerged as a widely used carbon-carbon bond formation method in organic synthesis.

A new method is described for the synthesis of fused and bridged ring systems based on the intramolecular addition of a vinyl radical to an α,β-unsaturated ketone. The method represents a general route to masked γ-diketones. In this approach a vinyl radical formed by trialkyltin hydride mediated homolysis of a vinyl halide, undergoes internal addition to a stereoproximal alkene moiety, followed by a hydrogen transfer to the addend radical.

The efficiency of the ring formation is enhanced by the kinetic preference of the vinyl radical to undergo addition to the radical acceptor alkene moiety, over the transfer of the hydrogen atom from the organostannane. This method illustrates the successful utilization of vinylogous reactivities in a

radical addition to α,β-enones, and proceeds in regioselective manner. In order to delineate the relationship between the substitution pattern of the acceptor alkene moiety and the mode of ring closure, substituted enones were subjected to carbocyclization. The utility of this annulating method in the synthesis of natural products was demonstrated by the syntheses of several highly functionalized, bridged bicyclic systems which were precursors for several terpenoids possessing antitumor and antifertility activity.

A significant part of our investigation includes the development of simple and general methods for gaining access to starting materials that are properly constituted to undergo the radical ring closure. The effort to prepare such materials demonstrated the value of the Birch reduction-alkylation sequence in the construction of the required properly substituted cyclohexenones.

This thesis is dedicated to my parents Zoe and Petros Yiannikouros who provided me with strength, pride, and most of all belief in personal dignity and integrity, in anything I undertake to do.

Acknowledgments

Accomplishing a dissertation thesis for my doctorate degree has been so far the most unique experience in the course of my professional advancement. The long rocky, uphill, and chokingly narrow road leading to my goal started becoming broader and smoother as soon as Dr. Vernon Box became my Ph.D. thesis advisor. I really can't think of anything sufficiently good to say concerning Dr. Vernon Box, who stood by me during the hard times of the past three years with patience and overwhelming determination to help me in making a scientist out of myself.

Dr. Nash Marinovic who provided the original plan for this work had also been my Ph.D. advisor before Dr. Vernon Box took over. He was the first one to teach me how to perform synthesis in Organic Chemistry.

My Ph.D. thesis committee members, Dr. William Berkovitz, Dr. Klaus Grohmann, and Dr. Neil McKelvie, whose constant concern and advice spared the strength and the will in me for fulfillment of my dream. I also would like to thank Dr. Herbert Meislich whose constant support and advice contributed a great deal in the accomplishment of this work.

Dr. Daniel Akins was very helpful with some word processing computer work and Dr. Theodore Axenrod provided to me the CHEMDRAW program which I used to create all the illustrations and the schemes that are in this thesis.

Special thanks to the department of chemistry at CCNY which provided to me laboratory space, chemicals, and financial assistance for this work.

Dr. David Cane, Brown University provided GC/MS analyses which were also very useful. Ramsey Pal was very helpful in the aquisition of almost all the mass spectra.

I would especially like to thank Christopher Nielsen for his assistance in editing of this thesis.

Last but very vital to me was the unlimited emotional and practical support offered to me by Georgia Charalambous, Melina Hatzopoulos, and Sasan Karimi.

Table of contents

CHAPTER 1

1.0.0. Birch Reduction in the Synthesis of Natural products.

1.0.1. Introduction.

Since 1949, when A. J. Birch introduced a reduction method using sodium in liquid ammonia, with ethanol as proton donor for benzenoid aromatic molecules, the Birch reduction has gained significant importance as a key reaction for the synthesis of natural products. In one simple reaction, it bridges the gulf between aromatic chemistry and those molecules which are readily available for the construction of alicyclic structures.

The Birch reduction also furnishes the facility to carry a synthon, which is inert towards an extensive array of reagents but which is also rich in latent functionality, through several stages of a protracted synthesis.

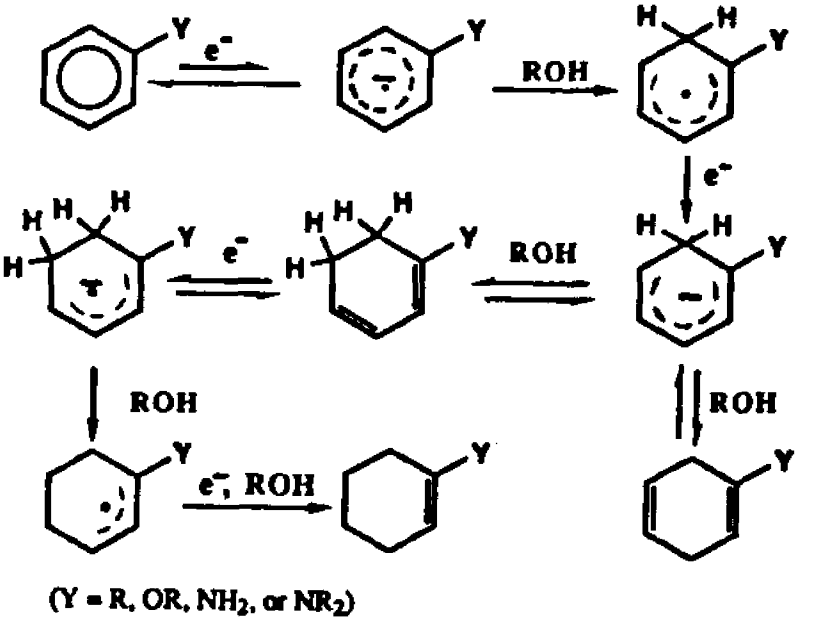
A large number of applications of the Birch reduction have been carried out using aromatic ethers and simple alkylbenzenes. Over the past decade, however, increasing attention has been given to other derivatives. New procedures have also been established for substrates such as aromatic acids, esters, and ketones, which until recently, have been regarded as unsuitable candidates for Birch reductions.

1.1.0. General Considerations

1.1.1. The Reduction Process

Metals from Groups I and II of the Periodic Table dissolve readily in liquid ammonia. The resulting solutions of solvated electrons are powerful reducing agents that can be used to perform selective reactions.

Scheme 1



(Y = R, OR, NH_2, or NR_2)

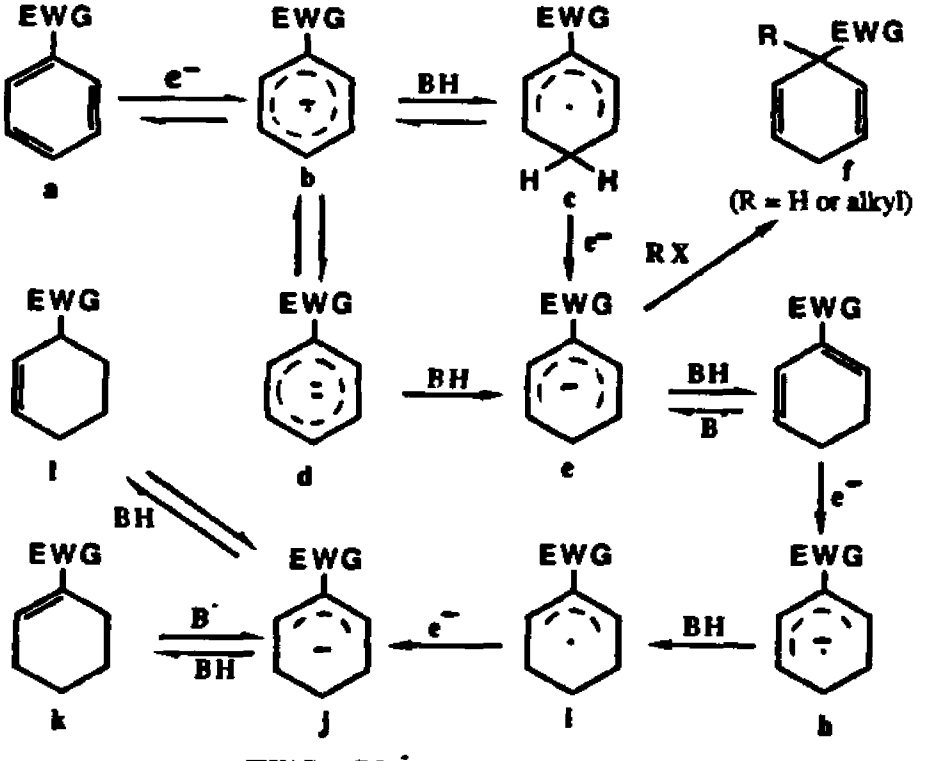
The reduction process, as applied to benzenoid substrates, is summarized[1] in Scheme 1. An electron is added in a reversible step to the LUMO of the molecule to form the radical anion, which is usually protonated and reduced further to a cyclohexadienyl anion.[2] Alternatively, the radical anion may be reduced further to a dianion,[3] which is then protonated to afford the same cyclohexadienyl anion. Protonation of this intermediate occurs

predominantly at the central carbon atom,[4] forming the unconjugated 1,4-diene, which is resistant to further reduction.

Clearly, the presence of electron releasing groups retards the electron transfer by elevating the LUMO. Therefore, for aromatic ethers and alkylbenzenes, it is necessary to displace the initial equilibrium between the substrate and the radical anion, through protonation of the radical anion by a stronger acid than ammonia ($pK_a = 35$). Alcohols ($pK_a = 16$-20) are normally used for this purpose.

With substrates that bear electron-withdrawing groups (EWG), the radical anion is formed in high enough concentration to be protonated by a proton donor or be further reduced to the dianion (Scheme 2).

Scheme 2



(EWG = CO_2^-, CO_2R, COR, or Ar)

When the substituent is an electron donor, the resulting anion radical is more basic than if the substituent was a EWG. If ammonia cannot protonate the radical anion when the substituent is an electron donor, it cannot protonate the radical anion which bears an EWG. Therefore the presence of a proton donor other than ammonia is necessary during the course of the reaction.

Over-reduction may occur through an initial protonation at the terminal atoms of the pentadienyl anion **e**, but occurs most frequently when the reaction medium is sufficiently basic to catalyse the rearrangement of 1-4-dienes to the 1,3-isomers[4] (**e→g**).

Many experimental procedures have been developed and these are described in several reviews.[5-15] The metals employed are usually lithium or sodium, but also include potassium and calcium. Protonating agents range from moderately acidic, such as ammonium salts and water, to weakly acidic, like ethanol and t-butanol. A wide range of co-solvents is also employed and iron salts are sometimes added to control reduction. In addition, aromatic systems that bear electron-withdrawing groups often lead to stable anionic intermediates, which can be alkylated by suitable alkylating agents.

Thus, it is generally concluded, this reaction must be carried out with meticulous care, since it has been shown that the selection of reaction conditions can afford a wide range of results. Of greater importance, however, are the mechanistic implications of these results. Thus, a general understanding of the overall reaction is needed to decide which experimental variables are of greatest importance to a particular reductive-alkylation scheme.

1.1.2. Scope and Limitations

Electron-releasing groups direct reduction to unsubstituted 2,5-positions, and, while alkyl groups retard reduction (t-butyl > isopropyl > ethyl > methyl), amino-groups and alkoxy-groups slightly accelerate the rate of reaction.[16] Phenols are rapidly ionized and are resistant to the addition of electrons.[17,18] In sharp contrast, β-naphthols are readily reduced, so furnishing the corresponding β-tetralones.[19-21]

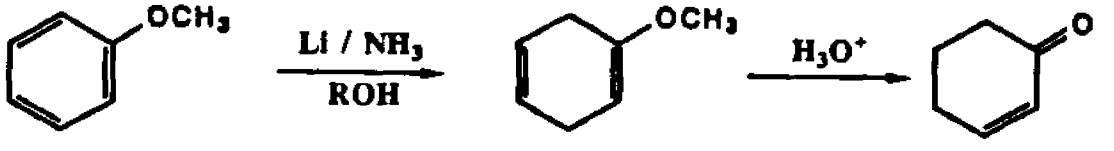
Electron withdrawing groups that allow delocalization of electrons accelerate reduction and afford 1,4-dihydro-derivatives (see Schemes 1 and 2). A major limitation to the choice of electron-withdrawing groups is the ease with which they themselves undergo reduction. In the absence of an electron-withdrawing group, it is usually difficult to reduce benzene rings that carry bulky substituents or that do not have two unsubstituted positions in a *para* relationship. Compounds with 1,2,3-trisubstituted patterns, for example, can normally be reduced only under forcing conditions.

A variety of secondary reactions may reduce the yield of a desired product, and in some cases may prevent its formation entirely. For example, it is possible for both aryl and benzylic heteroatom substituents to be hydrogenolized. Rearomatization may occur readily, usually because oxygen is present, but in some cases by the loss of a hydride ion. Tetrahydro-products often arise as a consequence of base-catalyzed conjugation of cyclohexa-1,4-dienes, or by an initial protonation at C-1 or C-5 of the intermediate pentadienyl anions.

The Birch reduction of aromatic hydrocarbons and ethers proceeds smoothly when the substitution pattern allows the addition of hydrogen to two unsubstituted positions in *para* relationship. thereby affording 2,5-

dihydro-derivatives. The utilization of anisole moieties as precursors to cyclohexenones has been applied to a wide variety of synthetic aims, but has been of very limited value with 1,2,3-trisubstituted patterns and more densely substituted derivatives (Scheme 3).

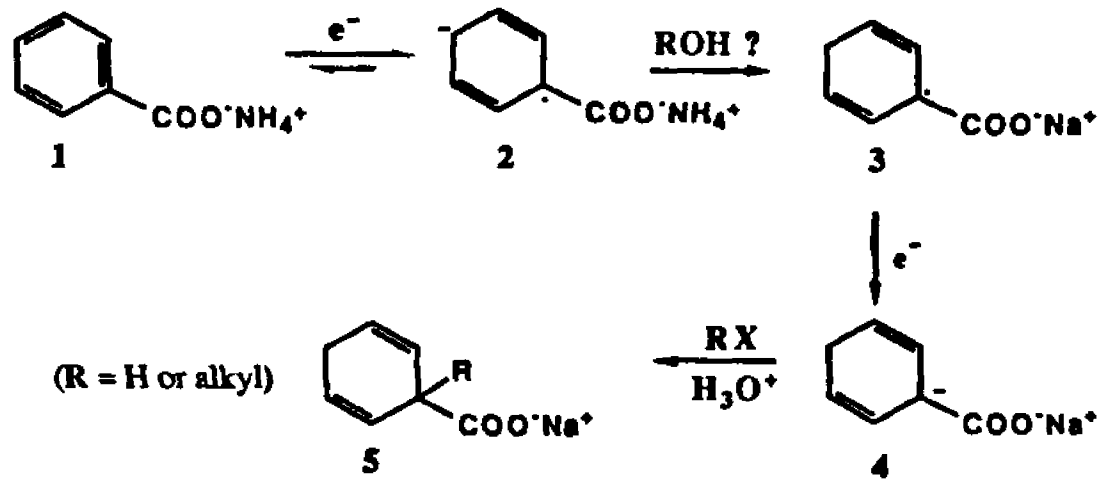
Scheme 3



Birch reduction of benzoic acid, with sodium in liquid ammonia and ethanol, affords 1,4-dihydrobenzoic acid in 89-95% yield[22,23] (Scheme 4). Initially, benzoic acid reacts with ammonia to form ammonium benzoate **1**, and then, a solvated electron is transferred into the LUMO to form the anion **2**. At this point, the radical anion picks up a proton from ethanol (or, in this case, the most acidic proton would come from the ammonium ion, if it has not reacted with the metal) to form the radical **3**. Immediately, another electron is transferred to form a stable carbanion **4**, which could either be quenched by a suitable alkylating agent, or could be protonated by adding saturated aqueous ammonium chloride to yield the carboxylic acid derivative **5**.

Reductive alkylation of benzoic acid derivatives have provided access to a wide variety of cyclohexenone derivatives.[24] It has been usefully applied in the last few years to the synthesis of several carboxylic natural products.[25]

Scheme 4

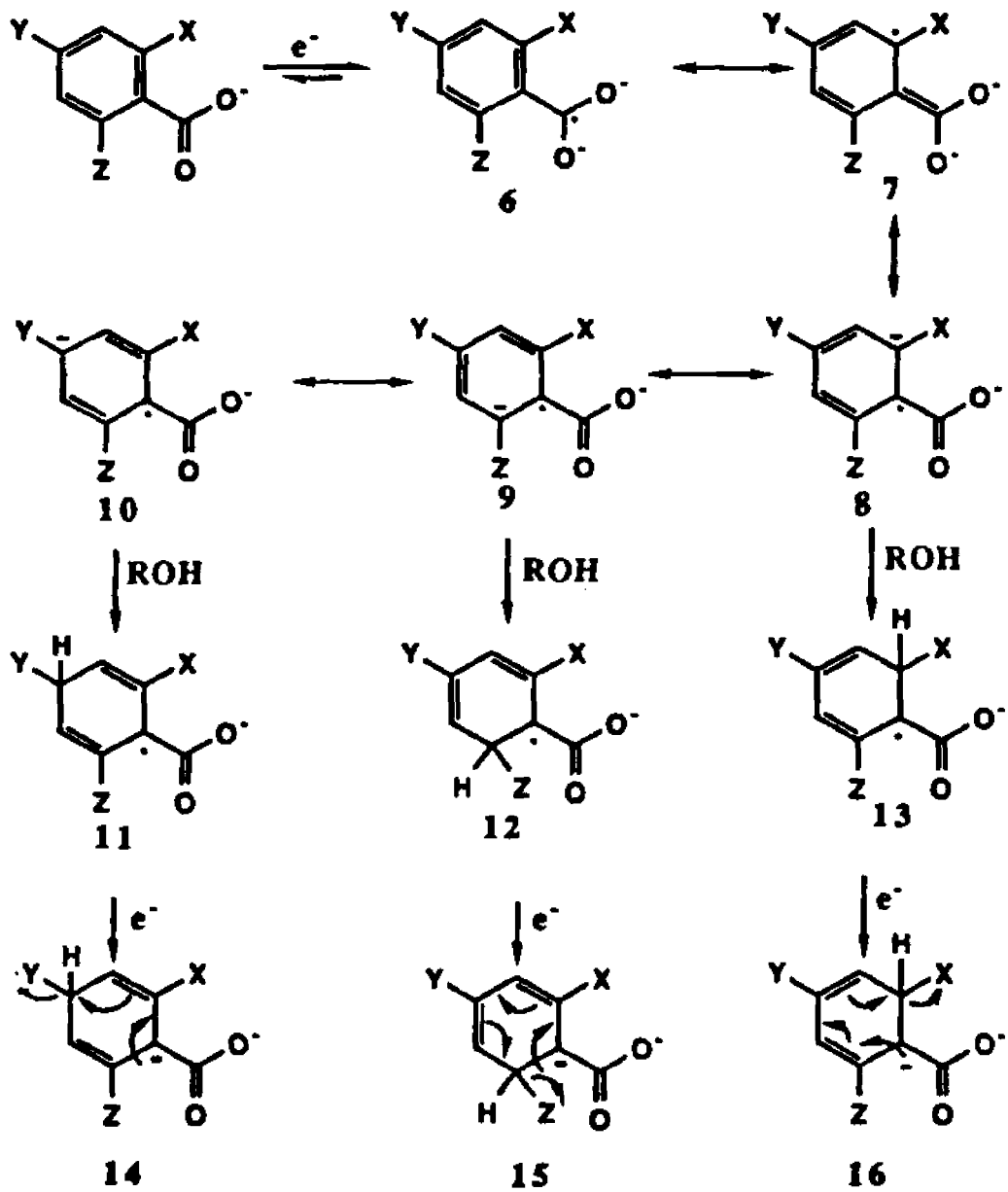


Careful reduction of benzoic acid derivatives in liquid ammonia, by lithium requires only *ca* 2.2 gram atom equivalents of metal, indicating that reduction of the substrate occurs much more readily than the reduction of the ammonium ions generated by the reaction of the acid with the ammonia.[26] It has been noted in the reductive alkylation of some benzoic acid derivatives[25c,27] that the addition of an alcohol is not necessary, however it may serve as a useful buffer and can often improve solubility. Nevertheless, the presence of an alcohol can be deleterious, since it allows isomerization of the initially formed 1,4-dihydro-isomer to the 3,4-isomer and, in this way, the possibility of further reduction.[28]

Some of the most synthetically useful groups of aromatic acids are those which also bear alkoxy functions, in that the reduced products are potential cyclohexenones. Nevertheless, oxidative rearomatization and over-reduction can occur because of the presence of the alkoxy groups. However, the main problem with anisoic acids is the potential for hydrogenolysis of the alkoxy function(s). As shown in Scheme 5, alkoxy-groups that are in a *meta*

relationship to the acyl-group do not present any difficulties, but *para*-substituents are invariably hydrogenolysed,[29,22] and *ortho*-substituents are often vulnerable to reductive cleavage.[30,31]

Scheme 5



Loss of 2-methoxy substituents is promoted by both 4- and 6-substituents and is unavoidable with 3-substituted derivatives due, presumably, to steric compression.[26] Substituents at C-5, however, retard hydrogenolysis of the 2-methoxy group, and a 5-methoxy substituent suppresses hydrogenolysis completely.[26] These complementary effects are consistent with the view that increased electron density at C-2 and C-5 in an intermediate radical anion **9**, would be favored by 3-, 4-, and 6-, substituents, and it would promote expulsion of the 2-methoxy group (**9**→**15**→**16** benzoate). Substituents at C-5 would disfavor an increased of electron density at C-2 and C-5, and it would suppress completely the expulsion of the said C-2 group.

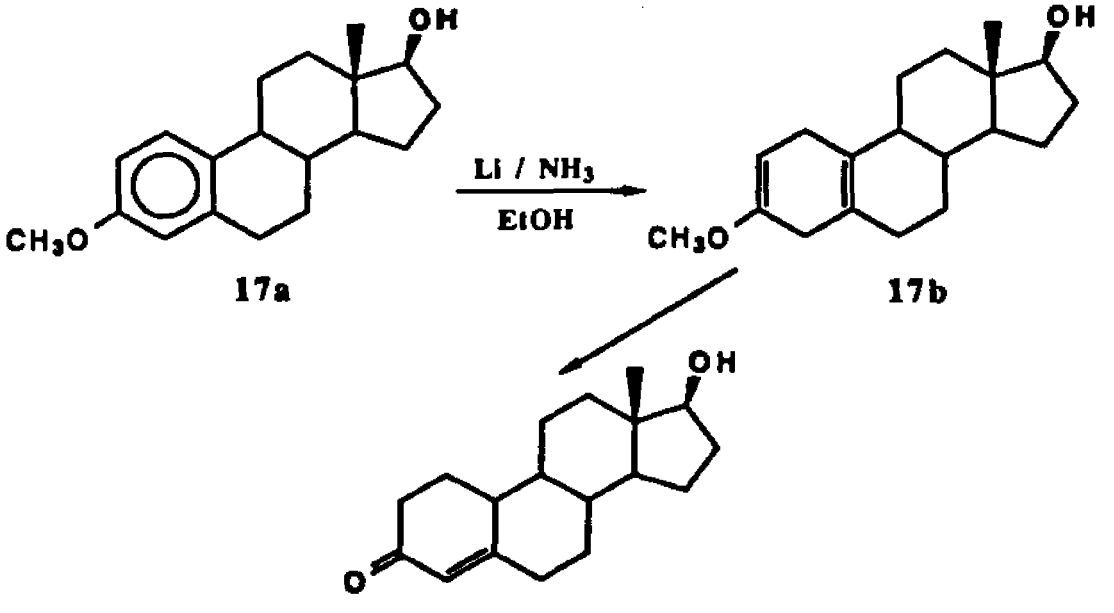
1.2.0. Synthetic Applications

1.2.1. Preparation of cyclohex-2-enones.

The use of anisoles, as synthetic equivalents to cyclohex-2-enones (Scheme 3), has been widespread since the original observations of Birch. There is a wealth of examples in the syntheses of steroids,[8,11,32] terpenes,[33,34] sesquiterpenes,[35] diterpenes,[36,37] diterpene alkaloids,[38] triterpenes,[39] and opium alkaloids.[40,41,42]

The Birch reduction[5] (Scheme 6) of the monomethyl ether of estradiol, **17a** with a solution of lithium metal in liquid ammonia, in the presence of an alcohol as a proton donor, provided the 1,4-dihydrobenzene derivative **17b** which upon acidic hydrolysis gave the enone **17**.

Scheme 6

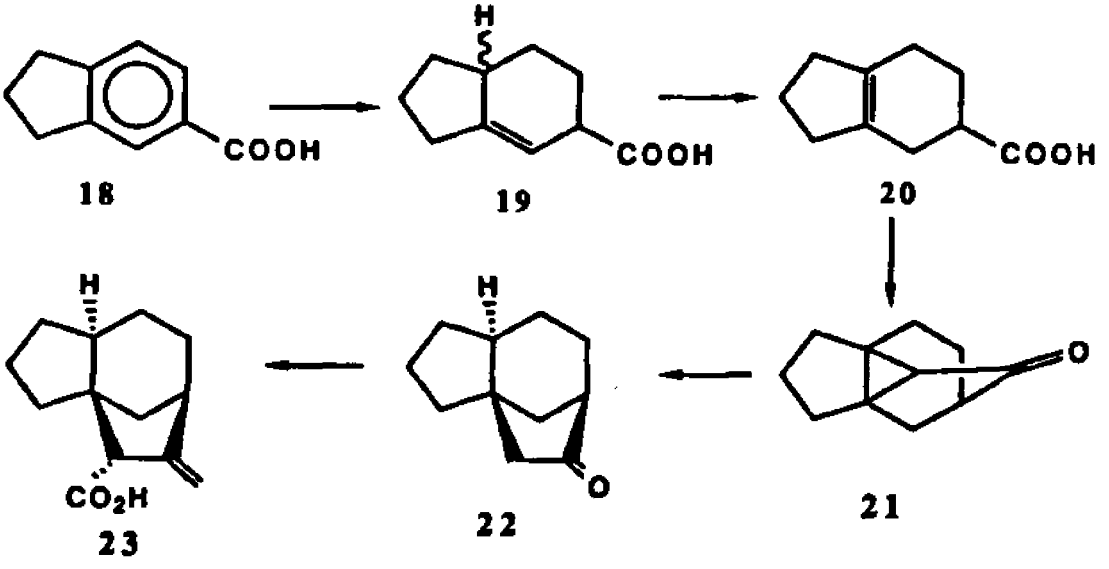


17a **17b** **17**

1.2.2. Reduction of aromatic carboxylic acids.

Indane-2-carboxylic acid **18** was converted into hydrindene acid **19** (Scheme 7) by reduction with lithium in ammonia at -78^{0}C followed by the addition of ethanol and then portions of ammonium chloride at intervals of five minutes. Compound **19** was then converted into **20**, which was utilized as a precursor[44,45] to the tricyclic acid **23**.

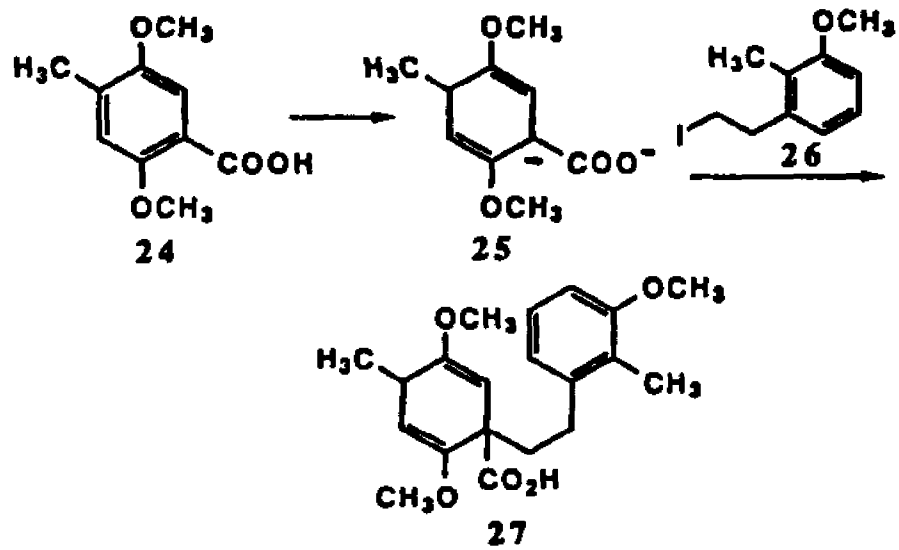
Scheme 7



In 1980 Mander and co-workers employed the Birch reduction-alkylation process in their explorations toward the total synthesis of the very interesting, antineoplastic co-metabolite, juncusol[46,47] (Scheme 8).

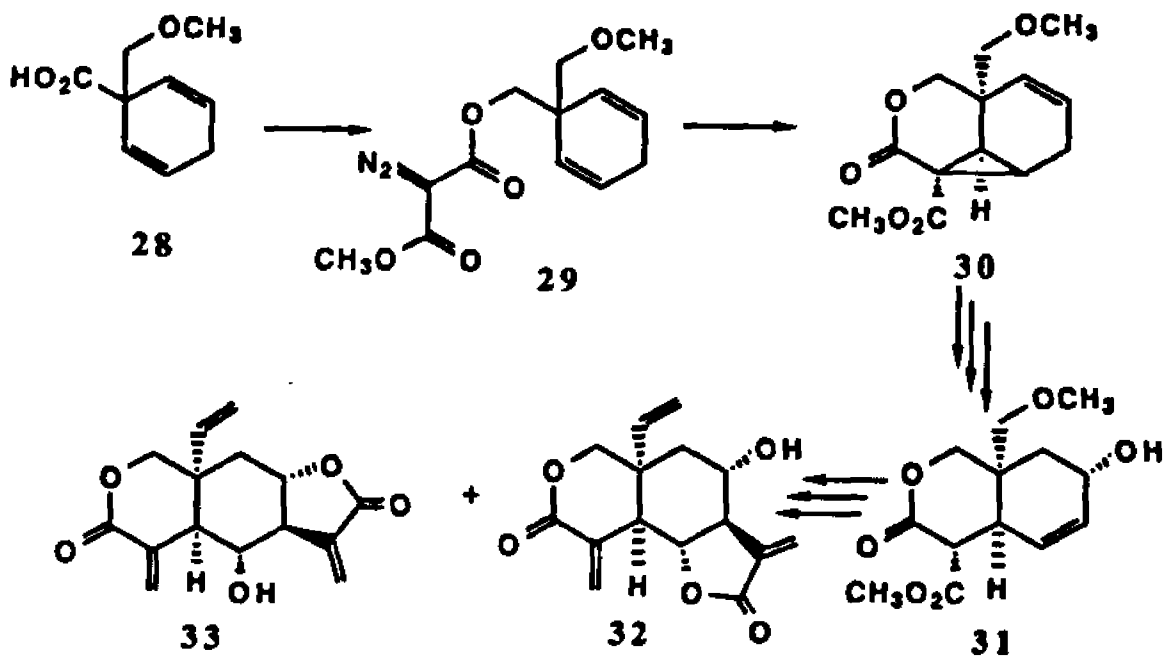
Thus, enediolate **25** was prepared by lithium ammonia reduction of 4-methyl-2,5-dimethoxy-benzoic acid **24** and alkylated in situ with alkyliodide **26**, to afford acid **27**, in 94% yield, after careful acidification to pH = 5.5.

Scheme 8



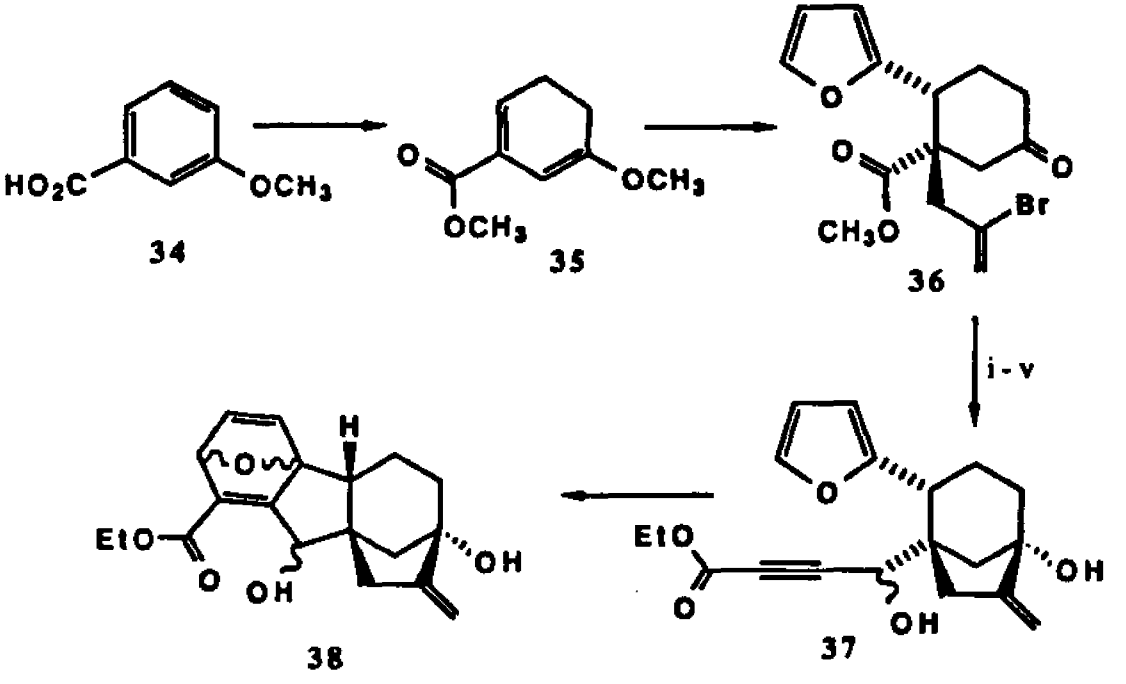
The *cis*-fused 2-oxadecalin-3-one system that is found in vernolepin has been constructed, in seven steps, from benzoic acid (Scheme 9). The dihydro-intermediate **28** could be obtained directly by trapping the anion, obtained from reduction of benzoic acid by lithium in liquid ammonia, with chloromethyl methyl ether. Subsequent transformation[48] afforded **31** and, eventually, vernolepin **32** and vernomenin **33**.

Scheme 9



One approach to the synthesis of gibberellins[50,51] is outlined in Scheme 10. Carefully controlled Birch reduction of 3-methoxybenzoic acid **34**, followed by esterification, provided **35**. The conjugate addition of the Grignard reagent[49] afforded the 3,4-disubstituted-3-methoxycarbonyl-cyclohexanone **36**.

Scheme 10

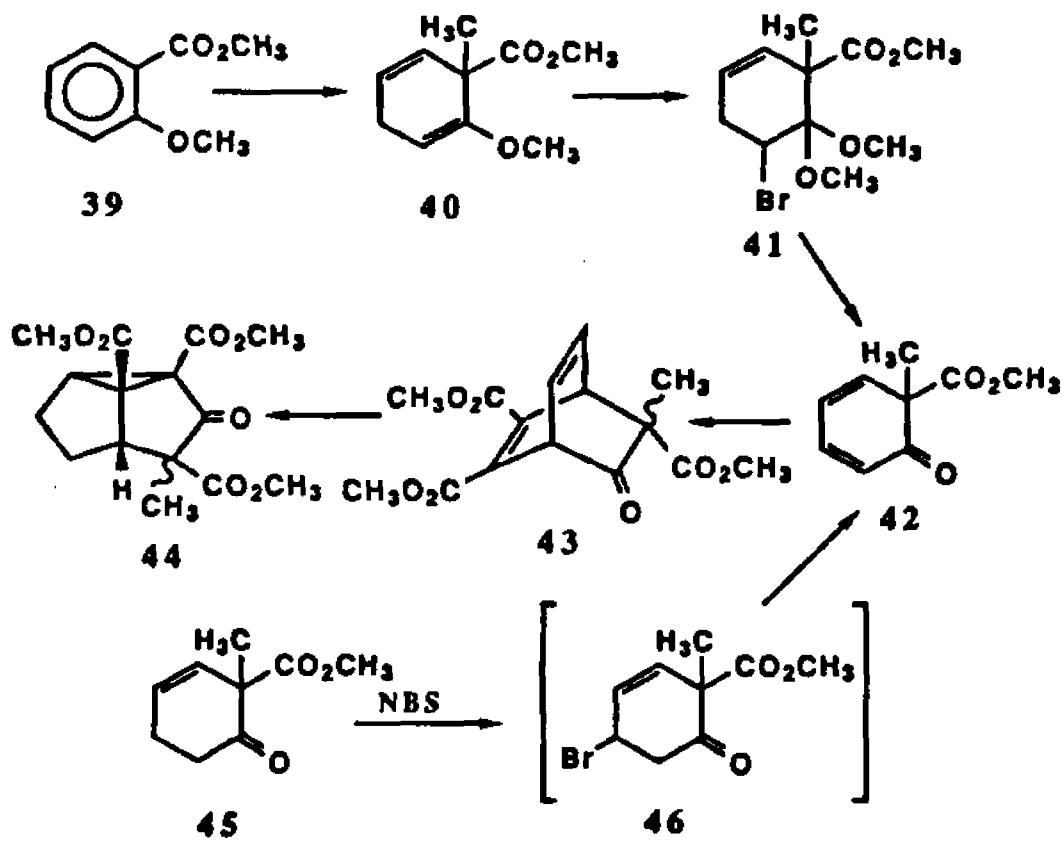


Reagents: i, n-Bu_2CuLi; ii, $LiAlH_4$; iii, pyridinium dichromate, pyridinium trifluoroacetate; iv, EtOC(O)C≡CLi; v, PhH, heat for 160 hours.

1.2.3. Reduction of Aromatic Carboxylic Esters.

A completely general procedure for the reduction of aromatic esters appears to be by use of sodium[52] or potassium[26], at low temperatures, in the presence of one equivalent of t-butyl alcohol. Even lithium has been shown to give excellent results, and it is often the preferred metal if the reduction is followed by alkylation.[53] This is because alkylation of potassium enolates is not always fruitful, and so exchange of the counter-ion with lithium bromide prior to this step has been recommended.[26]

Scheme 11



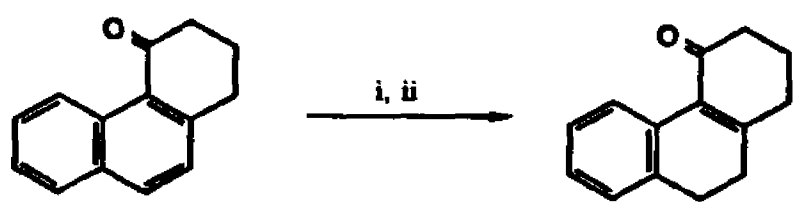
Reduction of aromatic esters, instead of acids, provides a number of potential advantages. The esters tend to be more soluble than carboxylate salts, and the products are more stable. This is especially true of methoxydihydrobenzoic acids, which may be prone to oxidative decarboxylation, or to the hydrolysis of enol ether functions during acidic work-up procedures. Moreover, with esters, hydrogenolysis of 2-alkoxy-substituents does not present the same difficulties as with acids.

The application of bromination-dehydrobromination sequences to the dihydro-aromatic ester **40**, (Scheme 11), has furnished the cyclohexadienone **42**. This compound readily engaged in [4+2] cycloadditions with, *inter alia*, dimethyl acetylene dicarboxylate, and gave the adduct **43**. The hydrogenation and photolysis[54] of **43** led to **44** by means of an oxadi-π-methane rearrangement.[55]

1.2.4. Reduction of Aromatic Ketones.

The reduction of the ring of aromatic ketones was once thought not to be feasible. The first indication that this was incorrect was provided by the reduction[56] of the hydrophenanthrenone **47** to **48** (Scheme 12).

Scheme 12



47 **48**

Reagents: i, M (M = Li, Na, or K) liq. NH_3; ii, NH_4Cl

Optimal procedures for the reduction and reductive-alkylation of aromatic ketones were first established by Watanade and Narisada for acetophenone and its methoxy-derivatives.[56]

Scheme 13

Reagents: i, K, liq. NH_3, t-BuOH; ii, *LiBr*; iii, R_2X

49 R_1 = H
50 R_1 = 5-OMe
51 R_1 = 6,7-$(OMe)_2$
52 R_1 = 5,6,7-$(Me)_3$

49a R_1 = H, R_2 = Me
50a R_1 = 5-OMe, R_2 = Me
51a R_1 = 7-OMe, R_2 = Me
52a R_1 = 5,7-$(OMe)_2$, R_2 = Me
53a R_1 = 5-OMe, R_2 = $-CH_2C(Br)=CH_2$

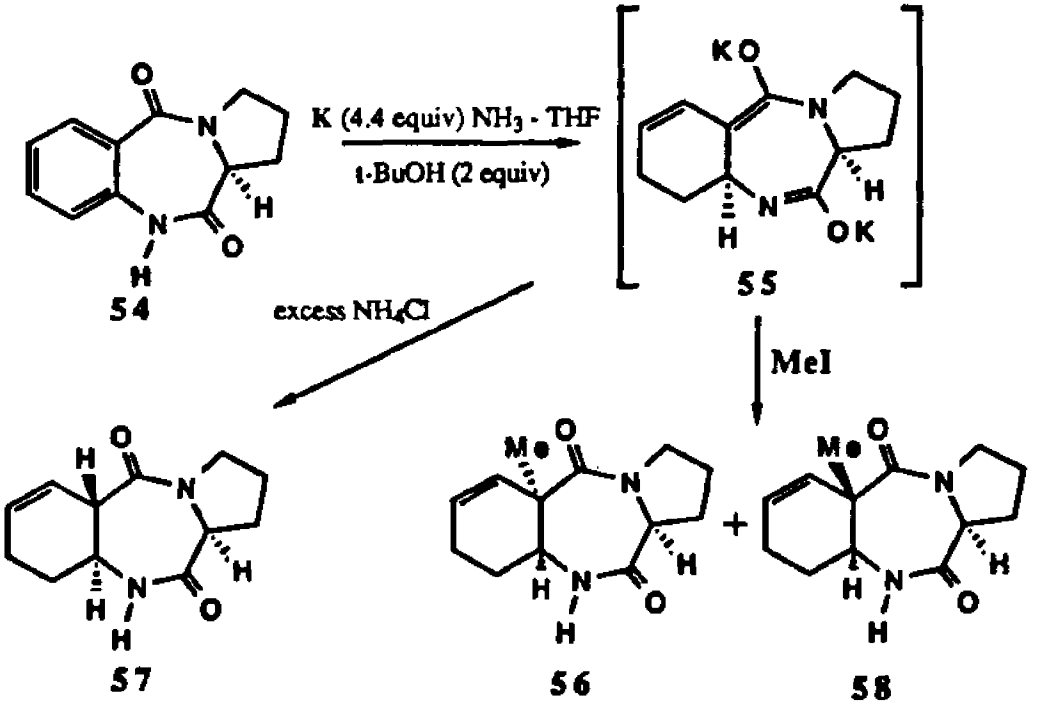
It has been reported that 1-tetralones are reduced by sodium or lithium in liquid ammonia at -33° C to corresponding tetralols or tetralins.[57] Modifications to the original procedure allowed the methoxylated derivatives **49 - 52** to be prepared in excellent yields[27] (Scheme 13).

1.2.5. Reduction of aromatic amides.

In 1987, A. G. Schultz and co-workers reported the enantioselective Birch reduction and reductive alkylation of anthranilic acid derivatives.[58] Reduction of pyrrolobenzodiazepine-5,11-dione **54** in NH_3 - THF with potassium (4.4 equiv) and t-BuOH (2.0 equiv) followed by alkylation with

methyl iodide at -78° C gave a-alkylation products 56 and 58 (56/58 = 85:15) via enolate 55. The stereoselectivity for alkylation of 55 was improved with more sterically demanding alkyl halides. On the protonation with excess of NH_4Cl at -78° C, enolate 55 gave trans-fused β,γ-unsaturated amide 57 in 73% yield (Scheme 14).

Scheme 14



REFERENCES

1. Zimmerman, H. E. in *Molecular Rearrangements*, ed. de Mayo, P., Wiley - Interscience, New York, 1963, Vol. 1, pp 347-352.
2. Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.*, 1980, 102, 3370.
3. Rabideau, P. W.; Peters, N. K.; Huser, D. L. *J. Org. Chem.*, 1981, 46, 1593.
4. Rabideau, P. W.; Huser, D. L. *J. Org. Chem.*, 1983, 48, 4266.
5. Birch, A. J. *Q. Rev., Chem. Soc.*, 1950, 4, 69.
6. Birch, A. J.; Smith, H. *Q. Rev., Chem. Soc.*, 1958, 7, 17.
7. Smith, H. in *Organic Reactions in Liquid Ammonia*, Wiley - Interscience, New York, 1963, Vol. 1, Part 2.
8. Kakis, F. J. in *Steroid Reactions*, ed. Djerassi, C. Holden Day, San Francisco, 1963, pp 267-298.
9. Harvey, R. G. *Synthesis*, 1970, 161.
10. Birch, A. J.; Subba Rao G. S. R. in *Advances in Organic Chemistry, Methods and Results*, ed. Taylor, E. C., Wiley - Interscience, New York, 1972, pp 1-65.
11. Dryden, H. L. in *Organic Reactions in Steroid Chemistry*, ed. Fried, J.; Edwards, J. A. Van Nostrand Reinhold, New York, 1972, Vol. 1, pp 1-60.
12. Birch, A. J. *J. Agric. Food Chem.*, 1974, 22, 162.
13. Subba Rao, G. S. R.; Pramod, K. *Proc. Indian Acad. Sci., Chem. Sci.*, 1984, 93, 573.
14. Birch, A. J.; Slobbe, *J. Heterocycles*, 1976, 5, 905.

15. Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.*, **1986**, 3, pp 35-85.
16. Krapcho, A. P.; Bothner-By, A. A. *J. Am. Chem. Soc.*, **1959**, 81, 3658.
17. Fried, J.; Abrahams, N. A.; Santhanakrishnan, T. S. *J. Am. Chem. Soc.*, **1967**, 89, 1044.
18. Radlick, P.; Crawford, H. T. *J. Org. Chem.*, **1972**, 37, 1669.
19. Birch, A. J. J. Chem. Soc., **1944**, 430.
20. Barltrop, J. A.; Saxton, J. E. J. Chem. Soc., 1952, 1038.
21. Nelson, N. A.; Hsi, R. S. P.; Schuck, J. M.; Khan, L. D. *J. Am. Chem. Soc.*, **1960**, 82, 2573.
22. Kuehne, M. E.; Lambert, B. F. *J. Am. Chem. Soc.*, **1959**, 81, 4278.
23. *Idem. Org. Syn.*, **1963**, 43, 22.
24. a)Taber, D. F. *J. Org. Chem.*, **1976**, 41, 2649. b) Birch, A. J.; Slobbe, J. *Aust. J. Chem.*, **1977**, 30, 1045. c) Hook, J. M.; Mander, L. N.; Urech, R. *Synthesis*, **1979**, 374. d) Hook, J. M.; Mander, L. N. *J. Org. Chem.*, **1980**, 45, 1722.
25. a) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.*, **1980**, 102, 5085. b) Cossey, A. L.; Gunter, M. J.; Mander, L. N. *Tetrahedron Lett.*, **1980**, 21, 3309. c) Hook, J. M.; Mander, L. N.; Urech, R. *J. Am. Chem. Soc.*, **1980**, 102, 6628. d) Gunter, M. J.; Mander, L. N. *Aust. J. Chem.*, **1981**, 34, 675.
26. Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.*, **1982**, 23, 1095.
27. Brown, J. M.; Cresp, J. M.; Mander, L. N. *J. Org. Chem.*, **1977**, 42, 3984.
28. de Mos, J. C.; van Bekkum, H.; van den Boch, C. B.; van Minnen-Pathuis, G.; van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas*, **1971**, 90, 137.
29. Birch, A. J.; Hextall, P.; Sternhell, S. *Aust. J. Chem.*, **1954**, 7, 256.
30. Birch, A. J.; Murray, A. R.; Smith, H. *J. Chem. Soc.*, **1951**, 1945.
31. House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.*, **1976**, 41,

2401.

32. Akhrem, A. A.; Titov, Y. A., in *Total Steroid Synthesis*, Plenum, New York, **1970**.
33. Soffer, M. D.; Jevnick, M. A. *J. Am. Chem. Soc.*, **1955**, *77*, 1003.
34. Thomas, A. F.; Willhalm, B.; Bowie, J. H. *J. Chem. Soc. B*, **1967**, 392.
35. Heathcock, C. H., in *The Total Synthesis of Natural Products*, ed. ApSimon, J. W., Wiley, New York, **1973**, Vol. 2, pp 197-558.
36. van Tamelen, E. E.; Taylor, E. G. *J. Am. Chem. Soc.*, **1980**, 102, 1202.
37. van Tamelen, E. E.; Carlson, J. G.; Russell, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.*, **1981**, 103, 4615.
38. Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T; Hayase, Y. *J. Am. Chem. Soc.*, **1967**, 89, 1482.
39. ApSimon, J. W.; Hooper, J.W., in *The Synthesis of Natural Products*, ed. ApSimon, J. W., New York, 1973, Vol. 2, pp 559-640.
40. Bayerman, H. C. Bvan Berkel, J.; Lie, T. S.; Maat, L.; Wessels, J. C. M. *Recl. Trav. Chim. Pays-Bas*, **1978**, 96, 127.
41. Hsu, F. L.; Rice, K. C.; Brossi, A. *Helv. Chim. Acta*, **1980**, 63, 2042.
42. Manmade, A.; Marshall, J. L.; Minns, R. A.; Dalzell, H.; Razdan, R. K. *J. Org. Chem.*, **1982**, 47, 1717.
43. Turner, J. V.; Anderson, B. F.; Mander, L. N. *Aust. J. Chem.*, **1980**, 33, 1061.
44. Mander, L. N.; Prager, R. H.; Turner, J. V. *Aust. J. Chem.*, **1974**, 27, 2645.
45. Cossey, A. L.; Gunter, M. J.; Mander, L. N. *Tetrahedron Lett.*, **1980**, 21, 3309.
46. Mander, L. N.; Hamilton, R. *J. Tetrahedron Lett.*, **1981**, 22, 4115.
47. Zutterman, F.; de Wilde, H. Mijngheer, R.; de Clercq, P.; Vandewalle,

M. *Tetrahedron*, **1979**, 25, 2389.

48. Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.*, **1977**, 42, 1794.
49. Grootaert, W. M.; de Clercq, P. J. *Tetrahedron Lett.*, **1982**, 23, 3291.
50. van Meerssche, M.; Declercq, J.-P.; Grootaert, W. M.; de Clercq, P. J. *Bull. Soc. Chim. Belg.*, **1982**, 91, 819.
51. Loewenthal, H. J. E., in *Guide for the Perplexed Organic Experimentalist*, Heyden, London, **1978**, pp 133-138.
52. Hamilton, R. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron*, **1986**, 42, 2881.
53. Schulzt, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.*, **1984**, 49, 4429.
54. Demuth, M.; Schaffner, K. *Angew. Chem.*, Int. ed. Engl., **1982**, 21, 820.
55. Mejer, S. *Bull. Acad. Pol. Sci. Chim..*, **1962**, 10, 469.
56. Narisada, M,; Watanade, F. *J. Org. Chem.*, **1973**, 38, 3887.
57. Hall, S. S.; Lipsky, S. D.; McEnroe, F. J.; Bartels, A. P. *J. Org. Chem.*, **1971**, 36, 2588.
58. Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, 109, 6493.

CHAPTER 2

2.0.0. Free Radical Carbocyclization

2.1.0. Introduction

Most organic free-radical reactions involve one or more of the following elementary mechanistic steps in which A, B, and D represent atoms or groups, not necessarily carbon-centered.

$A-B$	$A^{\cdot} + B^{\cdot}$	homolysis
$A^{\cdot} + B^{\cdot}$	$A-B$	coupling
$A - e^{-}$	A^{+}	electron transfer
$A^{\cdot} + e^{-}$	A^{-}	" "
$A^{\cdot} + B-D$	$A-B + D^{\cdot}$	atom or group transfer ($S_{RN}2$)
$A^{\cdot} + B=D$	$[A-B-D]^{\cdot}$	addition
$[A-B-D]^{\cdot}$	$A^{\cdot} + B \equiv D$	α-fission

A radical $A^{\cdot}$ generated in the presence of organic substrates may potentially be capable of undergoing a number of the above types of reactions; or, if only one reaction type is available, questions of regio- and stereo-selectivity may arise. Given a number of possible reaction pathways, how may one predict which will be preferred?

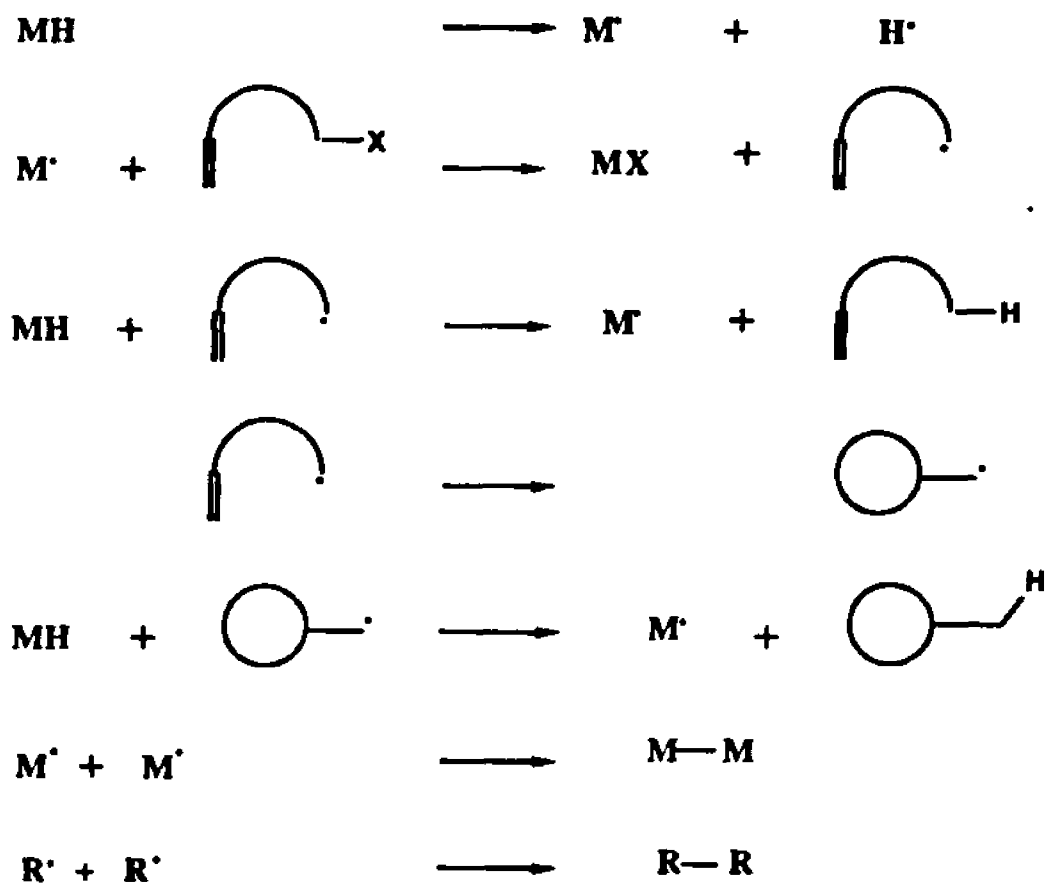
2.1.1. Addition of alkyl radical to a carbon-carbon double bond.

It has long been known that free radicals can add to double bonds. Such reaction comprise the basis for a wide variety of useful synthetic procedures including vinyl polymerization, anti-Markovnikov addition of hydrogen halides to olefins, and a host of other preparative synthetic reactions.[1-3] Radical additions to carbon-carbon double bonds can also occur intramolecularly, resulting in cyclized products. In recent years, intramolecular radical cyclization has become a major area of research interest. Many examples are now documented, several of which constitute useful synthetic procedures.[4-7]

Extensive research over the past twenty five years has resulted in a better understanding of the mechanism, kinetics, and thermodynamics of free radical cyclizations. These reactions, like other radical addition processes, proceed by a radical chain mechanism (Scheme 1), and follow a pathway which results in the formation of the most stable product. For example, the addition pathway leading to adducts that contain a tertiary radical will usually be favored over that resulting in formation of a secondary radical. However, regiochemical predictions based purely on thermodynamic control often break down for intramolecular and even acyclic cases because of a failure to account for steric and polar effects on the developing transition state.[2,8,9] A better analysis of the features affecting the regiochemistry of intramolecular carbon-carbon bond-forming radical addition should include four major factors:

a. **The strength of the bond being formed:** The radical usually bonds to the end of an olefin that results in a stronger carbon-carbon bond.

Scheme 1

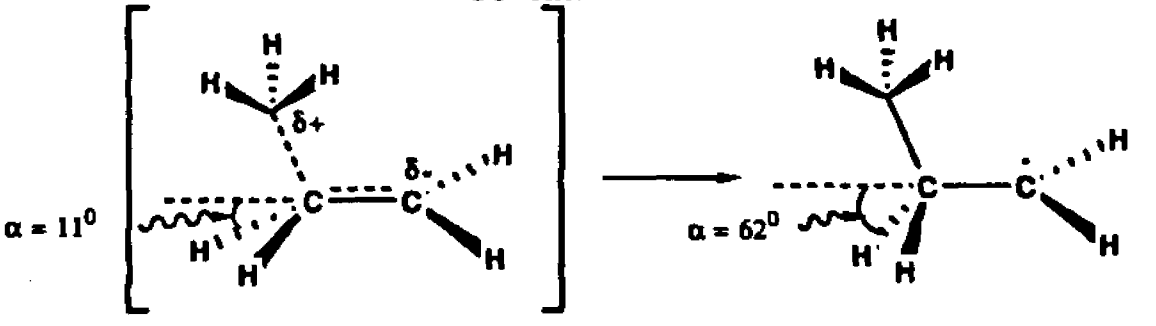


b. **Steric hindrance:** The radical avoids sterically crowded sites because of energetically unfavorable nonbonding interactions. These interactions may also contribute to an effective weakening of the carbon-carbon bond being formed.

c. **Polar effects:** Radicals containing electron withdrawing groups such as halogens are polarized so as to make the radical more stable (electrophilic). Such radicals are repulsed by olefin termini that also contain electron withdrawing groups.

d. **Stability of the addend radical:** The radical usually attacks the end of the olefin that results in the more stable addend radical. Such radical stability is usually measured by how effectively adjacent substituents can delocalize the free spin.[10,11]

Scheme 2



T S

No single factor can rationalize known trends in the regiochemistry of additions; rather, combinations of all four must be used. Equally important must be a consideration of the steric requirements for attainment of an optimal transition state geometry. A recent model (Scheme 2) of the transition complex for addition of the methyl radical to ethylene[12] incorporates the three participating carbon atoms at the vertices of a slightly obtuse triangle, lying in a plane orthogonal to that of the olefin's framework. The complex is dipolar and the incoming radical is usually computed to assume a fractional positive charge (i.e., it behaves as a nucleophile) whereas the ethylene moiety becomes slightly negative. The transition state formation involves the interaction of a semioccupied 2p orbital with one lobe of the unoccupied π^* orbital. This interaction defines both the shape and the polarity of the transition complex. The CCC bond angle is calculated to be close to the value in the product, with the methyl radical slightly hybridized in a product-like sp^3 center. The newly forming carbon-carbon bond is very long (2.3 A), however, and the rest of the transition state is estimated to be

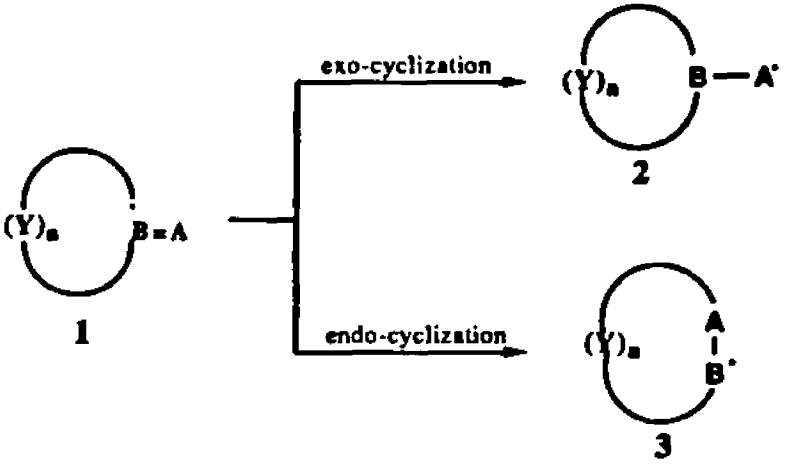
reactant-like. The carbon-carbon double bond length should be essentially unchanged from its normal value for a double bond (1.34A). The methylene group undergoing attack is slightly tilted out of the plane of the σ-ethylene framework by 11°, much less than it is in the final product (61°).

Ring-closure reactions respond in the same way as analogous intermolecular processes respond to both thermochemical factors and to steric and polar effects, but they are also subjected to additional constraints connected with the formation of cyclic systems.[14] For example, ring strain makes a direct contribution to $\Delta H^{\ddagger}$ for an intramolecular radical reaction, and this is reflected in the energy of the transition state. On this basis alone, the relative rates of formation of carbocyclic systems should be in the order of six- > seven- > four- > three-membered. However, entropy changes also make a major contribution to the free energy of activation. In general, intramolecular additions occur more readily than their intermolecular analogues because the latter involve a substantial loss of translational entropy, whereas the former involve only the loss of internal rotational degrees of freedom. Furthermore, the entropy change due to the loss of rotational freedom becomes increasingly unfavorable with increasing chain length. When both enthalpy and entropy changes are taken into account, it is seen that intramolecular addition occurs most rapidly at ordinary temperatures when the ring formed contains three, five, or six members.

Radical cyclization can occur only when a favorable transition state geometry can be reasonably achieved. This must occur with minimal increase in ring strain energy, and if two regiochemical modes of addition are available, the cyclization will proceed via the path with the lowest energy transition state. Such considerations lead to the proposal of various "rules"

for radical cyclization.[15] These rules predict that intramolecular additions under kinetic control in the lower alkenyl and alkynyl radicals and related species occur preferentially in the exo-mode (Scheme 3).

Scheme 3

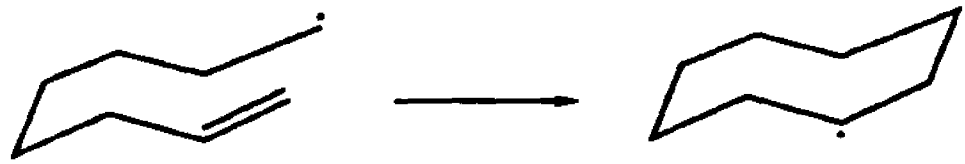


That is, exo-ring closure of **1** to **2** is kinetically favored over endo- ring closure of **1** to **3** for radicals of type **1** where Y is a chain of atoms n > 5. This kinetic preference exists because ring strain generated during attainment of the required transition state geometry for endo-adduct **3** far outweighs thermo-chemical and other factors disfavoring formation of the thermodynamically less stable exo-adduct **2**. Models and statistical calculations[13] show that this constrain is very severe for small rings, but less so for more flexible large rings. Butenyl and pentenyl radicals should therefore undergo specific exo-cyclization, but cyclization of longer chains may also afford endo-products.

Accurate kinetic data pertinent to this guideline are available only for the lower alkenyl radicals (Table 1),[16,17] which undergo regioselective exo-ring closure. However, the degree of preference for the exo-mode decreases along the series butenyl, pentenyl,hexenyl, and heptenyl. The regiospecific exo-ring

closure of the 7-octenyl radical **4a** probably reflects the existence of unfavorable interannular non-bonded interactions in the cyclic transition state leading to cyclooctyl radical **4** (Scheme 4).

Scheme 4



4a **4**

Table 1: Rate constants at 65° and activation papameters for ring-closure of ω-alkenyl radicals

Radical	% *exo*	K_{exo}	$\Delta H^{\#}_{exo}$	$\Delta S^{\#}_{exo}$	K_{endo}	$\Delta H^{\#}_{endo}$	$\Delta S^{\#}_{endo}$
3-butenyl	100	1.8×10^{4}	10.5	-10			
4-pentenyl	100	7.0×10^{-1}	16.0	-14			
5-hexenyl	98	3.6×10^{5}	6.1	-17	7.0×10^{3}	7.8	-20
6-heptenyl	85	1.1×10^{4}	7.5	-20	1.9×10^{3}	8.0	-22
7-octenyl	100	3.0×10^{2}	8.9	-23			

The kinetic data for cyclization of alkenyl radicals reflect the usual interplay of enthalpic and entropic factors. The value of $\Delta S^{\#}$ decreases monotonically down the series butenyl to octenyl. This is to be expected because ring closure of any particular radical, as compared with that of its next lower homolog, involves an additional loss of rotational freedom of one CH_2 rotor. The value of $\Delta H^{\#}$ however, appears to reflect approximately the heat of formation of the ring being generated. It is small for cyclopentyl and

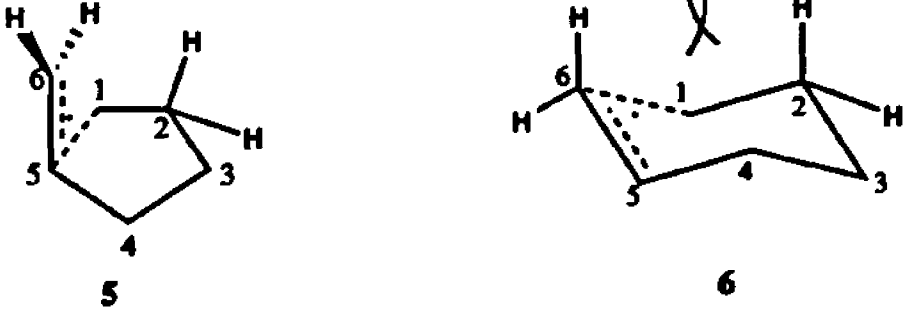
cyclohexyl rings, but much larger for three- or four-membered rings. The resultant rate constants for ring closure at ordinary temperature are in the order hexenyl > butenyl > heptenyl > octenyl > pentenyl.

2.1.2. The 5-Hexenyl Radical.

Several studies have been made to determine the factors which govern the regiochemical preference of the 5-hexenyl radicals. The factors include:

a. **Ring strain:** Less ring strain develops during 1,5-ring closure. Approach of the radical to the olefin must follow the strict stereo electronic requirements described earlier.[12] The 6-endo-cyclization requires such severe distortion of bond angles and distances that the alternative 5-exo-cyclization predominates.

Scheme 5

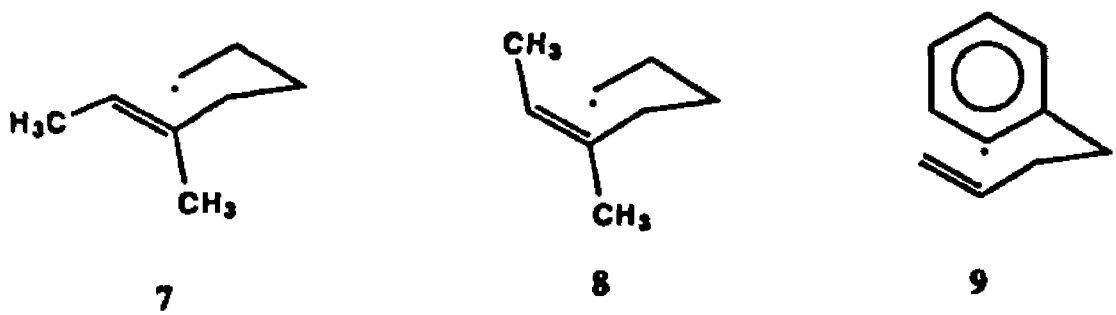


5 6

b. **Steric Interactions:** The formation of a six-membered ring is disfavored by nonbonding steric interactions between the pseudoaxial proton at the two position and the syn proton at six position[21] (Scheme 5). That is, transition state **5** is more favored than 6.

This rationale is supported by the fact that the disubstituted 5-hexenyl radical 7 (Scheme 6) cyclized to give both five- and six-membered ring adducts, whereas its geometric isomer 8, in which the 2,6 interaction should be more severe, undergoes solely 1,5-cyclization.[21] In contrast to this phenomena, alkenylaryl radical 9, which does not have a 2,6-interaction because it has no proton at the 2-position, also undergoes rapid and specific 1,5-ring closure.[22] From these examples, it seems clear that the most important effects in controlling the direction of cyclization are steric rather than electronic.

Scheme 6



7 8 9

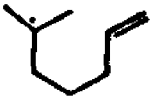
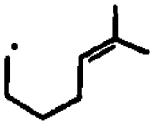
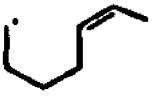
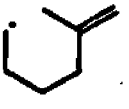
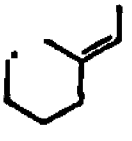
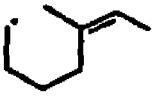
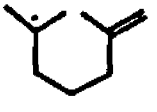
c. **Entropy:** Entropy calculations have shown that while 1,5-closure is favored over 1,6-closure, the magnitude of the difference in entropy for each pathway is quite small (2.8 Gibbs/mol) and the free energy of each cyclization is much more influenced by enthalpy changes (1,7 Kcal/mole) arising from steric and polar factors.[20]

2.1.3. Substituted 5-Hexenyl Radical

In an attempt to obtain more precise data concerning the magnitude of 2,6 non-bonding interactions in the transition state for the ring closure of 5-hexenyl radical, methyl-substituted radicals have been examined.[24,25] Several alkenyl bromides and tri-n-butyltin hydride have been used in order to determine the effect of substituents on the rates and regiochemistry of cyclization of the 5-hexenyl radical.[18,22,23] This was done through the effects, arising from non-bonding interactions on the energies of the various possible comformers of cyclic transition complexes.

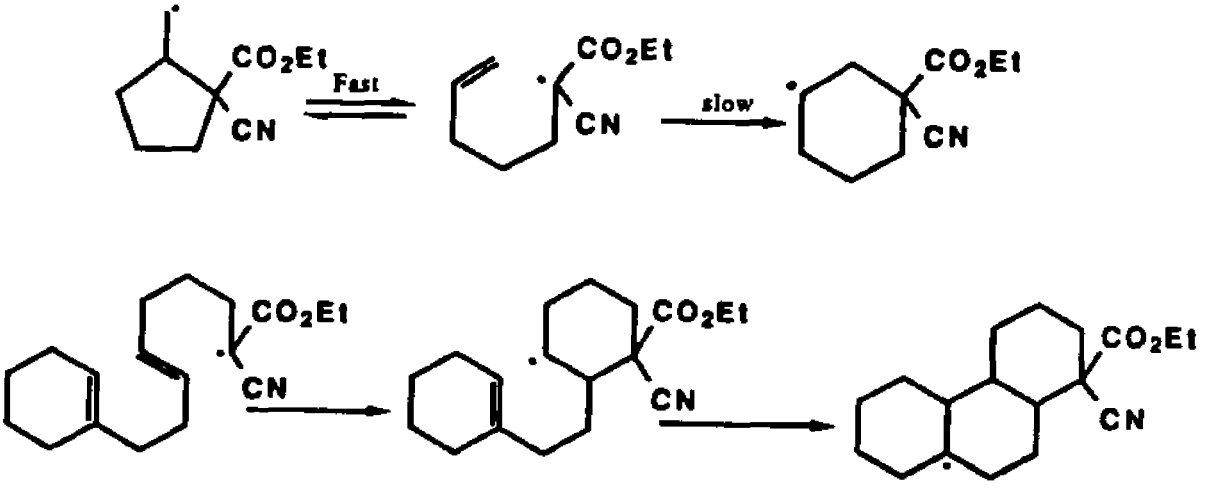
The effects of alkyl substituents at C-1 or C-6 in the 5-hexenyl radical, predicted on the basis of the thermochemical hypothesis that the rates of closely related reactions reflect the relative stabilities of reactants and products, are clear. The rate of 1,5-ring closure should be diminished by substitution at C-1 and enhanced by substitution at C-6. The experimental data (Table 2),[19] however, do not reveal such effects. There are at least two possible plausible explanations. First, it appears that homolytic addition proceeds through a very early transition state in which there is little change of configuration at C-1 or C-6 and little transfer of spin density.[12] Secondly, it seems possible that changes in energy arising from the interactions of substituents with fractional charges at C-1 and C-6 in the polar transition state (Scheme 2) will be in the opposite direction to those changes expected to result from interactions with the free spin. Consequently, the two effects tend to counterbalance each other.

Table 2: Relative Rates of Cyclization for 5-Hexenyl Radical (~60° C)

Radical	k1,5(rel)	k1,6(rel)	k1,6/k1,5	Ref.
	1	0.02	0.02	19
	1.4	0.02	0.014	19
	1.4	0.02	0.014	19
	2.4	< 0.01	< 0.005	19
	1.0	< 0.01	< 0.01	21
	0.022	0.04	1.8	19
	0.06	0.16	2.5	21
	0.11	0.20	1.7	21
	0.16	< 0.002	< 0.01	21
	< 0.0002	0.02	~ 100	19

Radicals containing substituents at C-1 (Scheme 7) are expected to exert a strong conjugative effect on the adjacent radical center. It is known[26] that these types of radical often afford mainly products of endo-ring closure. Such results are not incompatible with the concept of stereo-electronic control. Careful examination of their behavior suggests that exo-ring closure is the kinetically controlled process but, being freely reversible,[27] is often superseded by slow but essentially irreversible endo-ring closure.[28] The amount of 1,6-closure depends on the conditions used; with lower temperatures or more efficient hydrogen donors higher five-membered/six-membered ring ratios result. This type of cyclization is now used as a preparative method for the synthesis of six-membered rings.[27] These types of stabilized radicals have been used for the construction of interesting polycyclic ring systems related to a variety of terpenes (Scheme 7). It is interesting to note that each intermediate radical undergoes specific 1,6-ring closure, contrary to the behavior of similar unstabilized radicals.[37-41]

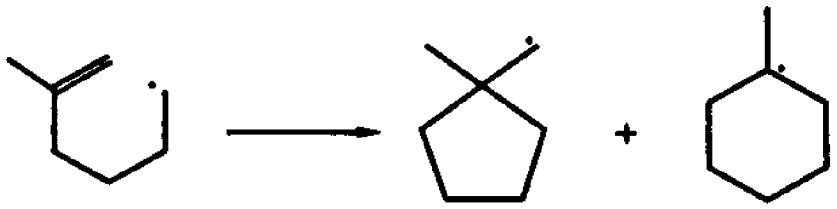
Scheme 7



Substitution at C-5 in 5-hexenyl and related radicals is a profound affect on the regioselectivity of ring closure. For example, reactions involving the

intermediacy of 5-methylhex-5-enyl radical **10** favor the formation of endo-products.[19] The thermochemical explanation for this phenomenon is that the difference in hyperconjugative stabilization between the tertiary radical **12** and the primary exo-product **11** is sufficient to outweigh those factors favoring exo-ring closure (Scheme 8). The kinetic data (Table 2) clearly show that the observed preference for endo-ring closure reflects not an enhanced rate of formation of **12** but a greatly retarded rate of 1,5-cyclization.

Scheme 8



10 **11** **12**

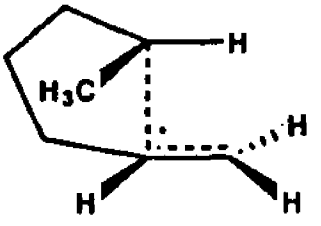
Intermolecular additions of alkyl radicals to olefins display a similar sensitivity to the presence of alkyl groups at the point of attack.[29] One can conclude that radical cyclizations, like any other addition process, are sensitive to a complex interplay of electronic and steric factors, and that any attempt to predict or rationalize regiochemical behavior on the basis of radical stability alone is tenuous at best.[30]

Geminal alkyl substituents also influence the rate of cyclization by exerting a so-called "gem-dialkyl effect." It has been shown that the 2,2-dimethyl- hex-5-enyl radical undergoes 1,5-cyclization about ten times faster than the 5-henexyl radical,[25] and that the 3-propylhex-5-enyl radial also shows an enhanced rate of ring closure.[31] Such increased rates are believed to result

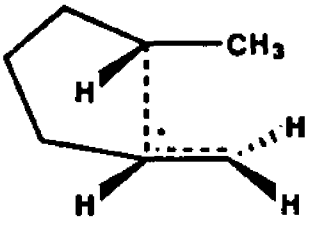
from relief of steric compression between geminal substituents during the course of cyclization.

5-hexenyl radicals and related species bearing a substituent at C-1 afford a mixture of *cis*- and *trans*-disubstituted compounds by 1,5-ring closure. Preferential formation of the trans-product would be expected, since the transition state for *trans*-cyclization **13** is less subjected to nonbonding interactions than that for *cis*- cyclization **14** (Scheme 9).

Scheme 9



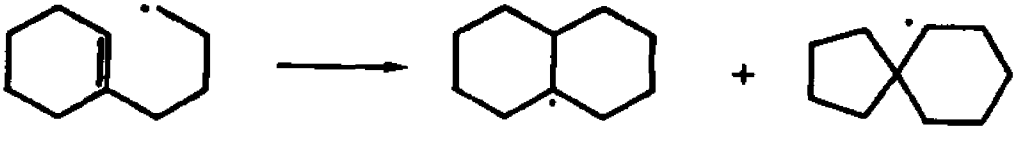
13



14

When a ring is incorporated into the 5-hexenyl radical system, intramolecular addition leads to the formation of bicyclic products. For example, cyclohexenylbutyl radical **15** (Scheme 10) still displays a slight preference for 1,5-ring closure[32] providing the spiro[4.5]decane system **17**. The rate of cyclization for this system is considerably slower than for a simple 5-hexenyl radical. The relative yields of *cis*- and *trans*-decalin formed from **16** depend on the efficiency of the hydrogen atom donor.

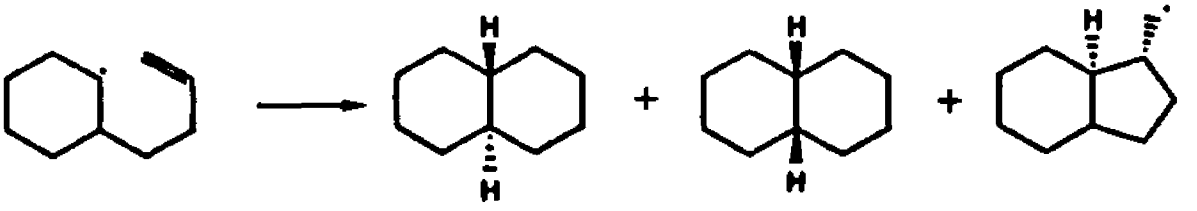
Scheme 10



15 **16** **17**

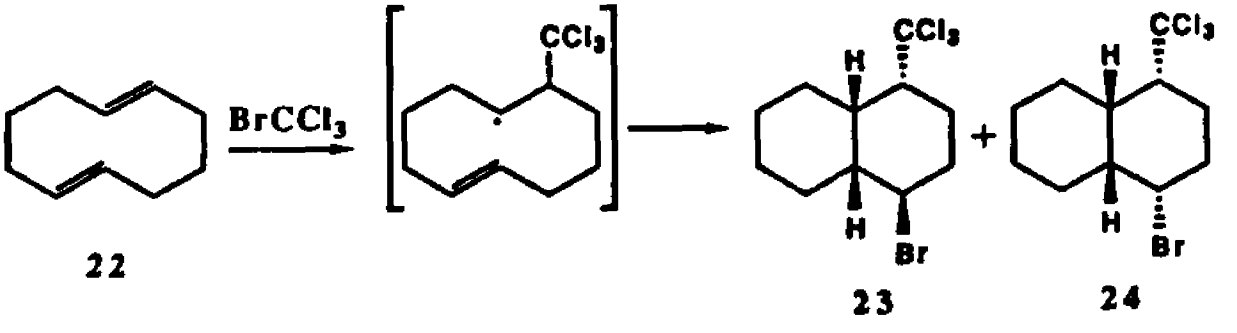
When the initial radical site is located in a ring, as in **18** (Scheme 11), the stereo-chemistry of the final product is determined by the cyclization process. While the stereochemical details of this reaction have not been worked out, there is a general agreement[33] that the major six-membered ring adduct is the *trans*-decalin radical **19** which suggests that endo-closure occured.

Scheme 11



Cis,trans-1,5-cyclodecadiene **22** cyclizes to the *cis*-fused decalins **23** and **24** via, 1,6-ring closure[34] (Scheme 12). The products obtained suggest a pathway involving regiospecific additions of the radical at the *cis*-olefin, followed by exclusive 1,6 stereospecific ring closure to give only *cis*-fused decalins.

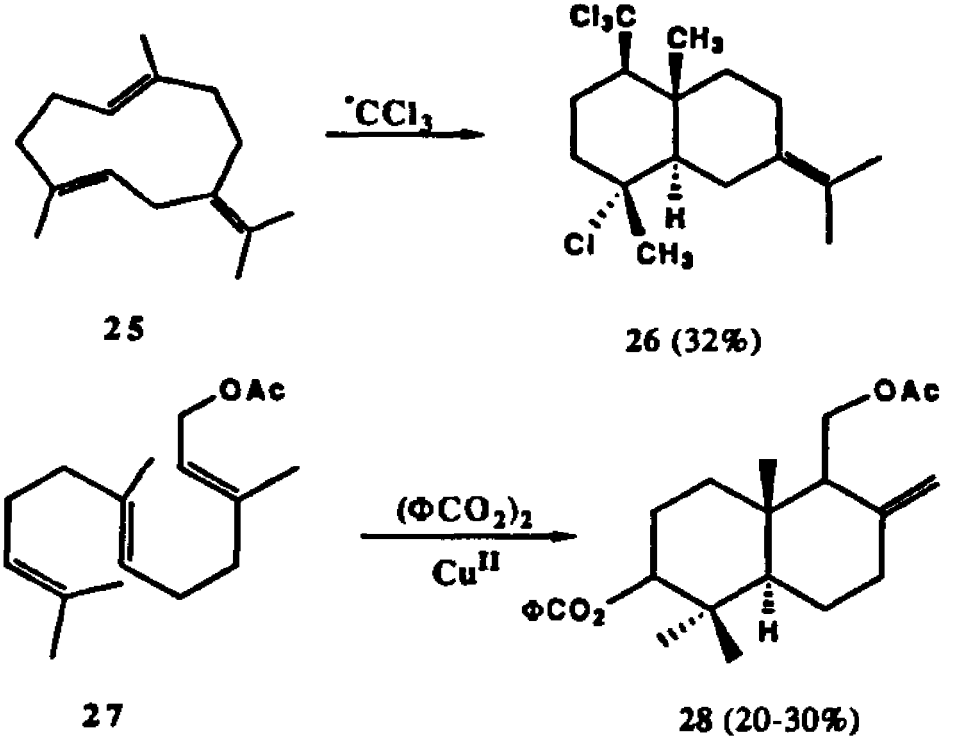
Scheme 12



Two other fascinating cyclizations that occur regio- and stereo-specifically are shown in Scheme 13. The addition of trichloromethyl radical or

benzoyloxy radical to germacratriene **25** or polyene **27** results[35, 36] in the specific formation of *trans*-decalins **26** and **28** respectively. In each case only one isomer was detected.

Scheme 13



25 **26 (32%)**

27 **28 (20-30%)**

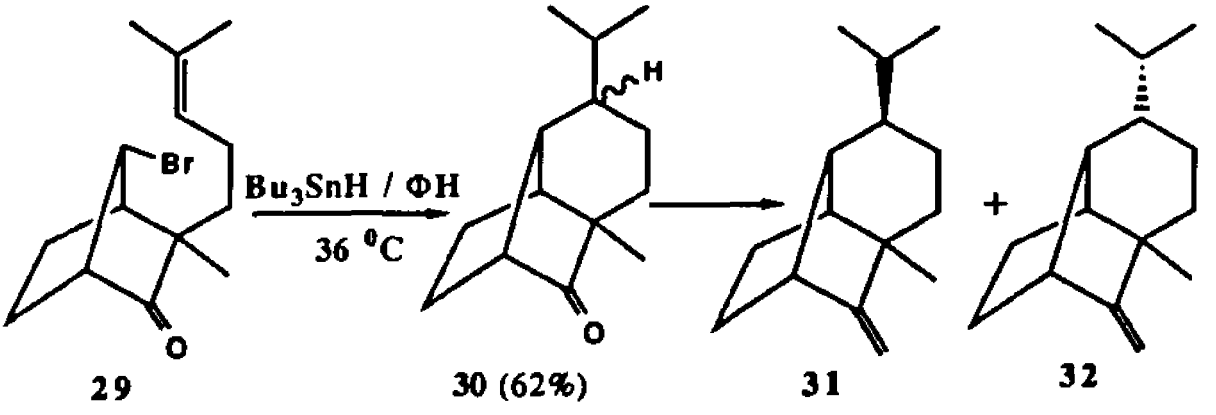
2.2.0. Intramolecular Radical Carbocyclization in Organic Synthesis

Although radical addition reactions have received widespread use in the fields of preparative organic chemistry[43] and vinyl polymerization, the applications of radical cyclization in organic synthesis have been limited. In the last few years, however, free-radical addition reactions have gained popularity, and their use in the construction of complex organic compounds is being evaluated by a number of research groups. Radical cyclization has been utilized extensively for cyclopolymerization,[44] but its contribution to

synthetic organic chemistry is confined to a small number of cases such as the Pschorr synthesis of phenanthrene derivatives.[45]

In spite of the promising work of Julia, Walling, Ingold and Beckwith, the use of free radical cyclizations in natural product synthesis design has only begun to surface.

Scheme 14

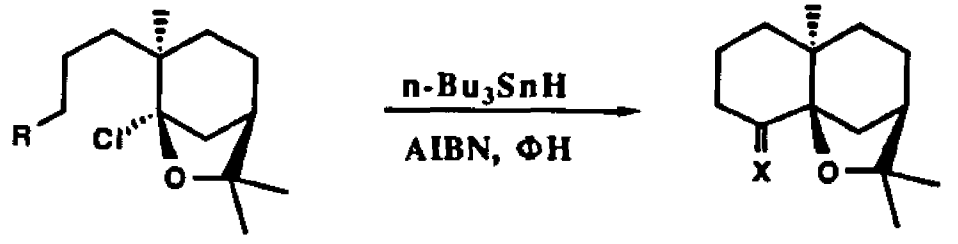


One conscious effort was the syntheses of the sesquiterpenes, sativene **31** and copacamphene **32** by Bakuzis and coworkers[42] (Scheme 14). The crucial step involved cyclization of the 7-norbornyl radical derived from the haloketone **29**, to tricyclic ketone **30**. The major flaw in this synthesis was a lack of stereoselectivity in the radical cyclization. It is possible that this inability to direct the stereochemical course of radical reactions has served as a deterrent to their use in the natural product synthesis.

Similar stereochemical problems were encountered[46] in a synthesis of dihydroagarofuran **34**. Cyclization of the α-chloroether **33** gave a mixture of stereoisomers **34** (47%) and **35** (20%) (Scheme 15). When acetylene **36** was used as the cyclization substrate, however, a simple solution to the stereochemical problem was achieved. Cyclization of **36** gave vinylsilane **37**

(72%) as a mixture of geometrical isomers. Protodesilylation of **37** and subsequent reduction of **38** with diimide gave dihydroagarofuran **34**, contaminated with less than 5% of **35**.

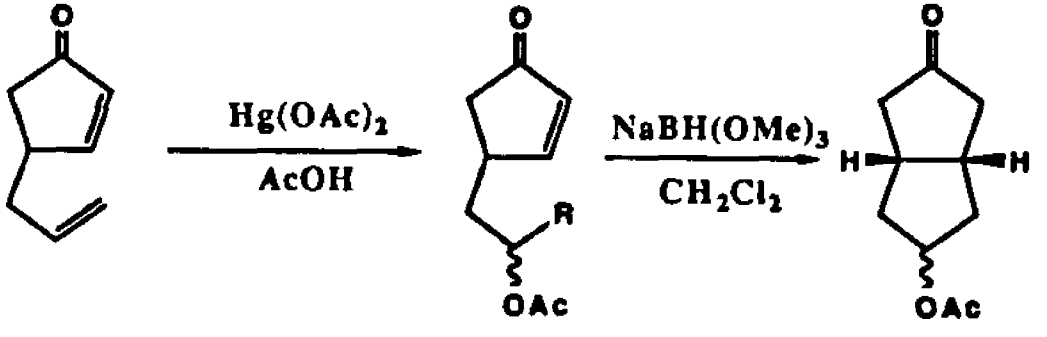
Scheme 15



33 R = $CH{=}CH_2$ **34** X = α-H, β -Me, **35** X = α-Me, β- H
36 R = $C{\equiv}CSiMe_3$ **37** X = $CHSiMe_3$, **38** X = CH_2

Another example of a bond construction that would be difficult to achieve by way of a polar coupling[47] is shown in Scheme 16. Reductive cyclization of the α-acetoxymercurial **40**, prepared by acetoxy-mercuration of dienone **39**, affords bicyclo[3.3.0]octane **43**, a substructure for a large number of

Scheme 16

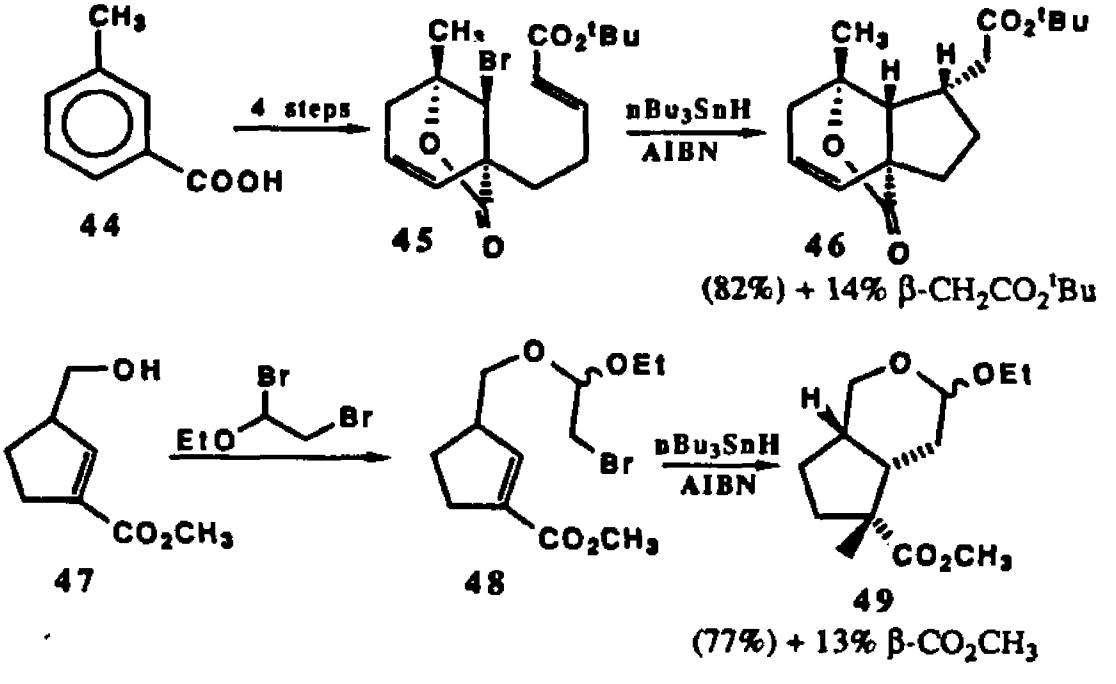


39 **40** R = CH_2HgOAc **43** (58%)
41 R = $CH_2^{\bullet}$
42 R = CH_2^{-}

natural products. This reaction presumably proceeds by cyclization of the intermediate α-acetoxy radical **41**, and a bond is formed between the radical center and an electrophilic fragment. Polar construction of the same bond by hypothetical α-acetoxy carbanion **42** would be doomed because the nucleophilic component would undergo self destruction as a result of a β-elimination process (**42** **39**). Thus, α-heteroatom substituted radicals can serve as surrogates for inaccessible or kinetically unstable nucleophiles.

Two other potentially useful transformations also involve conjugate addition of radicals (Scheme 17). In the conversion of **45** to the highly functionalized perhydroindane **46**, bond formation occurs at a sterically congested center and proceeds with good stereoselectivity.[48] Stereoselectivity is also seen in the cyclization[49] of bromoacetal **48**. Capture of the cyclized radical by tri-n-butyltin hydride, from the convex face of the initially formed bicyclic system, accounts for the observed stereoselectivity, **49**.

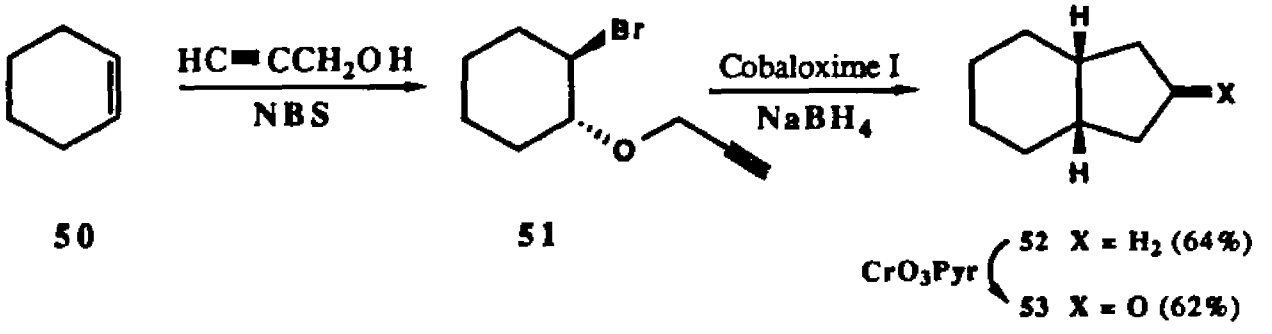
Scheme 17



One important aspect of free-radical cyclizations is the question of maintaining functionality in the product. In almost all the examples presented so far, the cyclizations were terminated by hydrogen atom transfer in a way which reduces the functionality in the product.[50,51]

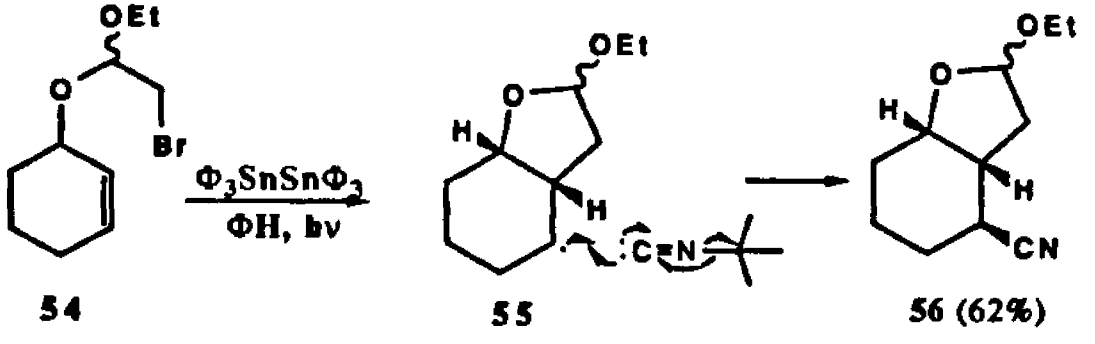
By increasing the unsaturation in the starting material **51** and further manipulation of the product results lactone **53** (scheme 18).

Scheme 18



An interesting example for producing residual functionality, is the regiospecific intermolecular trapping of a radical **56**, arising from cyclization reaction[50] of **55** (Scheme 19).

Scheme 19

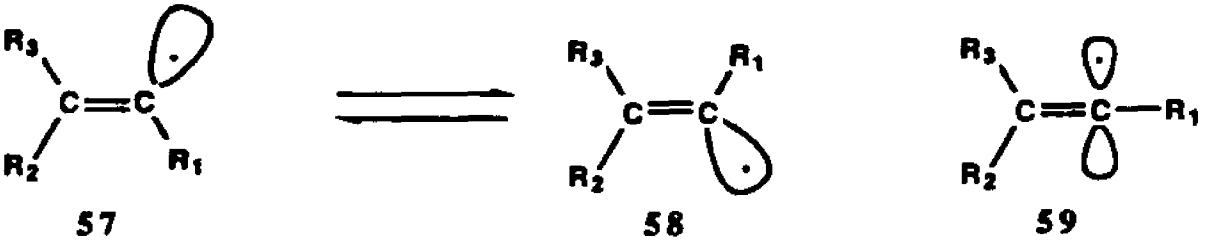


Recent interest in residual functionality has not been restricted to the unsaturated component of radical cyclizations. A number of vinyl radical cyclizations have been reported. The synthetic potential of the vinyl radicals gives us a reason to examine their properties before we describe of their reactions.

2.3.0. The Properties of Vinyl Radicals

Unlike alkyl radicals, relatively little is known about the properties of vinyl radicals. Crude estimates of radical stability are often based upon the dissociation energy of forming a radical from its parent hydrocarbon.[51] Such measurements estimate that the vinyl radical stability is very similar to alkyl radical stability. Extensive studies by ESR spectroscopy[52-55] have shown that vinyl radicals can be classified as either "bent" σ radicals **57** and **58**, or as "linear" π radicals **59** (Scheme 20). The singly occupied molecular orbital (SOMO) of the "bent" σ form possesses substantially more s-character. Both vinyl and 1-methylvinyl radicals have been shown to be of the "bent" σ type. E-Z isomerization of vinyl radicals occurs quite rapidly ($3x10^7$ to $3x10^9$ sec^{-1}), even at -180° C, and is only slightly slower for 1-methylvinyl radical.[30,31] The barrier to inversion has been estimated to be 2 kcal/mol.

Scheme 20



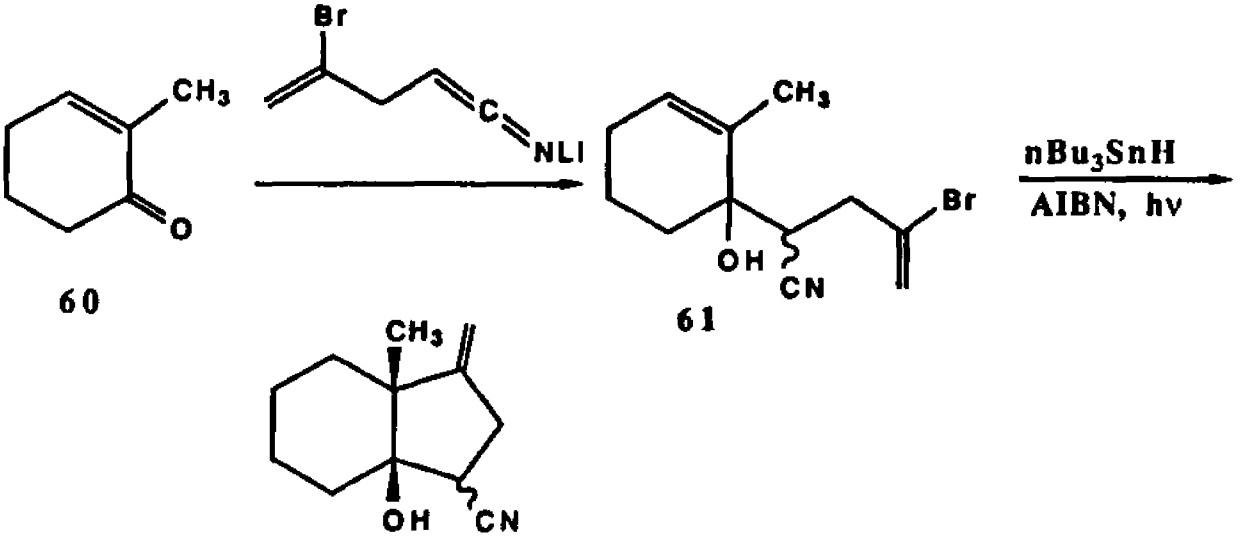
57 **58** **59**

Vinyl radicals that are subjected to steric crowding, or which contain spin-delocalizing groups (e.g. CO_2Me, Ar) are thought to have "linear" π comformations. Trapping studies of 1-methylvinyl and 1-phenylvinyl radicals generated from pure cis- or trans-adducts suggest a rapidly inverting "bent" σ conformation.[56-58,62,63] 1-Halovinyl or 1-methoxyvinyl radicals are also thought to have a "bent" σ conformation, but with much slower inversion rates.[59-61]

2.3.1. Intramolecular Carbocyclization of Vinyl Radicals

Stork has demonstrated a new type of annulation based on the intramolecular addition of vinyl radicals to olefins[62-65] (Scheme 21).

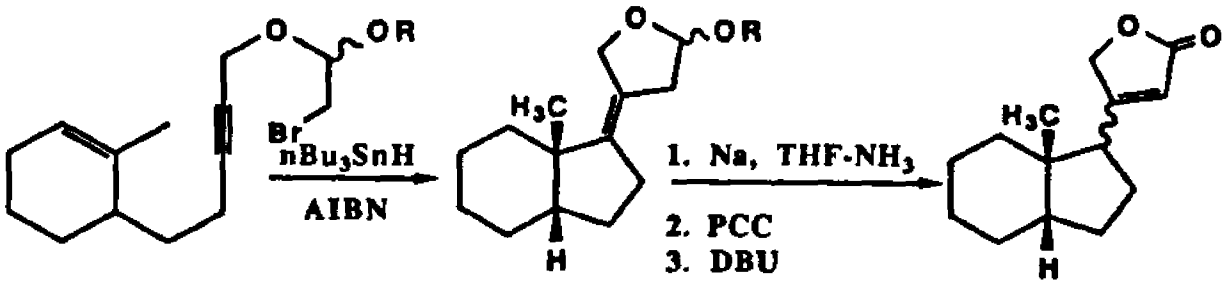
Scheme 21



These reactions, which serve as model studies for a synthetic approach to the cardiac aglycones, have several interesting features. The carbocyclizations produce quaternary centers without complications (Scheme 22). In addition,

the vinylic fragments of **62** and **64** occupy predictable sites in the products and provide a handle for further manipulation.

Scheme 22



63 **64 (75%)** **65 (50%)**

The importance of the methodology for the formation of carbocyclic rings to the synthesis of complex organic molecules has been well recognized.[66] Intramolecular addition of radicals to α,β-unsaturated carbonyl compounds, a reaction type of considerable synthetic potential in carbocyclization, has seen limited use in synthesis of natural products.[47]

REFERENCES

1. Abell, P. I., *Free Radicals*, ed. Kochi, J. K., John Wiley, New York, **1973**, Vol.2, ch. 13.
2. Tedder, J. M.; Walton, J. C., *Adv. Physical Org. Chem.*, **1978**, 16, 86; *Tetrahedron*, **1980**, 36, 701.
3. Minisci, F., *Acc. Chem. Res.*, **1975**, 8, 165.
4. Beckwith, A. L. J.; Ingold, K. U., *Rearrangements in Ground and Excited States*, ed. deMayo, Academic Press, New York, **1980**, Vol. 42-1, pp 182-220.
5. Nonhebel, D. C.; Walton, J. C., *Free Radical Chemistry*, Cambridge Univ. Press, New York, **1974**, ch. 14.
6. Wilt, J. W., *Free Radicals*, ed. Kochi, J. K., John Wiley, New York, **1973**, Vol. 1, pp 418-446.
7. a) Julia, M., *Pure and Applied Chem.*, **1974**, 40, 553; b) Julia, M., *Acc. Chem. Res.*, **1971**, 4, 386; c) Julia, M., *Pure and Applied Chem.*, **1967**, 15, 167; d) Julia, M., *Record of Chem. Prog.*, **1964**, 25, 1.
8. Walton, J. C., et al., *J. Chem. Soc. Perk. Trans. II*, **1975**, 320; *J. Chem. Res.*, **1977**, 5, 18; Tedder, M. H., et al., *J. Chem. Res.*, **1977**, 5, 165.
9. Minisci, F., et al., *Tetrahedron*, **1977**, 33, 793.
10. Mayo, F. R.; Walling, C., *Chem. Rev.*, **1950**, 46, 191.
11. Nonhebel, D. C.; Walton, J. C., *Free Radical Chemistry*, Cambridge Univ. Press, New York, **1974**, ch. 5.
12. a) Fujimoto, H.; Yamade, S.; Minato, T.; Fukui, K., *J. Am. Chem. Soc.*, **1972**, 94, 9205; b) Nagase, S.; Takatsuka, K.; Fueno, T., *ibid.*, **1976**, 98, 3838; c) Hoyland, J. R., *Theor. Chim. Acta*, **1971**, 22, 229; d) Dewar, M.

J. S.; Olivella, S., *J. Am. Chem. Soc.*, **1978**, 100, 5290.

13. Hamann, S. D.; Solomon, D, H.; Spurling, T. H., *Aust. J. Chem.*, **1978**, 29, 1975.
14. a) Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, **1962**; b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A., *Corformational Analysis*, Jonh Wiley, New York, **1965**, p. 19.
15. Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K., *Chem. Comm.*, **1980**, 482.
16. Beckwith, A. L. J.; Moad, G., *J. Chem. Soc. Chem. Comm.*, **1974**, 472.
17. Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K., *J. Am. Chem. Soc.*, **1980**, 102, 1734.
18. Jenking, C. L.; Kochi, J. K., *J. Am. Chem. Soc.*, **1972**, 94, 843.
19. Beckwith, A. L. J.; Blair, I. A.; Phillipou, G., *Tetrahedron Lett.*, **1974**, 2251.
20. Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A., *Tetrahedron*, **1975**, 31, 1737.
21. House, H. O.; Weeks, P. D., *J. Am. Chem. Soc.*, **1975**, 97, 2778.
22. Bartlett, P. D.; Clossen, W. D.; Gogdell, T. J., *J. Am. Chem. Soc.*, **1965**, 87, 1308.
23. Sheldon, R. A.; Kochi, J. K., *Org. React.*, **1972**, 19, 279.
24. Beckwith, A. L. J.; Lawrence, T., *J. Chem. Soc., Perkin Trans II*, **1979**, 1535.
25. Julia, M., *Pure and Applied Chem.*, **1974**, 40, 553; *Acc. Chem. Res.*, **1971**, 4, 386.
26. Julia, M.; Maumy, M.; Mion, L., *Bull. Soc. Chim. Fr.*, **1967**, 2641; Julia, M.; Maumy, M., *Ibid.*, **1969**, 2427.
27. Corfield, G. C., *Chem. Soc. Rev.*, **1972**, 1, 523.
28. Giese, B.; Meixner, J., *Tetrahedron Lett.*, **1977**, 2779.

29. Bonacic-Koutechk, V.; Koutesky, J.; Salem, L., *J. Am. Chem. Soc.*, **1977**, 99, 842.

30. Beckwith, A. L. J.; Moad, G., *J. Chem. Soc., Perkin Trans II*, **1975**, 1726.

31. Beckwith, A. L. J.; Gream, E.; Struble, D. L., *Aust. J. Chem.*, **1972**, 25, 1081.

32. Beckwith, A. L. J.; Phillipou, G., *Chem. Comm.*, **1973**, 280.

33. Pregaglia, G.; Regario, G., *Chem. Ind.* (Milan), **1963**, 45, 1065.

34. Brown, E. D.; Swan, T. W.; Sutherland, J. K.; Torre, A., *J. Chem. Soc., Perkin Trans I*, **1975**, 2326.

35. Breslow, R.; Olin, S. S.; Groves, T. J., *Tetrahedron Lett.*, **1968**, 1837.

36. Julia, M., *Acc. Chem. Res.*, **1971**, 4, 386.

37. Julia, M., *Rec. Chem. Prog.*, **1964**, 25, 1.

38. Julia, M.; Surzur, J.; Katz, L.; LeGoffic, F., *Bull. Soc. Chim. Fr.*, **1964**, 1116, 1122, and 1129.

39. Cekovic, Z., *Tetrahedron Lett.*, **1972**, 749.

40. Chatzopoulos, M.; Monthhead, J. P., C. R. Hebd. *Seances Acad. Sci. Ser. C*, **1975**, 29.

41. Surzur, J. M.; Torri, G., *Bull. Soc. Chim. Fr.*, **1970**, 3070.

42. Sosnousky, G., *Free Radical Reactions in Preparative Organic Chemistry*, Macmillan Co., New York, **1964**.

43. Cotter, R. J.; Matzer, M., *Ring-Forming Polymerization*, Acad. Press, New York, **1969**.

44. de Tar, D. F., *Org. Reactions*, **1957**, 9, 409; Abromovitch, R. A., *Adv. Free Radical Chem.*, **1967**, 2, 87.

45. Buchi, G.; Wuest, H., *ibid.*, **1979**, 44, 546.

46. Danishefsky, S.; Chackalamannil, S.; Uang, B. J., *ibid.*, **1982**, 47, 2231.

47. Hart, D. J.; Chuag, C. P., *ibid.*, **1983**, 48, 1782.

48. Stork, G.; Mook, R.; Biller, S. A.; Rychnousky, S. D., *J. Am. Chem. Soc.*, **1983**, 105, 3741.

49. Stork, G.; Sher, P. M., *J. Am. Chem. Soc.*, **1983**, 105, 6766.

50. Kochi, J. K., *Adv. Free Radical Chem.*, **1975**, 5, 189.

51. Fressenden, R. W.; Schuler, R. H., *J. Chem. Phys.*, **1963**, 39, 2147.

52. Kasai, R. H.; Whipple, E. B., *J. Am. Chem. Soc.*, **1967**, 89, 1033; Nagai, S.; Ohnishi, S.; Nitta, I., *Chem. Phys. Lett.*, **1972**, 13, 379.

53. Griller, D. Copper, J. W.; Ingold, K. U., *J. Am. Chem. Soc.*, **1975**, 97, 4269.

54. Nielson, G. W.; Symons, M. C. R., *J. Chem. Soc., Perkin Trans II*, **1973**, 1405.

55. Kampmeie, J. A.; Fantazier, R. M., *J. Am. Chem. Soc.*, **1966**, 88, 1959 and 5219.

56. Singer, L. A.; Chen, J., *Tetrahedron Lett.*, **1966**, 2089; *J. Am. Chem. Soc.*, **1966**, 88, 513; *Tetrahedron Lett.*, **1969**, 4849.

57. Liu, M. S.; Soloway, S.; Wedegaertner, D. K.; Ranpmeier, J. A., *J. Am. Chem. Soc.*, **1971**, 93, 3809.

58. Chnuki, T.; Yoshida, M.; Simamura, O., *Chem. Lett.*, **1972**, 797.

59. Singer, L. A.; Kong, N. P., *Tetrahedron Lett.*, **1967**, 643; *J. Am. Chem. Soc.*, **1967**, 89, 5251.

60. Kuivila, H. G., *Acc. Chem. Res.*, **1968**, 1, 299.

61. Whitesides, G. M.; Casey, C. P.; Krieger, J. K., *J. Am. Chem. Soc.*, **1971**, 93, 1379.

62. Stork, G., *Current Trends in Organic Chemistry*, ed. Nozaki, H., Pergamon, New York, **1983**, p 359.

63. Stork, G.; Williard, P. G., *J. Am. Chem. Soc.*, **1977**, 99, 7067.

64. Stork, G.; Baine, N. H., *ibid.*, **1982**, 104, 2321.

65. Stork, G.; Mook, R., *ibid.*, **1983**, 105, 3720.

66. Nonhebell, D. C.; Walto, J. C., *Free Radical Chemistry*, Cambridge Univ. Press, New York, 1974, ch. 5.

CHAPTER 3

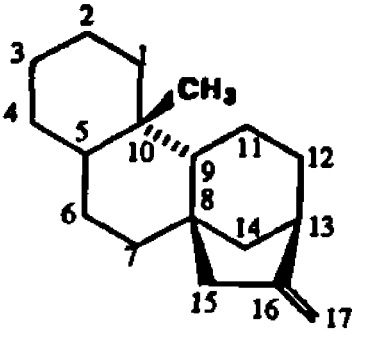
3.0.0. Introduction

The three-dimensionality of the chemical science is what for more than a century fascinated organic chemists. However, it has been during recent decades that the challenge of stereochemical control has come to the forefront of synthesis. The state of this art has become spectacularly sophisticated, notably in the construction of rigid well understood systems. What has evolved is the methodology for the stereocontrolled elaboration of cyclic bridged molecules. This area has become increasingly important as organic chemists focus their attention on the synthesis of natural products.

The striking biological properties and novel structural features of terpenes, diterpenes, terpenoids, and diterpenoids attracted the attention of organic chemists and serious intensive efforts commenced with the eluciation of the structure of several members of each of the above naturally existing families of organic molecules.

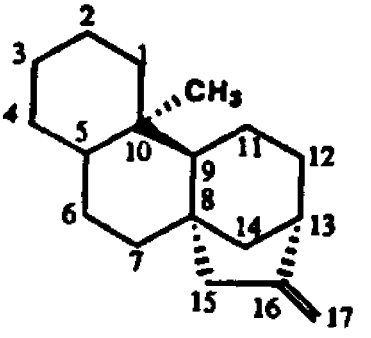
Kaurene **1** and ent-kaurene **2** derived diterpenoids are gibberellic acid **3** and shikodonin **4** respectively. Perhaps worthy of note is the presence in the gibberellin and shikodonin skeletons of the unusual bicyclo[3.2.1]octane unit, which has stimulated the design of many ingenious methods for the construction of such systems.

Scheme 1



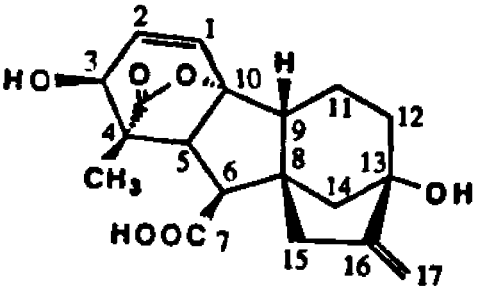
Kaurene

1



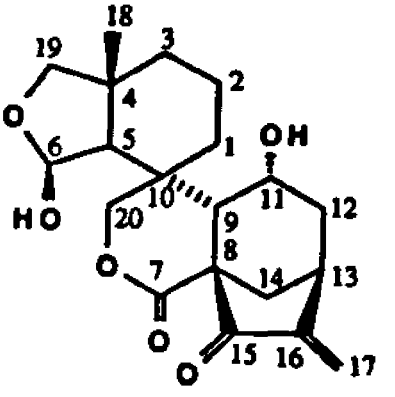
ent-Kaurene

2



Gibberellic acid

3



Shikodonin

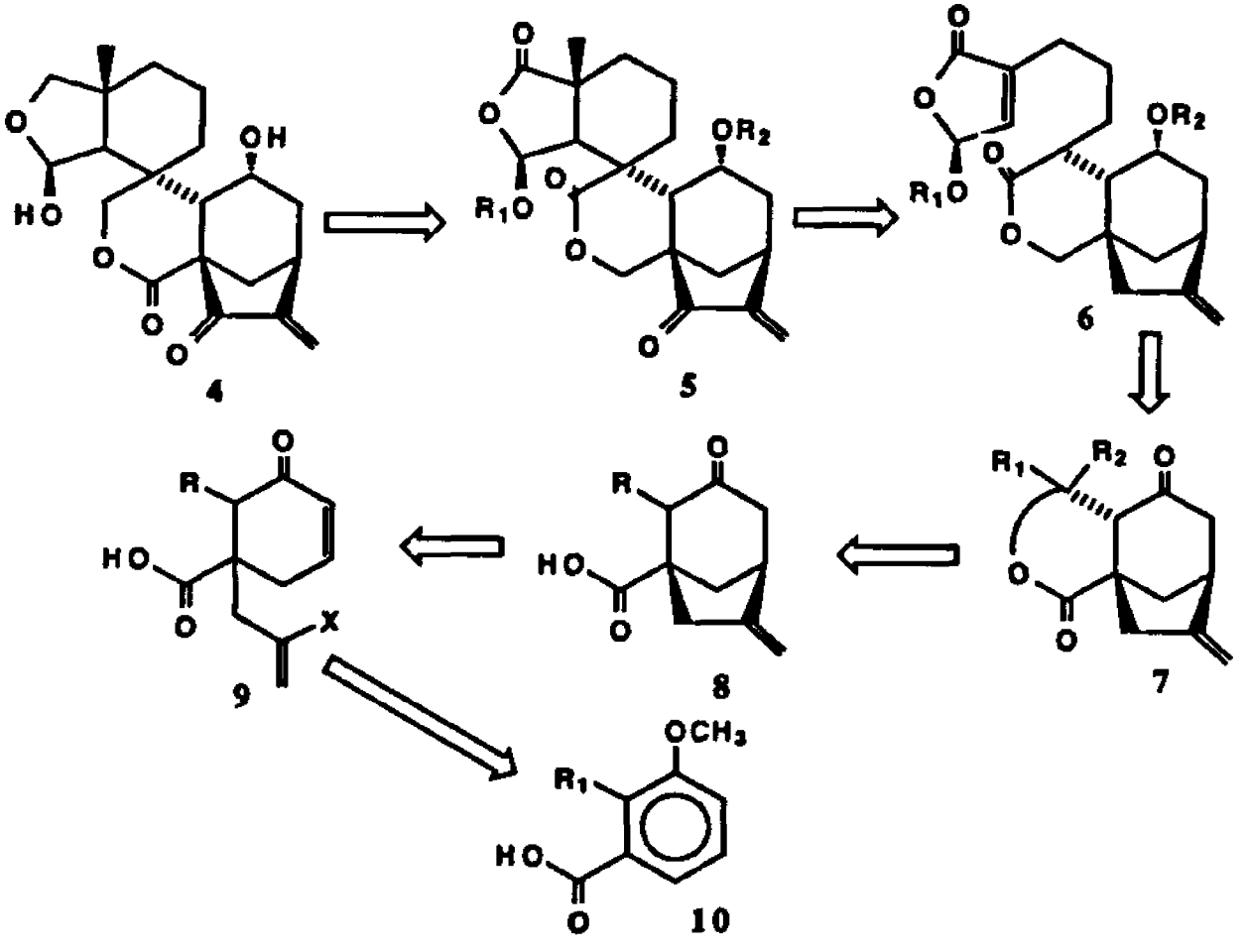
4

Our attempt includes a novel approach to the stereocontrolled synthesis of the bicyclo[3.2.1]octane unit and specifically focuses on the synthesis of a fragment (precursor) planned to be used for the total synthesis of shikodonin. In addition to the bicyclo[3.2.1]octane unit, shikodonin is of interest in that it is the first instance of an ent-kaurene type diterpenoid oxygenated at C-19 along with the unique spirosecokaurene structure.

3.1.0. Retrosynthetic analysis of shikodonin.

Our retrosynthetic analysis is shown in Scheme 2. Intramolecular Michael addition and methylation of developed carbanion of ester **6** should construct ring A giving ester **5**. Ester **6** should be available from the proper manipulation of the tricyclic ketone ester **7**. The key step in the synthesis involves the formation of a vinyl radical by trialkyltin hydride mediated homolysis of a vinyl halide **9** , followed by intramolecular addition to the stereoproximal alkene moiety and a hydrogen transfer to the addend radical, to give intermediate **8**.

Scheme 2



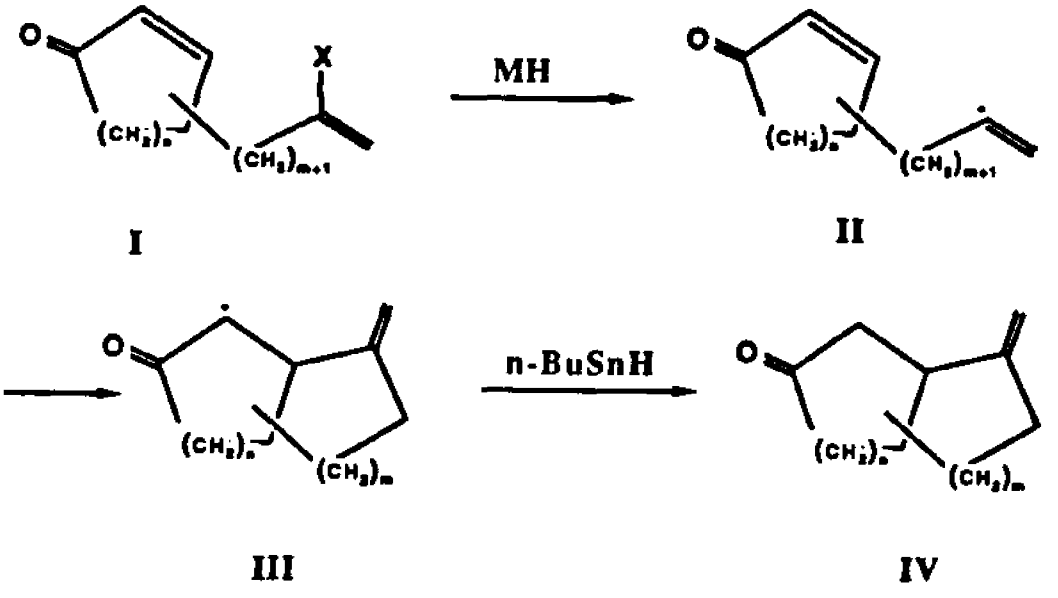
The structure of shikodonin includes eight chiral centers and the B and C rings of it join in cis-fusion. Unfortunately, in the BCD tricyclic system of shikodonin the cis-fused isomer is expected to be considerably more strained than the trans-isomer, and this point has important consequences in the chemistry of molecules incorporating this system. As we said, earlier, our purpose for this investigation was to construct a fragment which would include primarily the bicyclo[3.2.1]octane unit.

3.2.0 Presentation of the Problem

Our approach (Scheme 3) involved formation of a vinyl radical **II** by trialkyltin hydride[1,2] mediated homolysis of a vinyl halide **I**, followed by an internal addition to a stereoproximal acceptor alkene moiety and a hydrogen transfer to the addend **III**. A synthetically useful feature of this approach to carbocyclization is that the chemoselectivity of an organostannane assured the compatibility of the α,β-unsaturated carbonyl moiety until homolytic cleavage. The efficiency of ring formation is enhanced by the kinetic preference of vinyl radical **II** to undergo addition to an acceptor alkene moiety over transfer of the hydrogen atom from the organostannane,[3] and by effective delocalization[4] of the free spin by the adjacent carbonyl group in the addend radical **III**.

Such vinyl radical carbocyclizations offer tremendous potential for the total syntheses of natural products having complex ring systems. Moreover, the vinyl group introduced into the newly formed ring can provide a useful "handle" for a large variety of functional group transformations.

Scheme 3



I II III IV

After our literature research left us with a better understanding of the cyclization properties of alkyl and vinyl radicals, we were prepared to initiate an investigation of the intramolecular carbocyclization of vinyl radicals. This led to the synthesis of a key intermediate for the total synthesis of shikodonin.[5]

A significant part of our investigation includes the development of simple and general methods for gaining access to starting materials **9** that are properly constituted to undergo the radical ring closure. The effort of the preparation of such materials demonstrated the value of the Birch reduction-alkylation in the construction of the required properly substituted cyclohexenones.

REFERENCES

1. Stork, G., *Current Trends in Organic Chemistry*, ed. Nozaki, H., Pergamon, New York, **1983**, p 359.
2. Stork, G.; Williard, P. G., *J. Am. Chem. Soc.*, **1977**, *99*, 7067.
3. Stork, G.; Baine, N. H., *ibid.*, **1982**, *104*, 2321.
4. Stork, G.; Mook, R., *ibid.*, **1983**, 105, 3720.
5. Kubo, I. Pettei, M. J.; Hirotsu, K.; Tsujo, H.; Kubotah, T., *J. Am. Chem. Soc.*, **1980**, *45*, 4765.

CHAPTER 4

4.0.0. Introduction

Several naturally occuring compounds, especially a wide variety of important diterpenes, contain a bicyclo[3.2.1]octane system with a diversity of substitution patterns and stereochemistry.[1]

Among the different features of the synthesis of such systems, the phase in which the carbocyclic framework is assembled represents, in general, the most salient aspects of the sequence. We have therefore made the decision to center the discussion around the key-steps involved in constructing a bicyclic or tricyclic system. Secondly we will indicate the transformations leading to the crucial precursors.

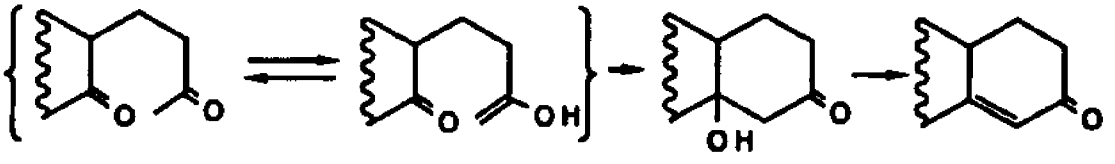
Annulation methods, during which a ring is attached on a pre-existing system, are generally recognized as such when the two new carbon-carbon bonds are formed in time-related processes. They can be simultaneous, consecutive or separated by only the few functionalization steps necessary for the final cyclization.

Although there are many routes to substituted bicyclo[3.2.1]octane systems, only few proceed with high stereoselectivity.[2] Recently, we devised new stereoselective preparations of substituted bicyclo[3.2.1]octanes. Here we describe the stereocontrolled synthesis of such systems starting with appropriately substituted aromatic compounds.

4.1.0. Preparation of a,b-unsaturated ketones

Our initial investigation of stereocontrolled synthesis of bicyclo[3.2.1]-octane systems began with the efforts leading to the synthesis of a,b-unsaturated cyclohexenones. Such enones are traditionally obtained[3] through the route 1 2 3, (Scheme 1), as well as by a Birch reduction of an appropriate substituted aromatic ether system (see scheme 3, chapter 1). Aromatic ethers containing a variety of substituents are quite easily, and regiospecifically prepared, and so the synthesis of enones from these systems, by Birch reduction, is synthetically advantageous. Accordingly, we describe below (i) the synthesis of systems such as 3; and (ii) the use of such systems in a new synthesis of bicyclo[3.2.1]octanes.

Scheme 1



1 **2** **3**

4.1.1. Reductive alkylation of 3-methoxybenzoic acid 4 and 3-methoxy-4-methylbenzoic acid 8

Convergent synthetic routes to the vinyl halide starting materials have been developed (Table 1). Thus, the Birch reduction and alkylation in situ of *m*-anisic acid 4 was a fast and easy method for the preparation of 1,4-cyclohexadiene derivatives.[4] Under standard reductive alkylation conditions,

which constituted the application of lithium, as a reducing metal, in a mixture of liquid ammonia and tetrahydrofuran in a 2:1 ratio, *m*-anisic acid gave compounds **5** in very good yields (Scheme 2). The interesting point we found, contrary to the one established in the literature,[4] is that we had no need for use of any other proton source beyond the proton provided by the benzoic acid itself. That indicates that the solvated electrons in ammonia react faster with the aromatic system than with the ammonium ion. Thus, the ammonium ion was the the source of the proton needed for the quenching of the developed radical anion during the reduction. The subsequent hydrolysis of **5** in a mixture of 2:1 THF:10% HCl_{aq} provided a,b-enone acids **6** via the unconjugated ketone **6a**. Treatment of **6** with diazomethane afforded the precursors of the bridge systems **7c**, **7d** and **7e**. Vinyl iodide **7e** was obtained upon alkylation of 1-carbomethoxy-3-methoxy-1,4-cyclohexadiene **5a** with 2-iodo-3-bromopropene[5] followed by treatment with acid.

Scheme 2

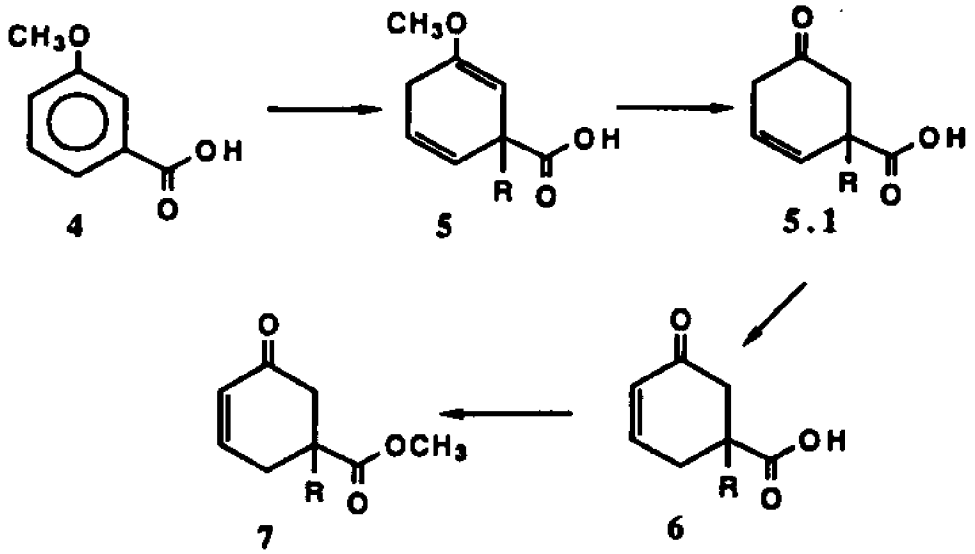
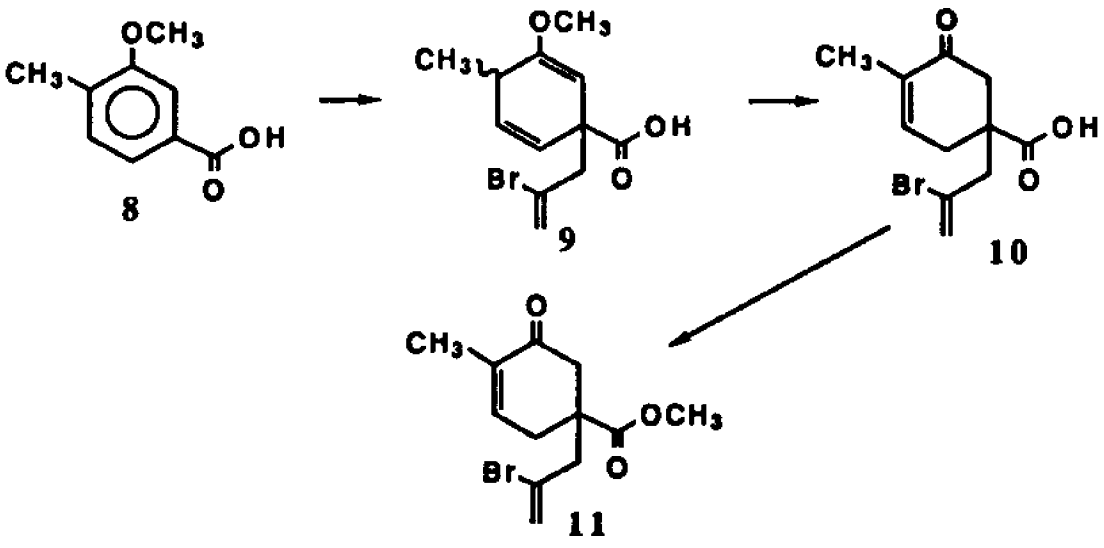


Table 1. Synthesis of α,β-unsaturated ketone derivatives

R	% yields of 7	
H-	93	a
CH_2=$CHCH_2$-	89	b
CH_2=$CClCH_2$-	86	c
CH_2=$CBrCH_2$-	77	d
CH_2=$ClCH_2$-	73	e
CH_3OOCCH_2-	83	f
$^tBuOOCCH_2$-	75	g
$PhCH_2OCH_2$-	78	h
HC≡CCH_2-	82	i
$CH_3CH_2OOCH_2$-	91	k

Scheme 3



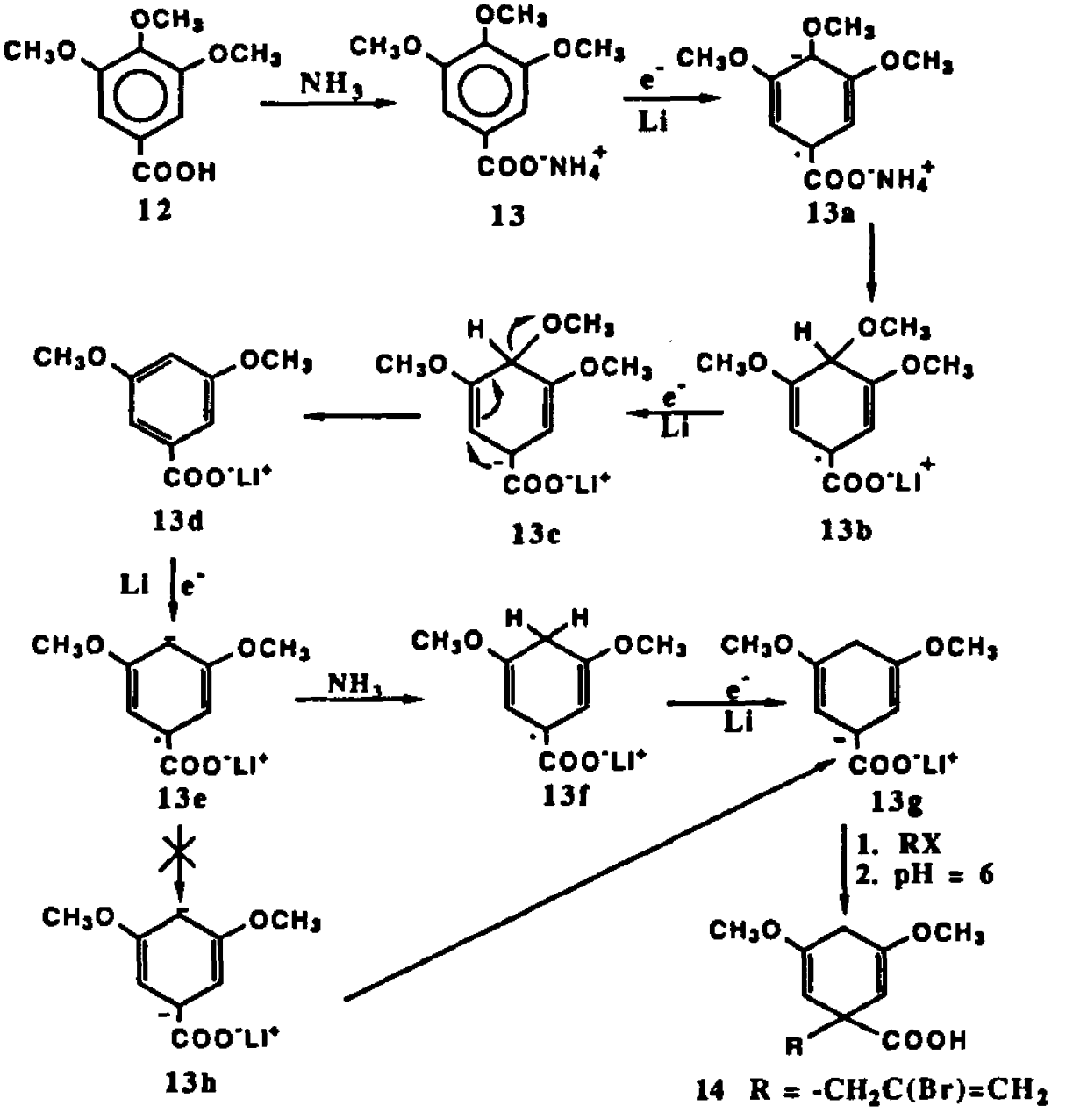
Similarly the substituted enone **11** was prepared in 75% overall yield from 3-methoxy-4-methyl-benzoic acid **8** (Scheme 3). The 1H NMR spectrum of the cyclohex-1,4-diene derivative **9** indicates that the developed carbanion after reduction is alkylated preferentially from the same side of the methyl group to give a 3:1 mixture of diastereoisomers of diene **9**. The explanation is that the carbanion is in the form of aggregates, leaving mostly the side with the methyl group pointing outside and therefore the observed ratio of isomers is resulted. In Chapter 9 the phenomenon of aggregation is well described and appears to be of a great synthetic importance.

4.1.2. Reductive alkylation of 3,4,5-trimethoxybenzoic acid 12

Several other new compounds were prepared[6] through reductive alkylation of 3,4,5-trimethoxybenzoic acid **12**. The mechanism of the reduction of the above compound is outlined below (Scheme 4). The ammonium benzoate **13** accepts an electron to give radical anion **13a** which is protonated by the proton provided by the ammonium salt to give the radical intermediate **13b** which subsequently accepts a second electron leading to **13c** which collapses to 3,5-dimethoxybenzoic acid lithium salt **13d** by extrusion of the methoxy group in the *para*-position. The compound **13d** begins a second cycle of reduction giving radical anion **13e** which is protonated by the ammonia to give **13f**. This indicates that the relative basicity of radical anion **13e** is higher than the basicity of ammonia. The following addition of an electron developed the carbanion **13g** which was alkylated in *situ* . After removal of ammonia and subsequent acidification (pH=6) the 1,4-cyclohexadiene derivative **14** was produced. The addition of an electron to

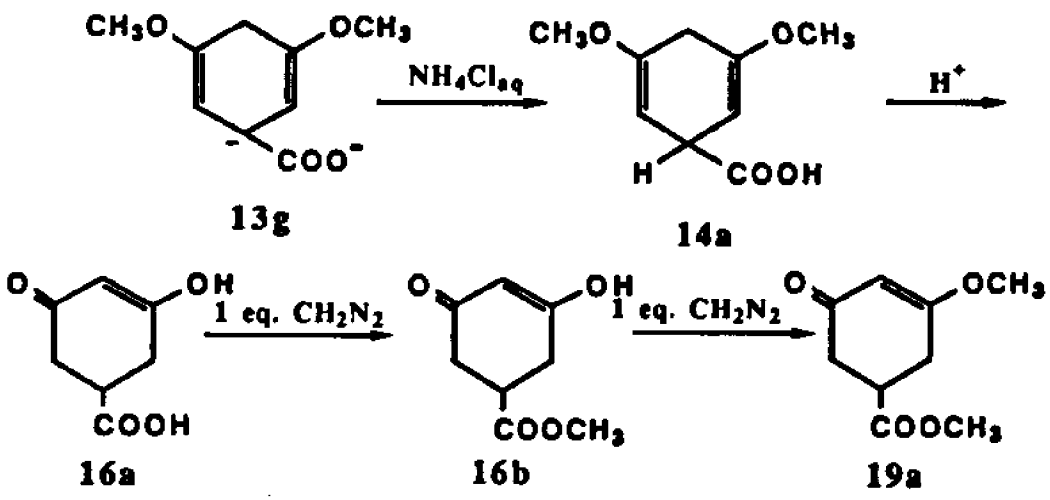
13e would have generated an antiaromatic intermediate 13h, which would be further destabilized by the two electron donating methoxy groups.

Scheme 4



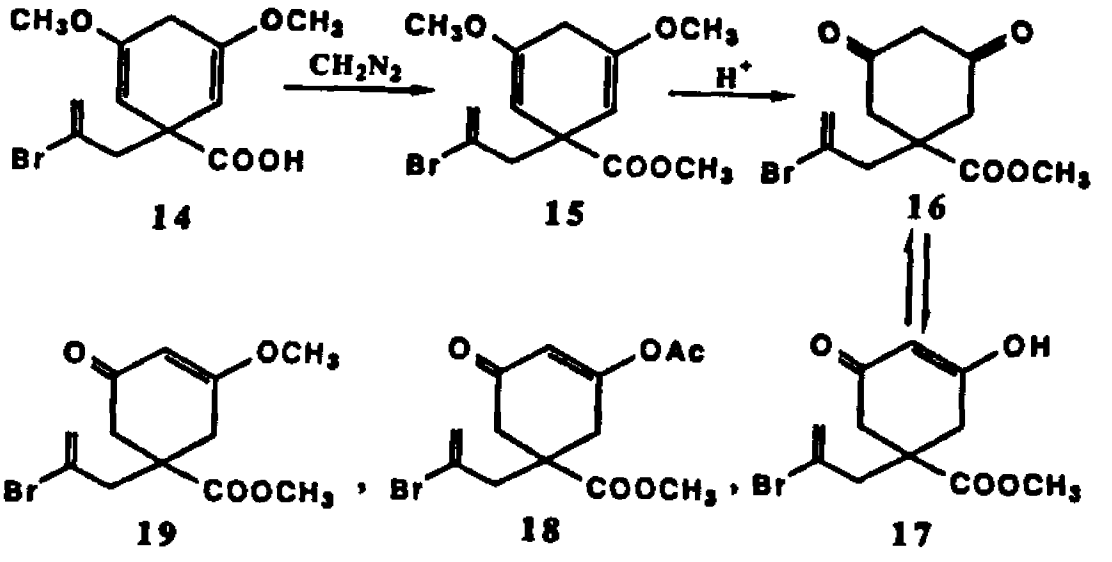
Carbanion **13g** was also quenched with a large excess of ammonium chloride saturated aqueous solution to give **14a** (R=H) which was then hydrolyzed and esterified with diazomethane to give **19a**. Two equivalents of diazomethane were required; the first one reacts with the carboxylic group to give the methyl ester and the second one reacts with the β-hydroxy enone to give β-methoxy enone. This was produced after an excess of diazomethane was used for the esterification of the carboxylic acid **16a** (Scheme 5).

Scheme 5



Compound **14** was esterified with diazomethane to give the methyl ester **15** (Scheme 6) which was then hydrolyzed to diketone **16**. This diketone existed in the enol form **17** in diethyl ether. The β-hydroxyl α,β-unsaturated ketone **17** provided compounds **18** and **19** by treatment with acetic anhydride and diazomethane respectively.

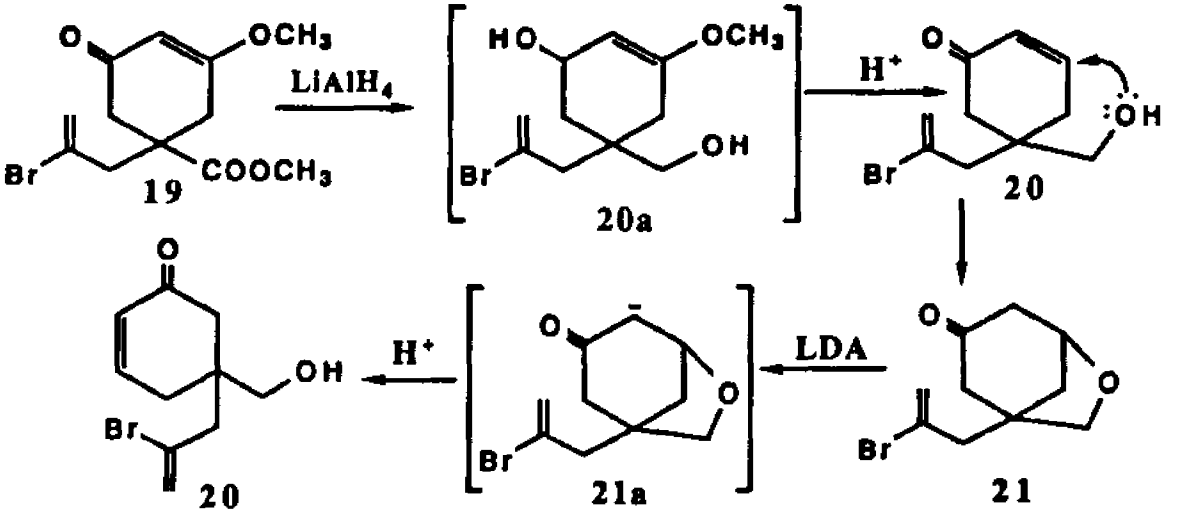
Scheme 6



Reduction of **19** with lithium aluminum hydride following by acidic hydrolysis[7] provided the alcohol **20**, which cyclized through intramolecular Michael addition, to compound **21** during the acidic work-up (Scheme 7).

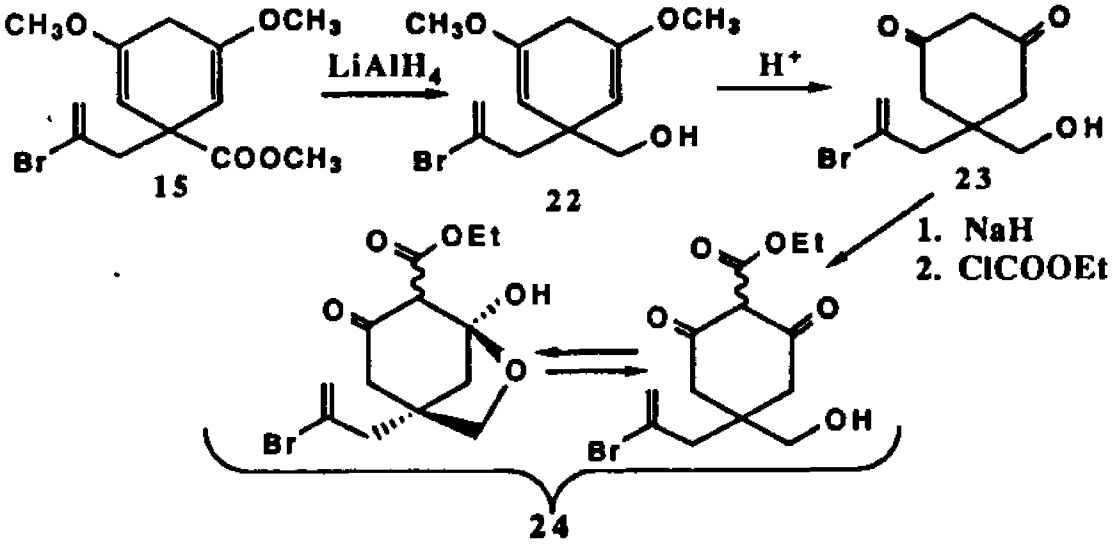
Compound **20** was recovered from **21** by treatment with lithium diisopropylamide and slowly neutralized to pH=7 at which **20** was stable. For that reason, in order to avoid wasting time and material, compound **20** was used without purification for the next reaction step as we will see in the following chapter.

Scheme 7



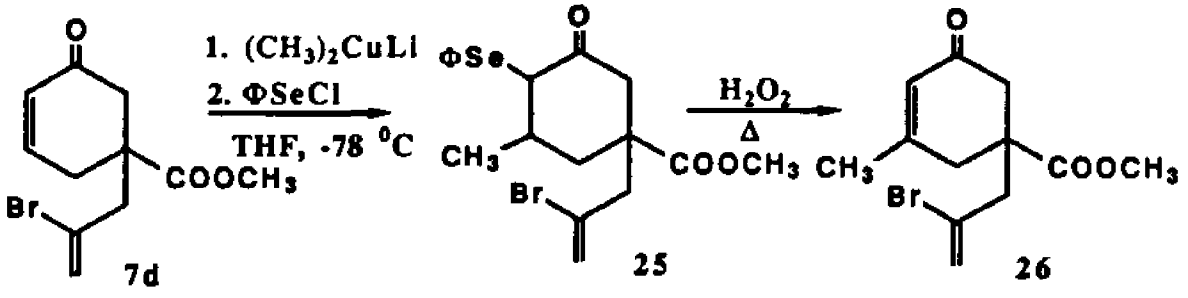
Compound **15** was reduced using lithium aluminum hydride to the alcohol **22**, which then was hydrolyzed to the diketone **23**. Treatment of **23** with NaH in THF at -20° C followed by addition of equivalent of ethyl chloroformate gave compound **24** in 74% yield (Scheme 8). There are two possible alkylations, the C-alkylation and the O-alkylation. The ^1H NMR suggests that the product is the one derived from C-alkylation.

Scheme 8



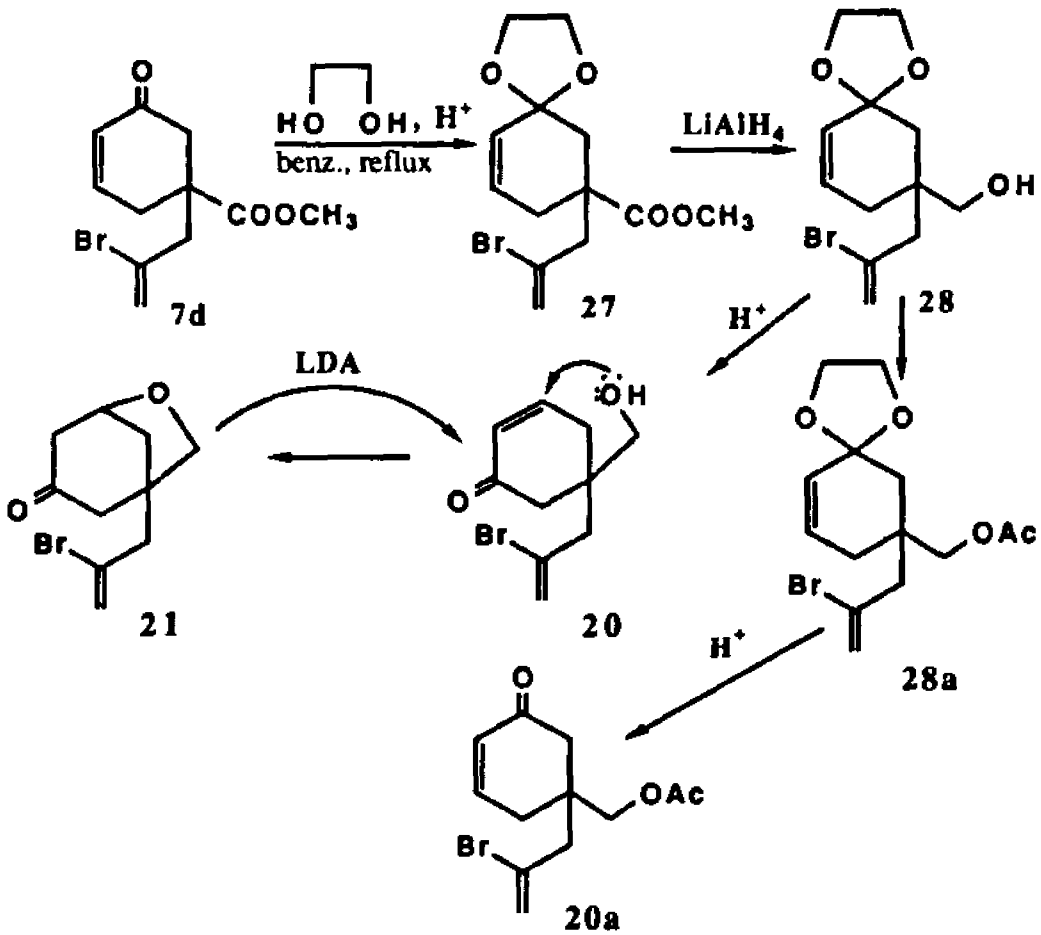
Compound **7d** was treated with lithium dimethylcuprate and quenched with phenyl selenium bromide[8] to give **25** which was then oxidized and heated to 100° C for an hour to provide compound **26** (Scheme 9).

Scheme 9



Compound **7d** was treated with ethylene glycol in refluxing benzene with a catalytic amount of PTSA to give ethylene ketal derivative **27** which then was reduced with lithium aluminum hydride to compound **28**. During hydrolysis of **28** in acidic conditions, compound **20** was converted to **21** and was recovered by treatment of **21** with base and slow acidification to pH=6 (Scheme 10).

Scheme 10



EXPERIMENTAL

General. Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton nuclear magnetic resonance (1H) spectra were determined on a Varian EM-360A (60 MHz), or on a IBM NR/300 FT NMR (270 MHz), or on a IBM WP/200-SY (200 MHz), and or on a JEOL/JNM/GX-400 FT NMR spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=double, t=triplet, q=quarter, m=multiplet, br=broad), assignment, integration, coupling constant. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer and on Finnigan CH5 single focusing mass spectrometer. Thin-Layer chromatography (TLC) was performed with 13181 silical gel with fluorescent indicator (Kodak) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silical gel 60 mesh. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY).

Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Birch reduction-alkylation of 3-methoxybenzoic acid.

Procedure A.

A 250-mL three-necked round-bottomed flask equipped with a dry ice-acetone condenser, was charged with *m*-methoxybenzoic acid **4** (1.52 g, 10.0 mmol) in 20 mL freshly distilled tetrahydrofuran under nitrogen atmosphere. To the above 55 mL solution ammonia, distilled over sodium metal at -78° C, was added. The reaction mixture became a clear solution and lithium metal, washed successively with hexane, methanol and hexane was added in small pieces at -78° C until the blue color persisted. The temperature was then raised to -33° C (refluxing ammonia) and the solution was stirred for 30 more minutes. The solution was again cooled down to -78° C, and 1.1 equivalents of 3-bromopropene, dissolved in 5 mL dry tetrahydrofuran, was injected into it, through a rubber septum. The solution was then allowed to warm up to room temperature in a working hood. After all ammonia evaporated, the solvent was removed by a rotary evaporator and the residue was dissolved in 20 mL of water. The aqueous solution was extracted three times with 20 mL-portions of ether and the extractions were discarded. The aqueous layer was transfer into a 500 mL Erlermeyer flask and 100 mL of ethyl acetate was added to it.

The cooled, magnetically stirred mixture was slowly acidified with 10% HCl_{aq} to pH=6.5 at 0° C. The stirring solution was then saturated with NaCl. At that point the entire mixture was transferred to a separatory funnel and it was extracted three times with 100 mL-portions of ethyl acetate. The combined organic extractions were washed twice with 50 mL-portions of water and once with 100 mL of brine and dried over magnesium sulfate. After filtration the solvent was removed by rotary evaporator, and dried under high vacuum to afford 1.92 g crude product **5b**. The crude product was

immediately submitted for hydrolysis by dissolving it in 20 mL of a mixture of THF:10% HCl_{aq} (2:1 ratio) and the solution was stirred for 6 hours at room temperature. The hydrolysis was monitored by TLC (1:2 ethyl acetate:hexane, $R_f = 0.8$ to $R_f = 0.4$) every half hour until all starting material was gone. To the reaction mixture was then added aqueous saturated solution of $NaHCO_3$ until the pH = 5.0 and then it was extracted again with three 50 mL-portions of ethyl acetate. The combined organic extract was dried over magnesium sulfate, and after filtration the solvent was removed by evaporation. The crude carboxylic acid derivative **6b** was then dissolved in 50 mL anhydrous diethyl ether and esterified using freshly prepared diazomethane solution in diethyl ether. After the solvent was removed the crude product was purified by column chromatography to afford 1.59 g of 1-methoxycarbonyl-1-propenyl-cyclohex-4-enone-3 **7b** (82% yield from 3-methoxybenzoic acid).

Identical procedures of Birch reduction-alkylation and hydrolysis were applied using different alkylation reagents (1.1 equiv) which provided analogous compounds useful for our research investigation. Analytical data for each of these compounds is given below. All reactions were run with 1.52 g of *m*-methoxybenzoic acid and yields, in brackets, are reported accordingly.

Compound **7b** (89%): ^1H NMR (60 MHz, $CDCl_3$, ppm): 6.85 (dt, 1H, J = 10 Hz, J = 4 Hz), 5.92 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.82-5.40 (m, 1H), 5.18 (s, 1H), 4.98 (dd, 1H, J = 7 Hz, J = 3 Hz), 3.65 (s, 3H), 3.0-2.1 (m, 6H); IR (neat, cm^{-1},): 3080 (w), 3030 (w), 2950 (m), 2900 (m), 2840 (m), 1725 (s), 1675 (s), 1635 (m), 1615 (w), 1440 (m), 1380 (m), 1335 (s), 1200 (s), 915 (m), 725 (m); mass spectrum, *m/z*: 194 (M), 162, 135, 107, 93, 91, 79, 59, 41, 40, 39 (100%); mass spectrum, exact mass calcd for $C_{11}H_{14}O_3$ *m/e* 194.0943, obsd *m/e* 194.0944.

Compound **6c** (90%): m.p. 150-151° C; 1H NMR (60 MHz, $CDCl_3$, ppm) 11.40-10.90 (br, 1H), 6.85 (dt, 1H, J = 10 Hz, J = 4 Hz), 5.90 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.23 (d, 1H, J = 1.5 Hz), 5.15 (br, 1H), 3.05-2.20 (m, 6H). Anal. Calcd for $C_{10}H_{11}O_3Cl_1$: C, 55.96; H, 5.17. Found: C, 55.48; H, 5.48.

Compound **7c** (86%): m.p. 75-76° C; ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 6.85 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.05 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.30 (d, 1H, J = 1.5 Hz), 5.15 (br, 1H), 6.67 (s, 3H), 3.15-2.3 (m, 6H); IR (sol. in $CHCl_3$, cm^{-1}) 3025 (w), 3000 (m), 2950 (m), 1725 (s), 1675 (s), 1630 (m), 1435 (m), 1385 (m), 1335 (m); mass spectrum, *m/z*: 230 (M^+, ^{37}Cl), 228 (M^+, ^{35}Cl), (230/228 = 1/3), 193, 153, 107, 91, 68, 41, 39. Anal. Calcd for $C_{11}H_{13}O_3Cl_1$: C, 57.78; H, 5.73. Found: C, 57.74; H, 5.65.

Compound **5d** (85%): ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 11.80 (s br, 1H), 5.85 (m, 2H), 5.50 (m, 2H), 4.80 (s br, 1H), 3.60 (s, 3H), 2.90 (s, 2H), 2.70 (s br, 2H).

Compound **6d** (79%): m.p. 180-181° C; ^{13}C NMR (200 MHz, $CDCl_3$, ppm, coupling) 196.43 (s), 174.22 (s), 147.27 (d), 128.90 (d), 125.00 (d), 126.51 (s), 118.58 (d), 52.39 (q), 48.19 (t), 44.58 (t), 33.78 (t); IR (KBr, cm^{-1}): 3250-2500 (br), 1715 (s), 1650 (m), 1640 (m), 1625 (w), 1450 (m), 1375 (m); ^{1}H NMR (60 MHz,$CDCl_3$, ppm): 10.85 (br, 1H), 6.95 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.10 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.55 (s, 2H), 3.10-2.25 (m, 6H). Anal. Calcd for $C_{10}H_{11}O_3Br_1$: C, 46.34; H, 4.28. Found: C, 46.42; H, 4.53.

Compound **7d** (77%): m.p. 108-109° C; ^{1}H NMR (60 MHz,$CDCl_3$, ppm) 6.95 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.10 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.55 (s, 2H), 3.65 (s, 3H), 3.10-2.25 (m, 6H); IR (sol. $CHCl_3$, cm^{-1}): 3050 (w), 3010 (m), 2960 (m), 1735

(s), 1690 (s), 1625 (m), 1440 (m), 1390 (m), 1340 (m), 1220 (s); mass spectrum, *m/z*: 275 (M^++1, ^{81}Br), 274 (M^+, ^{81}Br), 273 (M^++1, ^{79}Br), 272 (M^+, ^{79}Br), 225, 223, 193 (M^+ - Br, 100%), 153, 107, 105, 91, 79, 59, 41, 40, 39. Anal. Calcd for $C_{11}H_{13}O_3Br_1$: C, 48.37; H, 4.80. Found: C, 48.55; H, 5.02.

Compound **7f** (83%): ^1H NMR (60 MHz, $CDCl_3$, ppm): 6:90 (dt, 1H, J = 10 Hz, J = 4 Hz, 6.00 (dt, 1H, J = 10 Hz, J = 2 Hz), 3.65 (s, 3H), 3.60 (s, 3H), 3.15 - 2.30 (m, 6H); IR (neat, cm^{-1}): 3020 (w), 2955 (m), 2845 (w), 1740 (s), 1720 (s), 1685 (s), 1620 (m), 1440 (m), 1385 (s), 1365 (m); mass spectrum, *m/z* (relative intensity) 227 (M^++1, 1), 153 (100), 107 (100), 79 (97), 68 (99), 59 (99), 43 (79), 40 (100), 39 (100); mass spectrum, exact mass calcd for $C_{11}H_{14}O_5$ *m/e* 226.0841, obsd *m/e* 226.0845.

Compound **7g** (75%): mp 48-49° C; ^1H NMR (60 MHz, $CDCl_3$, ppm): 6.85 (dt, 1H, J = 10 Hz, J = 4 Hz), 5.95 (dt, 1H, J = 10 Hz, J = 2 Hz), 3.65 (s, 3H), 3.10 - 2.20 (m, 6H), 1.41 (s, 9H); IR ($CHCl_3$, cm^{-1}): 3025 (w), 3000 (m), 2980 (m), 2950 (w), 1735 (s), 1720 (s), 1680 (s), 1615 (m), 1435 (m), 1385 (m), 1365 (m); mass spectrum, *m/z* (relative intensity) 268 (M^+, traces), 153 (94), 107 (100), 68 (99), 57 (99), 43 (100), 41 (100), 40 (100), 39 (100); mass spectrum, exact mass calcd for $C_{14}H_{20}O_5$ *m/e* 268.1310, obsd *m/e* 268.1306.

Compound **6h** (80%): mp 96-97° C; ^1H NMR (60 MHz, $CDCl_3$, ppm): 10.10 (br, 1H), 7.30 (s, 5H), 6.85 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.05 (dt, 1H, J = 10 Hz, J = 2 Hz), 4.50 (s, 2H), 3.60 (s, 2H), 3.15 - 2.40 (m, 6H); IR ($CHCl_3$, cm^{-1}): 3400-2500 (s, br), 1710 (s), 1680 (s), 1620 (w), 1500 (m), 1455 (m), 1435 (m), 1415 (m), 1385 (m), 1365 (m); mass spectrum, *m/z* (relative intensity) 274 (M^+, 5), 243 (2), 153 (11), 91 (55), 85 (90), 83 (100), 47 (89).

Compound 7h (78%): ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 7.30 (s, 5H), 6.85 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.05 (dt, 1H, J = 10 Hz, J = 2 Hz), 4.50 (s, 2H), 3.65 (s, 3H), 3.55 (s, 2H), 3.10 - 2.35 (m, 6H); IR (neat, cm^{-1}): 3090 (w), 3070 (w), 3030 (m), 3000 (m), 2950 (m), 2900 (m), 2860 (w), 1735 (s), 1680 (s), 1620 (m), 1500 (s), 1455 (m), 1435 (m), 1410 (m), 1385 (m), 1365 (m), 1330 (m), 1300 (m); mass spectrum, exact mass calcd for $C_{16}H_{18}O_4$ *m/e* 274.1205, obsd *m/e* 274.1210.

Compound 7i (82%): ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 6.95 (dt, 1H, J = 10 Hz, J = 4 Hz), 5.95 (dt, 1H, J = 10 Hz, J = 2 Hz), 3.70 (s, 3H), 3.05 - 2.50 (m, 6H), 2.25 (t, 1H, J = 3 Hz); IR (neat, cm^{-1}): 3300 (s), 3050 (w), 2950 (m), 2900 (m), 2850 (w), 2125 (w), 1730 (s), 1680 (s), 1620 (w), 1440 (m), 1385 (m), 1340 (m); mass spectrum, *m/z* (relative intensity) 193 (M^++1, 30), 192 (M^+, 9), 153 (26), 133 (74), 105 (100), 104 (100), 93 (82), 79 (93), 77 (97), 68 (94), 59 (99), 41 (100), 40 (100), 39 (100); mass spectrum, exact mass calcd for $C_{11}H_{12}O_3$ *m/e* 192.0786, obsd *m/e* 192.0783.

Compound 5a (98%) after esterification with diazomethane: ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.80 (s, br, 2H), 4.7 (br, d, 1H, J = 3.5 Hz), 3.85 (m, 1H), 3.65 (s, 3H), 3.55 (s, 3H), 2.75 (br s, 1H), 2.60 (br s, 1H).

Synthesis of 1-methoxycarbonyl-1-(2-iodoprop-2-enyl)-cyclohex-4-en-3-one, 7e.

A 50 mL three-necked round bottom flask equipped with a condenser and a magnetic bar was charged with 0.77 mL (0.56 g, 5.5 mmol) dried diisopropylamine in 11 mL dried THF. The reaction flask was cooled to -78° C in a dry-ice acetone bath and then 5.0 mL (5.25 mmol) of 10.5 M solution of n-butyl lithium in hexane was injected through a rubber septum. The solution

was stirred for 30 min before a dropwise addition of 0.84 g (5.0 mmol) of methyl ester of **5a** dissolved in 10mL of THF. The reaction mixture was stirred for 45 min at -20° C and then after it was cooled to -78° C, 1.36 g (5.50 mmol) of 2-iodo-3-bromopropene in 5 mL of THF was added dropwise. The temperature was raised slowly to 0° C over 30 min period of time and the reaction mixture was continuously stirred for another hour. After 30 min stirring at room temperature 15 mL of saturated ammonium chloride was added and the solvent was removed by rotary evaporator. The residue was extracted with three 25 mL-portions of ethyl acetate and the combined extracts was dried over magnesium sulfate, filtered, concentrated, and purified by column chromatography (1:1 ethyl acetate : hexane, R_f = 0.3) to afforded 1.15 g (80% yield) of the methyl ester of **5e**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 6.05 (s br, 1H), 5.85-5.70 (m, 3H), 4.75 (s, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 2.85 (s br, 2H), 2.65 (s br, 2H); IR (neat, cm^{-1}): 3015 (m), 3000 (s), 2950 (s), 2900 (s), 2835 (m), 1730 (s), 1645 (m), 1605 (m), 1435 (s), 1390 (m), 1220 (s).

Acidic hydrolysis of the above compound gave compound **7e** (73%): ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 6.80 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.10 - 5.80 (m, 3H), 3.65 (s, 3H), 3.05 - 2.20 (m, 6H); IR ($CHCl_3$, cm^{-1}): 3045 (w), 2950 (m), 1725 (s), 1685 (s), 1610 (m), 1435 (s), 1385 (m).

Preparation of 1-methoxycarbonyl-1-(2-bromoprop-2-enyl)-4-methyl-cyclohex-4-en-3-one, 11.

The reductive-alkylation of 3-methoxy-4-methylbenzoic acid **8**, with 2,3-dibromopropene as alkylating reagent, was performed under the same conditions employed in procedure A, to give a diastereoisomeric mixture (1:2 ratio, from the ^{1}H NMR spectrum) of compound **9** in 94% yield. ^{1}H NMR (60

MHz, $CDCl_3$, ppm): 10.20 (br, 1H), 5.85-5.55 (m, 5H), 3.55 (s, 1H), 3.45 (s, 2H), 3.05-2.55 (m, 3H), 1.15 (d, 3H, J = 7 Hz).

The crude product **9** (2.70 g) was transferred into a 100 mL one-necked round-bottomed flask and mixed with 27 mL of a mixture of THF and 10% hydrochloric acid, 2:1 ratio. The reaction mixture was stirring for 6.5 h monitored by TLC (hexane : ethyl acetate 3:1 ratio, from R_f = 0.8 to R_f = 0.5, a sample from the reaction mixture was esterified with diazomethane before it was used for TLC) every half hour at room temperature. After workup, compound **10** was isolated in 96% yield. ^1H NMR (60 MHz, $CDCl_3$, ppm): 11.85 (br, 1H), 6.80 (br, 1H), 5.65 (m, 2H), 3.25-2.25 (m, 6H), 1.75 (br, 3H).

Compound **10** was then esterified with freshly prepared diazomethane in ether and the methyl ester derivative **11** was purified by column chromatography (silica gel, 1:2 ethyl acetate : hexane) to afford 2.62 g of product (87% yield from **8**). ^1H NMR (60 MHz, $CDCl_3$, ppm): 6.60 (m, 1H), 5.60 (m, 2H), 3.70 (s, 3H), 3.05-2.25 (m, 6H), 1.75 (m, 3H); IR (KBr, cm^{-1}): 3100 (w), 3020 (w, shoulder), 2950 (m), 2920 (m), 1730 (s), 1675 (s), 1620 (m); mass spectrum, exact mass calcd for $C_{12}H_{15}O_3Br_1$ *m/e* 286.0205, obsd *m/e* 286.0203.

Preparation of 1-methoxycarbonyl-1-(2-bromoprop-2-enyl)-5-methoxycyclohex-4-en-3-one, 19.

Procedure **A** was employed for the reduction of 3,4,5-trimethoxybenzoic acid **12** and alkylation, in situ, with 2,3-dibromopropene. This reaction provided the acid **14** in 86% yield. ^1H NMR (60 MHz, $CDCl_3$, ppm): 11.45 (br, 1H), 5.85 (s br, 2H), 5.05 (s br, 2H), 3.75 (s, 6H), 3.05 (s br, 2H), 2.90 (s br, 2H).

Compound **14** was esterified with diazomethane to give the methyl ester **15** in quantitative yield. ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.75 (s br, 2H), 4.90 (s br, 2H), 3.80 (s,3H), 3.75 (s, 6H), 2.95 (s, 2H), 2.80 (s br, 2H); ^{13}C NMR (200 MHz, $CDCl_3$, ppm): 175.06 (C-12), 153.07 (C-9), 128.24 (C-8), 120.78 (C-3, C-5), 94.48 (C-2, C-6), 54.31 (C-10, C-11), 52.23 (C-13), 50.16 (C-1), 30.97 (C-7); IR (neat, cm^{-1}): 3025 (m), 2975 (s), 2910 (s), 2840 (m), 1735 (s), 1700 (s), 1660 (m), 1625 (M), 1600 (w), 1450 (s), 1400 (s).

Compound **15** was then subjected to acidic hydrolysis, under previously described conditions, to give the diketone **16** in an equilibrium with the enol **17**: mp 166-167° C. Anal. Calcd for $C_{11}H_{13}O_4Br_1$: C, 45,69; H, 4.53; Br, 27.63. Found: C, 45.39; H, 4.46; Br, 27.14.

The diketone/enol **16/17** mixture was dissolved in ether and was treated with diazomethane at 0° C. After removal of the solvent the crude product was purified by column chromatography (silica gel, 1:1 hexane : ethyl acetate, $R_f = 0.35$) to give a solid (mp 65-66° C) compound **19** in 82% yield from **12**. ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.60 (s, 2H), 5.30 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.15-2.15 (m, 6H); IR (KBr, cm^{-1}): 3025 (w), 2950 (m), 2925 (m), 1735 (s), 1680 (s), 1625 (m), 1440 (s), 1380 (m), 1365 (s), 1220 (s), 1200 (s); mass spectrum, *m/z* (relative intensity) 304 (M^+, ^{81}Br, 0.5), 302 (M^+, ^{79}Br, 0.5), 273 (3), 271 (3), 223 (76), 193 (59), 183 (55), 167 (88), 165 (100); mass spectrum, exact mass, *m/e*, calcd for $C_{12}H_{15}O_4{}^{81}Br_1$ 304.0135, obsd *m/e* 304.0128.

Preparation of 1-methoxycarbonyl-5-methoxycyclohex-4-en-3-one, 19a.

The Birch reduction of 3,4,5-trimethoxybenzoic acid **12**, using procedure **A**, was attempted. Instead of alkylating the intermediate **13g**, it was quenched

by slowly adding saturated ammonium chloride solution in the reaction mixture. After removal of the ammonia and workup of the reaction compound **14a** was isolated: ^{1}H NMR (60 MHz,$CDCl_3$, ppm): 10.55 (br, 1H), 4.75 (d br, 2H, J = 4 Hz), 3.85 (m, 1H), 3.65 (s, 6H), 2.85 (s, br, 1H), 2.70 (s, br, 1H). Esterification of **14a** with diazomethane provides compound **15a**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 4.75 (d, 2H, J = 4 Hz), 3.85 (t, 1H, J = 4 Hz), 3.70 (s, 3H), 3.65 (s, 6H), 2.85 (s, br, 1H), 2.70 (s, br, 1H); IR (nujol, cm^{-1}): 3080 (w), 3000 (m), 2950 (s), 2900 (m), 2830 (m), 1735 (s), 1695 (m), 1660 (m), 1400 (m), 1210 (s), 1155 (s).

Hydrolysis of **14a** to **16a** was achieved by stirring it in a mixture of THF : 10% HCl_{aq} for 1.5 h at room temperature. The crude **16a** was esterified with diazomethane solution in ether at 0° C. The first equivalent of diazomethane gave **16b** and the second equivalent gave compound **19a**: mp 82-83° C; ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.45 (s, 1H), 3.80 (s, 6H), 3.10 (m, 1H), 2.85-2.45 (m, 4H). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 59.04; H, 6.58.

Preparation of 1-hydroxymethylene-1-(2-bromoprop-2-enyl)-3,5-dimethoxy-2,5-cyclohexadiene, 22.

A 100 mL three-necked round-bottomed flask, equipped with a condenser, was charged with 0.76 g (20.0 mmol) of lithium aluminum hydride suspended in 50 mL of anhydrous diethyl ether. To the above suspension, a solution of compound **15** (3.17 g, 10.0 mmol) in 25 mL diethyl ether was adding dropwise through an addition funnel, during 1h at 0° C. The reaction mixture was stirred for an additional hour at room temperature and then 10 mL water were added dropwise while the solution was being stirred, vigorously, during a 20 minutes period. The reaction mixture was then neutralized with 10% HCl_{aq}, to pH=7, and transferred into a separatory

funnel, where it was extracted with diethyl ether. The combined etherical extracts was dried over anhydrous magnesium sulfate. After filtration the crude product was concentrated, and then purified by column chromatography to give 2.69 g (93% yield) of compound **22**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.80 (s br, 2H), 4.70 (s br, 2H), 3.70 (s, 6H), 3.50 (s, 2H), 2.90 (s, 2H), 2.85 (s, 1H), 2.70 (s, 1H); IR (film, cm^{-1}): 3650-3200 (br), 3075 (w), 3015 (m), 2950 (s), 2825 (m), 1630 (m), 1600 (m).

Preparation of 24

After acidic hydrolysis of the hydroxymethylene derivative **22**, the crude product diketone **23** (1.87 g) was dissolved in 10 mL dried THF and this solution was added dropwise to a stirred suspension of NaH (0.20 g) in 30 mL dried THF, during 30 minutes at -20° C. The reaction mixture was allowed to stirr for another half hour at 0° C and then ethyl chloroformate (0.96 mL, 1.09 g, 10.0 mmol) was added by a syringe into it at -20° C. The solution was then stirred for an additional hour before work-up. The crude product was purified by column chromatography to afford 2.46 g of **24** (74% yield). ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.55 (s br, 2H), 4.15 (q, 2H, J = 6.5 Hz), 4.00-3.35 (m, 4H), 2.95 (s br, 2H), 2.70 (s, 2H), 2.50 (s, 2H), 1.23 (t, 3H, J = 6.5 Hz).

Preparation of 1-methoxycarbonyl-1-(2-bromoprop-2-enyl)-5-methyl-cyclohex-4-en-3-one, 26.

A 100 mL two-necked round-bottomed flask, equipped with condenser, was charged with methyllithium in hexane, 6.0 mL (1.6 M sol., 9.6 mmol) and 10 mL dried THF, under a nitrogen atmosphere. To this solution cuprous iodide, (0.857 g, 4.5 mmol) was slowly added at -40° C. The solution was stirred for 40 minutes at the same temperature and then compound **7d** (1.09 g,

4.0 mmol) in 10 mL of dried THF was added into it at -78° C. After stirring for an hour at -78° C, 1.18 g (5.0 mmol) of phenylselenium bromide was added and the reaction mixture was allowed to warm to room temperature. Saturated ammonium chloride solution was added to the reaction mixture and then it was transferred to a separatory funnel. The product was extracted with ethyl acetate. The organic layer was dried, filtered, concentrated and the crude product **25** was dissolved in 20 mL methylene chloride. Then 4.0 mL of 30% hydrogen peroxide were added and the reaction mixture was warm to 40° C. While the solution was stirring 0.748 ml of pyridine were added and the reaction mixture was allowed to stir for 40 more minutes. The mixture was then extracted with three 25 mL portions of ethyl acetate. The combined organic extracts was washed successively with 2% sodium hydroxide solution, 5% hydrochloric acid solution, brine, and then dried over magnesium sulfate, filtered, and purified by column chromatography (ethyl acetate : hexane, 1:2) to give 0.89 g (78% yield) of enone **26**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 5.85 (s br, 1H), 5.55 (s, 2H), 3.65 (s, 3H), 3.00-2.20 (m, 6H), 1.92 (s br, 3H).

Preparation of 1-methoxycarbonyl-1-(2-bromoprop-2-enyl)-5-aetoxy-cyclohex-4-en-3-one, 18.

To a 100 mL two-necked round-bottomed flask, equipped with a reflux condenser, compound **17**, (2.86 g, 10.0 mmol), dissolved in 40 mL chloroform was added. Dried pyridine (2.53 mL, 2.47 g, 30.0 mmol) was then added to the above solution, followed by a slow addition of 1.43 mL (1.57 g, 20.0 mmol) of acetyl chloride. This solution was refluxed for one hour and after it was cooled to room temperature, the pyridinium hydrogen chloride salt was removed by filtration. The reaction mixture was then dilute with chloroform and washed several times with sodium bicarbonate. The organic layer was

dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (1:2, ethyl acetate : hexane) to afford 2.67 g (81% yield) of compound **18**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 6.0 (s, 1H), 5.65 (s, 2H), 3.75 (s, 3H), 3.10-2.60 (m, 6H), 2.25 (s, 3H); IR (neat, cm^{-1}): 3015 (w), 2955 (m), 1770 (s), 1730 (s), 1670 (s), 1620 (m), 1430 (m), 1360 (s), 1180 (s), 1120 (s); mass spectrum, *m/z* (relative intensity) 300 (traces), 259 (8), 257 (8), 251 (35), 209 (50), 169 (30), 149 (44), 137 (32), 121 (100), 84 (65), 81 (31), 79 (35), 77 (50), 69 (100), 43 (100), 39 (100).

Preparation of 1-hydroxymethylene-1-(2-bromoprop-2-enyl)-cyclohex-4-en-3-one, 20.

To a cold (0° C), magnetically stirred suspension of lithium aluminum hydride (0.57 g, 15 mmol) in 45 mL of anhydrous ether, under nitrogen, a solution of ester **19** (3.04 g, 10 mmol, in 30 mL anhydrous ether) was added dropwise followed by a 30-min stirring at room temperature. Then 10 mL of water was added dropwise at 0° C, and the reaction mixture was stirred for 30 min at room temperature. Then 75 mL of saturated oxalic acid solution was added slowly followed by an additional 30-min stirring at room temperature. The reaction mixture was transferred in a separatory funnel and extracted with ether. The combined etherical extracts was washed with saturated sodium bicarbonate solution, then with brine, and dried over magnesium sulfate. After filtration, the solution was concentrated by rotor evaporator, and the liquid residue was purified by column chromatography (ethyl acetate : hexane, 1:1, R_f = 0.25) to give 2.309 g (95 %) of **20** as a colorless liquid: IR (neat, cm-1) 3600-3150 (br, s), 3040 (w), 2925 (m), 2880 (m), 1660 (s), 1620 (m),1390 (m); ^{1}H NMR (60 MHz, $CDCl_3$, ppm): 6.95 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.05 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.65 (s, 2H), 4.00 (s, br, 1H), 3.55 (s, 2H), 2.65 (s, 2H), 2.45 (m,

4H). Because of intramolecular Michael reaction leading to the conversion of **20** to the bicyclo compound **21**, no further analytical data were collected for **20**, and instead it was submitted to the next reaction step.

Preparation of 1-methoxycarbonyl-1-(2-bromoprop-2-enyl)-cyclohex-4-en-3-one, ethylene ketal, 27.

A 100 mL two-necked round bottom flask, equipped with a Dean-Stark water trap, was charged with 2.73 g (10 mmol) of compound **7d**, 86 mg (0.5 mmol) of PTSA, 0.93 g (15 mmol) of ethylene glycol, and 75 mL of anhydrous benzene. The solution was refluxed for 6 hours and the reaction was monitored by TLC. After the completion of the reaction the solution was neutralized by adding anhydrous sodium bicarbonate at 0° C and stirring for 15 min. The solvent was removed by distillation and the residue was extracted with three 50 mL-portions of ethyl acetate. The combined organic extracts was dried over magnesium sulfate. After filtration, and solvent removal the residue was purified by column chromatography to give 3.10 g (98 % yield) of **27** as a colorless liquid: IR (neat, cm^{-1}) 3040 (m), 2950 (s), 2900 (s), 1730 (s), 1655 (w), 1620 (m), 1440 (s), 1365 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.90 (m, 2H), 5.65 (s, br, 2H), 4.00 (m, 4H), 3.70 (s, 3H), 3.00-1.70 (m, 6H).

Lithium aluminum hydride reduction of **27** (634 mg, 2.0 mmol), in the usual way described earlier, gave the alcohol **28** (520 mg) 90% yield: IR (neat, cm^{-1}) 3650-3050 (br, s), 3020 (m), 2950 (s), 2880 (s), 1655 (w), 1620 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.90-5.65 (m, 4H), 4.00 (s, 4H), 3.60 (s, 2H), 2.80 (br, 1H), 2.70 (s, 2H), 2.30 (m, 2H), 1.85 (s, br, 2H).

Alcohol **28** (289 mg, 1.0 mmol) and 5 drops of pyridine were dissolved in 3 mL of acetic anhydride and the reaction mixture was allowed to stirr overnight. After workup of the reaction and purification of the product, 314 mg (95 % yield) of acetate **28a** was isolated: IR (neat, cm^{-1}) 3020 (m), 2950 (s), 2880 (s), 1745 (s), 1655 (w), 1620 (s); ^1H NMR (60 MHz, CDCl3, ppm) 5.85-5.65 (m, 4H), 3.95 (s, 4H), 3.60 (s, 2H), 2.70 (s, 2H), 2.30 (m, 2H), 2.10 (s, 3H), 1.85 (s, br, 2H).

Compound **28a** (297 mg, 0.9 mmol) was stirred in a 9 mL mixture of THF : 10% HCl, 2:1 ratio for 3 hours at room temperature. The reaction was monitored by TLC and after the completion of the reaction the reaction mixture was worked up. The acetate enone **20a** was isolated in 92 % yield (238 mg) as a colorless liquid: IR (neat, cm^{-1}) 3050 (w), 2990 (m), 2950 (m), 1745 (s), 1680 (s), 1625 (m); 1H NMR 6.95 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.15 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.65 (m, 2H), 4.10 (s, 2H), 2.70 (s, 2H), 2.50 (m, 4H), 2.10 (s, 3H).

REFERENCES

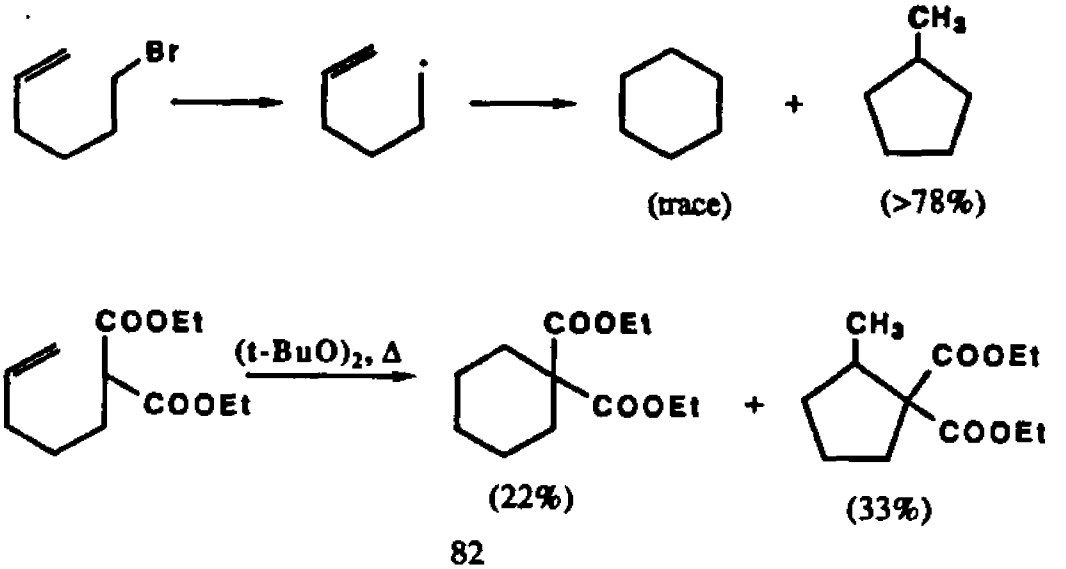
1. a. Krishnammorthy, H. N., Ed.; *Gibberellins and Plant Growth*. Wiley, New York, **1975**; b. Hedden, P. *ACS Symp. Ser.* **1979**, 111, 19; c. Hartsuck, J. A.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1963**, 85, 3414.
2. a. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, 100, 8031; b. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopolan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, 100, 8034; c. Quassem, M. A.; Othman, A. A.; Rogers, A. J. *Tetrahedron*, **1968**, 24, 4535; d. Turner, J. V.; Anderson, B. F.; Mander, L. N. *Aust. J. Chem.* **1980**, 33, 1061; e. Grootaert, W. M.; de Clercq, P. J. *Tetrahedron Lett.* **1982**, 23, 3291.
3. a. Rapson, W. S.; Robinson, R., *J. Chem. Soc.* **1935**, 57, 1285; b. Kende, A. S.; Constandinides, D.; Lee, S. J.; Liebeskind, L. *Tetrahedron Lett.*. **1975**, 6, 405; c. Banerjee, D. K.; Sarendranath V. *Indian J. Chem.* **1975**, 13, 201.
4. Biffin, M. E. C.; Moritz, A. G.; Paul, D. B., *Aust. J. Chem.*, **1972**, 25, 1329.
5. a. 3-Bromo-2-iodo-1-propene was prepared from 2-iodo-1-propene by mesylation and treatment with LiBr (91%); b. Gras, J.-L.; Kong Win Chang, Y. Y.; Bertand, M., *Tetrahedron Lett.*, **1982**, 38, 3571.
6. a. Van Tamelen, E.; Hildahl, G. T. *J. Am. Chem. Soc.* **1956**, 78, 4405; b. Smith, A. B.; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, 105, 575.
7. *Organic Synthesis*, Coll. Vol. V, pp 294-299.
8. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Sos.* **1975**, 97, 5446.

CHAPTER 5

5.0.0. Introduction

Until recently, most of the procedures used in synthesis for making carbon-carbon bonds, were based on ionic or concerted reactions. On the other hand, synthetic organic chemists have made only limited use of free radical, carbon-carbon bond-forming reactions in the synthesis of polyfunctional molecules. In the last few years however, free-radical addition reactions haved gained popularity, and their use in the construction of complex organic compounds is being evaluated by a number of research groups. The intramolecular addition of a free radical to a neighboring double bond, forming a carbocyclic structure, was widely studied through the efforts of Walling, Ingold, Beckwith, and Julia (see references in chapter 2). It has been shown that initial radical structure, steric effects resulting from olefin substitution patterns, and geometric constrains in the chain linking the olefin and radical center, are factors which govern the regiochemistry and stereochemistry of the cyclization (Scheme 1).[1-9]

Scheme 1

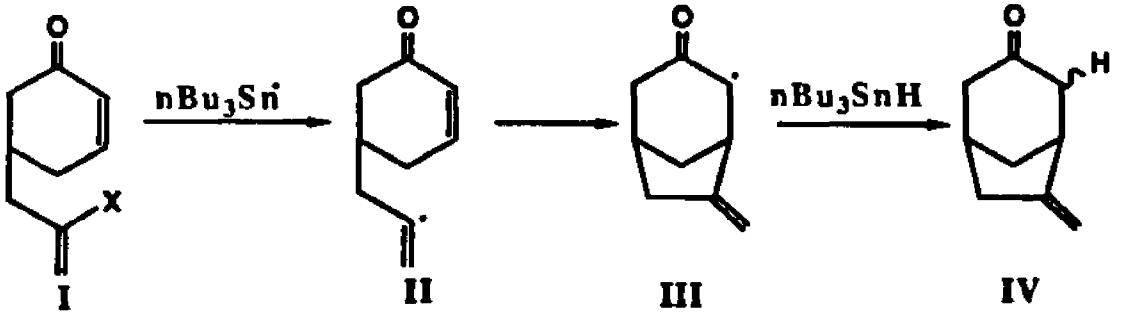


For example, the parent 5-hexenyl radical, derived from 5-hexenyl bromide gives almost exlusively methylcyclopentane and traces of cyclohexane.[1,10] In contrast, the radical derived from the diethyl malonate derivative affords a mixture of five- and six-membered ring products.[11]

5.1.0. Vinyl Radical Carbocyclization

The utilization of vinylogous reactivities in radical processes are difficult to realize selectively, since dimerization, disproportionation, polymerization, trapping of the radical by oxygen, and b-bond cleavage, often effectively compete with the terminating hydrogen atom transfer reaction.

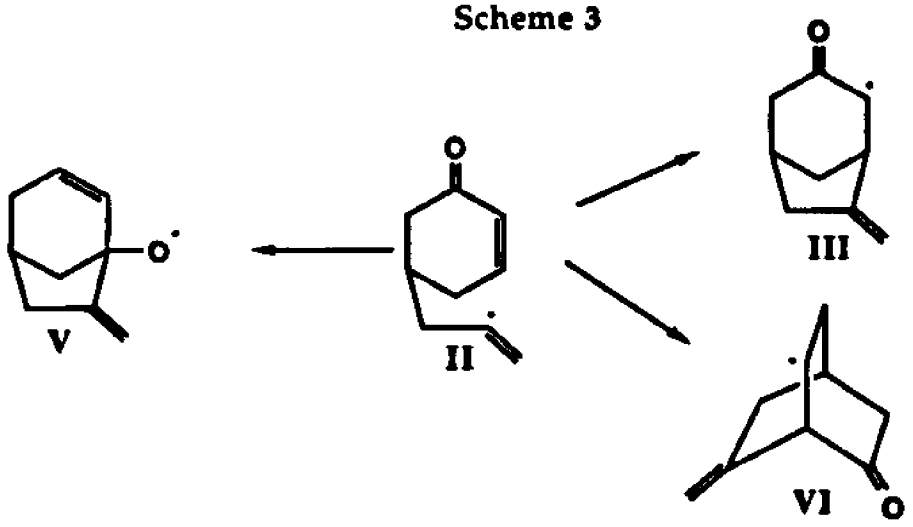
Scheme 2



Our approach (Scheme 2) involves formation of a vinyl radical **II** by AIBN catalyzed reaction of tri-n-butyltin hydride[12], with the vinyl halide **I** in benzene, followed by the internal addition of the radical to the stereoproximal acceptor alkene moiety. Hydrogen abstraction from the Bu_3SnH by the addend radical **III** completed one cycle of the radical chain. A synthetically useful feature of this approach to carbocyclization is that the chemoselectivity of the tri-n-butyltin radical for halogen abstraction, in the the presence of the α,β-unsaturated carbonyl moiety.

The efficiency of the new bond formation is enhanced by the kinetic preference of vinyl radical **II** to undergo intramolecular addition to the acceptor alkene moiety, rather than to participate in the intermolecular transfer of the hydrogen atom from the organostannane.[13] More importantly, the reaction is facilitated by the effective delocalization[14] of the carbon radical electron by the adjacent carbonyl group in the addend radical **III**. This resulted in the regioselective cyclization[15] to produce bridged ring system **IV**. The regiochemical preference had been anticipated since the three possible modes **III**, **V**, and **VI** for cyclization of the vinyl radical **II** reveals that the required disposition of the reactive centers is more readily accommodated in the transition state for the formation of the radical intermediate **III** (Scheme 3).[16]

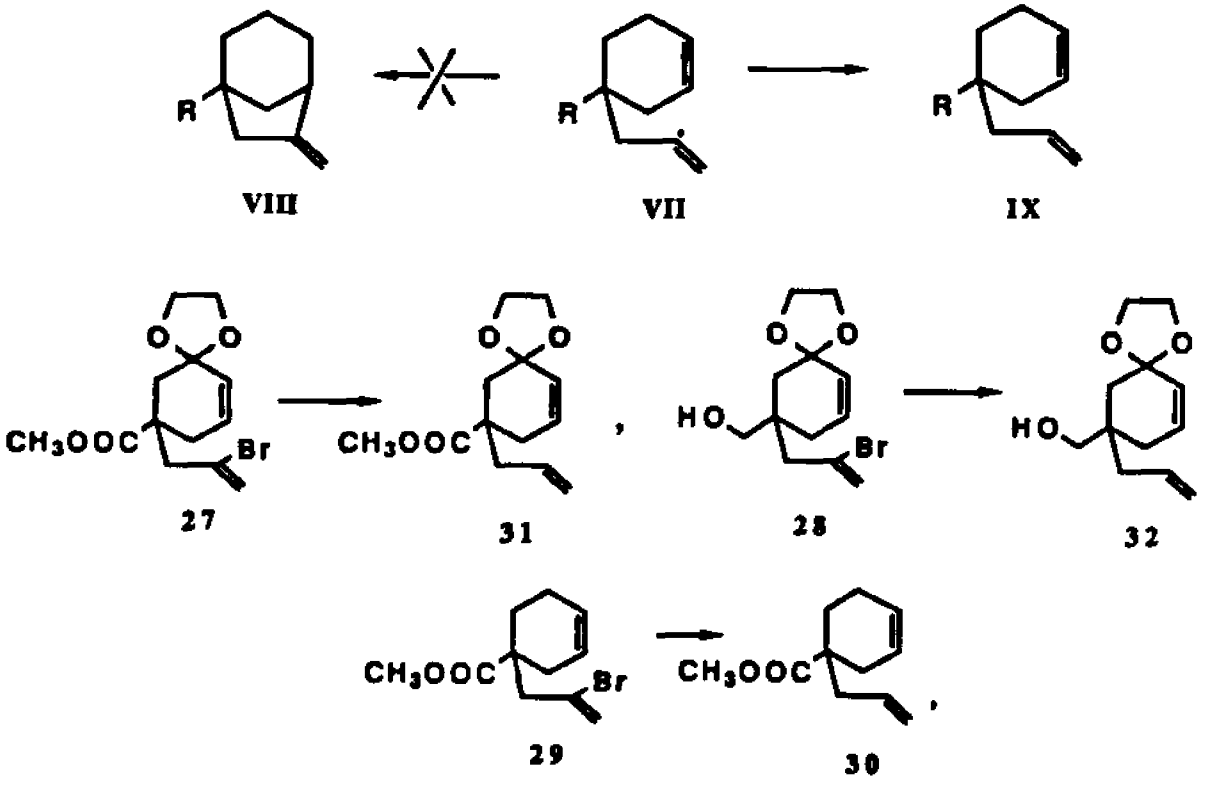
Scheme 3



The difference in energies of the possible intermediates **III**, **V**, and **VI** clearly favors the formation of **III** only. When the system is going to the TS leading to the bicyclo[3.2.1]octane the radical center developed in **III** enjoys delocalization involving the carbonyl group. On the other hand, the TS leading to the bicyclo[2.2.2]octane involves the development of an unstabilized radical **VI**.

Also, the possible modes of orbital interactions between a radical and a closed-shell molecule notwithstanding, the frontier orbitals of the acceptor α,β-unsaturated alkenes, have larger coefficients for the β-carbon.[17] Furthermore, the failure[18] of vinyl bromides **29**, **27**, and **28** to cyclize but instead give the reduced product **30**, **31**, and **32** respectively, suggests that the "vicinal" orbital interaction is a SOMO-LUMO interaction (Scheme 4). Also, looking at the intermediate radicals **VII** and **VIII**, **VII** should be more stable than **VIII** since there is no extra ring strain. Vinyl and alkyl radicals have relatively equal stabilities.[19]

Scheme 4



The influence of the nature of the halide on the efficiency of carbocyclization was investigated. The results indicated: a) the vinyl chloride function is the least useful vinyl radical precursor because of lower reactivity; vinyl bromides, being less sensitive to Birch reduction conditions and

synthetically more accessible than vinyl iodides are the vinyl radicals of choice. **b)** a major involvement of the **SOMO** of the tin radical with the **HOMO** of the vinyl halide, since both the ease of the abstraction of the halogens and the energies of the **HOMO** of the carbon-halogen bond,[20] fall in the order I > Br > Cl.

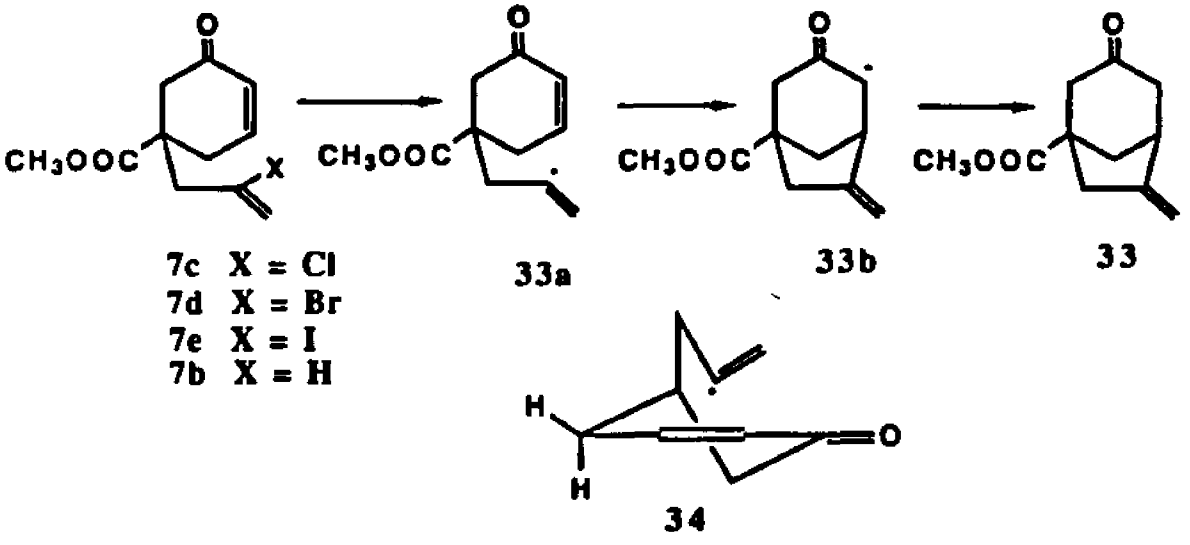
The choice of solvent was briefly examined. Benzene, being inert to radical intermediates and having a sufficiently high boiling point to facilitate initiation of homolytic cleavage of a hydrogen-tin bond, proved to be the optimum solvent. Methanol and toluene resulted in lower yields of cyclized material, probably because of their ability to donate hydrogen atoms.

The substantial concentration effect on the ratio of rates for the hydrogen atom transfer and carbocyclization, is consistent with trends noted in alkyl radical cyclization.[21] At 0.25 M stannane concentration, reaction of **7c** yielded only **7b** (71%); **7d** gave a mixture of **33** (54%) and **7b**. Yields of cyclized products increased by decreasing the stannane concentration and eventually, at 0.2 mM stannane concentration, **7c** gave **33** (69%) and **7b** (7%), while **7d** gave only cyclized product **33** in 82% yield. That was achieved by adding dropwise a 0.1 M solution of stannane in benzene to an appropriate refluxing dilute solution of starting material in benzene (25 mL of benzene per mmol of starting material). Decreasing the stannane concentration to 0.1 mM in the reactions of both **7c** and **7d** gave only the cyclic bridge product **33** (Scheme 5).

Conformational analysis of the intermediate vinyl radical **33a** demonstrates that in order to form the 1,3-five-membered ring product, the substituent bearing the radical must be an axial one **34**. In this conformation the axial hydrogen attached to C-6, which will be the more reactive hydrogen in a radical transfer process, appears to be remote to the vinyl radical.

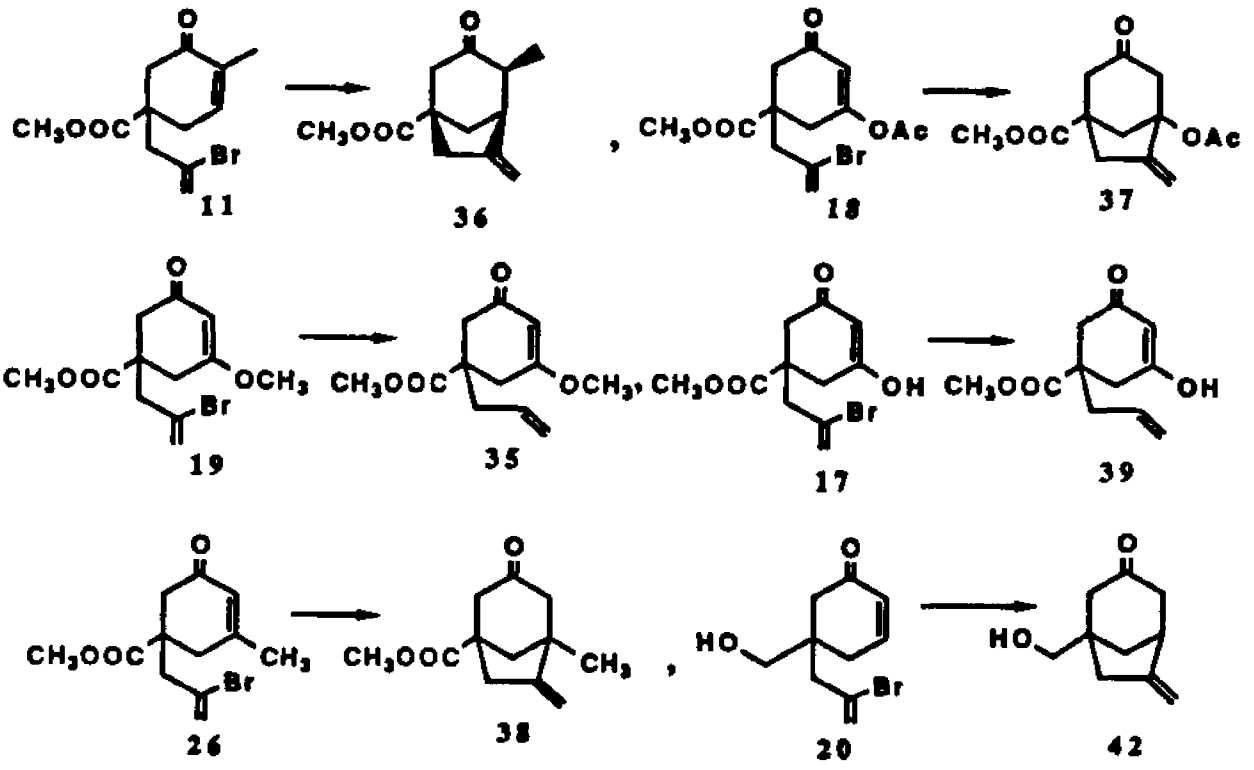
Because of this geometry, the vinyl radical intermediate cannot abstract the axial hydrogen at C-6 and because this side reaction could not occur increased the possibility for cyclization. Since this cyclization occurs via radical intermediate **33b**, the newly formed carbon-hydrogen bond will be stereorandom.

Scheme 5



In order to study the relationship between the substitution pattern of the acceptor alkene moiety and the mode of the ring closure, substituted enones **11, 17, 18, 19,** and **26** (Chapter 4) were treated with tri-n-butyltin hydride (Scheme 6). Under the standard conditions which we established for the free radical reaction, enone **11** gave 93% cyclized product **36**. The enones **17** and **19** gave only the alternative reduced products **39** and **35**. On the other hand **18** and **26** gave **37** and **38** respectively in very high yields. Compound **20** (Chapter 4) was subjected to the free radical cyclization immediately after it was prepared, without purification, to give the bicyclic bridged system **42** in 92% yield.

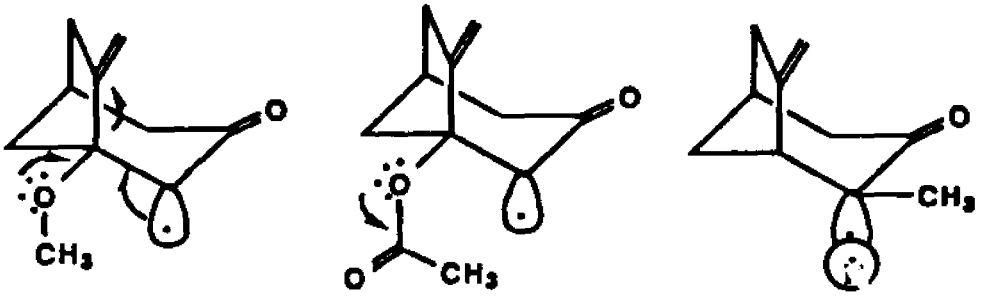
Scheme 6



The cyclization products which were obtained indicate the utility of activated olefins, substituted by π-electron acceptor groups, as cyclization substrates that will ensure regiochemical control of the ring closure. Also, it is clear that the strong electron donating hydroxy and methoxy groups on the β-position deactivate the radical acceptor alkene moiety in **17** and **19** so reduction takes place instead of cyclization . The acetate group in **18**, because of cross conjugation, leaves the olefin unaffected and cyclized product is the only one obtained. If we assume that cyclization takes place, then the intermediate radical **35a** is very unstable compared to **37a**, and in a reverse process gives the uncyclized reduced product (Scheme 7). In the enones **11** and **26** the methyl-substituent again does not affect the course of cyclization either electronically or sterically. Another interesting result came out of the cyclization of **11**, was that the transfer of hydrogen atom from the

organostannane came from the opposite side of the previous formed bond in compound **36**. That happened because of in the radical intermediate **36a** the electron spin must be axial to make delocalization possible, and so the hydrogen radical can approach from the axial side, opposite to the five-membered ring, leaving the methyl group equatorial (Scheme 7).

Scheme 7



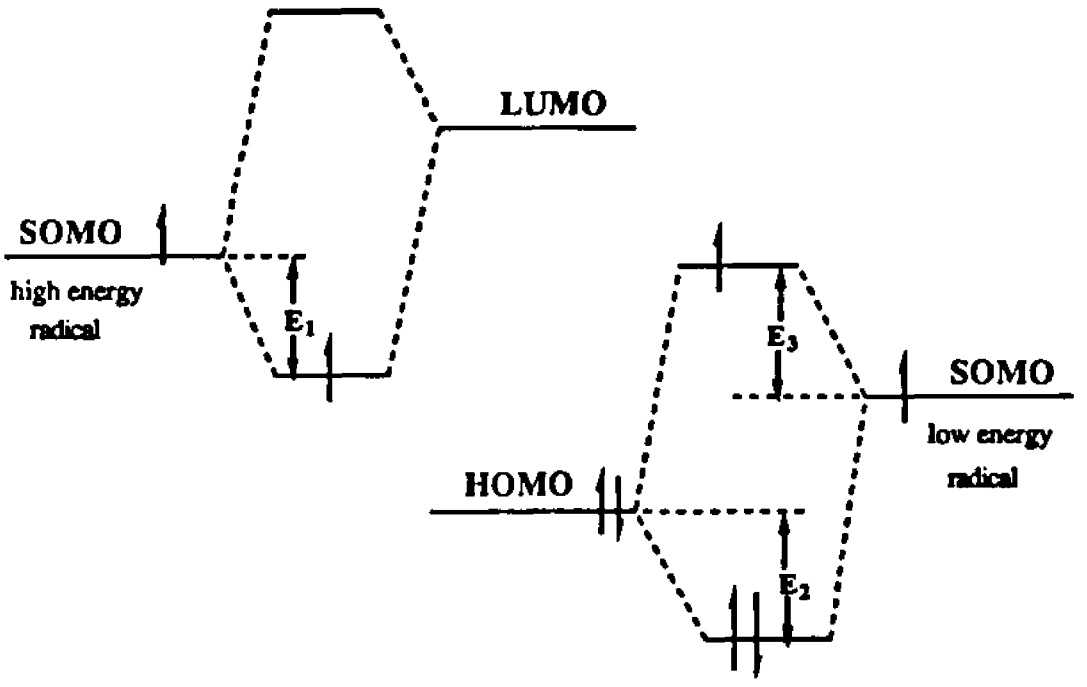
35a **37a** **36a**

An important asset which distinguishes vinyl radical cyclization from alkyl radical cyclization is the regiospecific incorporation of a double bond into the newly formed ring. This double bond has an important synthetic value since it can readily be transformed into a variety of functional groups.

All the results were matched with the expected ones based on the theoretical calculations published in the literature. Radicals, in general, are very soft entities and thus Coulombic forces are usually small while the frontier interactions remain large. Plainly, the frontier orbital of the radical is the singly occupied molecular orbital **SOMO**. This orbital will interact with either the **HOMO**, or the **LUMO** of the molecule which it is reacting with, as shown in Scheme 8. Whichever interaction will occur greater stability will be produced. The interaction with the **LUMO** will lead to a drop in energy (E1); but the interaction with the **HOMO** will also lead to a drop in energy (2E2 -

E3). Radicals with high-energy SOMO (nucleophilic character) will react faster with molecules having a low-energy LUMO (electrophilic character), and radicals with low-energy SOMO (electrophilic character) will react faster with molecules having high-energy HOMO (nucleophilic character).

Scheme 8



The high-energy SOMO (nucleophilic property) in the vinyl radicals will interact only with the low-energy LUMO (electrophilic property) of the alkene and as such are those bearing electron-withdrawing groups. The site of the attack is governed by the highest coefficient of the appropriate frontier orbital.[17]

The development of the stereochemical probe for the investigation of vinyl radical carbocyclization was based on three major considerations: a)

The attack angles of the reagents and the conformations of the allylic substituents in the transition structures for additions to unsaturated systems;[22] b) the factors controlling the competition between addition and hydrogen abstraction in reactions of vinyl radicals with akylethylenes;[23] and c) the substitution pattern of the alkylethylenes which will help to rationalize and predict the regioselectivities and stereo- selectivities of intramolecular vinyl radical additions. These were relevant to the understanding of radical attack angles in the addition reactions, conformational preferences in the transition structures, stereoselectivity in radical cyclizations,[24] and regioselectivity in radical additions.[25,26]

EXPERIMENTAL

General. Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton nuclear magnetic resonance (1H) spectra were determined on a Varian EM-360A (60 MHz), or on a IBM NR/300 FT NMR (270 MHz), or on a IBM WP/200-SY (200 MHz), and or on a JEOL/JNM/GX-400 FT NMR spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=double, t=triplet, q=quarter, m=multiplet, br=broad), assignment, integration, coupling constant. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer and on Finnigan CH5 single focusing mass spectrometer. Thin-Layer chromatography (TLC) was performed with 13181 silical gel with fluorescent indicator (Kodak) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silical gel 60 mesh. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY).

Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Preparation of 1-methoxycarbonyl-3-oxo-8-methylene-bicyclo-[3.2.1]-octane 33.

A 100-mL two-necked round bottom flask equipped with a magnetic stirring bar, rubber septum inlet, and a condenser is flushed with nitrogen and charged with ester **7d** (0.273 mg, 1.0 mmol) dissolved in benzene (45 mL dried by overnight refluxing over CaH_2). A separate solution constituted of tri-n-butyltin hydride (0.325 mL, 320 mg, 1.1 mmol), and AIBN (8.3 mg) as catalyst dissolved in benzene (15 mL).was prepared in an addition funnel fitted on the upper opening of the condenser. The reaction was brought to refluxing, and then the AIBN/Bu_3SnH solution in the addition funnel was added dropwise over 1 hour period of time. The reaction course was monitored by TLC and within 45 min all of the starting material had reacted. The solution was cooled, the solvent was removed in vacuo, and the liquid residue was purified by column chromatography (hexane:ethyl acetate 1:1, R_f = 0.35) to give 186 mg (96% yield) of compound **33** as colorless liquid: IR (neat, cm^{-1}) 3075 (w), 2950 (s), 1720 (s), 1710 (s), 1660 (m), 1435 (s), 1255 (s), 1225 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.00 (m, br, 2H), 3.75 (s, 3H), 3.10 (m, 1H), 3.75-2.00 (m, 8H); ^{13}C NMR ($CDCl_3$, ppm) 207.50, 174.62, 150.59, 108.55, 51.94, 50.43, 50.31, 49.70, 41.87, 41.27, 40.72; mass spectrum, exact mass calcd for $C_{11}H_{14}O_3$ *m/e* 194.0943, obsd *m/e* 194. 0944.

The following compounds were treated under identical free radical conditions to give cyclized products.

Compound **11** (2.87 g, 10.0 mmol) gave **36** (2.04 g, 98% yield) as a colorless liquid: IR (neat, cm^{-1}) 3060 (w), 2940 (s), 2915 (s), 1860 (m), 1725 (s), 1710 (s), 1650 (m); ^1H NMR (60 MHz, $CDCl_3$, ppm) 4.90 (s, br, 2H), 3.70 (s, 3H), 2.95-2.15

(m, 7H), 1.00 (d, 3H, *J*=6 Hz); mass spectrum, exact mass calcd for $C_{12}H_{14}O_3$ *m/e* 208.1099, obsd *m/e* 208.1098.

Compound **18** (3.31 g, 10.0 mmol) gave **37** (2.19 g, 87% yield) as a colorless liquid: IR (neat, cm^{-1}) 2960 (s), 2920 (m), 1850 (w), 1750 (s), 1735 (s), 1720 (s), 1660 (w), 1435 (s), 1370 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.25-5.05 (m, 2H), 3.80 (s, 3H), 2.90-2.25 (m, 8H), 2.10 (s, 3H); mass spectrum, exact mass calcd for $C_{13}H_{16}O_5$ *m/e* 252.0997, obsd *m/e* 252.1002.

Compound **26** (2.87 g, 10.0 mmol) gave **38** (1.91 g, 92% yield) as a colorless liquid: IR (neat, cm^{-1}) 3025 (w), 2950 (m), 2925 (m), 1860 (w), 1730 (s), 1725 (s), 1645 (w), 1435 (m); ^1H NMR (270 MHz, $CDCl_3$, ppm) 5.10 (s, 1H), 4.83 (d, 1H, *J*=13.2), 3.74 (s, 3H), 2.74 (d, 1H, *J*=15.92), 2.69 (d, 1H, *J* = 16.49), 2.42 (d, 1H, *J* = 16.81), 2.41 (d, 1H, *J* = 16.20), 2.19-2.10 (m, 2H), 1.98 (d, 1H, *J* = 10.16), 1.84 (dd, 1H, *J* = 10.16, *J* = 2.81), 1.71 (s, 3H); mass spectrum, exact mass calcd for $C_{12}H_{16}O_3$ *m/e* 208.1099, obsd *m/e* 208.1102.

Compound **20** (2.47 g, 10.0 mmol) gave **42** (1.54 g, 93% yield) as a colorless liquid: IR (neat, cm^{-1}) 3600-3200 (s, br), 3080 (w), 2940 (s), 2875 (m), 1715 (s), 1660 (w); ^1H NMR (270 MHz, $CDCl_3$, ppm) 4.97 (s, 1H), 4.88 (s, 1H), 3.83 (s, br, 1H), 3.53 (s, 2H), 2.99 (d, br, 1H, *J* = 2.11), 2.54-2.13 (m, 6H), 1.83 (s, br, 2H); ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 211.80, 152.22, 119.80, 108.16, 68.58, 50.86, 46.82, 42.14, 40.13, 39.68; mass spectrum, exact mass calcd for $C_{10}H_{14}O_2$ *m/e* 166.0994, obsd *m/e* 166.0998.

Compound **20a** (2.87 g, 10.0 mmol) gave **42a** (2.00 g, 96% yield) as a colorless liquid: IR (neat, cm^{-1}) 3080 (w), 2950 (s), 2890 (m), 1745 (s), 1720 (s),

1660 (w); ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 5.05-4.75 (m, 2H), 4.00 (s, 2H), 2.95 (m, 1H), 2.45-2.20 (m, 6H), 2.05 (s, 3H), 1.85 d, br, 2H); ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 209.06, 170.76, 151.50, 108.61, 69.83, 50.98, 50.79, 44.58, 41.97, 40.69, 40.31, 40.14; mass spectrum, exact mass calcd for $C_{12}H_{16}O_3$ *m/e* 208.1099, obsd *m/e* 208.1098.

REFERENCES

1. a. Walling, C; Pearson, M. S., *J. Am. Chem. Soc.*, **1964**, 86, 2262; b. Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J., *ibid.*, **1966**, 88, 5361; c. Walling, C.; Cioffari, A., *ibid.*, **1972**, 94, 6059.
2. Griller, D.; Ingold, K. U., *Acc. Chem. Res.*, **1980**, 13, 317.
3. Beckwith, A. L. J.; Blair, A. I.; Phillipou, G., *Tetrahedron Lett.*, **1974**, 2251.
4. Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K., *J. Chem. Soc., Chem. Comm.*, **1980**, 482.
5. Julia, M., *Rec. Chem. Prog.*, **1964**, 25, 3.
6. Julia, M., *Pure Appl. Chem.*, **1967**, 15, 167.
7. Julia, M., *Acc. Chem. Res.*, **1971**, 4, 386.
8. Julia, M., *Pure Appl. Chem.*, **1974**, 40, 553.
9. Julia, M.; Descoins, C.; Jacquet, B.; Uguen, D.; Groeger,F. A., *Tetrahedron*, **1975**, 31, 1737.
10. For reviews of the tin hydrides see Kuivila, H. G., *Synthesis*, **1970**, p. 499; *Acc. Chem. Res.*, **1968**, 1, 299. In many of the examples presented herein, tri-n-butyltin radicals were generated by abstraction of a hydrogen atom from tri-n-butyltin hydride by isobutyronitrile radicals, generated in turn from azo(bis)isobutyronitrile (AIBN)
11. Julia, M.; LeGoffic, F.; Katz, L., *Bull. Soc. Chim. Fr.*, **1964**, p. 1122.
12. a. Kuivila, H. G. *Acc. Chem. Res.* **1968**, 1, 299; b. White sides, G. M.; Casey,
C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, 93, 1379.
13. Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States;* de Mayo, Paul, Ed.; Academic Press: New York, 1980; Vol. 41-2, pp 180-181.

14. Nonhebel, D. C.; Walto, J. C. *Free Radical Chemistry;* Cambridge University Press: New York, 1974; ch. 5.

15. The stereochemistry of the ring junction is the consequence of geometrical constraints for the vinyl radical approach to the enone double bond.

16. a. Beckwith, A. L. J. *Tetrahedron* **1981**, 37, 3073; b. See, also, ref. 13, pp 182-220.

17. a. Fukui, K. *Acc. Chem. Res.* **1971**, 4, 57; b. Fujimoto, H.; Fukui, K. *Chemical Reactivity and Reaction Paths*, J. Wiley: New York, Klopman, G.; Ed., **1974**.

18. Baine, N. H. Ph. D. Thesis, Colombia University, 1981.

19. Benson, S. W., *Thermochemical Kinetics*, 2nd Ed., John Wiley, New York, 1976.

20. Fukui, K.; Kato, H.; Yonezawa, T. *Bull. Chem. Soc.* Japan **1960**, 33, 1197.

21. a. Julia, M. *Acc. Chem. Res.* **1971**, 4, 386; b. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, 94, 6059, 6064.

22. a. Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, 103, 2438; b. Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, 104, 7162; c. Houk, K. N. *Pure Appl. Chem.* **1983**, 55, 277; d. Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *THEOCHEM.* **1983**, 103, 197.

23. Houk, K. N. In *Frontier in Free Radical in Chemistry;* Pryor, W. A., Ed.; Academic: New York, **1983**; p 43 ff.

24. a. Beckwith, A. L. J. *Tetrahedron* **1981**, 37, 3073; b. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, 41, 3925; c. Surzur, J. -M., *Reactive Intermediates;* Abramovitch, R. A., Plenum: New York, **1982**; Vol. 2, pp 121-295.

25. a. Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, 36, 701; *Acc. Chem. Res.* **1976**, 9, 183 and references therein; b. Ruchard, C. *Fortschr. Chem. Forsch.* **1980**, 88, 1.

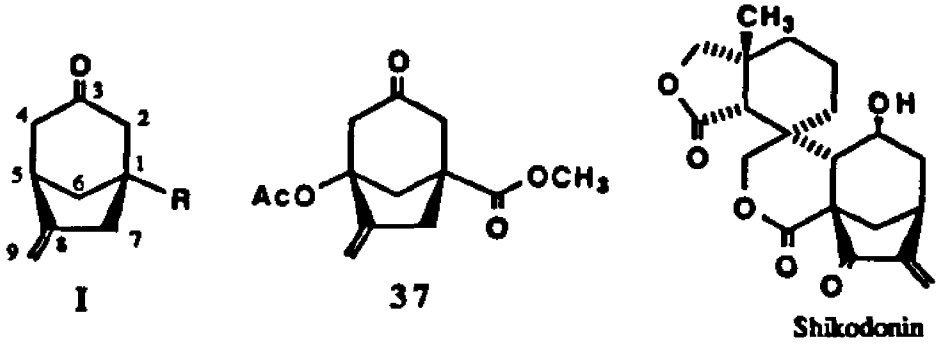
26. Delbecq, F.; Ilavsky, D.; Anh, N. T.; Lefour, J. M. *J. Am. Chem. Soc.* **1985**, 107, 1623.

CHAPTER 6

6.0.0. Introduction.

In this chapter we describe all efforts to utilize the bridged bicyclic systems for the synthesis of a tricyclic system found in many sesquiterpenes and diterpenoids. The potential utility of the free radical cyclization in the synthesis of such systems is underscored by the utilization of **37** for the preparation of a useful intermediate in the synthesis of gibberellic acid. A projected synthesis of shikodonin[1] could be achieved by introducing an acetic acid appendage at C-2 on such bicyclic systems (Scheme 1).

Scheme 1

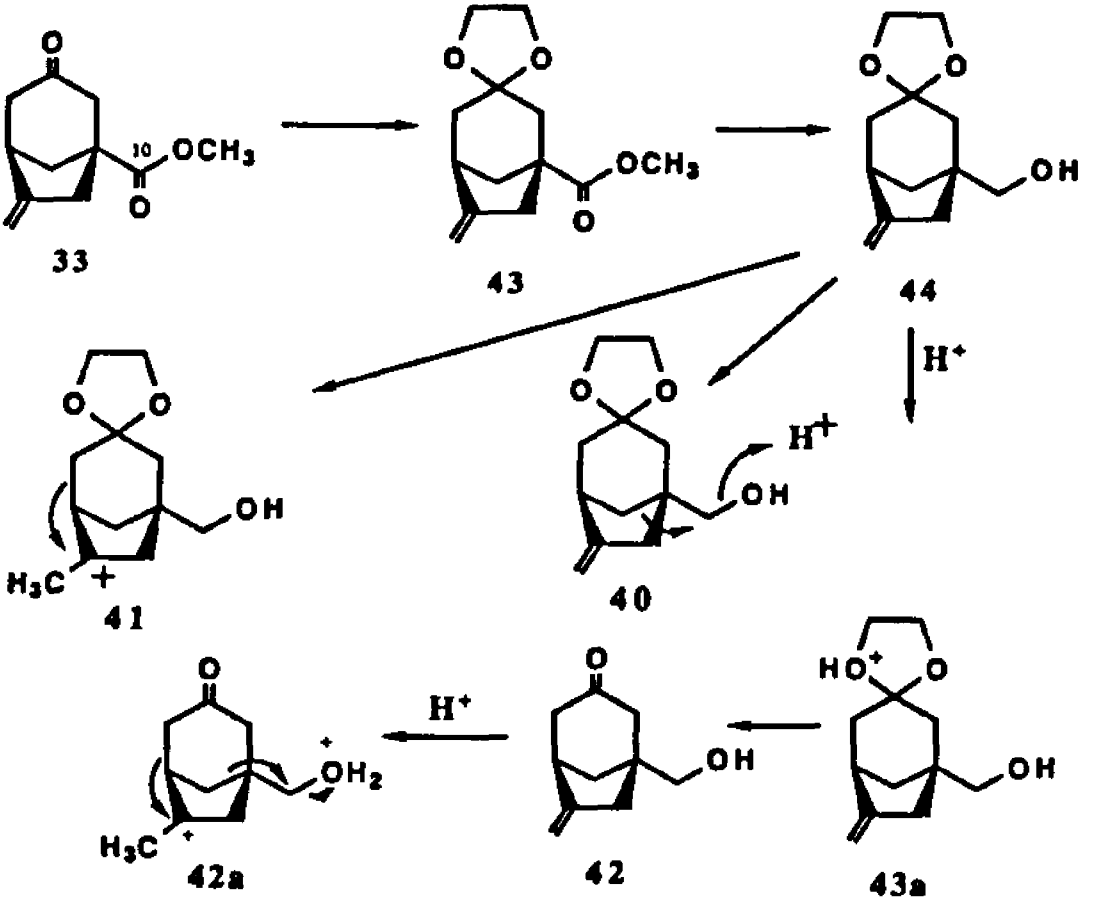


6.1.0. The chemistry of ester ketone 33 and hydroxymethyl ketone 42.

Our approach to highly functionalized tricyclic system began with the compound **33**. The reduction of the ethylene ketal **43** gave the hydroxymethylene ethylene ketal **44**. During hydrolysis of **44** several by-products were formed possibly by way of cationic rearrangements, due to the carbocations formed by the loss of the hydroxy group after it was protonated, as well as that formed by protonation of the double bond (Scheme 2). The

above transformations did not allow us to isolate more than 15% of the required bicyclic methylene hydroxy ketone **42**. Obviously the acid catalyzed transformation of the desired product (or even before formation of **42**) is a competing processes with the hydrolysis of the ethylene ketal **44**.

Scheme 2

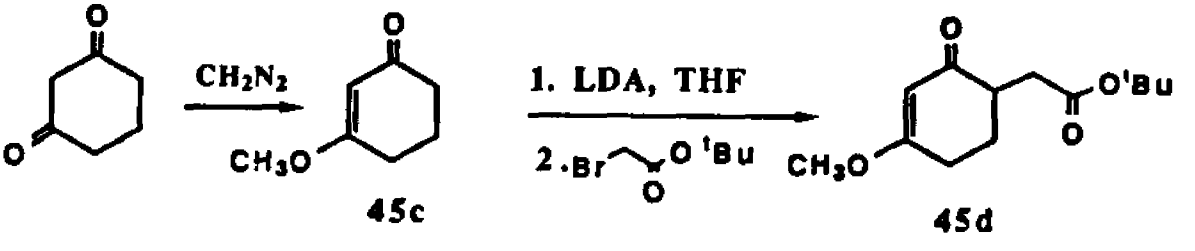


The above transformations demonstrated the sensitivity of **42** and **44** to acidic conditions. Exposure of these systems to any conditions that develop significant electron deficiency, for **42** at C-8 and C-10 and for **44** at C-3, C-8, and C-10, initiates a rearrangement of several bonds, resulting, possibly, in dimerization, polymerization, and other unwanted reactions. The bicyclic

system 42 should not be exposed to proton acidic conditions, which will cause these undesired transformations. As we described earlier (chapter 5, page 7) the bicyclic system 42 was prepared in a very efficient yield after free radical carbocyclization of the enone 20 (Chapter 4, Scheme 7).

In order to study the LDA alkylation of the hydroxy ketone 42, a model experiment was performed by converting the 1,3-cyclohexadione to 3-methoxycyclohex-2-en-1-one, 45c with diazomethane in THF in quantitative yield. The enone 45c was the treated with an equivalent amount of LDA in THF and at -78° C a solution of 1.1 equivalent of t-butyl bromoacetate was injected through a rubber septum. After workup the reaction provided compound 45d in excellent yield (94%) (Scheme 3).

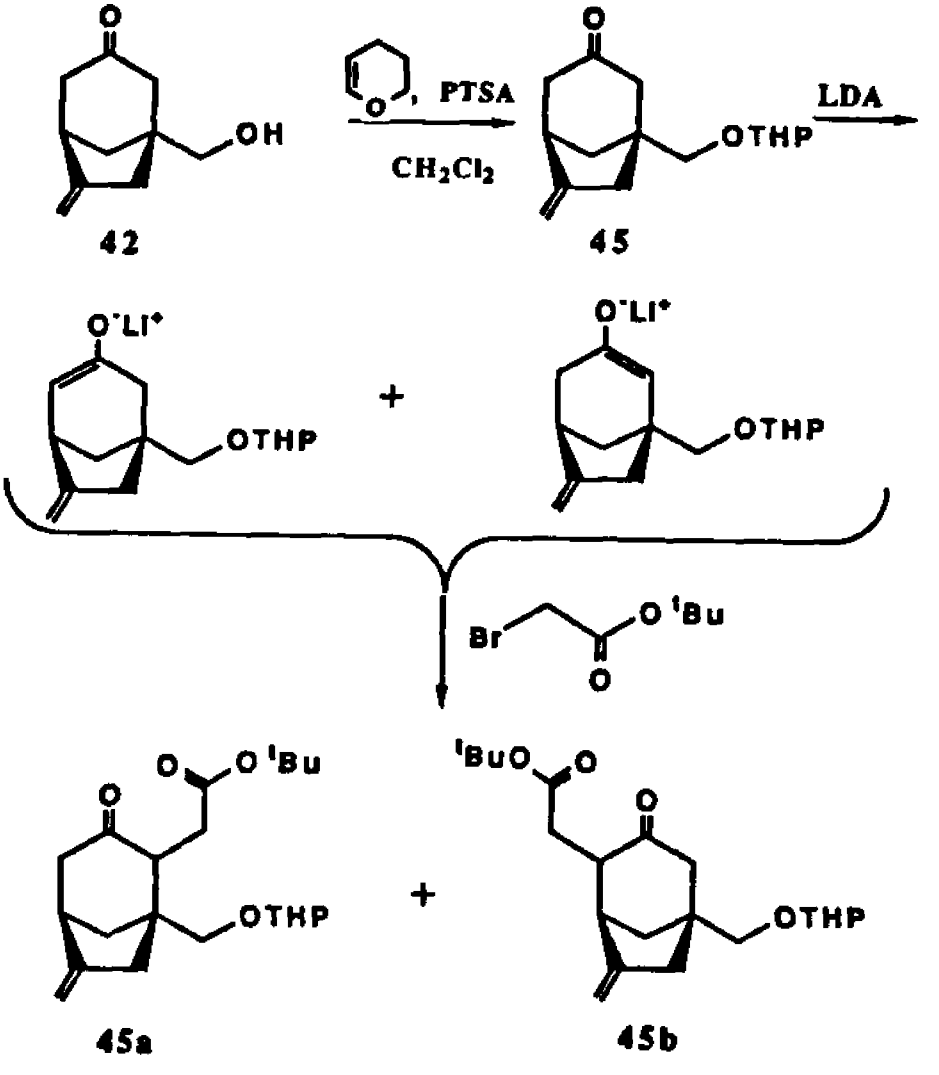
Scheme 3



After compound 42 was converted to tetrahydropyranyl derivative 45, we tried to alkylate it at C-2 by forming the lithium enolate using LDA in THF. As could have been predicted, alkylation was more efficient at C-4 than at C-2, because of less steric hindrance at C-4. C-2 is neopentyl-like carbon. The use of t-butyl bromoacetate as an alkylating reagent gave primarily C-4 alkylation, however this product proved very difficult to isolate from the isomeric material alkylated at C-2. The above results were proven from the ^1H NMR features of the mixture of 45a and 45b. From the the integration of the above NMR spectrum of the mixture, we estimated that 70% of the mixture was

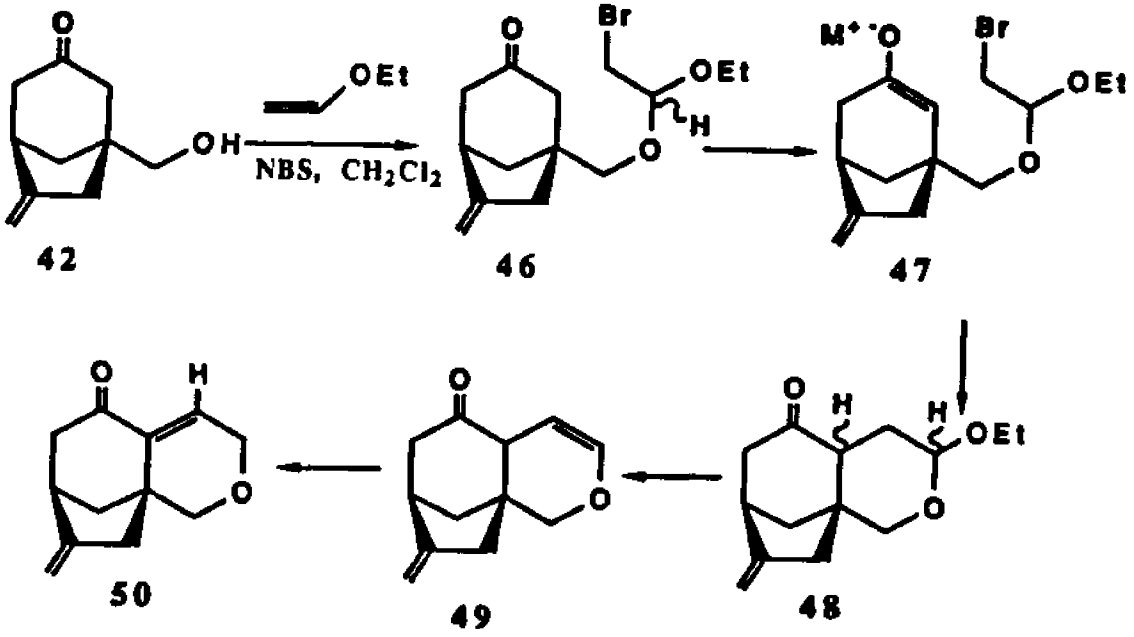
constituted from the undesired alkylated material **45b**. The orientation of the new substituent could be either equatorial, or axial and there was no obvious strategy to employ in order to control the formation of the axial one selectively (Scheme 4).

Scheme 4



We, therefore, concentrated on the use of the hydroxymethyl group as a handle in order to facilitate alkylation at the C-2 position. By attaching an appropriate substituent to the hydroxyl group we hoped to perform an intramolecular alkylation at C-2.

Scheme 5



For that purpose compound **46** was prepared by dissolving a mixture of **42** and ethyl vinyl ether in methylene chloride and adding slowly 1.1 equiv of N-bromosuccinimide at 0° C. After the floating succinimide was filtered out, the bromomethylene acetal **46** (as mixture of inseparable isomers) was chromatographically purified and was obtained in 92% yield. By injecting this compound into a stirring solution of freshly prepared LDA in THF at -78° C we expected the alkylation to take place by intramolecular axial approach[2] of the electrophilic bromomethylene group to the lithium enolate **47**. The selective approach should lead to tricyclic system **48**. Unfortunately, under the reaction conditions, probably excess of LDA caused elimination of an ethanol molecule to give a possible intermediate **49** which was isomerized to the more stable conjugated system **50** (Scheme 5). The only evidence we have for supporting the above suggestion was the ^1H NMR spectrum of the material which showed a quartet at δ 6.9 integrating for one proton. The reaction appeared to be extraordinarily sensitive to the exact choice of base. The bases NaH, KH, and DBU in ether at room temperature failed[3] to give any

of the desired product **48**. Similar treatment of the bromo-acetal **46** with two equivalents of potassium t-butoxide in benzene[4] for three hours at room temperature afforded the cyclized product **48** (78%).

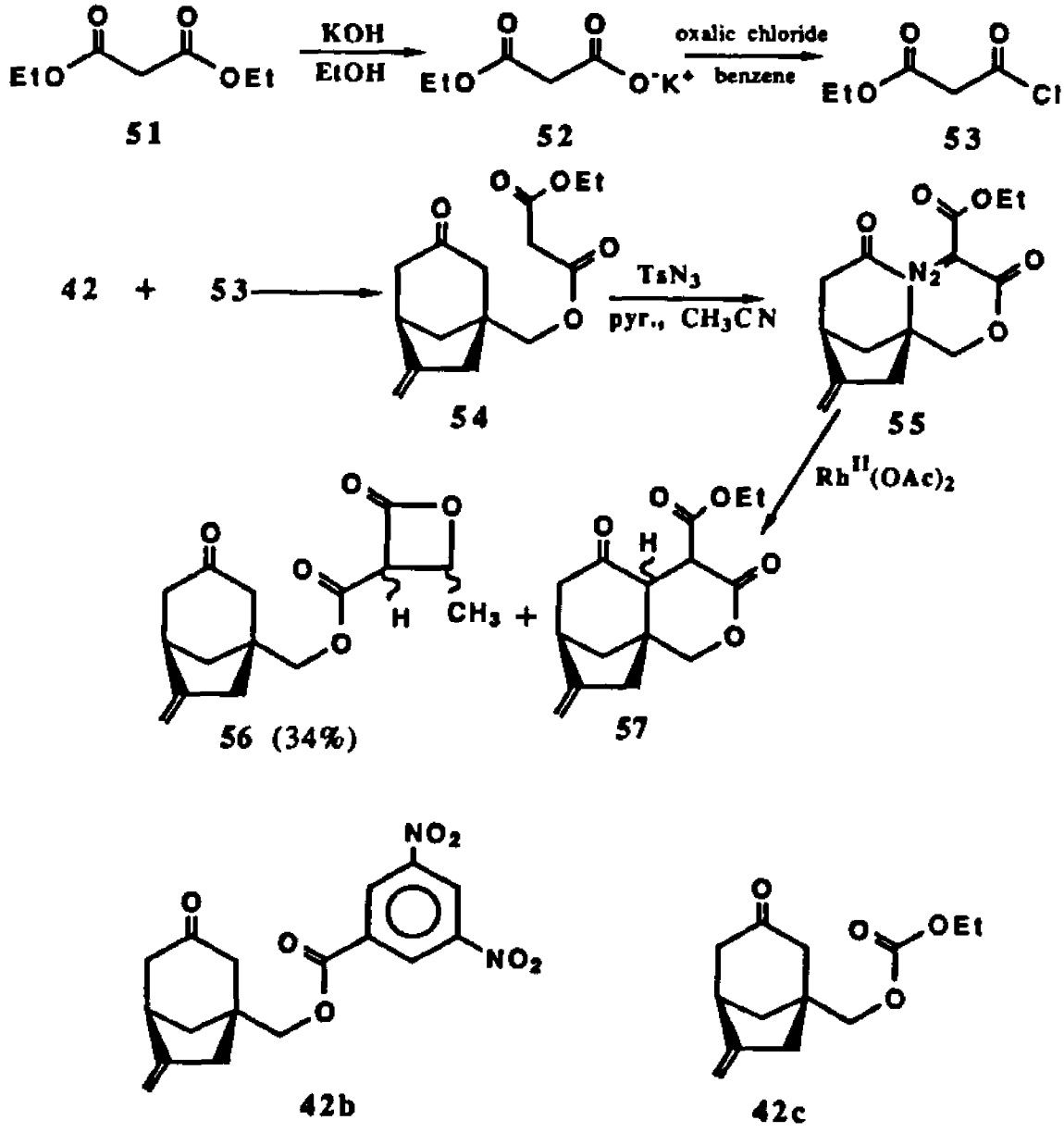
Although the preliminary results indicated that the above route could be very efficient, it was not fully investigated by us, because the presence of base after the formation of **48** would epimerize the chiral carbon at C-2 which again would complicate the subsequent investigations. We therefore decided to investigate another approach which would involve carbene insertion into a carbon-hydrogen bond at C-2 and which we thought would be more efficient since the axial hydrogen ought to be the more reactive one.

Ethyl malonoyl chloride **53** was prepared from diethylmalonate **51** which upon treatment with 1.0 equivalents of potassium hydroxide in ethanol gave ethyl potassium malonate salt **52**. The above salt was mixed in suspension with benzene and then oxaloyl chloride was added dropwise at 0^{o} C. After the solution was stirred for an hour the potassium chloride was filtered out and the benzene solution of malonoyl chloride was concentrated by rotary evaporator at 15^{o} C water bath (Scheme 6).

Ester **54** was prepared by treatment of **42** with ethyl malonoyl chloride in ether in the presence of an equivalent amount of pyridine at room temperature (compounds **42b** and **42c** were prepared under semilar conditions). Compound **54** was then treated with tosyl azide[5], in acetonitrile in the presence of triethylamine[6], at room temperature for 8 hours to give the diazomalonyl ester **55** in 95% yield. This greenish material was dissolved in dried methylene chloride and it was stirred for 2 hours at room temperature in the presence of rhodium diacetate dimer[7], as a catalyst, while the reaction was followed by TLC. After TLC showed that the UV active starting material had been used up, the reaction mixture was extracted with 4% HCl_{aq} and the

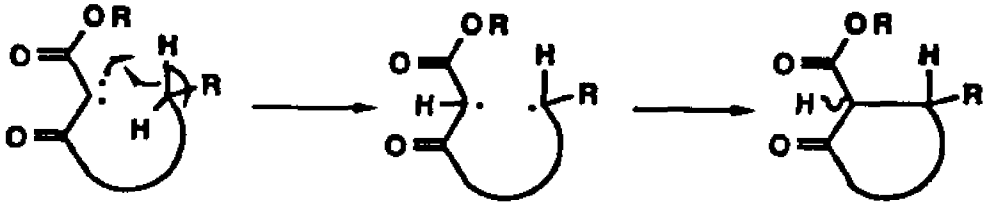
concentrated organic crude product was purified to afford 34% yield of the β-lactone **56**. The IR spectrum (1840 cm^{-1}) and the ^1H NMR (δ=1.32 doublet 3H, *J*=7.2 Hz) confirmed the formation of this lactone. We did not observe any formation of the cyclized compound **57**, and we do not know if any of it was formed under the above conditions.

Scheme 6



It is possible that the formation of **57** did not occur due to the unfavorable carbene insertion into a neopentyl carbon-hydrogen bond. We recognized that the formation of a four-membered ring lactone was a very new carbene insertion reaction, since previous[7] reports showed that all carbenes generated with rhodium diacetate as a catalyst inserted to form five-membered rings. However, we decided that there was no reason to continue trying to form the six-membered ring using rhodium diacetate as a catalyst since compound **57** was not formed in any appreciable yield (Scheme 7).

Scheme 7



X **XI** **XII**

The reactivity of the methylene group attached to a carboxylic group towards a carbene generated by rhodium diacetate to form a four-membered ring was a new process which needed further investigation, as well as application, in different systems. For example we considered the reactivity of the methylene group attached to an amide for the formation of β-lactam derivatives. Discussion of the work done in this direction will be presented at the end of this chapter.

The failure of the carbene insertion for the preparation of key intermediate for the total synthesis of shikodonin, indicated that other synthetic approaches should be explored. We realized that other attempts to utilize the bicyclic system **42** to produce the tricyclic intermediate would probably not lead to any reasonable success, since even if we did find a way to

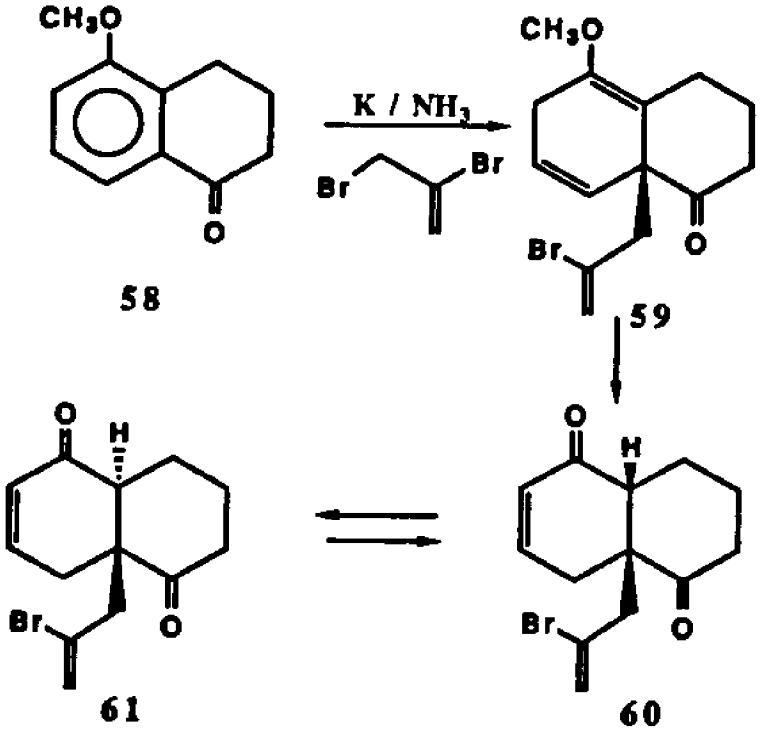
efficiently construct a tricyclic system, since there would be no way to ensure the formation of an axial carbon-carbon bond at C-2, because of epimerization at that carbon center.

We therefore decided that the most logical way to achieve our goal was to introduce the required substituent before we constructed the 1,3-fused five-membered ring onto the six-membered ring, by free radical cyclization.

6.2.0. Birch Reduction-Alkylation on 5-methoxy-tetralone, 58.

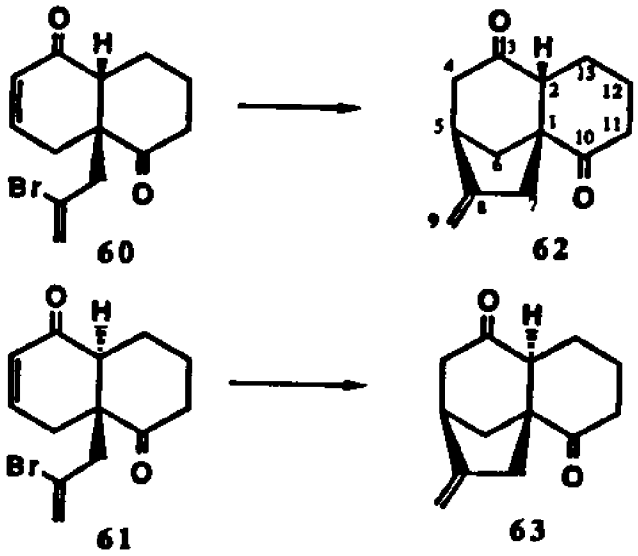
A review of studies on the Birch reduction[8] and alkylation, showed that successful reductive alkylations had been done on tetralone systems. 5-methoxy-tetralone has the required features so that after reductive alkylation the product would give the required carbon skeleton for the construction of a tricyclic system (Scheme 8).

Scheme 8



A successful reductive alkylation on 5-methoxy-tetralone **58** was performed by dissolving it in a mixture of 3:1 ammonia:THF and adding potassium metal until the blue color persisted at -78° C. After the mixture was stirred for 40 minutes at -33° C, the mixture was cooled to -78° C and the potassium counter-ion was replaced by lithium, by adding dried lithium bromide to the reaction mixture. After 30 minutes of stirring the ammonia was evaporated under a nitrogen atmosphere, then 2,3-dibromopropene was added at -78° C. A careful workup afforded compound **59** in 86% yield. The interesting points about the above reaction was that: **a)** we did not have to use any proton source other than ammonia; and **b)** ammonia should be removed before the alkylating reagent was injected into the reaction flask. Hydrolysis of **59** in a mixture of THF:10% HCl 2:1 ratio, gave a mixture of *cis*- and *trans*-**60** and **61** in approximately 1:1 ratio after stirring at room temperature for three hours. When the stirring continued for six more hours the ratio of **60**:**61** changed into 2:1. This mixture was separable by column chromatography (1:6 ethyl acetate:hexane, $R_f = 0.5$, $R_f = 0.4$). At this point we were not able to distinguish between the two isomers, but further chemistry would probably make the identification of the two isomers easier.

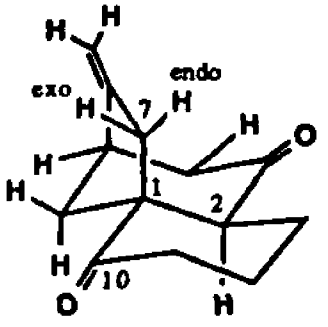
Scheme 9



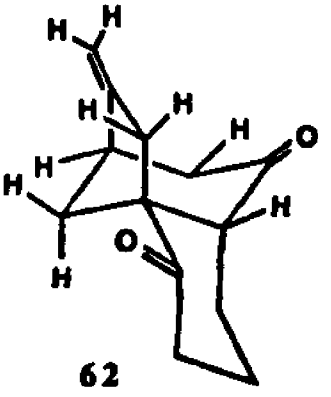
Compounds **60** and **61** were subjected to free radical cyclization conditions described earlier in chapter 2. The tricyclic diketone **63** was formed in 91% yield from **61** (upper spot on the TLC). Similarly the tricyclic system **62** was formed from **60** in 90% yield (Scheme 9).

A model of ketone **62** (*cis*-isomer) showed that the two hydrogens attached to C-7 ought to experience different magnetic fields from each other. The exo-hydrogen was located in the deshielding region of the carbonyl at C-10, therefore the chemical shift for this proton was δ 3.10 (dd, J = 18 Hz, J = 3 Hz), whereas for the endo-hydrogen the chemical shift was δ 2.6. In the *trans*-isomer **63** the two protons at C-7 give a broad signal which was integrated for two protons at δ 2.7 (Scheme 10).

Scheme 10



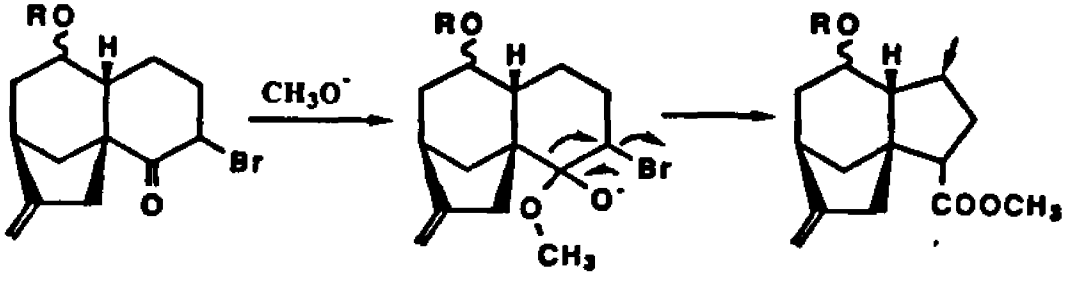
63



62

In order to use the tricyclic compound **62** for the projected synthesis, we would have to perform a ring contraction in order to convert it to the correct carbon skeleton. A possible plan for this is showed in scheme 11.

Scheme 11



Comparing the above results with what is projected to be done (see retrosynthetic analysis for the synthesis of key intermediates for total synthesis of natural products) it seemed that the system **63** could not be used for our planned synthesis because of the *trans-* conformation. For the tricyclic compound **62**, additional problems could be raised in the effort to differentiate between the two carbonyl group, as well as in making the C-10 a quarternary center. While it did not seem possible to make further plans for utilizing **62**, we had an insight into using a different aromatic system, which could be an aromatic ring fused to a five-membered ring. Since the six-membered ring gave a mixture of *cis-* and *trans-* ring-fused products in a 2:1 ratio, we reasoned that the indane-like system should only give the *cis-* isomer because in the indanes the *cis*-ring fusion is more stable than the *trans*-ring fusion. We therefore chose to use the 4-methoxyphthalide, as our starting compound.

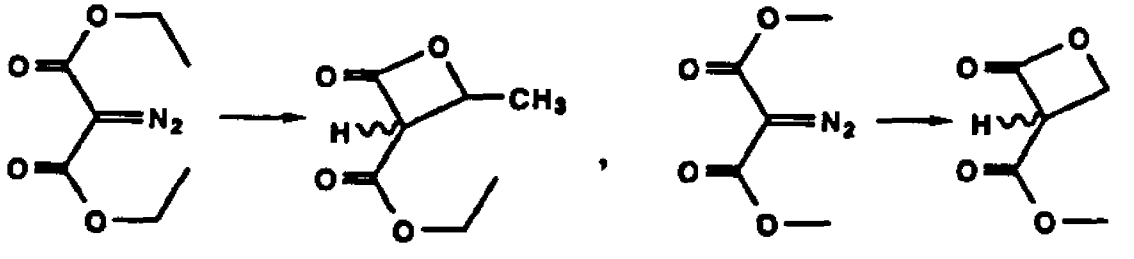
6.3.0. Carbenes for the synthesis of β-lactams.

In our efforts to utilize carbenes generated from diazomalonates after treatment with catalytic amount of rhodium diacetate for the formation of the tricyclic system **57**, we surprisingly observed the formation of a β-lactone derivative **56**. The appreciable yield (34%) in which **56** was formed indicated to us that the reaction could be used in more general way.

Therefore the compounds **64, 65, 66a,** and **67a** were prepared, via the same route described earlier for the synthesis of similar diazo compound **55** (Scheme 6).

Compound **64** was subjected to carbene insertion reaction conditions to give β-lactone **68** in quantitative yield. The formation of the four-membered lactone was confirmed by the strong absorption bands in the IR spectrum at 1840 cm^{-1} which corresponds to the carbonyl of the lactone ring. The ^1H NMR shows selectivity of *trans-* to *cis-* in a ratio almost 10:1 (Scheme 12). However, the hydrogen between the two carbonyl groups is highly epimerizable and, therefore, it probably plays a major role in this observed *cis-* to *trans-* ratio.

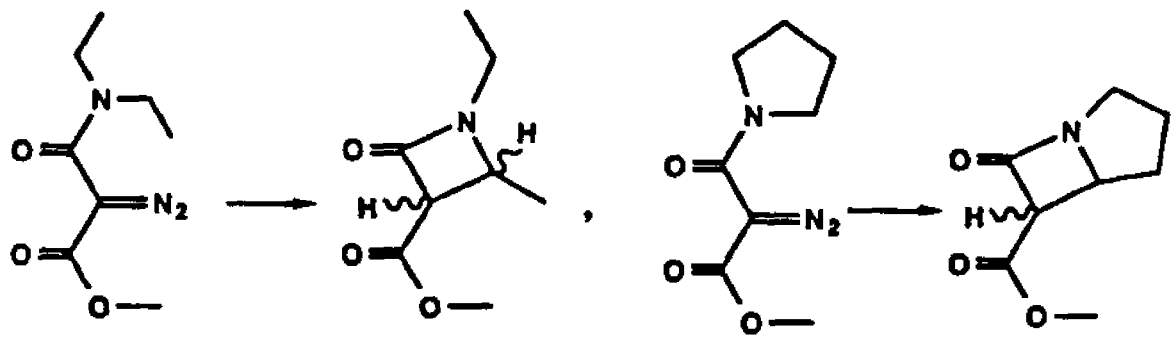
Scheme 12



Compound **65** gave the β-lactone **69** in an extremely slow reaction. After 24 hours more than 75% of the starting material was still unreacted.

Our efforts were then focused on the use of compounds **66a** and **67a** for the synthesis of β-lactams and penicillins analogues, as well as to examine the role of N or O in the reaction selectivity (scheme 13). The formation of the β-lactam **70** from **66a**, although a slow reaction, was quite successful. Again the ^{1}H NMR spectrum of **70** shows a high selectivity of the formation of *trans*- versus *cis*- product. The utility of **67a** for the synthesis of the penicillin analogue **71**, did not work. After 24 hours of stirring the reaction mixture remain unchanged and no formation of the lactam **71** was observed. A large strain of the five-membered ring should be the cause of this failure. However further investigation is necessary to prove if the replacement of the C-3 carbon with sulfur would reduce the strain and consequently would allow the formation of a true penicillin derivative.

Scheme 13



66a **70** (*cis*:*trans* 1:10) **67a** **71**

EXPERIMENTAL

General. Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton nuclear magnetic resonance (1H) spectra were determined on a Varian EM-360A (60 MHz), or on a IBM NR/300 FT NMR (270 MHz), or on a IBM WP/200-SY (200 MHz), and or on a JEOL/JNM/GX-400 FT NMR spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=double, t=triplet, q=quarter, m=multiplet, br=broad), assignment, integration, coupling constant. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer and on Finnigan CH5 single focusing mass spectrometer. Thin-Layer chromatography (TLC) was performed with 13181 silical gel with fluorescent indicator (Kodak) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silical gel 60 mesh. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY).

Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Preparation of 45.

Compound **42** (0.83 g, 5.0 mmol) and 3,4-dihydro-2H-pyrane (0.63 g, 7.5 mmol, 0.71 mL), (97%), were dissolved in dried methylene chloride (25 mL) under a nitrogen atmosphere at 0° C. To the above stirring solution, PTSA (20 mg) was added as catalyst. The reaction was monitored by TLC (hexane:ethyl acetate, 4:1, starting material's R_f = 0.35) every 15 min. The reaction was completed in 45 min. The reaction mixture was neutralized by the addition of few drops of pyridine and after 15 min of stirring at 0° C the solution was saturated with $NaHCO_3$. The stirring was continued for an additional 15 min and then water (10 mL). The reaction mixture was extracted with three 30-mL portions of diethyl ether. The combined organic extracts was dried, filtered, and concentrated by rotary evaporator. The liquid residue was chromatographically purified to give the colorless liquid tetrahydropyranyl derivative **45** in 96% yield (1.20 g): IR (neat, cm^{-1}) 3080 (w),2950 (s), 2870 (m), 1715 (s), 1660 (w); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.20-4.95 (m, 2H), 4.65 (s, br, 1H), 4.05-3.15 (m, 4H), 3.05 (m, 1H), 2.50-2.20 (m, 6H), 1.85 (s, br, 2H), 1.75-1.45 (m, 6H); mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ *m/e* 250.1569, obsd *m/e* 250.1572.

Preparation of acetate 42b.

A 100-mL three-necked round bottom flask equipped with a condenser and magnetic bar was charged with hydroxy ketone **42** (1.66 g, 10.0 mmol) dissolved in anhydrous diethyl ether (40 mL). To this solution were added, dropwise, two solutions, one made of pyridine (1.19 g, 15.0 mmol in 15 mL ether) and the other made of ethyl chloroformate (1.20 g, 11.0 mmol in 20 mL ether) at 0° C, over 1 hr, so that each addition ended simultaneously. After stirring for an additional 1 hr, the resulting precipitate was removed by

filtration. The filtrate was extracted with ether, the extract was washed with water, and then dried over magnesium sulfate. After filtration, the solvent was removed by rotary evaporator and the crude product was chromatographically purified (hexane:ethyl acetate, 3:1, R_f = 0.3) to give **42b** (2.31 g, 97% yield) as colorless liquid: IR (neat, cm^{-1}) 3090 (w), 3000 (m), 2960 (s), 2900 (m, shoulder), 1750 (s), 1715 (s), 1660 (w); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.15-4.85 (m, 2H), 4.10 (q, 2H, J = 6 Hz), 4.00 (s, 2H), 3.05 (m, 1H), 2.40-2.15 (s, br, 6H), 1.85 (d, br, 2H), 1.15 (t, 3H, J = 6 Hz); mass spectrum, exact mass calcd for $C_{13}H_{18}O_4$ *m/e* 238.1205, obsd *m/e* 238.1201.

Preparation of 46.

A 100-mL two-necked round-bottom flask, equipped with a condenser and magnetic bar, was charged with hydroxyl ketone **42** (1.66 g, 10.0 mmol) and bromosuccinimide (1.96 g, 11.0 mmol) in dry methylene chloride (60 mL) under nitrogen. Into this stirring solution was injected 1.15 mL (0.87 g, 12.0 mmol) of ethyl vinyl ether, through a rubber septum, at 0° C. The reaction mixture was stirred for 1 hr at room temperature, then the floating succinimide was removed by filtration, and the filtrate was concentrated by rotary evaporator. The residue was purified by column chromatography (hexane:ethyl acetate, 4:1, R_f = 0.35) to afford the bromo-acetal **46** (2.92 g, 92% yield) as a colorless liquid: IR (neat, cm^{-1}) 3090 (w), 3000 (s), 2950 (s), 2910 (s), 2880 (m), 1720 (s), 1660 (w); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.05-4.80 (m, 2H), 4.65 (t, 1H, J = 6 Hz), 3.75-3.35 (m, 6H), 2.95 (m, 1H), 2.45-2.15 (m, 6H), 1.90-1.65 (m, 2H), 1.20 (t, 3H, J = 6 Hz); mass spectrum, exact mass calcd for $C_{14}H_{21}O_3Br_1$ *m/e* 316.0674, obsd *m/e* 316.0671.

Preparation of compound 48.

The bromo-acetal **46** (1.59 g, 5.0 mmol), as a mixture of two diastereo-isomers, was dissolved in anhydrous benzene (50 mL), to which potassium tert-butoxide (1.12 g, 10.0 mmol) was added at room temperature. The reaction mixture was stirred for 3 hrs at room temperature and then 5% HCl (50 mL) was added at 0°C. The reaction mixture was extracted with three 30-mL portions of ethyl acetate, the combined organic layers was washed with saturated aqueous sodium bicarbonate, and dried over magnesium sulfate. Removal of the solvent gave the residue, which was purified by column chromatography (20% ether in methylene chloride) to afford the tricyclic compound **48** (2.22 g, 94% yield): IR (neat, cm^{-1}) 1720 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.05-4.80 (m, 2H), 4.70 (t, 1H, J = 5.5 Hz), 4.85-3.35 (m, 4H), 2.95 (m, 1H), 2.65-2.15 (m, 5H), 1.95-1.65 (m, 4H), 1.2 (t, 3H, J = 6 Hz).

Preparation of ethyl potassium malonate 52.

Potassium hydroxide (5.6 g, 100 mmol) was dissolved in 100 mL of absolute ethanol, and this solution was added dropwise to a stirred solution of diethylmalonate **51** (20.225 g, 100 mmol) in 100 mL absolute ethanol, at 0°C, during one hour. The reaction mixture was then allowed to warm up to room temperature and the stirring continued for an additional 1 hr. The white crystals of **52** were separated by vacuum filtration and dried under vacuum for 3 hrs.

Preparation of ethyl malonoyl chloride 53.

Oxaloyl chloride (3.18 g, 25 mmol) in 10 mL of dried benzene was added dropwise to a stirring suspension of ethyl potassium malonate **52** (2.42 g, 20 mmol) in dried benzene (50 mL) at 0°C during one hour. After the solution

had been stirred at room temperature for 1 hr, the solid residue was removed by filtration and the filtrate, which contained the product, was concentrated by rotary evaporation of the benzene to give **53** (3.61 g, 90% yield).

Preparation of 42c.

A 100-mL three-necked round bottom flask was charged with the hydroxy ketone **42** (1.66 g, 10.0 mmol) dissolved in methylene chloride (40 mL). To this stirring solution were added dropwise two solutions, of pyridine (1.19 g, 15.0 mmol in 15 mL methylene chloride) and 3,5-dinitrobenzoyl chloride (2.54 g, 11.0 mmol in 20 mL methylene chloride), at 0°C, during 1 hr, so that each addition ended simultaneously. After stirring for an additional 1 hr, the resulting precipitate was removed by filtration. The filtrate was extracted with methylene chloride, and the extract was washed with water, and dried over sodium sulfate. After filtration the solvent was removed by rotatory evaporator and the crude product was purified by recrystallization (hexane:ethyl alcohol, 1:3) to give white crystals of **42c** (m.p. 159-160° C): ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 9.20 (s, br, 3H), 5.05 (m, 2H), 4.45 (s, 2H), 3.05 (m, 1H), 2.50-2.25 (m, 2H), 2.20 (m, 6H); IR (neat, cm^{-1}) 3090 (w), 3020 (m), 2960 (s), 2890 (m), 1735 (s), 1715 (s), 1535 (s). Anal. Calcd for $C_{17}H_{16}O_7N_2$: C, 56.67; H, 4.48; N, 7.77. Found: C, 55.97; H, 4.50; N, 7.54.

Preparation of 54.

Under identical conditions as they are described above, compound **54** was prepared by treatment of **42** (1.66 g, 10.0 mmol) with ethyl malonoyl chloride **53** (1.66 g, 11.0 mmol) to give 2.58 g (92% yield) of colorless liquid: IR (neat, cm^{-1}) 3060 (w), 2970 (s), 2935 (s), 1745 (s), 1720 (s), 1655 (w); ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 5.10-4.85 (m, 2H), 4.15 (q, 2H, J = 6 Hz), 4.10 (s, 2H), 3.40 (s, 2H),

3.00 (m, 1H), 2.45-2.25 (m, 6H), 1.85-1.65 (m, 2H), 1.25 (t, 3H, J = 6 Hz); mass spectrum, exact mass calcd for $C_{15}H_{20}O_5$ *m/e* 2080.1311, obsd *m/e* 280.1313.

Preparation of amide 66 and 67.

Under the previously described conditions for the preparation of **54** we prepared the following compounds. For this, methyl malonoyl chloride was prepared in the same way as ethyl malonoyl chloride was prepared:

Compound **66** was prepared by treatment of methyl malonoyl chloride with two equivalents of diethylamine: IR (neat, cm^{-1}) 2970 (m), 2875 (m), 1710 (s), 1620 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 3.90 (s, 3H), 3.60 (s, 2H), 3.55 (q, 4H, J = 6 Hz), 1.50 (t, 6H, J = 6 Hz); mass spectrum, exact mass calcd for $C_8H_{15}O_3N_1$ *m/e* 173.1052, obsd *m/e* 173.1052.

Compound **67** was prepared by treatment of methyl malonoyl chloride with two equivalents of pyrrolidine: IR (neat, cm^{-1}) 2955 (m), 2880 (m), 1715 (s), 1615 (s); $_1H$ NMR (60 MHz, $CDCl_3$, ppm) 3.90 (s, 3H), 3.65 (m, 4H), 3.60 (s, 2H), 2.00 (m, 4H); mass spectrum, exact mass calcd for $C_8H_{13}O_3N_1$ *m/e* 171.0895, obsd *m/e* 171.0897.

Preparation of diazo compounds.

Compound 55.

Malonate **54** (2.80 g, 10.0 mmol) was dissolved in dried acetonitrile (30 mL), triethylamine (1.22 g, 12.0 mmol) and tosyl azide (2.37 g, 12.0 mmol) were each added to the solution. The mixture was stirred for 12 hours at room temperature. After evaporating the solvent, the reaction product was suspended in ether (50 mL) and the insoluble material was removed by

filtration. The filtrate was washed with 1 N NaOH, water and brine, and dried over magnesium sulfate. After filtration and removal of the solvent the residue was purified by column chromatography (hexane:ethyl acetate, 3:1, R_f = 0.45) to provide the diazo compound **55** (3.00 g, 98% yield) as a greenish liquid: IR (neat, cm^{-1}) 3050 (w), 2960 (m, shoulder) 2925 (s), 2120 (s), 1750 (s), 1725 (s), 1710 (s), 1680 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.15-4.85 (m, 2H), 4.30 (q, 2H, *J* = 6 Hz), 2.25 (s, 2H), 3.05 (m, 1H), 2.55-2.25 (m, 6H), 1.85-1.65 (m, 2H), 1.35 (t, 3H, *J* = 6 Hz); mass spectrum, exact mass calcd for $C_{15}H_{18}O_5N_2$ *m/e* 306.1216, obsd *m/e* 306.1212.

Preparation of 56.

The diazo **55** (1.53 g, 5.0 mmol) was dissolved in dried methylene chloride (15 mL) (passed through potassium carbonate column) under nitrogen. Then 10 mg (catalytic amount) of rhodium diacetate was added and the solution was stirred at room temperature for 1.5 hr. Gas evolution was observed and the mixture turned brown. The reaction's course was followed by TLC every 15 min. The diazo compound had reacted in 45 min. After that the reaction mixture was diluted with 4% aqueous HCl (20 mL) and the mixture was extracted with two 30-mL portions of methylene chloride. The combined organic extracts was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated by rotary evaporator. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate, 2:1, R_f=0.5) to give compound **56** (0.47 g, 34% yield). The compound was identified only by the presence of a doublet in the NMR spectrum at 1.75 ppm for the methyl group attached to the β-lactone as well as the absorbance in the IR spectrum at 1840 cm^{-1}.

Under the same conditions used for the preparation of the diazo-compound **55** we prepared the following diazo-compounds.

Compound **64**: IR (neat, cm^{-1}) 2985 (s), 2940 (m), 2810 (w), 2140 (s), 1730 (s), 1680 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 3.95 (q, 4H, J = 6 Hz), 1.20 (t, 6H, J = 6 Hz); mass spectrum, exact mass calcd for $C_7H_{10}O_4N_2$ *m/e* 186.0641, obsd *m/e* 186.0637.

Compound **66a**: IR (neat, cm^{-1}) 2960 (m), 2870 (w), 2110 (s), 1710 (s), 1620 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 3.90 (s, 3H), 3.60 (q, 4H, J = 6 Hz), 1.45 (t, 6H, J = 6 Hz); mass spectrum, exact mass calcd for $C_8H_{13}O_3N_3$ *m/e* 199.0957, obsd *m/e* 199.0961.

Compound **67a**: IR (neat, cm^{-1}) 2950 (m), 2870 (w), 2105 (s), 1705 (s), 1605 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 3.95 (s, 3H), 3.50 (m, 4H), 2.10 (m, 4H); mass spectrum, exact mass calcd for $C_8H_{11}O_3N_3$ *m/e* 197.0800, obsd *m/e* 197.0804.

Compound **64** was treated with rhodium diacetate, as was described in the preparation of **56**, to give the β-lactone **68** in quantitative yield: IR (neat, cm^{-1}) 2970 (s), 2925 (m), 1835 (s), 1730 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 4.90 (dq, 1H, J = 4 Hz, J = 6 Hz), 4.30 (q, 2H, J = 7 Hz), 4.15 (d, 1H, J = 4 Hz), 1.65 (d, 3H, J = 6 Hz), 1.35 (t, 3H, J = 7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 164.18, 162.52, 71.13, 62.21, 61.54, 19.49, 13.88; mass spectrum, exact mass calcd for $C_7H_{10}O_4$ *m/e* 158.0579, obsd *m/e* 158.0575.

Similarly β-lactam **70** was formed from **66a** by treatment with rhodium diacetate in methylene chloride at room temperature for 12 hrs. After workup 60% of the starting material was recovered and the rest was converted quantitatively to **70**: IR (neat, cm^{-1}) 2960 (m), 2930 (m), 2870 (w), 1755 (s), 1725 (s); ^1H NMR (200 MHz, $CDCl_3$, ppm) 3.94 (dq, 1H, J = 2.25 Hz, J = 6.17 Hz), 3.34 (s, 3H), 3.52 (d, 1H, J = 2.25 Hz), 3.37 (dt, 1H, J = 21.54 Hz, J = 7.26 Hz), 3.08 (dt, 1H, J = 21.17 Hz, J = 6.92 Hz), 1.36 (d, 3H, J = 6.17 Hz), 1.18 (t, 3H, J = 7.32); mass spectrum, exact mass calcd for $C_8H_{13}O_3N_1$ *m/e* 171.0895, obsd *m/e* 171.0896.

Preparation of 45d (lithium diisopropylamide, LDA, alkylation of 3-methoxycyclohex-2-en-1-one, 45c)

A dry, 250-mL, three-necked, round bottomed flask was equipped with a magnetic bar, and a condenser, which was fitted with a three-way adapter. The other two necks were each fitted with a rubber septum. The air in the system is replaced by alternatively evacuating and filling the system with dry nitrogen, three times; a rubber balloon filled with dry nitrogen, attached to the three-way adapter, was used to maintain a positive pressure of nitrogen throughout the reaction. The flask was charged with 50 mL of dry THF, freshly distilled from sodium and benzophenone, and 1.11 g (1.54 mL, 11 mmol) of dry diisopropylamine, distilled from calcium hydride. The flask was cooled to 0°C in an ice bath. A 10.5-M hexane solution of n-butyllithium (1.0 mL, 10.5 mmol) was added dropwise with stirring over a 20-min period. The resulting lithium diisopropylamide was cooled to -78°C in a dry ice-acetone bath. After an hour a solution of 1.26 g (10.0 mmol) of 3-methoxy-cyclohex-2-en-1-one in 40 mL of dry THF was added dropwise with stirring at -78°C over a 1 hr period. The solution was stirred at -78°C for 30 min followed

by rapid addition of 2.15 g (1.78 mL, 11.0 mmol) of tert-butyl-bromoacetate. After 5 min, the cooling bath was removed, the mixture was allowed to warm to room temperature, and was stirred overnight. The reaction was quenched with 30 mL of water and the organic layer was extracted four times with 20 mL of diethyl ether. The combined organic extracts was washed twice with 20 mL of water, once with 15 mL of brine, and dried over magnesium sulfate. After filtration the solvent was removed by rotary evaporator followed by chromatographic purification to afford **72** (2.26 g, 94% yield) as a colorless liquid: IR (neat, cm^{-1}) 3070 (w), 2980 (m), 1740 (s), 1665 (s), 1620 (m); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.75 (s, 1H), 4.05 (s, 3H), 3.35-2.10 (m, 7H), 1.55 (s, 9H); mass spectrum, exact mass calcd for $C_{13}H_{20}O_4$ *m/e* 240.1361, obsd *m/e* 240.1363.

Preparation of 60.

A 100-mL three-necked round bottomed flask equipped with a dry ice-condenser and a magnetic bar was charged with 5-methoxy-1-tetralone **58** (1.76 g, 10.0 mmol) dissolved in dry THF (25 mL), under nitrogen. Into this solution, 55 mL of dry ammonia was distilled (from sodium metal) at -78°C. Then, potassium metal (858 mg, 22.0 mmol) that had been washed in hexane, was carefully added in small pieces. After the solution turned blue, indicating that enough metal had been added for the reduction, the solution was stirred for 45 min at -33°C, and then the ammonia was allowed to evaporate in the hood aided by a stream of nitrogen. Traces of ammonia were removed by evacuating the flask. The solution was cooled to -78°C and anhydrous lithium bromide (0.96 g, 11.0 mmol) was added. The solution was stirred for 15 min and 2,3-dibromopropene (2.2 g, 1.1 mL, 11 mmol) was added rapidly at -78°C. The solution was stirred for 30 min at -78°C and then for additional 45 min at room temperature. The solvent was removed in vacuo and the

residue was diluted with 50 mL of water before it was extracted with three 30-mL portions of ethyl acetate. The combined organic extracts was dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography to give **59** (2.55 g, 86% yield) as a colorless liquid: IR (neat, cm^{-1}) 3040 (m), 2930 (s), 2860 (m), 2830 (m), 1700 (s), 1650 (m), 1620 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.85 (s, m, 2H), 5.50 (s, 2H), 3.55 (s, 3H), 3.15-1.85 (m, 10H).

Compound **59** (2.55 g, 8.6 mmol) was dissolved by stirring in 26 mL of 10% HCl:THF, 1:2 ratio. Hydrolysis was completed in 6 hrs and after workup the products **60** (upper spot on TLC, 1.58 g, 56% yield from **58**) and **61** (lower spot on TLC, 0.71 g, 25% yield from **58**) were separated by chromatography. Compound **60** which we suspected to be the *cis*-isomer had the following spectroscopic data: IR (neat, cm^{-1}) 3050 (w), 2950 (s), 2880 (m), 1710 (s), 1675 (s), 1625 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm), 6.90 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.05 (dt, 1H, J = 10 Hz, J = 2 Hz), 5.60 (s, 2H), 3.10-1.85 (m, 11H).

Preparation of diketone 62.

Compound **60** (0.57 g, 2.1 mmol) was transformed to the tricyclic compound **62** (0.41 g, 96% yield) with tri-n-butyltin hydride in benzene under previously described conditions: IR (neat, cm^{-1}) 3080 (w), 2950 (s), 2870 (m), 1740 (shoulder), 1705 (s), 1660 (m); ^1H NMR (200 MHz, $CDCl_3$, ppm) 4.98 (s, br, 1H), 4.92 (s, br, 1H), 3.20 (ddd, 1H, H-7_{ex}, $J_{(H\text{-}7_{ex},\ H\text{-}7_{en})}$=16.12, $J_{(H\text{-}7_{ex},\ H\text{-}9)}$=2.90, $J_{(H\text{-}7_{ex},\ H\text{-}9)}$=2.90), 2.98 (m, 1H, H-5), 2.61 (dd, 1H, H-4_{eq}, $J_{(H\text{-}4_{eq},\ H\text{-}4_{ax})}$=19.53, $J_{(H\text{-}4eq,\ H\text{-}5)}$=5.86), 2.52-2.32 (m, 5H), 2.16-1.16 (m, 6H);

REFERENCES

1. Kubo, I.; Pettei, M. J.; Hirotsu, K.; Tsuji, H.; Kubota, T., *J. Am. Chem. Soc.*, **1978**, 100, 628.
2. Kieczykowski, G. R.; Schlessinger, R, H., *J. Am. Chem. Soc.*, **1978**, 100, 782.
3. Kuo, F., Ph.D. Thesis, Purdue University, **1986**.
4. Kuo, F.; Fuchs, P. L., *J. Am. Chem. Soc.*, **1987**, 109, 1122.
5. For the preparation of Tosyl Azide see *Org. Synth.*, Coll. Vol. V, p. 179.
6. Iio, H.; Isobe, M.; Kawai, T.; Goto, T., *Tetrahedron*, **1979**, 35, 941.
7. Taber, D. F.; Petty, E. H., *J. Org. Chem.*, **1982**, 47, 4808.
8. Brown, J. M.; Cresp, T. M.; Mander, L. N., *J. Org. Chem.*, **1977**, 42, 3984.

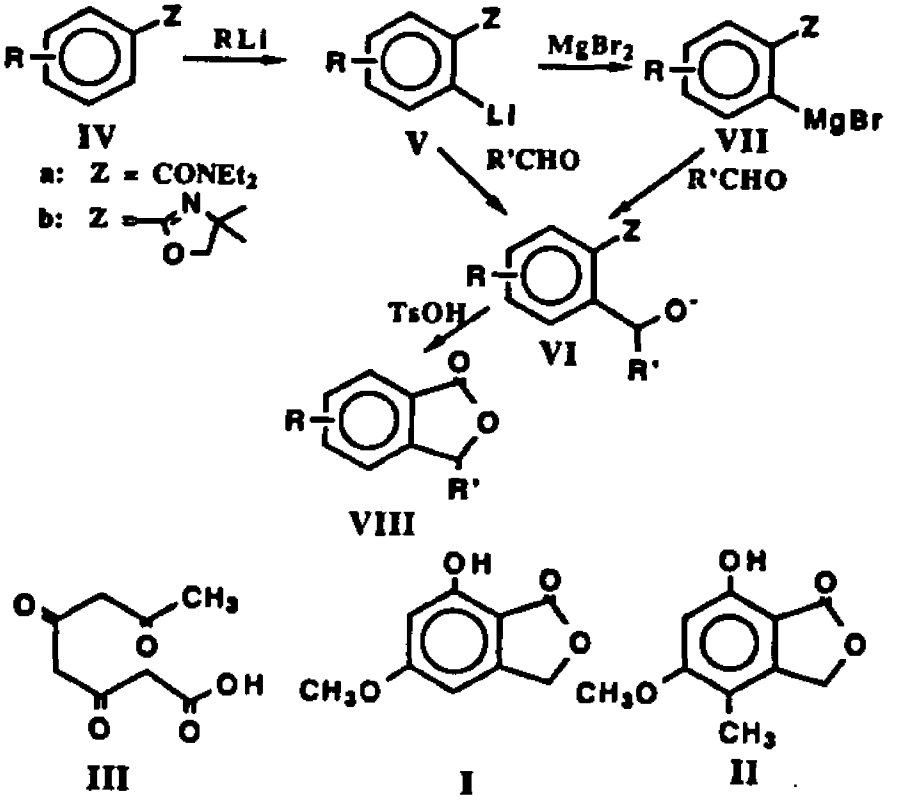
CHAPTER 7

SYNTHESIS OF PHTHALIDES

7.0.0. Introduction

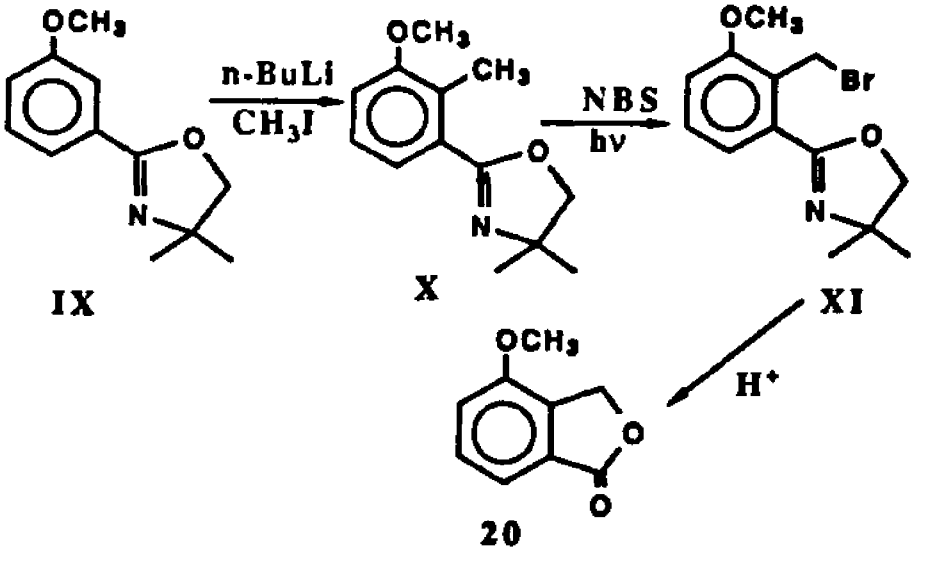
Several members of the phthalide family are naturally occuring compounds, like 5-methoxy-7-hydroxyphthalide[1] I, 4-methyl-5-methoxy-7-hydroxyphthalide[2] II, and many others.[3] These phthalides are derived biosynthetically[4] by the cyclization of a regular polyketide chain III with one secondary modification: oxidation of $-CH_3$ to $-CH_2OH$, a process that is a commonplace in nature.

Scheme 1



Several, synthetic organic chemists have reported almost identical approaches to the synthesis of phthalides in the chemical literature, namely synthesis from N,N-dialkylbenzamide by an *ortho* lithiation reaction, followed by hydroxyalkylation.[5] Snieckus and co-workers[6], by using the tertiary amide IV as an effective *ortho* metalation director, have demonstrated its utility for the construction of phthalides (Scheme 1). The *ortho*-lithiated benzamide V undergoes transmetalation with $MgBr_2{\cdot}2Et_2O$ to give VII. After quenching with different electrophiles, the resulting products VI were converted into phthalides VIII. Attempts to go directly from V to VI without performing lithium-magnesium transmetalation failed to give *ortho*-substituted products.

Scheme 2

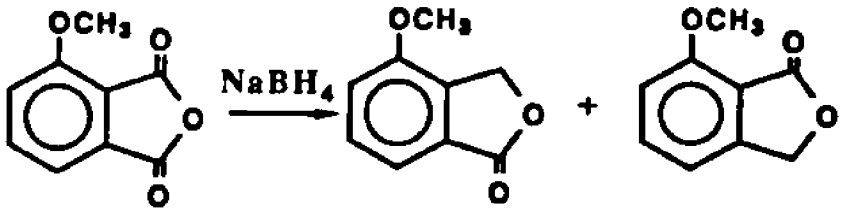


The preparation of 4-methoxyphthalide 20 was achieved[7] by treating the oxazoline IX with n-butyllithium at -45°C, followed by the addition of methyl iodide to give derivative X in 90% yield (Scheme 2). Bromination using NBS

gave the bromomethyl oxazoline XI, which was hydrolyzed in aqueous acid to give 20 in 94% yield.

The reduction of 3-methoxyphthalic anhydride XII can yield two isomeric lactones[8], 4-methoxyphthalide 20 and 7-methoxyphthalide 21. The regioselectivity of such a reduction depends on the metal hydride that is used. For example, sodium borohydride reduction gave a 87:13 ratio of 20 versus 21. The selectivity is dued to the chelation between the boron atom and the oxygen of the methoxy group (Scheme 3).

Scheme 3



XII 20 21

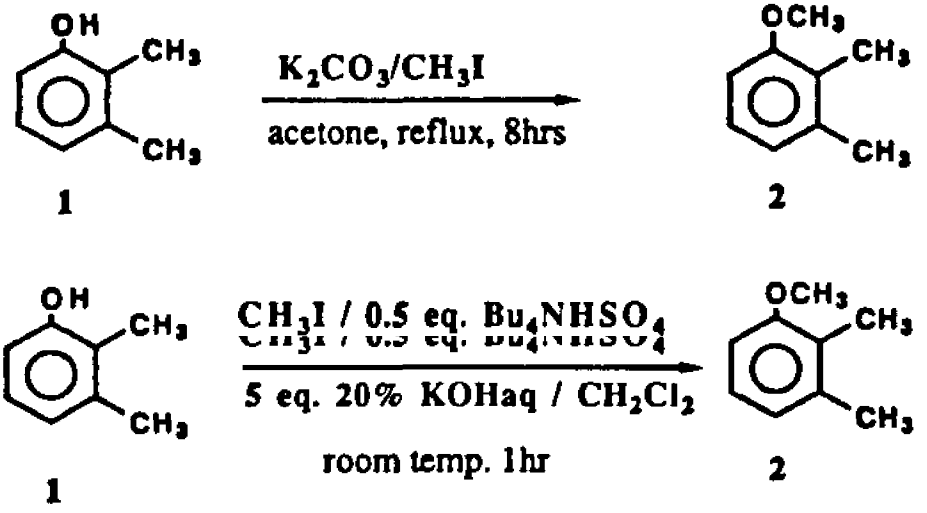
7.1.0. The synthesis of 4-methoxyphthalide 20.

Here we describe a new, versatile, and direct approach to the synthesis of 4-methoxyphthalide, which is also applicable to the preparation of several other phthalides.

Retrosynthetically, a phthalide can be regarded as being derived from an ortho-dialkylbenzene. These dialkylbenzenes are commercially available, or can be produced by simple synthesis via Diels-Alder reactions, or Friedel-Crafts alkylations of suitable compounds.

This retrosynthetic analysis led us to consider using 2,3-dimethylanisole **2**, which was prepared in our laboratory by the methylation of commercially available 2,3-dimethylphenol **1**, as shown in scheme 4.

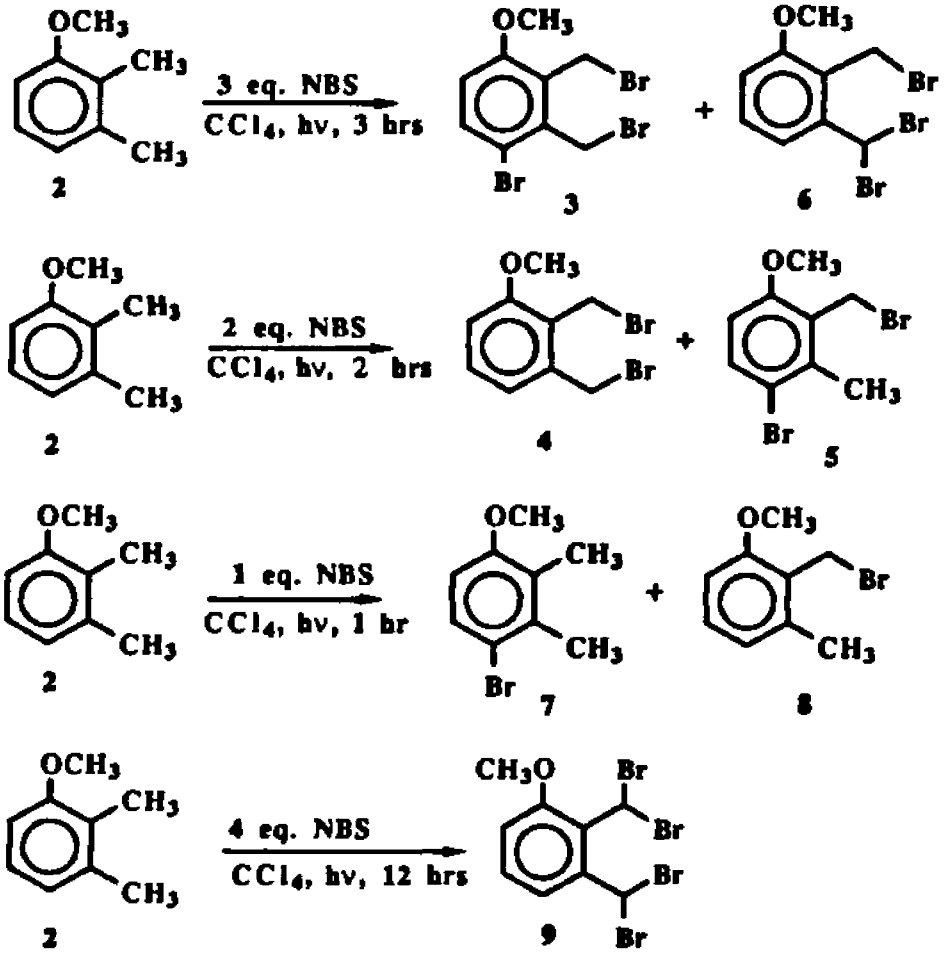
Scheme 4



One mole of 2,3-dimethylanisole **2** was subjected to allylic bromination with three equivalents of N-bromosuccinimide in carbon tetrachloride (0.1M). The formation of 2,3-bis(bromomethyl)-4-bromoanisole **3** was

different from previously reported results[9] in which 2-bromomethyl-3-dibromomethylphenyl acetate was prepared, and this dibromo compound was not ideal for our proposed synthesis (Scheme 5).

Scheme 5



Before we continued our investigation, we ascertained the experimental conditions which favored free radical over electrophilic aromatic substitution.

The electrophilic substitution of an aromatic ring by NBS in nonpolar solvents such as CCl_4 is well documented.[10] But even though we performed our experiments under conditions where NBS was supposed to react through a free-radical mechanism, we still observed a significant occurrence of electrophilic aromatic substitution.

Two equivalents of NBS reacted through a free-radical mechanism whereas the third equivalent engaged in an electrophilic substitution on the aromatic ring.

We first investigated using a 1:1 molar ratio between the aromatic substrate and NBS in various concentrations in CCl_4. Table I shows that the concentration of 2,3-dimethylanisole **2** in CCl_4 is the only factor which influences the ratio between the electrophilic substitution product and the benzyl bromide derivative. With increasing concentration of 2,3-dimethylanisole **2** in CCl_4, the amount of 2-bromomethyl-3-methylanisole **8** formed was reduced. Adding NBS to pure (100%) dimethylanisole **2** resulted in a violent reaction and dense fumes of HBr were liberated, giving 2,3-dimethyl-4- bromoanisole **7** as the only detected product.

Our conclusion was that as the average polarity of the reaction mixture increased, the rate of the electrophilic attack on the aromatic ring increased much faster than the rate of the free radical processes. With a 1:1 molar ratio of 2,3-dimethylanisole 2 to NBS, the optimal concentration of the dimethylanisole **2** solution for the formation of 2-bromomethyl-3-methylanisole **8** was 0.1 M. At any higher concentration, 4-bromo-2,3-dimethylanisole **7** was detected along with **8**.

Table I

a. Using 1.0 equiv. of NBS.

Concentration of **2** in CCl4	product **7**	product **8.**
neat	100%	0%
1.0 M	95%	5%
0.1 M	0%	100%

b. Using 2.0 equiv. of NBS.

	product **4**	product **5**	product **8.**
1.0 M	60%	30%	10%
0.1 M	90%	10%	0%
0.05 M	100%	0%	0%

c. Using 3.0 equiv. of NBS.

	product 3	product **4**	product 5	product **6.**
1.0 M	100%	0%	0%	0%
0.1 M	90%	5%	5%	0%
0.05 M	60%	30%	0%	10%
0.025 M	0%	10%	0%	90%

When 2 equivalents of NBS were used and the concentration of the starting material was above 0.05 M, three compounds were formed, 2,3-bis(bromomethyl)anisole **4**, 4-bromo-2-bromomethyl-3-methylanisole **5**, and 2-bromomethyl-3-methylanisole **8**.

When 3 equivalents of NBS were used and the concentration of the starting material was above 0.025 M, again compounds **3, 4, and 5** were formed along with the desired product, 2-bromomethyl- 3,3-dibromomethyl-anisole **6**. At 0.02 M concentration the tribromo compound **6** was the only one formed (100%).

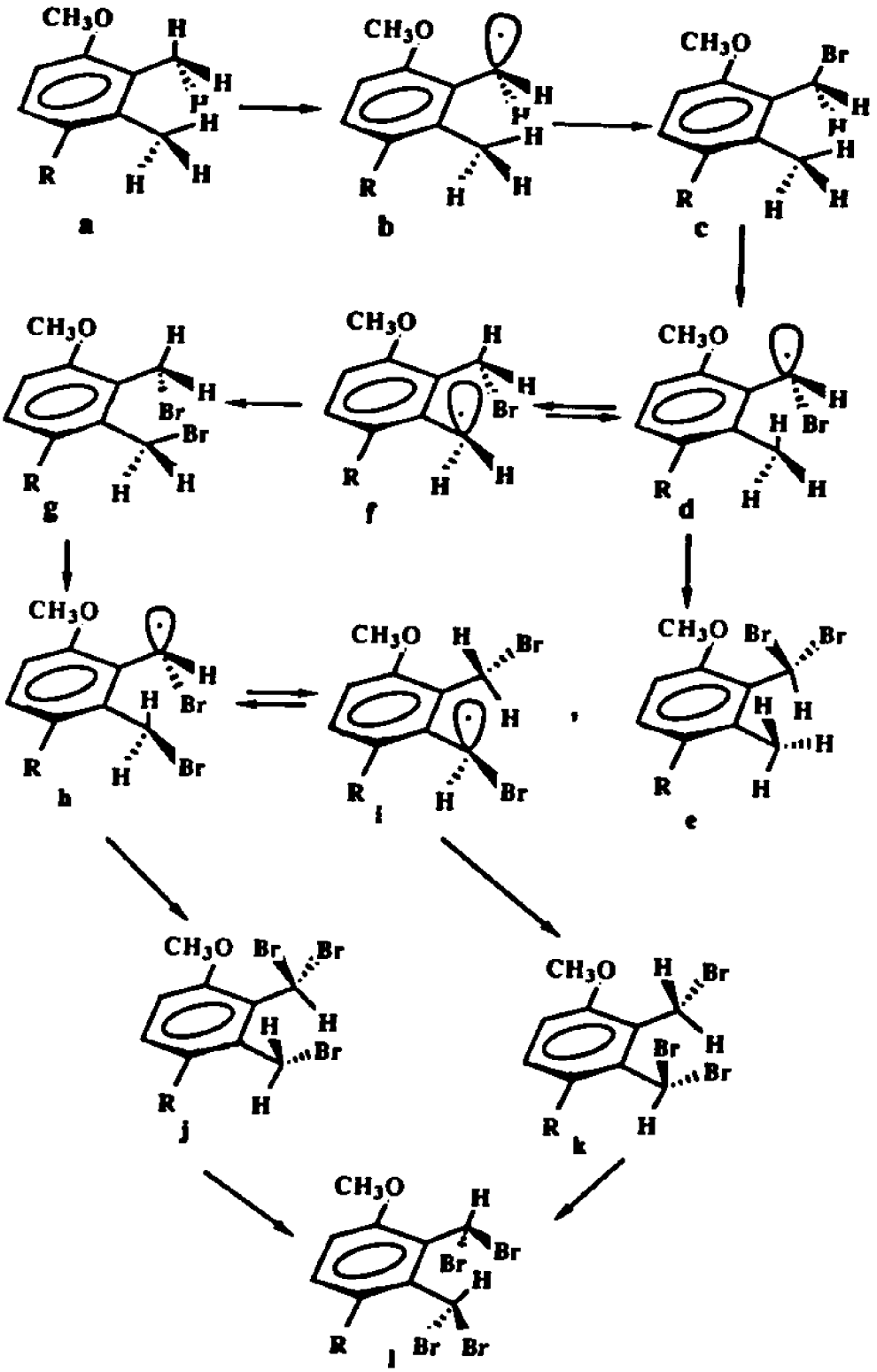
The tribromo-derivative **3** was subjected to further allylic bromination conditions by dissolving it in CCl_4 (0.025 M) and adding one equivalent of NBS. The solution was irradiated with a sunlight 250 watt lamp for 12 hours and, after removal of the solvent, the starting material was recovered without any further detectable bromination.

On the other hand, tribromo-derivative **6**, after 12 hours of irradiation, under the same conditions for allylic bromination with NBS underwent further bromination to provide 2,3-bis(dibromomethyl)-anisole **9**. After the last results were substantiated, we were able to derive a feasible mechanism for this sequence of brominations.

7.1.1. Proposed allylic bromination mechanism

The dimethylphenol derivative **a** (Scheme 6), during the propagation step of the free radical reaction, provided the most stable radical **b**, which then gave a monobromo derivative **c**. Compound **c** produced a new radical **d**, which can rearrange to radical **f**. These two radicals, **d** and **f**, would give the dibromo derivatives **e** and **g** respectively. The radical **f** should be less stable, and more reactive, than the radical **d**. Radical **d** should be more hindered than radical **f**. Thus the kinetically controlled processes favoured the formation of **g** from radical **f** and no **e** was observed in the reaction mixture.

Scheme 6



Compound **g** produced the radical **h**, which is in equilibrium with the radical **i**. If **R = H** then radical **i** reacts to give compound **k**, but if **R = Br** (Br is a large electron rich substituent) then radical **h** cannot easily give compound **j**, because of stereo-electronic interactions between the methoxy group and the 2-dibromomethyl-substituent, and radical **i** cannot easily give compound **k**, because of similar stereo-electronic interactions between the large 4-bromo-substituent and the 3-dibromomethyl substituent.

Therefore, if a bromine substituent is introduced on the 4-position of the aromatic ring, it then becomes very difficult to introduce a third bromine atom onto the side chains by free radical reaction.

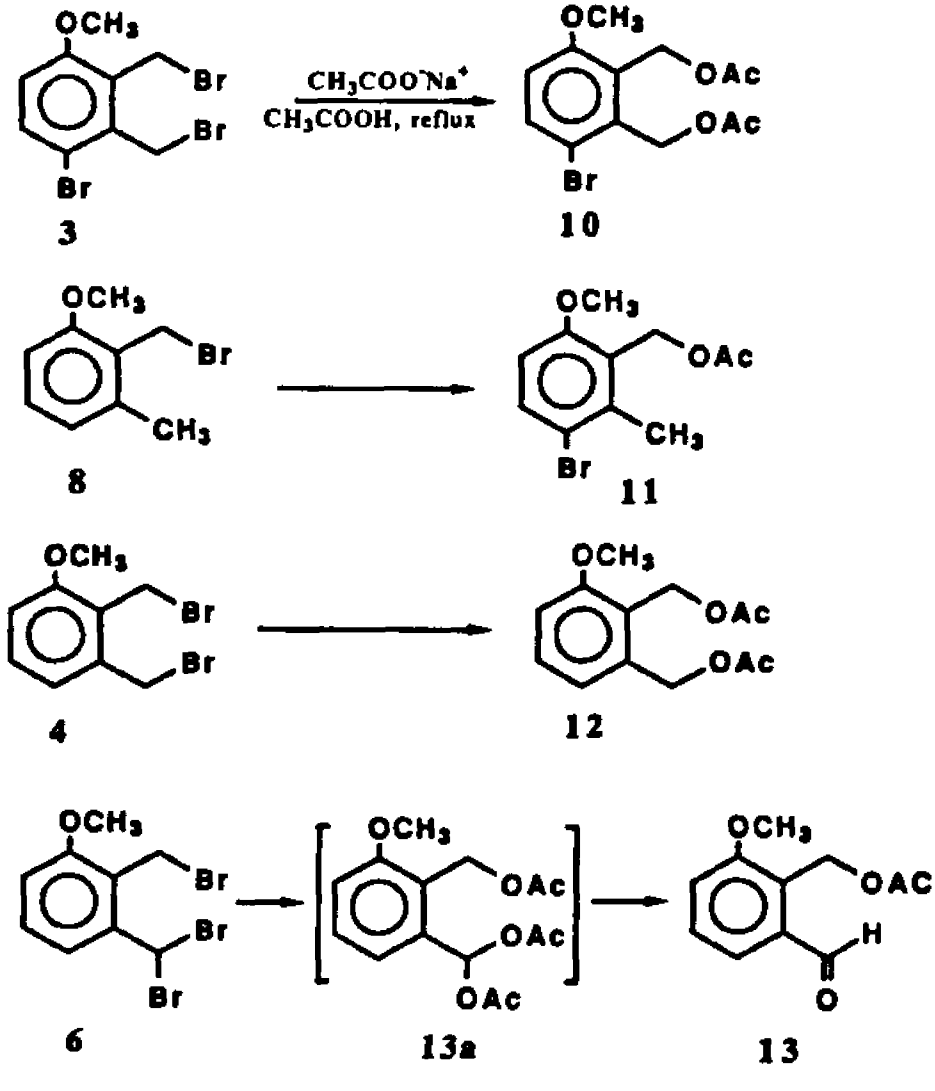
On the other hand, when **R=H** the compound **k**, by a fourth bromination gave compound **9**, which has a gearlike[11] structure in which CH hydrogen on the 2-dibromomethyl group is tucked into the cleft[12] formed by the two lone pair electrons of the 1-methoxy oxygen, and the hydrogen of the other 3-dibromomethyl group is tucked into the cleft formed by the two bromines of the neighboring group. The two dibromomethyl groups and the methoxy group form a tightly interlocking cyclic tongue-and-groove arrangement by virtue of cooperative nonbonded repulsions.

Thus it seems that the 4-bromine atom is a more efficient blocker of bromination on the 3-bromomethyl group than the 1-methoxy group is on the bromination of the 2-bromomethyl group. At present, this difference in reactivities seems largely due to the greater steric bulk of, and the greater electron density surrounding the bromine as compared to oxygen.

7.2.0. Formation of acetates 10, 12, and 13.

The nucleophilic substitution of the bromides by NaOAc in DMF, at 100° C, after 2 hours, gave the expected acetates **10, 11, 12,** and **13.** We were not able to isolate and characterize the triacetate **13a,** so we applied different conditions for the same bromine displacement, using glacial acetic acid instead of DMF as solvent. Although the reaction was much cleaner under the new conditions, we still were not able to isolate compound **13a** (Scheme 7). Acetate derivatives **10** and **12** were solids and were recrystallized from a mixture of hexane and ethyl acetate.

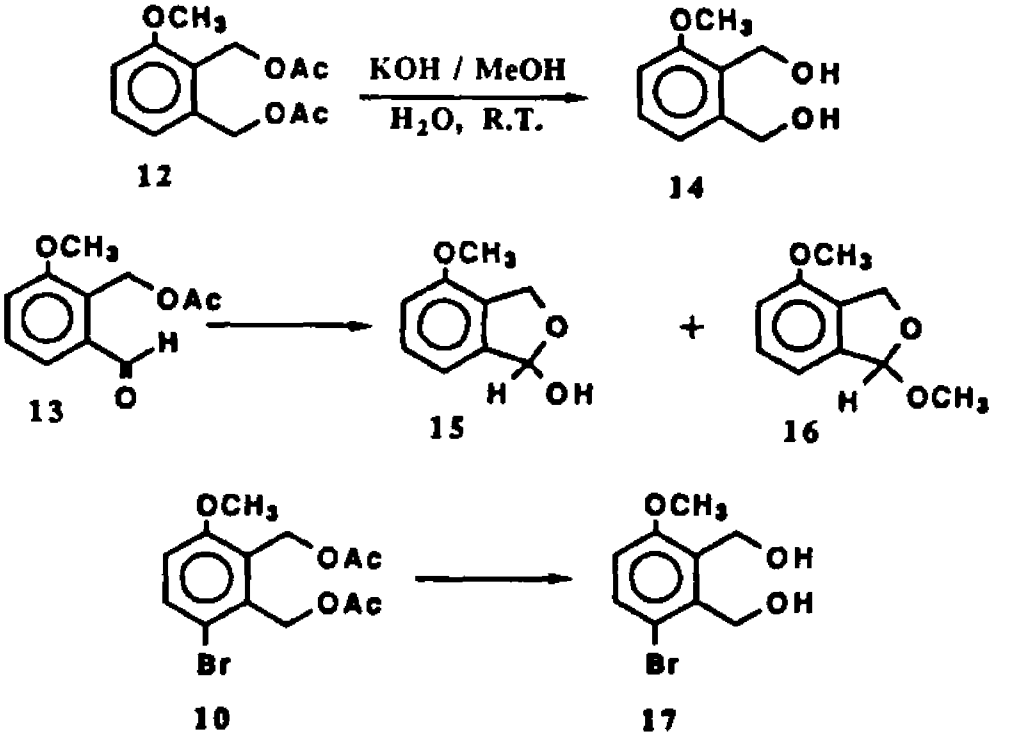
Scheme 7



7.3.0. Hydrolysis of acetates 10, 12, and 13.

The diacetate derivative **12** was hydrolyzed using potassium carbonate in aqueous methanol at room temperature to give 2,3-bis(hydroxymethyl)-anisole **14** in very good yield (92%) after chromatographic separation. Acetate **13** was also hydrolyzed under the same conditions to give **15** as major product (60%), and **16** as a minor product (30%). The longer the reaction ran, the more compound **16** was formed. Acetate **10**, on the other hand, gave the 4-bromo-2,3- bis(hydroxymethyl)anisole **17** in a high yield (95%) (Scheme 8).

Scheme 8

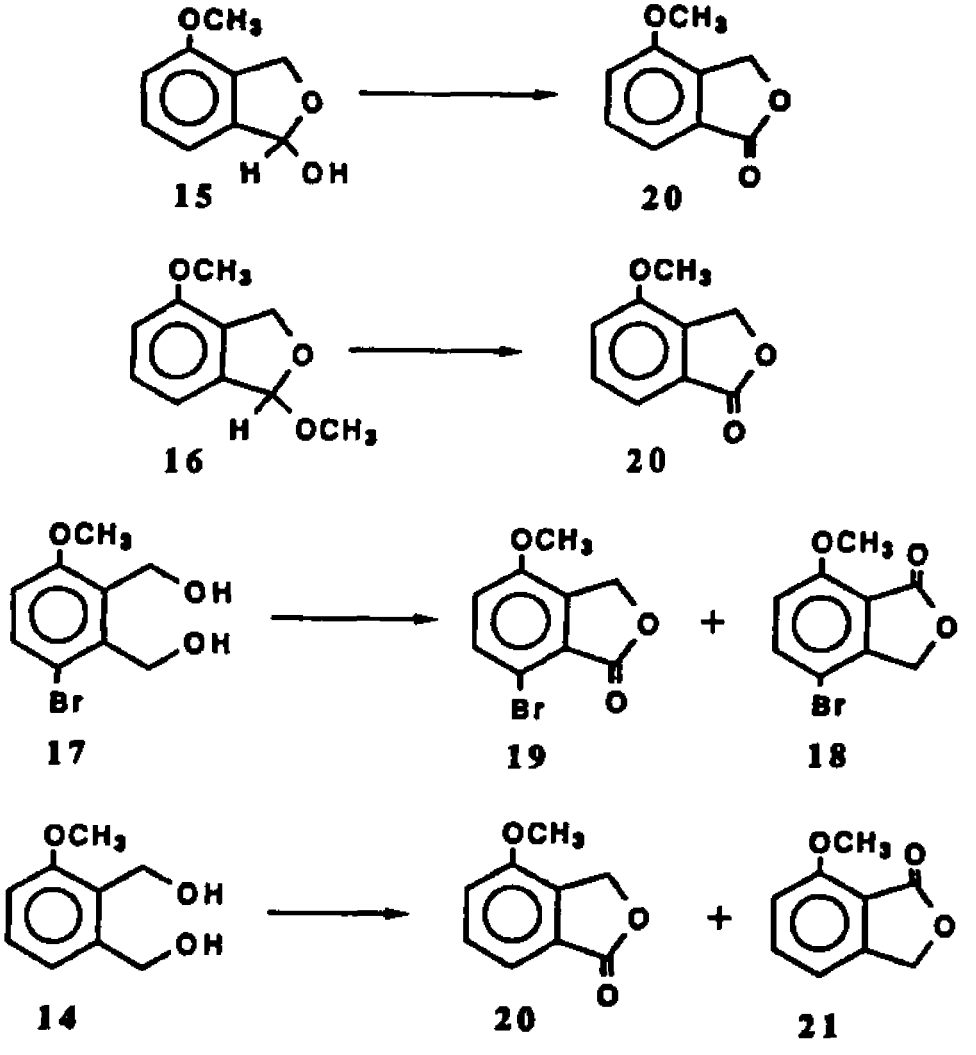


7.4.0. Oxidation of 14, 15, 16, and 17.

Oxidation of **15**, using Jones reagent at room temperature, gave the compound **20** (98%). Although several research groups[5,6,7] reported the preparation of compound **20**, none of those groups gave full spectroscopic and analytical data for it. The structures of compounds **15** and **16** are

unequivocally supported by all the spectroscopic and analytical data, and the preparation of the tribromo-compound 6 parallels that of the Spanish investigators.[9] Compound **15** can produce only one phthalide, namely compound **20**. The similar oxidation of **17** at room temperature gave **18** (80%) and **19** (20%).

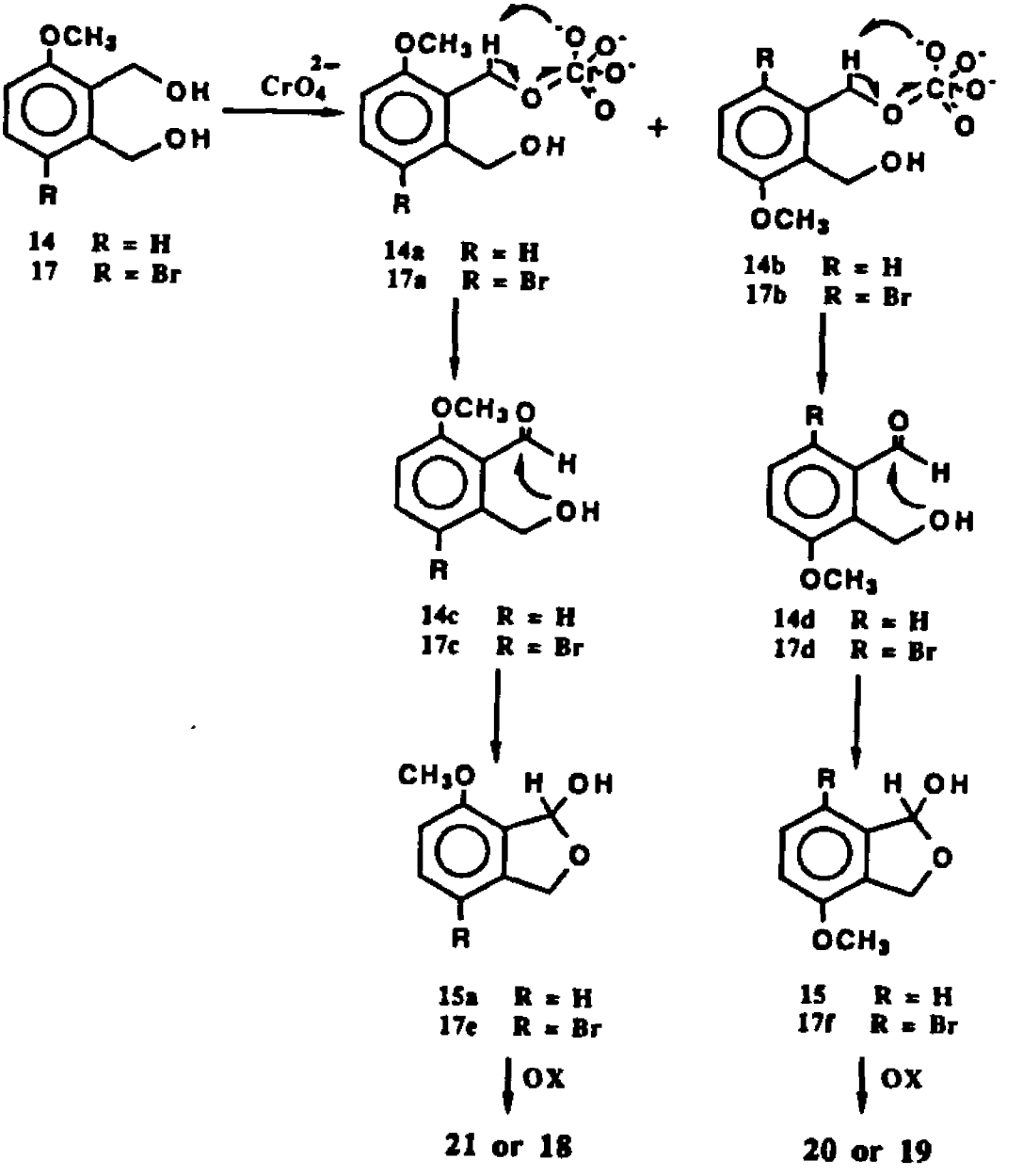
Scheme 9



Oxidation[13] of the diol **14**, at 0°C, gave a mixture of 4-methoxyphthalide **20** (20%) and 7-methoxyphthalide **21** (80%). When the reaction was conducted in refluxing acetone, then the ratio between the two phthalides was inverted from that obtained at 0°C (Scheme 9).

The oxidation of diol **14**, using an approximately stoichiometric amount of the oxidizing reagent, resulted in the isolation of small amounts of the hemiacetal **15**. The yield of compound **15** was not determined.

Scheme 10



The oxidation is apparently subject to kinetic control, rather than thermodynamic control, since the less hindered hydroxymethyl group of compound **14** is oxidized faster at high temperatures, to produce the less stable *meta*-alkoxyaldehyde. At low temperatures, the more hindered hydroxymethyl group became the more reactive center, producing the more stable *ortho*-alkoxyaldehyde.

Indeed, it is well known that the Cr^{VI} oxidations are usually kinetically controlled processes.[14] At low temperatures, the formation of the kinetically controlled product **14c** is preferred, while at high temperatures, the formation of the thermodynamically controlled product **14d** is preferred.

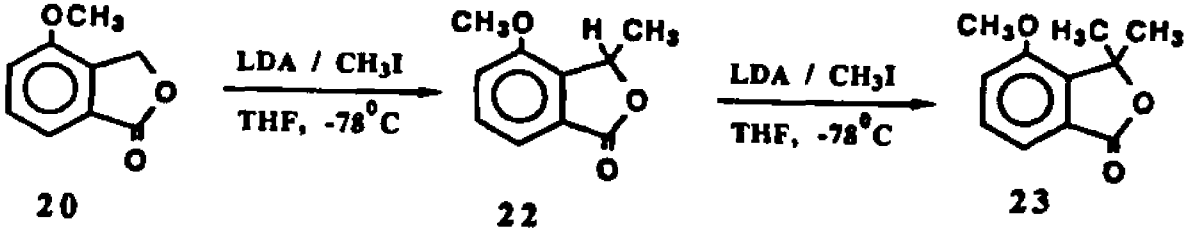
The isolation of the hemiacetal **15** confirms that a complete oxidation went through a hemiacetal intermediate to give the final products **20**. Analogous hemiacetal intermediate **15a** should formed before a complete oxidation gave **21** (Scheme 10).

In the case of the oxidation of **17**, there is no kinetic preference because of the presence of a large substituent at the 4-position, therefore changing the temperature of the reaction should not result in a significant variation of the product distribution. Thus we get at any temperature, as a major product, the thermodynamically controlled product **17c** and of course after the oxidation was completed the 7-bromo-4-methoxyphthalide **18** was isolated in over 90% yield with 4-bromo-7-methoxyphthalide **19** 10% yield.

7.5.0. Methylation of 4-methoxyphthalide 20.

Alkylation of **20**, using LDA in THF at -78° C with methyl iodide, gave compound **22** in 92% yield[15] (Scheme 11). A second methylation took place under the same conditions, which gave 3,3-dimethyl-4-methoxyphthalide **23** in 87% yield.

Scheme 11



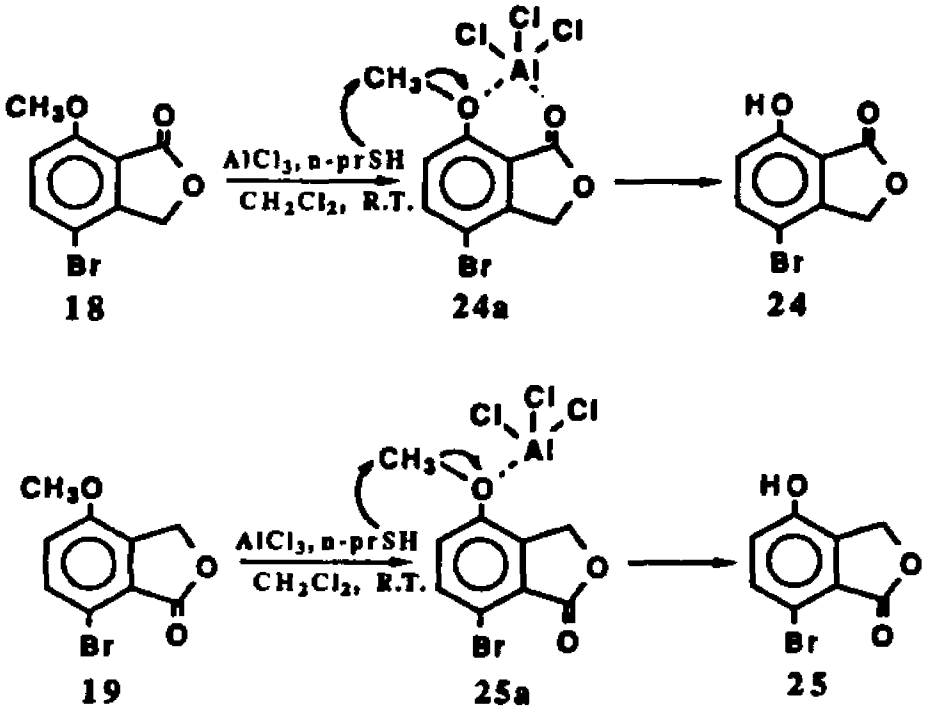
7.6.0. Demethylation of 4-bromo-7-methoxyphthalide, 18.

The structural assignments for the two monobromophthalides were not unambiguously achieved by use of the NMR and IR spectroscopic data. Thus, we attempted to reduce the 4-bromo-7-methoxyphthalide **18** and the 7-bromo-4-methoxyphthalide **19** to the phthalides **21** and **20** respectively, under free radical reaction using 2 equivalents of nBu_3SnH and catalytic amount of AIBN in refluxing benzene. Surprisingly, we recovered only the starting materials.

The demethylation of **18** with n-propanethiol and anhydrous $AlCl_3$ in CH_2Cl_2 at 0°C gave, in 15 minutes, 4-bromo-7-hydroxyphthalide **24** in quantitative yield.[16] Under the same conditions, the reaction with **19** was very slow, and after 8 hours all the starting material was converted to 7-bromo-4-hydroxyphthalide **25** (Scheme 12).

The faster reaction of compound **18** confirmed the structural assignment because demethylations are known to be rapid when the reaction proceeds via a chelated intermediate, like intermediate **24a**.

Scheme 12



We have described above a new approach to the preparation of phthalides. These and related compounds have received considerable attention as valuable intermediates in the synthesis of several biologically active compounds.[5c,7,15b] In the following chapter, it will be demonstrated how 4-methoxyphthalide **20** was used to synthesize some complex molecules. These very important intermediates were needed for an investigation of alternative routes toward the total syntheses of natural products, such as shikodonin.[17]

EXPERIMENTAL

General. Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton nuclear magnetic resonance (1H) spectra were determined on a Varian EM-360A (60 MHz), or on a IBM NR/300 FT NMR (270 MHz), or on a IBM WP/200-SY (200 MHz), and or on a JEOL/JNM/GX-400 FT NMR spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=double, t=triplet, q=quarter, m=multiplet, br=broad), assignment, integration, coupling constant. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer and on Finnigan CH5 single focusing mass spectrometer. Thin-Layer chromatography (TLC) was performed with 13181 silical gel with fluorescent indicator (Kodak) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silical gel 60 mesh. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY).

Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Preparation of 2,3-dimethylanisole 2.

A. To a solution of 2,3-dimethyphenol **1** (12.20 g, 100.0 mmol) in acetone (300 mL) was added anhydrous potassium carbonate (41.40 g, 300 mmol) and methyliodide (42.60 g, 300 mmol). The mixture was refluxing overnight, and after filtration, and removal of the solvent, the liquid residue was distilled at low pressure (15 mm Hg, 110° C) to give 13.4 g (99% yield) of 2,3-dimethylanisole **2**: IR (neat, cm^{-1}) 3000 (m), 2945 (s), 2850 (w), 2835 (m), 1585 (s), 1470 (s), 1305 (m), 1260 (s), 1105 (s), 1015 (m), 770 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 6.90 (t, 1H, J = 8 Hz), 6.65-6.45 (m, 2H), 3.70 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H).

B. To a stirring solution of 2,3-dimethylphenol **1** (12.20 g, 100 mmol) and tetra-n-butylammonium hydrogen sulfate (3.40 g, 10 mmol) in 200 mL of methylene chloride was added KOH (28.0 g, 0.5 mol) in 140 mL of water (20% solution). Methyliodide (21.3 g, 150 mmol) was added to the above stirring biphasic solution and the mixture was stirred for 2 hrs at room temperature. The solution was then left to stand and the two layers were separated. After the methylene chloride was evaporated the residue was dissolved in diethyl ether (200 mL) and the tetrabutylammonium iodide and other inorganic salts were precipitated and filtered out. The etherical solution was concentrated and distilled to give 13.6 g (100% yield) of 2,3-dimethylanisole **2**.

Preparation of 2,3-bis(bromomethyl)anisole 4.

A 2-L one-necked, round bottomed flask was charged with 2,3-dimethyl-anisole **2** (13.62 g, 100 mmol) and N-bromosuccinimide (37.38 g, 210 mmol) in 1.5 L of dry carbon tetrachloride. The mixture was irradiated and heated with a Flood sunlight lamp while it was stirring under nitrogen for 2.5 hrs. After

the solution was cooled to room temperature, the suspensed succinimide was removed by filtration and the solvent was removed by rotary evaporator. The yellowish residue was recrystallized from petroleum ether and diethyl ether (5:1 ratio) to give compound **4** (27.06 g, 92% yield) as white crystals (m.p. 69-70° C): IR (nujol, cm^{-1}) 1590 (m), 1285 (m); ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.50 (t, 1H, J = 8 Hz), 7.15 (d, 1H, J = 8 Hz), 7.05 (d, 1H, J = 8 Hz), 4.90 (s, 2H), 4.75 (s, 2H), 3.95 (s, 3H).

The preparation of other brominated materials.

The same procedure described above was used for the preparation of all the following bromo-compounds. Variations in the concentration of 2,3-dimethylanisole **2** in CCl_4 and the number of equivalents of NBS as well led to different products as is shown below.

Compound 3.

2,3-Dimethylanisole **2** (1.36 g, 10.0 mmol) in 50 mL of dry CCl_4 and 3.1 equiv of NBS (5.52 g, 31.0 mmol) gave 3.73 g (100% yield) of tribromo compound **3** as white crystals (recrystallized from hexane : chloroform, 2:1), m.p. 102-103 ^{0}C: ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.50 (d, 1H, J = 9 Hz), 6.70 (d, 1H, J = 9 Hz), 4.75 (s, 2H), 4.70 (s, 2H), 3.85 (s, 3H). Anal. Calcd for $C_9H_9O_1Br_3$: C, 28.99; H, 2.43; Br, 64.29. Found: C, 29.27; H, 2.22; Br, 64.35.

Compound 6.

2,3-Dimethylanisole **2** (1.36 g, 10.0 mmol) in 400 mL of dry CCl_4 and 3.1 equiv of NBS (5.52 g, 31.0 mmol) gave 3.66 g (98% yield) of tribromo compound **6**, which was recrystallized from hexane : chloroform (5:1, ratio) as white crystals (m.p. 84-85° C): IR (nujol, cm^{-1}) 1585 (w), 1280 (m); ^1H NMR (60

MHz, $CDCl_3$, ppm) 7.55 (dd, 1H, J = 8 Hz, J = 2.5 Hz), 7.35 (t, 1H, J = 8 Hz), 7.05 (s, 1H), 6.85 (dd, 1H, J = 8 Hz, J = 2.5 Hz), 4.65 (s, 2H), 3.90 (s, 3H). Anal. Calcd for $C_9H_9O_1Br_3$: C, 28.99; H, 2.43; Br, 64.29. Found: C, 29.27; H, 2.22; Br, 64.35.

Compound 7

One equivalent (1.78 g, 10.0 mmol) of NBS was adding slowly in small portions to stirring 2,3-dimethylanisole **2** (1.36 g, 10.0 mmol) at 0°C. The reaction was highly exothermic and a rapid formation of dense fumes of HBr were observed during the addition of NBS. The reaction mixture was allowed to warm to room temperature and after an hour 100 mL of CCl_4 were added while stirring. The floating succinimide was removed by filtration and the solvent was evaporated in vacuo to give 4-bromo-2,3-dimethylanisole **7** (2.15 g, 100% yield): ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 7.25 (d, 1H, J = 8 Hz), 6.40 (d, 1H, J = 8 Hz), 3.70 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H).

Compound 8.

2,3-Dimethylanisole **2** (1.36 g, 10.0 mmol) in 100 mL of dry CCl_4 and 1.1 equiv of NBS (1.96 g, 11.0 mmol) gave 2.15 g (100% yield) of monobromo-compound **8**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 7.15 (t, 1H, J = 8 Hz), 6.85-6.55 (m, 2H), 4.55 (s, 2H), 3.80 (s, 3H), 2.35 (s,3H).

Compound 9.

Compound **9** was prepared from **6** under allylic bromination conditions. The reaction was run overnight and the yield was over 98%. The compound was recrystallized from chloroform to give white needle crystals (m.p. 149-150 ^{0}C):IR (nujol, cm^{-1}) 1585 (w), 1290 (m), 1265 (m), 1140 (m), 1060 (m); ^{1}H NMR

(60 MHz, $CDCl_3$, ppm) 7.65 (s, 1H), 7.45 (s, 1H), 7.55-6.75 (m, 3H), 3.90 (s, 3H). Anal. Calcd for $C_9H_8O_1Br_4$: C, 23.93; H, 1.78. Found: C, 24.42; H, 1.84.

Preparation of acetates 10, 12, and 13.

Compound 6 (18.65 g, 50.0 mmol) and anhydrous sodium acetate (3.6 equiv, 14.94 g, 180.0 mmol) were dissolved in of glacial acetic acid (250 mL). The magnetically stirred solution was refluxed for 3 hrs and then the acetic acid and acetic anhydride were removed by distillation. The residue was dissolved in ethyl acetate and the inorganic salts (sodium bromide and sodium acetate) were removed by filtration. The organic solution was mixed with 4% HCl (100 mL) and extracted with three 100 mL-portions of ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and purified by column chromatography (hexane:ethyl acetate, 1.5:1, R_f=0.4) to give acetate **13** (10.10 g, 97% yield) as a viscous liquid which solidified when refrigerated: IR (nujol, cm^{-1}) 1765 (s), 1690 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 10.15 (s, 1H), 7.60 (m, 2H), 7.30 (m, 1H), 5.60 (s, 2H), 3.90 (s, 3H), 2.05 (s, 3H); mass spectrum, exact mass calcd for $C_{11}H_{12}O_4$ *m/e* 208.0736, obsd *m/e* 208.0735.

The following bromo-compounds were acetolysed under the same conditions described above. Yields were greater than 95%.

Compound **4** gave **12** (m.p. 90-91°C): ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.65-6.70 (m, 3H), 5.30 (s, 2H), 5.20 (s, 2H), 3.85 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.37; H, 6.32.

Compound **3** gave **10** (m.p. 133-134° C): ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 7.60 (d, 1H, J = 9 Hz), 6.85 (d, 1H, J = 9 Hz), 5.30 (s, 2H), 5.25 (s, 2H), 3.85 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 170.60, 170.41, 157.87, 135.67, 134.19, 126.06, 116.92, 113.14, 63.14, 57.78, 56.11, 20.88, 20.72. Anal. Calcd for $C_{11}H_{15}O_5Br_1$: C, 47.15; H, 4.57. Found: C, 46.71, H, 4.53.

General procedure for hydrolysis of acetoxy derivatives 10, 12, and 13. Preparation of 14.

A 500-mL round bottomed flask, equipped with a magnetic bar, was charged with compound **12** (12.60 g, 50.0 mmol) dissolved in 250 mL methanol. To this solution was added potassium carbonate (15.18 g, 110.0 mmol), and while stirring water was added slowly until the solution just become clouding. The mixture was stirred for 4 hrs at room temperature monitored by TLC. After all starting material had reacted most of the methanol was removed by rotary evaporator. The residue was transferred to a separatory funnel and it was extracted three times with 100-mL portions of chloroform. The combined organic extracts was washed twice with water and once with brine, dried over magnesium sulfate, filtered and concentrated by rotary evaporator. The yellowish residue was recrystallized from a mixture of chloroform and hexane (1:1 ratio) to afford 7.64 g (91% yield) of the diol **14** (m.p. 96-97° C) ^{1}H NMR (60 MHz, $CDCl_3$, 1 drop D_2O, ppm) 7.25-6.60 (m, 3H), 4.80 (s, 2H), 4.75 (s, 2H), 3.85 (s, 3H). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.40; H, 7.29.

Preparation of 17.

Compound **10** gave the diol **17** (m.p. 130-131° C): ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 7.40 (d, 1H, J = 8.5 Hz), 6.65 (d, 1H, J = 8.5 Hz), 4.85 (s, 2H), 4.80 (s, 2H), 3.80

(s, 3H), 2.80 (br, 2H). Anal. Calcd for $C_9H_{11}Br_1O_3$: C, 43.75; H, 4.49. Found: C, 43.80; H, 4.28.

Preparation of 15 and 16.

Compound **13** gave a separable mixture of **15** (85%) and **16** (15%).

Compound **15** (m.p. 111-112° C) IR ($CHCl_3$, cm^{-1}) 3600-3150 (br), 2950 (m), 2900 (w), 2870 (w), 1585 (s), 1460 (s); ^1H NMR (270 MHz, $CDCl_3$, 1 drop D_2O, ppm) 7.23 (t, 1H, J = 8.3 Hz), 6.98 (d, 1H, J = 7.5 Hz), 6.75 (d, 1H, J = 8.0 Hz), 6.59 (d, 1H, J = 2.1 Hz), 5.23 (dd, 1H, J = 12.9, J = 2.0 Hz), 5.05 (d, 1H, J = 12.9 Hz), 3.81 (s, 3H). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 64.87; H, 6.18.

Compound **16**: ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.40-6.70 (m, 3H), 6.15 (d, 1H, J = 2 Hz), 5.05 (d, 1H, J = 2 Hz), 5.05 (s, 1H), 3.80 (s, 3H), 3.40 (s, 3H).

General procedure for Jones Oxidation.

Oxidation of 14.

A 500-mL round bottomed flask equipped with a condenser and a magnetic bar was charged with **14** (8.30 g, 50.0 mmol) dissolved in 250 mL of acetone. To this refluxing solution, Jones reagent was added dropwise, until the reaction mixture retained a red/orange color (*ca* 25 mL of 3 M sol.). The reaction mixture was stirred for 30 min and the excess of Jones reagen was destroyed with isopropyl alcohol. Acetone was then removed by rotary evaporation and the residue was dissolved in 50 mL of water. The mixture was extracted with three 50-mL portions of chloroform, dried over magnesium sulfate, filtered, and concentrated by rotary evaporator. The solid crude product was chromatographically separated (silica gel, 1:1 hexane:ethyl

acetate, $R_{f_1} = 0.6$, $R_{f_2} = 0.3$) into two components (combined weight 7.87 g, yield 96%).

The component with the higher R_f was identified as the 4-methoxyphthalide **20** (85%) (m.p. 128-129°C): IR (KBr, cm^{-1}) 2975 (s), 2940 (s), 2855 (s), 1785 (s); ^1H NMR (270 MHz, $CDCl_3$, ppm) 7.52-7.45 (m, 2H), 7.12 (dd, 1H, J = 5.8 Hz, J = 1.7 Hz), 5.24 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 171.16, 154.26, 134.90, 130.85, 127.23, 117.04, 114.84, 68.11, 55.65. Anal. Calcd for C9H8O3: C, 65.84; H, 4.91. Found: C, 65.42; H, 4.85.

The component with the lower R_f value identified as the 7-methoxyphthalide **21** (15%) (m.p. 108-109°C): IR (KBr, cm^{-1}) 1780; ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.50 (t, 1H, J = 8 Hz), 6.90 (d, 1H, J = 8 Hz), 6.80 (d, 1H, J = 8 Hz), 5.22 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 169.22, 158.71, 149.45, 136.34, 113.78, 113.19, 110.61, 68.82, 55.99.

Oxidation of 15 and 16.

Both compounds **15** and **16** after oxidation gave a single product, identified as the 4-methoxyphthalide **20**, in quantitative yield.

Oxidation of 17.

Compound **17** after oxidation, at room temperature, gave a mixture of 4-bromo-7-methoxyphthalide **18** (90% yield) and 7-bromo-4-methoxyphthalide **19** (10% yield).

Compound **18** gave the following analytical data: m.p. 197-198°C; IR ($CDCl_3$, cm^{-1}) 1775 (s); ^1H NMR (270 MHz, DMSO, ppm) 7.73 (dd, 1H, J = 7.84

Hz, J = 1.11 Hz), 6.97 (d, 1H, J = 7.77 Hz), 5.14 (s, 2H), 3.99 (s, 3H). Anal. Calcd for $C_9H_7Br_1O_3$: C, 44.48; H, 2.90; Br, 32.87. Found: C, 44.58; H, 2.53; Br, 33.00.

Compound **19** (m.p. 207-208° C): IR (nujol, cm^{-1}) 1780 (s); 1H NMR (270 MHz, DMSO, ppm) 7.68 (d, 1H, J = 7.66 Hz), 7.26 (d, 1H, J = 7.62 Hz), 5.26 (s, 2H), 3.92 (s, 3H); Anal. Calcd for $C_9H_7Br_1O_3$: C, 44.48; H, 2.90; Br, 32.87. Found: C, 44.13; H, 2.82.

Preparation of 3-methyl-4-methoxyphthalide 22.

A dry, 250-mL, three-necked, round bottomed flask is equipped with a magnetic stirrer, and a condenser which is fitted with a three-ways adapter. The other two necks were each fitted with a rubber septum. The air in the system was replaced by alternately evacuating and filling the system with dry nitrogen, via the three-ways adapter, and a positive pressure of nitrogen was maintained throughout the reaction. The flask was charged with 50 mL of anhydrous tetrahydrofuran, freshly distilled from sodium and benzophenone, and 1.11 g. (1.54 mL, 11 mmol) of anhydrous diisopropylamine, distilled from calcium hydride. The flask was cooled to 0° C with an ice bath. A 10.5 M hexane solution of n-butyllithium (1.0 mL, 10.5 mmol) was added dropwise to the stirred reaction mixture, during 20 minutes. The resulting lithium diisopropylamide was cooled to -78° C with a dry ice-acetone bath. After an hour a solution of 1.65 g (10.0 mmol) of 4-methoxyphthalide **20** in 40 mL of anhydrous tetrahydrofuran was added dropwise, at -78° C during 30 minutes, followed by the rapid addition of 2.98 g (1.36 mL, 1 mmol) of methyl iodide. After 5 min, the cooling bath was removed, the mixture was allowed to warm to room temperature, and was stirred overnight. The reaction was quenched with 30 mL of water and the organic phase was separated. The

organic phases were combined and washed twice with 20 mL of water, once with 15 mL of brine, and dried over magnesium sulfate. Solvent removal on a rotary evaporator, followed by chromatographic purification, afforded 3-methyl-4-methoxyphthalide **22** (1.67 g, 94%) as white crystals, m.p. 96-97°C; IR (nujol, cm^{-1}) 1780; ^1H NMR (270 MHz, $CDCl_3$, ppm) 7.47 (d, 1H, J = 1.53 Hz), 7.46 (s, 1H), 7.09 (dd, 1H, J = 4.60 Hz, J = 3.23 Hz), 5.55 (q, 1H, J = 6.57 Hz), 3.92 (s, 3H), 1.65 (d, 3H, J = 6.58 Hz). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.25; H, 5.55.

Preparation of 3,3-dimethyl-4-methoxyphthalide 23.

Compound **22** was further alkylated under the above described conditions with methyl iodide to give the 3,3-dimethyl-4-methoxyphthalide **23** in excellent yield (87%): m.p. 74 -75°C; IR (nujol, cm^{-1}) 1775 (s); ^1H NMR (270 MHz, $CDCl_3$, ppm) 7.48-7.42 (m, 2H), 7.10 (dd, 1H, J = 5.42 Hz, J = 2.1 Hz), 3.93 (s, 3H), 1.69 (s, 6H); ^{13}C NMR (270 MHz, $CDCl_3$, ppm) 169.75, 153.89, 130.81, 130.67, 117.12, 115.19, 114.93, 85.40, 55.57, 25.31. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 67.92; H, 6.22.

Preparation of 4-bromo-7-hydroxyphthalide 24.

Demethylation of 4-bromo-7-methoxyphthalide 18.

A stirred solution of anhydrous aluminum chloride (1.47 g, 11.0 mmol) in n-propanethiol (0.84 g, 1.02 mL, 11.0 mmol) cooled in ice-water bath was prepared. To the above solution was added compound **18** (2.43 g, 10.0 mmol) dissolved in 20 mL of CH_2Cl_2 during 15 minutes, and the reaction mixture was stirred for another 15 minutes at room temperature. The reaction mixture was poured into water, acidified with 10% HCl, and extracted twice with 30-mL portions of dichloromethane. The combined organic extracts was

shaken with brine, dried over magnesium sulfate, filtered, and then evaporated to leave a crude solid material, which was purified with chromatography over a silical gel column to give compound **24** (2.24 g, 98% yield) (m.p. 166-167° C): IR (nujol, cm^{-1}) 3600-3050 (br), 1765 (s); ^1H NMR (270 MHz, DMSO, ppm) 7.58 (d, 1H, J = 8.67 Hz), 6.91 (d, 1H, J = 8.56 Hz), 5.11 (s, 2H), 3.55 (br, 1H). Anal. Calcd for $C_8H_5O_3Br_1$: C, 41.91; H, 2.20; Br, 34.89. Found: C, 40.76; H, 2.34; Br, 34.50.

Preparation of 4-hydroxy-7-bromophthalide 25.

The same reaction was performed with compound **19**, to give, after 8 hrs, compound **25**: ^1H NMR (60 MHz, DMSO, ppm) 7.55 (d, 1H, J = 8.4 Hz), 7.10 (d, 1H, J = 8.4 Hz), 5.30 (s, 2H).

REFERENCES

1. Talaparta, B.; Roy, M. K.; Talaparta, S. K. *In. J. Chem.* Vol. 19B, **1980**, 927.
2. Auricchio, S.; Ricca, A.; de Pava, O. V. *J. Org. Chem.* **1983**, 48, 602.
3. a. Harland, P. A.; Hodge, P. *Chem. Comm. Synth.* **1982**, 223; b. Miller, D. G.; Trenbeath, S.; Sih, C. J. *Tetrahedron Lett.* **1976**, 20, 1637.
4. Geissman, T. A.; Crout, D. H. G. *Organic Chemistry of secondary plant metabolism*, ed. Freeman-Cooper, San Francisco, **1969**, p. 102.
5. a. Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, 48, 2349; b. Narasimhan, N. S.; Mali, R. S.; Kulkarni, B. K.; Gupta, P. K. *In. J. Chem.* Vol. 22B, 1983, 1257; c. Narasimhan, N. S.; Kusurkar, S. S. *In. J. Chem.* Vol. 22B, **1983**, 349.
6. Sibi, M. P.; Miah, J.; Snieckus, V. *J. Org. Chem. 1984*, 49, 737.
7. Meyers, A. I.; Avila, W. A. *J. Org. Chem.* **1981**, 46, 3881.
8. Soucy, C.; Favreau, D; Kayser, M. M. *J. Org. Chem.* **1987**, 52, 129.
9. Farina, F.; Primo, J.; Torres, T. *Chem. Lett.* **1980**, 77.
10. a. Mitchell, R. H.; Lai, Y.-H.; Williams, R. V. *J. Org. Chem.* **1979**, 44, 4733; b. Djerassi, C. *Chem. Rev.* **1948**, 48, 271.
11. Siegel, J.; Gutierrez, A.; Schweizer, W. B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* **1986**, 108, 1569.
12. Berg, U.; Liljefors, T.; Roussel, C.; Sandstrom, *J. Acc. Chem. Res.* **1985**, 18, 80, and references therein.
13. Bhattacharjee, D.; Popp, F. D. *J. Heterocyclic Chem.* **1980**, 17, 315.
14. Oxidation with Jones reagent (Cr^{VI}).
15. a. Trost, B. M.; Rivers, G. T.; Gold, G. M. *J. Org. Chem.* **1980**, 45, 1835; b. Mahalingam, S.; Kuzma, P. C.; Lee, J. Y.-C.; Harris, T. M. *J. Am. Chem.*

Soc. **1985**, *107*, 7760.

16. Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275.

CHAPTER 8

8.0.0. REDUCTIVE - ALKYLATION OF PHTHALIDES

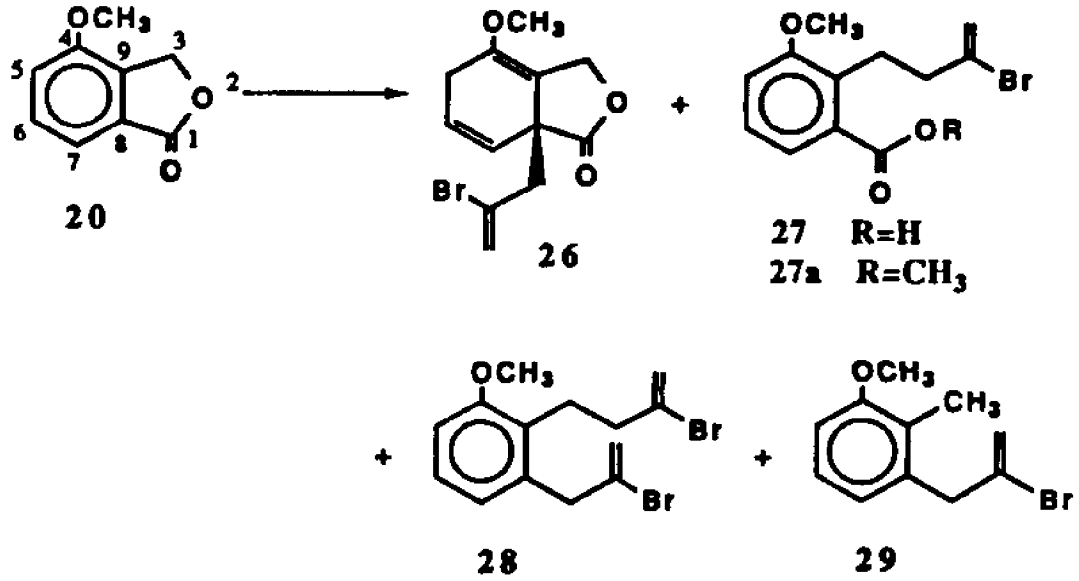
8.1.0. Reduction of 4-methoxyphthalide 20

No successful Birch reduction of 4-methoxyphthalide **20** to a 2,5-cyclohexadiene derivative **26** appears in the chemical literature up to today. We describe here a long and successful investigation for the reduction of **20**, and its derivatives under Birch reduction conditions.

Standard conditions of Birch reduction-alkylation were applied to 4-methoxyphthalide **20** (Scheme 1) (see procedure B in experimental section). The starting material was dissolved in 80 mL of a mixture of ammonia:THF 2:1 ratio in the presence of 1.1 equivalents of t-butyl alcohol as a proton donor. Potassium metal was added at approximately 2.2 equivalents, and the alkylating reagent was added immediately after the addition of the metal. After workup of the reaction, very little of the desired compound **26** was isolated (15% yield). Instead, compounds **27**, **28**, and **29** were isolated in 15%, 25%, and 20% yields respectively. Twenty percent of the starting material was recovered. From a preliminary investigation of the reaction conditions we demonstrated that it was essential to have a proton donor in the reaction flask before potassium metal was added, otherwise the reaction was very messy and we were not able to isolate any products under those conditions.

The compounds **27, 28,** and **29** were materials produced "after" the cleavage of the bond between C-3 and O. We thought that we could solve the problem if we put some steric restrictions on that bond.

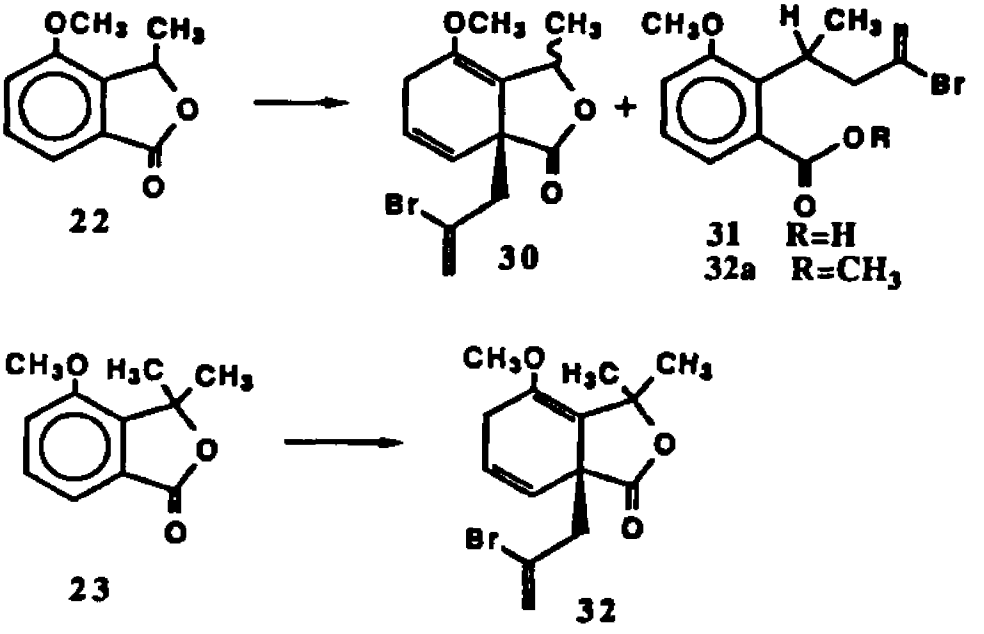
Scheme 1



8.1.1. Reduction of phthalides 22 and 23.

Two previously synthesized compounds, 3-methyl-4-methoxy- phthalide **22** and 3,3-dimethyl-4-methoxyphthalide **23**, were ideally suitable for the investigation of the mechanism for the cleavage of the C_3-O bond. The Birch reduction-alkylation of compound **22** under the conditions described in procedure **B** gave compound **30** in 35% yield, **31** in 30% yield and 30% starting material, but no decarboxylated compound was detected. Compound **30** appeared as a mixture of diastereoisomers (almost 1:1 ratio). Similarly, the reaction was also run with compound **23** under the same conditions to give only the alkylated reduction product **32** in 85% yield, based on the recovered starting material (Scheme 2).

Scheme 2

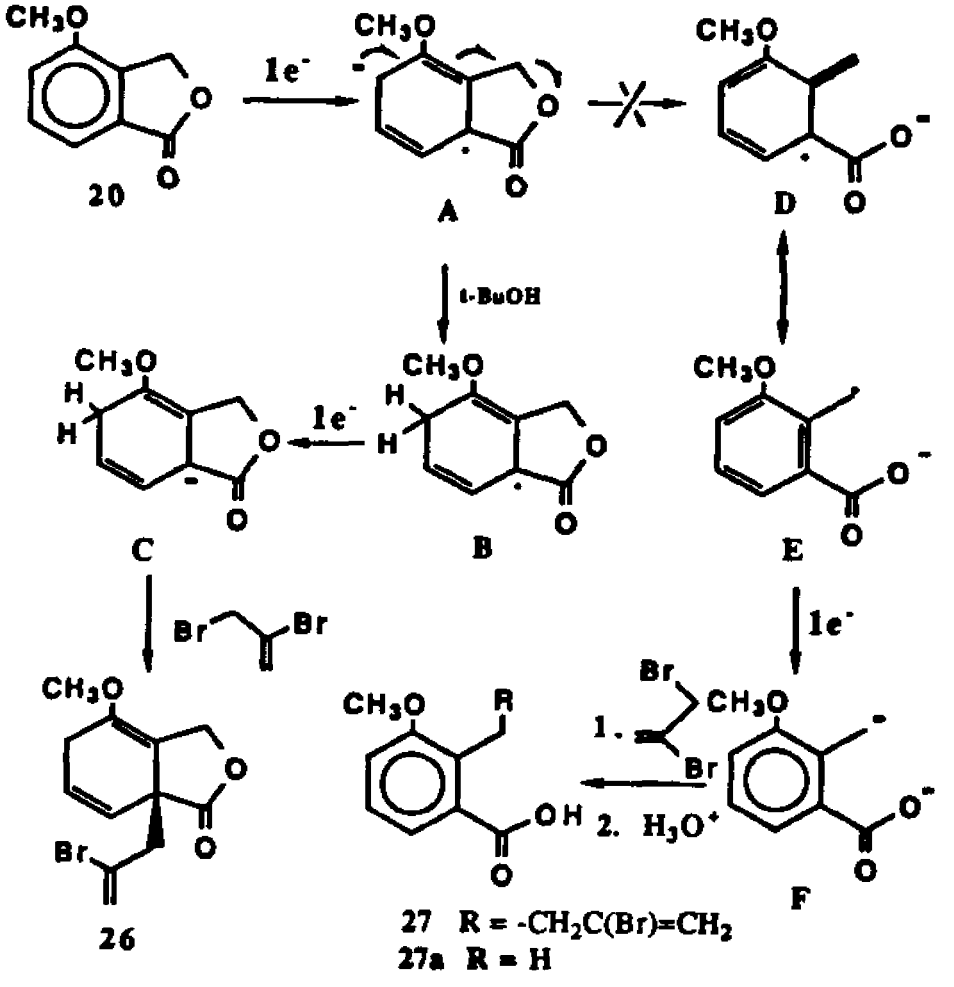


8.2.0. Mechanistic interpretation of Birch reduction of phthalides.

In order to understand the processes leading to the decarboxylated products 28 and 29 we examined the mechanism of the Birch reduction process (Scheme 3). After the addition of one equivalent of potassium to 4-methoxyphthalide 20, the radical anion A is formed. The C-3, O-2 bond is not flexible enough to go out of the plane of the six-membered ring, which has a planar structure because of resonance, the radical anion intermediate A cannot then suffer cleavage to give D. The ideal geometry of the C-3, O-2 bond, for cleavage to occur, is for this bond to be perpendicular to the six-membered ring, and with A this is impossible. On the other hand, A can be protonated by the t-butyl alcohol to give the radical intermediate B. The latter then accepts another electron from a second equivalent of potassium metal to form the carbanion C,which is subsequently alkylated to give compound 26. The radical carboxylate ion D if it is formed has a resonance form, the benzyl radical derivative E, which also accepts another electron from the medium to

generate the carbanion F. This carbanion can be alkylated to provide the benzoic acid derivative 27 after acidification. The last mechanistic interpretation for the formation of 27 is highly unlikely since we are doubtful about the possibility of the formation of D from A.

Scheme 3



8.2.1. Relative reactivity of 26, 30, and 32 towards potassium t-butoxide.

So far, we have been able to give a possible mechanistic explanation as to how compounds 26 and 27 are formed, even though the formation of intermediate D does not look feasible due to the planar geometry of radical

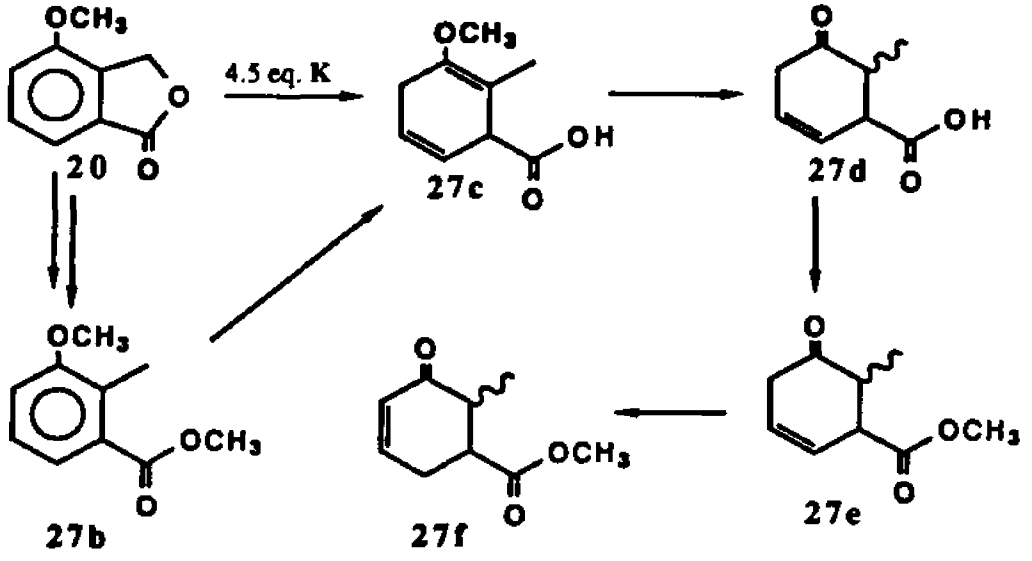
anion **A**. However, the formation of 3-methoxy-2-methylbenzoic acid **27b** from the reaction of 4-methoxyphthalide, in the absence of a proton donor and alkylating reagent (scheme 4), was still not sufficient to prove that cleavage occurs from radical anion intermediate **A** as well.

As previously mentioned, compound **22** gave the benzoic acid derivative **31** along with **30** but did not give any decarboxylated material. On the other hand, compound **23** gave neither a carboxylic acid derivative nor a decarboxylated one. Compound **23** gave only the 2,5-cyclohexadiene derivative **32**. Clearly, the methyl substituents which are attached to C-3 on 4-methoxy- phthalide changed the course of the reaction pathway in the formation of some of the products. The absence of a benzoic acid derivative after the reaction with compound **23** is evidence that the two 3-methyl substituents prevent sufficient distortion of the C_3-O bond from planar geometry. At this point, we were still not able to give any mechanistic explanation for the formation of the decarboxylated materials **28** and **29**, but we suspected that a better understanding of the mechanism for the formation of the carboxylic acid derivatives would come out of the working mechanism which provides the decarboxylated derivatives as well.

Oxidative decarboxylation is a well-known procedure and has been purposely done many times during the course of the Birch reactions. In our case, this was not what we experienced, because we made sure that we ran the reaction under an inert nitrogen atmosphere. Although we suspected, at this point, that a part of the problem involved using t-BuOH as a proton donor, we were unable to develop a mechanistic rationalization without putting too much speculative thought into it. Therefore, we decided to search for an answer to this question through further experimentation.

The next logical step was to replace the proton donor with a more acidic one, and thus ammonium acetate was chosen (see procedure C in the experimental section). We thought that lithium was the only choice we had of reductant, because it would react more slowly with ammonium acetate than with potassium. So we used lithium instead of potassium as a reducing metal. The results of the new procedure overwhelmingly proved that we were on the right track. Applying the new reaction conditions, we observed no detectable formation of the compounds **28** and **29**. Also, formation of the benzoic acid derivatives **27** and **31** was minimized to below 5% in both reactions with compounds **20** and **22**. An interesting observation under the above conditions was that compound **30** was formed in a higher (3:1) stereoselective ratio.

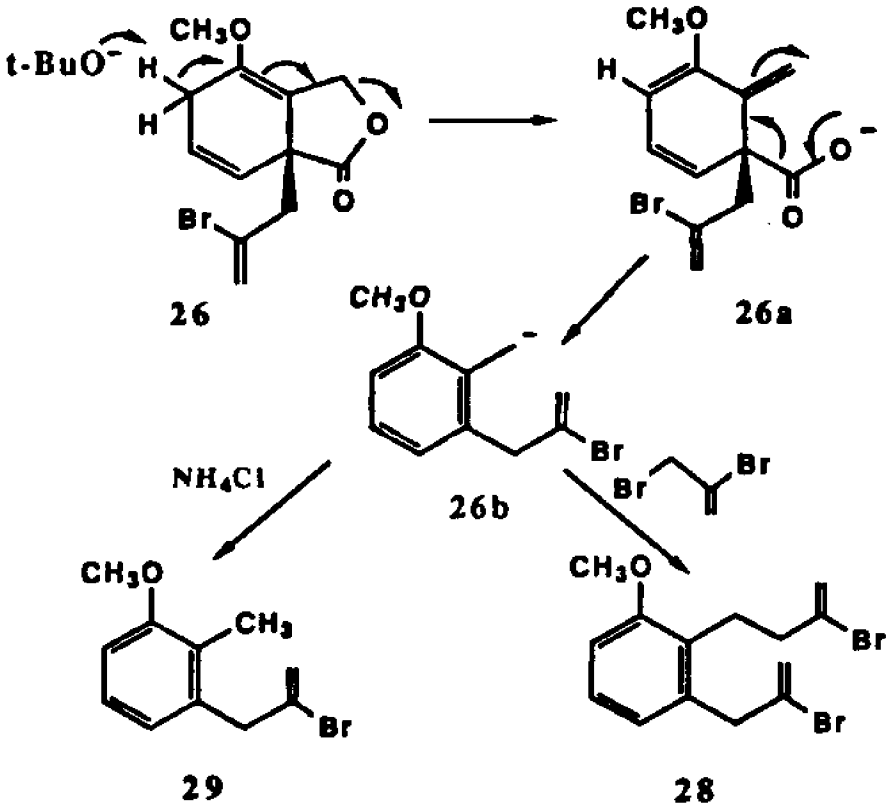
Scheme 4



Having all these results in mind, we were able to say that decarboxylation is taking place after product **26** is formed (Scheme 5). The molecular models of compound **26** shows that the planar structure no longer exists. The strong base, potassium t-butoxide, which is generated after the proton transfer from

t-BuOH to the radical anion **A**, can cause the cleavage of the single bond between C-3 and O in **26** to give the intermediate **26a**. This can easily undergo decarboxylation to give a stable benzyl anion **26b**, which can be alkylated by an excess of 2,3-dibromopropene or can be protonated during the workup of the reaction to give compounds **28** and **29** respectively. The fact that compound **22** does not undergo any decarboxylation could be a clue to the question of which diastereoisomer is formed predominantly, and we will try to describe the mechanism of the formation of compound **30** as well (Scheme 5).

Scheme 5

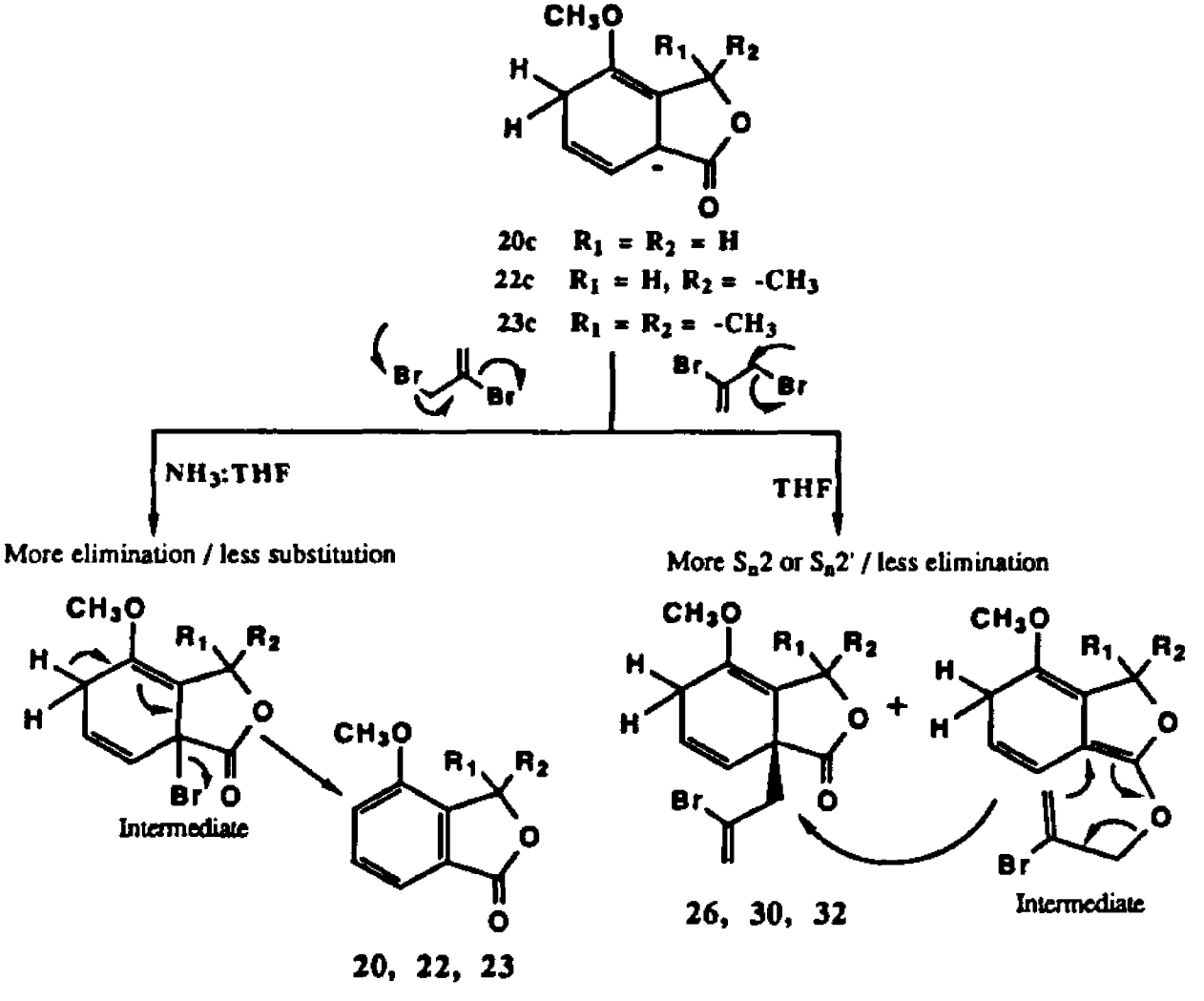


8.2.2. Role of ammonia towards alkylation.

Starting materials were recovered from all reactions run with the three phthalides **20, 22,** and **23**. By changing the ratio THF: ammonia to 1:1 (from 1:3) we favoured the formation of the products versus the starting material

(see procedure D in the experimental section). Under the new conditions, the solvation of lithium in the reaction mixture was very difficult, and the reaction was not as clean, probably causing over-reduction. Of course, we realized that ammonia favoured the elimination reaction over substitution (Scheme 6).

Scheme 6



After observing the increased formation of products **26, 30, and 32**, we felt that if we removed the ammonia before adding the alkylating reagent 2,3-dibromopropene, we could maximize the yields of the above products.

The reductive-alkylation reactions were repeated according to procedure E, where ammonia was removed completely before the addition of the alkylating reagent at -78°C. The products **26, 30,** and **32** were formed in more than 90% yields and no starting materials were recovered. In one case, the addition of 2.3-dibromopropene, was done at -20°C and again about 20% starting material was recovered, showing clearly that temperature is an additional factor along with ammonia that promotes elimination over substitution.

8.2.3. Role of counter-ion towards alkylation.

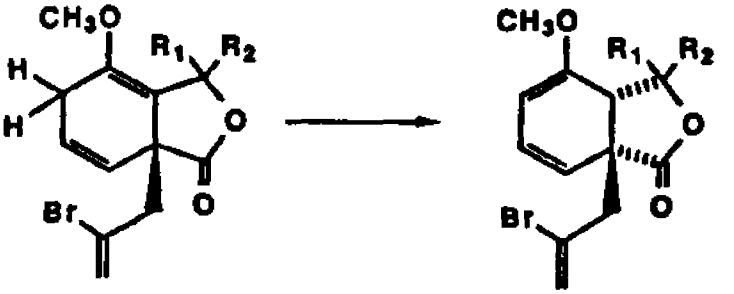
In the past, it was an accepted experimental fact that the potassium counter-ion should be replaced by adding lithium salt(s) to the reaction flask before alkylation was done[1]. In spite of contrary, known experimental procedures, we used potassium as a reducing metal in the presence of ammonium acetate and without doing the above exchange between potassium and lithium. We alkylated the potassium enolate to get 94% yield of **30**. Also, we observed that potassium reacts much faster with the aromatic nucleus than with the ammonium acetate. The excess of ammonium acetate reacted after the reduction of the benzenoid nucleus was completed, giving a release of hydrogen gas from the reaction mixture.

8.3.0. Hydrolysis of 26, 30, and 32.

The compounds **26, 30,** and **32** were purified and stored in the refrigerator. After a day, even though the compounds were free from solvent, we observed a transformation (Scheme 7) of compounds **26, 30,** and **32** to the

conjugated 1,3-diene derivatives 33, 34, and 35 respectively. These dienes with their fixed substitution pattern could be used in the future in a predesigned Diels-Alder reaction. The products from such a reaction would be of great importance.

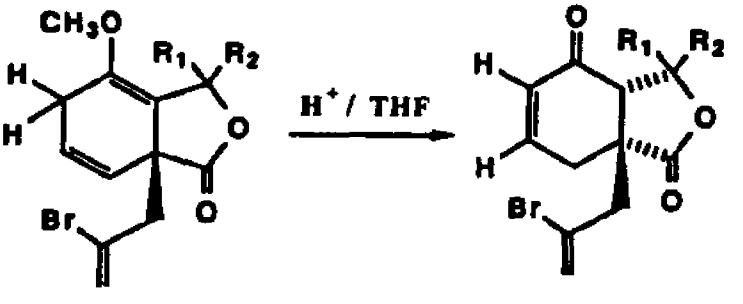
Scheme 7



26, 30, 32 33, 34, 35

The hydrolysis of compound **26** was achieved by dissolving the compound in 10 mL of a mixture of THF : 10%HCl_{aq} 2:1 ratio for every gram and stirring for six hours at room temperature. This gave the α,β-unsaturated cyclohexenone derivative **36**. The same was done with compounds **30** and **32** to give compounds **37** and **38** respectively (Scheme 8).

Scheme 8



26, 30, 32

36 $R_1 = R_2 = H$
37 $R_1 = H, R_2 = CH_3$
38 $R_1 = R_2 = CH_3$

The above hydrolyses were followed by TLC until all starting material was gone. We did not observe any hydrolysis of the γ-lactone ring and the desired products were formed in quantitative yields. These compounds were purified and identified before they were subjected to the free-radical carbocyclization. Also in all three compounds **36, 37,** and **38** we observed only the *cis*-ring fusion and none of the *trans*-ring fusion (IR 1760-1765 cm^{-1} for C=O of the γ-lactones).

8.4.0. Determination of the diastereoisomers 37.

At this point we think it is necessary to describe the evidence for the presence of a pair of diastereoisomers of **37**. Birch reduction-alkylation of **22**, through procedure **B**, gave **30** in 35% yield. This gummy mixture of isomers was not separable by column chromatography. The ^1H NMR spectrum of **30** is characterized by several peaks which are indicative of the presence of two diastereoisomers. At δ 1.65 there is a doublet (1.5 H) and and at δ 1.80 there is another doublet (1.5 H) which has an almost equal integrated area (together three protons). These two peaks represent the methyl group attached to C-12. Similarly there are two peaks for the methoxy group, one at δ 3.50 and another one at δ 3.65, again with almost equal integrated areas (together three protons). From δ 2.45 to 3.15 there are another four protons (H-4 and H-7). From δ 5.20 to 5.40 there is a multiple peak for one proton (H-12). At δ 5.60 there is a broad-singlet peak for two protons (H-9), and at δ 6.00 there is another broad-singlet peak for two protons (H-5, H-6). Comparing the above chemical shifts of the mixture of isomers produced from procedure **C** makes it clear that one isomer was formed predominantly. The chemical shifts for the methyl group remain the same except that the integrated areas now are

8/1 for δ 1.65/1.80 peaks and the methoxy group gives 1/8 for δ 3.50/3.65 peaks. This is very strong evidence that the alkylation of the developed carbanion after Birch reduction gives a mixture of diastereoisomers and depending on the conditions used, we get one of them predominantly. The answer to which is which would come through further ^{1}H NMR analyses.

Furthermore the hydrolysis of the two diastereoisomeric mixtures **30** from procedures **B** and **C** again gave inseparable mixtures of diastereoisomers **37**, in exactly the same ratio as in **30**. The ^{1}H NMR spectrum analysis shows that the chemical shift for the methyl group attached to C-12 shifted upfield from δ 1.65 to δ 1.32 and for the other isomer the methyl group at δ 1.80 shifted to δ 1.60. The two octets for H-12 at δ 4.50 and δ 5.00, indicate that the isomer with the H-12 proton which falls under the shielding, anisotropic effect of the carbonyl would be shifted more upfield than the proton which falls more in the deshielding region of the carbonyl.

Model structures of the two diastereoisomers of **37** show that in the isomer with the H-12 in endo (*cis* to the side six-membered ring) position this proton will always be shielded by the carbonyl at C-3 no matter what the conformation is, whereas in the other isomer with the H-12 in exo position, the proton will be a greater distance from the carbonyl and not as shielded. From the ^{1}H NMR spectra of **30** and **37** we can see that the major isomer is the one with the methyl group attached to C-12 in the endo position.

The unexpected transformation of **30** to **34** can easily be seen by comparing the spectra of the two compounds. When the methyl group attached to C-12 is in the endo position in **34**, it experiences increased shielding from the conjugated system in the cyclohexadiene ring to give a doublet at δ 1.19. In the other isomer the same methyl group in the exo

position gives a doublet at δ 1.64. Again the major isomer is the one with the methyl group at C-12 in the endo position. This true because the methyl group falls in the shielding anisotropic region of the two conjugated double bonds of the six-membered ring. For an ease comparison of the proton chemical shifts for the various compounds mentioned above the tables **8.1**, **8.2**, **8.3**, and **8.4** are provided at the end of this section.

The reduction-alkylation of **22** under the conditions described in procedure E gave **30** as a mixture of diastereoisomers with a 1:10 ratio of exo versus endo-isomer in 92% total yield. The reaction was repeated according procedure **E** with a slight modification during the final stage. Immediately after the alkylating reagent was injected, a large amount of ethyl acetate was added to the reaction mixture with vigorous stirring at -78°C (procedure **F**). What was isolated was another mixture of diastereoisomers of **30** in a 6:4 ratio exo- to endo-isomer. With these modifications of the conditions we gained some control over the ratio of the two diastereoisomers and also were able to describe a possible mechanism of the observed selectivity. Originally we thought that a simple steric hindrance would give preferential electrophilic approach to the carbanion but the 1,3-interaction in a five-membered ring is not of enough importance to give the ratio of 1:10 exo- versus endo-isomer. Additionally we have a variety of ratios dependant on the conditions we apply. These two reasons were the evidence that we should search for a different mechanism which would rationalize all the experimental results,

Remarkably, when ammonium acetate was used as a proton donor the exo:endo ratio was 7:93 (compare this with the 1:1 ratio exo:endo when t-butyl alcohol was used as a proton donor, procedure **B**). Therefore, having all this evidence in mind, we concluded that the first product which is formed in the

reaction flask is the alkylated cyclohexadiene derivatives (26, 30), and from that, based on the conditions used the other products are derived.

The ratio of diastereoisomers formed should be close to 6:4 and, under the conditions of the reaction, conversion of the exo-product to the endo-product occurs. This is possible if the glycal-like group of product 30 is activated under the reaction conditions. In fact, this is the only way to explain the exo to endo transformation. The methyl enol ether group will facilitate cleavage of the C-12 to oxygen bond and, in the absence of a strong base, the carboxylate anion will recyclize to the most stable diastereoisomer, which from all the data we collected so far, is the endo-product 30 (Scheme 10).

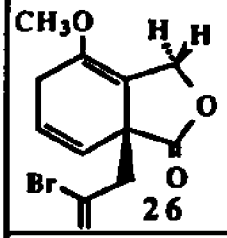
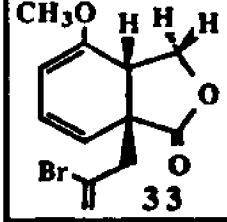
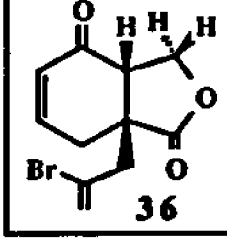
Table 8.1	H-2	H-4	H-5	H-6	H-12	H-13	H-14
 26		2.81 (2H) m	6.10 m	6.00 d	4.45 (ex) d 4.40 (en) d		
 33	3.39 d	5.07 d	6.12 dd	5.03 d	4.55 (ex) dd 3.88 (en) d d		
 36	3.44 t	6.16 dt	6.99 dt	2.87 (2H) m	4.55 (ex) m 4.53 (en) m		

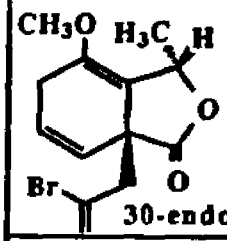
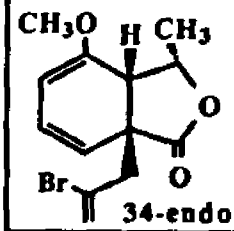
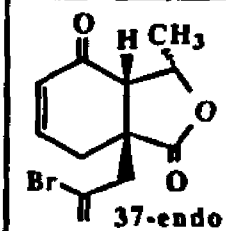
Table 8.2	H-2	H-4	H-5	H-6	H-12	H-13	H-14
 30-endo		2.80 (2H) m	6.10 m	6.00 d	5.15 (ex) d	1.65 (en) d	
 34-endo	3.51 d	5.19 d	6.01 dd	5.13 d	4.84 dq	1.16 d	
 37-endo	3.57 d	6.23 ddd	6.94 ddd	2.60 (ax) ddd 2.68 (eq) ddd	4.98 dq	1.32 d	

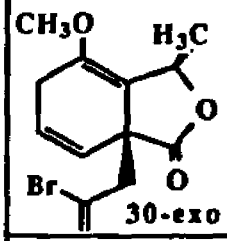
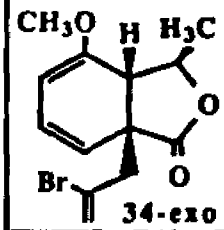
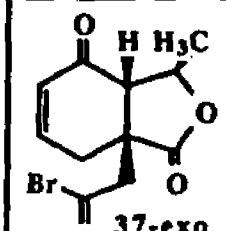
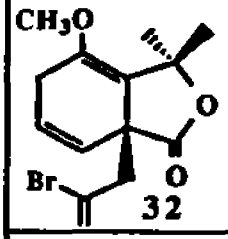
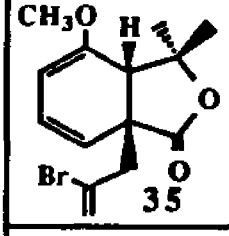
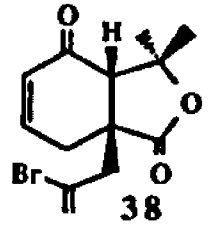
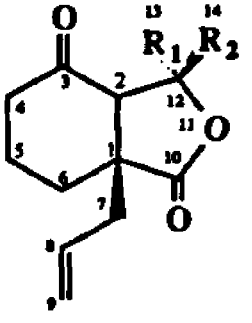
Table 8.3	H-2	H-4	H-5	H-6	H-12	H-13	H-14
 30-exo		2.80, 2H m	6.10 m	6.00 d	4.90 d		1.80 d
 34-exo	3.51 d	5.19 d	6.01 dd	5.13 d	4.22 dq		1.51 d
 37-exo	3.57 d	6.23 ddd	6.94 ddd	2.60 (ax) ddd 2.68 (eq) ddd	4.49 dq		1.59 d

Table 8.4	H-2	H-4	H-5	H-6	H-12	H-13	H-14
 32		2.85 (2H) dd	5.98 m	6.01 d		1.65 (en) s	1.70 s
 35	3.12 s	5.19 d	6.02 dd	5.14 d		1.22 s	1.57 s
 38	3.20 s	6.24 ddd	6.95 ddd	2.62 (2H) ddd		1.29 s	1.70 s



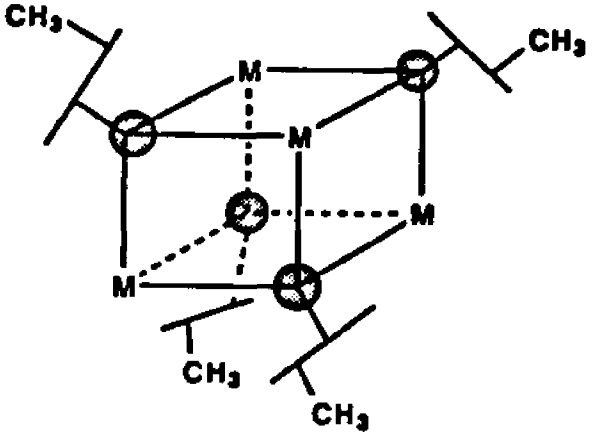
8.5.0. Transformation of exo-isomer (30) to endo-isomer (30).

Compound **30**, by the active glycal-like system, opens the γ-lactone ring to give intermediate **39a** which equilibriates to **39b** through **41** and **42**. This opening of the lactone ring occurs in the highly polar conditions of the reaction mixture and, of course, in the presence of a Lewis acid M^+ ($M^+ = Li^+$

or K^+). The longer the product 30 experiences these conditions the more equilibration between **39a** and **39b** will occur.

When the equilibration process is interrupted by transferring the product into ethyl acetate, the ratio of exo to endo is 6:4 (procedure F). This indicates that electrophilic approach to the carbanion **22c** is preferable from the same side of the planar carbanion as the C-12 methyl group is. The conjugation of the pair of electron on C-1 is what forced the whole molecule to have a planar geometry with the sole exception of the methyl group at C-12. The only way to rationalize the stereoselectivity is that the carbanion forms an aggregate, in which the methyl group at C-12 is the only substituent on the carbanion **22c** (p. 164) which sticks out of the plane of the aggregate of this carbanion. We speculate that these aggregates **40** should only leave free for the approaching electrophile the side where the methyl group is located. Obviously, this happens because the bulky methyl group needs more room and since it is the hydrophobic part of the molecule it would be better solvated in the solvent (THF) while the polar part anion would coordinate with the metal ions inside the aggregates **40** (Scheme 9).

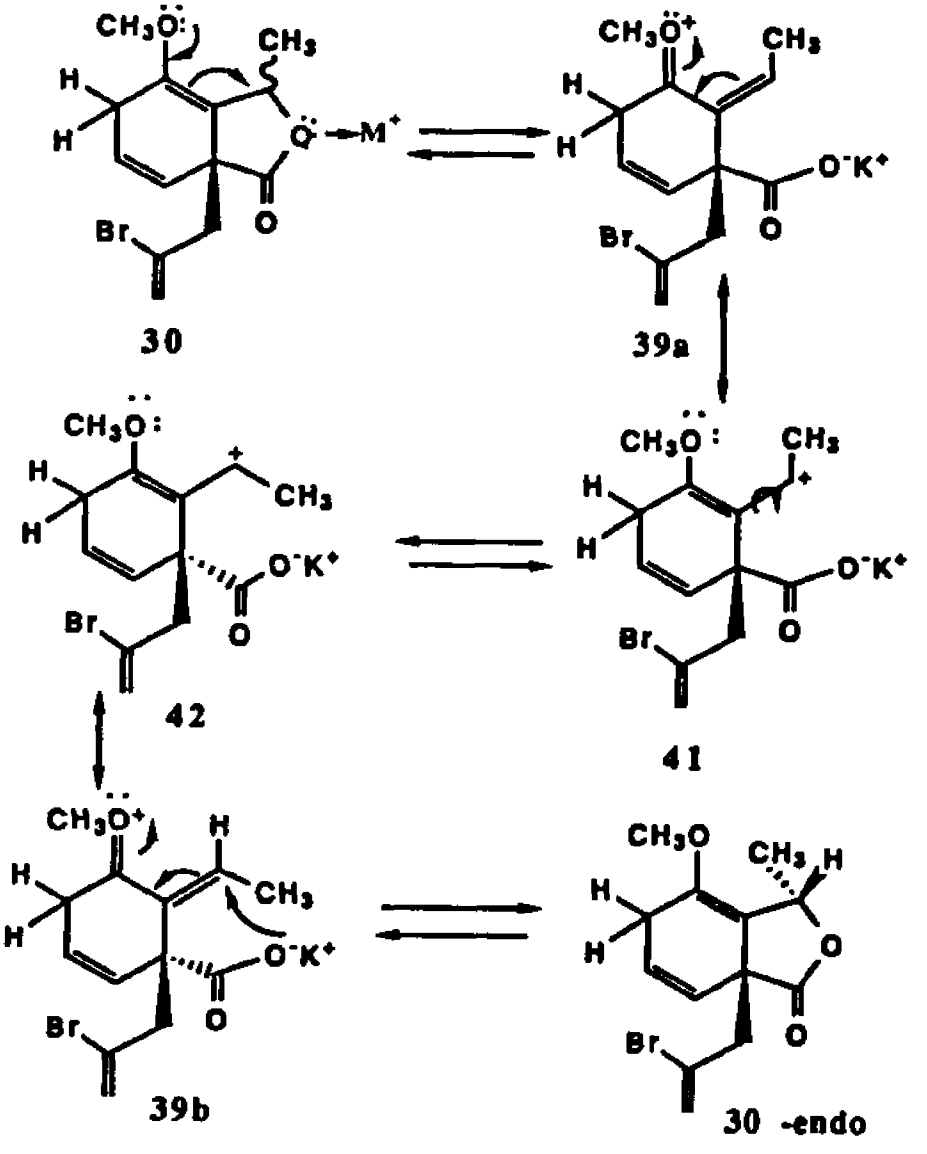
Scheme 9



aggregate **40**

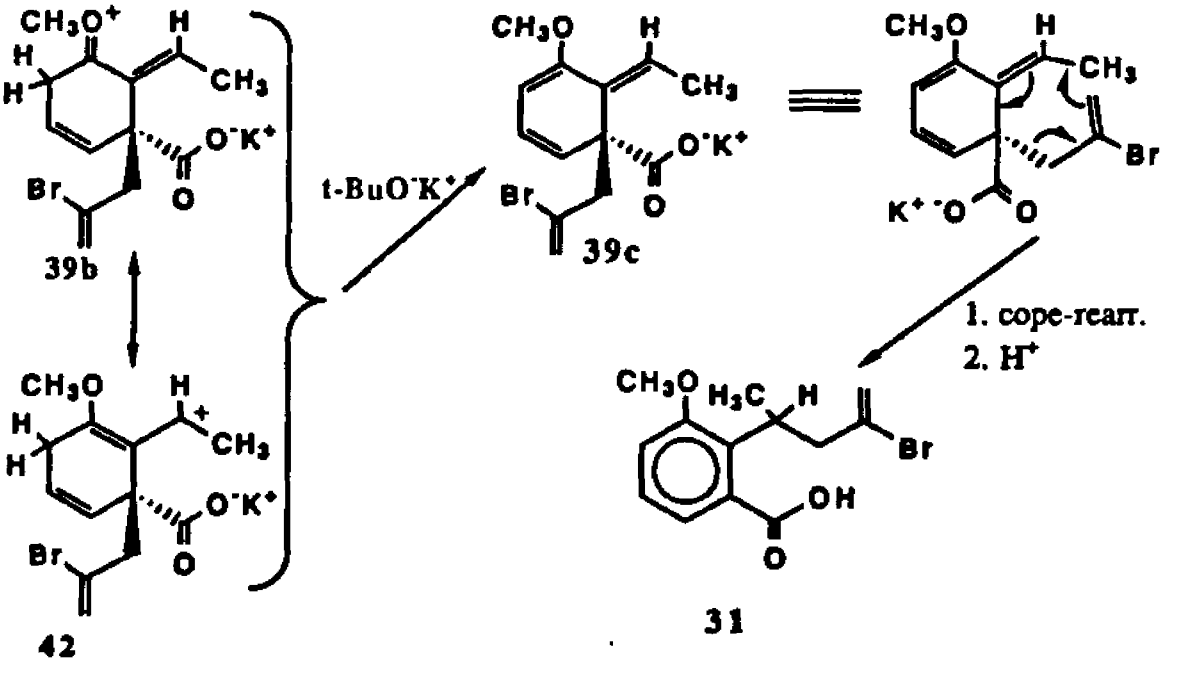
As soon as the lactone ring opens two things may happen: a) in the presence of a strong base, like potassium t-butoxide, elimination would give intermediate **39c**. This rearomatized by Cope rearrangement to give the carboxylic acid derivative **31**; b) In the absence of a strong base the opened form **39a** and **39b** would recyclized to give the endo-product **30**. This happens because **39a** experiences a strong steric interaction between the methyl group at C-12 and the methoxy group at C-3 so that intermediate **39b**, the most stable, is the one which gives endo-product **30** through resonance form **42** (Scheme 10).

Scheme 10



As we already said we did not observe any decarboxylation during the Birch reduction-alkylation of **22**. This did not occur because the carboxylate group is not perpendicular to the six-membered ring (conformation needed for decarboxylation to occur) due to the the methyl group at C-12 which bisects the dihedral angle formed by the carboxylate and the allylbromide groups (shown in **39c**). The Cope rearrangement on the other hand can easily occur because of a better interaction of the molecular orbitals involved (Scheme 11). At this point we want to say that Cope rearrangement is involved in the formation of **27** as well from intermediate **26a** (see Scheme 5)

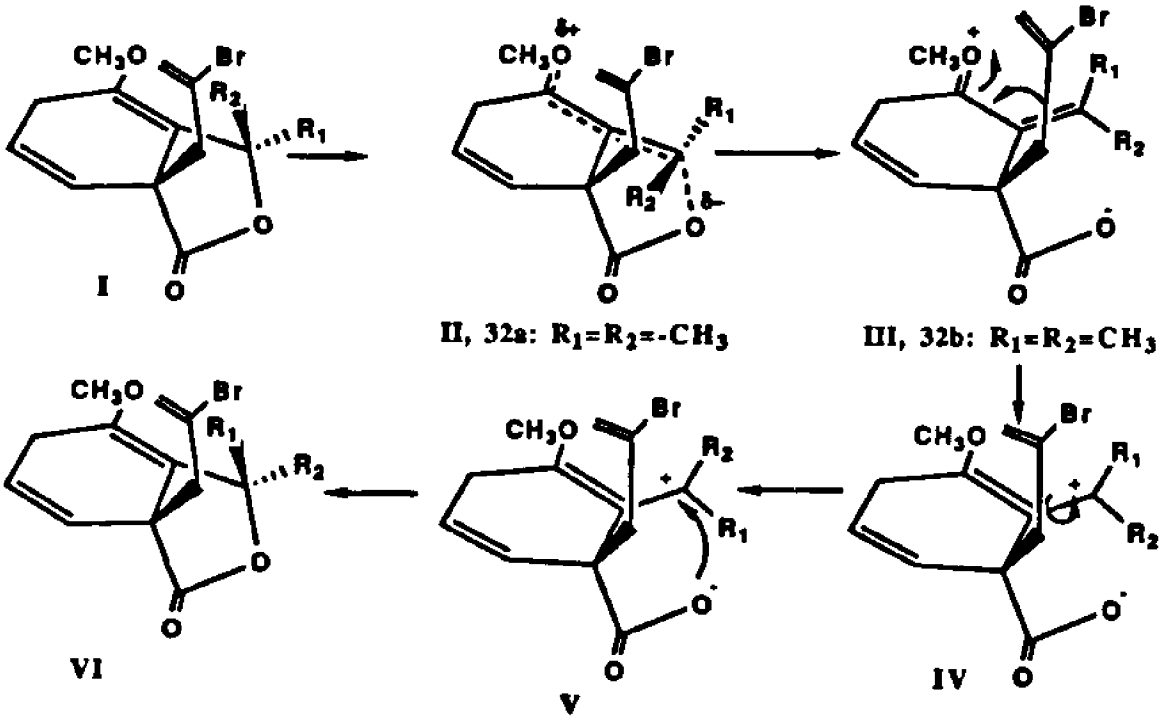
Scheme 11



At this point we suggest that compound **32** cannot undergo through the opened-ring structure intermediate **32b** because the gem-dimethyl group would experience severe steric interactions during the transition state **32a** with both the vinylbromide and the methoxy groups (Scheme 12). This

might be the reason that we did not observe any decarboxylation or any Cope rearrangement for the reaction with compound **23**. It is clear after all that the intermediate **26a** (Scheme 5) is formed predominantly from **26** if t-butanol is used as a proton source to give compounds **27, 28,** and **29**.

Scheme 12



Having a complete understanding of the entire mechanism of Birch reduction-alkylation on phthalides we were ready to continue our investigation by performing a free radical carbocyclization on compounds **36, 37,** and **38**. Access to these precursors allows us to perform a thorough investigation of projected syntheses of natural products.

EXPERIMENTAL

General. Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton nuclear magnetic resonance (1H) spectra were determined on a Varian EM-360A (60 MHz), or on a IBM NR/300 FT NMR (270 MHz), or on a IBM WP/200-SY (200 MHz), and or on a JEOL/JNM/GX-400 FT NMR spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=double, t=triplet, q=quarter, m=multiplet, br=broad), assignment, integration, coupling constant. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer and on Finnigan CH5 single focusing mass spectrometer. Thin-Layer chromatography (TLC) was performed with 13181 silical gel with fluorescent indicator (Kodak) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silical gel 60 mesh. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY).

Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Reduction with potassium (K).

Procedure B.

Reaction with 4-methoxyphthalide 20.

The material to be reduced (10.0 mmol) was placed in a 100 mL, three-necked, round-bottom flask, under a nitrogen atmosphere, and dissolved in 20 mL of dried THF. Then 1.1 equiv of dried t-BuOH was added to the mixture. This solution was cooled to -78°C, and 60 mL of dried ammonia was distilled into the reaction flask (ammonia was dried with sodium metal and a catalytic amount of ferric chloride). Potassium metal was then added in small pieces until the blue color persisted (*ca.* 2.2 equiv) at -78°C. After 5 minutes of stirring, 1.1 equiv (11.0 mmol) of 2,3-dibromopropene was injected into the reaction mixture and stirring was continued for additional 15 minutes before the ammonia was allowed to evaporate. After the addition of 10 mL of saturated ammonium chloride (aq.), the mixture was further diluted with 25 mL of water and extracted with three 50 mL-portions of ethyl acetate. The combined organic extracts was dried over magnesium sulfate, filtered, and concentrated. The crude gum was chromatographically separated to give starting material (0.69 g, 42%), compound **26** (0.44 g, 15%), compound **28** (0.72 g, 20%), and compound **29** (0.24 g, 10%).

The aqueous layer was acidified with 10% HCl_{aq} to pH=4 and then was extracted with three 40-mL portions of ethyl acetate. The combined organic extracts was dried, filtered, and concentrated. The crude residue was dissolved in 30 mL of anhydrous diethyl ether and treated with freshly prepared etherical diazomethane solution at 0°C. This gave crude **27a**, which was chromatographically purified (0.39 g, 13%).

Procedure B-1

A 100-mL three-necked round bottomed flask equipped with a magnetic bar and a dry-ice condenser was charged with 1.6 g (10.0 mmol) of 4-methoxy-phthalide 20 and 0.81 g (11.0 mmol) of t-butanol dissolved in 20 mL dry THF and the solution was cooled to -78° C. Into this mixture, 60 mL liquid ammonia was distilled from sodium metal and then potassium metal (0.82 g, 22.0 mmol) was added in small pieces until the blue color persisted. After 30 minutes of stirring at -78° C the solution was left to warm to -33° C and stirring was continued for additional 30 minutes. To the reaction mixture was then added dropwise with a pipet 10 mL saturated ammonium chloride at -33° C. Ammonia was then allowed to evaporate under the hood. The reaction mixture was concentrated by a rotatory evaporator, the residue was diluted with 25 mL of water, and then was transferred into a separatory funnel, where it was extracted with three 25-mL portions of diethyl ether. The organic extracts was discarded and the aqueous layer was transferred in a 250 mL Erlemeyer flask. Sodium chloride was added until the solution was saturated and 100 mL ethyl acetate was added to the mixture. The mixture was cooled to 0° C and 10% HCl_{aq} solution was added until the pH was 5. The mixture was then transferred into a separatory funnel and extracted twice with 50-mL portions of ethyl acetate. The combined organic extracts was dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in 25 mL of ether and treated with freshly prepared etherical diazomethane solution. After solvent removal, the crude product was purified by column chromatography to give 0.90 g (50% yield) of 2-methyl-3-methoxybenzoic acid methyl ester **27b**. ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.30 - 6.85 (m, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 2.45 (s, 3H).

Preparation of enone 27e.

The above procedure **B-1** was applied to 4-methoxyphthalide **20** (1.64 g, 10.0 mmol) with a minor modification. Instead of using 1.1 equiv. of t-butanol, 3.3 equiv. were used, and accordingly, 4.5 equiv. of potassium metal were required. Compound **27c** presumably was produced, before the methyl enol ether was hydrolyzed to give the β,γ-unsaturated ketone **27d** (0.59 g, 35% yield), which was esterified with diazomethane to **27e**. IR (neat, cm^{-1}) 3050 (w), 2950 (m), 1725 (s), 1600 (w); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.90 (m, 2H), 3.75 (s, 3H), 3.90 - 3.50 (m, 2H), 2.95 (d, 2H, J = 2 Hz), 1.20 (d, 3H, J = 7 Hz). Isomerization of **27e** in 6.0 mL mixture of 10% HCl_{aq} : THF (1 : 2) at room temperature after 6 hours gave the α,β-unsaturated ketone **27f**, in quantitative yield. IR (neat, cm^{-1}) 3050 (w), 2950 (m), 1735 (s), 1680 (s), 1590 (w); ^1H NMR (60 MHz, $CDCl_3$, ppm) 6.90 (dt, 1H, J = 10 Hz, J = 4 Hz), 6.10 (dt, 1H, J = 10 Hz, J = 2 Hz), 3.95 (s, 3H), 2.90 - 2.60 (m, 4H), 1.25 (m, 3H); mass spectrum, exact mass, *m/e*, calcd for $C_9H_{12}O_3$: 168.0786, obsd: 168.0788.

Reaction with 3-methyl-4-methoxyphthalide 22.

Procedure **B** was applied to 3-methyl-4-methoxyphthalide **22** (1.78 g, 10.0 mmol), and 0.89 g (50%) of the starting material was recovered. The compounds **30** (0.75 g, 25%), and **31** (0.69 g, 22%) were isolated. Compound **31** especially was isolated from the aqueous layer after acidification and extraction with ethyl acetate. Compound **31** was esterified with diazomethane to give methyl ester **31a**.

Reaction with 3,3-dimethyl-4-methoxyphthalide 23.

Procedure **B** was applied to 3,3-dimethyl-4-methoxyphthalide **23** (1.92 g, 10.0 mmol), and 1.25 g (65%) of the starting material was recovered. The only other compound isolated was **32** in 32% (1.0 g) yield.

Reduction with lithium metal (Li).

Procedure C.

Reaction with 4-methoxyphthalide 20.

4-Methoxyphthalide **20** (1.64 g, 10.0 mmol) was placed in a 100 mL, three-necked, round-bottom flask along with 1.1 equiv of dried (anhydrous) ammonium acetate. To this mixture, 20 mL of dried THF were added and then 60 mL of dried ammonia were distilled into the solution while it was stirring at -78°C. To this solution, lithium metal, (washed in hexane, methanol, and hexane successively), was added, in small pieces until the blue color persisted. After the blue solution was stirred for 5 minutes, 1.1 equiv of 2.3-dibromopropene was added at -78°C. The ammonia was allowed to evaporate and the solution warmed to room temperature. Then 15 mL of saturated ammonium chloride (aq.) was added and, after it had been diluted with water (20 mL), the solution was extracted with three 50-mL portions of ethyl acetate. The combined organic extracts was dried, filtered, and concentrated. The crude residue was then chromatographically separated to give starting material **20**, approximately 60% (0.98 g), and compound **26** in 32% (0.92 g) yield. The aqueous layer was acidified and extracted with three 25-mL portions of ethyl acetate. The combined organic extracts was dried, filtered, and concentrated to give a small amount (ca 100 mg) of a liquid residue. After analysis, it was found to be the benzoic acid derivative **27**, in less than 5% (0.15 g) yield.

Reaction with 3-methyl-4-methoxyphthalide 22.

Procedure C was applied to 3-methyl-4-methoxyphthalide **22** (1.78 g, 10.0 mmol). Approximately 60% (1.07 g) of the starting material was recovered and compound **30** in 35% (1.05 g) yield. Compound **31** was isolated in less than 5% (0.15 g) yield from the aqueous layer after it was acidified and extracted with ethyl acetate.

Reaction with 3,3-dimethyl-4-methoxyphthalide 23.

Under the same conditions as described in procedure C, the reaction of 3,3-dimethyl-4-methoxyphthalide **23** gave starting material at about 60% (1.15 g) yield. The only other product isolated was compound **32** in 35% (1.10 g) yield.

Procedure D.

Reaction with 4-methoxyphthalide 20.

4-Methoxyphthalide 20 (1.64 g, 10.0 mmol) and ammonium acetate (0.850 g, 11 mmol) were placed in a 100 mL, three-necked, round- bottom flask under a nitrogen atmosphere. After the addition of 30 mL of dried THF, the reaction mixture was cooled to -78°C, and 30 mL of dried liquid ammonia was transferred into the reaction flask while it was stirring. Then lithium metal was added in small pieces until the reaction mixture turned blue and the stirring was continued for 5 more minutes. After that, 2,3-dibromo-propene (1.1 mL, 2.2 g, 11.0 mmol) was injected into the reaction mixture, which was stirred 10 minutes more, and then the ammonia was left to evaporate in a hood. Then 15 mL of saturated ammonium chloride (aq.) was added, followed by 30 mL of water. The mixture was extracted with three 50 mL-portions of ethyl acetate. The combined organic extracts was dried, filtered,

and concentrated. After chromatographic purification of the brownish residue, 35% (0.57 g) of the starting material and 43% (1.23 g) of compound **26** were isolated. The aqueous layer was then checked for any acidic organic product, but none was detected.

Reaction with 3-methyl-4-methoxyphthalide 22.

Under the conditions of procedure D, the reaction of 3-methyl-4-methoxyphthalide **22** (1.78 g, 10.0 mmol) gave back 34% (0.61 g) of the starting material and compound **30** as the only product in 46% (1.38 g) yield.

Reaction with 3,3-dimethyl-4-methoxyphthalide 23.

After the reaction was run with compound **23** (1.92 g, 10.0 mmol), 40% (0.77 g) of the starting material was recovered and compound **32** was isolated as the only product in 50% (1.58 g) yield.

Procedure E.

Reaction with 4-methoxyphthalide 20.

A 100 mL, three-necked, round-bottom flask was charged with 4-methoxyphthalide **20** (1.64 g, 10.0 mmol) and ammonium chloride (0.850 g, 11.0 mmol). To this mixture were added 20 mL of dried THF, and then 60 mL of dried ammonia was transferred, by distillation from sodium metal, to the reaction flask at -78° C. While this mixture was stirring at -78° C, lithium metal was added, in small pieces, until the blue color of the solution was maintained. The solution was then stirred for an additional 15 minutes at -78° C, and the excess of electrons was destroyed by dropwise addition, from a syringe, of 1,2-dibromoethane, after which the ammonia was left to evaporate. During the evaporation of ammonia the pressure in the reaction

flask was kept positive by passing of a stream of dried nitrogen, through it and the last traces of ammonia were removed by warming the reaction flask up to 50° C. Then the reaction mixture was cooled down to -78° C, and 1.1 mL (11.0 mmol) of 2,3-dibromopropene were added dropwise over 2 minutes. After 10 minutes of stirring, the solution was allowed to warm up to room temperature and 15 mL of $NaCl_{aq}$ saturated solution were added before it was further diluted with 30 mL of water. The solution was then transferred to a separatory funnel and was extracted with three 50-mL portions of ethyl acetate. The combined organic extracts was dried, filtered, concentrated, and chromatographically purified to afford 2.53 g of compound **26** (88% yield).

Reaction with 3-methyl-4-methoxyphthalide 22.

Procedure E was applied for the reduction-alkylation of 3-methyl-4-methoxyphthalide **22** (1.78 g, 10.0 mmol) to give, after isolation, compound **30** in 91% yield (2.72 g).

Reaction with 3,3-dimethyl-4-methoxyphthalide 23.

Under the same conditions of procedure E, the reductive-alkylation of compound **23** (1.92 g, 10.0 mmol) gave compound **32** (3.02 g, 96% yield).

Procedure F.

Procedure F is a modified procedure E, in which instead of lithium, potassium is used as a reducing metal. Compound **20** (1.64 g, 10.0 mmol) gave 2.61 g of **26** (91% yield), compound **22** gave 2.84 g of **30** (94% yield), and compound **23** gave 3.00 g of **32** (95% yield). Some starting materials (0.08 - 0.10 g, 5%) were recovered.

Procedure G.

Reaction with 3-methyl-4-methoxyphthalide 22.

A 100 mL, three-necked, round-bottom flask was charged with 1.78 g (10.0 mmol) of compound **22** and 0.850 g (11.0 mmol) of ammonium chloride. To this mixture were added 20 mL of dried THF, and then 60 mL of dried ammonia was transferred by distillation from sodium metal to the reaction flask at -78° C. While this mixture was stirring at -78° C, lithium metal was added, in small pieces, until the blue color of the solution was maintained. The solution was then stirred for an additional 15 minutes at -78° C, and the excess of electrons was destroyed by dropwise addition, from a syringe, of 1,2-dibromoethane, after which the ammonia was left to evaporate. During the evaporation of ammonia the pressure in the reaction flask was kept positive, by passage of a stream of dried nitrogen through it, and the last traces of ammonia were removed by warming the reaction flask up to 50° C. Then the reaction mixture was cooled down to -78° C, and 1.1 mL (11.0 mmol) of 2,3-dibromopropene were added rapidly while the reaction mixture was stirring vigorously. After one minute of stirring, the solution was diluted with 150 mL of ethyl acetate and slowly was allowed to warm up to room temperature and 15 mL of $NaCl_{aq}$ saturated solution were added before it was further diluted with 30 mL of water. The solution was then transferred to a separatory funnel and was separated. The organic layer was dried over magnesium sulfate, filtered, concentrated, and chromatographically purified to afford 2.77 g of compound **30** (92% yield). From the ^1H NMR shows that **30** is a mixture of diastereoisomers endo:exo 6:4 ratio.

Spectroscopic and analytical data:

Compound **26** (liquid): IR (neat, cm^{-1}) 2960 (w), 2940 (m), 1765 (s), 1620 (m); ^1H NMR (60 MHz, $CDCl_3$, ppm) 5.85 (s, br, 2H), 5.50 (m, 2H), 4.90 (m, 2H), 3.65 (s, 3H), 2.70 (m, 4H); mass spectrum, *m/z* (relative intensity): 286 (M^+, ^{81}Br, 2.9), 284 (M^+, ^{79}Br, 4), 148 (9.7), 121 (100), 115 (13.1), 107 (18.4), 92 (18.3), 91 (82.3).

Compound **27a** (liquid): IR (neat, cm^{-1}) 3000 (w), 2940 (m), 2840 (w), 1625 (m), 1585 (s), 1460 (s), 1255 (s), 1100 (s), 890 (s); ^1H NMR (300 MHz, $CDCl_3$, ppm) 7.38 (d, 1H, J = 8 Hz), 7.20 (t, 1H, J = 8 Hz), 6.97 (d, 1H, J = 8 Hz), 5.58 (d, 1H, J = 2 Hz), 5.49 (d, 1H, J = 2 Hz), 3.88 (s, 3H), 3.82 (s, 3H), 3.15 (t, 2H, J = 8 Hz), 2.66 (t, 2H, J = 8 Hz). Compound **27** (solid, m.p. 106-107 ^0C); ^1H NMR (60 MHz, $CDCl_3$, ppm) 11.30 (br, 1H), 7.20-7.10 (m, 3H), 5.60 (sbr, 1H), 5.40 (m, 1H), 3.85 (s, 3H), 3.45-3.10 (m, 2H), 2.90-2.50 (m, 2H). Anal. Calcd for $C_{12}H_{13}Br_1O_3$: C, 50.55; H, 4.60. Found: C, 50.78; H, 4.70.

Compound **28** (liquid): IR (neat, cm^{-1}) 3000 (w), 2940 (m), 2840 (w), 1580 (s), 1460 (s), 1435 (m), 1260 (s), 1100 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.20-6.60 (m, 3H), 5.50-5.30 (m, 4H), 3.80 (s, 3H), 3.75 (s, br, 2H), 3.00-2.40 (m, 4H); mass spectrum, *m/z* (relative intensity) 362 (M^+, 2 x ^{81}Br, 23.4), 360 (M^+, ^{79}Br, ^{81}Br, 45.1), 358 (M^+, 2 x ^{79}Br, 24.2), 199 (22.4), 161 (24.5), 160 (65.9), 159 (100), 158 (35.2), 145 (56.2), 144 (65.5), 131 (31.9), 130 (38.0), 129 (60.0), 128 (63.2), 127 (63.0), 117 (42.2), 116 (54.1), 115 (65.2), 91 (53.4).

Compound **29** (liquid): IR (neat, cm^{-1}) 3000 (w), 2930 (m), 2835 (w), 1625 (m), 1580 (s), 1460 (s), 1435 (m), 1235 (s), 1100 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.10 (m, 1H), 6.80 (m, 2H), 5.50 (m, 1H, 5.40 (m, 1H), 3.95 (s, 3H), 3.80 (m,

2H), 2.30 (s, 3H); mass spectrum, *m/z* (relative intensity) 242 (M^+, ^{81}Br, 84.4), 240 (M^+, ^{79}Br, 85.4), 161 (100), 160 (74.7), 146 (82.2), 145 (81.0), 135 (71.0), 131 (84.0), 128 (79.7), 117 (82.7), 115 (86.3), 105 (81.5), 91 (84.9).

Compound **30** (liquid): IR (neat, cm^{-1}) 1770 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 6.00 (s, 2H), 5.55 (s,m, 2H), 5.20 (m, 1H), 3.65 (s, 3H), 2.90-2.65 (m,4H), 1.60 (d, 3H, J = 7 Hz).

Compound **31a** (liquid): IR (neat, cm^{-1}) 2950 (m), 2840 (w), 1720 (s), 1625 (m), 1580 (m), 1455 (m), 1435 (m), 1305 (m), 1285 (s), 1260 (s), 1060 (s); ^1H NMR (60 MHz, $CDCl_3$, ppm) 7.20-6.80 (m, 3H), 5.40 (s br, 1H), 5.25 (s br, 1H), 4.55 (m, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 2.85 (m, m, 2H), 1.35 (d, 3H, J = 7 Hz).

Compound **32** (liquid): IR (neat, cm^{-1}) 3030 (w), 2960 (m), 2925 (m), 2840 (w), 1760 (s), 1695 (m), 1620 (m); ^1H NMR (270 MHz, $CDCl_3$, ppm) 6.01 (s, m, 2H), 5.60 (s, 1H), 5.59 (s, 1H), 3.64 (s, 3H), 2.86 - 2.81 (m, 4H), 1.70 (s, 3H), 1.64 (s, 3H).

Compound **33** (liquid): IR (neat, cm^{-1}) 3040 (w), 3000 (w), 2960 (m), 2940 (m), 2910 (m), 2840 (w), 1765 (s), 1645 (m), 1620 (m); ^1H NMR (270 MHz, $CDCl_3$, ppm) 6.12 (dd, 1H, H-5, J_{H_5, H_6} = 6.6 Hz, J_{H_5, H_4} = 9.3 Hz), 5.65 (s, 1H, H-9), 5.54 (d, 1H, H-9, J_{H_9, H_7} = 1.6 Hz), 5.08 (d, 1H, H-6, J_{H_6, H_5} = 6.6 Hz), 5.03 (d, 1H, H-4, J_{H_4, H_5} = 9.3 Hz), 4.55 (dd, 1H, H-10ex, $J_{H_{10ex}, H_{10en}}$ = 9.5 Hz, J_{H_{10ex}, H_2} = 8.5 Hz), 3.87 (dd, 1H, H-10en, $J_{H_{10en}, H_{10ex}}$ = 9.4 Hz, J_{H_{10en}, H_2} = 8.5 Hz), 3.61 (s, 3H), 3.38 (dd, 1H, H-2, $J_{H_2, H_{10ex}}$ = 9.45 Hz, $J_{H_2, H_{10en}}$ = 9.45 Hz), 2.91 (d, 1H, H-7, J_{H_7, H_7} = 14.76 Hz), 2.69 (d, 1H, H-7, J_{H_7, H_7} = 14.79 Hz).

Compound 34 (liquid): IR (neat, cm^{-1}) 2920 (m), 2840 (m), 1760 (s), 1650 (m), 1620 (m), 1585 (s); ^1H NMR (270 MHz, $CDCl_3$,) δ 6.01 (dd, 1H, H-5, $J_{H5, H4}$ = 6.5 Hz, $J_{H5, H6}$ = 9.3 Hz), 5.65 (s, 1H, H-9), 5.57 (d, 1H, H-9, $J_{H9, H7}$ = 1.6 Hz), 5.20 (d, 1H, H-6, $J_{H6, H5}$ = 9.3 Hz), 5.13 (d, 1H, H-4, $J_{H4, H5}$ = 6.5 Hz), 4.83 (dq, 1H, H-10, $J_{H10, H2}$ = 9.5 Hz, $J_{H10, H12}$ = 6.6 Hz), 3.65 (s, 3H),3.51 (d, 1H, H-2, $J_{H2, H10}$ = 9.5 Hz), 2.94 (dd, 1H, H-7, $J_{H7, H7}$ = 14.7 Hz, $J_{H7,H9}$ = 0.8 Hz), 2.64 (d, 1H, H-7, $J_{H7, H7}$ = 14.7 Hz), 1.16 (d, 3H, H-12, $J_{H12, H10}$ = 6.6.

Compound 35 (liquid): IR (neat, cm^{-1}) 2920 (m), 2840 (m), 1760 (s), 1650 (m), 1620 (m), 1585 (s); ^1H NMR (270 MHz, $CDCl_3$) δ 6.02 (m, 1H, H-5), 5.66 (s, 1H, H-9), 5.59 (s, 1H, H-9), 5.17 (m, 2H, H-4, H-6), 3.65 (s, 3H), 3.12 (s, 1H, H-2), 3.00 (d, 1H, H-7, $J_{H7, H7}$ = 13.2 Hz), 2.63 (d, 1H, H-7, $J_{H7, H7}$ = 13.2 Hz), 1.57 (s, 3H, H-13), 1.22 (s, 3H, H-12)

Compound 36 (liquid): IR (neat, cm^{-1}) 2920 (m), 1770 (s), 1670 (s), 1620 (m); ^1H NMR (270 MHz, $CDCl_3$, ppm) 6.99 (dt, 1H, H-5, $J_{H5, H4}$ = 10.1 Hz, $J_{H5, H6}$ = 4.36 Hz), 6.17 (dt, 1H, H-4, $J_{H4, H5}$ = 9.6 Hz, $J_{H4,H6}$ = 2.2 Hz), 5.77 (s, 1H, H-9), 5.70 (d, 1H, H-9, $J_{H9, H7}$ = 2.0 Hz), 4.59 - 4.48 (m, 2H, H-10), 3.45 (dd, 1H, H-2, $J_{H2, H10ex}$ = 7.0 Hz, $J_{H2, H10en}$ = 7.0 Hz), 2.96 - 2.67 (m, 4H, H-7, H-6); mass spectrum, exact mass calcd for $C_{11}H_{11}O_3Br_1$ *m/e* 269.9892, obsd *m/e* 269.9889.

Compound 37 (solid: m.p. 100 - 101° C): IR (KBr, cm^{-1}) 2950 (m), 2920 (m), 1850 (m), 1765 (s), 1665 (s), 1620 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (ddd, 1H, H-5, $J_{H5, H4}$ = 10.3 Hz, $J_{H5, H6en}$ = 4.4 Hz, $J_{H5, H6ex}$ = 3.3 Hz), 6.25 (ddd, 1H, H-4, $J_{H4, H5}$ = 10.3 Hz, $J_{H4, H6en}$ = 2.0 Hz, $J_{H4, H6ex}$ = 2.0 Hz), 5.74 (d, 1H, H-9, $J_{H9, H7}$ = 1.0 Hz), 5.63 (d, 1H, H-9, $J_{H9, H7}$ = 2.0 Hz), 4.98 (dq, 1H, H-10ex, $J_{H10ex, H12}$ = 6.8 Hz, $J_{H10ex, H2}$ = 8.8 Hz), 3.57 (d, 1H, H-2, $J_{H2, H10ex}$ = 8.8 Hz), 3.01 (dd, 1H, H-7, $J_{H7, H7}$ =

14.6 Hz, $J_{H7, H9}$ = 1.0 Hz), 2.85 (d, 1H, H-7, $J_{H7, H7}$ = 14.6 Hz), 2.68 (ddd, 1H, H-6ex, $J_{H6ex, H6en}$ = 19.1 Hz, $J_{H6ex, H5}$ = 3.4 Hz, $J_{H6ex, H4}$ = 2.0 Hz), 2.60 (ddd, 1H, H-6en, $J_{H6en, H6ex}$ = 19.1 Hz, $J_{H6en, H5}$ = 4.4 Hz, $J_{H6en, H4}$ = 2.0 Hz), 1.32 (d, 3H, H-12). Anal. Calcd for $C_{12}H_{13}Br_1O_3$: C, 50.56; H, 4.59; Br, 28.02. Found C, 50.60; H, 4.38; Br, 27.61.

Compound 38: IR (neat, cm^{-1}) 2980 (m), 2925 (m), 1760 (s), 1665 (s), 1620 (m); ^1H NMR (60 MHz, $CDCl_3$) δ 6.95 (dt, 1H, H-5, $J_{H5, H4}$ = 10 Hz, $J_{H5, H6}$ = 4 Hz), 6.25 (dt, 1H, H-4, $J_{H4, H5}$ = 10 Hz, $J_{H5, H6}$ = 2 Hz), 5.75 (s, br, 1H, H-9), 5.60 (d, 1H, H-9, $J_{H9, H7}$ = 2 Hz), 3.20 (s, 1H, H-2), 3.10 (d, 1H, H-7, $J_{H7, H7}$ = 14.5 Hz), 2.85 (d, 1H, H-7, $J_{H7, H7}$ = 14.5 Hz), 2.60 (dd, 2H, H-6, $J_{H6, H5}$ = 4.0 Hz, $J_{H6, H4}$ = 2.0 Hz), 1.29 (s, 3H, H-12).

REFERENCES

1. Moody, C. J.; Toczek, J. *Tetrahedron Lett.*, **1986**, *27*, 5253.

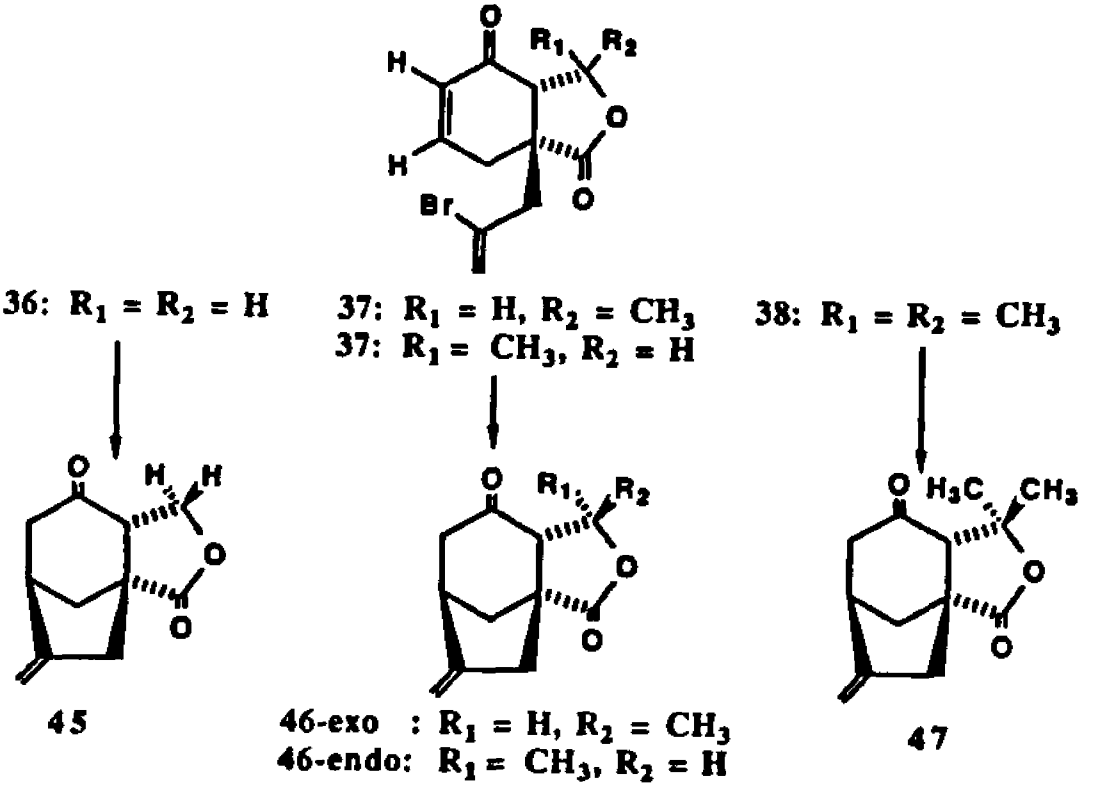
CHAPTER 9

9.0.0. FREE - RADICAL CARBOCYCLIZATION ON 36, 37, and 38

9.1.0. Formation of 45, 46, and 47

The compound 36 was dissolved in dried benzene at a concentration of approximately 0.03 M and a mixture of 1.1 equiv of tri-n-butyltin hydride and 0.01 equiv of AIBN in dried benzene (0.1 M) was added to it over 40 minutes while the solution was at reflux. The reaction mixture was stirred for additional 30 minutes at reflux before workup. The cyclization gave the tricyclic compound 45 in quantitative yield. Similarly the compounds 37 and 38 gave the tricyclic systems 46 and 47 respectively (Scheme 1).

Scheme 1

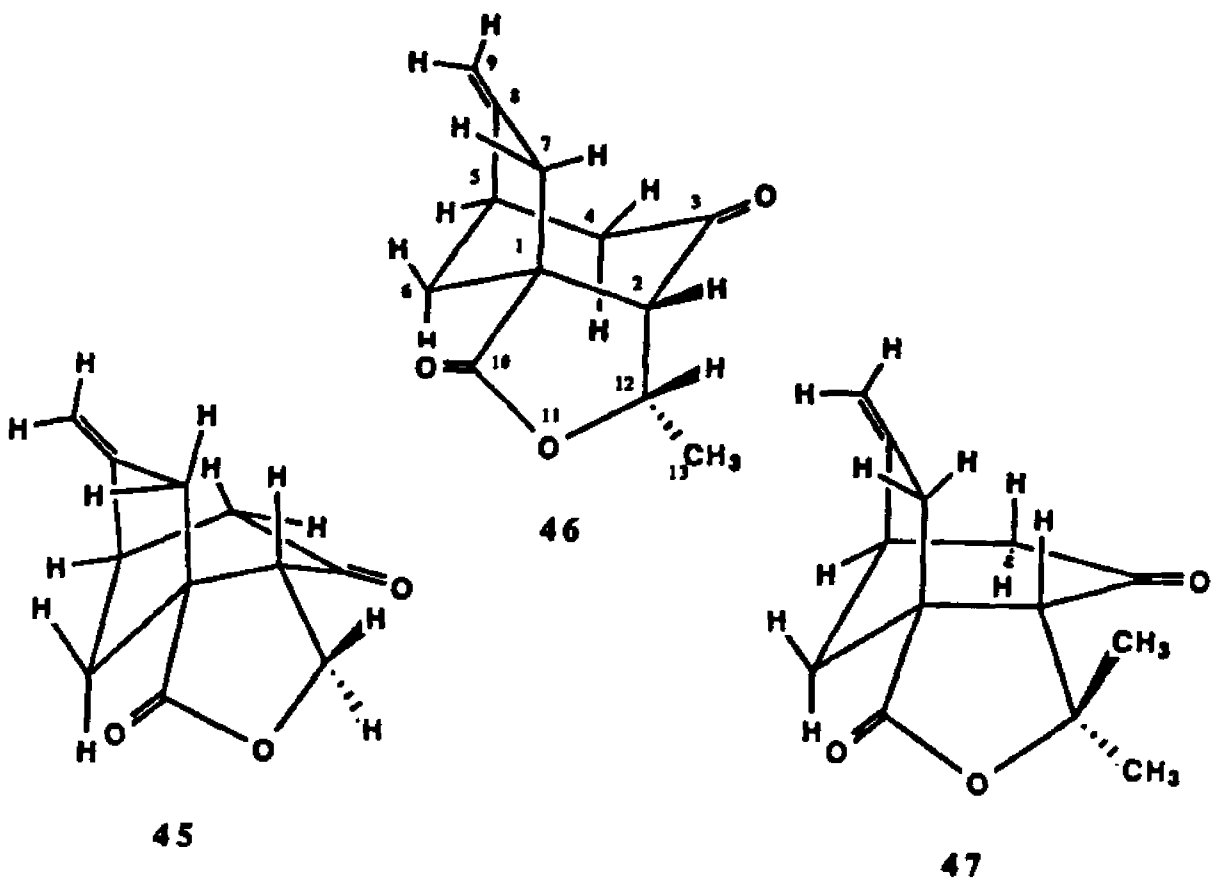


9.2.0. NMR data in determining the conformation of 45, 46, and 47

The carbocyclizations of **36, 37,** and **38** under the standard cyclization conditions were complete within two hours, providing the tricyclic systems **45, 46,** and **47** in over 90% yields. Cyclization was confirmed by the change of the IR carbonyl absorption bands characteristic of cyclohexenone (1680 cm^{-1}) transformation to cyclohexanone (1710 cm^{-1}). The stereochemistry of each of the tricyclic systems was assigned on the basis of ^1H NMR analysis (Scheme 2). The chemical shifts for every proton in each of the three compounds are given in the following table for a better and clearer comparison. The chemical shifts are supported by scrutinized decoupling and NOE experiments. In **45** irradiation at δ 1.81 simplifies the peak at δ 2.08 from dddd to mbr as well as the peak at δ 2.55 from ddd to dd. That suggests that the peak at δ 1.81 is due to H-6_{ax} proton which couples with H_{6eq} at δ 2.08 and also with a long range coupling with H-7_{en}. With irradiation at δ 2.08 the peak at δ 1.81 (H-6_{ax}) from dd becomes d and the peak at δ 3.15 (H-5) from ddd becomes dd. There is also indication that a long range coupling exists between this proton (H-6_{eq}) and the protons at δ 2.52 (H-4_{ax}) and at δ 3.08 (H-2) because their peak patterns become simpler. The above gives the first clue that the six-membered ring in **45** is in a boat conformation. If it was a chair, then there should be couple with the proton at δ 2.72. The latter conclusion becomes clearer when irradiation is taking place at δ 2.72 (H-4_{eq}) when coupling with the proton at δ 3.15 (H-5) changes from ddd to dd. Irradiation at δ 3.01 (H-7_{ex}) decouples the proton at δ 2.55 (H-7_{en}) from ddd to dd. Decoupling of the proton at δ 3.08 (H-2) converts the peaks at δ 4.14 and δ 4.59 from dd to just d for both. The irradiation at δ 3.15 (H-5) decouples the proton at δ 2.72 (H-4_{eq}) from dd to d and the proton at δ 2.08 (H-6_{eq}) from dddd becomes dd.

Irradiation at δ 4.14 (H-12_{ax}) decouples the proton at δ 4.59 (H-12_{eq}) from dd to d and the proton at δ 3.08 (H-2) from dd becomes d as well. The same effect is observed when the proton at δ 4.59 (H-12_{eq}) is irradiated. The proton at δ 4.14 (H-12_{ax}) from dd becomes d and the proton at δ 3.08 (H-2) from dd becomes again d. When we irradiated at the terminal vinyl protons at δ 5.19 (H-9) the ddd at δ 3.01 (H-7_{ex}) becomes just a doublet. Performing all these decoupling experiments we were able to confirm the structure and partially the conformation of the tricyclic system **45**. The fact that δ 3.01 (H-7_{ex}) does not couple with δ 3.08 (H-2) along with the 1765 cm^{-1} absorbance of the carbonyl of the lactone ring in the IR spectrum, confirms the *cis*-junction between the six-membered ring and the γ-lactone ring.

Scheme 2

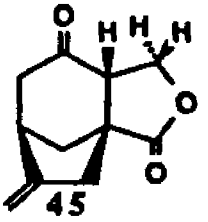
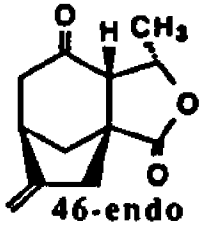
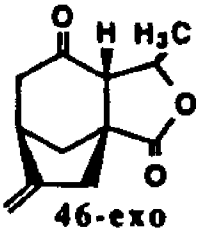
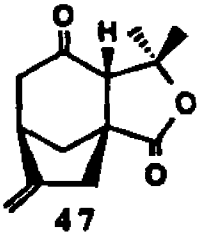


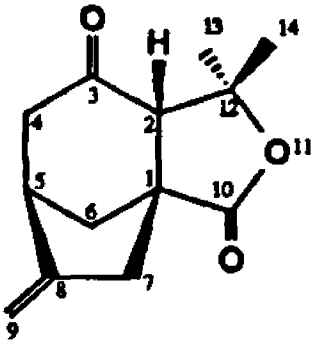
45 **46** **47**

The variation of H-2 chemical shift in the three tricyclic systems indicates that the conformation of the cyclohexanone ring varies from **45** (δ 3.08) to **46** (δ 3.11) to **47** (δ 2.68). There are two planes which determine the position of the carbonyl within the molecule, the *xy* and the *xz* planes. In **45** and **46** the H-2 is closer to the *xy* plane and in **47** the H-2 is closer to the *xz* plane. Model structures of the three systems show that in order to get the corresponding chemical shifts of H-2, **45** should have a boat conformation which also matches the rest of the NMR analytical data. System **46** should have a chair-like conformation since the endo C_{12}-methyl group forces the carbonyl out of its way. In **47** the two C_{12}-methyl groups force the carbonyl group to bisect the dihedral angle formed by them, and that brings the C_2-H bond parallel to the *xz* plane of the carbonyl in which the H-2 experiences a shielding effect. For better comparison of the chemical shifts between the various protons of the three tricyclic systems **45**, **46**, and **47** the table **9.1** is provided.

The positive Nuclear Overhouser Effect (NOE) of the peak at δ 1.93 (H-6_{ax}), when the doublet peak at δ 1.36 (C_{12}-methyl group) was irradiated in **46**, indicates that this methyl group is in the endo position. The same NOE experiment was conducted in **47** and we observed a positive effect of the peak at 1.96 (H_{6ax}) when irradiation took place at δ 1.37 (C_{12}-methyl group) and a large positive effect of the peak at δ 2.68 (H-2) when irradiation took place at δ 1.63 (C_{12}-methyl group). The above NOE results reveals the positions of the corresponding methyl groups. The methyl group at δ 1.37 is the endo (C-13) and the methyl group at δ 1.63 is the exo (C-14). These models demonstrated the great ease and efficiency with which complex tricyclic bridged systems can be constructed by means of vinyl radical cyclization after a properly

substituted precursor was synthesized. These ring systems comprise the C-D ring system of a large variety of diterpenoids with antitumor activity.

Table 9.1	H-2	H-4	H-5	H-6	H-12	H-13	H-14
 45	3.08 ddd	2.52 (ax) d	3.15 dddd	1.81 (ax) dd	4.14 (en) dd		
		2.72 (eq) dd		2.08 (eq) dddd	4.59 (ex) dd		
 46-endo	3.11 dd	2.56 (2H) m	3.13 br	1.93 (ax) dd	4.96 dq	1.36 d	
				2.27 (eq) dddd			
 46-exo					4.50 dq	1.60 d	
 47	2.68 d	2.53 (2H) m	3.10 m	1.96 (ax) dd		1.37 s	1.63 s
				2.22 (eq) dddd			



47

CONCLUSIONS

This body of work has provided: a) an understanding of the properties of the Birch reduction-alkylation of different aromatic systems and b) an understanding of the properties of the intramolecular addition reaction of vinyl radicals to olefins. Several important observations can be summarized as follows:

1. **Birch reduction-alkylation:**

   a) We have demonstrated that in the reduction of benzoic acid derivatives no additional proton source is required. Instead, the proton from the acid is provided for the reduction as ammonium ion.

   b) In the presence of ammonium ion the metal (lithium, sodium, and potassium) reacts faster with the aromatic ring and the ammonium ion reacts faster with the radical anion developed after the first electron is provided by the metal to the aromatic system.

   c) Potassium enolates with esters can undergo C-alkylation and replacement of the potassium counter-ion with lithium ion is not necessary.

   d) Carbanions after Birch reduction are in aggregates and thus alkylation occurs in a selective fashion (formation of diastereoisomers).

e) We have demonstrated for the first time that a Birch reaction can be used for synthesis of substituted aromatic materials.

2. **Free radical carbocyclization:**

a) We have demonstrated that a vinyl radical cyclization can be used for the construction of a five-membered ring in a 1,3-junction to a six-membered ring, in quantitatively yield.

b) The vinyl radical is a generally high energy species (electron rich) and as such would react rapidly with low energy alkenes (electron poor or electrophilic center).

c) The cyclization of vinyl chlorides occurs in excellent yields but slower than it does with vinyl bromides and iodides.

d) The alkyl-substituents on the alkene moiety have no effect on the cyclization, but electron donating substituents on the β-position lead to the reduction of the vinyl halide to a vinyl group.

e) The concentration of the tri-n-butyltin hydride in the reaction flask is a crucial key to a successful cyclization of the developed vinyl radical.

f) The intramolecular cyclization of vinyl radicals holds great potential for the synthesis of complex molecules. The method offers several advantages, including:

1. Generally high yields.

2. Mild Conditions - The reaction proceeds under neutral conditions which reduce the possibility of epimerization of acid or base labile centers.

3. Versatility - The cyclization was compatible with a variety of functionalities, including alcohols, esters, ketones, and other acid or base sensitive groups.

4. Stereospecificity - Properly designed vinyl radical precursors can be used for the stereospecific construction of complex molecules.

These results illustrate the stereospecific construction of bicyclo[3.2.1]octanes with a definite substitution pattern. The work done by us with phthalides proved that simple molecules can be properly used with inexpensive reagents to construct a well designed carbon-skeleton in a three dimensional stereocontrolled fashion, required in the synthesis of natural products. The successful Birch reduction-alkylation of phthalides on the other hand tells us that there is valuable chemistry left to be done with simple molecules which is being overlooked by many research groups.

EXPERIMENTAL

General. Melting points were determined in open capillaries by using a Uni-melt Thomas Hoover capillary melting apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 247 grating spectrophotometer. Proton nuclear magnetic resonance (1H) spectra were determined on a Varian EM-360A (60 MHz), or on a IBM NR/300 FT NMR (270 MHz), or on a IBM WP/200-SY (200 MHz), and or on a JEOL/JNM/GX-400 FT NMR spectrometer (400 MHz). Chemical shifts are reported in parts per million (ppm; δ values) downfield from internal tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=double, t=triplet, q=quarter, m=multiplet, br=broad), assignment, integration, coupling constant. Mass spectra were measured on an AEI MS-902S double focusing high resolution mass spectrometer and on Finnigan CH5 single focusing mass spectrometer. Thin-Layer chromatography (TLC) was performed with 13181 silical gel with fluorescent indicator (Kodak) as the adsorbant in 0.2 mm thick, plastic-backed plates. Column chromatography was performed with silical gel 60 mesh. Combustion analyses were performed by Schwarzkoff Microanalytical Laboratory (New York, NY).

Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium benzophenone ketyl under an atmosphere of dry nitrogen. All other solvents used were purified by distillation under a nitrogen atmosphere from calcium hydride before use.

Free radical carbocyclization of 36, 37, and 38.

Cyclization of 36.

A 250 mL two-necked round-bottomed flask equipped with a magnetic stirring bar, rubber septum inlet, and a condenser was charged with compound **36** (0.542 g, 2.0 mmol) dissolved in dry benzene (90 mL) under a nitrogen atmosphere. A separated solution constituted of tri-n-butyltin hydride (0.640 g, 2.2 mmol) and a catalytic amount of AIBN (15 mg) dissolved in benzene (30 mL) was prepared in an additional funnel fitted on the upper opening of the condenser. The reaction was brought to refluxing, and after then the AIBN/Bu_3SnH solution in the additional funnel was added dropwise over 1 hour period of time. The reaction course was monitored by TLC and within 30 min all of the starting material had reacted. The solution was cooled, the solvent was removed by rotary evaporator, and the residue was purified by column chromatography (hexane:ethyl acetate 1.5:1, Rf = 0.4) to give of the tricyclic compound **45** (0.365 g, 95% yield, m.p. 118 - 119° C): IR (KBr, cm^{-1}) 2980 (w), 2920 (w), 1765 (s), 1700 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (dd, 1H, H-9, $J_{H9, H7ex}$ = 2.9 Hz, $J_{H9, H7en}$ = 2.9 Hz), 5.16 (dd, 1H, H-9, $J_{H9, H7ex}$ = 2.9 Hz, $J_{H9, H7en}$ = 2.0 Hz), 4.59 (dd, 1H, H-10ex, $J_{H10ex, H10en}$ = 10.3 Hz, $J_{H10ex, H2}$ = 10.3 Hz), 4.14 (dd, 1H, H-10en, $J_{H10en, H10ex}$ = 10.3 Hz, $J_{H10en, H2}$ = 10.3 Hz), 3.15 (dddd, 1H, H-5, $J_{H5, H6eq}$ = 5.4 Hz, $J_{H5, H6ax}$ = ? Hz, $J_{H5, H4eq}$ = 5.9 Hz, $J_{H5, H4ax}$ = ? Hz), 3.08 (ddd, 1H, H-2, $J_{H2, H10ex}$ = 10.3 Hz, $J_{H2, H10en}$ = 10.3 Hz, $J_{H2, H6eq}$ = 2.45 Hz), 3.01 (ddd, 1H, H-7ex, $J_{H7ex, H7en}$ = 16.1 Hz, $J_{H7ex, H9}$ = 2.9 Hz, $J_{H7ex, H9}$ = 2.9 Hz), 2.72 (dd, 1H, H-4eq, $J_{H4eq, H4ax}$ = 19.5 Hz, $J_{H4eq, H5}$ = 5.9 Hz), 2.55 (ddd, 1H, H-7en, $J_{H7en, H7ex}$ = 16.1 Hz, $J_{H7en, H6ax}$ = 2.9 Hz, $J_{H7en, H9}$ = 2.0 Hz), 2.52 (d, 1H, H-4ax, $J_{H4ax, H4eq}$ = 19.1 Hz), 2.08 (dddd, 1H, H-6eq, $J_{H6eq, H6ax}$ = 11.7 Hz, $J_{H6eq, H5}$ = 5.4 Hz, $J_{H6eq, H4eq}$ = 2.5 Hz, $J_{H6eq, H2}$ = 2.5 Hz), 1.81 (dd, 1H, H-6ax, $J_{H6ax, H6eq}$ = 11.7 Hz,

$J_{H6ax, H7en}$ = 2.9 Hz). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.56; H, 6.25.

Under identical conditions described above compound **37** (0.285 g, 1.0 mmol) gave compound **46** (0.198g, 96% yield, m.p. 145 - 146° C): IR (KBr, cm^{-1}) 3070 (w), 2940 (m), 1760 (s), 1700 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, br, 1H, H-9), 5.15 (s, br, 1H, H-9), 4.96 (dq, 1H, H-10, $J_{H10, H2}$ = 9.8 Hz, $J_{H10, H12}$ = 6.1 Hz), 3.13 (s, br, 1H, H-5), 3.11 (dd, 1H, H-2, $J_{H2, H10}$ = 9.8 Hz, $J_{H2, H6eq}$ = ? Hz), 2.98 (ddd, 1H, H-7ex, $J_{H7ex, H7en}$ = 16.0 Hz, $J_{H7ex, H9?}$ = 2.6 Hz, $J_{H7ex, H9?}$ = 2.6 Hz), 2.56 (m, 2H, H-4), 2.47 (dd, 1H, H-7en, $J_{H7en, H7ex}$ = 15.9 Hz, $J_{H7en, H6ax}$ = 2.6 Hz), 2.27 (dddd, 1H, H-6eq, $J_{H6eq, H6ax}$ = 11.9 Hz, $J_{H6eq, H5}$ = 5.5 Hz, $J_{H6eq, H2}$ = ? Hz, $J_{H6eq, H4eq}$ = ? Hz), 1.93 (dd, 1H, H-6ax, $J_{H6ax, H6eq}$ = 11.9 Hz, $J_{H6ax, H7en}$ = 2.6 Hz), 1.36 (d, 3H, H-12, $J_{H12, H10}$ = 6.1 Hz); mass spectrum, exact mass calcd for $C_{12}H_{14}O_3$ *m/e* 206.0943, obsd *m/e* 206.947. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.79; H, 6.84.

Similarly compound **38** (0.299 g, 1.0 mmol) gave compound **47** (0.212 g, 97% yield, m.p. 101 - 102° C): IR (KBr, cm^{-1}) 2960 (m), 2920 (w), 1765 (s), 1700 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (m, 1H, H-9), 5.13 (m, 1H, H-9), 3.10 (m, 1H, H-5), 2.98 (ddd, 1H, H-7ex, $J_{H7ex, H7en}$ = 16.0 Hz, $J_{H7ex, H9?}$ = 3.0 Hz, $J_{H7ex, H9?}$ = 3.0 Hz), 2.68 (d, 1H, H-2, $J_{H2, H6eq}$ = 1.5 Hz), 2.54 - 2.52 (m, 2H, H-4), 2.46 (ddd, H-7en, $J_{H7en, H7ex}$ = 16.0 Hz, $J_{H7en, H9?}$ = 1.2 Hz, $J_{H7en, H9?}$ = 1.2 Hz), 2.22 (dddd, 1H, H-6, $J_{H6eq, H6ax}$ = 11.9 Hz, $J_{H6eq, H5}$ = 5.6 Hz, $J_{H6eq, H2}$ = 2.5 Hz, $J_{H6eq, H4eq}$ = 1.7 Hz), 1.96 (dd, 1H, H-6ax, $J_{H6ax, H6eq}$ = 11.9 Hz, $J_{H6ax, H5}$ = 2.9 Hz), 1.63 (s, 3H, H-13), 1.37 (s, 3H, H-12). Anal. Calcd for $C_{13}H_{18}O_4$ ($C_{13}H_{16}O_3$ + H_2O): C, 65.53; H, 7.61. Found: C, 65.37; H, 7.55.

BIBLIOGRAPHY

Abell, P. I., *Free Radicals*, ed. Kochi, J. K., John Wiley, New York, **1973**, Vol.2, ch. 13.

Akhrem, A. A.; Titov, Y. A., in *Total Steroid Synthesis*, Plenum, New York, **1970**.

ApSimon, J. W.; Hooper, J.W., in *The Synthesis of Natural Products*, ed. ApSimon, J. W., New York, **1973**, Vol. 2, pp 559-640.

Auricchio, S.; Ricca, A.; de Pava, O. V. *J. Org. Chem.* **1983**, 48, 602.

Baine, N. H. Ph. D. Thesis, Colombia University, **1981**.

Banerjee, D. K.; Sarendranath V. *Indian J. Chem.* **1975**, 13, 201.

Barltrop, J. A.; Saxton, J. E. J. Chem. Soc., **1952**, 1038.

Bartlett, P. D.; Clossen, W. D.; Gogdell, T. J., *J. Am. Chem. Soc.*, **1965**, 87, 1308.

Bayerman, H. C. Bvan Berkel, J.; Lie, T. S.; Maat, L.; Wessels, J. C. M. *Recl. Trav. Chim. Pays-Bas*, **1978**, 96, 127.

Beckwith, A. L. J. *Tetrahedron* **1981**, 37, 3073.

Beckwith, A. L. J.; Blair, A. I.; Phillipou, G., *Tetrahedron Lett.*, **1974**, 2251.

Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K., *Chem. Comm.*, **1980**, 482.

Beckwith, A. L. J.; Gream, E.; Struble, D. L., *Aust. J. Chem.*, **1972**, 25, 1081.

Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States*; de Mayo, Paul, Ed.; Academic Press: New York, **1980**; Vol. 41-2, pp 180-181.

Beckwith, A. L. J.; Ingold, K. U., *Rearrangements in Ground and Excited States*, ed. deMayo, Academic Press, New York, **1980**, Vol. 42-1, pp 182-220.

Beckwith, A. L. J.; Lawrence, T., *J. Chem. Soc., Perkin Trans II*, **1979**, 1535.

Beckwith, A. L. J.; Moad, G., *J. Chem. Soc. Chem. Comm.*, **1974**, 472.

Beckwith, A. L. J.; Moad, G., *J. Chem. Soc., Perkin Trans II*, **1975**, 1726.

Beckwith, A. L. J.; Phillipou, G., *Chem. Comm.*, **1973**, 280.

Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, 41, 3925.

Benson, S. W., *Thermochemical Kinetics*, 2nd Ed., John Wiley, New York, **1976**.

Berg, U.; Liljefors, T.; Roussel, C.; Sandstrom, *J. Acc. Chem. Res.* **1985**, 18, 80.

Bhattacharjee, D.; Popp, F. D. *J. Heterocyclic Chem.* **1980**, 17, 315.

Biffin, M. E. C.; Moritz, A. G.; Paul, D. B., *Aust. J. Chem.*, **1972**, 25, 1329.

Birch, A. J. *J. Agric. Food Chem.*, **1974**, 22, 162.

Birch, A. J. J. Chem. Soc., **1944**, 430.

Birch, A. J. *Q. Rev., Chem. Soc.*, **1950**, 4, 69.

Birch, A. J.; Hextall, P.; Sternhell, S. *Aust. J. Chem.*, **1954**, 7, 256.

Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.*, **1980**, 102, 3370.

Birch, A. J.; Murray, A. R.; Smith, H. *J. Chem. Soc.*, **1951**, 1945.

Birch, A. J.; Slobbe, J. *Aust. J. Chem.*, **1977**, 30, 1045.

Birch, A. J.; Slobbe, *J. Heterocycles*, **1976**, 5, 905.

Birch, A. J.; Smith, H. *Q. Rev., Chem. Soc.*, **1958**, 7, 17.

Birch, A. J.; Subba Rao G. S. R. in *Advances in Organic Chemistry, Methods and Results*, ed. Taylor, E. C., Wiley - Interscience, New York, **1972**, pp 1-65.

Bonacic-Koutechk, V.; Koutesky, J.; Salem, L., *J. Am. Chem. Soc.*, **1977**, 99, 842.

Breslow, R.; Olin, S. S.; Groves, T. J., *Tetrahedron Lett.*, **1968**, 1837.

Brown, E. D.; Swan, T. W.; Sutherland, J. K.; Torre, A., *J. Chem. Soc., Perkin Trans I*, **1975**, 2326.

Brown, J. M.; Cresp, T. M.; Mander, L. N., *J. Org. Chem.*, **1977**, 42, 3984.

Buchi, G.; Wuest, H., *ibid.*, **1979**, 44, 546.

Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, 103, 2438.

Cekovic, Z., *Tetrahedron Lett.*, **1972**, 749.

Chatzopoulos, M.; Monthhead, J. P., C. R. Hebd. *Seances Acad. Sci. Ser. C*, **1975**, 29.

Chnuki, T.; Yoshida, M.; Simamura, O., *Chem. Lett.*, **1972**, 797.

Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopolan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, 100, 8034.

Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, 100, 8031.

Corfield, G. C., *Chem. Soc. Rev.*, **1972**, 1, 523.

Cossey, A. L.; Gunter, M. J.; Mander, L. N. *Tetrahedron Lett.*, **1980**, 21, 3309.

Cotter, R. J.; Matzer, M., *Ring-Forming Polymerization*, Acad. Press, New York, **1969**.

Danishefsky, S.; Chackalamannil, S.; Uang, B. J., *ibid.*, **1982**, 47, 2231.

de Mos, J. C.; van Bekkum, H.; van den Boch, C. B.; van Minnen-Pathuis, G.; van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas*, **1971**, 90, 137.

de Tar, D. F., *Org. Reactions*, **1957**, 9, 409; Abromovitch, R. A., *Adv. Free Radical Chem.*, **1967**, 2, 87.

Delbecq, F.; Ilavsky, D.; Anh, N. T.; Lefour, J. M. *J. Am. Chem. Soc.* **1985**, 107, 1623.

Demuth, M.; Schaffner, K. *Angew. Chem.*, Int. ed. Engl., **1982**, 21, 820.

Dewar, M. J. S.; Olivella, S., *J. Am. Chem. Soc.*, **1978**, 100, 5290.

Djerassi, C. *Chem. Rev.* **1948**, 48, 271.

Dryden, H. L. in *Organic Reactions in Steroid Chemistry*, ed. Fried, J.; Edwards, J. A. Van Nostrand Reinhold, New York, **1972**, Vol. 1, pp 1-60.

Effio, A.; Griller, D.; Ingold, K. U.; Beckwith, A. L. J.; Serelis, A. K., *J. Am. Chem. Soc.*, **1980**, 102, 1734.

Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, **1962**.

Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison,G. A., *Corformational Analysis*, Jonh Wiley, New York, **1965**, p. 19.

Farina, F.; Primo, J.; Torres, T. *Chem. Lett.* **1980**, 77.

Fressenden, R. W.; Schuler, R. H., *J. Chem. Phys.*, **1963**, 39, 2147.

Fried, J.; Abrahams, N. A.; Santhanakrishnan, T. S. *J. Am. Chem. Soc.*, **1967**, 89, 1044.

Fujimoto, H.; Fukui, K. *Chemical Reactivity and Reaction Paths*, J. Wiley: New York, Klopman, G.; Ed., **1974**.

Fujimoto, H.; Yamade, S.; Minato, T.; Fukui, K., *J. Am. Chem. Soc.*, **1972**, 94, 9205.

Fukui, K. *Acc. Chem. Res.* **1971**, 4, 57.

Fukui, K.; Kato, H.; Yonezawa, T. *Bull. Chem. Soc.* Japan **1960**, 33, 1197.

Geissman, T. A.; Crout, D. H. G. *Organic Chemistry of secondary plant metabolism*, ed. Freeman-Cooper, San Francisco, **1969**, p. 102.

Giese, B.; Meixner, J., *Tetrahedron Lett.*, **1977**, 2779.

Gras, J.-L.; Kong Win Chang, Y. Y.; Bertand, M., *Tetrahedron Lett.*, **1982**, 38, 3571.

Griller, D. Copper, J. W.; Ingold, K. U., *J. Am. Chem. Soc.*, **1975**, 97, 4269.

Griller, D.; Ingold, K. U., *Acc. Chem. Res.*, **1980**, 13, 317.

Grootaert, W. M.; de Clercq, P. J. *Tetrahedron Lett.*, **1982**, 23, 3291.

Gunter, M. J.; Mander, L. N. *Aust. J. Chem.*, **1981**, 34, 675.

Hall, S. S.; Lipsky, S. D.; McEnroe, F. J.; Bartels, A. P. *J. Org. Chem.*, **1971**, 36, 2588.

Hamann, S. D.; Solomon, D, H.; Spurling, T. H., *Aust. J. Chem.*, **1978**, 29, 1975.

Hamilton, R. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron*, **1986**, 42, 2881.

Harland, P. A.; Hodge, P. *Chem. Comm. Synth.* **1982**, 223.

Hart, D. J.; Chuag, C. P., *ibid.*, **1983**, 48, 1782.

Hartsuck, J. A.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1963**, 85, 3414.

Harvey, R. G. *Synthesis*, **1970**, 161.

Heathcock, C. H., in *The Total Synthesis of Natural Products*, ed. ApSimon, J. W., Wiley, New York, **1973**, Vol. 2, pp 197-558.

Hedden, P. *ACS Symp. Ser.* **1979**, 111, 19.

Hook, J. M.; Mander, L. N. *J. Org. Chem.*, **1980**, 45, 1722.

Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.*, **1986**, 3, pp 35-85.

Hook, J. M.; Mander, L. N.; Urech, R. *J. Am. Chem. Soc.*, **1980**, 102, 6628.

Hook, J. M.; Mander, L. N.; Urech, R. *Synthesis*, **1979**, 374.

Hook, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.*, **1982**, 23, 1095.

Houk, K. N. In *Frontier in Free Radical in Chemistry*; Pryor, W. A., Ed.; Academic: New York, **1983**; p 43 ff.

Houk, K. N. *Pure Appl. Chem.* **1983**, 55, 277; d. Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *THEOCHEM.* **1983**, 103, 197.

House, H. O.; Strickland, R. C.; Zaiko, E. J. *J. Org. Chem.*, **1976**, 41, 2401.

House, H. O.; Weeks, P. D., *J. Am. Chem. Soc.*, **1975**, 97, 2778.

Hoyland, J. R., *Theor. Chim. Acta*, **1971**, 22, 229.

Hsu, F. L.; Rice, K. C.; Brossi, A. *Helv. Chim. Acta*, **1980**, 63, 2042.

Idem. Org. Syn., **1963**, 43, 22.

Iio, H.; Isobe, M.; Kawai, T.; Goto, T., *Tetrahedron*, **1979**, 35, 941.

Jenking, C. L.; Kochi, J. K., *J. Am. Chem. Soc.*, **1972**, 94, 843.

Julia, M. *Acc. Chem. Res.* **1971**, 4, 386.

Julia, M., *Pure and Applied Chem.*, **1967**, 15, 167.

Julia, M., *Pure and Applied Chem.*, **1974**, 40, 553.

Julia, M., *Rec. Chem. Prog.*, **1964**, 25, 1.

Julia, M., *Rec. Chem. Prog.*, **1964**, 25, 3.

Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A., *Tetrahedron*, **1975**, 31, 1737.

Julia, M.; Descoins, C.; Jacquet, B.; Uguen, D.; Groeger,F. A., *Tetrahedron*, **1975**, 31, 1737.

Julia, M.; LeGoffic, F.; Katz, L., *Bull. Soc. Chim. Fr.*, **1964**, p. 1122.

Julia, M.; Maumy, M.; Mion, L., *Bull. Soc. Chim. Fr.*, **1967**, 2641; Julia, M.; Maumy, M., *Ibid.*, **1969**, 2427.

Julia, M.; Surzur, J.; Katz, L.; LeGoffic, F., *Bull. Soc. Chim. Fr.*, **1964**, 1116, 1122, and 1129.

Kakis, F. J. in *Steroid Reactions*, ed. Djerassi, C. Holden Day, San Francisco, **1963**, pp 267-298.

Kampmeie, J. A.; Fantazier, R. M., *J. Am. Chem. Soc.*, **1966**, 88, 1959 and 5219.

Kasai, R. H.; Whipple, E. B., *J. Am. Chem. Soc.*, **1967**, 89, 1033.

Kende, A. S.; Constandinides, D.; Lee, S. J.; Liebeskind, L. *Tetrahedron Lett.*. **1975**, 6, 405

Kieczykowski, G. R.; Schlessinger, R, H., *J. Am. Chem. Soc.*, **1978**, 100, 782.

Kochi, J. K., *Adv. Free Radical Chem.*, **1975**, 5, 189.

Krapcho, A. P.; Bothner-By, A. A. *J. Am. Chem. Soc.*, **1959**, 81, 3658.

Krishnammorthy, H. N., Ed.; *Gibberellins and Plant Growth*. Wiley, New York, **1975**.

Kubo, I. Pettei, M. J.; Hirotsu, K.; Tsujo, H.; Kubotah, T., *J. Am. Chem. Soc.*, **1980**, 45, 4765.

Kubo, I.; Pettei, M. J.; Hirotsu, K.; Tsuji, H.; Kubota, T., *J. Am. Chem. Soc.*, **1978**, 100, 628.

Kuehne, M. E.; Lambert, B. F. *J. Am. Chem. Soc.*, **1959**, 81, 4278.

Kuivila, H. G., *Acc. Chem. Res.*, **1968**, 1, 299.

Kuivila, H. G., *Synthesis*, **1970**, p. 499; *Acc. Chem. Res.*, **1968**, 1, 299.

Kuo, F., Ph.D. Thesis, Purdue University, **1986**.

Kuo, F.; Fuchs, P. L., *J. Am. Chem. Soc.*, **1987**, 109, 1122.

Liu, M. S.; Soloway, S.; Wedegaertner, D. K.; Ranpmeier, J. A., *J. Am. Chem. Soc.*, **1971**, 93, 3809.

Loewenthal, H. J. E., in *Guide for the Perplexed Organic Experimentalist*, Heyden, London, **1978**, pp 133-138.

Mahalingam, S.; Kuzma, P. C.; Lee, J. Y.-C.; Harris, T. M. *J. Am. Chem. Soc.* **1985**, 107, 7760.

Mander, L. N.; Hamilton, R. *J. Tetrahedron Lett.*, **1981**, 22, 4115.

Mander, L. N.; Prager, R. H.; Turner, J. V. *Aust. J. Chem.*, **1974**, 27, 2645.

Manmade, A.; Marshall, J. L.; Minns, R. A.; Dalzell, H.; Razdan, R. K. *J. Org. Chem.*, **1982**, 47, 1717.

Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.*, **1977**, 42, 1794.

Mayo, F. R.; Walling, C., *Chem. Rev.*, **1950**, 46, 191.

Mejer, S. *Bull. Acad. Pol. Sci. Chim..*, **1962**, 10, 469.

Meyers, A. I.; Avila, W. A. *J. Org. Chem.* **1981**, 46, 3881.

Miller, D. G.; Trenbeath, S.; Sih, C. J. *Tetrahedron Lett.* **1976**, 20, 1637.

Minisci, F., *Acc. Chem. Res.*, **1975**, 8, 165.

Minisci, F., et al., *Tetrahedron*, **1977**, 33, 793.

Mitchell, R. H.; Lai, Y.-H.; Williams, R. V. *J. Org. Chem.* **1979**, 44, 4733.

Moody, C. J.; Toczek, J. *Tetrahedron Lett.*, **1986**, 27, 5253.

Nagai, S.; Ohnishi, S.; Nitta, I., *Chem. Phys. Lett.*, **1972**, 13, 379.

Nagase, S.; Takatsuka, K.; Fueno, T., *ibid.*, **1976**, 98, 3838.

Nagata, W.; Sugasawa, T.; Narisada, M.; Wakabayashi, T; Hayase, Y. *J. Am. Chem. Soc.*, **1967**, 89, 1482.

Narasimhan, N. S.; Kusurkar, S. S. *In. J. Chem.* Vol. 22B, **1983**, 349.

Narasimhan, N. S.; Mali, R. S.; Kulkarni, B. K.; Gupta, P. K. *In. J. Chem.* Vol. 22B, **1983**, 1257.

Narisada, M,; Watanade, F. *J. Org. Chem.*, **1973**, 38, 3887.

Nelson, N. A.; Hsi, R. S. P.; Schuck, J. M.; Khan, L. D. *J. Am. Chem. Soc.*, **1960**, 82, 2573.

Nielson, G. W.; Symons, M. C. R., *J. Chem. Soc., Perkin Trans II*, **1973**, 1405.

Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, 45, 4275.

Nonhebel, D. C.; Walton, J. C., *Free Radical Chemistry*, Cambridge Univ. Press, New York, **1974**, ch. 5.

Nonhebel, D. C.; Walton, J. C., *Free Radical Chemistry*, Cambridge Univ. Press, New York, **1974**, ch. 14.

Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, 104, 7162.

Pregaglia, G.; Regario, G., *Chem. Ind.* (Milan), **1963**, 45, 1065.

Quassem, M. A.; Othman, A. A.; Rogers, A. J. *Tetrahedron*, **1968**, 24, 4535.

Rabideau, P. W.; Huser, D. L. *J. Org. Chem.*, **1983**, 48, 4266.

Rabideau, P. W.; Peters, N. K.; Huser, D. L. *J. Org. Chem.*, **1981**, 46, 1593.

Radlick, P.; Crawford, H. T. *J. Org. Chem.*, **1972**, 37, 1669.

Rapson, W. S.; Robinson, R., *J. Chem. Soc.* **1935**, 57, 1285.

Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Sos.* **1975**, 97, 5446.

Ruchard, C. *Fortschr. Chem. Forsch.* **1980**, 88, 1.

Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, 109, 6493.

Schulzt, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.*, **1984**, 49, 4429.

Sheldon, R. A.; Kochi, J. K., *Org. React.*, **1972**, 19, 279.

Sibi, M. P.; Miah, J.; Snieckus, V. *J. Org. Chem.* **1984**, 49, 737.

Siegel, J.; Gutierrez, A.; Schweizer, W. B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* **1986**, 108, 1569.

Singer, L. A.; Chen, J., *Tetrahedron Lett.*, **1966**, 2089; *J. Am. Chem. Soc.*, **1966**, 88, 513; *Tetrahedron Lett.*, **1969**, 4849.

Singer, L. A.; Kong, N. P., *Tetrahedron Lett.*, **1967**, 643; *J. Am. Chem. Soc.*, **1967**, 89, 5251.

Smith, A. B.; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, 105, 575.

Smith, H. in *Organic Reactions in Liquid Ammonia*, Wiley - Interscience, New York, **1963**, Vol. 1, Part 2.

Soffer, M. D.; Jevnick, M. A. *J. Am. Chem. Soc.*, **1955**, 77, 1003.

Sosnousky, G., *Free Radical Reactions in Preparative Organic Chemistry*, Macmillan Co., New York, **1964**.

Soucy, C.; Favreau, D; Kayser, M. M. *J. Org. Chem.* **1987**, 52, 129.

Stork, G., *Current Trends in Organic Chemistry*, ed. Nozaki, H., Pergamon, New York, **1983**, p 359.

Stork, G.; Baine, N. H., *ibid.*, **1982**, 104, 2321.

Stork, G.; Mook, R., *ibid.*, **1983**, 105, 3720.

Stork, G.; Mook, R.; Biller, S. A.; Rychnousky, S. D., *J. Am. Chem. Soc.*, **1983**, 105, 3741.

Stork, G.; Sher, P. M., *J. Am. Chem. Soc.*, **1983**, 105, 6766.

Stork, G.; Williard, P. G., *J. Am. Chem. Soc.*, **1977**, 99, 7067.

Subba Rao, G. S. R.; Pramod, K. *Proc. Indian Acad. Sci., Chem. Sci.*, **1984**, 93, 573.

Surzur, J. -M., *Reactive Intermediates*; Abramovitch, R. A., Plenum: New York, **1982**; Vol. 2, pp 121-295.

Surzur, J. M.; Torri, G., *Bull. Soc. Chim. Fr.*, **1970**, 3070.

Taber, D. F. *J. Org. Chem.*, **1976**, 41, 2649.

Taber, D. F.; Petty, E. H., *J. Org. Chem.*, **1982**, 47, 4808.

Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.*, **1980**, 102, 5085.

Talaparta, B.; Roy, M. K.; Talaparta, S. K. *In. J. Chem.* Vol. 19B, **1980**, 927.

Tedder, J. M.; Walton, J. C. *Tetrahedron* **1980**, 36, 701; *Acc. Chem. Res.* **1976**, 9, 183.

Tedder, J. M.; Walton, J. C., *Adv. Physical Org. Chem.*, **1978**, 16, 86; *Tetrahedron*, **1980**, 36, 701.

Tedder, M. H. *J. Chem. Res.*, **1977**, 5, 165.

Thomas, A. F.; Willhalm, B.; Bowie, J. H. *J. Chem. Soc. B*, **1967**, 392.

Trost, B. M.; Rivers, G. T.; Gold, G. M. *J. Org. Chem.* **1980**, 45, 1835.

Turner, J. V.; Anderson, B. F.; Mander, L. N. *Aust. J. Chem.*, **1980**, 33, 1061.

Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, 48, 2349.

Van Meerssche, M.; Declercq, J.-P.; Grootaert, W. M.; de Clercq, P. J. *Bull. Soc. Chim. Belg.*, **1982**, 91, 819.

Van Tamelen, E. E.; Carlson, J. G.; Russell, R. K.; Zawacky, S. R. *J. Am. Chem. Soc.*, **1981**, 103, 4615.

Van Tamelen, E. E.; Taylor, E. G. *J. Am. Chem. Soc.*, **1980**, 102, 1202.

Van Tamelen, E.; Hildahl, G. T. *J. Am. Chem. Soc.* **1956**, 78, 4405;

Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, 94, 6059, 6064.

Walling, C.; Cioffari, A., *ibid.*, **1972**, 94, 6059.

Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J., *ibid.*, **1966**, 88, 5361.

Walling, C; Pearson, M. S., *J. Am. Chem. Soc.*, **1964**, 86, 2262.

Walton, J. C., et al., *J. Chem. Soc. Perk. Trans. II*, **1975**, 320; *J. Chem. Res.*, **1977**, 5, 18.

White sides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, 93, 1379.

Wilt, J. W., *Free Radicals*, ed. Kochi, J. K., John Wiley, New York, **1973**, Vol. 1, pp 418-446.

Zimmerman, H. E. in *Molecular Rearrangements*, ed. de Mayo, P., Wiley - Interscience, New York, **1963**, Vol. 1, pp 347-352.

Zutterman, F.; de Wilde, H. Mijngheer, R.; de Clercq, P.; Vandewalle, M. *Tetrahedron*, **1979**, 25, 2389.