NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canada

ISBN 0-315-89649-3

Canada

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

ABSTRACT

CHAPTER 1:

A brief overview of the preparation and uses of o-quinodimethanes and benzocyclobutenes is presented.

CHAPTER 2:

The preparation of benzylidenebenzocyclobutene analogs from acetylenic precursors is presented. The strategy initially involves addition of tributyltin hydride to acetylenes via free-radical or palladium catalysed processes. The resulting vinylstannanes then undergo an intramolecular Stille coupling to yield benzocyclobutenes. For (o-bromoaryl)phenylalkynones, both steps were mediated by palladium catalysis, thus leading to a convenient one-pot synthesis of 2-benzylidenebenzocyclobutenones.

CHAPTER 3:

In order to overcome difficulties in scaling up the preparation of 2-benzylidenbenzocyclobutenones as described in Chapter 2, the reaction in question is examined in greater detail. Although the problems involved were not ultimately eliminated, a greater understanding of the parameters involved points to areas for further experimentation.

Attempts to prepare benzocyclobutene derivatives via a double Stille coupling strategy using a vinyldistannane are then discussed. Several other miscellaneous attempts at benzocyclobutene syntheses are also investigated.

CHAPTER 4:

A proposed scheme for utilizing 2-benzylidenebenzocyclobutenones as precursors to regioisomeric anthraquinones is presented. The key step in this scheme involves oxidative removal of the benzylidene functionality. Although this transformation was not successful, an interesting rearrangement is found to occur upon ozonolysis of various benzylidenebenzocylobutene derivatives. Complete

assignment of the ^{13}C and ^{1}H NMR resonances of one of these rearrangement products is described using the FLOCK pulse sequence.

CHAPTER 5:

The thermolysis of aryl, vinyl and alkynyl benzylidenebenzocyclobutenols is described. Oxidative removal of the benzylidene functionality after thermolytic ring expansion of the phenyl and vinyl precursors provides anthraquinone and naphthoquinone, respectively.

CHAPTER 6:

The anionic cleavage of several benzylidenebenzocyclobutenols is presented. The stereochemistry of the benzylidene group is used as a mechanistic probe to differentiate between a carbanionic and an electrocyclic pathway for the opening of the cyclobutene ring. For all derivatives studied, the carbanionic mechanism is shown to operate.

The Z to E isomerization of lithium benzylidenebenzocyclobutenoxide is postulated to proceed via a carbanionic ring opening-vinyl anion isomerization-ring closure sequence. Trapping of the putative aldehyde intermediate with excess methyl lithium supports this mechanism.

CHAPTER 7:

The photoisomerization and photodimerization of benzylidene-benzocyclobutenones is discussed. Trapping studies and laser flash photolysis experiments point to the the involvement of a ketene-allene as a major intermediate in the isomerization process.

CHAPTER 8:

A method is described which allows visualization of column chromatography by use of a quartz column and addition of a fluorescent indicator to commercial adsorbents.

The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore all progress depends on the unreasonable.

George Bernard Shaw

If man could be crossed with the cat it would improve man but it would deteriorate the cat.

Mark Twain

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. Tony Durst for his guidance, support and encouragement while allowing me enough freedom to ascend some of my own learning curves.

I am also very grateful to Dr. Scaiano for the use of his laser flash photolysis apparatus and the several valuable discussions we have had concerning the photochemical aspects of my project. My collaboration with Ron Boch concerning the laser studies has been one of the most rewarding and exciting periods of my graduate work. It is truly a pleasure to work with a researcher such as Ron who shares a genuine interest in a project and has the perseverance to keep pushing it forward.

Tony Williams is thanked for opening my eyes and my imagination to the largely underused potential of NMR in structure elucidation. His friendship and our intensely stimulating exchange of ideas will always be treasured.

Richard Connors has been a close personal friend during the past four years. By means of our discussions we have navigated through concept spaces that neither one of us would likely have found alone. I hope that this synergy will continue.

I would like to express a very special gratitude to Yvonne Lear for her friendship and support over the past year. Her company has added much color to my life and I sincerely hope that our friendship will continue to grow.

I would like to thank my mother, father and brother for their great support and encouragement not only over the course of my graduate work but through all the steps leading to this point.

Finally, I must express my gratitude to my precious cat Indole for her inexhaustible affection and delightful company.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	azabis(isobutyronitrile)
Ar	aryl
Bu	butyl
°C	degrees Celsius
CI	chemical ionization
cm	centimeters
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DTBP	di-t-butylphenol
EG	ethylene glycol
EI	electron impact
eq.	equivalents
GC	gas chromatograph
h	hours
Hz	Hertz
HRMS	high resolution mass spectrum
int	integration
IR	infrared
J	coupling constant
m	multiplet
M	molar
M^+	parent molecular ion
m/e	mass/elementary charge
min	minutes
mmol	millimoles

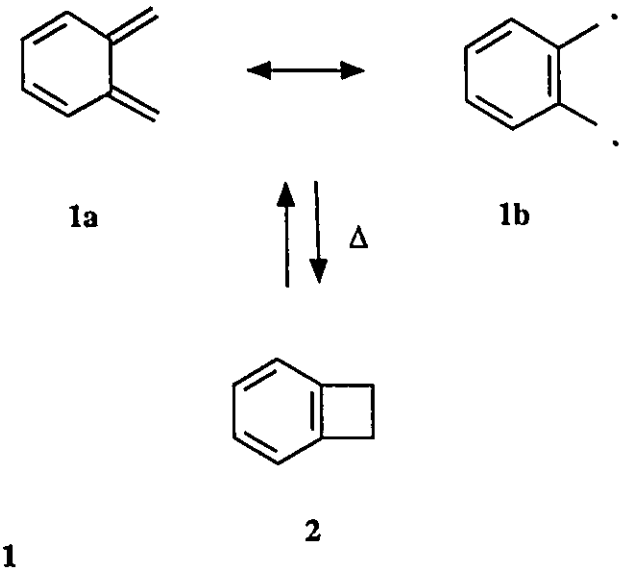
mp	melting point
Pr	propyl
MS	mass spectroscopy
µs	microseconds
nm	nanometers
NMR	nuclear magnetic resonance
ns	nanoseconds
p	page
q	quartet
rx	reaction
s	seconds or singlet
t	triplet
t-Bu	tertiary butyl
tfc	tris[3-(trifluoromethylhydroxymethylene)-camphorato]
THF	tetrahydrofuran

General organization:

Each chapter is treated as an independent unit. All numbers relating to structures, figures, tables or references are only valid within the same chapter. The experimental section and references are found at the end of each chapter. The experimental details for the preparation of a compound is given only once in the first chapter in which it appears.

CHAPTER 1: INTRODUCTION

o-Quinodimethanes are highly reactive intermediates which have been used extensively as dienophiles in Diels-Alder reactions.[1-3] The parent compound, o-xylylene **1**, has been isolated and studied in a glassy matrix at -196°C.[4] It has been shown to be planar and posess a singlet ground state, best represented by resonance contributor **1a**, but can exhibit biradicaloid behaviour, demonstrating a significant contribution from **1b**.



Scheme 1

o-Quinodimethanes exist in thermal equilibrium with benzocyclobutenes **2** (Scheme 1). For the parent o-xylylene **1**, although possessing a 10 kcal/mol higher energy than benzocyclobutene, there is a considerable activation barrier of 30 kcal/mol for ring closure[5] (Fig 1). Therefore, o-xylylene produces benzocyclobutene only when it is generated at very high temperatures (300-600°C) (Scheme 2). At lower temperatures, dimers are formed preferentially. Since dimer **4** cannot be formed from a thermally disallowed [4π+4π] cyclization, it must arise from the biradical intermediate **3**. It has been suggested that dimer **5** also arises from this same biradical intermediate. An interesting temperature dependence exists for the type of dimer formed. At lower

temperatures(-78-0°C) dimer **5** is formed preferentially, whereas at higher temperatures(0-200°C) dimer **4** is favoured.[6]

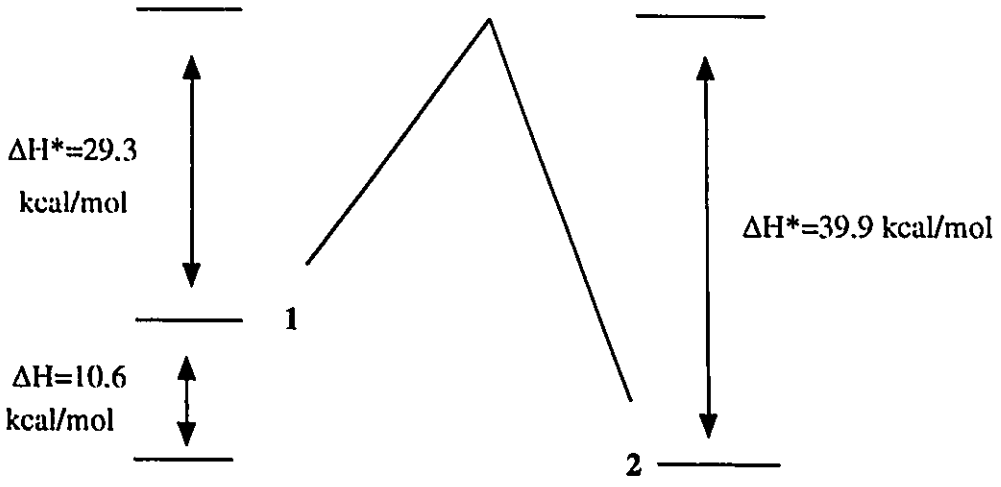
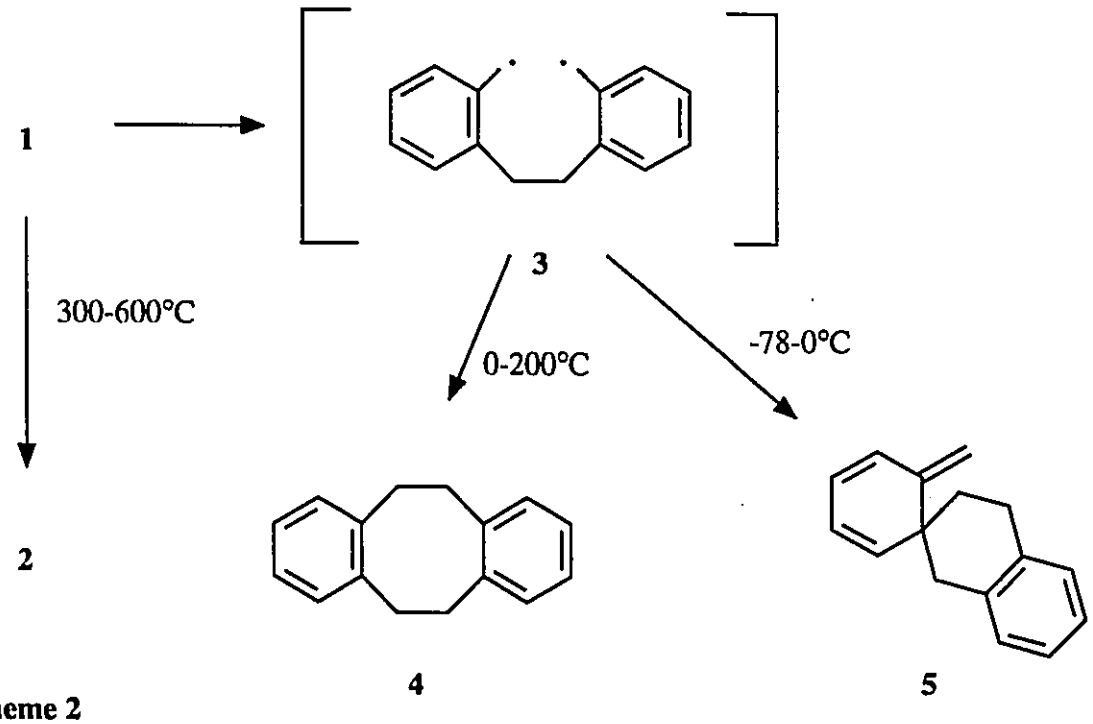


Fig 1

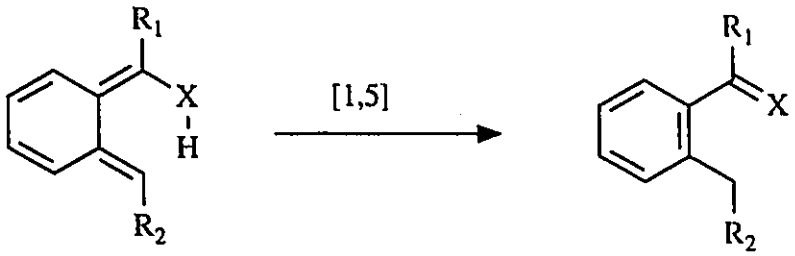


Scheme 2

The activation energy for the interconversion of substituted o-quinodimethanes and

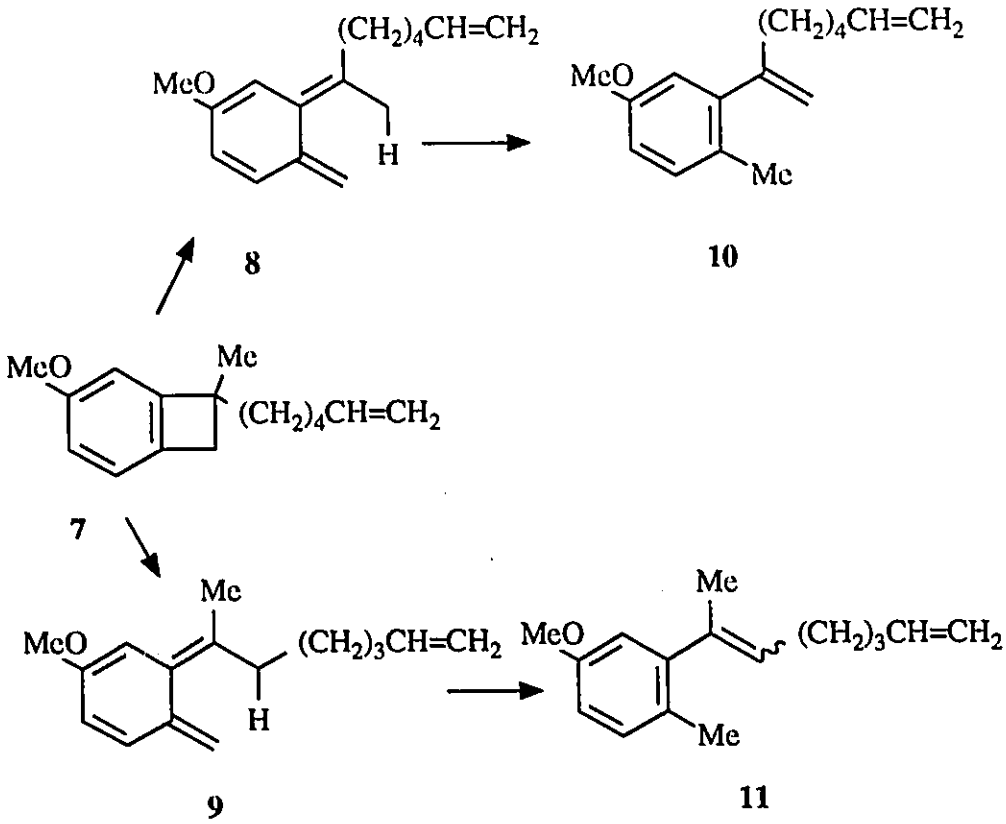
benzocyclobutenes is generally much lower than for the parent compounds. For example, a methoxy substituent on the cyclobutene ring lowers the activation energy by 9 kcal/mol.[7] This property allows the preparation of benzocyclobutenes from o-quinodimethane intermediates and the use of benzocyclobutenes as precursors to o-quinodimethanes at reasonable temperatures without significant competing dimerization.

Even if dimerization is suppressed, a [1,5] suprafacial hydrogen shift may become a significant side reaction for certain o-quinodimethanes. This will occur for intermediates of type **6**, where X may be oxygen or an alkyl group (Scheme 3). For example, generation of o-quinodimethanes **8** and **9** by thermolysis of benzocyclobutene **7** did not yield intramolecular Diels-Alder adducts but rather solely products **10** and **11** from [1,5] hydrogen shifts[8] (Scheme 4). Similarily, attempts to trap o-quinodimethanes generated from benzocyclobutenol **12** with unactivated dienophiles only yielded the aldehyde **13**[9] (Scheme 5).

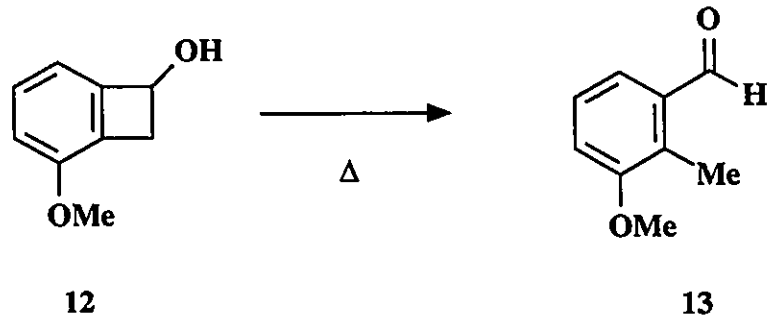


6

Scheme 3



Scheme 4



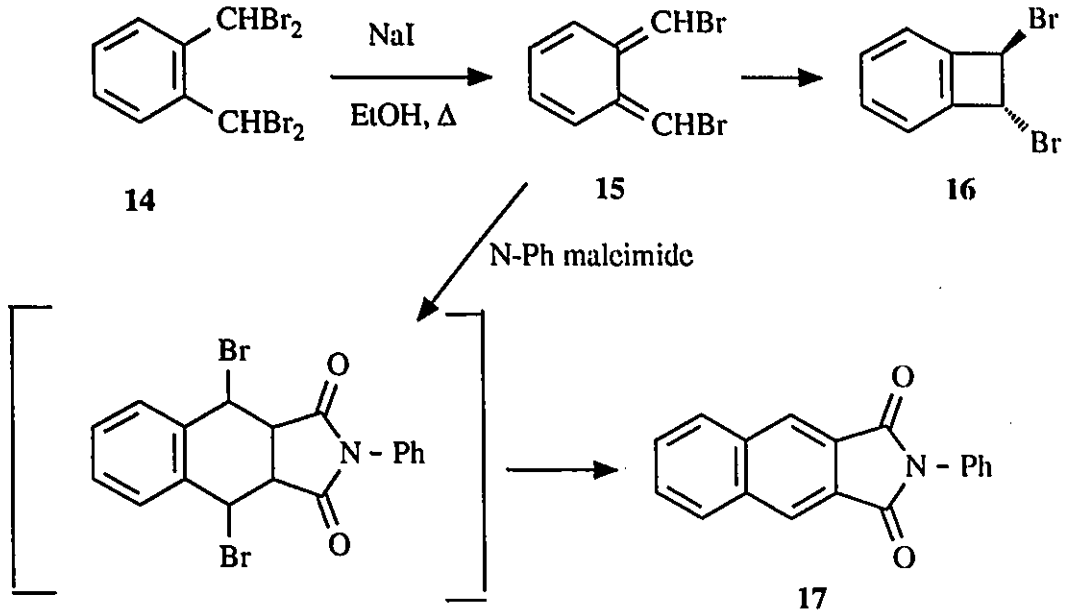
Scheme 5

Generation of o-quinodimethanes:

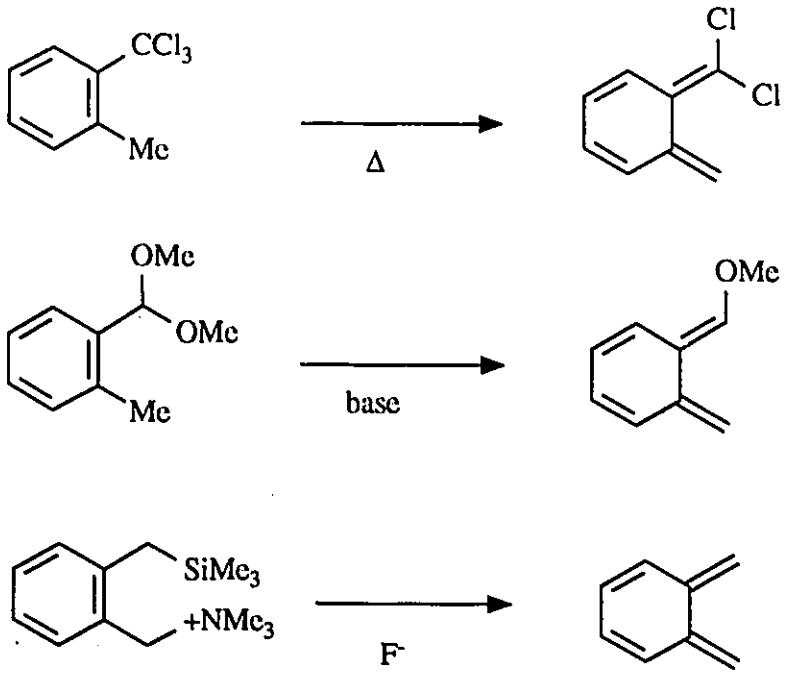
Despite the above limitations, o-quinodimethanes are nevertheless extremely useful intermediates and consequently considerable efforts have been expended towards developing methods for their generation.[1-3] The most general methods are discussed briefly below.

1) 1,4-elimination:

The first o-quinodimethane to be identified as an intermediate was the dibromoderivative **15**, prepared by the treatment of α,α,α',α'-tetrabromo-o-xylene **14** with sodium iodide in refluxing ethanol[10] (Scheme 6). In the absense of a dienophile, the benzocyclobutene **16** was obtained. When a typical dienophile such as N-phenylmaleimide was present, the o-quinodimethane intermediate was trapped to yield **17**.[11] Other 1,4 elimination strategies have been developed such as thermal elimination of HCl,[12-14] base[15-17] and fluoride[18-19] induced elimination (Scheme 7).



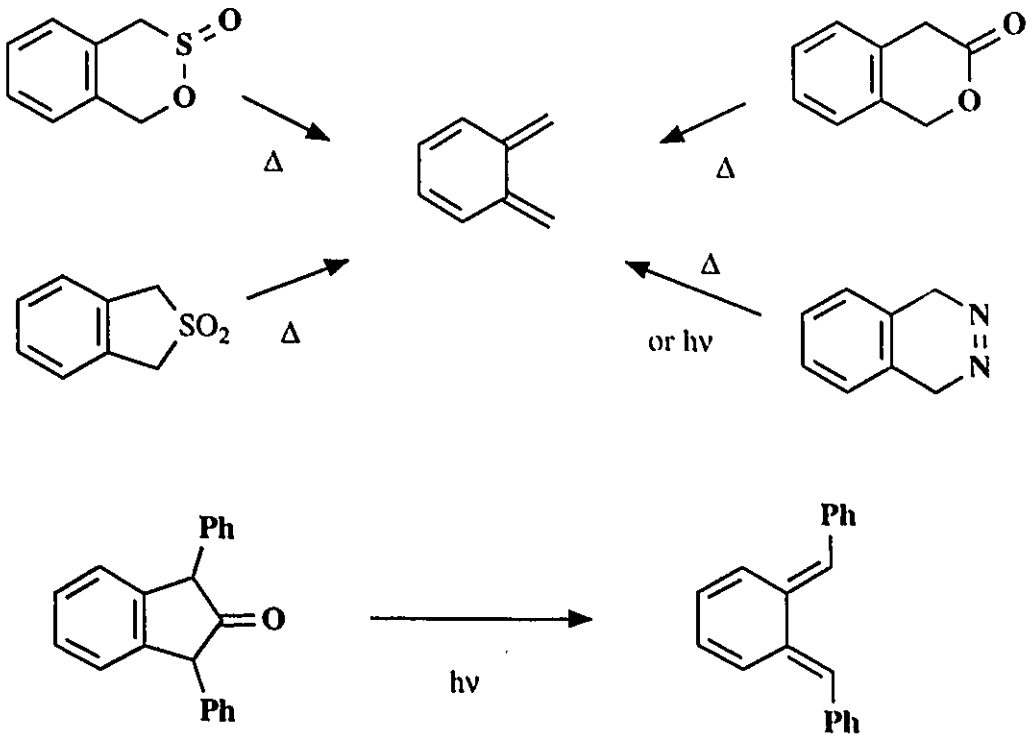
Scheme 6



Scheme 7

2) Extrusion reactions:

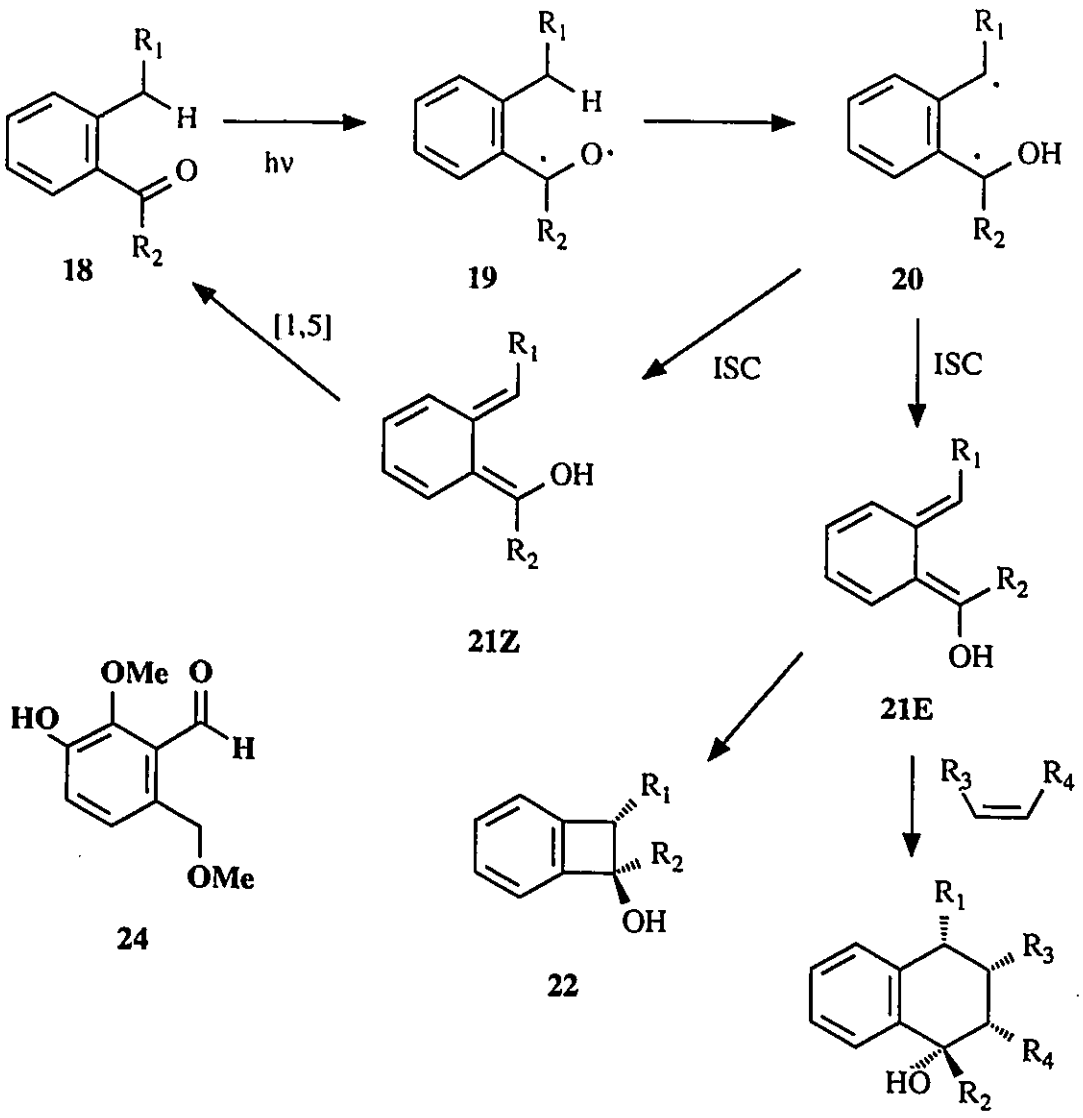
The thermal or photochemical extrusion of gaseous molecules such as N_2[4,20], CO_2[21-22], SO_2[21,23-28] or CO[29] from suitable precursors can be a very effective method of generating o-quinodimethanes (Scheme 8). The photochemical extrusion reactions are highly valued in mechanistic studies since the o-quinodimethane intermediates can be generated at very low temperatures in matrices to allow spectroscopic characterization of the isolated molecules.



Scheme 8

3) Photoenolisation:

Irradiatiation of o-alkylated phenylketones **18** can generate o-quinodimethanes by a process similar to a Norrish Type II cleavage[30-32] (Scheme 9). Excitation of the carbonyl to an $n\pi^*$ triplet **19** subsequently allows abstraction of a benzyl hydrogen to generate the triplet biradical **20**, which then decays to the o-quinodimethanes **21E** and **21Z**. The Z intermediate is quite short-lived and quickly reverts to **18** by a [1,5] hydrogen shift. Thus it is intermediate **21E** which is generally trapped by dienophiles to yield **23** or to benzocylobutenols **24** in their absence. However, there is one report where the Z isomer was trapped intramolecularily.[33] Very recently, evidence has been presented which suggests that for methoxy precursors such as **24** benzocyclobutenes can still be formed without o-quinodimethane intermediates.[34] The mechanism involved would be analogous to cyclobutanol formation from aliphatic ketones.[35]

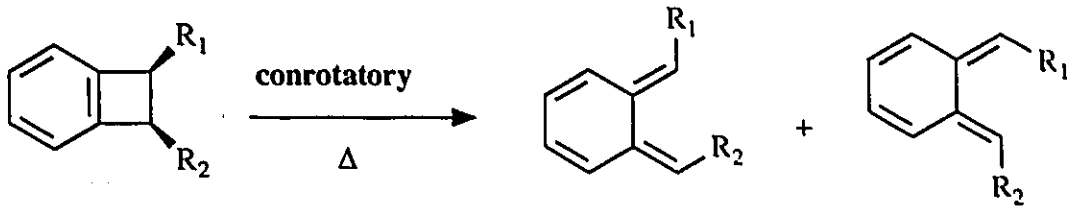


Scheme 9

4) Thermolysis of benzocyclobutenes:

As mentioned previously, benzocyclobutenes and o-quinodimethanes are in thermal equilibrium. This means that benzocyclobutenes are often used as precusors to o-quinodimethanes. The opening of a benzocyclobutene can be regarded as a thermally allowed 4 π conrotatory electrocyclic process. Consequently, although both methylene units in the cyclobutene ring must rotate in the same direction, one direction is generally preferred (Scheme 10). This preference is dependent on the substituents on the cyclobutene ring and has been termed torquoselectivity. Although previously thought to be sterically driven, the torquoselectivity of a group has now been established to be

primarily an electronic effect.[36-42] In general, electron donating groups such as alkyl, alcohols, halogens and amines rotate outward, whereas electron accepting groups such as formyl, iminium and boranes rotate inward. This has been rationalized on theoretical grounds. Upon inward rotation electron donating groups tend to destabilize the transition state of ring opening by interacting with the two electrons of the breaking sigma bond, causing unfavourable antiaromatic four electron interactions. Conversely, electron accepting groups cause stabilizing aromatic two electron interactions upon inward rotation.



R_1-outward **R_1-inward**

Scheme 10

Substituents can also have a profound effect on the temperature at which benzocyclobutenes open. For example, given a reaction time of 18 h, benzocylobutenes with the following substituents on the cyclobutene ring will open at these temperatures: NH_2 (25°C), OH (80°C), NHCOR (110°C), COR (150°C), CH_2R (180°C) and H (200°C).[3] An empirical correlation has been found to predict the activation energy and the torquoselectivity of ring opening depending upon the additive effects of substituents on the cyclobutene ring. The values for a few substituents are listed in Table 1.[41]

Table 1: Effect on activation energy* of the ring opening of substituted cyclobutenes

Substituent	outward rotation	inward rotation
CH_3	+3	-1
Cl	+6	-3
OR	+5	-9

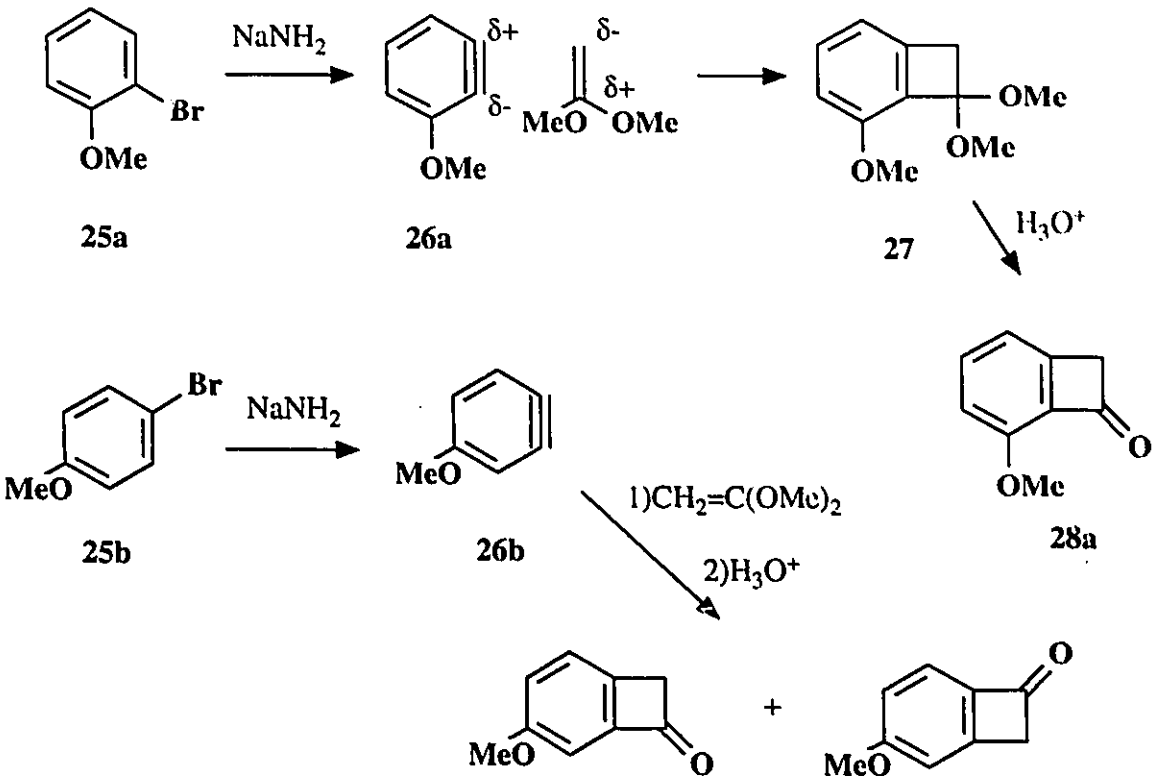
*** relative to H**

Preparation of Benzocyclobutenes:

Because of their importance as precursors to o-quinodimethanes, many additional methods for the preparation of benzocyclobutenes have been developped.

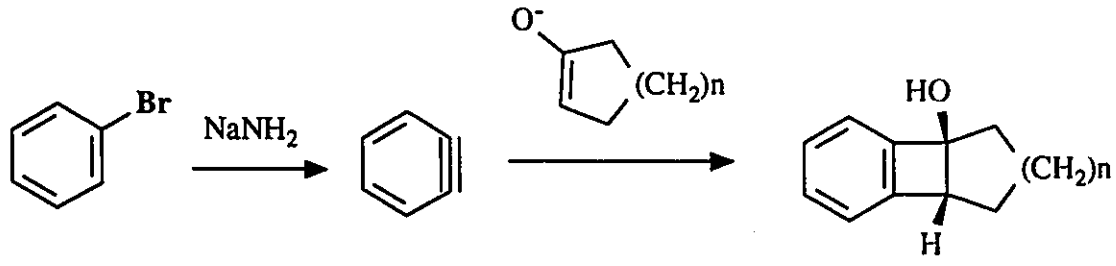
1) Reaction of benzyne and alkenes:

Many benzocyclobutenes are best prepared by the generation of benzyne in the presence of a suitable alkene.[43-45] This method is especially useful for the preparation of benzocyclobutenones, where a substituted bromobenzene derivative **25** can both direct the sodamide generation of the benzyne intermediate **26** as well as the regioselectivity of the 1,1-dimethoxyethene addition (Scheme 11). For example, through resonance and inductive effects, a methoxy substituent will polarize the adjacent benzyne functionality in **26b** so that cycloaddition takes place regioselectively. The resulting dimethylketal **27** is then easily hydrolysed to the benzocyclobutenone **28a**. However, if the methoxy group is farther removed, as in **25b**, addition will be non-specific.[43]



Scheme 11 **28b** **28c**

The preparation of fused benzocyclobutenols of the type **29** have also been studied in detail by Caubere[45-46] (Scheme 12). These are prepared from sodamide generated benzyne intermediates and cyclic ketone enolates. However, this is effective only for rings where n=1-3.

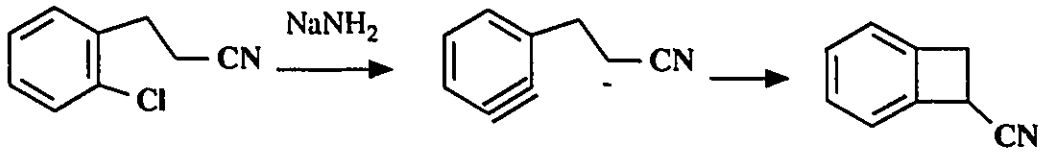


Scheme 12 **29**

2) Anionic cyclization with benzyne intermediates:

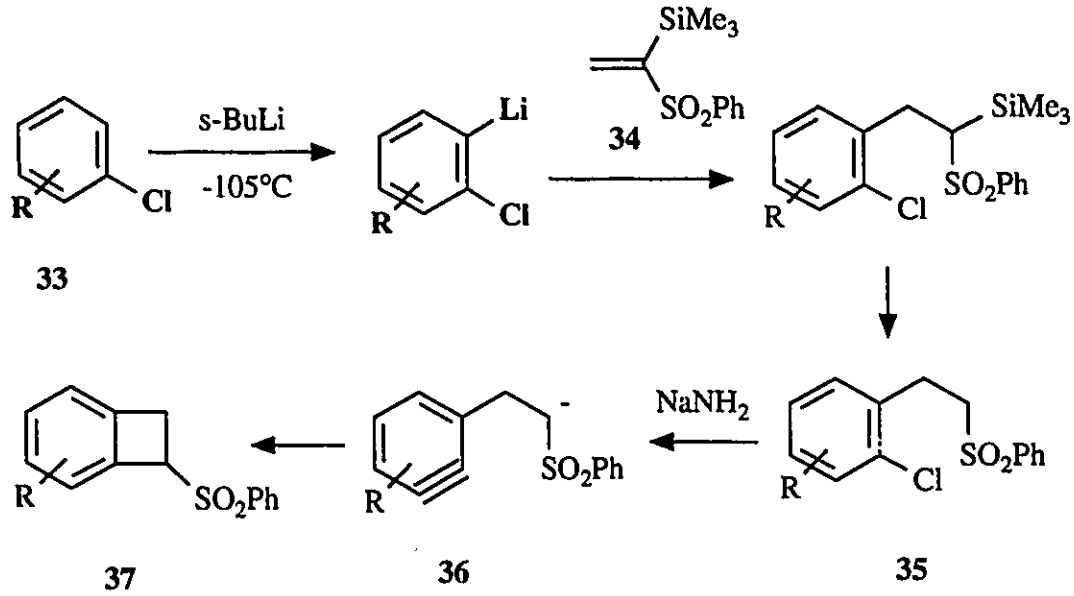
The most convenient method of preparing 1-cyanobenzocyclobutene **32** is the treatment of o-(2-cyanoethyl)-chlorobenzene **30** with sodamide (Scheme 13). The

intermediate benzyne **31** suffers a nucleophilic attack by the carbanion adjacent to the nitrile.[47] This method has recently been generalized by Iwao[48] by the predictable ortholithiation of chlorobenzenes **33** at -105°C followed by nucleophilic attack on silylsulphonylalkene **34** and desilylation to the sulfone **35**. Treatment with sodamide then generates the benzocyclobutene **37** via a benzyne intermediate **36** (Scheme 14).



30 **31** **32**

Scheme 13



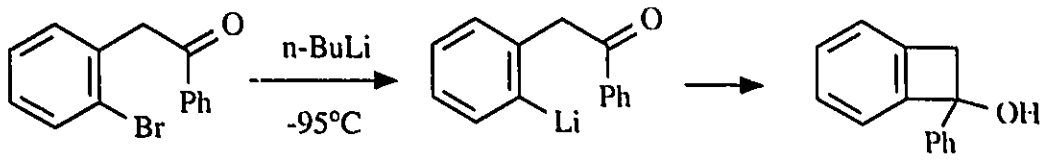
33 **37** **36** **35**

Scheme 14

3) Anionic cyclization without benzyne intermediacy:

Benzocylobutenes can also be prepared by metal-halogen exchange of halobenzenes with a suitable electrophile on a side chain ortho to the halide on the benzene ring. Thus, treatment of aryl bromide **38** at -95°C with butyllithium allows metal-halogen exchange to occur before attack of the alkyllithium on the ketone functionality (Scheme 15). The resulting aryllithium **39** then cyclizes to the

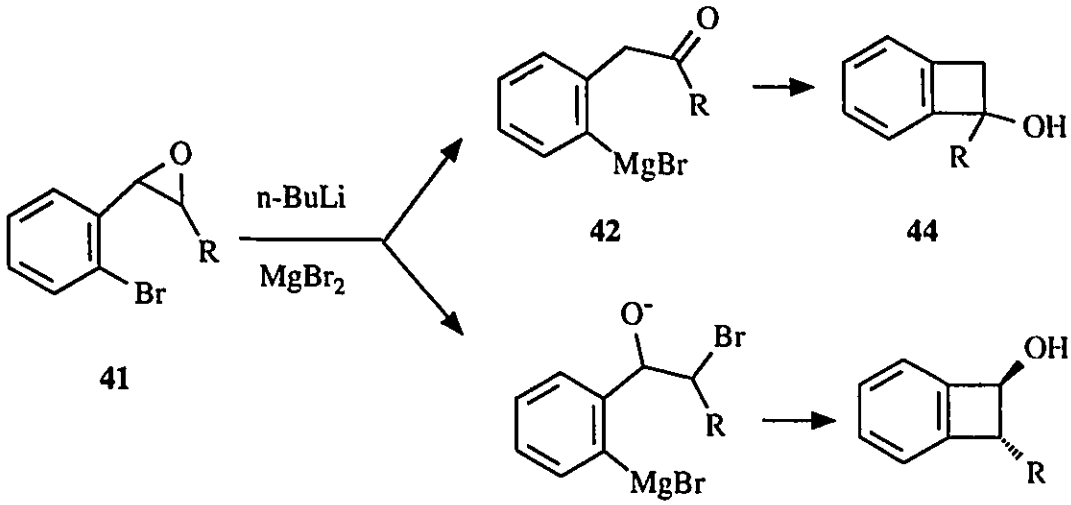
benzocyclobutenol **40**.[49]



38 **39** **40**

Scheme 15

Another approach involves the conversion of the styrene epoxides **41** with butyllithium and magnesium bromide to the benzocyclobutenols **44** and **45** (Scheme 16). The reaction is thought to proceed partly by rearrangement of the epoxide to ketone **42** mediated by magnesium bromide and partly by halogen opening of the epoxide to **43**.[50-51]



41 **42** **44** **43** **45**

Scheme 16

Other methods of benzocyclobutene preparation exist, often involving aromatisation of cycloalkane precursors.[52-55] However, these more circuitous approaches are not likely to compete with the more general and straightforward methods mentioned previously.

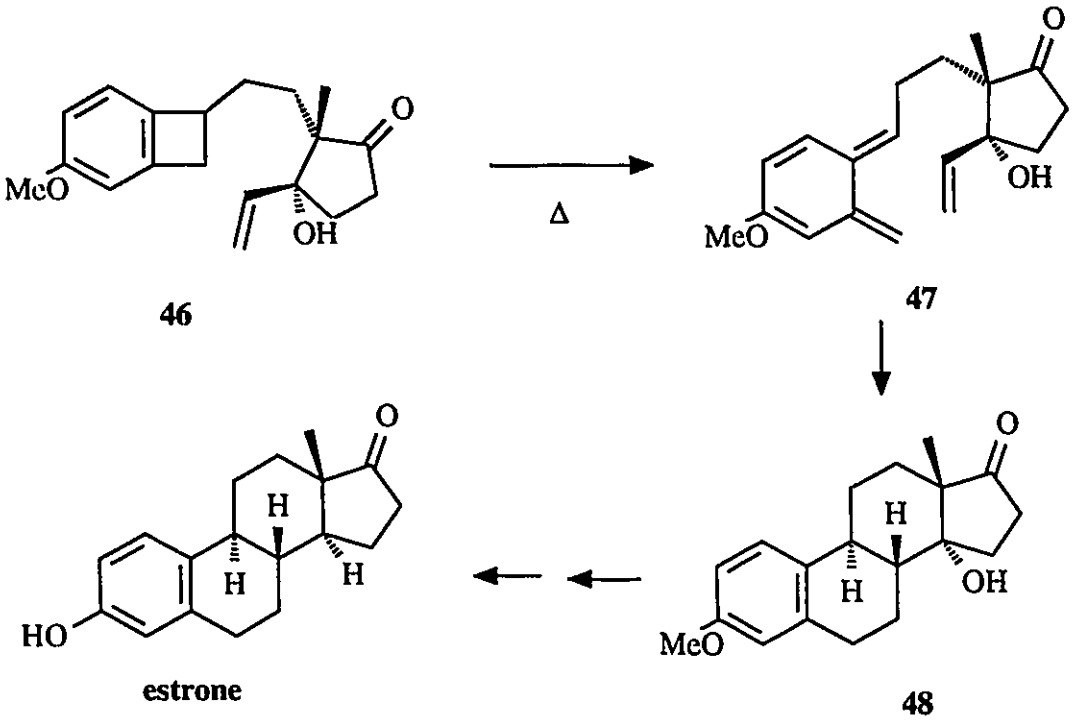
Examples of synthetic applications

In order to illustrate the versatility of orthoquinodimethanes in organic synthesis, a few examples will be given where their intermediacy played a key role in natural product

syntheses.

1) Estrone:

The application of o-quinodimethanes to the preparation of steroids has proven to be quite fruitful.[56] For example, thermolysis of the benzocylobutene precursor **46** provided a key intermediate **48** in the synthesis of estrone with the desired stereochemistry via the o-quinodimethane **47**[57] (Scheme 17). Much work has been done on the stereochemical control of the intramolecular Diels-Alder reaction of the o-quinodimethane, which is quite important in the formation of the steroid nucleus. For example, by simply changing a keto linker group for a methylene, a predictable reversal in stereochemistry is often observed.[3,58-60]

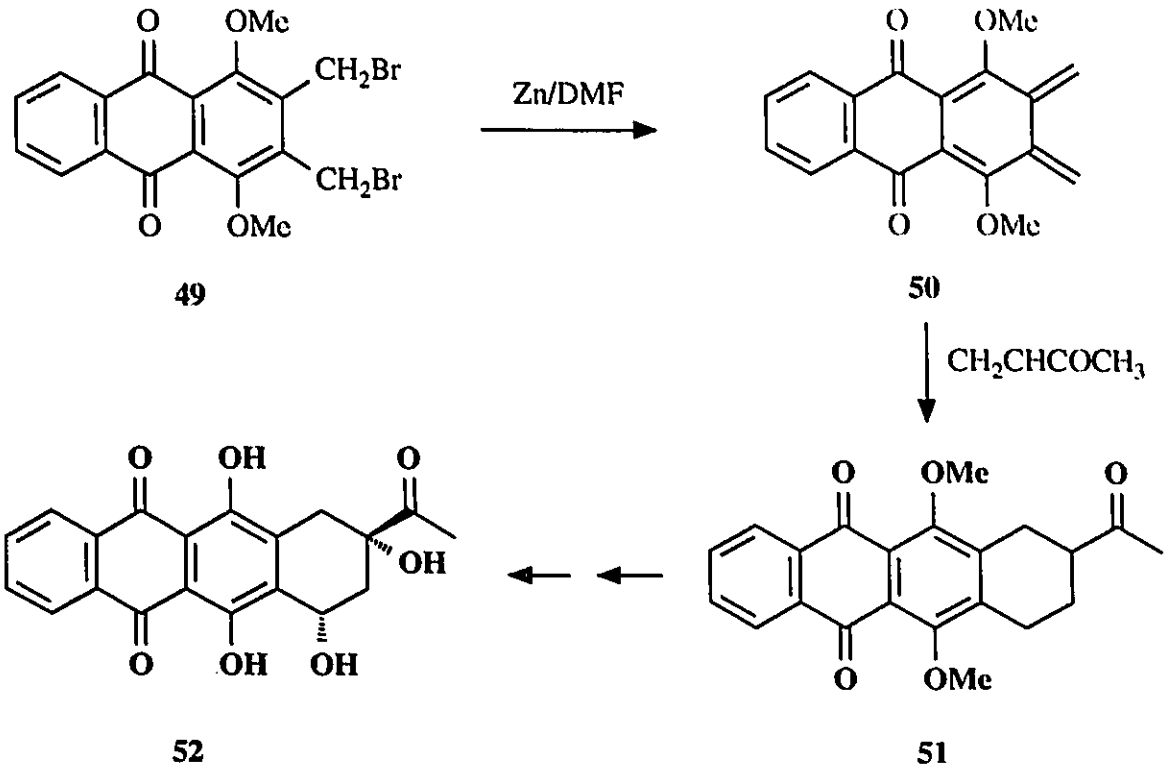


Scheme 17

2) 4-demethoxydaunomycinone:

Anthracycline antibiotics are good candidates for targets via an intermolecular Diels-Alder strategy using an o-quinodimethane (Scheme 18). For example, a zinc induced 1,4 elimination of bromine from precursor **49** led to o-quinodimethane

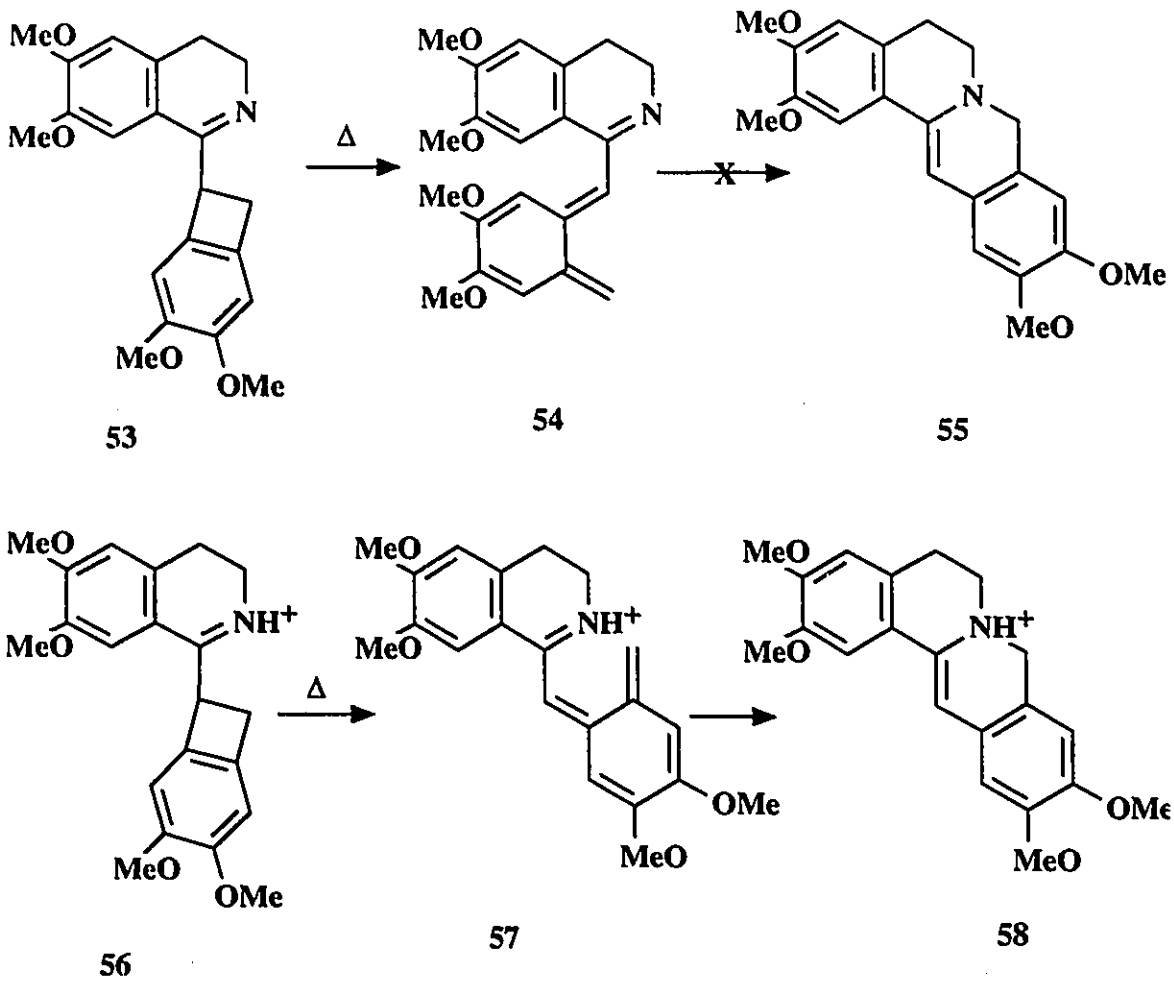
intermediate **50**, which was trapped by methyl vinyl ketone to yield the key intermediate **51** in the preparation of 4-demethoxydaunomycinone **52**.[61]



Scheme 18

3) Protoberberine:

A recent example demonstrates how the understanding of torquoselectivity has allowed control in the synthesis of a natural product. When imine **53** was thermolysed, no protoberberine **55** was formed (Scheme 19). This was rationalized on the basis that the expected outward rotation of the iminium moiety to **54** would not allow cyclization on geometric grounds. However, when the imine was treated with acid, the resulting iminium group in **56** was now highly electron accepting and rotated inward to **57** upon thermolysis. Subsequently cyclization gave the desired product **58**.[36]


MeO
MeO
N
Δ
MeO
MeO
MeO
MeO
N
X
MeO
MeO
N
OMe
MeO
53
54
55
MeO
MeO
NH+
Δ
MeO
MeO
NH+
OMe
MeO
MeO
MeO
NH+
OMe
MeO
56
57
58

Scheme 19

REFERENCES:

1. McCullough, J.J. *Acc. Chem. Res.* **1980**, 13, 270.

2. Charlton, J.L.; Alauddin, M.M. *Tetrahedron*, **1987**, 43, 2873.

3. Oppolzer, W. *Synthesis*, **1978**, 793.

4. Flynn, C.R.; Michl, J. *J. Am. Chem. Soc.* **1974**, 96, 3280.

5. Roth, W.R.; Biermann, M. *Chem. Ber.* **1978**, 111, 3892.

6. Errede, L.A. *J. Am. Chem. Soc.* **1961**, 83, 949.

7. Arnold, B.J.; Sammes, P.G.; Wallace, T.W. *J. Chem. Soc. Perkin Trans. 1* **1974**, 409.

8. Kametani, T.; Tsubuki, M.; Shiratori, Y.; Kato, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1977**, 42, 2672.

9. Kametani, T.; Honda, T.; Matsumoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1383.

10. Cava, M.P.; Napier, D.R. *J. Am. Chem. Soc.* **1956**, 78, 500.

11. Cava, M.P.; Deana, A.A. *J. Am. Chem. Soc.* **1959**, 81, 6458.

12. Hart, H.; Fish, R.W. *J. Am. Chem. Soc.* **1960**, 749.

13. Hart, H.; Hartlage, J.A.; Fish, R.W.; Rafos, R.R. *J. Org. Chem.* **1966**, 31, 2244.

14. Schiess, P.; Heitzmann, M. *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 469.

15. Moss, R.J.; Rickborn, B. *J. Org. Chem.* **1986**, 51, 1992.

16. Moss, R.J.; White, R.O. Rickborn, B. *J. Org. Chem.* **1985**, 50, 5132.

17. Moss, R.J.; Rickborn, B. *J. Org. Chem.* **1984**, 49, 3694.

18. Ito, Y.; Amino, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, 105, 1586.

19. Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, 103, 476.

20. Shabarov, Y.S.; Vasil'ev, N.I.; Levina, R.Y. *Zh. Obshch. Khim.* **1961**, 31, 2478.

21. Oppolzer, W. *Heterocycles*, **1980**, 14, 1615.

22. Das, K.G.; Afzal, J.; Hazra, B.G.; Bhawal, B.M. *Synth. Commun.* **1983**, 13, 787.

23. Durst, T.; Charlton, J.; Mount, D.B. *Can. J. Chem.* **1986**, 64, 246.

24. Charlton, J.L.; Alauddin, M.M.; Penner, *Can. J. Chem.* **1986**, 64, 793.

25. Hrytsak, M.; Etkin, N.; Durst, T.; *Tetrahedron Lett.* **1986**, 27, 5679.

26. Askan, S.; Lee, S.; Perkins, R.R.; Scheffer, J.R. *Can. J. Chem.* **1985**, 63, 3526.

27. Durst, T.; Kozma, E.C.; Charlton, J. *J. Org. Chem.* **1985**, 50, 4829.

28. Charlton, J.; Durst, T. *Tetrahedron Lett.* **1984**, 25, 5287.

29. Quinkert, G.; Opitz, K.; Wiersdorff, W.W.; Weintich, J. *Tetrahedron Lett.* **1963**, 1862.

30. Wagner, P.J.; Subrahmanyanm, D.; Park, B.-S. *J. Am. Chem. Soc.* **1991**, 113, 709.

31. Yoshioka, M.; Arai, M.; Nishizawa, K.; Hasegawa, T. *J. Chem. Soc., Chem. Commun.* **1990**, 374.

32. Sammes, P.G. *Tetrahedron*, **1976**, 32, 405.

33. Quinkert, G. *Chimia*, **1977**, 31, 225.

34. Coll, G.; Costa, A.; Deya, P.M..; Flexas, F.; Rotger, C.; Saa, J.M. *J. Org. Chem.* **1992**, 57, 6222.

35. March, J. Advanced Organic Chemistry, Third Edition, John Wiley & Sons, New York, **1985**, p. 214.

36. Jefford, C.W.; Bernardienelli, G.; Wang, Y.; Spellmeyer, D.C.; Buda, A.B.; Houk, K.N. *J. Am. Chem. Soc.* **1992**, 114, 1157.

37. Buda, A.B.; Wang, Y.; Houk, K.N. *J. Org. Chem.*, **1989**, 54, 2264.

38. Houk, K.N.; Spellmeyer, D.C.; Jefford, C.W.; Rimbault, C.G.; Wang, Y.; Miller, R.D. *J. Org. Chem.*, **1988**, 53, 2127.

39. Rudolf, K.; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* **1987**, 52, 3708.

40. Rondan, N.G.; Houk, K.N. *J. Am. Chem. Soc.* **1985**, 107, 2099.

41. Kirmse, W.; Rondan, N.G.; Houk, K.N. *J. Am. Chem. Soc.* **1984**, 106, 7989.

42. Dolbier, W.R.Jr.; Koroniak, H. *J. Am. Chem. Soc.* **1984**, 106, 1871.

43. Liebeskind, L.S.; Lescosky, L.J.; McSwain, C.M.Jr. *J. Org. Chem.* **1989**, 54, 1435.

44. Barton, J.W.; Shepherd, M.K. *J. Chem. Soc., Perkin Trans.I*, **1987**, 1561.

45. Gregoire, B.; Carre, M.-C.; Caubere, P. *J. Org. Chem.* **1986**, 51, 1419.

46. Caubere, P. *Top. Cur. Chem.* **1978**, 73, 72.

47. Raklick, P.; Brown, L.R. *J. Org. Chem.* **1973**, 38, 3412.

48. Iwao, M. *J. Org. Chem.* **1990**, 55, 3622.

49. Aidmen, I.S.; Narasimhan, N.S. *Tetrahedron Lett.* **1991**, 2171.

50. Dhawan, K.L.; Gowland, B.D.; Durst, T. *J. Org. Chem.* **1980**, 45, 924.

51. Jung, M.E.; Lam, P.Y.; Mansuri, M.M.; Speltz, L.M. *J. Org. Chem.* **1985**, 50, 1087.

52. Klundt, I.L. *Chemical Reviews* **1970**, 70, 472.

53. Schmidt, A.H.; Kunz, C. *Synthesis*, **1991**, 78.

54. South, M.S.; Liebeskind, L.S. *J. Org. Chem.* **1982**, 47, 3815.

55. Amupitan, J.O.; Stansfield, F. *J. Chem. Soc. Perkin. Trans. 1* **1974**, 1949.

56. Funk, R.L.; Vollhardt, K.P.C. *Chem. Soc. Rev.* **1980**, 41.

57. Kametani, T.; Nemoto, H.; Ishikawa, K.; Shiroyama, H.; Matsumoto, K.; Fukumoto, K.; Satoh, F.; Inoue, H. *J. Am. Chem. Soc.* **1977**, 99, 3461.

58. Fallis, A.G. *Can. J. Chem.* **1984**, 62, 183.

59. Craig, D. *Chem. Soc. Rev.* **1987**, 16, 187.

60. Oppolzer, W. *Tetrahedron Lett.* **1974**, 1001.

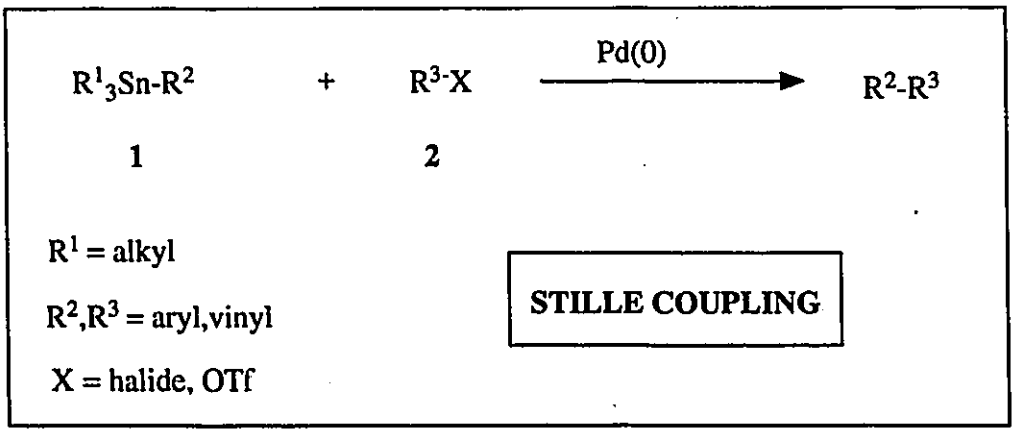
61. Alder, K, Fremery, M. *Tetrahedron*, **1961**, 14, 190.

CHAPTER 2: PREPARATION OF BENZYLIDEBENZOCYCLOBUTENE ANALOGS[1]

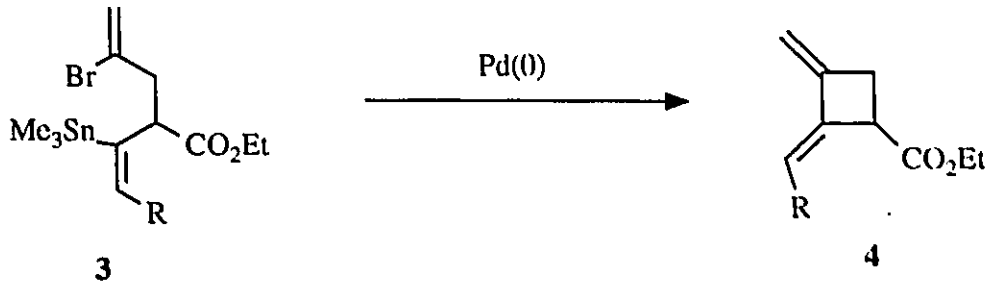
Introduction

As has been demonstrated in the introduction the o-quinodimethane strategy has been successfully applied to the rapid assembly of complex structures. A major drawback, despite considerable efforts over the past two decades has been the availability of efficient syntheses of precursors to suitably substituted o-quinodimethanes.

In recent years, transition metals have played an increasing role in versatile and selective carbon-carbon bond formation. For example, Stille[2-11] has made great use of palladium for the coupling of aryl and vinyl stannanes **1** with aryl or vinyl halides and triflates **2** (Scheme 1). Application of this methodology to the formation of benzocyclobutenes could potentially lead to new pathways to these important intermediates. These expectations were further encouraged by recent work by Piers and Lu[12], who utilized a Stille coupling reaction to make 2-alkylidene-3-methylene-cyclobutanecarboxylates **4** from vinylbromide vinylstannane precursors **3** (Scheme 2).



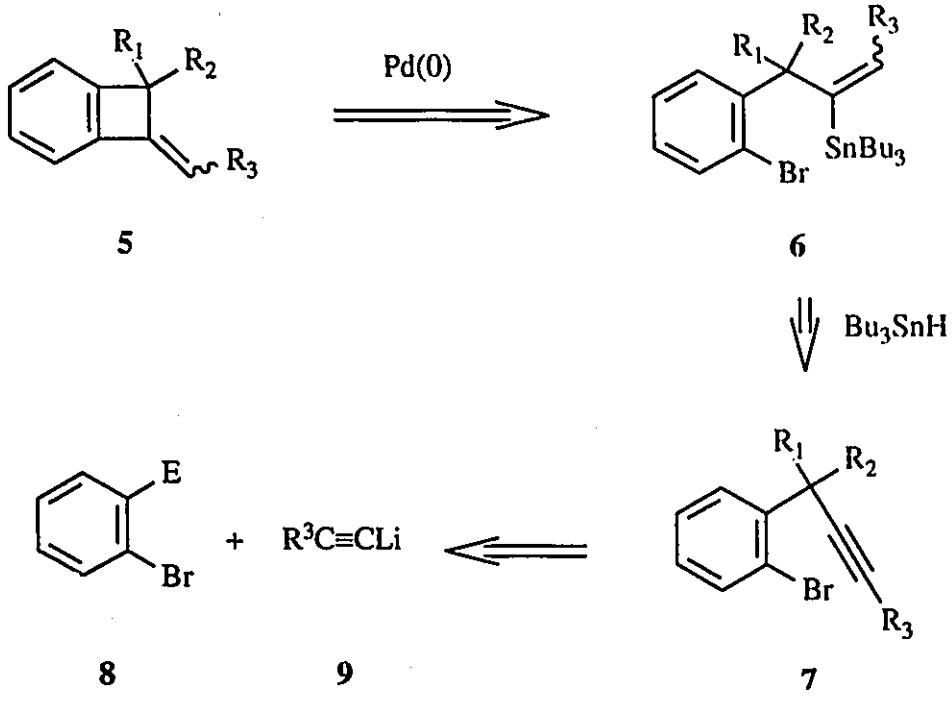
Scheme 1



3 4

Scheme 2

In order to apply this methodology to benzocyclobutene formation, a reasonable retrosynthetic analysis from **5** points to an arylbromide vinylstannane intermediate **6**, which should be conveniently prepared by tributylhydride addition to acetylenes such as **7**. Such acetylenes should in turn be available from coupling of acetylides **8** with benzylic electrophiles **9** (Scheme 3).



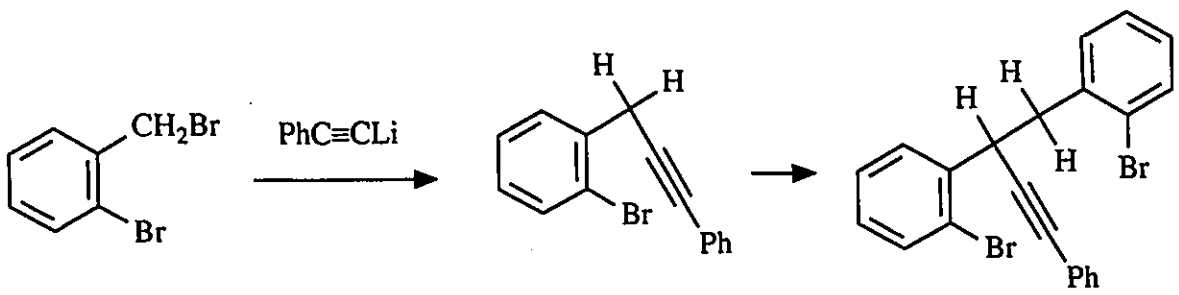
5 6 8 9 7

E= $CBrR^1R^2$,COR^1,etc.

Scheme 3

Results

The above synthetic strategy was explored by investigating the addition of tributyltin hydride under free radical conditions to acetylenes such as **7**. In an initial experiment, 2-bromobenzyl bromide **10** was added to a lithium phenylacetylide solution in THF (Scheme 4). The major product, as judged by TLC, was isolated and identified as **12** (16% yield), which presumably arose via deprotonation and benzylation of the initially formed **11** at the benzylic position. The structrure of **12** was deduced on the basis of the NMR evidence. The ^{1}H NMR spectrum revealed a characteristic -$CHCH_2$- coupling pattern: a resonance at δ 4.76 (1H, dd, 4.6 and 4.8 Hz) coupling with the diastereotopic methylene protons and a multiplet at δ 3.27 integrating to 2 protons. The remainder of the ^{1}H NMR consisted of the expected aromatic resonances δ 7.1-7.8 (13H). A DEPT experiment clearly showed the acetylenic carbons at δ 90 and δ 84. Five other quaternary carbons were identified: the two at δ 140.4 and δ 137.9 attributable to the C-Br carbons. At higher field, the expected methylene carbon appeared at δ 42.5 and the methine carbon at δ 38.2.

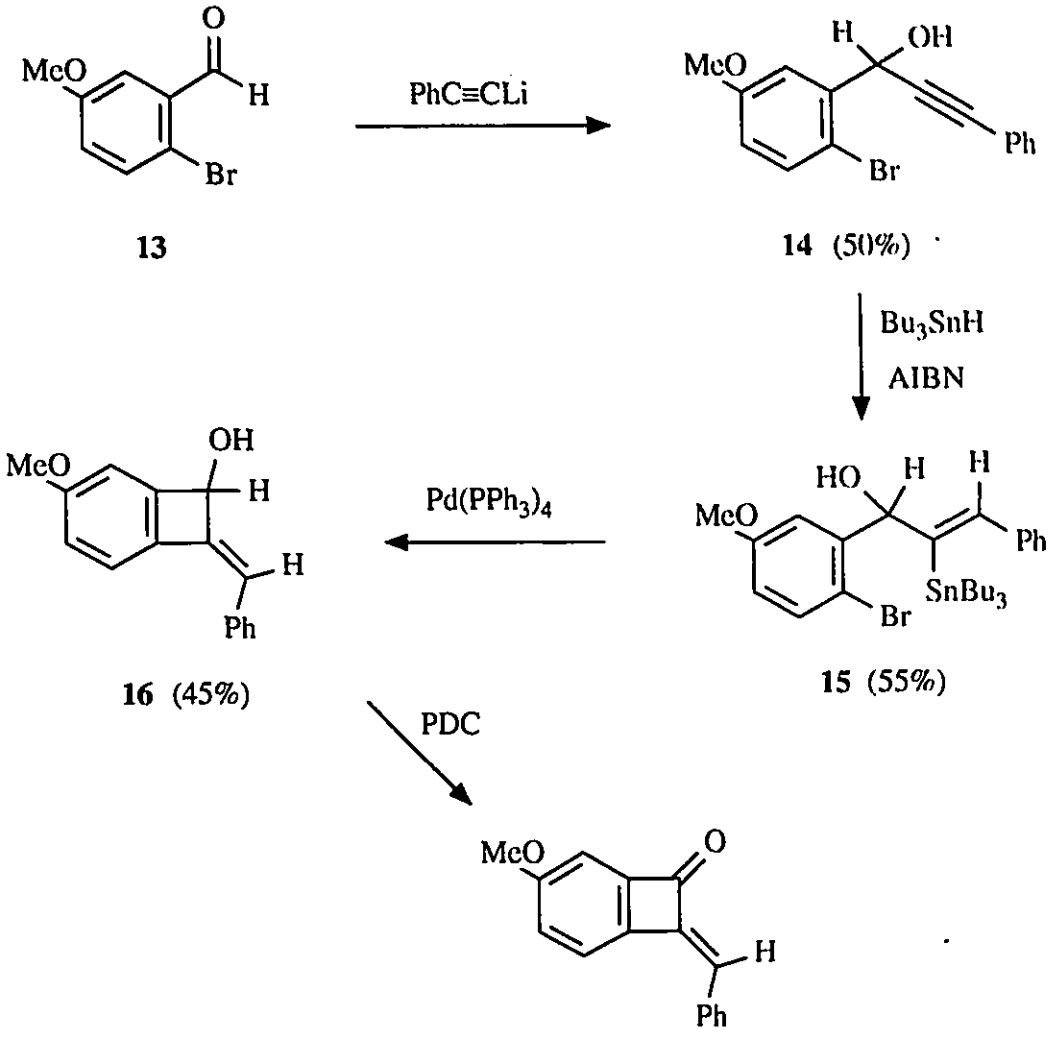


10 **11** **12**

Scheme 4

In order to circumvent the problem of multiple alkylation, carbonyl electrophiles were next explored. For example, the bromomethoxy aldehyde **13** yielded alkynol **14** in 50% yield when treated with lithium phenlylacetylide (Scheme 5). This product was characterized by ^{1}H NMR: δ 2.6 (s, 1H, OH), 3.80 (s, 3H, OMe), 5.93 (s, 1H, benzylic), 7.54 (dd, J = 8.8, 3.1 Hz, 1H), 7.5-7.2 (m, 7H). Treatment of alkynol **14** with tributyltin

hydride and AIBN in refluxing benzene afforded the stannylated adduct **15** in 55% yield. The regiochemistry of the addition was determined on the basis of the ^{1}H NMR spectrum: δ 0.5-1.6 (m, 27H, $SnBu_3$), 2.09 (d, J = 5.2Hz, 1H, OH), 3.78 (s, 3H, OMe), 5.72 (dd, J = 5.3, 1.7 Hz, J_{Sn-H}= 22 Hz, 1H, allyl), 6.70 (dd, J = 8.3, 3.1 Hz, 1H), 7.07 (d, J = 3.1 Hz, 1H), 7.22 (m, 6H), 7.43 (d, J = 8.7 Hz, 1H) (see Fig 1). The benzylic hydrogen was easily identified by its 5.3 Hz coupling with the alcoholic hydrogen. It couples with the alkenyl hydrogen (centered at δ 7.29 based on the centre of Sn-H coupling) with J = 1.7 Hz, which is reasonable only for a 4 bond coupling, thus establishing the assigned regiochemistry.



13 **14** (50%) **15** (55%) **16** (45%) **17**

Scheme 5

The stereochemistry of **15** was deduced from the average of the ^{117}Sn and ^{119}Sn couplings with the vinyl hydrogen of about 120 Hz typical[13] for a trans relationship. A cis Sn-H stereochemistry would have yielded a value of about 60Hz. The only tin isotopes present in significant proportions capable of ^1H NMR coupling (I = 1/2) are ^{117}Sn and ^{119}Sn, with abundances of 7.6% and 8.6% respectively, relative to the total natural isotopic constitution of this element.[14] Thus the Sn-H coupled resonances in the ^1H NMR spectrum can be identified as a pair of broad satellites around a peak with a total integration amounting to about 20% of the peak in question (see Figs 1 and 2). These satellites represent the combined ^{117}Sn-^1H and ^{119}Sn-^1H couplings which are often too close for resolution. In cases where these couplings can be resolved, the reported Sn-H coupling values correspond to an average of the ^{117}Sn-^1H and ^{119}Sn-^1H couplings.

Treatment of **15** with $Pd(PPh_3)_4$ in refluxing toluene effected the anticipated cyclization to benzocyclobutenol **16** in 45% yield. It was characterized by ^1H NMR: δ 2.5 (d, J = 7.7 Hz, 1H, OH), 3.79 (s, 3H, OMe), 5.42 (d, J = 7.3 Hz, 1H, benzylic), 6.36 (s, 1H, CHPh), 6.89 (m, 2H), 7.2-7.6 (m, 6H). The ^{13}C NMR showed the expected 14 resonances. Oxidation with PDC afforded benzocyclobutenone **17**, which was identified by spectral comparison with the same product prepared from an alternate route and characterized later in this chapter (see **46E** in Scheme 12). The stereochemistry of oxidation product **17** corroborates the assignment of the stereochemistry of **15** and **16**.

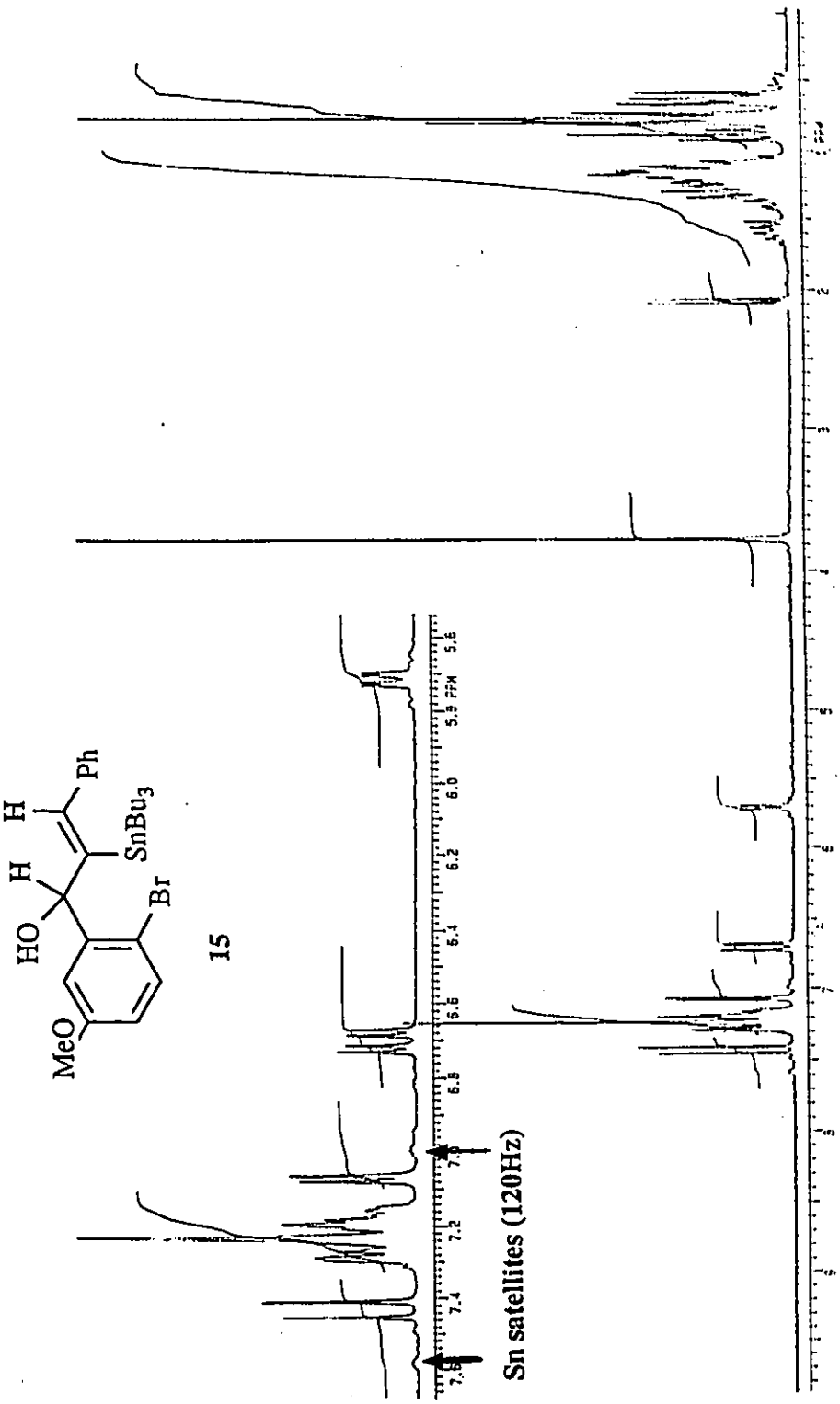
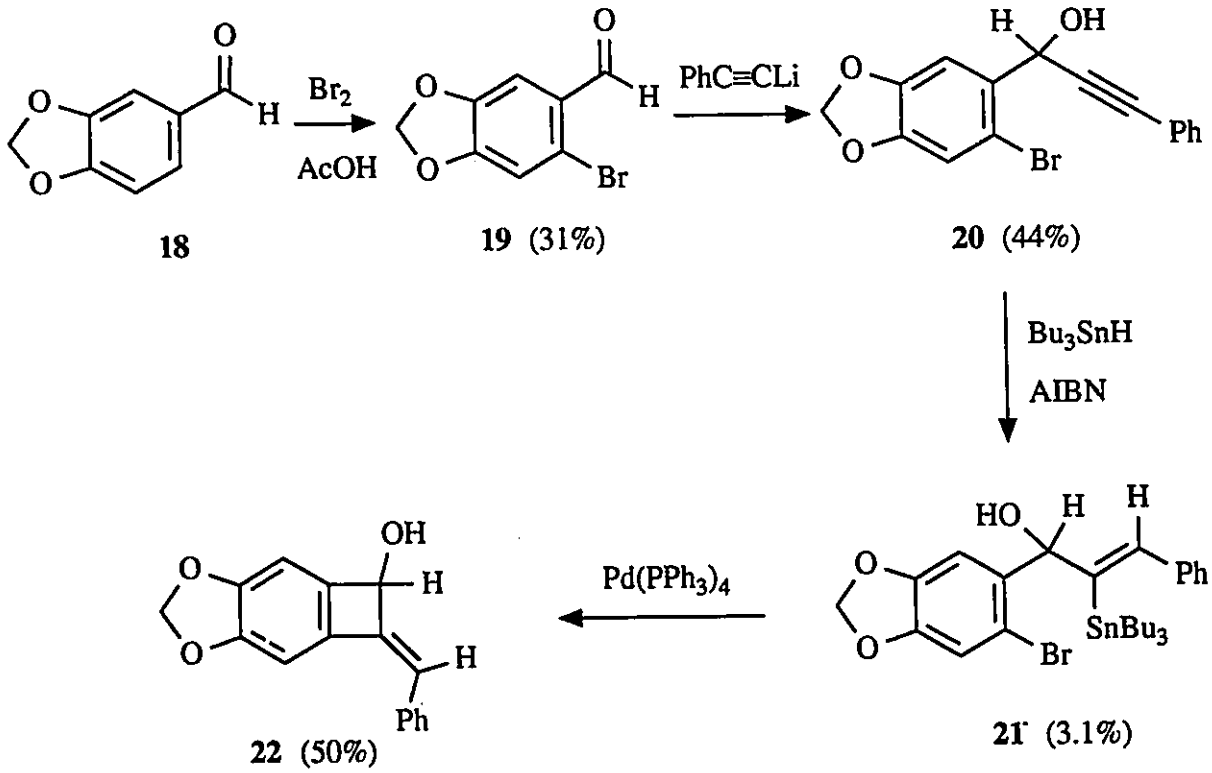


Fig 1: ^{1}H NMR of 15

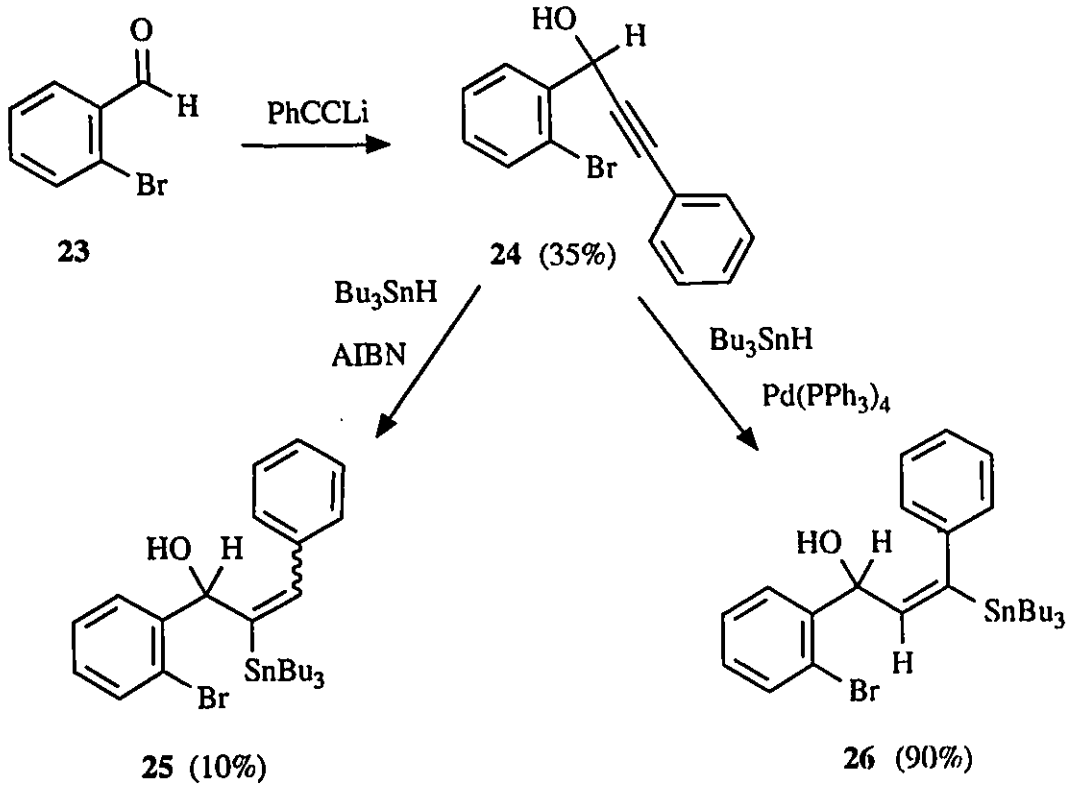
In order to explore the generality of this methodology, various other substrates were investigated. The methylenedioxy alkynol alcohol **20** was prepared in 44% yield from the aldehyde **19**, readily available from the bromination of piperonal **18**[15] (Scheme 6). Surprisingly, free radical addition of tributyltin hydride to **20** was much more difficult than with the methoxy alkynol **14**. Under conditions similar to those used for the preparation of **15**, the only tin adduct isolated was **21** in 3.1% yield with 30% recovery of starting material. The structure of vinylstannane **21** was acertained by its ^{1}H NMR spectrum: δ 0.4-1.4 (m, 27H, $SnBu_3$), 2.02 (d, J = 5 Hz, 1H, OH), 5.71 (dd, J = 5, 1 Hz, J_{Sn-H}= 20 Hz, 1H, allylic), 5.95 (s, 2H, -OCH_2O-), 6.98 (s, 1H), 7.01 (s, 1H), 7.1-7.3 (m, 5H), 7.33 (d, J = 1Hz, J_{Sn-H}= 120 Hz, 1H). Treatment of **21** with $Pd(PPh_3)_4$ in refluxing toluene afforded benzocyclobutenol **22** in 50% yield. ^{1}H NMR: δ 2.26 (d, J= 10.4 Hz, 1H, OH), 5.32 (d, J = 10.4 Hz, 1H, benzylic), 5.93 (s, 2H, -OCH_2O-), 6.32 (s, 1H, CHPh), 6.86 (s, 1H), 6.96 (s, 1H), 7.2-7.5 (m, 5H).



Scheme 6

The unsubstituted alkynol **24**, prepared by treating 2-bromobenzaldehyde **23** with

lithium phenylacetylide, was obtained as a slightly orangish oil in 35% isolated yield after distillation at 180°C/1 torr (Scheme 7). ^{1}H NMR for **24**: δ 2.74 (s, 1H, OH), 5.99 (s, 1H, benzylic), 7.2-7.8 (m, 9H). Treatment of **24** with tributyltin hydride and AIBN in refluxing benzene yielded in one chromatographic fraction evidence that **25** had formed in an estimated 10% yield. Specifically, in the ^{1}H NMR, a doublet at δ 5.75 (d, J = 8 Hz, 1H, benzylic) coupled only with the hydroxyl hydrogen at δ 2.21 (d, 1H, J = 8 Hz, OH), supporting the assigned regiochemistry. However, the aromatic region obscured any Sn-H coupling, thus the stereochemistry could not be determined. Due to the low yield obtained and the uncertainty concerning its structure, the cyclization of **25** was not attempted.



Scheme 7

Although the cyclization of vinylstannane intermediates to benzocyclobutenes was proven possible, serious difficulties were encountered in the hydrostannation step. In order to overcome this, an alternative to free-radical hydrostannation was explored. It had been established that tributyltin hydride could add to acetylenes regioselectively in a

palladium catalysed process.[16-17] Since the cyclization step can also be mediated by a palladium catalyst, it was conceivable that the addition and cyclization steps could occur in one pot.

Thus, the unsubstituted acetylenic alcohol **24** was studied first (Scheme 7). When treated with tributyltin hydride and $Pd(PPh_3)_4$ in benzene at room temperature, the reaction was complete within a few minutes, as judged by TLC. After chromatography, vinylstannane **26** was obtained in 90% yield. The regiochemistry of the addition was established by the 8.1 Hz coupling between the vinylic and benzylic hydrogens, consistent with a 3-bond coupling. The expected syn addition was confirmed by the 60 Hz Sn-H coupling between the stannyl group and vinylic hydrogen (see Fig 2). ^1H NMR δ 0.7-1.5 (m, 27H, $SnBu_3$), 2.03 (d, J = 3.8 Hz, 1H, OH), 5.46 (dd, J = 3.3, 8.1 Hz, 1H, benzylic), 5.95 (d, J= 8.1 Hz, J_{Sn-H}= 60 Hz, 1H, vinylic), 6.9-7.6 (m, 9H). Upon treatment with $Pd(PPh_3)_4$ in a variety of solvents such as DMF, $CDCl_3$, THF and benzene, no cyclization products were detected. This further supports the stereo- and regiochemical assignments for **26** since the other possible hydrostannation products should have yielded 4 or 5 membered rings. The trans relationship between the stannyl group and the benzyl moiety makes it geometrically impossible for cylization to occur.

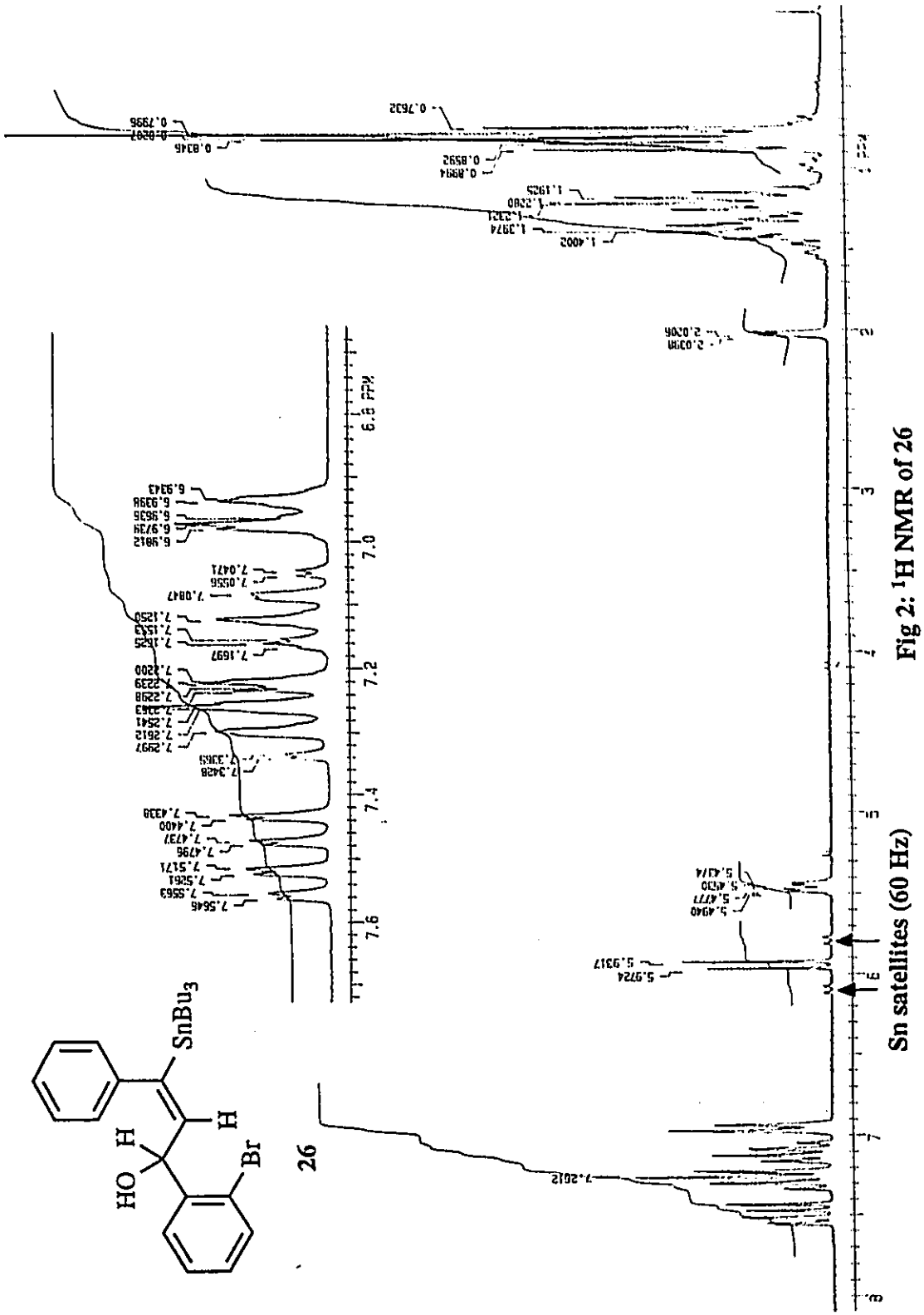
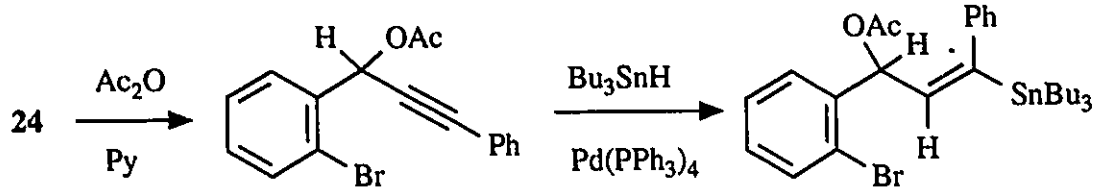


Fig 2: ^{1}H NMR of 26

It was hoped that acetate derivatives might give better hydrostannation results. Thus, the acetate **27** was prepared in 69% yield from the alcohol **24** (Scheme 8); ^{1}H NMR of **27**: δ 2.13 (s, 3H, $OCOCH_3$), 6.90 (s, 1H, benzylic), 7.2-7.9 (m, 9H). Unfortunately, treatment with tributyltin hydride and $Pd(PPh_3)_4$ afforded vinylstannane **28** in 12% yield, again with an undesirable regiochemistry for cyclization. ^{1}H NMR of **28**: δ 0.7-1.5 (m, 27H, $SnBu_3$), 1.97 (s, 3H, $OCOCH_3$), 5.92 (d, J = 7.9 Hz, J_{Sn-H}= 60 Hz, 1H, vinylic), 6.42 (d, J = 7.9 Hz, 1H, allylic), 6.8-7.6 (m, 9H).

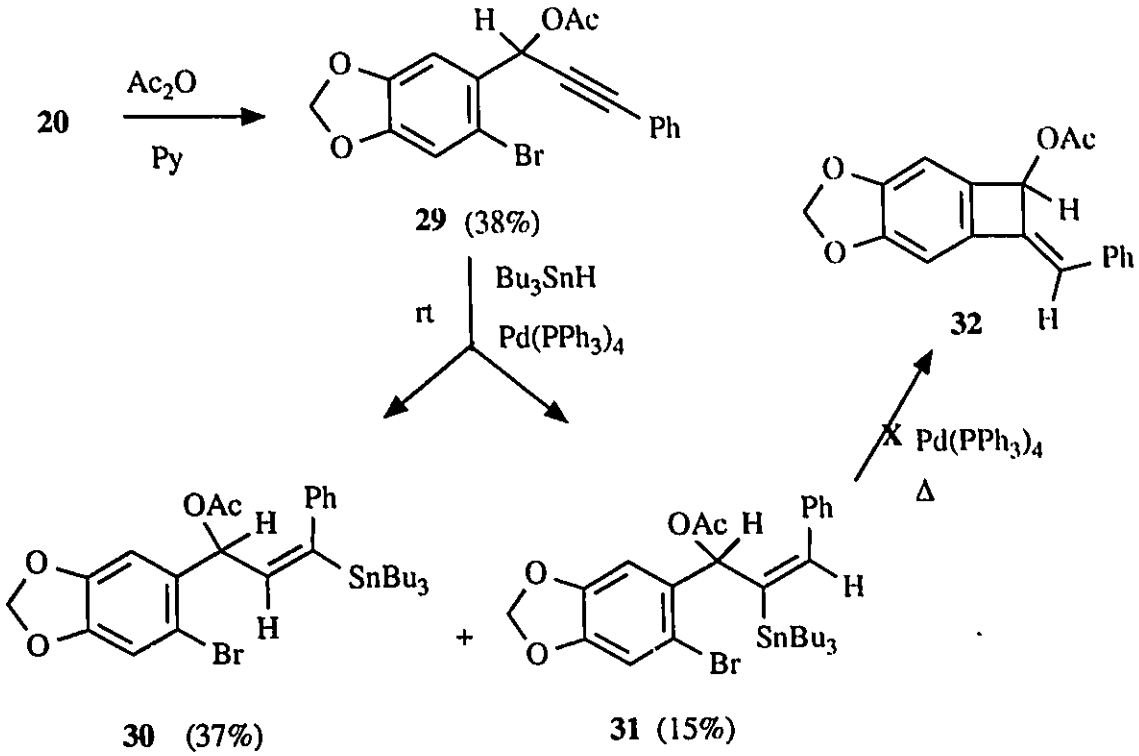


27 (69%) **28** (12%)

Scheme 8

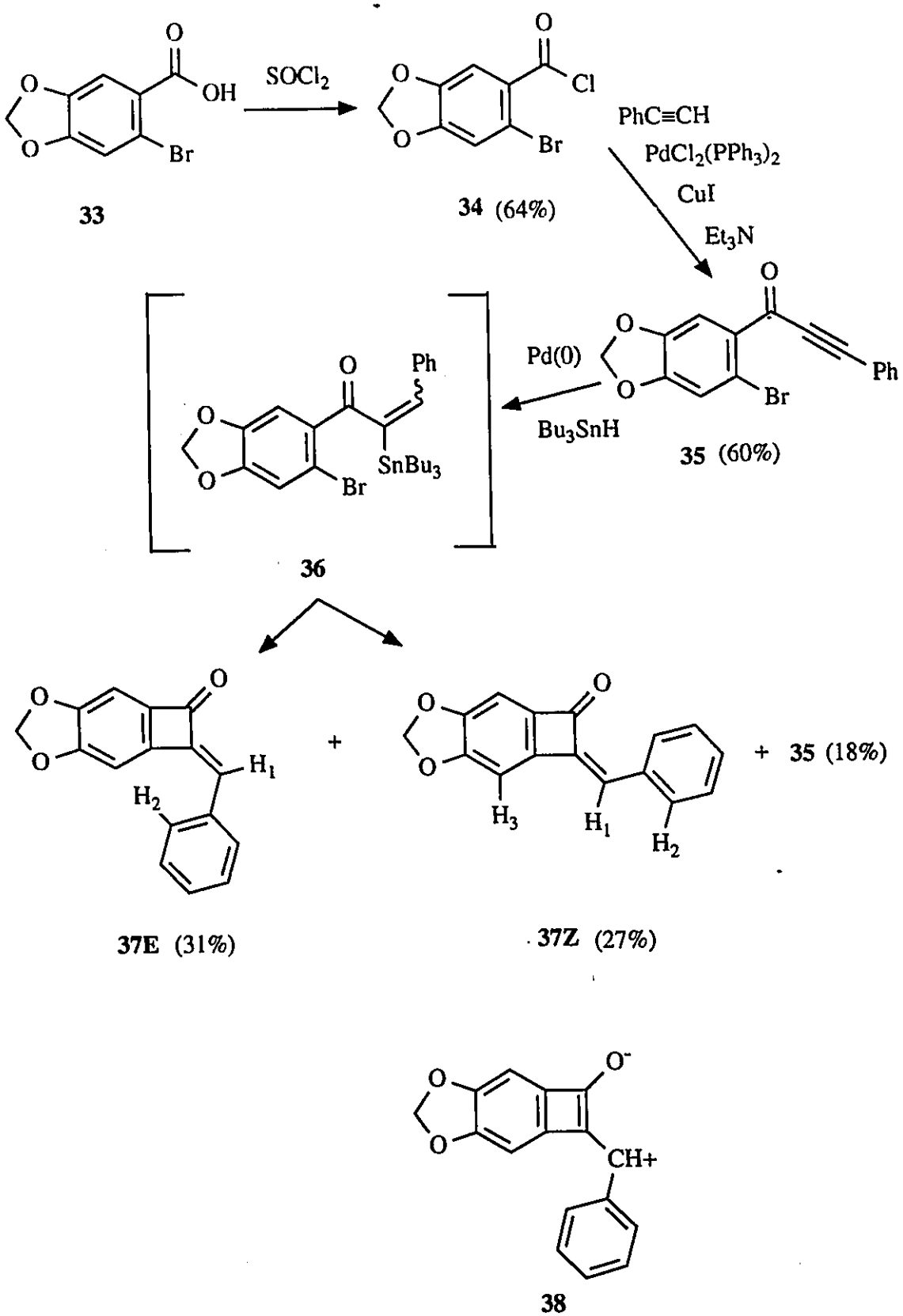
Acetylation of **20** with acetic anhydride in pyridine yielded **29** in 38% yield (Scheme 9). ^{1}H NMR of **29**: δ 2.25(s, 3H, $OCOCH_3$), 6.15(s, 2H, $-OCH_2O-$), 6.95(s, 1H), 7.20(s, 1H), 7.3-8.0(m, 6H). Treatment with tributyltin hydride and $Pd(PPh_3)_4$ at rt yielded the regioisomeric vinylstannanes **30** and **31** in 37% and 15% yield, respectively along with 25% recovered starting material. Their stereochemistry was assigned by their ^{1}H NMR spectra. Both were shown to bear a cis relationship between the vinyl hydrogen and the tin group, with Sn-H couplings of about 60Hz. The regiochemical assignments were made based on the coupling constant between the vinylic and benzylic hydrogens, being much larger in **30** than **31**. Thus, for **30**, ^{1}H NMR: δ 0.7-1.5 (m, 27H, $SnBu_3$), 1.95 (s, 3H, $OCOCH_3$), 5.84 (d, J = 7.8 Hz, J_{Sn-H}= 60 Hz, 1H, vinylic), 5.94 (m, 2H, $-OCH_2O-$), 6.34 (d, J = 7.8 Hz, 1H, benzylic), 6.8-7.3 (m, 7H). For **31**, ^{1}H NMR: δ 0.7-1.6 (m, 27H), 1.98 (s, 3H, $OCOCH_3$), 5.95 (s, 2H, $-OCH_2O-$), 6.84 (m, 2H, J_{Sn-H}= 60 Hz, vinylic + benzylic), 6.90 (s, 1H), 6.98 (s, 1H), 7.0-7.3 (m, 5H). Attempts to cyclize **31** to the benzocyclobutenol **32** by treatment with $Pd(Ph_3)_4$ in refluxing toluene or warm DMF led

only to intractable products. Perhaps this is due to competing oxidative addition of Pd(0) onto the allylic acetate functionality leading to polymeric products.



Scheme 9

Alkynones were next studied as substrates. Attempts to oxidize alkynol **20** with PDC yielded only intractable products. However, another strategy involving coupling of an acetylene with an acid chloride did prove to be highly successful and convenient[18] (Scheme 10). Thus, treatment of the acid chloride **34**, obtained in 64% as white crystals by refluxing the acid **33** in thionyl chloride followed by crystallization from hexanes/ethyl acetate, with phenylacetylene and a $PdCl_2(PPh_3)_2$/CuI/PPh_3 catalytic mixture in triethylamine at room temperature overnight yielded alkynone **35** as golden crystals in 60% yield after crystallization. The mother liquor was shown to contain an additional 33% of **35** thus giving a total yield of 93%. ^{1}H NMR for **35**: δ 6.07(s, 2H, -OCH_2O-), 7.10(s, 1H), 7.40(m, 4H), 7.61(m, 2H).



33

34 (64%)

35 (60%)

36

37E (31%)

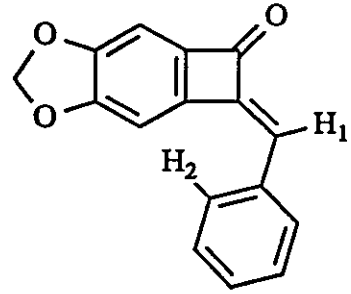
37Z (27%)

38

Scheme 10

In this case, the addition-cyclization sequence was successful. Treatment of alkynone **35** with tributyltin hydride, $PdCl_2(PPh_3)_2$ and triphenylphosphine in toluene at room temperature for 5 minutes followed by refluxing for 1 h afforded the desired benzylidenebenzocyclobutenones **37E** and **37Z** in 31% and 27% yields, respectively, presumably via intermediate **36**. Starting material was recovered in 18%, which corresponds to a combined yield of cyclized product of 70% based on unrecovered starting material. IR bands in the 1750-1760 cm^{-1} range for both **37E** and **37Z** are characteristic of the strained cyclobutenone structure. Based on the high wavenumber carbonyl bands, one can conclude that alkene conjugation is virtually absent, presumably due to unfavourable anti-aromatic resonance structures such as **38**.

Stereochemical assignments were based on NOE studies. Irradiation of the benzylidene hydrogen H_1 of **37E** at δ 6.62 showed enhancement only of the resonance from the ortho hydrogens on the phenyl ring H_2 at δ 7.50. Similarily, irradiation of H_1 of **37Z** at δ 6.29 led to enhancement of the phenyl ortho hydrogens H_2 at δ 7.88 but also of H_3 at δ 6.96. Thus a deshielding effect of the carbonyl oxygen on the benzylidene hydrogen H_1 of the E isomer of about 0.3 ppm could be used for the stereochemical identification of other substituted benzylidenebenzocylobutenones. The rest of the spectral data supported the assigned structures (see Figs 3-6 for ^1H and ^{13}C spectra of **37E** and **37Z**).

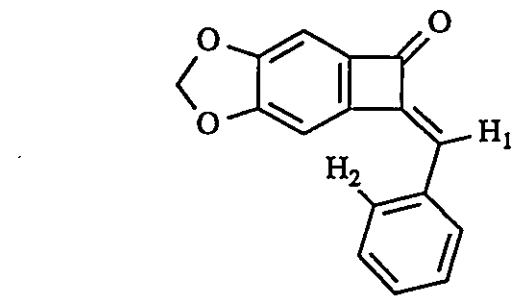


37E

VARIAN XL-300
SPECTRAL LINES FOR TH= 14.98
REL= 2528.6 RFP= 2171.6

INDEX	FREQ	PPM	INTENSITY
01	2256.11	7.522	48.309
02	2254.10	7.515	69.011
03	2252.58	7.510	18.512
04	2247.18	7.492	111.498
05	2246.37	7.489	89.499
06	2230.50	7.436	69.225
07	2228.84	7.431	17.551
08	2223.28	7.412	121.541
09	2221.79	7.407	44.979
10	2217.09	7.392	27.199
11	2215.58	7.387	54.832
12	2200.30	7.336	26.939
13	2198.95	7.331	50.093
14	2197.56	7.327	22.186
15	2193.87	7.314	18.405
16	2191.54	7.307	50.753
17	2184.35	7.283	18.970
18	2176.75	7.257	134.787
19	2172.01	7.241	270.950
20	2085.90	6.954	195.670
21	2085.12	6.952	206.406
22	1986.21	6.622	133.838
23	1838.00	6.128	762.010

Fig 3: ^{1}H NMR of 37E



37E

VARIAN XL-300
SPECTRAL LINES FOR TH= 8.24
RFL= 6158.2 RFP= 5808.0

INDEX	FREQ	PPM	INTENSITY
01	13905.1	184.347	13.005
02	11799.1	156.426	30.244
03	11618.1	154.027	32.127
04	11404.2	151.191	26.836
05	11347.9	150.445	33.944
06	11034.6	146.291	31.189
07	10203.7	135.275	43.415
08	9707.9	128.703	123.126
09	9662.1	128.096	63.932
10	9657.0	128.027	126.438
11	8651.5	114.698	34.759
12	7743.8	102.663	55.572
13	7740.2	102.616	72.603
14	7735.7	102.556	15.525
15	7653.4	101.464	34.633
16	5839.2	77.413	120.469
17	5807.2	76.989	124.879
18	5775.2	76.564	119.159

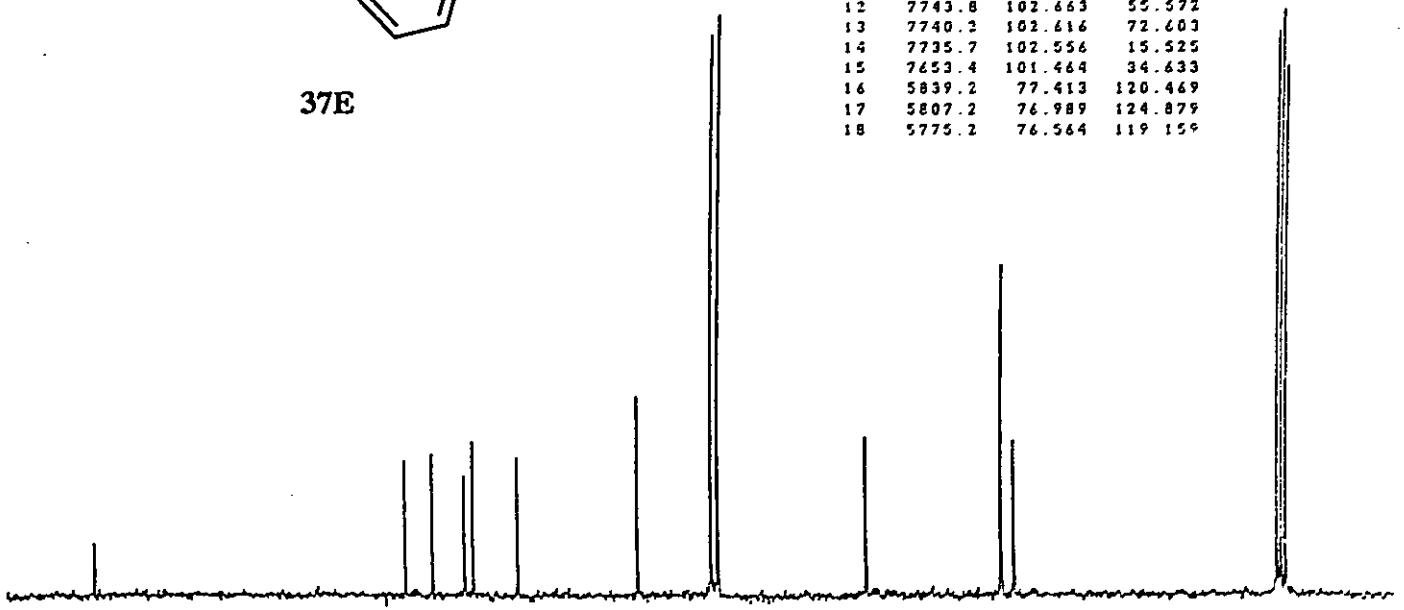


Fig 4: ^{13}C NMR of 37E

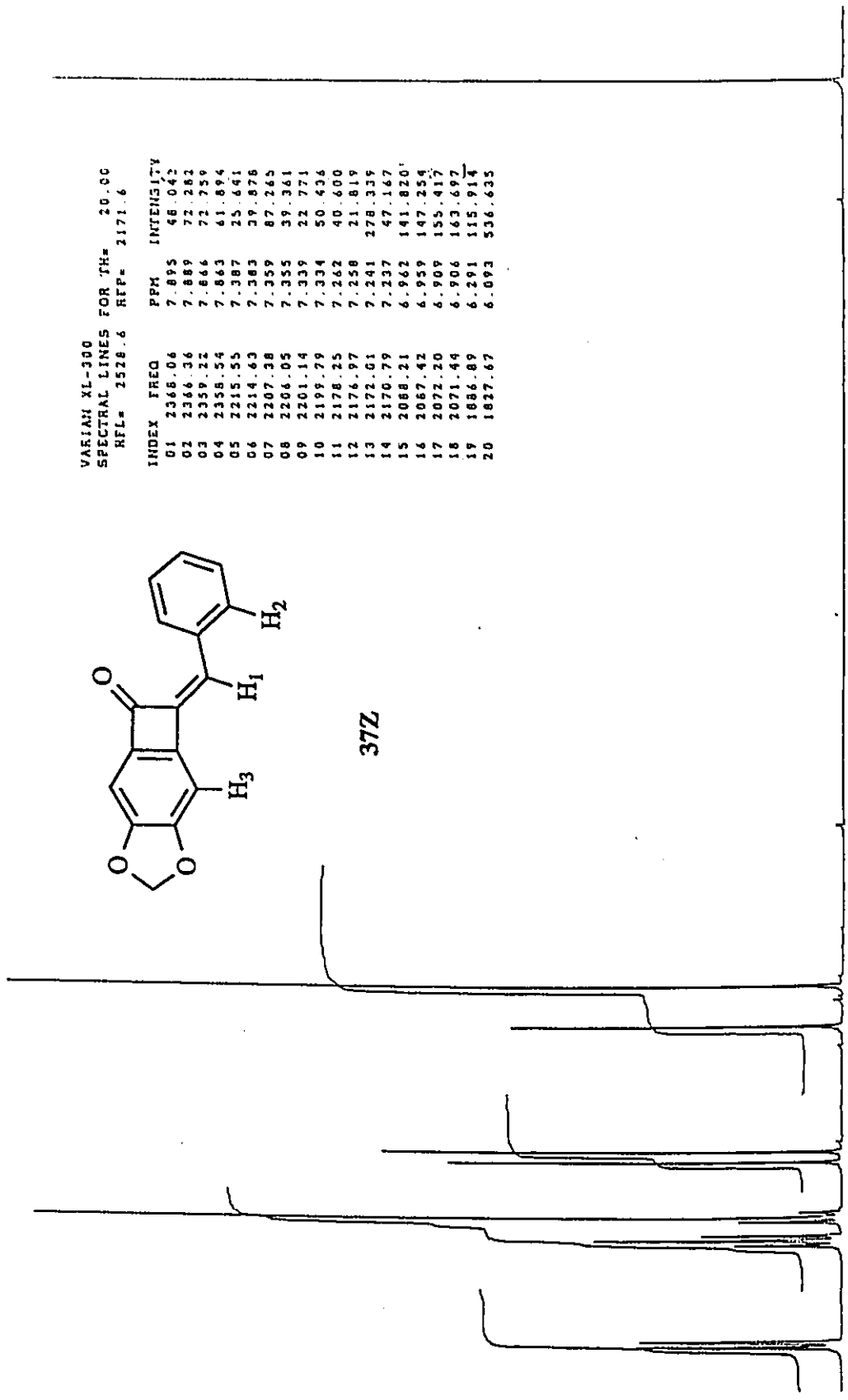


Fig 5: ^{1}H NMR of 37Z

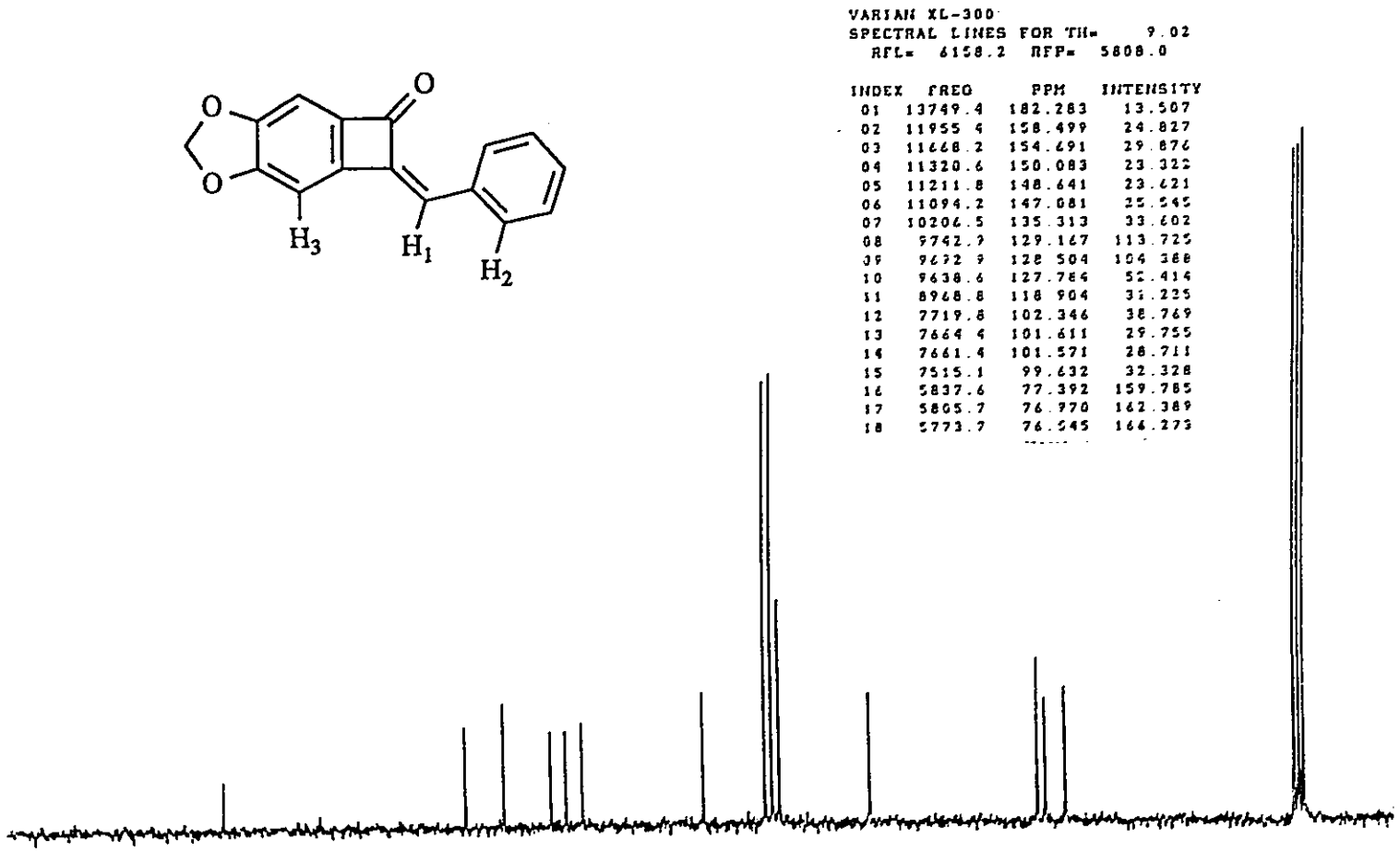
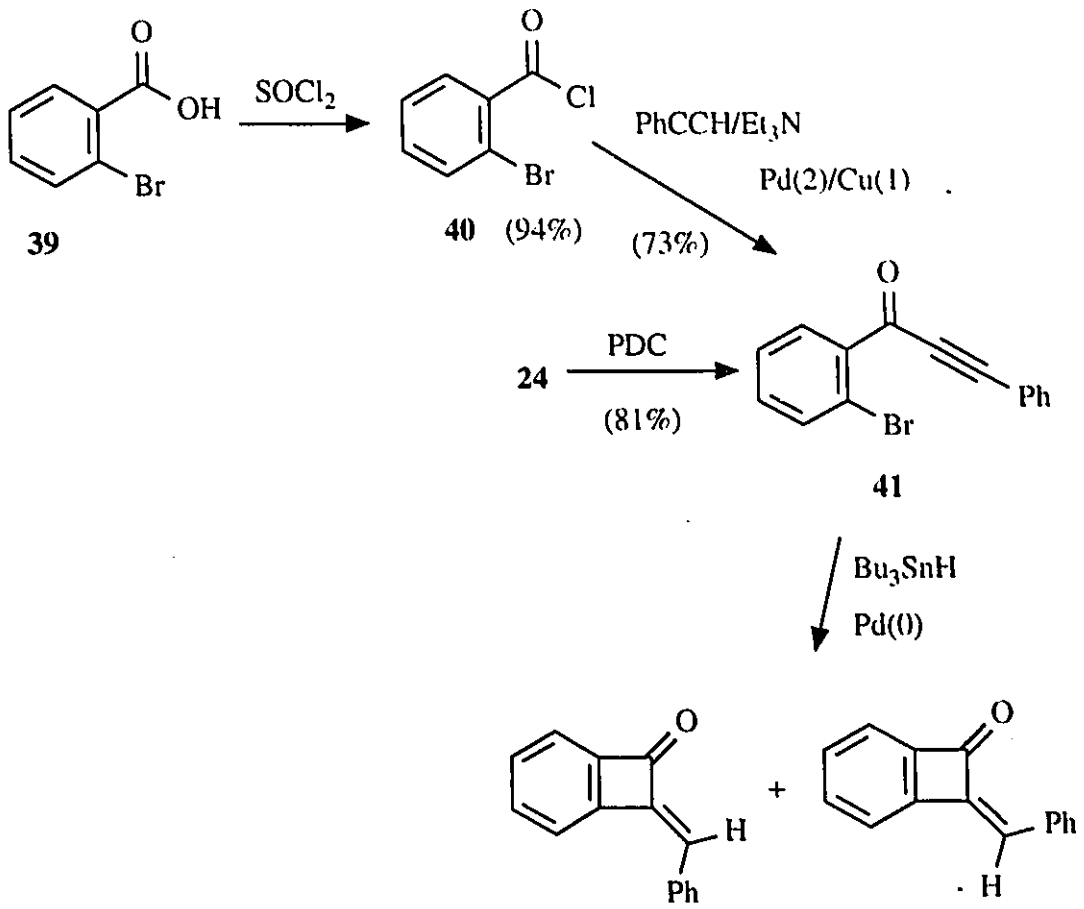


Fig 6: ^{13}C NMR of 37Z

The unsubstituted alkynone **41** was obtained in 81% yield via PDC oxidation of the alkynol **24** (Scheme 11). However, the route from 2-bromobenzoic acid **39** proved to be more economical and convenient. Thus, 2-bromobenzoyl chloride **40** (IR: 1787 cm^{-1}), obtained in 94% yield after treatment of **39** with thionyl chloride followed by distillation, was coupled with phenylacetylene using the Pd(2)/Cu(1) system in triethylamine to afford alkynone **41** in 73% yield; ^1H NMR δ 7.2-7.4 (m, 5H), 7.5-7.7 (m, 3H), 8.05 (m, 1H). Cyclization proceeded to give **42E** and **42Z** in a 1.5:1 E/Z ratio with a 70% combined yield. The stereochemical assignments were initially based on the deshielding effect of the carbonyl oxygen on the benzylidene hydrogen of **42E**, which appeared about 0.3 ppm lower field than for **42Z**. This assignment was later confirmed by an X-ray crystal determination for **42E** (see Fig 7). The characteristic high carbonyl stretching frequencies (1768 $cm^{-1}$for **42E** and 1757 cm^{-1} for **42Z**) were also present. The remainder of the spectral evidence supported the assigned structures (see experimental section).



Scheme 11

42E (42%) **42Z** (28%)

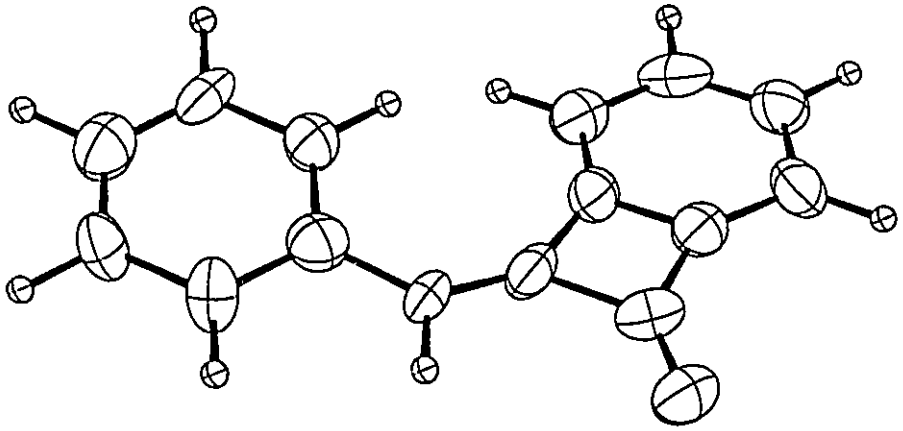
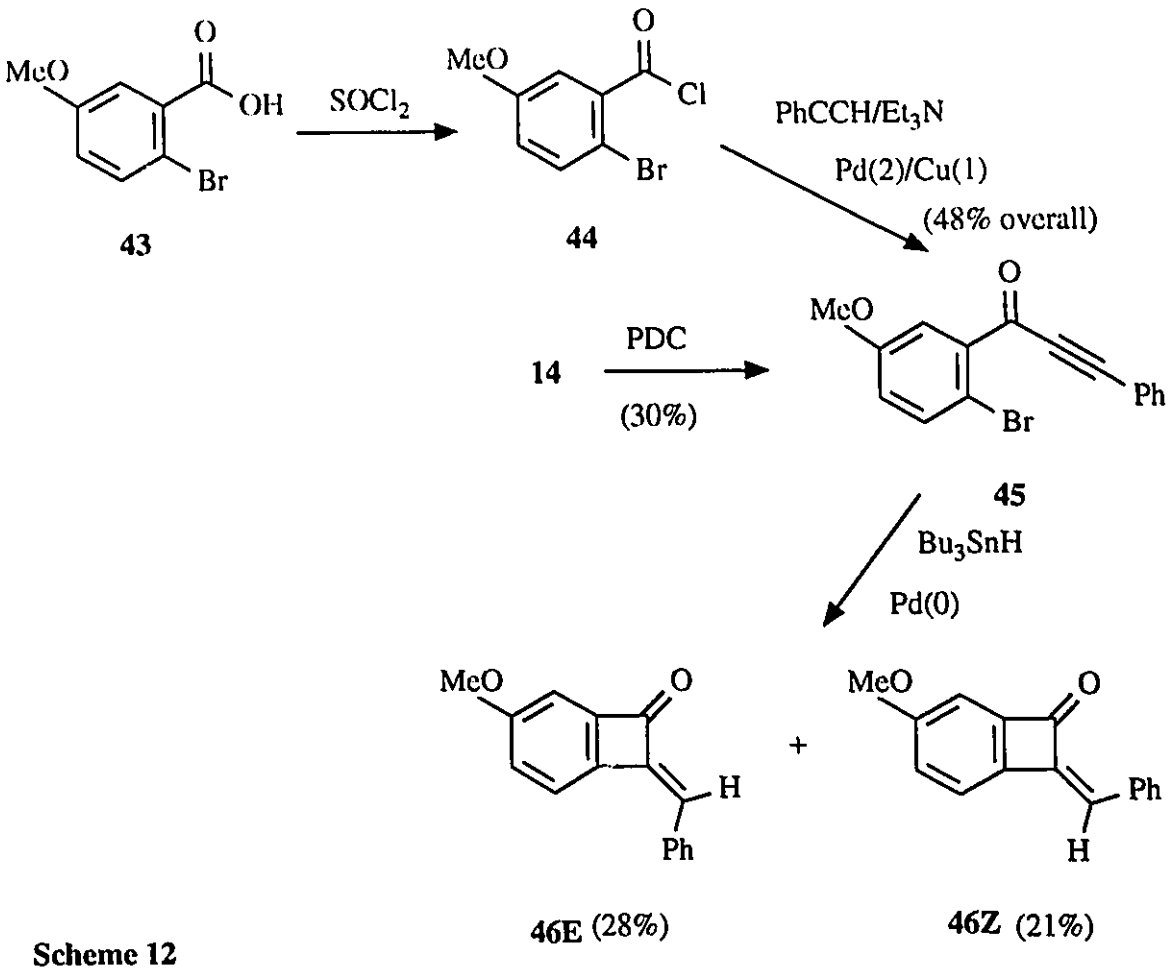


Fig 7: ORTEP diagram of 42E

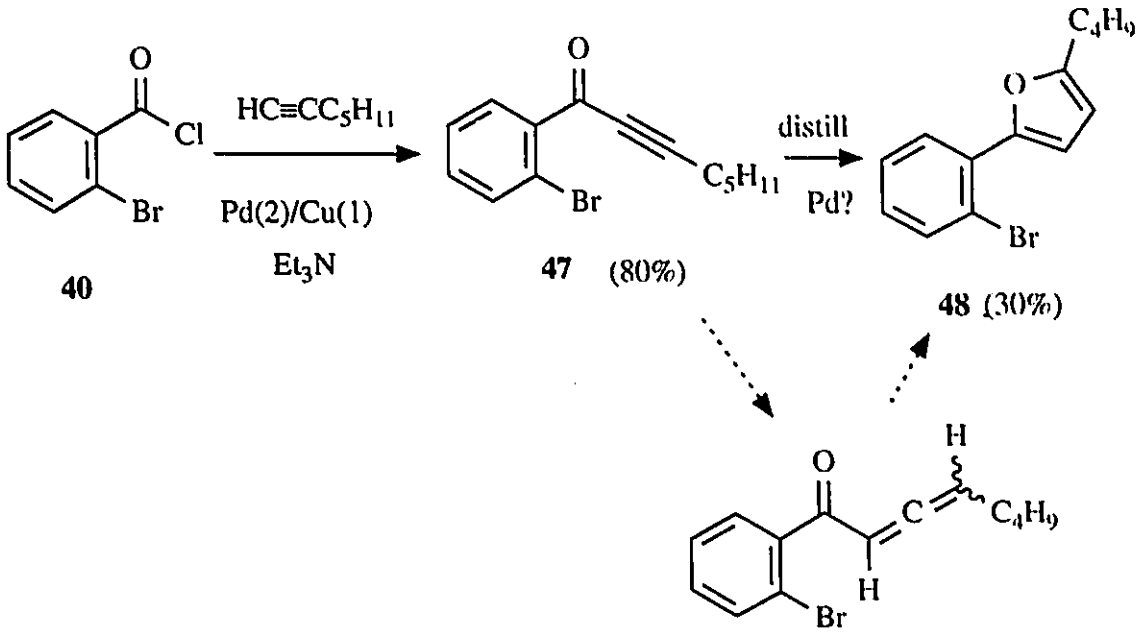
In the 3-methoxy series, alkynone **45** was prepared by PDC oxidation of alkynol **14** in 30% yield (Scheme 12). Alternatively, **45** was obtained in 48% yield as a tan solid from the acid **43** without purifying the intermediate acid chloride **44**. For **45**: ^{1}H NMR δ 3.83 (s, 3H), 6.92 (dd, J = 8.8, 3.1 Hz, 1H), 7.3-7.7 (m, 7H). Cyclization via the Bu_3SnH/Pd(0) protocol yielded benzylidenebenzocyclobutenone **46E** and **46Z** in a 49% combined yield (1.3:1 E/Z). In this case the stereoisomers proved to be inseparable on a preparative scale by chromatography in a number of solvent systems. For analytical purposes, a small amounts of each isomer were obtained using a Chromatotron plate with 10:1:1 hexanes/methylene chloride/ether as eluent. The non-overlapping fractions contained sufficient material for characterization. The stereochemical identification was based on the deshielding effect of the carbonyl oxygen on the benzylidene hydrogen of the E isomer (δ 6.69) compared to δ 6.37 for **46Z**. Both benzocyclobutenones showed the expected high carbonyl stretching frequencies: 1765 cm^{-1} for **46E** and 1766 cm^{-1} for **46Z**.



Scheme 12

We attempted to extent this methodology to other acetylene moieties. Thus, 1-heptyne was coupled with 2-bromobenzoyl chloride to yield alkynone **47** in appoximately 80% yield (Scheme 13), as judged by ^{1}H NMR: δ 0.87 (t, 7 Hz, 3H, CH_3), 1.2-1.4 (m, 4H, -CH_2-CH_2-Me), 1.5-1.7 (m, 2H, -CH_2-Pr), 2.42 (t, J = 7 Hz, 2H, -CH_2-Bu), 7.2-7.4 (m, 2H), 7.62 (dd, J = 0.7, 6.2 Hz, 1H), 7.96 (dd, J = 1.8, 7.5 Hz). Upon attempted distillation of **47** an interesting cyclization occured and furan **48** was collected in 30% yield. Its structure was deduced from several key features of the spectral data. Firstly, based on the ^{1}H NMR the product contained one fewer methylene units than **47**. Second, **47** and **48** had the same molecular mass as determined by mass spectrometry. Third, no carbonyl or alkyne functionalities were present as acertained by ^{13}C NMR or IR. Furthermore, an APT experiment revealed resonances characteristic[19] of the furan ring: two quaternaries at 156 and 140 ppm and two methine carbons at 111 and 107 ppm,

corresponding respectively to the carbons alpha and beta to the furan oxygen. The remaining spectral data are consistent with the structural assignment of **48** (see experimental section).

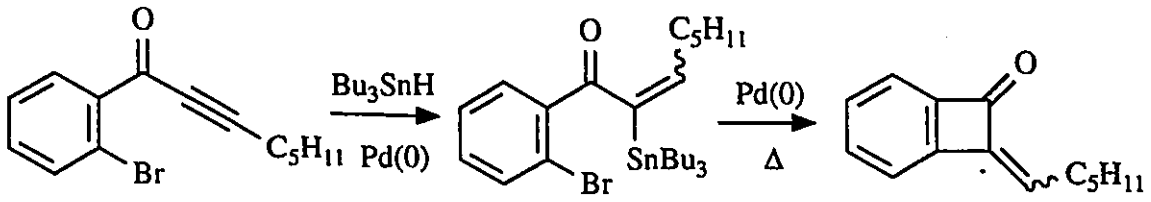


Scheme 13

This cyclization may occur via an allenyl ketone intermediate **49**, catalyzed by traces of palladium present during the distillation. The conversion of alkynones to furans via Pd (0) catalysis has been reported by Huang *et al.*[20] The authors suggest that palladium is responsible for the rearrangement of the akynone to the allenone (i.e. **47** -> **49**) but have not determined whether catalysis is required for the cyclization of the allenone to the furan (i.e. **49** -> **48**).

Chromatography of **47** afforded sufficient material for an attempted cyclization to a benzocyclobutenone, although most of the material decomposed on the silica gel. Addition of tributyltin hydride at room temperature resulted in the disapperance of the 2207(C≡C) and 1652 cm^{-1}(C=O) IR bands and the appearance of a strong band at 1641 cm^{-1}(CO) corresponding to the vinylstannane species **50** (Scheme 14). When refluxed for

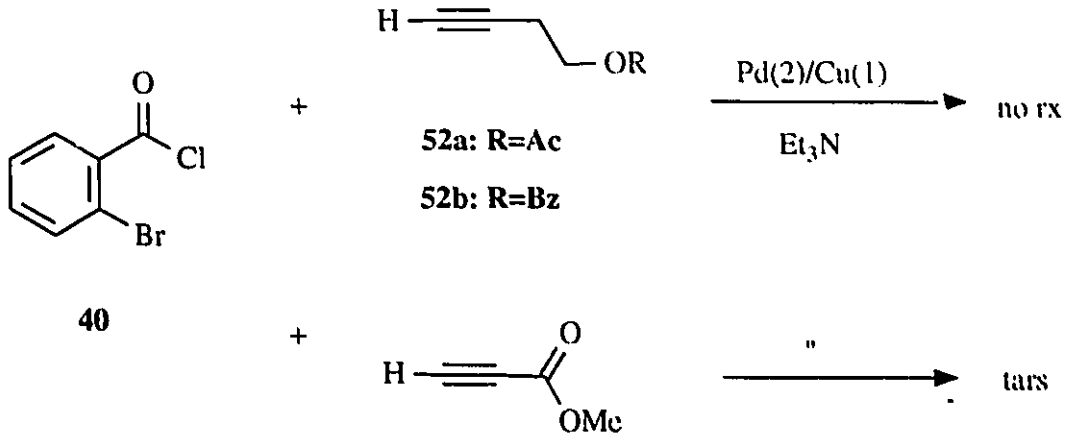
5h, the mixture generated a strong band at 1766 cm^{-1}, expected for the alkylidenebenzocyclobutenone **51**. However, attempted chromatographic purification generated a variety of products having carbonyl frequencies at 1774, 1760; 1752, 1750, 1746 and 1727 cm^{-1}. Rechromatography of the fractions having the highest C=O frequency again afforded a mixture of compounds having a similar set of multiple carbonyl frequencies. None of these fraction was pure enough for thorough characterization. However, one small fraction with a 1766 cm^{-1} peak also provided a peak at 200 m/e in the MS, corresponding to M^+ for **51**. Also, an ^1H NMR of this same fraction yielded a resonance at δ 5.91 (t, J = 8 Hz) which could be attributable to the vinyl hydrogen in **51**.



47 **50** **51**

Scheme 14

Attempts to prepare other alkynone derivatives via the Pd(2)/Cu(1) protocol met with failure (Scheme 15). For example, mixing 2-bromobenzoyl chloride **40** with either the acetyl or benzyl derivatives **52a** and **52b** led to no observable coupling, as acertained by IR monitoring. Attempts to couple **40** with methyl propriolate **53** led only to tar formation. However, this was found to occur with triethylamine and methyl propriolate alone, and thus precludes the use of this alkyne in these coupling procedures requiring triethylamine as base.



Scheme 15

Thus far only the syntheses of the 2-benzylidene- benzocyclobutenones were reliable. It was therefore decided to concentrate on the chemistry of this class of compounds rather than continue working on new synthetic approaches. These mechanistic studies constitute subsequent chapters in this thesis.

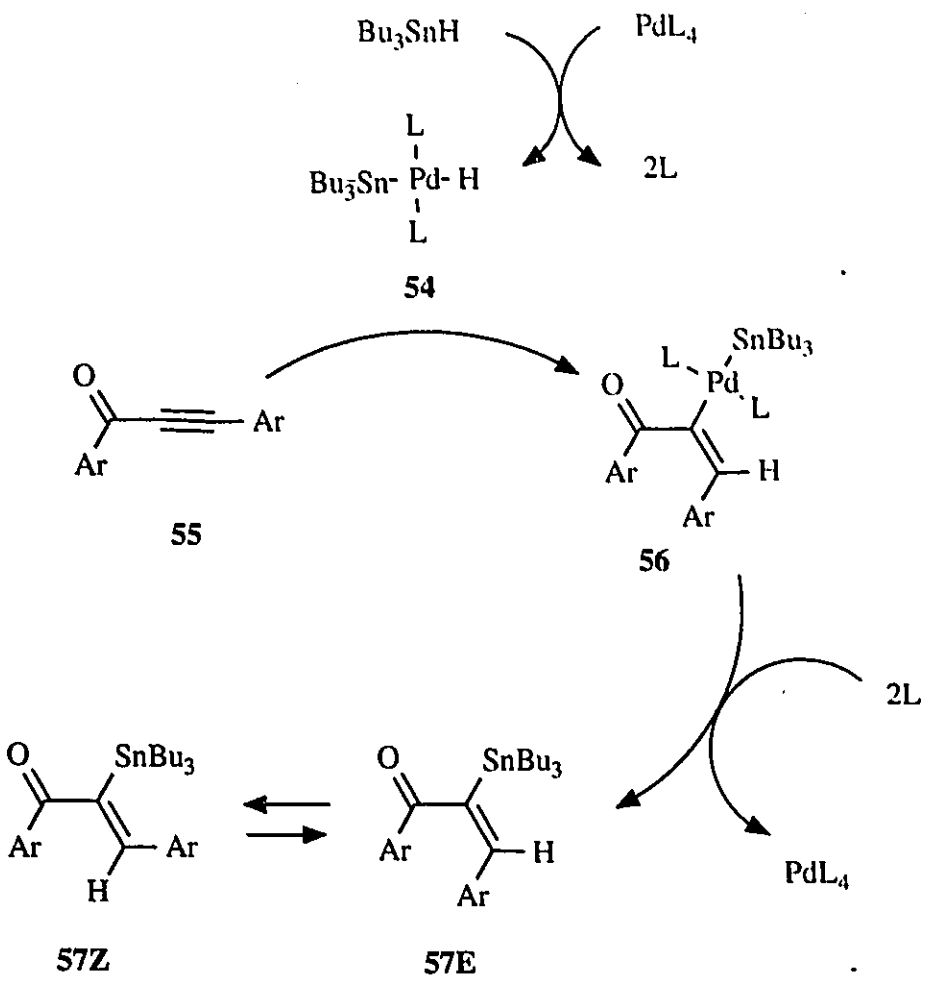
Mechanistic considerations

The overall process can be broken down into two steps: the tributylhydride addition and the cyclization of the vinylstannane. The regioselectivity of the first step was difficult to anticipate based on the work of Zhang *et al.*[16-17] who studied the palladium-mediated addition of tributyltin hydride to a variety of alkynes. They found that both phenyl and benzoyl substituents directed the stannyl group alpha. It was pleasing to observe that a competition between these groups led to the desired intermediate with the stannyl group alpha to the benzoyl group. This is also consistent with the observed behaviour of tributylhydride to act as a hydride donor in the presence of palladium and thus add the hydride in a Michael fashion. In fact, α,β-unsaturated ketones are quickly reduced to saturated ketones using this reagent mixture,[21-23] which demonstrates the necessity of utilizing an acetylene linkage in this one pot procedure.

According to this mechanism, however, addition should occur with stereoselectively with the tin moiety and the hydride being delivered on the same side of the acetylene bond. This was indeed observed for all cases except for the

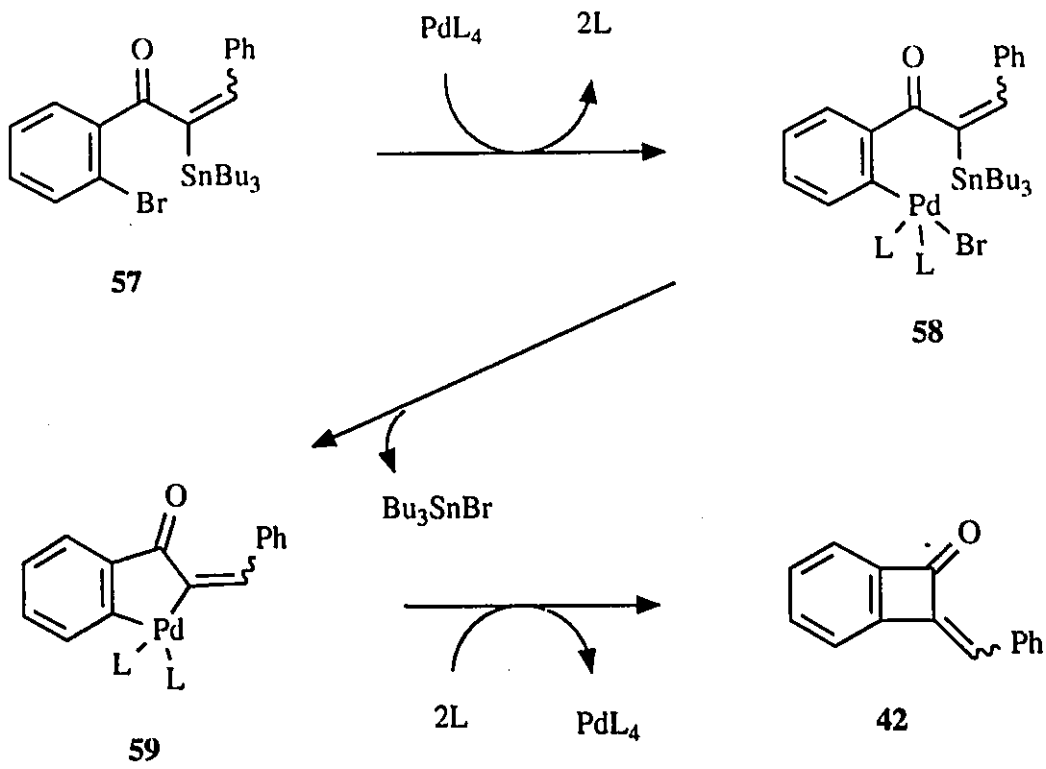
benzoylacetylenes. The authors suggest that addition does in fact take place stereoselectively but the configurationally labile vinylstannane quickly isomerizes to mixtures of E and Z isomers.[16] This would account for the isomeric mixtures obtained in the preparation of benzylidenebenzocyclobutenones.

The mechanistic details should be similar to those postulated in the palladium-mediated vinylation,[24-26] carbonylation[27] or arylation[28-29] of acetylenes. First, tributyltin hydride reduces the Pd(II) species present as $PdCl_2(PPh_3)_2$ to the zero valent $Pd(PPh_3)_4$. It is usually preferable to generate the Pd(0) species *in situ* since $PdCl_2(PPh_3)_2$ has a longer shelf life than $Pd(PPh_3)_4$. Secondly, the Pd(0) species inserts into the Sn-H bond of tributyltin hydride to generate **54**, which subsequently adds across the acetylene bond of **55** in a syn manner with the hydride acting as a Michael donor (Scheme 16). Reductive elimination of palladium from **56** would then yield the vinylstannane **57E**, which would then readily isomerize to an equilibrium between **57E** and **57Z**.



Scheme 16

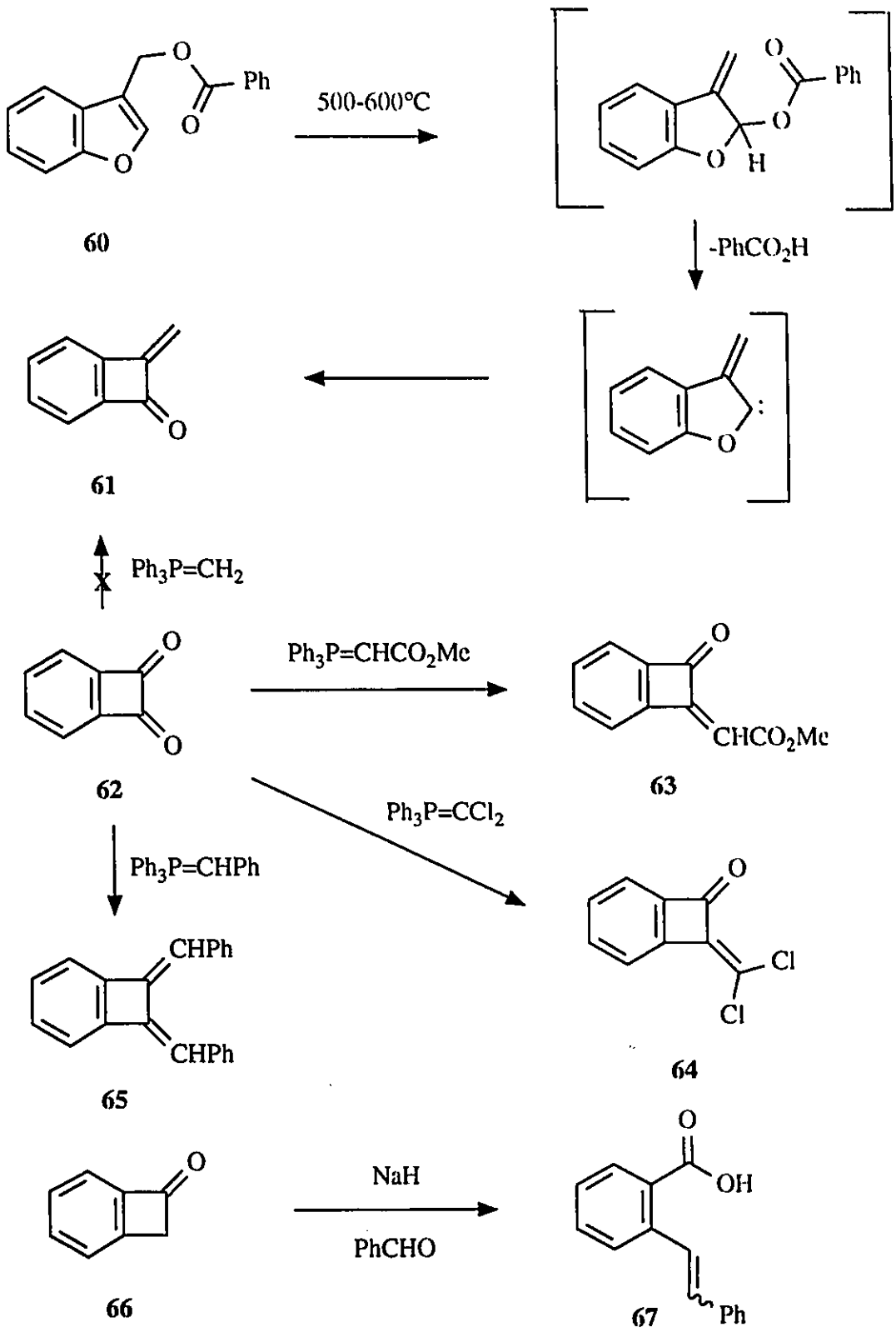
The cyclization step, an intramolecular Stille coupling, does not occur at room temperature but requires refluxing tolune. The mechanism of this coupling reaction has been studied in detail.[2-12] In the present example it involves oxidative addition of the Pd(0) species to the arylbromide bond of **57** to yield intermediate **58** followed by transmetallation of the vinylstannane moiety to produce species **59** (Scheme 17). Reductive elimination regenerates the Pd(0) species and yields the benzylidenbenzocyclobutenones **42**.



Scheme 17

Previous methylenecyclobutenone syntheses

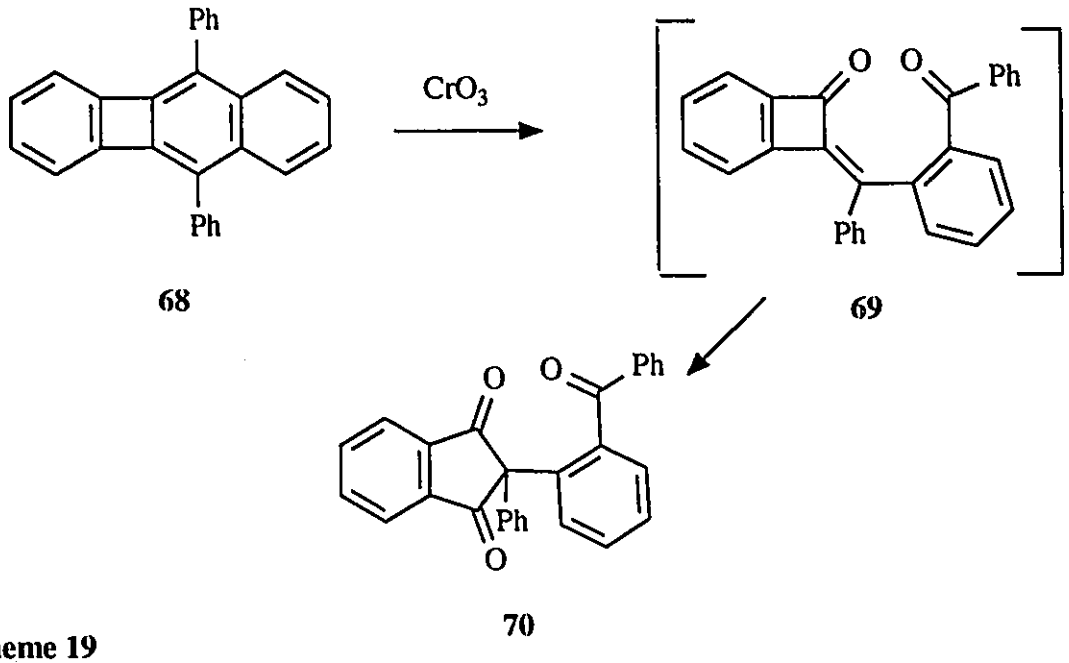
Surprisingly, there have been few reports of methylenebenzocylobutenone preparations[32] (Scheme 18). Methylenebenzocyclobutenone **61** has been prepared in low yield by Trahavovsky[30] via flash vacuum pyrolysis of 3-[(benzoyloxy)-methyl]benzofuran **60**. The Wittig approach to these compounds has only been partially successful. For example, treatment of benzocyclobutenedione **62** with methylenetriphenylphosphine did not yield methylenebenzocyclobutenone **61**, although triphenylphosphine oxide was formed in the reaction. However, the less nucleophilic triphenylphosphinecarbomethoxymethylene and triphenylphosphinedichloromethylene did yield the respective Wittig adducts **63** and **64**.[31-32] Treatment of benzozyclobutenedione with triphenylphosphinebenzylidene led to 1,2-dibenzylidenebenzocylobutene **65** in low yield (25%).[32] Finally, an aldol condensation route between benzocyclobutenone **66** and benzaldehyde only led to the ring opened product **67**.[33]



Scheme 18

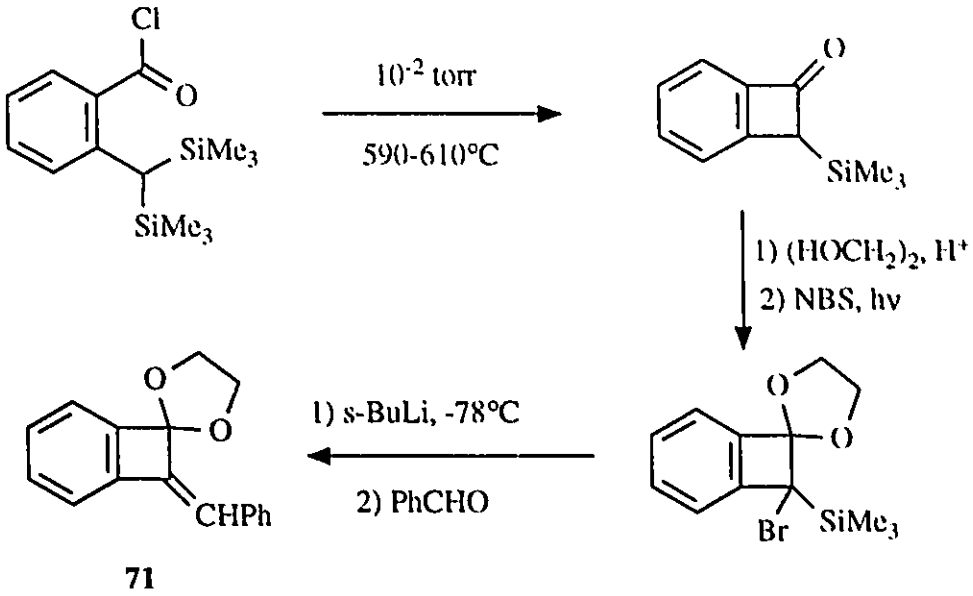
A benzylidenebenzocylobutenone analog **69** has been postulated as an intermediate

in the CrO_3 oxidation of the biphenylene **68** to compound **70**[34] (Scheme 19). There is one report of the preparation of the ethylene glycol ketal of benzylidenebenzocyclobutenone **71** via a Perterson olefination strategy[35] (Scheme 20). However, the synthesis requires several steps and involves vacuum flash pyrolysis, which would probably limit its generality as compared to the milder palladium-mediated process.



68 **69** **70**

Scheme 19


Cl
O
SiMe3
SiMe3
10-2 torr
590-610°C
O
SiMe3
1) (HOCH2)2, H+
2) NBS, hv
O
O
Br
SiMe3
1) s-BuLi, -78°C
2) PhCHO
O
O
CHPh

71

Scheme 20

EXPERIMENTAL

General: Solvents for the extractions and chromatographiic purifications were routinely distilled prior to use. ^{1}H and ^{13}C NMR spectra were obtained either on a Varian XL-300 or a Gemini-200 spectrometer. Reagent-grade toluene kept over 4A molecular sieves was used without prior distillation. Triethylamine was distilled from $LiAlH_4$ and kept under N_2 over 4A molecular sieves.

Reaction of 10 with lithium phenylacetylide: Phenylacetylene (0.22 mL, 2.0 mmol) was added to a solution of nBuLi (2.5 M, 0.80 mL, 2.0 mmol) in 2 mL of THF at -78°C and stirred for 5 min. To this solution was then added 2-bromobenzyl bromide **10** (600 mg, 2.4 mmol) in 2 mL of THF. After 5 min at -78°C the mixture was allowed to warm to rt and stirred for 18 h. The reaction mixture was partitioned between ether and water. The ether layer was washed with water, dried over $MgSO_4$ then evaporated to yield a brown oil (346 mg). This mixture was separated on a Chromatotron plate with hexanes as eluent. The major band was collected and evaporated to a colorless oil identified as **12** (141 mg, 16% yield). ^{1}H NMR δ 3.27 (m, 2H, $-CH_2-$), 4.76 (dd, J = 4.6, 4.8Hz, 1H, $-C\underline{H}CH_2-$), 7.1-7.4 (m, 10H), 7.55(m, 2H), 7.72 (dd, J = 1.8, 7.8 Hz, 1H); ^{13}C NMR (DEPT) δ 38.2(CH), 42.5(CH_2), 84.1(C≡C), 89.9(C≡C), 123.4(q), 123.7(q), 125.4(q), 127.1(CH), 127.9(CH), 128.0(CH), 128.3(CH), 128.4(CH), 128.7(CH), 130.0(CH), 131.7(CH), 131.9(CH), 132.8(CH), 132.9(CH), 137.9(C-Br), 140.4(C-Br); MS (m/e, int) 440 (0.8, M^+ for $^{79}Br+^{81}Br$), 340 (15, M^+-PhC≡CH for $2x^{81}Br$), 338 (26, M^+-PhC≡CH for $^{79}Br+^{81}Br$), 336 (14, M^+-PhC≡CH for $2x^{79}Br$), 178 (100, M^+-PhC≡CH-2xBr).

Preparation of alkynol 14: To a solution of nBuLi (2.15 M, 11.9 mL, 25.5 mmol) in 30 mL of THF at -78C was added phenylacetylene (2.81 mL, 25.5 mmol) over 5 min. The solution was stirred for 10 min then the bromomethoxy aldehyde **13** (5.49g, 25.5 mmol) in 30 mL of THF was introduced dropwise over 15 min. The mixture was stirred for an additional 15 min at -78C then quenched with 20 mL of saturated aqueous NH_4Cl. Partitioning of the reaction mixture between ether and water followed by drying of the organic phase with $MgSO_4$ yielded a brown oil (7.65 g). Chromatography on silica gel

with 3:1 hexanes/ethyl acetate yielded alkynol **14** as a brownish oil (4.12 g, 50% yield). ^{1}H NMR δ 2.6 (s, 1H, OH), 3.80(s, 3H, OMe), 5.93(s, 1H, benzylic), 7.54(dd, J = 8.8, 3.1 Hz, 1H), 7.5-7.2(m, 7H); MS (m/e, int) 318 (28, M^+ for ^{81}Br), 316 (29, M^+ for ^{79}Br), 237 (100, M^+-Br).

Free-radical hydrostannation of 14: Alcohol **14** (1.48g, 4.7 mmol), Bu_3SnH (1.75 mL, 7.0 mmol) and azobis(isobutyronitrile) (59 mg, 0.47 mmol) were refluxed in 50 mL of benzene under N_2 for 2.5h. The solvent was removed under reduced pressure, and the residue was chromatographed on a 4 mm Chromatotron plate with 6:1 hexanes/ethyl acetate as eluent. The adduct **14** was obtained in 55% yield. with tributylhydride and AIBN in refluxing benzene afforded the stannylated adduct **15** in 55% yield. ^{1}H NMR δ 0.5-1.6(m, 27H, $SnBu_3$), 2.09(d, J = 5.2Hz, 1H, OH), 3.78(s, 3H, OMe), 5.72(dd, J = 5.3, 1.7 Hz, J_{Sn-H}= 22 Hz, 1H, allyl), 6.70(dd, J = 8.3, 3.1 Hz, 1H), 7.07(d, J = 3.1 Hz, 1H), 7.22 (m, 6H), 7.43(d, J = 8.7 Hz, 1H).

Cyclization of 15: Adduct **15** (290 mg, 0.48 mmol), 2,6-di-*tert*-butylphenol (a few crystals), and $Pd(PPh_3)_4$ (28 mg) were refluxed in 25 mL of toluene for 4.5 h, and the solvent was removed under reduced pressure. The residue was chromatographed on a 2 mm Chromatotron plate with 3:1 hexanes/ethyl acetate as eluent to afford 45% of **16**: ^{1}H NMR δ 2.5(d, J=7.7Hz, 1H, OH), 3.79(s, 3H, OMe), 5.42(d, J=7.3Hz, 1H, benzylic), 6.36(s, 1H, CHPh), 6.89(m, 2H), 7.2-7.6(m, 6H); ^{13}C NMR δ 55.4, 75.3, 107.0, 117.3, 117.6, 123.1, 127.0, 127.5, 128.6, 135.7, 137.2, 143.1, 152.6, 161.2; MS (m/e, int) 238 (100, M^+).

Oxidation of 16: Alcohol **16** (143 mg, 0.60 mmol), pyridinium dichromate (343 mg, 0.91 mmol) and sodium acetate (14 mg, 0.17 mmol) were stirred in 50 mL of CH_2Cl_2 at rt for 20 h. Evaporation of the solvent yielded a black gum which was stirred in ether/ethyl acetate until a black powder formed after 4 h. The mixture was filtered over Celite then passed through a siliga gel plug with 1:1 hexanes/ethyl acetate as eluent. Evaporation of the desired fraction yielded ketone **17** (114 mg, 0.48 mmol, 80% yield). The ^{1}H NMR and IR data for **17** were identical to **46E** (*vide infra*).

Preparation of 19: To a solution of piperonal **18** (15.0 g, 0.10 mol) in 100 mL of glacial acetic acid was added dropwise Br_2 (5.1 mL, 0.10 mol). The mixture was stirred at rt under N_2 for 28h then 300 mL of water were added. The reddish precipitate which formed was filtered then dissolved in CH_2Cl_2 and washed with water. The organic phase was dried with $MgSO_4$, evaporated and the residue crystallized from CH_2Cl_2/hexanes to yield **19** (7.0g, 31 mmol, 31% yield) as orangish white needles. ^1H NMR δ 6.04 (s, 2H, $-OCH_2O-$), 7.00 (s, 1H), 7.30 (s, 1H), 10.12 (s, 1H, CHO).

Preparation of alkynol 20: The same procedure as for the preparation of **14** was used with the aldehyde **19**. In this case, chromatography was done with 5:1 hexanes/ethyl acetate as eluent yielding **20** in 44% yield as a brown oil: ^1H NMR: δ 2.68 (d, J =5 Hz, 1H, OH), 5.92(d, J = 5Hz, 1H, benzylic), 5.96(s, 2H, $-OCH_2O-$), 6.98(s, 1H), 7.2-7.5(m, 6H); MS (m/e, int) 332 (13, M^+ for ^{81}Br), 330 (14, M^+ for ^{79}Br), 251 (100, M^+-Br).

Free radical hydrostannation of 20: The same conditions as for **14** were used except that the mixture was refluxed for 4 h and the chromatographic separation was carried out with 5:1 hexanes/ethyl acetate. In one fraction, 30 % of **20** was recovered. The only other identifiable product obtained was vinylstannane **21** in 3.1% yield: ^1H NMR δ 0.4-1.4 (m, 27H, $SnBu_3$), 2.02 (d, J = 5 Hz, 1H, OH), 5.71 (dd, J = 5, 1 Hz, J_{Sn-H}= 20 Hz, 1H, allylic), 5.95 (s, 2H, $-OCH_2O-$), 6.98 (s, 1H), 7.01 (s, 1H), 7.1-7.3 (m, 5H), 7.33 (d, J=1Hz, J_{Sn-H}= 120 Hz, 1H).

Cyclization of 21: The same conditions as for the cyclization of **15** were used. Chromatography was carried out in 5:1 hexanes/ethyl acetate to yield benzocyclobutenol **22** in 50% yield: ^1H NMR δ 2.26 (d, J = 10.4 Hz, 1H, OH), 5.32 (d, J = 10.4 Hz, 1H, benzylic), 5.93 (s, 2H, $-OCH_2O-$), 6.32 (s, 1H, CHPh), 6.86 (s, 1H), 6.96 (s, 1H), 7.2-7.5 (m, 5H); ^{13}C NMR δ 74.4, 101.0, 102.9, 104.0, 116.7, 127.0, 127.5, 128.6, 137.0, 137.1, 142.6, 145.4, 149.0, 149.5.

Preparation of alkynol 24: The same procedure as for the preparation of **14** was used with the aldehyde **23**. In this case, distillation under reduced pressure (1 torr/180C) yielded alkynol **24** in 35% yield as a slightly orangish oil: ^1H NMR δ 2.74 (s, 1H, OH),

5.99 (s, 1H, benzylic), 7.2-7.8 (m, 9H); IR (CH_2Cl_2, cm^{-1}) 3600 (O-H), 2240 (C≡C); MS (m/e, int) 288 (5, M^+ for ^{81}Br), 286 (6, M^+ for ^{79}Br), 207 (100, M^+-Br).

Free-radical hydrostannation of 24: The same conditions as for **14** were used except that the mixture was refluxed for 3 h and the chromatographic separation was carried out with 9:1 hexanes/ethyl acetate. One fraction appeared to consist of a mixture of Bu_3SnBr and vinylstannane **25** (estimated 10% yield). ^1H NMR, δ 0.5-1.7(m, 107H = 27H of **25** + 3 x 27H of Bu_3SnBr), 2.1 (d, 1H, J = 8 Hz, OH), 5.75 (d, J = 8 Hz, J_{Sn-H}= 24 Hz, 1H, benzylic) 7.1-7.6 (m, 9H); MS (m/e, int) 521 (26, M^+-Bu for **25**), 313 (48, M^+-Bu for Bu_3SnBr)

Palladium catalysed hydrostannation of 24: To a solution of alkynol **24** (0.55g, 1.9 mmol) and $Pd(Ph_3)_4$ (62 mg, 54 μmol in 25 mL of benzene was added Bu_3SnH (0.60 mL, 2.2 mmol). The resulting deep red solution was stirred for 10 min then the solvent was evaporated under reduced pressure. The residue was chromatographed on a 4 mm Chromatotron plate with 9:1 hexanes/ethyl acetate as eluent to yield **26** as a yellowish oil (1.0 g, 90% yield): ^1H NMR δ 0.7-1.5 (m, 27H, $SnBu_3$), 2.03 (d, J = 3.8 Hz, 1H, OH), 5.46 (dd, J = 3.3, 8.1 Hz, 1H, benzylic), 5.95 (d, J= 8.1 Hz, J_{Sn-H}= 60 Hz, 1H, vinylic), 6.9-7.6 (m, 9H); MS (m/e, int) 520 (34, M^+-Bu).

Preparation of 27: A solution of alkynol **24** (0.34 g, 1.2 mmol) and acetic anhydride (2.0 g) in 15 mL of pyridine was stirred at rt for 1h. To the reaction mixture was then added 100 mL of water followed by extraction with ether twice. The organic phase was washed with 3N HCl then with water, dried over $MgSO_4$ and then evaporated to yellowish oil identified as **27** (0.27 g, 69% yield): ^1H NMR δ 2.13 (s, 3H, $OCOCH_3$), 6.90 (s, 1H, benzylic), 7.2-7.9 (m, 9H); IR (CH_2Cl_2, cm^{-1}) 2242 (C≡C), 1750 (C=O); MS (m/e, int) 330 (16, M^+ for ^{81}Br), 328 (16, M^+ for ^{79}Br), 288 (19, M^+- MeCHO for ^{81}Br), 286 (19, M^+- MeCHO for ^{79}Br), 207 (52, M^+- MeCHO-Br), 189 (75, M^+- $MeCO_2H$-Br), 43 (100, $MeCO^+$).

Palladium catalysed hydrostannation of 27: The same conditions as for **24** were used except that chromatography was carried out in 40:1 hexanes/ethyl acetate to afford

vinylstannane **28** in 12% yield: ^{1}H NMR δ 0.7-1.5 (m, 27H, $SnBu_3$), 1.97 (s, 3H, $OCOCH_3$), 5.92 (d, J = 7.9 Hz, J_{Sn-H}= 60 Hz, 1H, vinylic), 6.42 (d, J = 7.9 Hz, 1H, allylic), 6.8-7.6 (m, 9H); IR (CH_2Cl_2, cm^{-1}) 1740 (OAc).

Preparation of 29: A solution of alkynol **20** (0.95 g, 2.9 mmol) and acetic anhydride (4.0 g) in 10 mL of pyridine was refluxed for 15 min. After cooling to rt, 30 mL of H_2O were added and an orangish precipitate was collected. Crystallization from ethanol yielded **29** as white crystals (409 mg, 1.10 mmol, 38% yield): ^{1}H NMR δ 2.25 (s, 3H, $OCOCH_3$), 6.15 (s, 2H, $-OCH_2O-$), 6.95 (s, 1H), 7.20 (s, 1H), 7.3-8.0 (m, 6H); IR (CH_2Cl_2, cm-1) 2230(C≡C), 1745($OCOCH_3$); MS (m/e, int) 374 (30, M^+ for ^{81}Br), 374 (31, M^+ for ^{79}Br), 315 (41, M^+-MeCO for ^{81}Br), 313 (37, M^+-MeCO for ^{79}Br), 251 (100).

Palladium catalysed hydrostannation of 29: The same conditions as for **24** were used except that the purification was carried out with 20:1 hexanes/ethyl acetate to yield the vinylstannanes **30** and **31** in 37% and 15% yield, respectively along with 25% recovered starting material.

30: ^{1}H NMR δ 0.7-1.5 (m, 27H, $SnBu_3$), 1.95 (s, 3H, $OCOCH_3$), 5.84 (d, J = 7.8 Hz, J_{Sn-H}= 60 Hz, 1H, vinylic), 5.94 (m, 2H, $-OCH_2O-$), 6.34 (d, J = 7.8 Hz, 1H, benzylic), 6.8-7.3 (m, 7H).

31: ^{1}H NMR: δ 0.7-1.6 (m, 27H, $SnBu_3$), 1.98 (s, 3H, $OCOCH_3$), 5.95 (s, 2H, $-OCH_2O-$), 6.84 (m, 2H, J_{Sn-H}= 60 Hz, vinylic + benzylic), 6.90 (s, 1H), 6.98 (s, 1H), 7.0-7.3 (m, 5H).

Preparation of acid chloride 34: The acid **33** (8.66 g, 35.5 mmol) was refluxed in 20 mL of $SOCl_2$ for 1.5 h under a N_2 bleed. Carbon tetrachloride (30 mL) was added and the mixture was then evaporated under reduced pressure. The residue was crystallized from hexanes/ethyl acetate to yield acid chloride **34** (5.97 g, 22.7 mmol, 64% yield) as white crystals: ^{1}H NMR δ 6.10 (s, 2H, $-OCH_2O-$), 7.09 (s, 1H), 7.59 (s, 1H); IR (CH_2Cl_2, cm^{-1}) 1785 (COCl); MS (m/e) 264 (17, M^+ for ^{81}Br and ^{35}Cl), 262 (13, M^+ for ^{79}Br and ^{35}Cl), 229 (97, M^+-Cl for ^{81}Br), 227 (100, M^+-Cl for ^{79}Br).

Preparation of 35: Triethylamine (20 mL) was added to a mixture of **34** (5.87 g,

22.3 mmol), phenylacetylene (2.30 g, 22.5 mmol), $PdCl_2(PPh_3)_2$ (20 mg), CuI (20 mg) and PPh_3 (20 mg). The mixture was stirred at rt for 23h. Methanol (15 mL) was added and the solvents evaporated under reduced pressure. Ethyl acetate was added to the residue and the white precipitate was filtered off and washed with 200 mL of ethyl acetate. Evaporation of the filtrate followed by crystallization of the residue with hexanes/ethyl acetate yielded alkynone **35** (2.42 g, 13.4 mmol, 60% yield) as golden crystals: mp 101°C; ^{1}H NMR δ 6.07 (s, 2H, -OCH_2O-), 7.10 (s, 1H), 7.40 (m, 4H), 7.61 (m, 2H); IR (CH_2Cl_2, cm^{-1}) 1641 (C=O), 2188 (C≡C); MS (m/e, int) 330 (40, M^+ for ^{81}Br), 328 (40, M^+ for ^{79}Br), 302 (41, M^+-CO for ^{81}Br), 300 (41, M^+-CO for ^{79}Br), 163 (46), 129 (100); HRMS $C_{16}H_9{}^{81}BrO_3$ 329.9716 (calcd), 329.9714 (found); $C_{16}H_9{}^{79}BrO_3$ 327.9735 (calcd), 327.9732 (found). The mother liquor was shown to contain an additional 33% of **35** thus giving a total yield of 93%.

Cyclization of 35: Tributyltin hydride (2.0 mL, 7.3 mmol) was added via syringe to a solution of ynone **35** (2.1 g, 6.1 mmol), $PdCl_2(PPh_3)_2$ (0.08 g) and PPh_3 (0.08 g) in 25 mL of toluene. The turbid solution was stirred at rt for 5 min then refluxed for 1 h. After evaporation of the solvent, the residue was separated on a Chromatotron plate with eluent of increasing polarity starting from pure hexanes to hexanes/CH_2Cl_2 mixtures. The E isomer was separated but the Z isomer was contaminated with unreacted ynone. In all, the cyclized products were obtained in 58% yield (1.1:1 E/Z ratio), together with 18% recovered starting material. Samples for analytical purposes were prepared by recrystallization from hexanes/ethyl acetate for **37E** and hexanes/CH_2Cl_2 for **37Z**.

37E: mp 131°C; ^{1}H NMR δ 6.13 (s, 2H, -OCH_2O-), 6.62 (s, 1H, H_1), 6.95 (s, 1H), 7.26 (s, 1H), 7.31 (m, 1H), 7.41 (m, 2H), 7.50 (m, 2H, H_2); ^{13}C NMR δ 101.5, 102.6, 102.7, 114.7, 128.0, 128.1, 128.7, 135.3, 146.3, 150.4, 151.2, 154.0, 156.4, 184.3; IR (CH_2Cl_2, cm^{-1}) 1761 (CO); MS (m/e, int) 250 (100, M^+), 222 (44, M^+-CO), 163 (63); HRMS $C_{16}H_{10}O_3$ 250.0630 (calcd), 250.0649 (found).

37Z: mp 130°C; ^{1}H NMR δ 6.09 (s, 2H, -OCH_2O-), 6.29 (s, 1H, H_1), 6.91 (d, J = 0.8 Hz, 1H), 6.96 (d, J = 0.8 Hz, 1H, H_3), 7.24 (m, 1H), 7.36 (m, 2H), 7.88 (m, 2H, H_2);

^{13}C NMR δ 99.6, 101.6, 102.3, 118.9, 127.8, 128.5, 129.2, 135.3, 147.1, 148.6, 150.1, 154.7, 158.5, 182.3; IR (CH_2Cl_2, cm^{-1}) 1750 cm^{-1}; MS (m/e, int) 250 (100, M^+), 222 (39, M^+-CO), 163 (67); $C_{16}H_{10}O_3$ 250.0630 (calcd), 250.0622 (found).

Preparation of acid chloride 40: The same procedure as for **34** was used except that the purification was carried out by distillation (150-160 °C/ 1 torr) to yield **40** in 94% yield: ^1H NMR δ 7.3-7.5 (m, 2H), 7.6-7.7 (m, 1H), 8.0-8.1 (m, 1H); IR (CH_2Cl_2, cm^{-1}) 1787 (C=O).

Preparation of 41:

a) from 40: The same procedure as for **35** was used except that purification was carried out by distillation to yield **41** in 73% yield: ^1H NMR δ 7.2-7.4 (m, 5H), 7.5-7.7 (m, 3H), 8.05 (m, 1H); IR (CH_2Cl_2, cm^{-1}) 2200 (C≡C), 1653 (CO); MS (m/e, int) 286 (20, M^+ for ^{81}Br), 284 (20), M^+ for ^{79}Br), 258 (37, M^+-CO for ^{79}Br), 256 (37, M^+-CO for ^{81}Br), 202 (57), 129 (100); HRMS $C_{15}H_9{}^{81}BrO$ 285.9576 (calcd), 285.9797 (found); $C_{15}H_9{}^{79}BrO$ 283.9837 (calcd), 283.9837 (found).

b) from 24: A mixture of alkynol **24** (1.08 g, 3.76 mmol), sodium acetate (0.09 g), alumina (0.40 g) and finely ground PDC (2.12 g, 5.64 mmol) was stirred in 15 mL of CH_2Cl_2 for 3 h at rt. The reaction mixture was then filtered over Celite, the filtrate was evaporated and the resulting residue was chromatographed on silica gel with 1:1 hexanes/ethyl acetate as eluent to yield **41** in 81% yield.

Cyclization of 41: The same procedure as for the cyclization of **35** was used except that the products were separated on a Chromatotron plate with 6:1 hexanes/CH_2Cl_2 as eluent to yield **42E** and **42Z** in 70% combined yield (E/Z ratio of 1.5 : 1). Samples of each were crystallized from ether/hexanes.

42E: mp 91°C; ^1H NMR δ 6.86 (s, 1H, CHPh), 7.36 (m, 1H), 7.45 (m, 3H), 7.55 (m, 2H), 7.62 (m, 2H), 7.86 (m, 1H); ^{13}C NMR δ 119.1, 121.1, 121.6, 128.5, 128.7, 128.8, 130.1, 134.7, 134.8, 148.3, 156.7, 158.3, 187.0; IR (CH_2Cl_2, cm^{-1}) 1768 (CO); MS (m/e, int) 206 (65, M^+), 178(100); HRMS $C_{15}H_{10}O$ 206.0732 (calcd), 206.0752 (found).

42Z: mp 120°C; ^1H NMR δ 6.55 (s, 1H, CHPh), 7.3 (m, 2H), 7.4 (m, 2H), 7.5 (m,

3H), 7.94 (m, 2H); ^{13}C NMR δ 118.7, 121.2, 123.1, 128.6, 129.4(x2), 129.6, 135.0, 135.2, 149.1, 154.4, 160.1, 184.8; IR (CH_2Cl_2, cm^{-1}) 1757 (CO); MS (m/e, int) 206 (67, M^+), 178 (100); HRMS $C_{15}H_{10}O$ 206.0732 (calcd), 206.0752 (found).

Preparation of 45:

a) from 43: The same procedure as for the preparation of acid chloride **34** was used except that the intermediate **44** was not purified. Instead, after evaporation of the solvent, the residue was diluted twice with 25 mL of CCl_4 and evaporated under reduced pressure, finally at 1 torr for 1 h. The crude acid chloride was then coupled with phenylacetylene under the same conditions as **34**. Purification was carried out by silica gel chromatography with ether/ethyl acetate, with an increasing proportion of ethyl acetate, followed by crystallization from hexanes/ether to yield **45** as tan crystals (48% yield from **43**): mp 51°C; ^1H NMR δ 3.83 (s, 3H), 6.92 (dd, J = 8.8, 3.1 Hz, 1H), 7.3-7.7 (m, 7H); IR (CH_2Cl_2, cm^{-1}) 2210 (C≡C), 1652 (C=O); MS (m/e, int) 316 (34, M^+ for ^{81}Br), 314 (34, M^+ for ^{81}Br), 288 (20, M^+-CO for ^{81}Br), 286 (20, M^+-CO for ^{79}Br), 235 (23), 129 (100); HRMS $C_{16}H_{11}{}^{81}BrO_2$ 315.9923 (calcd), 315.9926 (found); $C_{16}H_{11}{}^{79}BrO_2$ 313.9942 (calcd), $C_{16}H_{11}{}^{79}BrO_2$ 313.9942 (calcd), 313.9923 (found).

b) from 14: The same PDC oxidation procedure was used as for alkynol **24** to provide alkynone **45** in 30% yield.

Cyclization of 45: The same procedure as for the cyclization of **35** was used except that the solution was stirred at rt for 3 h then refluxed for 2 h. Flash silica gel chromatography in 2:1 hexanes/ethyl acetate afforded a 1.3:1 mixture of **46E/46Z** (49% yield) as a yellow solid. To obtain analytical data for each pure isomer, a small quantity of the mixture (150 mg) was separated on a Chromatotron plate (4 mm) using 10:1:1 hexanes/CH_2Cl_2/ether. The nonoverlapping fractions were further purified by crystallization from ether/hexanes to give each isomer in pure form.

46E: mp 127°C; ^1H NMR δ 3.86 (s, 3H, OCH_3), 6.69 (s, 1H, CHPh), 7.03 (dd, J = 2.1, 0.8 Hz, 1H), 7.32 (m, 1H), 7.43 (m, 2H), 7.56 (m, 2H), 7.78 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 55.8, 104.0, 115.6, 122.8, 123.2, 128.1, 128.3, 128.7, 135.2, 147.2, 152.1, 158.5,

161.5, 186.5; IR (CH_2Cl_2, cm^{-1}) 1765 (C=O); MS (m/e, int) 236 (95, M^+), 221 (15), 208 (40), 165 (100); HRMS $C_{16}H_{12}O_2$ 236.0837 (calcd), 236.0837 (found)

46Z: mp 143°C; ^1H NMR δ 3.84 (s, 3H, OCH_3), 6.37 (s, 1H, CHPh), 6.98 (dd, J = 2.2, 0.8 Hz, 1H), 7.09 (dd, J = 8.1, 0.8 Hz, 1H), 7.25 (m, 1H), 7.37 (m, 2H), 7.46 (dd, J = 0.8, 8.1 Hz, 1H), 7.89 (m, 2H); ^{13}C NMR δ 55.8, 103.9, 199.9, 120.0, 124.2, 127.9, 128.5, 129.1, 135.3, 148.0, 154.0, 156.0, 161.2, 184.5; IR (CH_2Cl_2, cm^{-1}) 1766 (C=O); MS (m/e, int) 236 (100, M^+), 221 (16), 208 (42), 193 (100), 165 (98); HRMS $C_{16}H_{12}O_2$ 236.0837 (calcd), 236.0836 (found).

Preparation of 47: Under the same conditions used for preparation of **35**, 2-bromobenzoyl chloride **40** was coupled with 1-heptyne. After evaporation of the solvent, the residue was partitioned between ethyl acetate and water. The water layer was washed with ether and CH_2Cl_2. The organic washings were collected and filtered over $MgSO_4$ and silica gel. Evaporation of the solvents yielded alkynone **47** in about 80% yield (ca. 90% pure by ^1H NMR): ^1H NMR: δ 0.87 (t, 7 Hz, 3H, CH_3), 1.2-1.4 (m, 4H, $-CH_2-CH_2-Me$), 1.5-1.7 (m, 2H, $-CH_2-Pr$), 2.42 (t, J = 7 Hz, 2H, $-CH_2-Bu$), 7.2-7.4 (m, 2H), 7.62 (dd, J = 0.7, 6.2 Hz, 1H), 7.96 (dd, J = 1.8, 7.5 Hz); IR (CH_2Cl_2, cm^{-1}) 2220 (C≡C), 1660 (C=O). Purification by silica gel chromatography was impractical because of the apparent instability of **47** to prolonged exposure to silica gel

Preparation of 48: Attempted distillation (140°C/1-3 torr) of **47** from the crude mixture obtained as described above yielded exclusively the furan **48** in 30% yield as the only distillable product. Much decomposition was also noted in the distillation flask. ^1H NMR δ 0.94 (t, J = 7.3 Hz, 3H, CH_3), 1.3-1.5 (m, 2H, $-CH_2-Me$), 1.6-1.8 (m, 2H, $-CH_2-Et$), 2.68 (t, J = 7.4 Hz, 2H, $-CH_2-Pr$), 6.10 (d, J = 3.3 Hz, 1H, furan), 7.05 (t, J = 8 Hz, 1H), 7.09 (d, J = 3.5 Hz, 1H, furan), 7.31 (t, J = 8 Hz), 7.60 (d, J = 8 Hz, 1H), 7.77 (d, J = 8 Hz, 1H); ^{13}C NMR (DEPT) δ 13.9(CH_3), 22.4(CH_2), 27.9(CH_2), 30.2(CH_2), 106.7(furan CH), 111.4(furan CH), 119.0(C-Br), 127.2(CH), 127.6(CH), 128.1(CH), 131.3(Q), 134.0(CH), 149.1(furan Q), 156.5(furan Q); IR (CH_2Cl_2, cm^{-1}) 1560, 1540, 1469, 1019; MS (m/e, int) 280 (32, M^+ for ^{81}Br), 278 (34, M^+ for ^{79}Br), 237 (99, M^+-Pr for

^{81}Br), 237 (100, M^+-Pr for ^{79}Br), 128 (85).

REFERENCES

1. Bradley, J.C.; Durst, T. *J. Org. Chem.* **1991**, 56, 5459.

2. Stille, J.K. *Pure and Appl. Chem.* **1985**, 57, 1771.

3. Farina, V.; Krishnan, B. *J. Am. Chem Soc.* **1991**, 113, 9585.

4. Farina, V.; Roth, G.P. *Tetrahedron Lett.* **1991**, 32, 4243.

5. Echevarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* **1988**, 110, 1557.

6. Farina, V.; Baker, S.R.; Benigni, D.A.; Sapino, C.Jr. *Tetrahedron Lett.* **1988**, 29, 5739.

7. Stille, J.K.; Groh, B.L. *J. Am. Chem. Soc.* **1987**, 109, 813.

8. McKean, D.R.; Parrinello, G.; Renaldo, A.F.; Stille, J.K. *J. Org. Chem.* **1987**, 52, 422.

9. Scott, W.J.; Stille, J.K. *J. Am. Chem. Soc.* **1986**, **108**, 3033.

10. Stille, J.K. *Angew. Chem. Int. Ed. Engl.* **1986**, 508.

11. Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, 105, 6129.

12. Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1988**, 53, 926.

13. Leusink, A.J.; Budding, H.A.; Marsman, J.W. *J. Organometal. Chem.* **1967**, 9, 285.

14. Harris, R.K.; Mann, B.E. NMR and the Periodic Table, Academic Press, New York, **1978**, p. 342.

15. Orr, A.; Robinson, R.; Williams, M. *J. Chem. Soc.* **1917**, 946.

16. Zhang, H.X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, 55, 1857.

17. Zhang,H.X.; Guibe, F.; Balavoive, G. *Tetrahedron Lett.* **1988**, 29, 619.

18. Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synth. Commun.* **1977**, 777.

19. Katritzky, A.R.; Rees, C.W. Comprehensive Heterocyclic Chemistry, v. 4, Part 3, Permagon Press, New York, **1984**, p. 565.

20. Seng, H.; Shouyuan, L.; Huang, Y.Z. *Tetrahedron Lett.* **1986**, 27, 4893.

21. Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, 48, 3545.

22. Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, 23, 1825.

23. Kleinan, E.; Gleize, A. *Tetrahedron Lett.* **1982**, 23, 477.

24. Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron Lett.* **1989**, 30, 3465.

25. Trost, B.M.; Lee, D.C. *J. Am. Chem. Soc.* **1988**, 110, 7255.

26. Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, 29, 4325.

27. Samsel, E.G.; Norton, J.R. *J. Am. Chem. Soc.* **1984**, 106, 5505.

28. Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, 55, 4846.

29. Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, 111, 3454.

30. Trahavovsky, W.S.; Amah, A.N.; Cassady, T.J. *J. Am. Chem. Soc.* **1984**, 106, 2696.

31. Cava, M.P. Pohl, R.J.; Mitchell, M.J. *J. Am. Chem. Soc.* **1963**, 85, 2080.

32. Cava, M.P.; Mitchell, M.J. Cyclobutadiene and Related Compounds, Academic Press, New York, N.Y., **1967**, pp. 219-241.

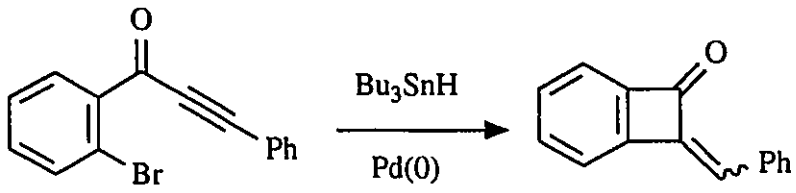
33. Bertelli, D.J.; Crews, P. *J. Am. Chem. Soc.* **1968**, 90, 3889.

34. Cava, M.P.; Pohlke, R. *J. Org. Chem.* **1962**, 27, 1564.

35. Chenard, B.L.; Slapak, C.; Anderson, D.K.; Swenton, J.S. *J. Chem. Soc. Chem. Comm.* **1981**, 179.

CHAPTER 3: ATTEMPTS AT OPTIMIZATION AND ALTERNATIVE PREPARATION OF BENZYLIDENEBENZOCYCLOBUTENONES

After initial success in preparing several analogs of benzylidene-benzocyclobutenones, attempts to scale up proved quite frustrating. For example for the cyclization of the unsubstituted alkynone **1** to benzocyclobutenes **2** (Scheme 1), yields of 50-70% were frequently obtained for 0.5-3 g of **1**; 30-40% were typical for 5-10 g, whereas trials with 20-45 g have yielded less than 10%. In addition, the yields for the small scale reactions were also quite poor on occasion. In order to attempt to understand and hopefully remedy the source of these problems, the reaction in question was more thoroughly studied.



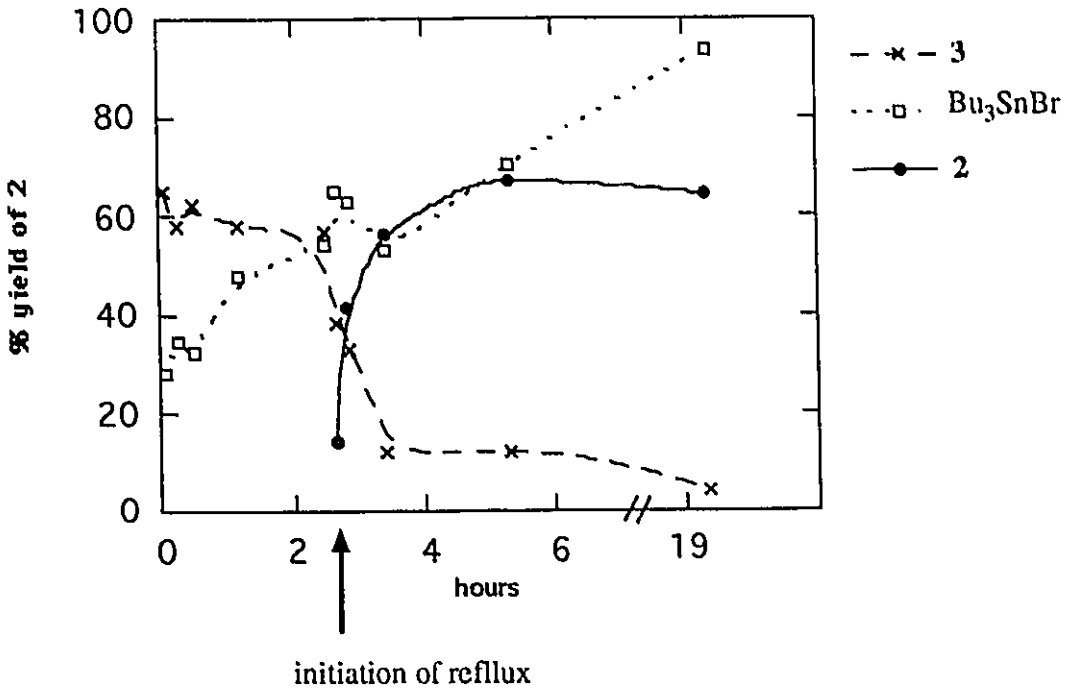
1 **2**

Scheme 1

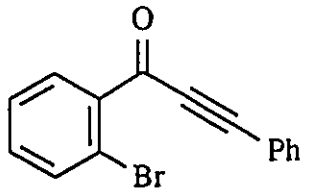
Results

Thus, tributyltin hydride (1.1 eq.) was added to a 0.12 M toluene solution of alkynone **1** (408 mg, 1.43 mmol) with $PdCl_2(PPh_3)_2$(0.05 eq) and PPh_3(0.10 eq) over a few seconds. The progress of the reaction was then monitored by taking measured aliquots, filtering these through a small plug of silica gel followed by ethyl acetate elution and adding a measured amount of naphthalene as an internal standard for GC analysis. Thus, a profile for the reaction was possible and revealed several important features (see Fig 1).

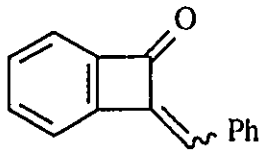
Fig 1: Reaction Profile for Cyclization of 1 -> 2*



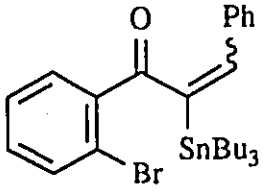
*yield valid for 2 (naphtalene as internal GC standard); all other yields are arbitrary



1

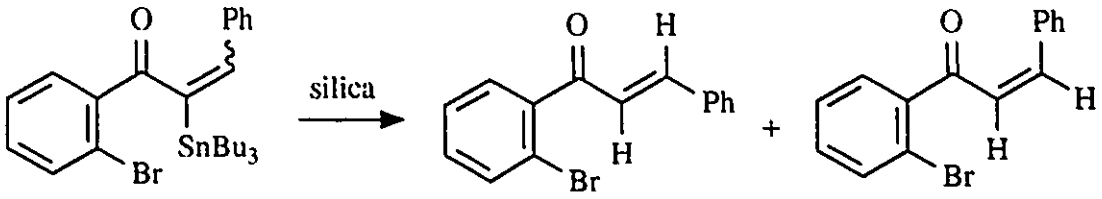


2



3

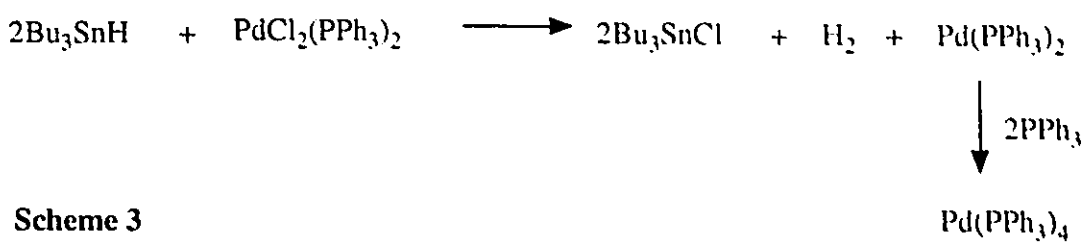
First, disappearance of the alkynone **1** occured within 5 minutes after the addition of tributyltin hydride with the concomittant appearance of a new major peak. It was possible to resolve this new peak by GC-MS into two components with identical cleavage patterns corresponding to alkenes **4E** and **4Z** (M^+ for both at 288) (Scheme 2). These are the expected products from the silica induced protolysis of vinylstannanes **3**; α-tributylstannyl conjugated enones are extremely sensitive to acidic conditions and generally hydrolyse readily on silica gel.[1]



3 **4E** **4Z**

Scheme 2

Second, tributyltin chloride was also detected by GC-MS, originating from the reduction of the $PdCl_2(PPh_3)_2$ catalyst[1] (Scheme 3). Most interestingly, tributyltin bromide **6** was also formed at room temperature and continued to increase over 2.5 h at room temperature although the peak corresponding to vinylstannane **3** remained constant and no cyclized products **2** were detected during this interval. Several other minor products were also detected by GC but have not been identified. It is thus tentitavely proposed that the source of this initially formed tributyltin bromide is either Pd mediated[2-3] or free radical[4-7] mechanisms leading to scission of the Ar-Br bond of some side-products initially formed in the reaction. Since the vinylstannane intermediates **3** did not seem to be affected by these processes, limiting the reaction time at room temperature should have no effect on the yield of the desired cyclization products **2**.



Scheme 3

Shortly after the initiation of refluxing, the peak corresponding to cyclized products **2** began to grow, the tributyltin bromide peak increased and the vinylstannane peak correspondingly diminished. Within 3 h, the formation of **2** leveled off to a maximum of 67% yield. Extended refluxing for 19 h revealed no significant loss of product, indicating that prolonged heating is not a factor of lower yields under these conditions.

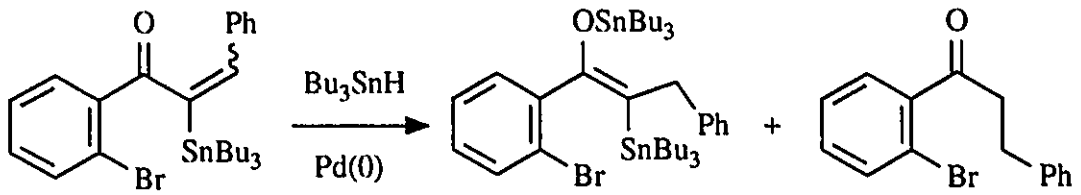
In the course of routine preparation of **2**, it was noticed that lower yields frequently corresponded to incomplete addition of tributyltin hydride to the acetylene, as judged by lack of complete disappearance of the 2200 cm^{-1} peak. This may have been attributable to the competing conversion of tributyltin hydride to hexabutyldistannane and hydrogen catalyzed by metals such as soluble Pd(0)[8] (Scheme 4).

Scheme 4

However, when the reaction was carried out in a flask sealed with a septum and equiped with a syringe to measure gas evolution, no significant amount of gas other than that expected from the reduction of the palladium catalyst was observed. Nevertheless, it is possible that trace quantities of precipitated metals in the catalyst or in the equipment used could cause accelerated decomposition of tributyltin hydride on occasion. This speculation is supported by the frequent observation of bubbling in a syringe containing tributyltin hydride.

In an attempt to compete with this decompostion when it occurs, effects of excess tributyltin hydride were examined. Thus the amount of tributyltin hydride was increased

to 2.1 eq. After 20 min at room temperature, the peak corresponding to the vinylstannanes **3** was reduced to one third compared to the control experiment. The yield of cyclized material after 60 min refluxing was reduced by a similar amount to 21%. These results are assumed to be due at least in part to hydrostannation of vinylstannanes **3** to the stannyl ethers **5**, which are expected to hydrolyse to the reduced compound **6**[9-12] (Scheme 5). No attempt was made to identify **5** or **6** in this reaction.



3 **5** **6**

Scheme 5

When the reaction was carried out at 0°C for 2.5 h followed by refluxing for 1 h a slightly lower yield (49%) was obtained. Addition of the radical inhibitor DTBP had no significant effect on yield (59%). Very slow addition of tributyltin hydride (over 20 min) tended to lower yields considerably (<30%) whereas adding the palladium catalyst to the solution with pre-mixed tributyltin hydride and DTBP gave results identical to rapid addition of tributyltin hydride.

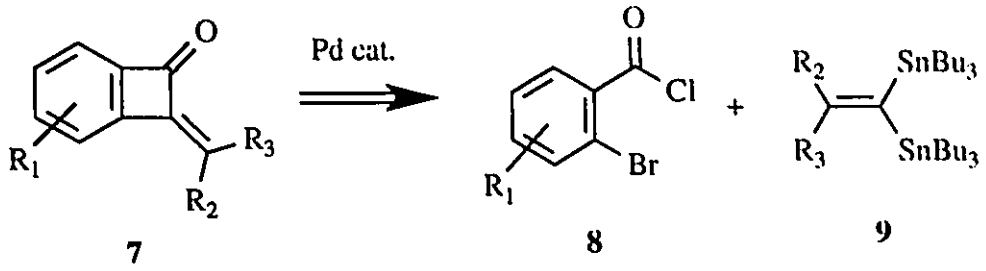
Conclusion

Thus, despite an increased appreciation of the factors which affect the yield of **2**, scale-up reactions were still largely unsatisfactory. Nevertheless, enough has been learned concerning the reaction profile to illuminate more promising approaches towards optimization. Specifically, a key factor determining the overall yield of cyclization product seems to be competition of the hydrostannation step with other side reactions. Perhaps a greater specificity could be obtained at much lower temperatures or in different solvents or different ligands in coordination with the palladium catalyst.

OTHER APPROACHES TO BENZYLIDENEBENZOCYCLOBUTENES

Double Stille Coupling

Due to the interesting reactivity and potentially useful synthetic applications of methylenebenzocyclobutenones **7**, other methods were sought to generate them. One potentially more general strategy involves a double Stille coupling using a geminally disubstituted vinyldistannane such as **9** and a suitably substituted aryl substrate (Scheme 6). Since Stille[13] had already reported that acyl chlorides couple readily with organostannanes in the presence of a palladium catalyst, 2-bromobenzoyl chlorides **8** and vinyldistannanes **9** were considered promising coupling partners.

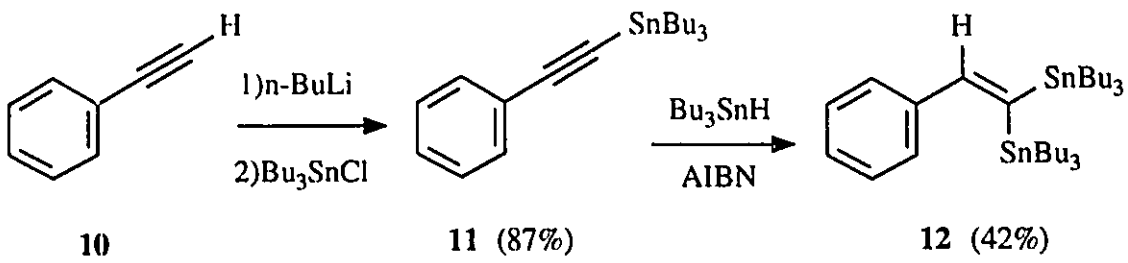


7 **8** **9**

Scheme 6

Results

The required bis(stannyl)styrene **12** was prepared in two steps from phenylacetylene **10** (Scheme 7). The first step involves formation of phenylacetylide anion followed by reaction with tributyltin chloride to obtain the stannylacetylene **11** in 87% yield. It was found to be more convenient to add a slight excess of phenylacetylene relative to n-BuLi to prevent formation of tetrabutyltin. Although **11** can be distilled (0.08 torr/ 140°C), it is difficult to prevent contamination by tetrabutyltin during the distillation. Stannylacetylene **11** was characterized by MS (all for ^{120}Sn): 335 (M^+-Bu), 278 (M^+- 2Bu + H), 221 (M^+-3Bu). As is typical for all tributyltin compounds studied in this project, the molecular ion peak is not observed, since it loses readily one butyl group in the mass spectrometer. ^1H NMR for **11**: δ 0.7-1.8 (m, 27H, $SnBu_3$), 7.24 (m, 3H), 7.42 (m, 2H); IR: 2132 cm^{-1}(C≡C).



10 **11** (87%) **12** (42%)

Scheme 7

The second step was achieved by free radical addition of tributyltin hydride to stannylacetylene **11**, initiated by AIBN. The bis(stannyl)styrene **12** obtained proved to be quite difficult to purify. Distillation occured at 0.1-0.2 torr/190-210°C but led to significant decompostion, especially if a careful fractional distillation was attempted. Due to the extremely non-polar nature of these compounds, attempted separation on silica gel in pure hexanes was unsuccessful, since the components all had R_f's near 1. Reverse phase silica gel separations were also attempted in numerous solvent systems ($MeOH/H_2O/MeCN/EtOH$) without success. Thus, for analytical determinations the purest distillation fraction was used. It was judged to be 70% pure by ^1H NMR integration of the vinylic hydrogen with diphenylacetic acid as internal standard. The major single contaminant was the stannylacetylene **11** (about 12% by GC).

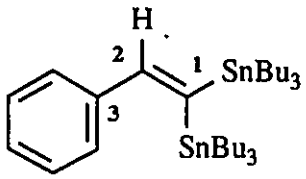
The mass spectrum of **12** showed a peaks at 624 (M^+-Bu) and 567 (M^+-2Bu) in a complex isotopic distribution pattern corresponding to various combinations of two tin isotopes. The ^1H NMR of **12** had the following resonances: δ 7.86 (s, J_{Sn-H}= 100, 176 Hz, 1H, vinyl), 7.2 (m, 5H), 0.6-1.7 (m, 54H, $SnBu_3$). The Sn-H couplings of 100 and 176 Hz are attributable to the cis and trans couplings, respectively. These couplings are much larger than for monostannylated alkenes which is attributable to the electropositive nature of the additional tin substituent.[14] In order to assign unambiguously the regiochemistry of tributyltin hydride addition, a DEPT experiment was carried out, yielding the following ^{13}C NMR data: δ 10.6 (CH_2), 11.8 (CH_2), 13.6 (CH_3), 13.7 (CH_3), 27.39 (CH_2), 27.43 (CH_2), 126.9 (CH, Ar), 127.0 (2 x CH, Ar), 127.9 (2 x CH, Ar), 144.0 (q, $^3J_{Sn-C}$= 48, 83

Hz, Ar), 150.9 (q, $^{1}J_{Sn-C}$= 214, 220 Hz, vinyl), 156.6 (CH, $^{2}J_{Sn-C}$= 15, 30 Hz). The two unaccounted methylene units are presumably located at fields higher than -5 ppm and were thus not observed in the ^{13}C NMR window taken.

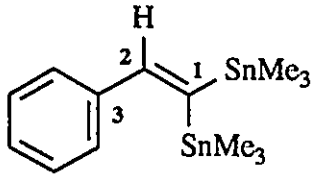
In addition both ^{117}Sn and ^{119}Sn NMR spectra were aquired and revealed the following shifts (relative to tetramethyltin): ^{117}Sn δ -17.3, -42.6; ^{119}Sn δ -20.8, -46.1. Combining the information obtained from these spectra allows for the assignment of the following coupling constants: ^{117}Sn-^{117}Sn (385 Hz); ^{119}Sn-^{119}Sn (400 Hz); ^{117}Sn-^{119}Sn (382 Hz). Homonuclear couplings in these spectra were identified by the AB system produced; heteronuclear couplings appeared as simple doublets symmetric about the major peak. Salient spectral data for **12** are summarized in Table 1, with comparisons to the reported corresponding values for the bis(trimethylstannyl) analog **13**.[15] Although there is good qualitative agreement between the two sets of data, it is interesting to note significant quantitative differences between trimethyl- and tributylstannyl analogs.

Table 1: Selected spectral data of vinyldistannanes

parameter	12	13
C(1) (ppm) C(2) (ppm) C(3) (ppm)	150.9 156.6 144.0	150.8 155.6 143.1
$^{1}J_{Sn\text{-}C(1)}$ (Hz)	220	404
$^{2}J_{Sn\text{-}C(2)}$ (Hz)	30	26
$^{3}J_{Sn\text{-}C(3)}$ (Hz)	48,83	55,100
^{119}Sn (ppm)	-20.8 -46.1	-9.6 -38.0
$^{2}J(^{119}Sn\text{-}^{119}Sn)$(Hz)	400	580

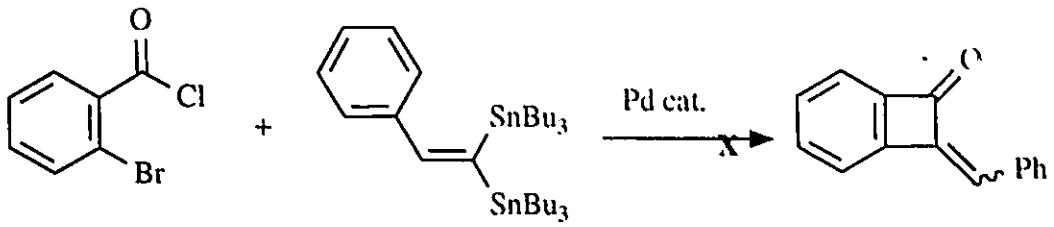


12



13

The reaction between 2-bromobenzoyl chloride **14** and vinyldistannane **12** in refluxing toluene with $Pd(PPh_3)_4$ was monitored by GC (Scheme 8). The reaction was quite sluggish, requiring 41 h for the disappearance of starting materials. The major products observed by GC-MS were tributyltin bromide and tributyltin chloride, indicating that some type of coupling had occured at both the acyl and aryl positions. However, no benzylidenebenzocylobutenones **2** were detected. Other catalysts such as $Pd(AsPh_3)_2Cl_2$, $Pd(PCy_3)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ were substituted without success.



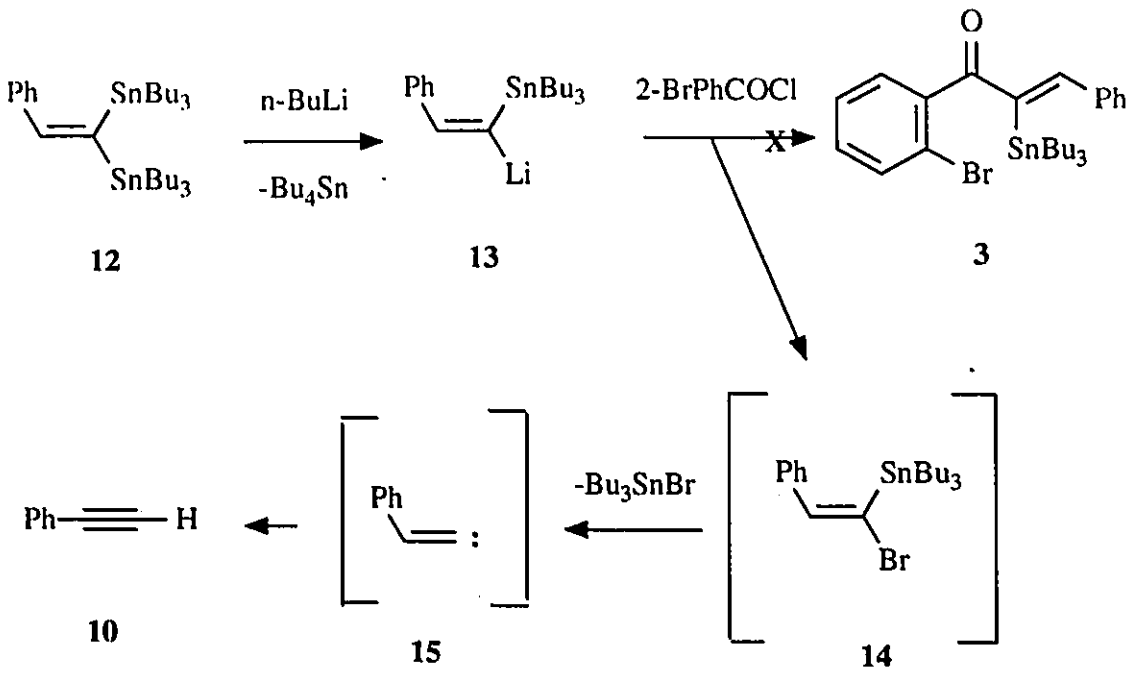
14 **12** **2**

Scheme 8

Since the trimethylstannyl analog **13** was shown[16] to undergo a double Stille coupling reaction with allyl bromide, it is possible that the greater steric bulk of the tributylstannyl groups excessively hindered the reactivity of **12**. Support for this hypothesis is the observation[16] that the stannylsilyl derivative $PhCH=C(SiMe_3)(SnMe_3)$ did not undergo the expected Stille coupling with allyl bromide, presumably due to steric inhibition.

Another approach in utilizing bis(stannyl)alkenes to prepare benzocylobutenes was then attempted involving the transmetallation[17-20] of one stannyl group with lithium by treatment with n-BuLi, followed by condensation with an appropriately substituted electrophile and subsequent cyclization with a palladium catalyst.

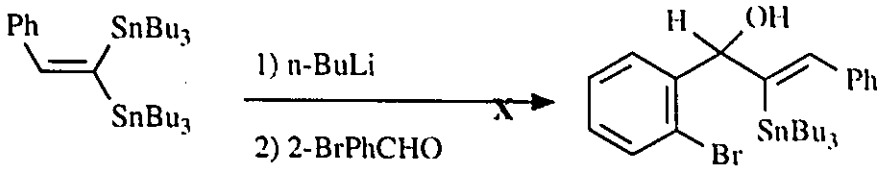
Thus, treatment of **12** at -78°C with 2 eq n-BuLi generated a brownish-orange color, probably indicative of formation of organolithium species **16**. Quenching with 3 equivalents of 2-bromobenzoyl chloride at -78°C discharged the color within a few minutes. GC and GC-MS analysis of the mixture indicated that metal exchange had occurred by the presence of tetrabutyltin and the near complete disappearance of vinyldistannane **12**. IR analysis did not reveal the expected carbonyl stretch at 1640 cm^{-1} previously assigned to vinylstannane **3**. In addition, filtering and evaporation of the solution followed by refluxing in toluene with $Pd(PPh_3)_4$ did not yield any of the cyclized compound **2**, expected if vinylstannane **3** had been formed.



Scheme 9

The GC-MS chromatogram also detected the formation of tributyltin bromide, which might be expected to form via metal-halogen exchange to stannylbromide **14** followed by elimination[1,21] to carbene **15** and rearrangement to phenylacetylene **10**. Although **10** was detected by GC-MS, it could also have formed from the stannylacetylene **11**, present as an impurity in the starting material. It is possible that the steric crowding of the tributyltin group in vinyllithium **13** significantly favors metal-halogen exchange over nucleophilic behaviour,[20] which is responsible for the failure of this reaction.

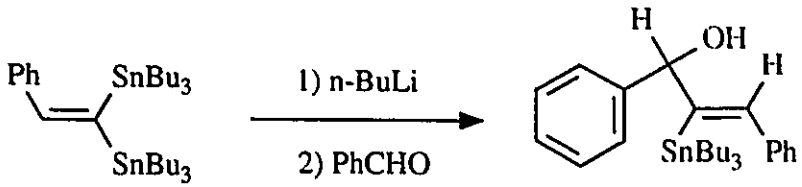
Similarily, quenching with o-bromobenzaldehyde did not yield any alcohol **16**, as judged by comparison of the crude ^{1}H NMR spectrum with that of previously prepared **16**[22] (Scheme 10).



12 **16**

Scheme 10

In order to determine whether the presence of the aryl bromine played a key role in the failure of the previous reactions, benzaldehyde was used as the quenching agent (Scheme 11). In this case, alcohol **17** was isolated in 30% yield. Its structure is supported by the ^{1}H NMR data: δ 0.7-1.3 (m, 27H, $SnBu_3$), 2.04 (d, J=4.1 Hz, 1H, OH), 5.46 (d, J= 3.9 Hz, J_{Sn-H}= 46 Hz, 1H, allylic), 7.2-7.4 (m, 10H, aryl), 7.50 (s, J_{Sn-H}= 120 Hz, trans vinylic). Thus, this result supports the hypothesis that metal-halogen side reactions may be responsible for the failure of the previous reactions.

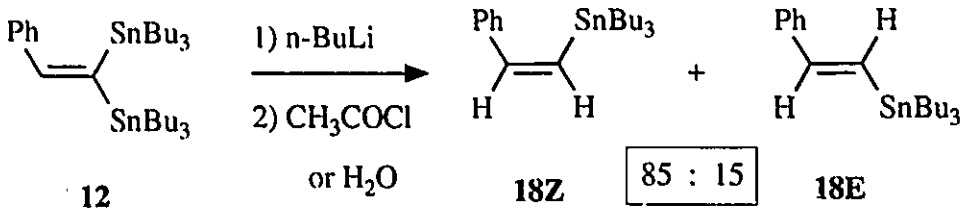


12 **17** (30%)

Scheme 11

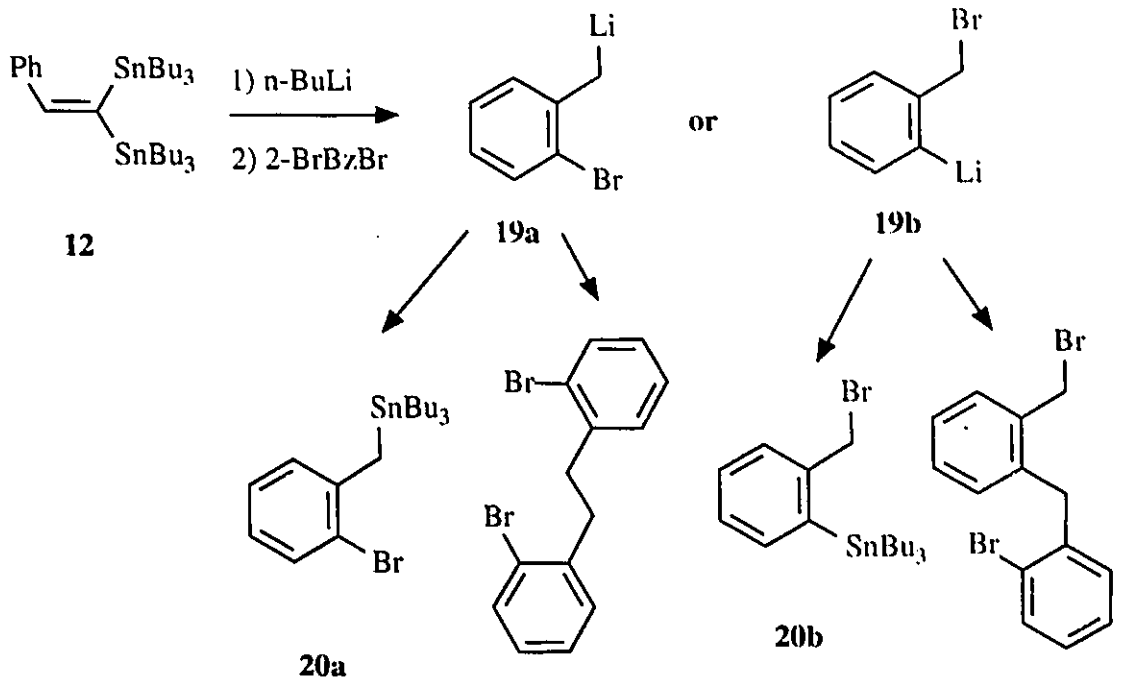
Attempts to trap anion **13** with acetyl chloride yielded mainly vinylstannane **18Z**, as judged by ^{1}H NMR (Scheme 12). The stereochemistry was assigned based on the Sn-H couplings. The hydrogen alpha to the stannyl group was located at δ 6.17 (d, J = 13.7 Hz, $^2J_{Sn-H}$= 60 Hz), with a typical[15] value for geminal coupling. The hydrogen beta to the stannyl group showed a typical[14] trans Sn-H coupling: δ 7.62 (d, 13.7 Hz, $^3J_{Sn-H}$= 120 Hz). In addition the GC-MS showed two peaks with identical cleavage patterns corresponding to **18Z** and **18E**: 337 (M^+-Bu). The ratio of the two peaks as acertained by GC was 85:15, corresponding to the ratio of **18Z** to **18E**. The same ratio was obtained by quenching with water. This is consistent with metal-halogen exchange taking place preferentially from

the less hindered side of **12**, with little or no inversion of **13** at -78°C. This behaviour of course reflects an increase of basicity at the expense of nucleophilicity incurred by the steric importance of the tributyltin group. Thus ketene is a presumed by-product of the reaction with acetyl chloride. Similar difficulties have previously been encoutered with sterically encumbered nucleophiles and enolizable electrophiles.[20]



Scheme 12

Finally, 2-bromobenzylbromide was used as the quenching agent (Scheme 13). GC-MS revealed two major peaks attributable to stannanes **20a** or **20b** (m/e 403, M^+-Bu) and a dibromo product **21a** or **21b** (m/e 340, M^+). These would result from coupling of the lithio derivatives **19a** and **19b** with tributyltin bromide and 2-bromobenzyl bromide, respectively. The formation of these transmetallated intermediates as well as tributyltin bromide is postulated to proceed via a mechanism similar to that proposed previously.(see Scheme 9)



Scheme 13

Conclusion

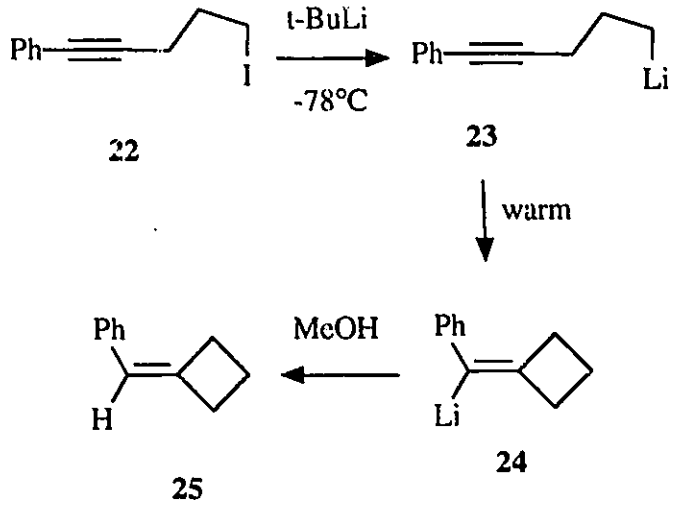
Due to serious difficulties in purification and the ready propensity of vinyldistannane **12** to polymerize as a white insoluble precicipate after several weeks storage, the synthetic strategy of using terminally disubstituted vinyldistannanes to prepare benzocyclobutenes was abandoned. The overall disappointing results using either a double Stille coupling strategy or a sequential metal exchange/Stille coupling protocol further discourage this approach.

Miscellaneous Approaches

Anionic Cyclization

Always being in search of alternate methods to generate benzocyclobutenes, we were quite interested in a recent report by Bailey *et al*[23] in which benzylidenecyclobutane

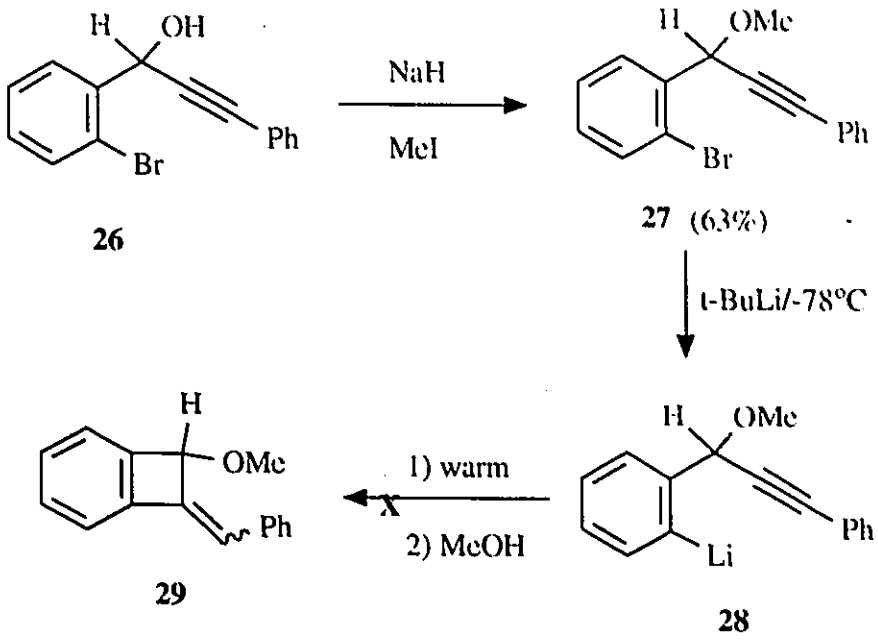
25 was obtained by a 4-exo-dig anionic cyclization of intermediate **23** to vinyllithium **24**, prepared by metal-halogen exchange of alkyl iodide **22** (Scheme 14). Interestingly, the method was only successful for the phenyl analog.



Scheme 14

Results

It was obvious that such an approach could yield a much more convenient method of generating benzylidenebenzocyclobutenes. The substrate chosen was methoxy acetylene **27**, obtained in 63% yield by treating the alcohol **26** with sodium hydride and methyl iodide in THF. ^{1}H NMR for **27**: δ 3.54 (s, 3H, OCH_3), 5.59 (s, 1H, CHOMe), 7.1-7.7 (m, 9H). Treatment of **27** with t-BuLi in 3:2 n-pentane/ether at -78°C presumably generated the lithiated derivative **28** (Scheme 15). The mixture was then warmed to room temperature and quenched with methanol. The crude ^{1}H NMR spectrum did not display the expected pair of singlets at *ca.* 5.5 and 6.5 ppm corresponding to the vinylic and benzylic hydrogens of methoxybenzocyclobutene **29**. Instead, a complex mixture was obtained, as evidenced by multiple methoxy peaks in the 3-4 ppm region.



26 **27** (63%) **29** **28**

Scheme 15

In a previous study[24] on a similar type of reaction involving a heteroatom linker between the aromatic ring and the acetylene functionality, only 5-endo-dig cyclization of **30** to **31** was observed (Scheme 16). In these cases the presence of the heteroatom may have played a role in directing the cyclization pathway. However, a fixed angle of 120° in the aryllithium substrates such as **28** and **30** as opposed to the smaller 108° angle in alkyllithium **23** may be severely detrimental to attaining a suitable geometry for 4-exo-dig cyclization.

30 **31**

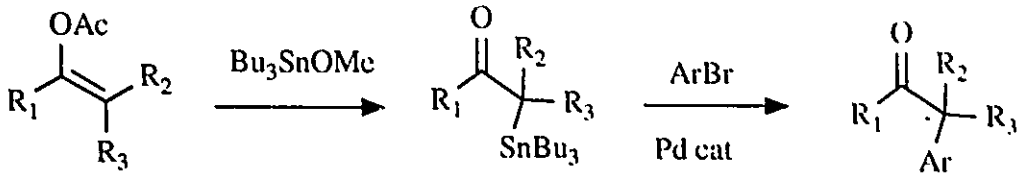
X= O,S,NMe

Scheme 16

Enol Acetate approach

Another potentially simple approach to the preparation of benzocyclobutenes was

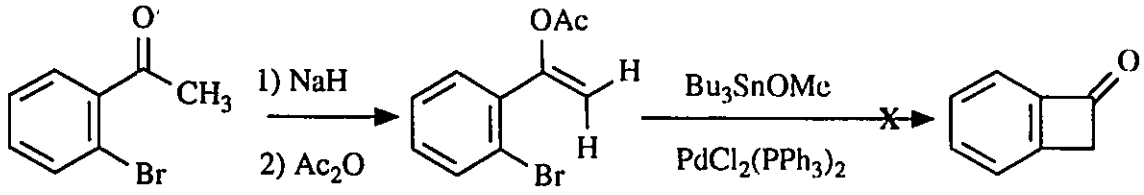
suggested by the work of Migita,[25] who devised a procedure for the conversion of enol acetates to α-arylketones (Scheme 17). This method involves treatment of the enol acetate **32** with tributyltin methoxide, which generates a ketostannane intermediate **33**. Presence of a palladium catalyst in the mixture then effects a Stille coupling with an aryl bromide to the α-arylketone **34**.



32 **33** **34**

Scheme 17

We thus attempted an intramolecular version of this coupling by first preparing the enol acetate **36** from 2'-bromoacetophenone **35**. This was accomplished in 67% yield by treatment with NaH followed by acetic anhydride. ^{1}H NMR for **36**: δ 2.13 (s, 3H, $OCOCH_3$), 5.13 (d, J = 1.8 Hz, 1H, vinylic), 5.23 (d, J = 1.8 Hz, 1H, vinylic), 7.2-7.6 (m, 4H). IR 1760 cm^{-1} (OAc). Other methods were much less effective: isopropenyl acetate/p-TsOH[26] (14%); acetic anhydride/pyridine (<5%); acetic anhydride/p-TsOH[26] (41%).



35 **36** (93%) **37**

Scheme 18

Refluxing a toluene solution of tributyltin methoxide and enol acetate **36** in the presence of $PdCl_2(PPh_3)_2$ for 3 h led to the formation of tributyltin bromide, as determined by GC-MS. This indicates that some form of coupling had occured. However, an IR

spectrum revealed only a very weak peak at 1780 cm^{-1} which could correspond to benzocyclobutenone **37**.[27] Refluxing for an additional 8h led to disappearance of the 1780 cm^{-1} peak. ^1H NMR and TLC indicated that a complex mixture of products had formed. It is possible that **46** was indeed formed but was unstable under these conditions.

CONCLUSION

Results from the optimization study and the various attempts at alternate preparation of the title compounds **2** did not lead to large scale access to these compounds or their derivatives. However, for the mechanistic and exploratory studies which follow reliable small scale preparations were satisfactory and thus no further attempts at scaling up or finding alternative preparative routes were investigated.

EXPERIMENTAL

General: Same as specified in Chapter 2. A Varian 3400 GC was used with OV-17 packing. The initial column temperature was set at 100°C followed by ramping up to 285°C at 20°C/min immediately after injection of the sample. ^{117}Sn and ^{119}Sn NMR spectra were obtained on a Varian XL-300 spectrometer with tetramethyltin as reference.

Preparation of 1: see preparation of **41** in Chapter 2.

Typical procedure for optimization experiments: Tributyltin hydride (0.42 mL, 1.57 mmol, 1.1 eq.) was added to 12 mL of a 0.12 M toluene solution of alkynone **1** (408 mg, 1.43 mmol, 1 eq.) with $PdCl_2(PPh_3)_2$(50 mg, 0.071 mmol, 0.05 eq) and PPh_3(37 mg, 0.14 mmol, 0.10 eq) over a few seconds. The progress of the reaction was then monitored by taking 100 µL aliquots of the reaction mixture, filtering these through a Pasteur pipette plug of silica gel (0.5 g, 230-400 mesh) followed by elution with 2 mL of ethyl acetate. This was done in order to prevent metal contamination of the GC column. One equivalent of naphthalene (100 µL from a 0.12 M ethyl acetate solution) was then added to the eluted aliquot and the resulting sample was analysed by GC. Absolute yields for **2** were obtained by prior GC calibration of pure compound against naphthalene. The amounts of **3** (based on the combined integration of **4E** and **4Z**) and Bu_3SnBr reported were not calibrated and thus only represent relative change during the course of the reaction. The products reported were identified by their GC-MS cleavage patterns:

Bu_3SnCl: (m/e, int) 269 (100, M^+-Bu for ^{120}Sn and ^{35}Cl), 213 (58, M^+- 2Bu + H for ^{120}Sn and ^{35}Cl), 177 (50, M^+- 2 Bu - Cl for ^{120}Sn), 155 (44, M^+- 3 Bu for ^{120}Sn and ^{35}Cl), 57 (88, Bu^+).

Bu_3SnBr: (m/e, int) 313 (100, M^+-Bu for ^{120}Sn and ^{79}Br), 257 (58, M^+- 2Bu + H for ^{120}Sn and ^{79}Br), 199 (44, M^+- 3 Bu for ^{120}Sn and ^{79}Br), 177 (36, M^+- 2 Bu - Br for ^{120}Sn), 57 (64, Bu^+).

4E or **4Z**: (m/e, int) 288 (57, M^+ for ^{81}Br), 287 (79, M^+-H for ^{81}Br), 286 (57, M^+ for ^{79}Br), 285 (73, M^+ for ^{79}Br), 131 (100, M^+-PhBr), 103 (82, M^+-PhBr-CO), 77 (63, Ph^+).

Preparation of 11: To a solution of phenylacetylene (5.05 g, 49.5 mmol) in 100 mL of THF at -78°C was added n-BuLi (2.3 M in hexanes, 19.4 mL, 44.6 mmol) over 20 min. The resulting solution was stirred at -78°C for a further 20 min then tributyltin chloride (13.4 mL, 49.5 mmol) was added over 5 min. The reaction mixture was allowed to warm to rt, stirred overnight then partitioned between 150 mL of CH_2Cl_2 and 50 mL of water. The organic phase was washed with 50 mL of brine then dried over $MgSO_4$. The solvents were evaported and the residue distilled at 0.08 torr/140°C to yield **11** (16.95 g, 87% yield) as a colorless oil: ^{1}H NMR δ 0.7-1.8 (m, 27H, $SnBu_3$), 7.24 (m, 3H), 7.42 (m, 2H); IR (CH_2Cl_2, cm^{-1}) 2132 (C≡C). MS (m/e, int) 335 (100, M^+-Bu for ^{120}Sn), 279 (54, M^+-2 Bu + H for ^{120}Sn), 221 (99, M^+- 3 Bu for ^{120}Sn).

Preparation of 12: A mixture of **11** (0.70 g, 1.43 mmol), tributyltin hydride (0.70 mL, 2.6 mmol) and azabis(isobutyronitrile) (50 mg) was heated in an oil bath for 21h. The reaction mixture was then distilled under reduced pressure yielding the purest fraction of **12** at 0.1-0.2 torr/190-210C: 0.58g (70% pure by GC and ^{1}H NMR with diphenylacetic acid as internal standard, 0.60 mmol, 42% yield): ^{1}H NMR δ 7.86 (s, J_{Sn-H}= 100, 176 Hz, 1H, vinyl), 7.2 (m, 5H), 0.6-1.7 (m, 54H, $SnBu_3$); ^{13}C NMR (DEPT) δ 10.6 (CH_2), 11.8 (CH_2), 13.6 (CH_3), 13.7 (CH_3), 27.39 (CH_2), 27.43 (CH_2), 126.9 (CH, Ar), 127.0 (2 x CH, Ar), 127.9 (2 x CH, Ar), 144.0 (q, $^3J_{Sn-C}$= 48, 83 Hz, Ar), 150.9 (q, $^1J_{Sn-C}$= 214, 220 Hz, vinyl), 156.6 (CH, $^2J_{Sn-C}$= 15, 30 Hz); MS (m/e, int) 624 (41, M^+-Bu) and 567 (10, M^+-2Bu). ^{117}Sn NMR δ -17.3, -42.6; ^{119}Sn NMR δ -20.8, -46.1; the following couplings were obtained from a combination of the ^{117}Sn and ^{119}Sn spectra: ^{117}Sn-^{117}Sn (385 Hz); ^{119}Sn-^{119}Sn (400 Hz); ^{117}Sn-^{119}Sn (382 Hz).

Preparation of 14: see preparation of **40** in Chapter 2.

Attempted Coupling of 12 and 14: A solution of **12** (97.7 mg, 0.14 mmol), **14** (38.3 mg, 0.17 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.0095 mmol) was refluxed under N_2. After 17 h, a GC sample revealed the presence of significant amounts of starting materials. After 41 h, GC analysis showed consumption of starting materials with the formation of two major peaks, identified by GC-MS as tributyltin chloride and tributyltin bromide in

approximately a 2:1 ratio. GC-MS also indicated the absence of **2**.

Coupling of transmetallated 12 with 2-bromobenzoyl chloride: To a solution of **12** (447 mg, 0.46 mmol) in 5 mL of THF at -78°C was added n-BuLi (2.44 M in hexanes, 0.34 mL, 0.83 mmol). The brownish-orange solution which formed was stirred for 2.5 h at -78C, quenched with 2-bromobenzoyl chloride (0.15 mL, 1.29 mmol), which discharged the color. The reaction mixture was stirred at -78°C for a further 1.5 h then partitioned between saturated aqueous $NaHCO_3$ and ether. The organic phase was dried over $MgSO_4$ and the solvents evaporated to yield an oily residue. Analysis of the crude reaction mixture by GC indicated almost complete disappearance of vinyldistannane **12** and the formation of tetrabutyltin (GC-MS (m/e, int) 291 (50, M^+-Bu for ^{120}Sn), 235 (90, M^+- 2 Bu + H for ^{120}Sn), 177 (100, M^+- 3 Bu for ^{120}Sn)). Also detected in significant amounts were tributyltin bromide and phenylacetylene (GC-MS (m/e, int) 102 (100, M^+). IR analysis did not reveal the expected carbonyl stretch at 1640 cm^{-1} previously assigned to vinylstannane **3**.

Coupling with 2-bromobenzaldehyde: The same procedure as above was used with 2-bromobenzaldehyde except that a saturated NH_4Cl solution was used in place of $NaHCO_3$. Comparison of the crude ^1H NMR spectrum with that of previously prepared **16**[22] indicated that no significant amount of this compound had formed.

Coupling with benzaldehyde: Qenching with benzaldehyde yielded alcohol **17** in 30% yield after chromatography with 1:1 hexanes/CH_2Cl_2 as eluent: ^1H NMR δ 0.7-1.3 (m, 27H, $SnBu_3$), 2.04 (d, J=4.1 Hz, 1H, OH), 5.46 (d, J= 3.9 Hz, J_{Sn-H}= 46 Hz, 1H, allylic), 7.2-7.4 (m, 10H, aryl), 7.50 (s, J_{Sn-H}= 120 Hz, trans vinylic).

Quenching with NH_4Cl: Using saturated aqueous NH_4Cl as the quenching agent followed by the usual work-up procedure gave a crude mixture with two peaks in the ^1H NMR characteristic of **18Z**: δ 6.17 (d, J = 13.7 Hz, $^2J_{Sn-H}$= 60 Hz) and 7.62 (d, 13.7 Hz, $^3J_{Sn-H}$= 120 Hz). The GC-MS showed two peaks with identical cleavage patterns corresponding to **18Z** and **18E**: (m/e, int) 337 (100, M^+-Bu for ^{120}Sn), 279 (35, M^+- 2 Bu - H for ^{120}Sn), 223 (61, M^+- 3 Bu for ^{120}Sn). The ratio of the two peaks as

acertained by GC was 85:15, corresponding to the ratio of **18Z** to **18E**.

Qenching with acetyl chloride: Using acetyl chloride as the quenching agent yielded results similar to the NH_4Cl quenching experiment except that the reaction was not as clean as judged by ^1H NMR and GC.

Coupling with 2-bromobenzyl bromide: With 2-bromobenzyl bromide as the quenching agent, GC-MS revealed two major peaks. One corresponded to stannane **20a** or **20b**: (m/e, int) 403 (64, M^+-Bu for ^{120}Sn and ^{79}Br), 347 (19, M^+- 2 Bu + H for ^{120}Sn and ^{79}Br), 291 (29, $Bu_3{}^{120}Sn^+$), 235 (65, $Bu_2{}^{120}SnH^+$), 199 (39,$^{120}Sn^{79}Br^+$), 179 (100, $Bu^{120}SnH_2{}^+$), 121 (42, $^{120}SnH^+$), 91 (54. Bn^+). The other peak corresponded to one of the dibromides **21a** or **21b**: (m/e, int) 342 (6, M^+ for $^{81}Br^{81}Br$), 340 (13, M^+ for $^{79}Br^{81}Br$), 338 (7, M^+ for $^{79}Br^{79}Br$), 261 (10, M^+-Br for ^{81}Br), 259 (10, M^+ for ^{79}Br), 171 (96, M^+- 2-BrBn for ^{81}Br), 169 (100, M^+- 2-BrBn for ^{79}Br), 90 (37, $C_7H_6{}^+$).

Preparation of 26: see preparation of **24** in Chapter 2.

Preparation of 27: A mixture of alcohol **26** (433 mg, 1.5 mmol), NaH (312 mg, 7.8 mmol) and MeI (2 mL) in 10 mL of THF was stirred at rt for 3h. The reaction mixture was then carefully quenched with saturated aqueous NH_4Cl and extracted with 3 x 30 mL of ether. The organic phases were combined, dried over $MgSO_4$, the solvents evaporated and the residue chromatographed with 1:1 hexanes/CH_2Cl_2 to yield the methoxy acetylene **27** (283 mg, 63% yield): ^1H NMR δ 3.54 (s, 3H, OCH_3), 5.59 (s, 1H, CHOMe), 7.1-7.7 (m, 9H).

Attempted anionic cyclization of 27: To a solution of **27** (84.6 mg, 0.28 mmol) in 4 mL of dry ether and 6 mL of pentane was added t-BuLi (1.7 M in hexanes, 0.62 mmol) at -78°C. The mixture was stirred at -78C for 20 min, allowed to warm to room temperature for 1 h then quenched with methanol. After work-up of the reaction mixture by the usual ether/water protocol, a ^1H NMR spectrum of the reaction mixture did not display the expected pair of singlets at *ca.* 5.5 and 6.5 ppm corresponding to the vinylic and benzylic hydrogens of methoxybenzocyclobutene **29**. Instead, a complex mixture was obtained, as evidenced by multiple methoxy peaks in the 3-4 ppm region.

Preparation of 36: To a solution of 2'-bromoacetophenone **35** (1.20 g, 6.03 mmol) in 10 mL of THF was added NaH (60% oil suspension, 384 mg, 12.8 mmol). The reaction mixture was stirred at rt for 40 min then added to 10 g of acetic anhydride. An aqueous $NaHCO_3$ solution was slowly added after 10 min followed by solid $NaHCO_3$ until gas evolution was subsiding. The mixture was left overnight then extracted with ether. The organic phase was washed with water (3x) then dried over $MgSO_4$. The solvents were removed under reduced pressure and the residue distilled at 2 torr/110°C to yield This was accomplished in 93% yield **36** (0.96 g, 4.0 mmol, 67% yield) as a colorless oil: ^{1}H NMR δ 2.13 (s, 3H, $OCOCH_3$), 5.13 (d, J = 1.8 Hz, 1H, vinylic), 5.23 (d, J = 1.8 Hz, 1H, vinylic), 7.2-7.6 (m, 4H); IR (CH_2Cl_2, cm^{-1}) 1760 (OAc).

Attempted cyclization of 36: A mixture of enol acetate **36** (276 mg, 1.15 mmol), tributyltin methoxide (330 µL, 1.15mmol), $PdCl_2(PPh_3)_2$ (86.7 mg, 0.12 mmol) in 5 mL of toluene was refluxed for 3 h. The formation of tributyltin bromide was indicated by GC-MS (after filtering through a small plug of silica gel with ethyl acetate as eluent to remove metals). An IR spectrum revealed only a very weak peak at 1780 cm^{-1}. Refluxing for an additional 8h led to disappearance of the 1780 cm^{-1} peak. ^{1}H NMR and TLC indicated that a complex mixture of products had formed.

REFERENCES

1. Zhang, H.X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, 55, 1857.

2. Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, 55, 4846.

3. Kalinin, V.N. *Synthesis* **1992**, 413.

4. Clark, A.; Jones, K. *Tetrahedron Lett.* **1989**, 30, 5485.

5. Curran, D.P. *Synthesis*, **1988**, 417.

6. Curran, D.P. *Synthesis*, **1988**, 489.

7. Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, 25, 2575.

8. Dangles, O.; Guibe, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, 52, 4984.

9. Keinan, E.; Gleize, P.A. *Tetrahedron Lett.* **1982**, 477.

10. Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, 1825.

11. Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, 48, 3545.

12. Yang, T.X.; Four, P.; Guibe, F.; Balavoine, G. *Nouv. J. Chim.* **1984**, 8, 611.

13. Labadie, J.W.; Stille, J.K. *J. Am. Chem. Soc.* **1983**, 105, 6129.

14. Leusink, A.J.; Budding, H.A.; Marsman, J.W. *J. Organometal. Chem.* **1967**, 9, 285.

15. Mitchell, T.N.; Amamria, A.; Fabisch, B. *J. Organometal. Chem.* **1983**, 259, 157.

16. Mitchell, T.N.; Reimann, W. *Organometallics* **1986**, 5, 1991.

17. Mitchell, T.N.; Reimann, W. *J. Organometal. Chem.* **1985**, 281, 163.

18. Amamria, A.; Mitchell, T.N. *J. Organometal. Chem.* **1981**, 210, C17.

19. Mitchell, T.N.; Reimann, W. *J. Organometal. Chem.* **1987**, 322, 141.

20. Mitchell, T.N.; Reimann, W. *J. Organometal. Chem.* **1987**, 322, 151.

21. Mitchell, T.N.; Amamria, A. *J. Organometal. Chem.* **1983**, 256, 37.

22. see compound **25** in Chapter 2.

23. Bailey, W.F.; Ovaska, T.V. *Tetrahedron Lett.* **1990**, 31, 627.

24. Johnson, F.; Subramanian, R. *J. Org. Chem.* **1986**, 51, 5041.

25. Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *J. Chem. Soc., Chem. Commun.* **1983**, 344.

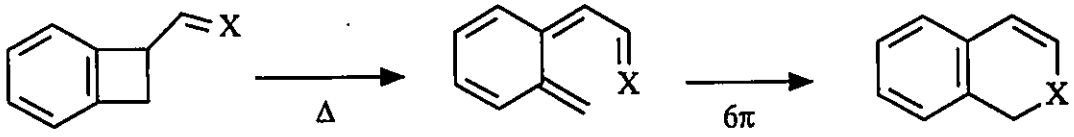
26. House, H.O.; Kramar, V. *J. Org. Chem.* **1963**, 28, 3362.

27. Cava, M.P.; Muth, K. *J. Am. Chem. Soc.* **1960**, 82, 652.

CHAPTER 4: ATTEMPTS AT REGIOSELECTIVE ANTHRAQUINONE PREPARATIONS

Introduction

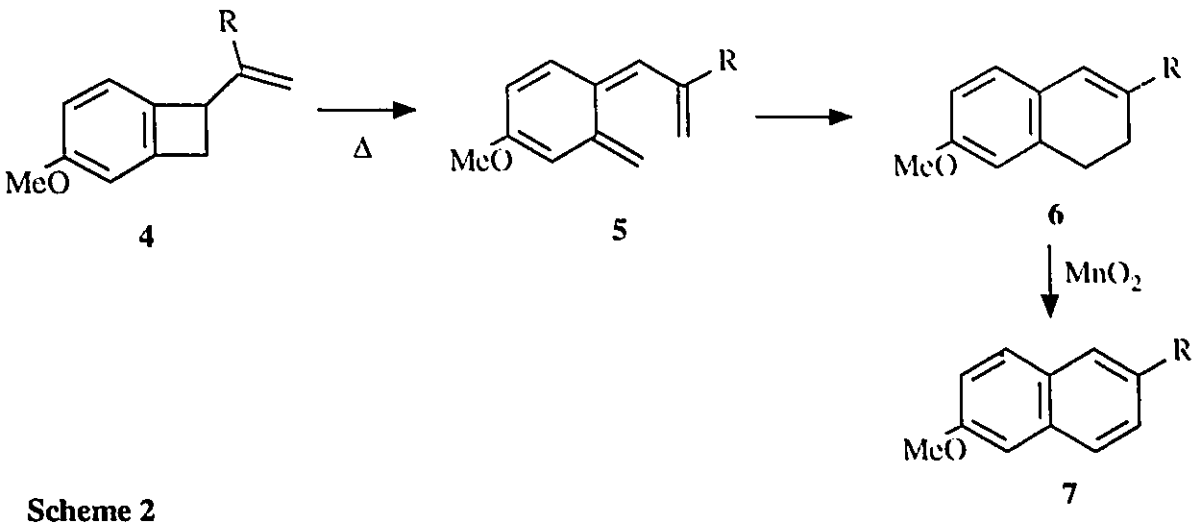
When an unsaturated linkage is directly attached to the cyclobutene ring in benzocyclobutenes such as **1**, thermal generation of the o-quinodimethane **2** is generally rapidly followed by 6π electrocyclic ring closure to **3**[1-6] (Scheme 1). This is often a very convenient way of generating naphtalene derivatives, as well as heterocycles. For example, in the synthesis of naproxen **7** (R = $CHMeCO_2H$), benzocyclobutenes such as **4** were thermolysed to the dihydronaphthalenes **6** via o-quinodimethanes **5**. Subsequent dehydrogenation with MnO_2 yielded the naphthalenes **7**[1] (Scheme 2). Thermolysis of oxime derivatives **8** generates isoquinolines **11** after cyclization of o-quinodimethane **9** and dehydration of intermediate **10**[2] (Scheme 3). By a judicious choice of substituents based on torquoselective ability, either a heterocyclic or carbon skeleton can be obtained. When the carboxylic acid **12a** is thermolysed, inward rotation of the carboxylic group to **13** is followed by cyclization to **14**, which then undergoes a [1,5] hydrogen shift to the alkylidene isochromanone **15** (Scheme 4). However, by simply esterifying the carboxylic functionality to **12b**, the opposite torquoselectivity is observed to generate o-quinodimethane **16**, which yields the dihydronaphtalenes **17**.[3]



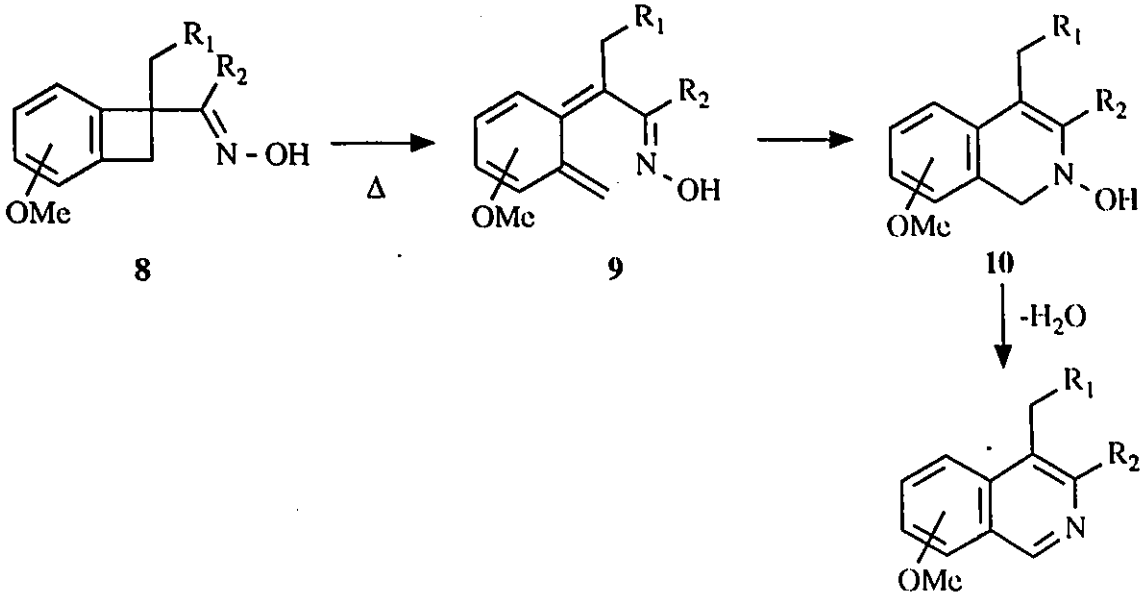
1 **2** **3**

X = CHR, NOH, O

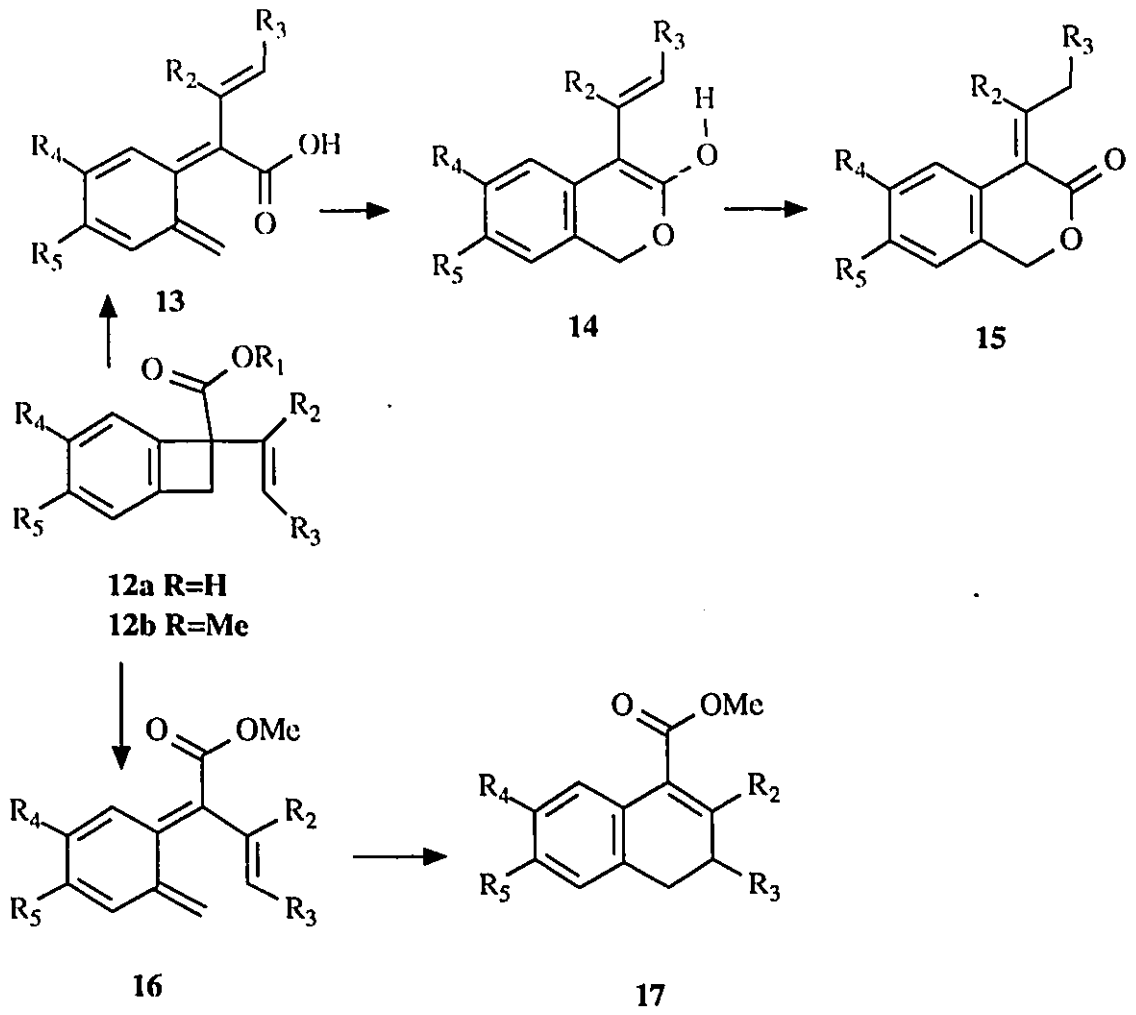
Scheme 1



Scheme 2

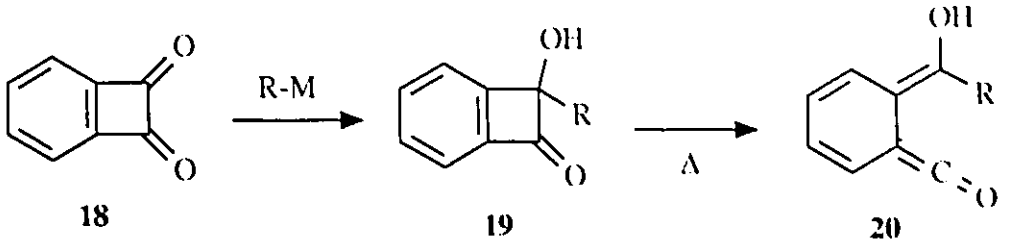


Scheme 3



Scheme 4

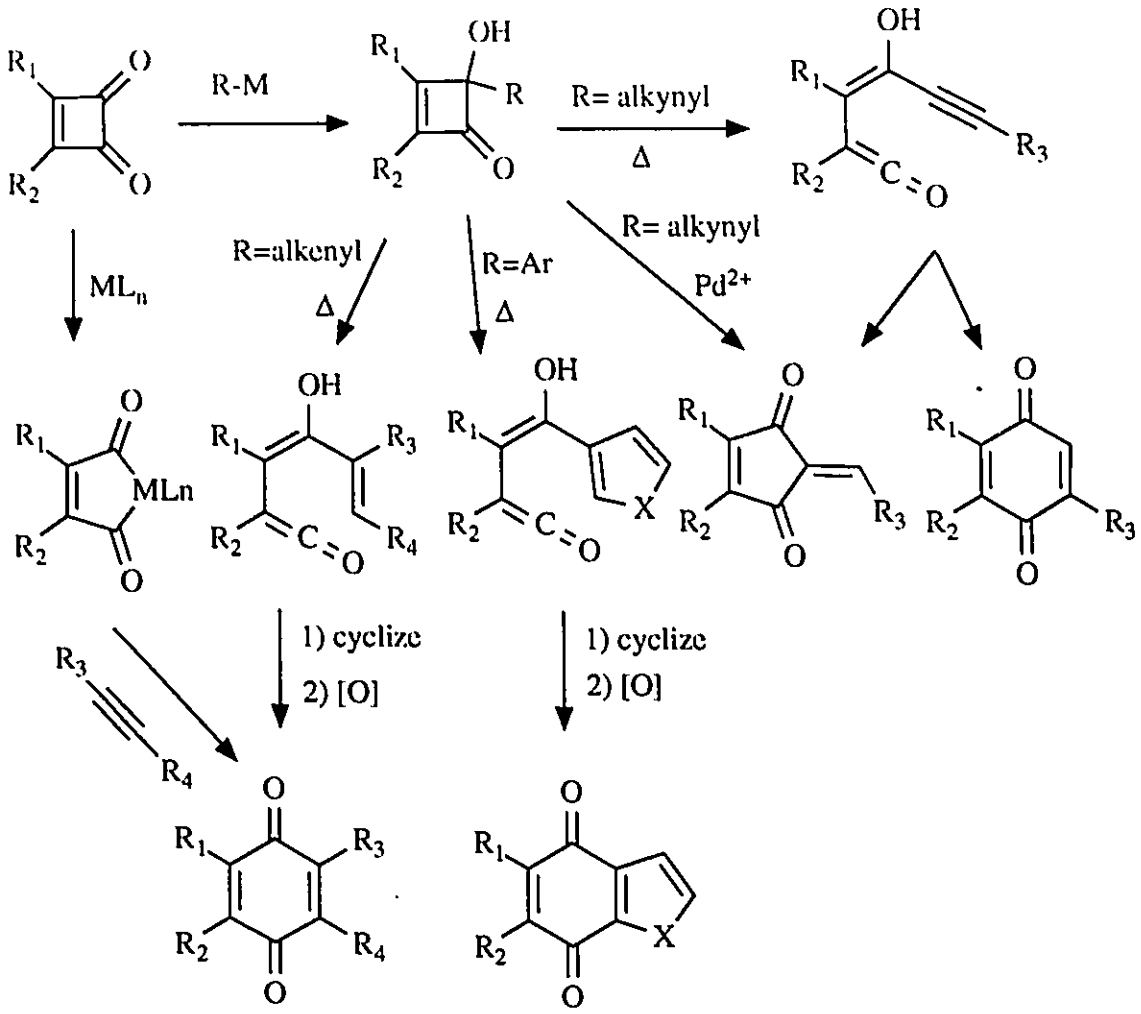
An important challenge of this electrocyclic cyclization strategy is the introduction of the unsaturated linkage to the cyclobutene ring. A powerful stategy for its introduction has been the condensation of organometallic reagents with benzocyclobutenedione derivatives **18** (Scheme 5). In addition to the convenience of this methodology, two other major advantages are gained. First, the resulting alcohols **19** usually open to the o-quinodimethanes **20** at lower temperatures, due to the activation energy lowering effect of the alcohol substituent. Second, due to the strong electon-donating capacity of oxygen, it will tend to rotate outward upon ring opening, thus forcing the unsaturated linkage to rotate inward and participate in the 6π electrocyclic ring closure.



18 **19** **20**

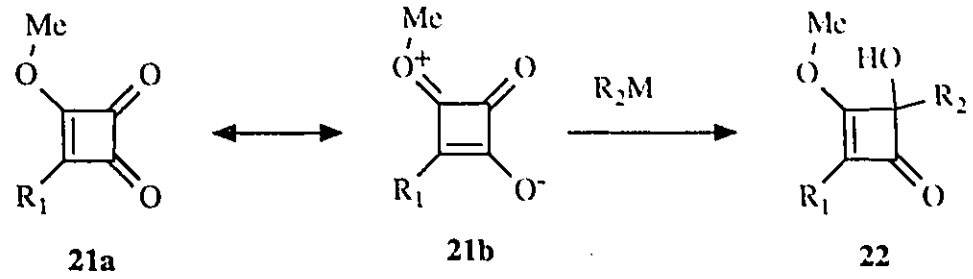
Scheme 5

Such a strategy has been thoroughly exploited for cyclobutenediones[7-8,23-30] and to a lesser extent for benzocyclobutenedione[7,19-22,25,31-32] derivatives by Moore and Liebeskind and has resulted in an effective synthesis of quinones and alkylidenediones. These precursors have proven to be a rich source for synthetic manipulations (Scheme 6). They yield not only quinones and alkylidenediones upon thermolysis[7-22] of alkenyl, aryl and alkynyl adducts, but metal mediated ring expansion[23-25] as well as metal insersion[25-32] of the dione precursors have greatly added to the synthetic versatility of these compounds.



Scheme 6

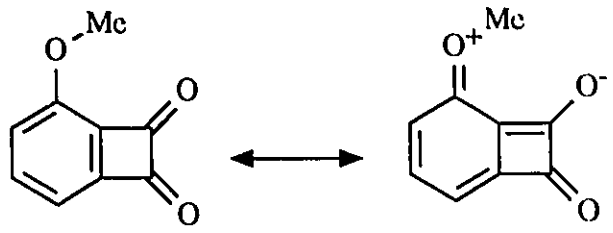
In order to prepare quinones regioselectively, the two carbonyls in the cyclobutenedione ring must be readily differentiable. This is usually straightforward for cyclobutenediones since the substituents on the ring can have a profound electronic effect on one of the carbonyls. For example, the methoxy substituent in **21** will render one carbonyl group much less susceptible to nucleophilic attack through the vinylogous conjugation in **21b** (Scheme 7). Treatment with a nucleophile will then afford adduct **22** regioselectively.[13]



21a **21b** **22**

Scheme 7

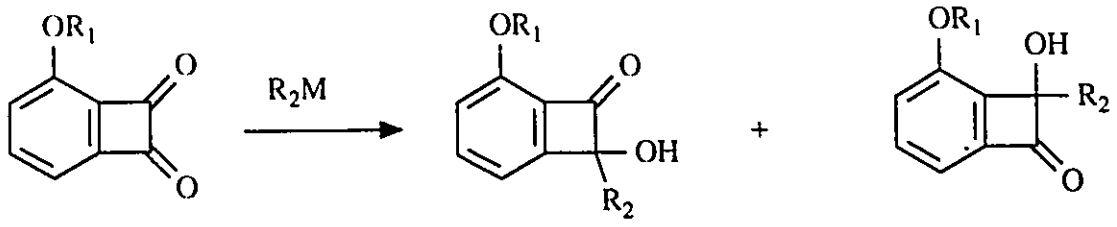
For benzocyclobutediones, substituents on the aromatic ring have a far smaller effect on the reactivity the carbonyl groups because of the disruption of aromaticity in resonance hybrids such as **23b**. In order to overcome the problem of regioselectivity, several approaches have been utilized and are illustrated below.



23a **23b**

1) Steric strategy

In studies directed towards acertaining the directing effect of a methoxy substituent, benzocyclobutenedione **24a** was treated with various aryl and alkynyl nucleophiles[19,20,22] (Scheme 8). It was found that the addition was regiospecific in favour of attack at the more electrophilic carbonyl, but in ratios that varied from 2:1 to 6.6:1. When the reaction was carried out at a lower temperature (-100°C), regioselectivity was greatly improved but at the cost of a significant decrease in yield. Introduction of a severely sterically demanding group such as TBDMS (**24b**) was successful in further encouraging attack at the farther removed carbonyl group to yield regioselectivities of > 20:1.



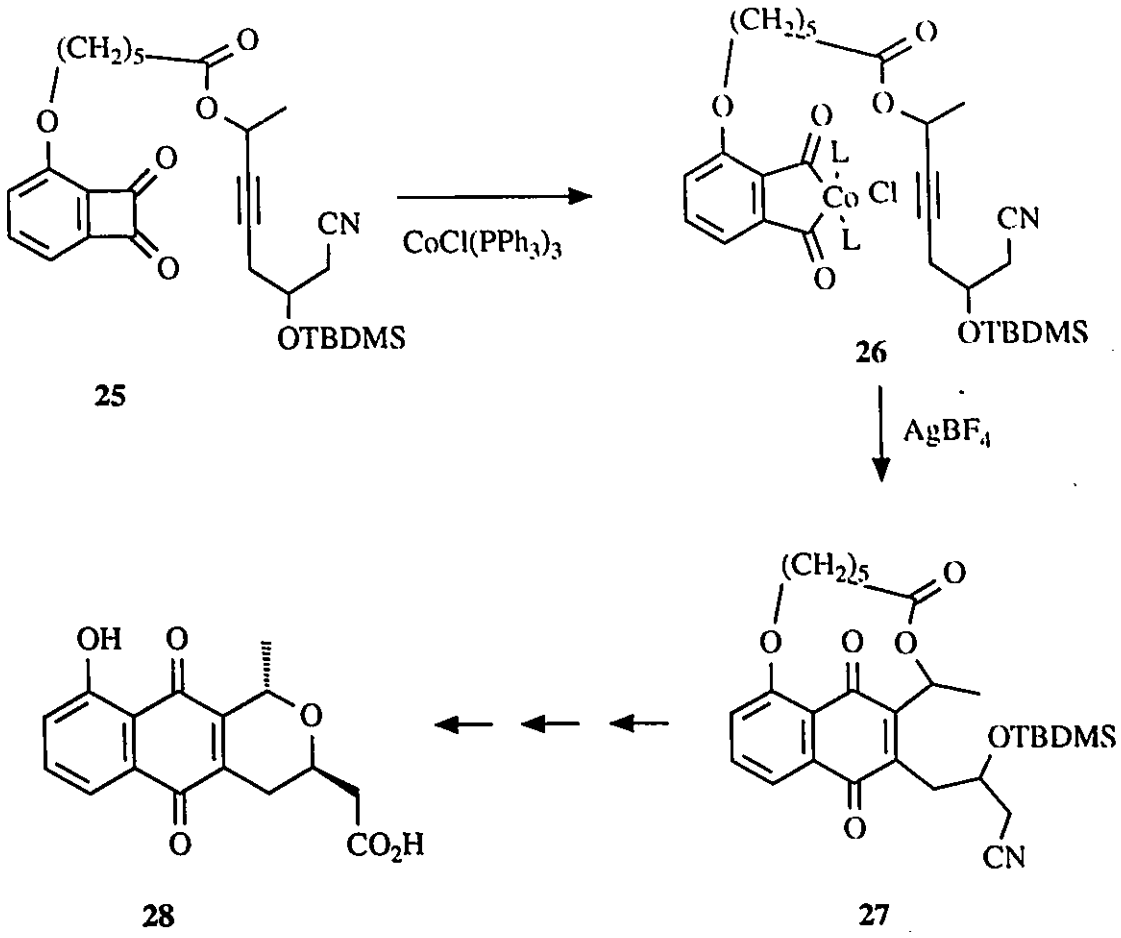
24a R_1= Me	2-6.6	:	1
24b R_1= TBDMS	>20	:	1

Scheme 8

There are three major limitations to this approach. First, only substituents ortho to the carbonyl group can significantly direct the regioselectivity. Second, the sequence involves several steps to protect and deprotect the desired position. Third, the silylation methodology is only applicaple to phenolic precursors.

2) Tether strategy

In one synthesis of nanaomycin A, a benzocyclobutenedione metal insertion approach was used[31](Scheme 9). In order to ensure regioselective addition of the alkyne moiety, a tether was introduced joining the alkyne with the phenolic position on the benzocyclobutenedione **25**. Thus, after metal insertion to **26**, the alkyne group was in a proper position to add with the desired regioselectivity to **27**. Further elaboration yielded nanaomycin A **28**.



25 26 27 28

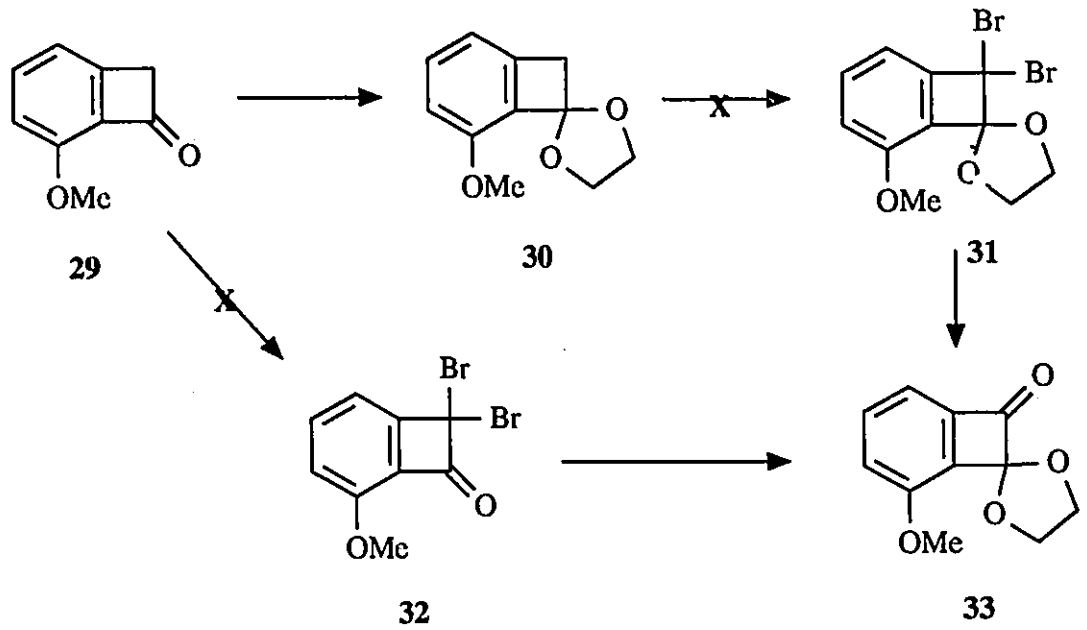
Scheme 9

As with the steric approach, this method is of limited general utility since it may be difficult to extend the tether concept to groups other than phenolic substituents on the benzocyclobutenedione precursor. In addition, considerable deprotective transformations are required to remove the tether and complete the functionalization of to the target molecule. A possible advantage of this method over the steric strategy is that a phenolic position meta to the cyclobutene ring may still allow regioselective alkyne addition. However, a much longer tether would be needed and might require considerable trial and error for each particular alkyne moiety.

3) Regioselective preparation of precursor

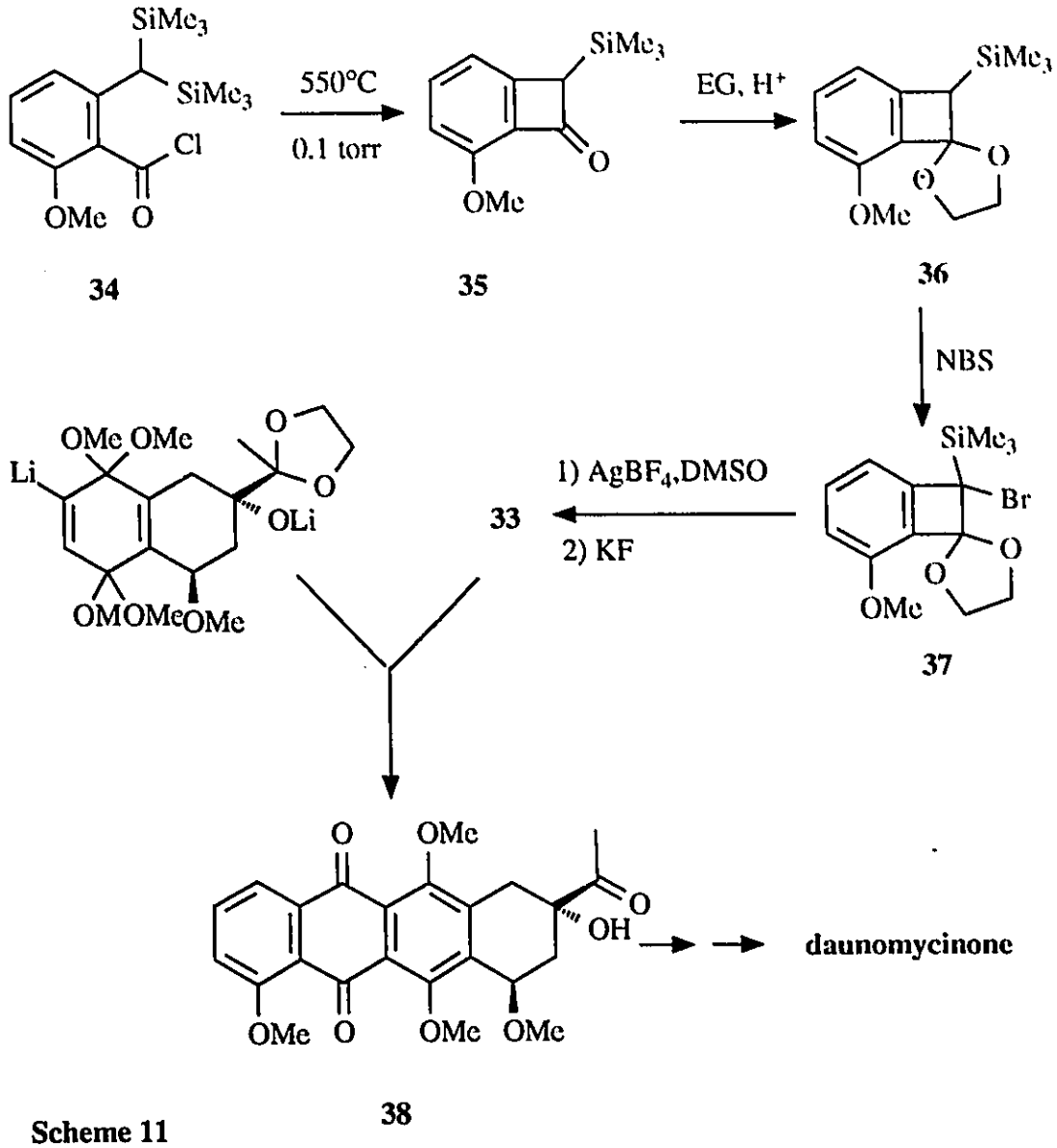
Another approach involves preparation of a selectively monoprotected benzocylobutenedione without going through the dione intermediate. Initial attempts to

accomplish this were directed towards the synthesis of daunomycinone,[33] an anthracycline antibiotic with antineoplastic activity. A required intermediate in this synthesis was the monoketalized benzocyclobutenedione **33** (Scheme 10). A likely precursor for this intermediate is benzocyclobutenone **29**, which is available from the regiospecific reaction between 2-bromoanisole and 1,1-dimethoxyethene via benzyne intermediacy.[34,35] However, various attempts to brominate or oxidize the benzylic position of ketal **30** or to ketalize dibromo compound **32** were unsuccessful.



Scheme 10

Therefore, another route (Scheme 11) was found which involved vacuum pyrolysis of the bis-silylated acid chloride **34**, which underwent preferential elimination of trimethylsilyl chloride to benzocyclobutenone **35.** Ketalization to **36** followed by bromination yielded the bromosilyl derivative **37.** Oxidative desilylation similar to a Swern oxidation led to the desired intermediate **33**, which was then converted to the key daunomycinone precursor **38.**



Scheme 11

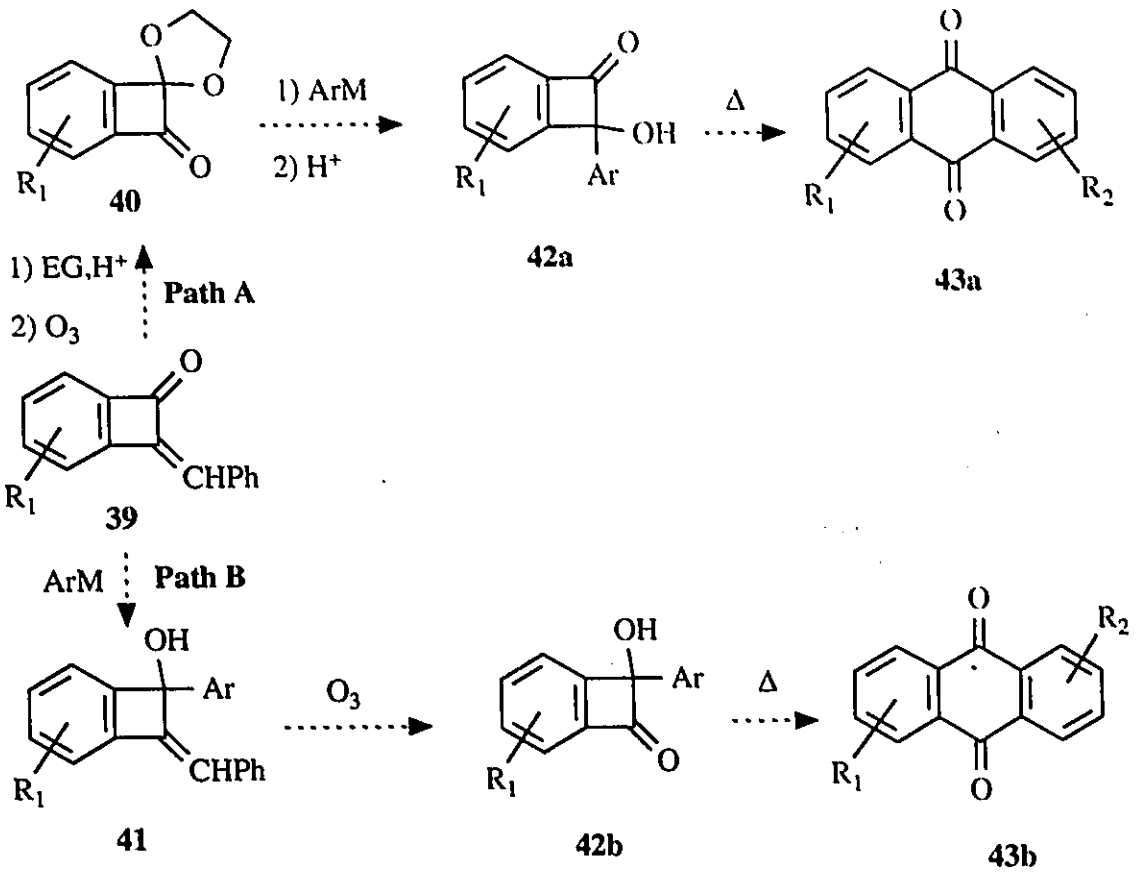
This approach offers the advantage that the regioselectivity is independent of steric or electronic effects imparted by the substituents on the benzocyclobutenedione aromatic ring. Instead, this control is effected by a suitable choice of substituted aromatic precursors.

The example cited above, however, does suffer from certain limitations. First, the pyrolysis methodology used may not be suitable for precursors sensitive to such temperature extremes. Second, this particular approach does not readily permit the protection of either carbonyl from the same precursor. Such a possibility would greatly

add to the versatility of this general strategy.

Overview of synthetic strategy

Based on the above examination of several existing approaches to the regioselective use or functionalization of benzocyclobutenediones, it is clear that new approaches would be of considerable value. In this connection, the benzylidenebenzocyclobutenones which are the subject of this thesis offer a new variant on the third strategy mentioned in the introduction. If the benzylidene functionality is considered as a protected carbonyl group, Scheme 12 outlines the proposed synthetic transformations which could lead to anthraquinones regioselectively. Path A involves initial protection of the ketone functionality of a substituted benzylidenebenzocyclobutenone **39** by ketalization followed by oxidative removal of the benzylidene group (e.g. ozonolysis) to yield intermediate **40**. Condensation with a substituted aryl lithium or Grignard followed by deprotection should then afford alcohol **42a**. Alternatively, by Path B, initial treatment with the aryl carbanion followed by the oxidative step would be expected to yield the regioisomeric **42b** via **41**. The intermediates **42a** and **42b** would be the key targets in this synthetic scheme since such compounds have previously been thermolysed to anthraquinones **43a** and **43b**.[19,20,22]



Scheme 12

Two factors suggest that such a strategy is worthy of investigation. First, the palladium-mediated cyclization is mild and is likely to be tolerant of a greater number of functional groups than the thermolysis approach in Scheme 11. Second, access to either regioisomeric anthraquinones is, in principle, possible from a common precursor.

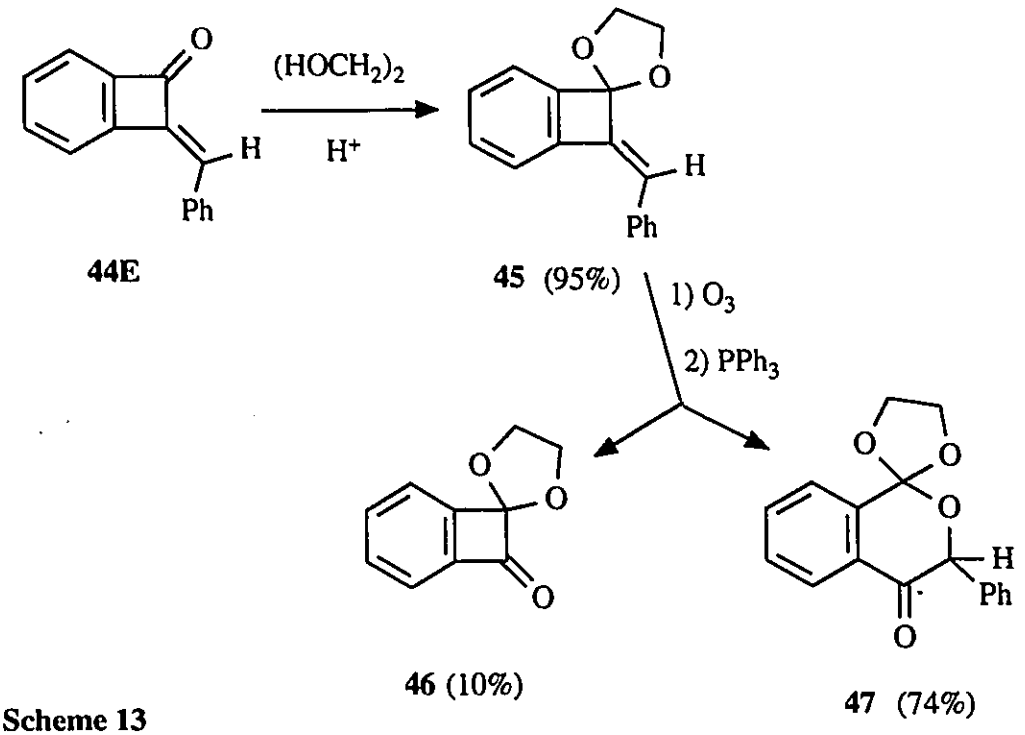
Results

In order to test out the feasabiliby of this proposed synthetic scheme, unsubstituted derivatives were first investigated. As will be described in detail below, the ketalization step in Path A and the preparation of the alcohol intermediate in Path B proceeded smoothly. The first steps in our synthetic strategy thus established, oxidative removal of the benzylidene functionality was next explored.

1) Ozonolysis

Ozonolysis of ketal **45**, prepared in 95% yield from ketone **44E**, at -78°C followed by triphenylphosphine work-up afforded the expected monoprotected

benzocylobutenedione **46** (IR 1774 cm^{-1}, MS (CI, m/e) 177 (M^++1)) in only 10% yield (Scheme 13). The major product proved to be the orthoester **47**, obtained in 74% yield. Because this was an unusual product for an ozonolysis reaction, rigorous proof of its structure was required. This was accomplished by various NMR experiments:



Scheme 13

The most useful of these was the FLOCK[36] experiment, so-called because it makes use of BIRD pulses sequences. Since it is used in several instances in this project, a description of the experiment follows. FLOCK is a 2D NMR experiment, correlating long-range C-H couplings. Consequently, it is an extremely powerful tool for structure elucidation, since it allows one to effectively "walk" around the carbon skeleton of a molecule and thus unambiguous assignment often becomes possible, even for complex structures.

The intensity of C-H correlations depends on the optimized coupling frequency which is determined by varying delays in the pulse sequence.[37] However, there is a complex dependence between the intensity of the signal and the optimization value for a given coupling constant. The result is that optimization values slightly off the actual

coupling constant may give decievingly low responses. For example, in the case of a response curve such as in Fig 1, where the actual coupling constant is 11.1 Hz, optimization at 10.4 or 11.8 Hz would yield only minimal signal intensities. In another scenario, as in Fig 2, optimization near 3.5 Hz would yield strong signals even though the actual coupling is 10 Hz.

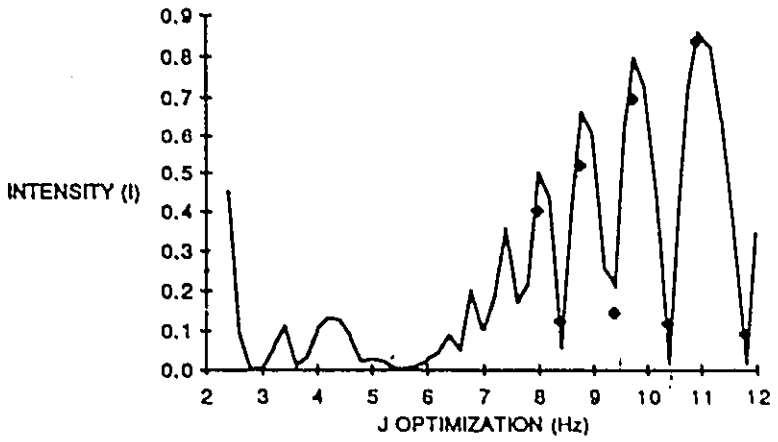


Fig 1

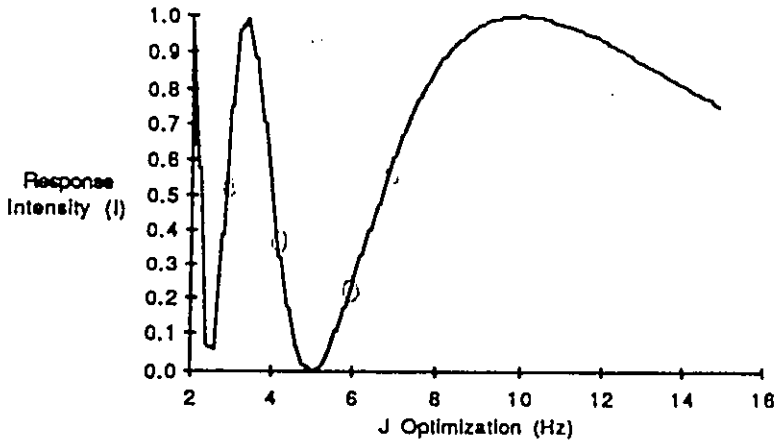


Fig 2

Figs 1 & 2 : Variations in sensitivity to long range C-H coupling depending on optimization frequency

In order to ensure that all correlations were accounted for, a coupled ^{13}C NMR spectrum was taken and FLOCK experiments with various optimization frequencies were performed until all correlations were accounted for. The FLOCK correlations were based on two reliable empirical rules: in benzene ring systems, only 3-bond couplings (5-9Hz) are observed; all other couplings are 2 and 3-bonds. This information coupled with HETCOR correlations allowed for complete and unambiguous assignment of structure **47** (see Fig 3 and Table 1). C-14 and C-15 were distinguished based on the assumption that only one hydrogen (H_{15b}) is close enough to the phenyl ring to experience a deshielding effect. The other 3 methylene hydrogens all appear overlapping at a slightly higher field.

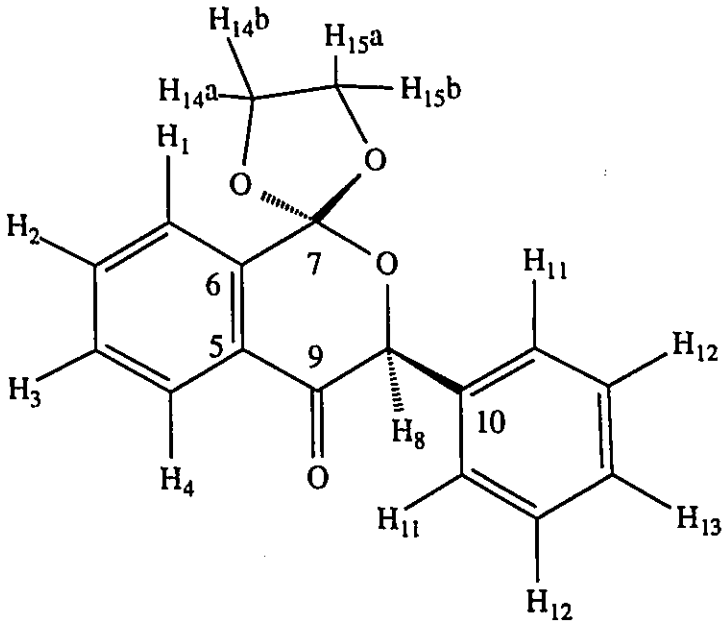


Fig 3: Numbering system for structure 47

Table 1: Assignments* for structure 47

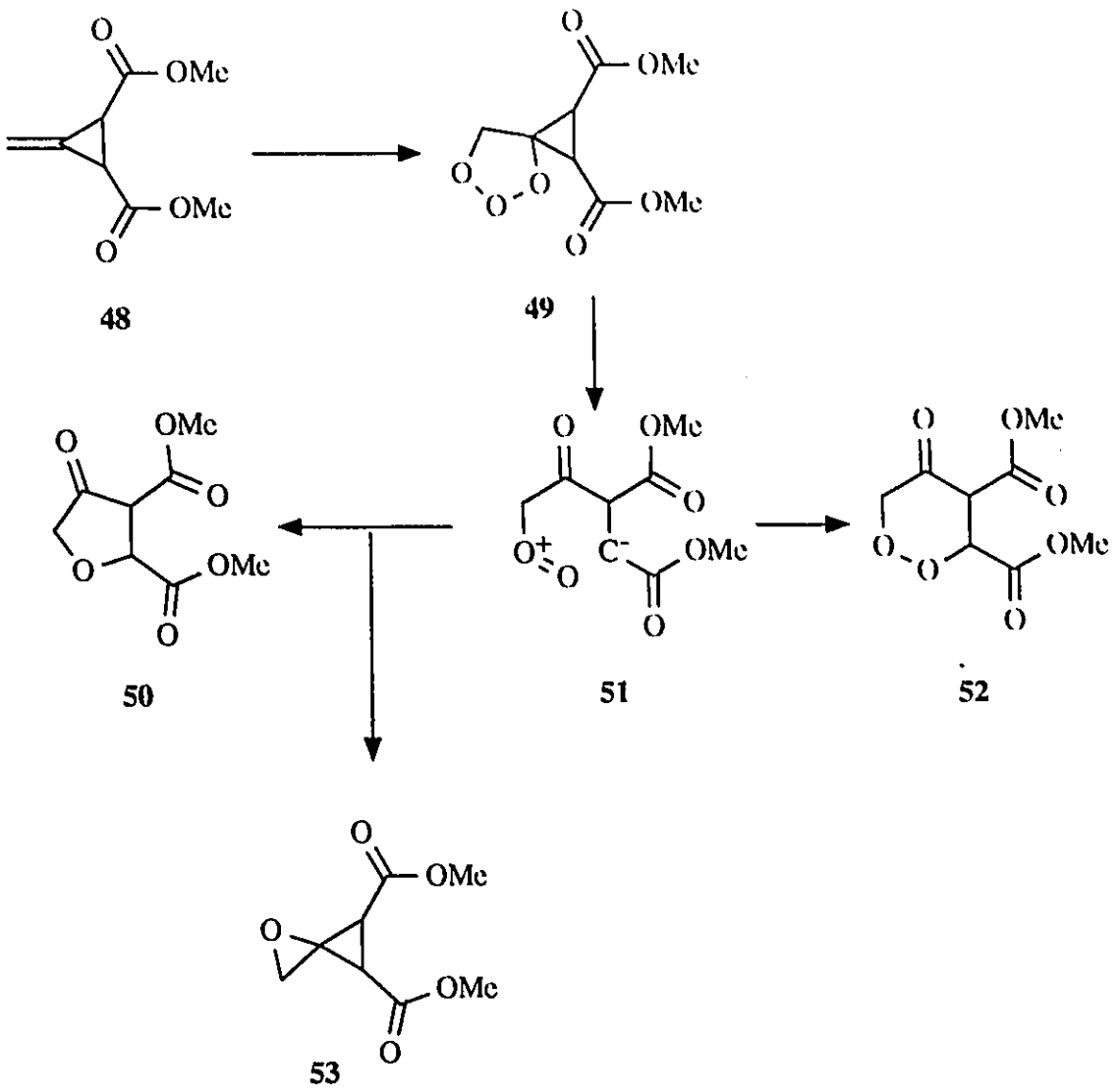
position	^{1}HMR shift (ppm)	^{13}CMR shift (ppm)	^{13}CMR coupl. (Hz)	FLOCK C-H correlations 3.0Hz	4.5Hz	6.0Hz	7.5Hz	13Hz
1	7.65(d)	124.86	164(d)					
			6.9(d)	3	3	3	3	3
2	7.7(m)	134.47	162(d)					
			8.2(d)	4	4	4	4	4
3	7.55(m)	130.16	146(d)					
			7.0(d)	1	1	1	1	1
4	7.96(d)	126.50	164(d)					
			5.4(d)	2	2	2	2	2
5	-	130.23	7.8(d)	1,3	1,3	1,3	1,3	1,3
			5.1(d)					
6	-	137.93	7.1(t)		2	4	4	
7	-	117.34	2.2(t)		1,14	14		14
8	5.67(s)	80.52	144(d)					
			3.9(t)		11			
9	-	193.57	3.9(t)	4,8	4,8	4,8	4,8	
10	-	135.76	12(d)		8	8	8,12	8,12
			6(d)					
11	ca7.4(m)	127.96	(m)		8,11,	8,11,	8,11,	8,11,
					13	13	13	13
12	ca7.35(m)	128.33	(m)		12	12	12	12
13	ca7.35(m)	128.44	(m)		11	11	11	11
14	4.3(m)	64.23	152(t)					
			2.2(t)	15		15		
15	4.4(2m)	64.77	152(t)					
			2.2(t)	14				

*Overlapping correlations were assigned based on expected couplings.

Inspection of Table 1 shows that multiple FLOCK experiments were necessary to reveal all correlations. For example, C-6 correlates only with H-2 at 4.5 Hz and only with

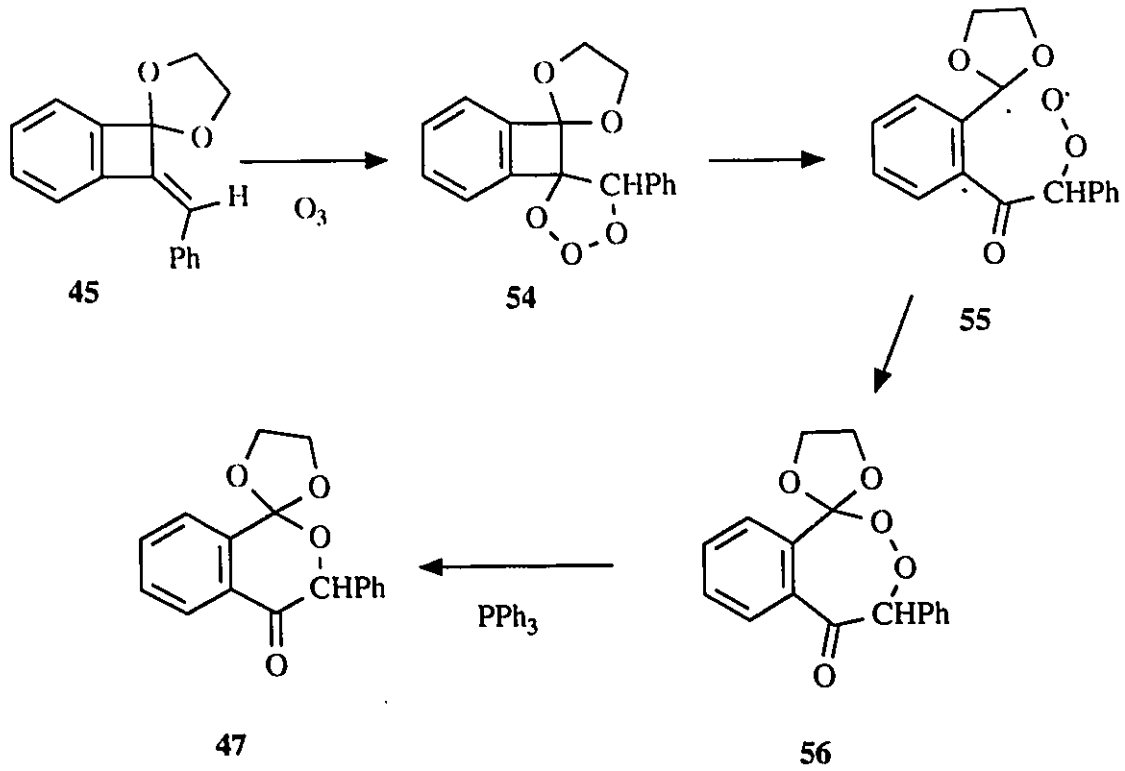
H-4 at 6.0 and 7.5 Hz, although both these couplings are about 7 Hz (as acertained from the 7.1 Hz triplet in the coupled ^{13}C NMR). It is interesting to note that certain correlations appear to exhibit a complex dependence on the optimization frequency, as predicted in Figs 1 and 2. For example, correlations between C-7 and H-14 or between C-14 and H-15 show two maxima with the chosen optimization frequencies.

In the search for other similar rearrangements during ozonolyses, only one other example surfaced.[38] It concerns another strained system, the dimethyl ester of Feist's acid **48** (Scheme 14). The products observed after ozonolysis were **50**, **52** and **53**. A mechanism was proposed to account for all products, with a common intermediate **51** arising from cleavage of the primairy ozonide **49**. Although an ionic mechanism was proposed, given the available information, it seems at least equally probable that radical processes are responsible for the observed products.



Scheme 14

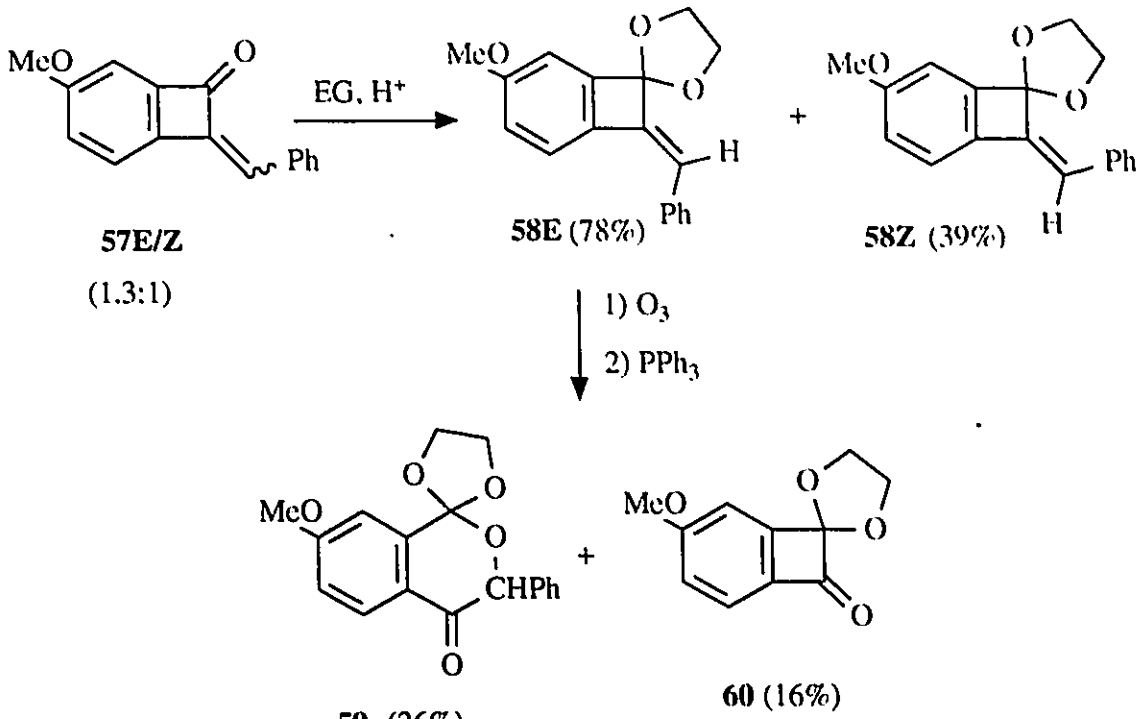
A radical mechanism seems especially likely for the ozonolysis of ketal **45**, given the stabilizing influence of α-oxy substituents. Scheme 15 depicts the proposed mechanism. Primary ozonide **54** cleaves homolytically to diradical **55**, driven by the stability of the α-dioxyradical and the release of ring strain. Intramolecular radical recombination leads to peroxide **56**, which is reduced to orthoester **47** by quenching of the reaction with triphenylphosphine.



45 54 55 56 47

Scheme 15

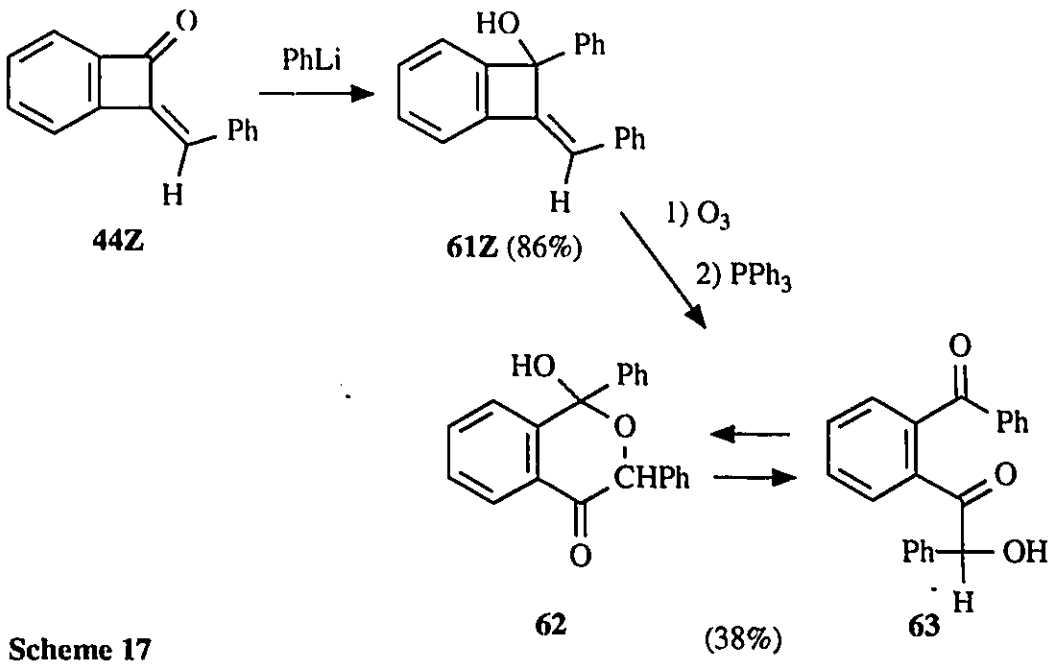
We studied next the ozonolysis of the methoxy analog **58E**. In order to prepare this compound, it was necessary to ketalize the inseparable 1.3:1 mixture of **57E/57Z** (see **46E** and **46Z** in Chapter 2, p. 42). Fortunately, it was possible to separate **58E** and **58Z** which were obtained in 78% and 39% yield, respectively. The stereochemical assignment for these ketals was made on the basis of the shielding influence of the ketal oxygens on the benzylidene hydrogen of **58E**, which appeared at δ 6.39 compared to δ 6.46 for **58Z**. A similar shielding effect of 0.1-0.2 ppm is observed for the various benzylidenebenzocyclobutenol derivatives prepared in this thesis. In addition, this assignment is supported by the greater proportion of **58E** to **58Z** isolated, reflecting the initial 1.3:1 ratio of **57E/57Z**.



Scheme 16

Ozonolysis of **57E** provided the orthoester **59** in 26% yield, which was characterized based on the similarity of its spectral data with **47**. Specifically, **58** showed a carbonyl absorption at 1691 cm^{-1} (compared to 1702 cm^{-1} for **47**), a benzylic resonance at δ 5.60 (compared to δ 5.67 for **47**) and a base peak at 313 (CI, M^++1) in the mass spectrometer. The desired benzocyclobutenone **60** (IR: 1772 cm^{-1}, MS (m/e) 206 (M^+)) was obtained in only 16% yield.

Alcohol **61Z** was prepared in 86% yield by the reaction of phenyllithium with ketone **44E**. Ozonolysis of **61Z** yielded a major fraction giving a mass of 317 m/e (CI, M^+ + 1), corresponding to a 38% yield of hemiketal **62** or the acyclic **63**. Analysis of this fraction by ^1H NMR revealed two benzylic hydrogens, appearing as singlets at δ 5.81 and δ 5.98 in a 1.3 : 1 ratio. The IR showed two carbonyl peaks at 1697 and 1675 cm^{-1}. Although this may be attributable to the two diastereomers of **62**, the large difference in these absorptions suggests the presence of the acyclic isomer **63**. Thus we propose that the two benzylic resonances in the ^1H NMR reflect an equilibrium between **63** and only one diastereomer of **62** (presumably the one with the two phenyl rings anti).

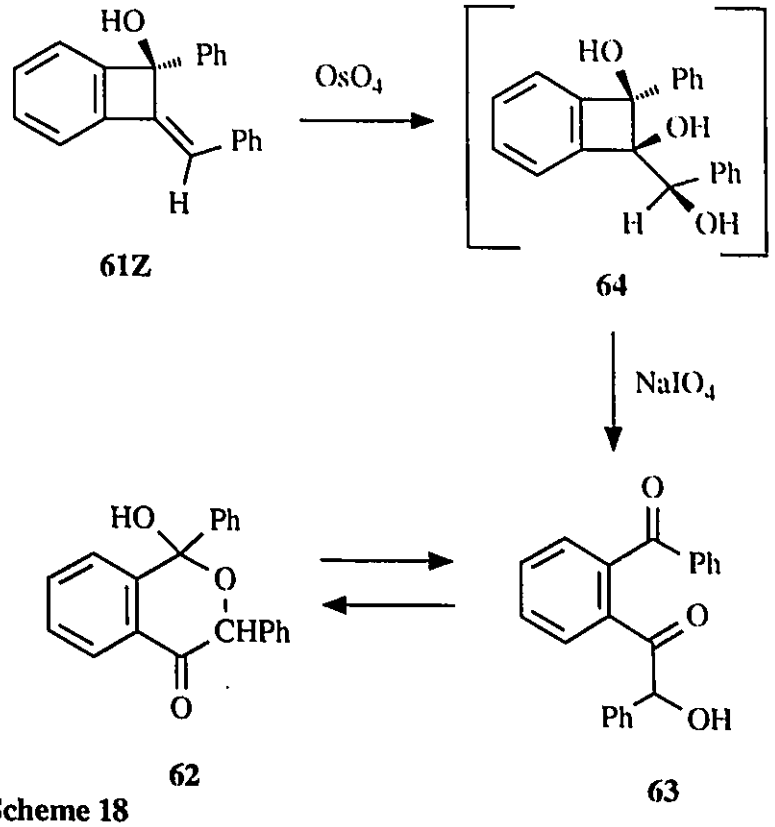


44Z **61Z** (86%) **62** (38%) **63**

Scheme 17

2) Other oxidative methods

Other methods of oxidizing the benzylidene group were explored. Inspection by ^1H NMR (singlets at δ 5.81 and 5.97) and IR (1698, 1673 cm^{-1}) of the crude reaction mixture obtained from the osmium tetroxide/periodate oxidation[39] of alcohol **61Z** indicated the formation of hemiketal **62** and its acyclic form **63** (Scheme 18). No carbonyl stretchings were observed > 1730 cm^{-1}, which would be expected if a benzocyclobutenone system was present in significant amounts. This conversion presumably occurs via triol **64**, which then suffers oxidative cleavage of the cyclobutene ring by periodate to yield **63** in preference to scission of the exocyclic diol. Subsequent cyclization leads to an equilibrium between **62** and **63**.

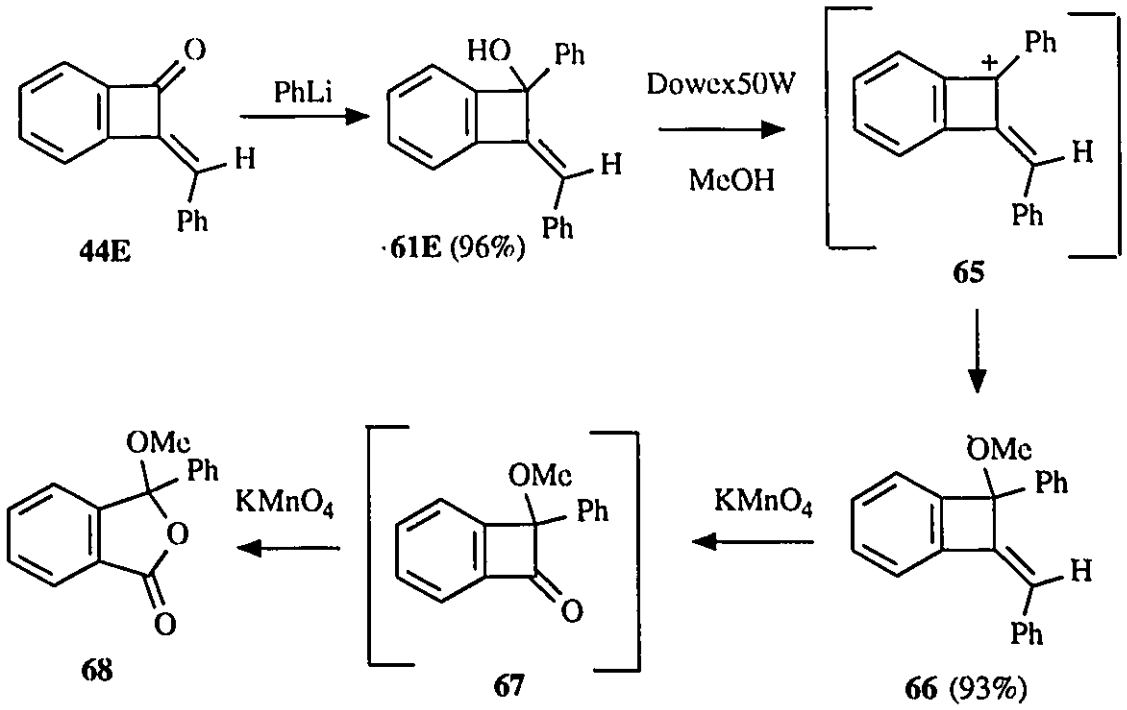


61Z **64** **62** **63**

Scheme 18

In order for this route to take place in preference to cleavage of the exocyclic diol requires a syn relationship between the hydroxy groups on the cyclobutene ring in **64**.[40] This in turn implies almost exclusive attack of the osmium tetroxide on the same face as the hydroxy functionality in **61Z**, perhaps due to severe steric constraints imparted by the phenyl ring on the opposite face of the molecule[41] or coordinative assistance from the hydroxy group.

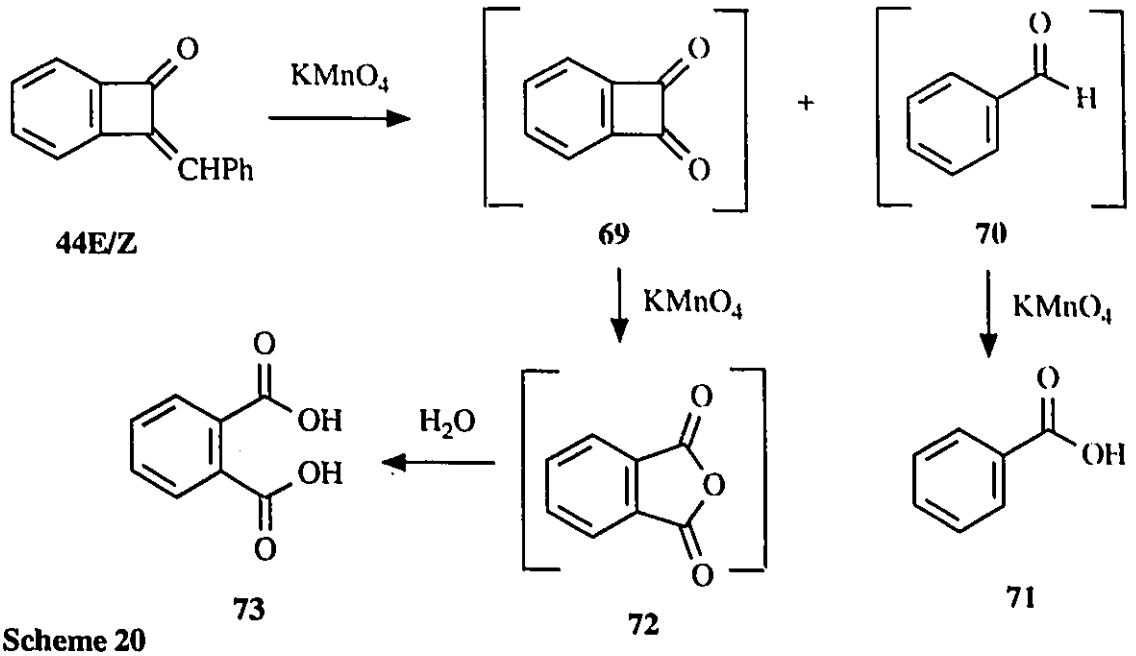
In order to avoid such side reactions, the alcohol **61E** (prepared in 96% yield from **44E**) was protected as a methyl ether **66** by refluxing it methanol in the presence of Dowex resin through the intermediacy of benzylic carbocation **65**[42] (Scheme 19). Treatment of methyl ether **66** with 2 equivalents of permanganate in a water/methylene chloride system with tetrabutylammonium chloride as phase transfer catalyst[43] converted it to the phthalide deriative **68**, as evidenced from analysis of the crude reaction mixture (IR: 1774 cm^{-1}, MS (CI): 241 (100, M^++1)).



Scheme 19

It is possible that the desired benzocyclobutenone **67** was initially formed then converted to **68** by permanganate. There is a precedent for the conversion of cyclobutanones to butyrolactones via sulfochromic acid oxidation.[44] Interestingly, this Baeyer-Villiger type of ring expansion observed for cyclobutanones does not extend to cyclopentanones, indicating that ring strain may be a necessary driving force for the reaction to occur.

Permanganate oxidation of the parent ketones **44E** and **44Z** under the same phase-transfer conditions as for **66** yielded no benzocyclobutenedione **69** (no C=O ν > 1750 cm^{-1} in the crude mixture). The products obtained were phthalic **73** and benzoic acids **71** (Scheme 20). It is possible that the initially formed benzocyclobutenedione **69** suffered a permanganate-mediated ring expansion to phthalic anhydride **72**, following a similar mechanism to that proposed for **67**. This is not unreasonable considering that α-diketones yield anhydrides upon Baeyer-Villiger oxidation.[45] Subsequent hydrolysis of **72** would yield the observed phthalic acid **73**. Oxidation of benzaldehyde **70** would give benzoic acid **71**.



Scheme 20

Conclusion

Although the full objectives proposed in Scheme 12 were not met, several oxidative ring expansion reactions of mechanistic interest were revealed. Furthermore, all of the required steps in our synthetic scheme proceeded smoothly except for the oxidative removal of the benzylidene group. Thus, if this final hurdle could be overcome, the regioselective synthesis of anthraquinones from benzylidenebenzocyclobutenones would certainly become feasible. However, continued attempts at oxidative cleavage were abandoned in favor of pursuing the more encouraging results obtained from other projects which will be described in subsequent chapters.

EXPERIMENTAL

General. Same as specified in Chapter 2 with the following additions. The FLOCK experiment and coupled ^{13}C NMR spectra were taken on the Varian XL-300 instrument.

Preparation of 44E/Z: see preparation of **42E/Z** in Chapter 2.

Preparation of ketal 45: A solution of **44E** (95.7 mg, 0.47 mol), p-toluenesulfonic acid monohydrate (24.0 mg, 0.13 mmol) and ethylene glycol (1.5 mL) was refluxed in 30 mL of toluene under Dean-Stark conditions. After 4.5 h, the reaction mixture was washed twice with saturated aqueous $NaHCO_3$ then filtered over $MgSO_4$. The filtrate was evaporated then chromatographed on a Chromatotron plate to yield recovered **44E** (23.8 mg, 25%) and **45** (82.1 mg, 71% yield or 95% based on unrecovered starting material) as a colorless oil: ^1H NMR δ 4.26 (m, 4H, O-CH_2CH_2-O), 6.54 (s, 1H, CHPh), 7.2-7.4 (m, 6H), 7.55 (m, 3H); ^{13}C NMR δ 65.9, 112.1, 118.4, 121.0, 121.5, 127.5, 127.9, 128.5, 129.9, 131.0, 136.5, 145.2, 145.8, 152.0.

Ozonolysis of 45: A solution of **45** (68 mg, 0.27 mmol) and methanol (0.5 mL) in 15 mL of CH_2Cl_2 was placed in a gas bubbler and cooled to -78°C under a stream of N_2. Ozone was bubbled in for 15 min, at which time the solution was deep blue. The reaction mixture was kept at -78°C for an additional 25 min under a stream of N_2 then quenched with triphenylphosphine (130 mg, 0.50 mmol) in 2 mL of CH_2Cl_2. After warming to rt, the reaction mixture was evaporated then chromatographed on a Chromatotron plate (3:1 hexanes/CH_2Cl_2) to yield the following compounds:

46 (5.0 mg, 0.028 mmol, 10% yield): ^1H NMR δ 4.25 (4H, m), 7.5-7.8 (4H, m); IR (CH_2Cl_2, cm^{-1}) 1774; MS (CI)(m/e, int) 177 (100, M^++1).

47 (54.9 mg, 0.20 mmol, 74% yield): ^1H and ^{13}C NMR: see Table 1; IR (CH_2Cl_2, cm^{-1}) 1702 (C=O), 1604, 1073 (C-O); MS (CI)(m/e, int) 283 (100, M^++1), 193 (22); MS (EI)(m/e, int) 222 (7, M^+-$C_2H_4O_2$), 176 (54, M^+-PhCHO), 148 (100, M^+-PhCHO-CO), 104 (46).

Preparation of 57E/Z: see preparation of **46E/Z** in Chapter 2.

Preparation of ketal 58E: The same procedure as for the preparation of **45** was used on a 1.3:1 mixture of **57E** and **57Z**. The chromatography was carried out with hexanes/CH_2Cl_2/ether (10:1:1) as eluent to yield **58E** (78% yield from **57E**) and **58Z** (39% yield from **57Z**).

For **58E**: ^{1}H NMR δ 3.81 (s, 3H, OMe), 4.25 (m, 4H, O-CH_2CH_2-O), 6.39 (s, 1H, CHPh), 6.87 (d, J = 1.4 Hz, 1H), 6.94 (dd, J = 2.2, 8.3 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.3-7.6 (m, 5H); IR (CH_2Cl_2, cm^{-1}) 1596, 1478, 1032; MS (m/e, int) 280 (41, M^+), 252 (100, M^+-C_2H_4), 129 (57); HRMS $C_{18}H_{16}O_3$ 280.1099 (calcd), 280.1095 (found).

For **58Z**: ^{1}H NMR δ 3.80 (s, 3H, OMe), 4.27 (m, 4H, O-CH_2CH_2-O), 6.46 (s, 1H, CHPh), 6.79(d, J = 3 Hz, 1H), 6.92 (dd, J = 3, 8 Hz, 1H), 7.1-7.35 (m, 4H), 7.55 (d, J = 7 Hz, 2H); IR (CH_2Cl_2, cm^{-1}) 1592, 1476, 1008; MS (m/e, int) 280 (47, M^+), 252 (100, M^+-C_2H_4), 129 (61); HRMS $C_{18}H_{16}O_3$ 280.1099 (calcd), 280.1083 (found).

Ozonolysis of 58E: A solution of **58E** (37.4 mg, 0.13 mmol) in 15 mL of methanol was placed in a gas bubbler and cooled under a stream of N_2 to -78°C. Ozone was then bubbled in for 10 min and the resulting deep blue solution was purged with N_2 for 5 min. Triphenylphosphine (71.4 mg, 0.27 mmol) was then added in 2 mL of CH_2Cl_2 and the mixture was allowed to warm to rt. The solvent was evaporated and the residue chromatographed on a Chromatotron plate (5:1 hexanes/EtOAc -> pure EtOAc) to yield the following compounds:

59 (11.0 mg, 26% yield) as a white solid: ^{1}H NMR δ 3.90 (s, 3H, OMe), 4.2-4.5 (m, 4H, -OCH_2CH_2O-), 5.60 (s, 1H, CHPh), 7.05 (m, 2H), 7.3-7.5 (m, 5H), 7.92 (d, J = 8.4 Hz, 1H); IR (CH_2Cl_2, cm^{-1}) 1691, 1604, 1073; MS (CI)(m/e, int) 313 (100, M^++1).

60 (4.3 mg, 16% yield): ^{1}H NMR δ 3.89 (3H, s, OMe), 4.24 (4H, m, -OCH_2CH_2O-), 7.11 (1H, s), 7.13 (1H, dd, J = 2.1, 8.1 Hz), 7.45 (1H, dd, J = 1.2, 8.1 Hz); IR (CH_2Cl_2, cm^{-1}) 1772; MS (m/e, int) 206 (32, M^+), 178 (98, M^+-CO), 134 (100).

Preparation of 61E: n-BuLi (2.15 M in hexanes, 1.5 mL, 3.23 mmol) was added to a solution of bromobenzene (0.55g, 3.5 mmol) in 5 mL of THF at -78°C. The solution was stirred at -78°C for 15 min, and then a solution of **44E** (180 mg, 0.88 mmol) in 15 mL

of THF, precooled to -78°C, was added via cannula over 15 min. The mixture was stirred for an additional 30 min at -78°C, quenched by dropwise addition of saturated NH_4Cl, warmed to rt, extracted into ether, dried over $MgSO_4$, and evaporated. Purification of the remaining brown oil by flash chromatography (1:1 hexanes-CH_2Cl_2) gave **61E** (241 mg, 96%) as a colorless oil: ^1H NMR δ 2.93 (1H, s), 6.46 (1H, s), 7.2-7.7 (14H, m); ^{13}C NMR δ 85.88, 119.69, 121.81, 122.14, 125.84, 127.45, 127.58, 127.81, 127.82, 128.26, 128.55, 130.17, 136.69, 141.86, 144.07, 148.40, 153.75; IR (CH_2Cl_2, cm^{-1}) 3574 (OH), 1046 (C-O); MS (m/e, int) 284 (100, M^+), 207 (32), 178 (32), 150 (10), 105 (20), 51 (27); HRMS $C_{21}H_{16}O$ 284.1201 (calcd), 284.1176 (found).

Preparation of 61Z: The same procedure as for **61E** was used with **44Z** except that the mixture was allowed to warm to rt for 10 min then partioned between ether and saturated NH_4Cl solution. Chromatography with 1:1 hexanes/CH_2Cl_2 afforded **61Z** in 86% yield: ^1H NMR δ 2.95 (1H, br s, OH), 6.69 (1H, s, CHPh), 7.1-7.6 (14H, m); IR (CH_2Cl_2, cm^{-1}) 3576, 1599, 1045.

Ozonolysis of 61Z: The same procedure as for the ozonolysis of **58E** was used except that the chromatography was carried out in 6:1 -> 3:1 hexanes/EtOAc to yield mixture of **62** and **63** in 38% yield as a 1.3:1 mixture: ^1H NMR δ 3.35 (br s, OH), 4.25 (br s, OH), 5.81 (s, CHPh), 5.98 (s, CHPh), 6.8-8.1 (m); IR (CH_2Cl_2, cm^{-1}) 3522 (OH), 1697 (C=O), 1675 (C=O), 1599, 1070; MS (CI)(m/e, int) 317(33, M^++1), 299 (94, M^+-H_2O), 211 (100).

Reaction of 61Z with OsO_4/$NaIO_4$: To a solution of **61Z** (10.7 mg, 38 μmol) in 0.75 mL of dioxane and 0.25 mL of water was added $NaIO_4$ (37 mg, 0.17 mmol) and a crystal of OsO_4. The reaction mixture was stirred for 3.5 h then partitioned between 10 mL of ether and 10 mL of water. The aqueous layer was washer twice with ether then the combined organic phases were washed once with water, dried over $MgSO_4$ and evaporated. The residue was analysed by ^1H NMR with the major components identified as **62** and **63**, characterized principally by the two singlets at δ 5.81 and 5.97. The IR of the crude reaction mixture also displayed strong carbonyl absorptions at 1698 and 1673

cm^{-1}, also characteristic of **62** and **63**. No carbonyl stretchings were observed >1730 cm^{-1}, which would be expected if a benzocyclobutenone system was present in significant amounts.

Preparation of 66: A mixture of **61E** (23.2 mg, 0.082 mmol) and Dowex 50W acidic resin (60 mg) was refluxed in 5 mL of methanol. After 3 h, the resin was filtered off and washed with methanol. The filtrate was evaporated to yield **66** (22.8 mg, 0.077 mmol, 93% yield) as a white solid: ^{1}H NMR δ 3.40 (s, 3H, OMe), 6.41 (s, 1H, CHPh), 7.2-7.7 (m, 14H); MS (m/e, int) 298 (40, M^+), 283 (97, M^+-Me), 267 (100, M^+-OMe), 265 (69), 252 (37), 178 (31), 77 (39); HRMS $C_{22}H_{18}O$ 298.1358 (calcd), 298.1362 (found).

Reaction of 66 with $KMnO_4$: A mixture of **66** (20.0 mg, 0.067 mmol), $KMnO_4$ (21.2 mg, 0.14 mmol) and Bu_4NCl (1 crystal) was vigorously stirred in 2 mL of CH_2Cl_2 and 3 mL of water. After 3 days, the mixture was partitioned between 25 mL of ether and 25 mL of water, the water layer was washed with ether, the combined organic phases were dried over $MgSO_4$ and evaporated to yield a residue. Analysis of the crude reaction mixture by ^{1}H NMR indicated the presence of some starting material as well as a major OMe peak at δ 3.29. Inspection of the IR revealed only one major carbonyl streching band at 1774 cm^{-1}. In the mass spectrum (CI), the base peak was located at 241 m/e. This spectral information is consistent with the formation of phtalide **68** as opposed to the benzocyclobutenone **67**.

Reaction of 44E and 44Z with $KMnO_4$: The same conditions as described for **66** were used for **44E** and **44Z**, except that the aqueous layers were acidified with dilute HCl during the work-up. Both reactions yielded the same products. An IR spectrum of the crude reaction mixtures revealed carbonyl stretchings at 1692 cm^{-1} only, indicating that no benzocyclobutenedione had formed. A ^{1}H NMR spectrum of the mixture in acetone-d_6 was consistent with a 1:1 mixture of phtalic **73** and benzoic **71** acids: ^{1}H NMR δ 6.2 (3H, br s, CO_2H), 7.47-7.57 (2H, m), 7.60-7.70 (3H, m), 7.75-7.85 (2H, m), 8.02-8.10 (2H, m); IR (m/e, int) 122 (89, M^+ for $PhCO_2H$), 105 (100), 77 (77), 51 (35).

REFERENCES

1. Shishido, K.; Yamashita, A.; Hiroya, K.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1990**, 469.

2. Shishido, K.; Hiroya, K.; Fukumoto, K.J. *Heterocycles*, **1989**, 28(1), 39.

3. Shishido, K.; Komatsu, H.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1987**, 2117.

4. Shishido, K.; Komatsu, H.; Fukumoto, K.; Kametani, T. *Heterocycles* **1989**, 28(1), 43.

5. Shishido, K.; Yamashita, A.; Hiroya, K.; Keiichiro, F. *Tetrahedron*, **1989**, 45, 5791.

6. Hickman, D.; Wallace, T.W.; Wardleworth, J.M. *Tetrahedron Lett.* **1991**, 32, 819.

7. Liebeskind, L.S. *Tetrahedron*, **1989**, 45, 3053.

8. Perri, S.T.; Moore, H.W. *J. Am. Chem. Soc.* **1990**, 112, 1897.

9. Xia, H.; Moore, H.W. *J. Org. Chem.* **1992**, 57, 3765. cb/6

10. Enhsen, A.; Karabelas, K.; Heerding, J.M.; Moore, H.W. *J. Org. Chem.* **1990**, 55, 1177.

11. Selwood, D.L.; Jandu, K.S. *Heterocycles*, **1988**, 27, 1191.

12. Perri, S.T.; Dyke, H.J.; Moore, H.W. *J. Org. Chem.* **1989**, 54, 2032.

13. Foland, L.D.; Karlsson, J.O.; Perri, S.T.; Schwabe, R.; Xu, S.L.; Patil, S.; Moore, H.W. *J. Am. Chem. Soc.* **1989**, 111, 975.

14. Moore, H.W.; Perri, S.T. *J. Org. Chem.* **1988**, 53, 996.

15. Reed, M.W.; Moore, H.W. *J. Org. Chem.* **1988**, 53, 4166.

16. Reed, M.W.; Moore, H.W. *J. Org. Chem.* **1987**, 52, 3491.

17. Perri, S.T.; Moore, H.W. *Tetrahedron Lett.* **1987**, 28, 4507.

18. Karlsson, J.O.; Nguyen, N.V.; Foland, L.D.; Moore, H.W. *J. Am. Chem. Soc.* **1985**, 107, 3392.

19. Liebeskind, L.S. Iyer, S.; Jewell, C.F.Jr. *J. Org. Chem.* **1986**, 51, 3065.

20. Foland, L.D.; Decker, O.H.W.; Moore, H.W. *J. Am. Chem. Soc.* **1989**, 111,

989.

21. Perri, S.T.; Foland, L.D.; Decker, O.H.W.; Moore, H.W. *J. Org. Chem.* **1986**, 51, 3067.

22. Decker, O.H.W.; Moore, H.W. *J. Org. Chem.* **1987**, 52, 1174.

23. Liebeskind, L.S.; Mitchell, D.; Foster, B.S. *J. Am. Chem. Soc.* **1987**, 109, 7908.

24. Mitchell, D; Liebeskind, L.S. *J. Am. Chem. Soc.* **1990**, 112, 291.

25. Liebeskind, L.S.; Chidambaram, R.; Mitchell, D.; Foster, B.S. *Pure & Appl. Chem.* **1988**, 60, 27.

26. Huffman, M.A.; Liebeskind, L.S. *Organometallics*, **1990**, 9, 2194.

27. Iyer, S.; Liebeskind, L.S. *J. Am. Chem. Soc.* **1987**, 109, 2759.

28. Liebeskind, L.S.; Chidambaram, R. *J. Am. Chem. Soc.* **1987**, 109, 5025.

29. Jewell, C.F.Jr.; Liebeskind, L.S.; Williamson, M. *J. Am. Chem. Soc.* **1985**, 107, 6715.

30. Cho, S.H.; Wirtz, K.R.; Liebeskind, L.S. *Organometallics*, **1990**, 9, 3067.

31. Liebeskind, L.S.; Baysdon, S.L.; South, M.S.; Iyer, S. *Tetrahedron*, **1985**, 41, 5839.

32. Liebeskind, L.S.; Baysdon, S.L.; South, M.S. *J. Am. Chem. Soc.* **1980**, 102, 7398.

33. Swenton, J.S.; Anderson, D.K.; Jackson, D.K.; Narasimhan, L. *J. Org. Chem.* **1981**, 46, 4825.

34. Liebeskind, L.S.; Lescosky, L.J.; McSwain, C.M.Jr. *J. Org. Chem.* **1989**, 54, 1435.

35. Stevens, R.V.; Bisacchi, G.S.; *J. Org. Chem.* **1982**, 47, 2393.

36. Reynolds, W.F.; McLean, S.; Perpick-Dumont, M.; Enriquez, R.G. *Mag. Res. Chem.* **1989**, 27, 162.

37. Martin, G.E.; Zektzer, A.S. *Mag. Res. Chem.* **1988**, 26, 631.

38. Bailey, P.S. Ozonation in Organic Chemistry, v. 1, Academic Press, New York, **1978**, p. 178.

39. Pappo, R.; Allen D.S.Jr.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.* **1956**, 21, 478.

40. March, J. Advanced Organic Chemistry, 3rd Ed. John Wiley & Sons, New York, **1985**, p. 1063.

41. see Ref. 40, p. 733.

42. Arnold, B.J.; Sammes, P.G.; Wallace, T.W. *J. Chem. Soc. Perkin Trans. I.* **1974**, 415.

43. Trahanovsky, W.S. Oxidation in Organic Chemistry, Part D, Academic Press, New York, **1982**, p. 147.

44. Jeanne-Carlier, R.; Bourelle-Wargnier, F. *Tetrahedron Lett.* **1975**, 22, 1842.

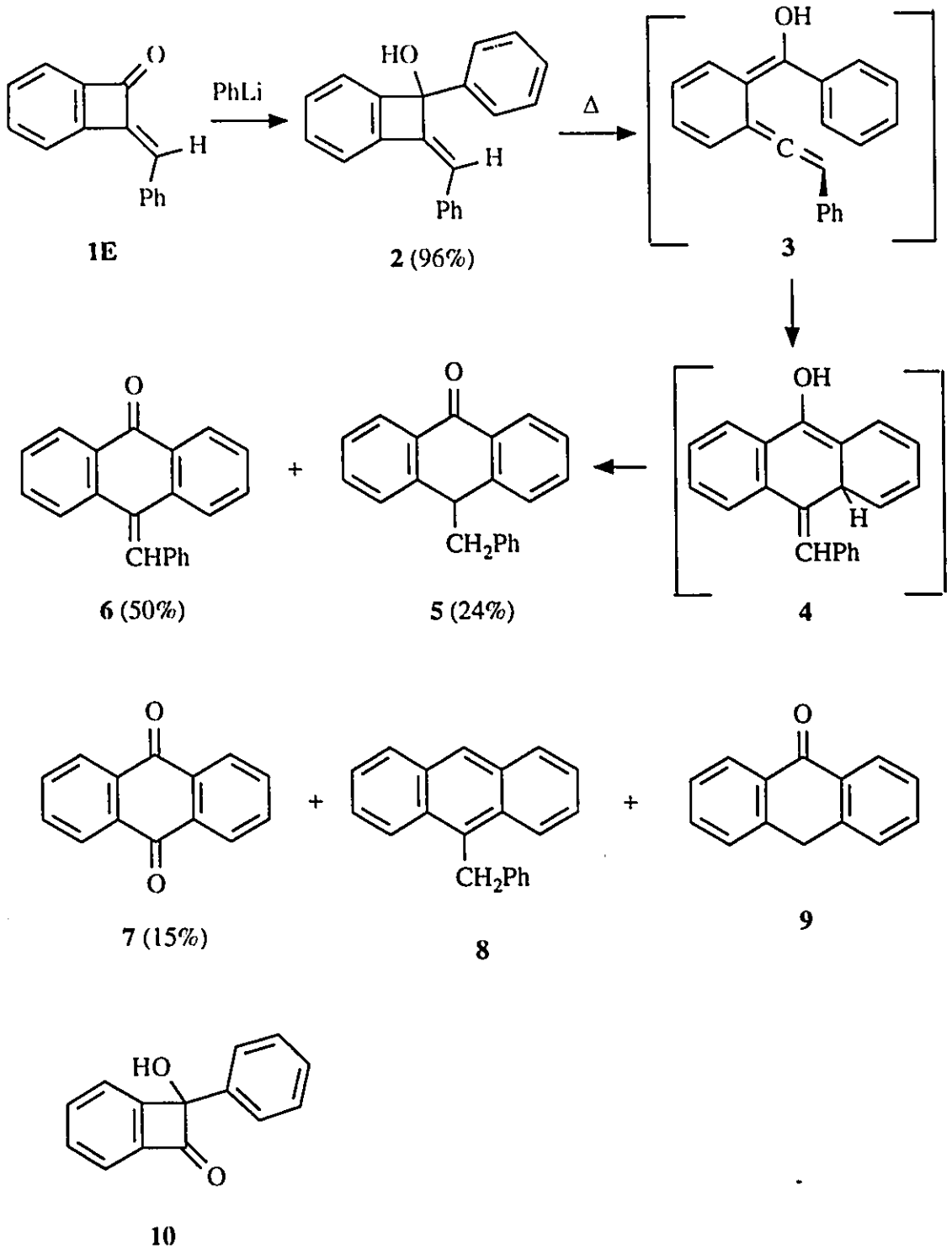
45. see Ref. 40, p. 990.

CHAPTER 5: THERMOLYSIS OF BENZYLIDENEBENZOCYCLOBUTENONE DERIVATIVES[1]

Due to the difficulties encountered in the oxidative removal of the benzylidene group from the cyclobutene ring, another strategy was taken to explore the possibility of removing this group after ring expansion had occured. Thus a variety of adducts were prepared by condensation of an organolithium or Grignard reagent with benzylidenebenzocyclobutenones and the resulting alcohols were thermolysed.

Phenyl adduct

Phenylcarbinol **2** was prepared in 96% yield by treating **1E** with phenyllithium at -78°C (Scheme 1). When **2** was refluxed for 16h in decalin, 10-benzylideneanthrone **6** was obtained in 40-65% yields (GC estimation). Variable amounts of 10-benzylanthrone **5**, anthraquinone **7**, 9-benzylanthracene **8** and anthrone **9** were also formed. Isolation of these products via chromatography was impractical due to overlapping R_f's in a number of solvent systems and the known instabiliby of **6** to silica gel.[2] However, it was possible to isolate **6** and **7** by fractional crystallization. The remaining products were identified by comparison of GC-MS data with those from either authentic materials or reports in the literature. The mechanism for the formation of these materials is unclear at the present time, although the intermediacy of **3** and **4** is proposed. Free radical involvement is unlikely since addition of 2,6-di-*t*-butylphenol had no significant effect on the outcome of the thermolysis. It should be noted that ring opening of **10** occurs at 160°C (refluxing xylene) within 20 min[3] compared to 16h at 190°C for **2**.



1E **2** (96%) **3** **4** **6** (50%) **5** (24%) **7** (15%) **8** **9** **10**

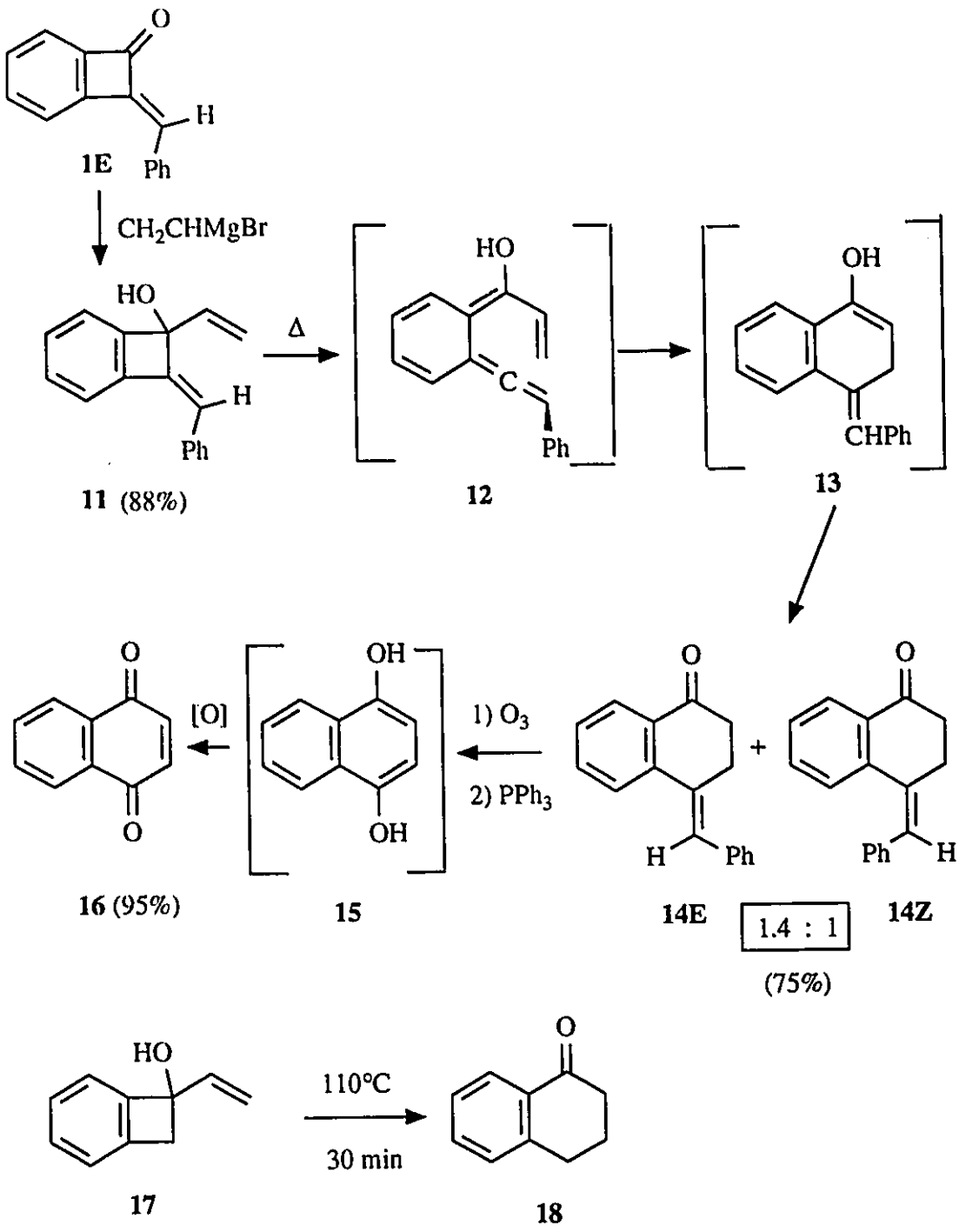
Scheme 1

Ozonolysis of **6** gave **7** in essentially quantitiative yield as judged by GC analysis. In principle this shows that the benzylidene group in **2** can serve as a masked carbonyl funtionality via a thermolysis-oxidation procedure.

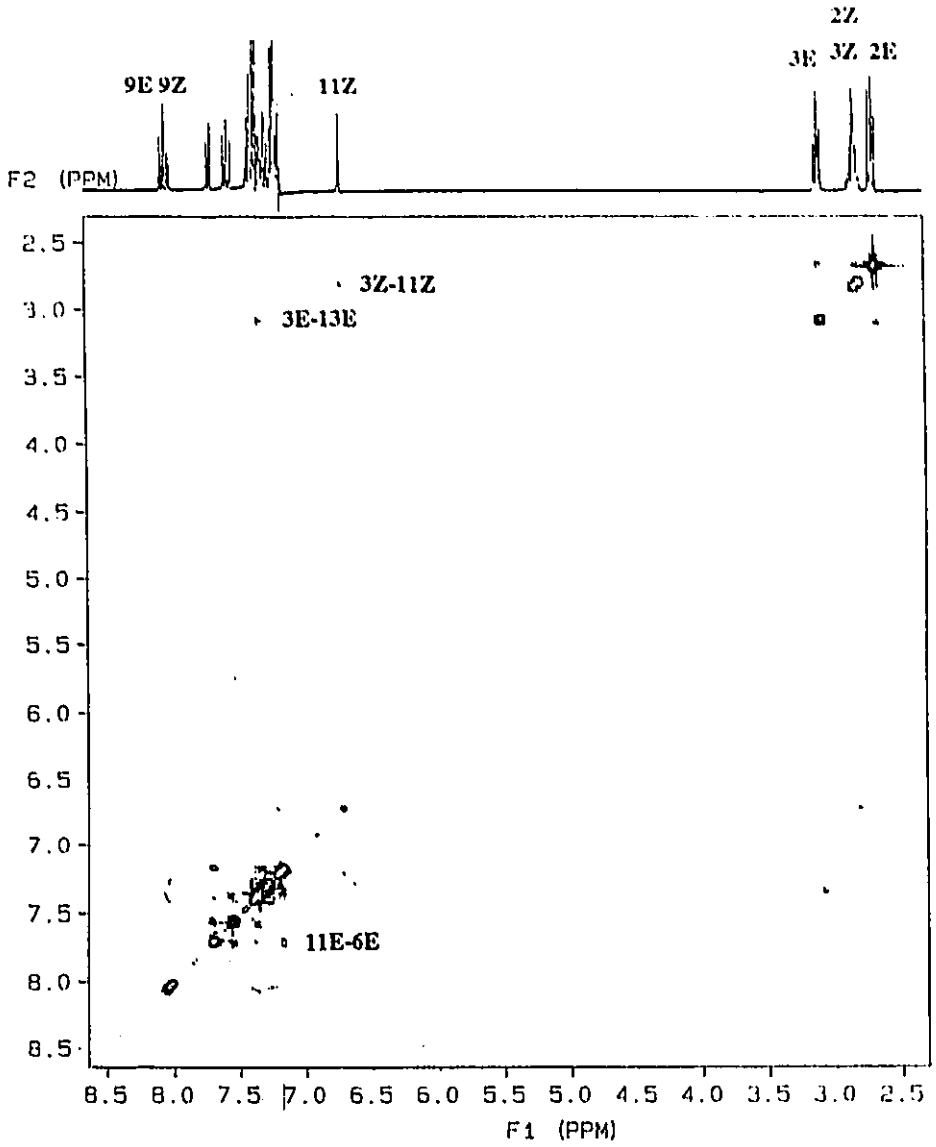
Vinyl adduct

The tertiary alcohol **11**, obtained in 88% yield by treatment of **1E** with vinylmagnesium bromide, required heating in refluxing decalin (190°C) for 30 min for conversion to a 1.4:1 mixture (as judged by integration of the high field portion of the ^{1}H NMR spectrum) of E- and Z-4-benzylidene-1-tetralones **14E/Z**, in 75% yield (Scheme 2). Inspection of the NOESY (Fig 1) allowed identification of the minor component as the Z isomer with a correlation between H-3 and H-11. For the E isomer, a correlation was found between H-3 and the ortho phenyl hydrogens H-13. In addition, a correlation between the singlet at δ 7.17 and the doublet at δ 7.70 could be assigned to H-11 and H-6 respectively for the major E isomer. With these key assignments and a combination of 2-D NMR experiments such as COSY(H-H) (Fig 2), HETCOR(C-H, 1 bond corr.) (Fig 3) and FLOCK[4](C-H, mainly 3-bond corr.) (Fig 4), it was possible to assign the carbon and proton shifts for each isomer. These results are summarized in Table 1.

In refluxing xylene(160°C), the conversion of **11** to **14** was 90% complete (80% isolated products) by ^{1}H NMR after 28h. This contrasts with the 30 min at 110°C required to transform 1-vinylbenzocyclobuten-1-ol **17** into 1-tetralone **18**[5] and again illustrates the greater difficuly in generating the allenyl analogs of o-quinodimethane, e.g. **12**. Interestingly, the initial cyclization product **12** undergoes preferential reprotonation to **13** rather than aromatization to 4-benzyl-1-naphthol. Ozonolysis of **14** gave 1,4-naphthoquinone **16** in near quantitative yield presumably via in situ oxidation of the initially formed 1,4-dihydroxynaphthalene **15**.


O
H
Ph
1E
CH2CHMgBr
HO
H
Ph
11 (88%)
Δ
HO
C
Ph
12
OH
CHPh
13
O
O
[O]
OH
OH
1) O3
2) PPh3
O
O
+
H
Ph
Ph
H
16 (95%)
15
14E
1.4 : 1
14Z
(75%)
HO
110°C
30 min
O
17
18

Scheme 2



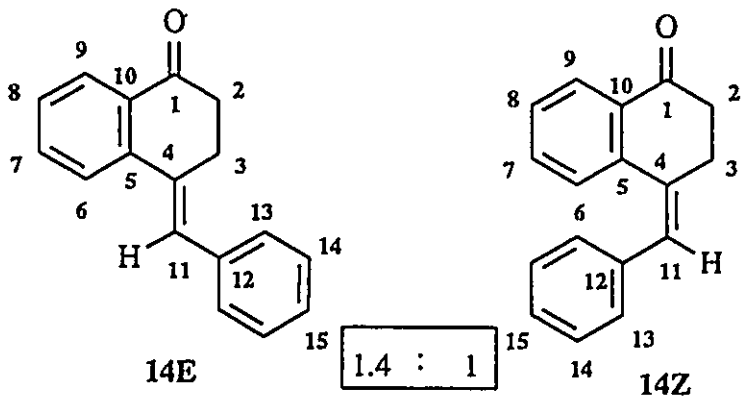


Fig 1: NOESY of 14E/Z

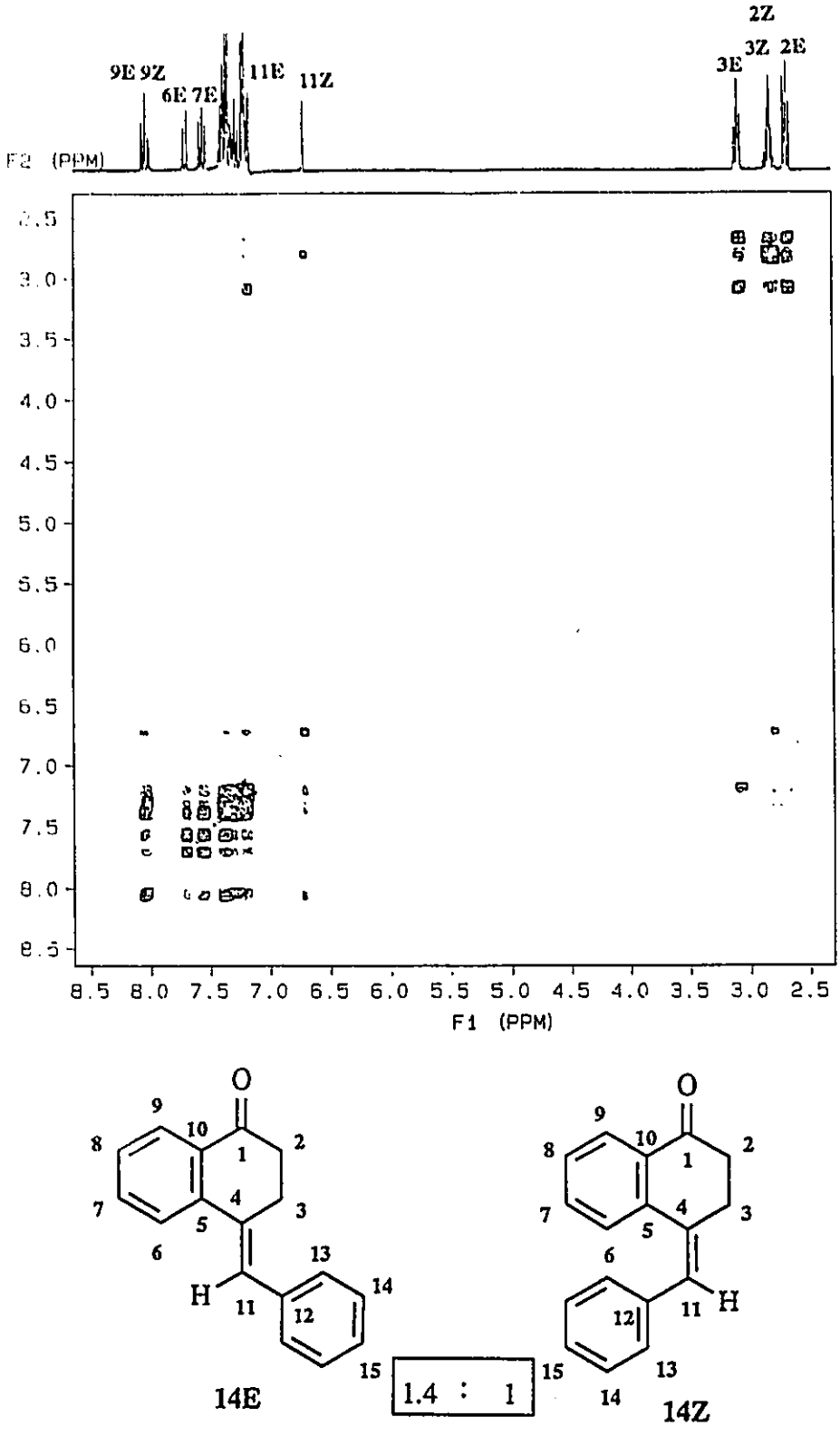
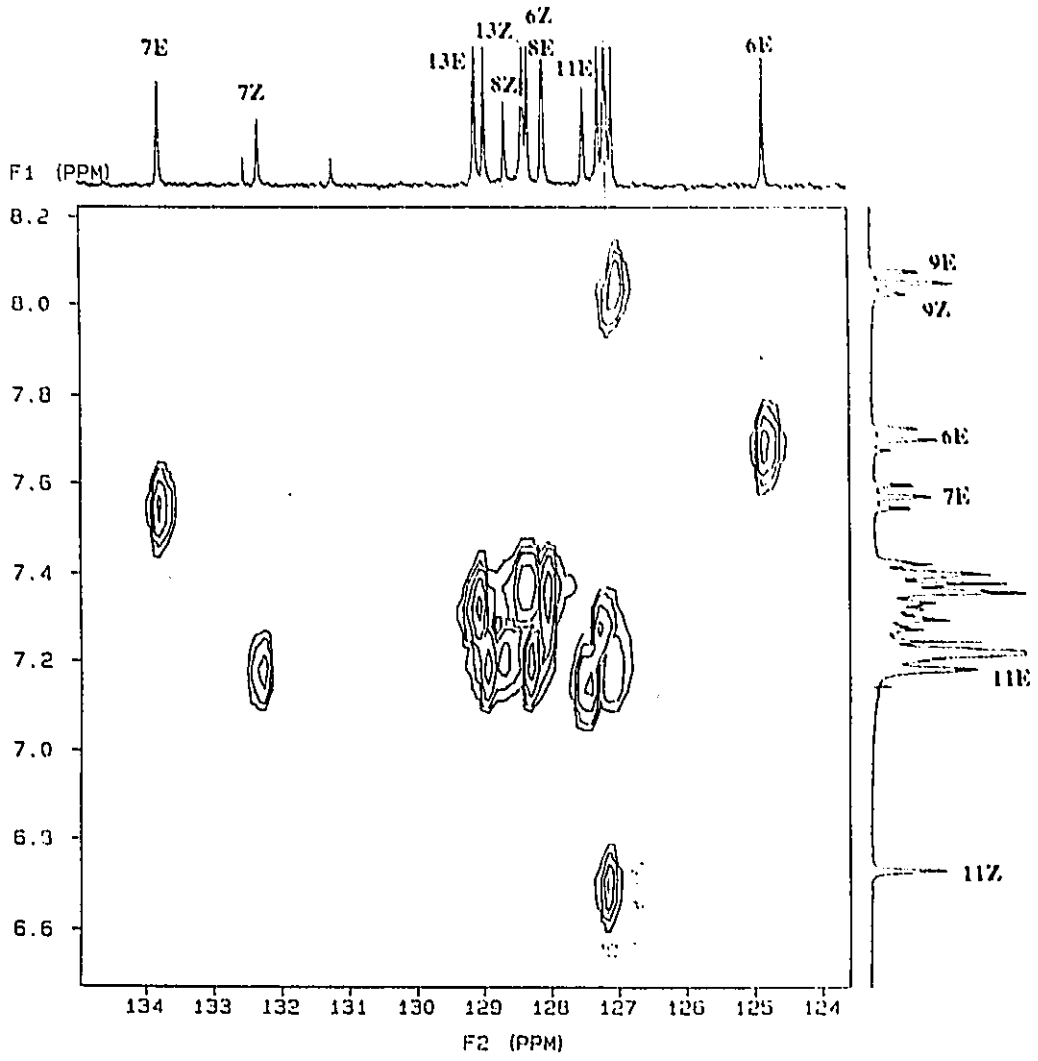


Fig 2: COSY of 14E/Z



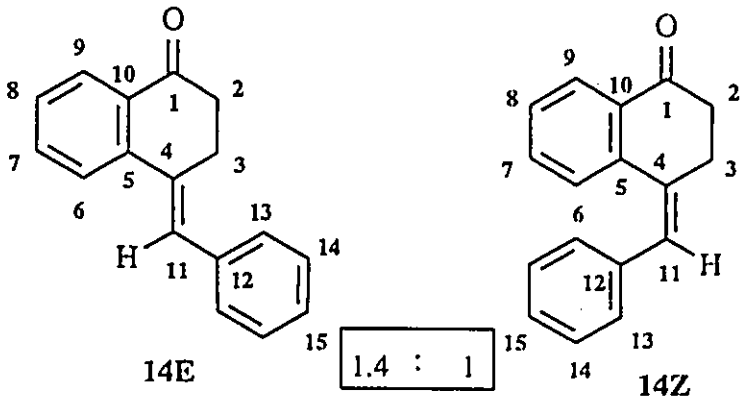
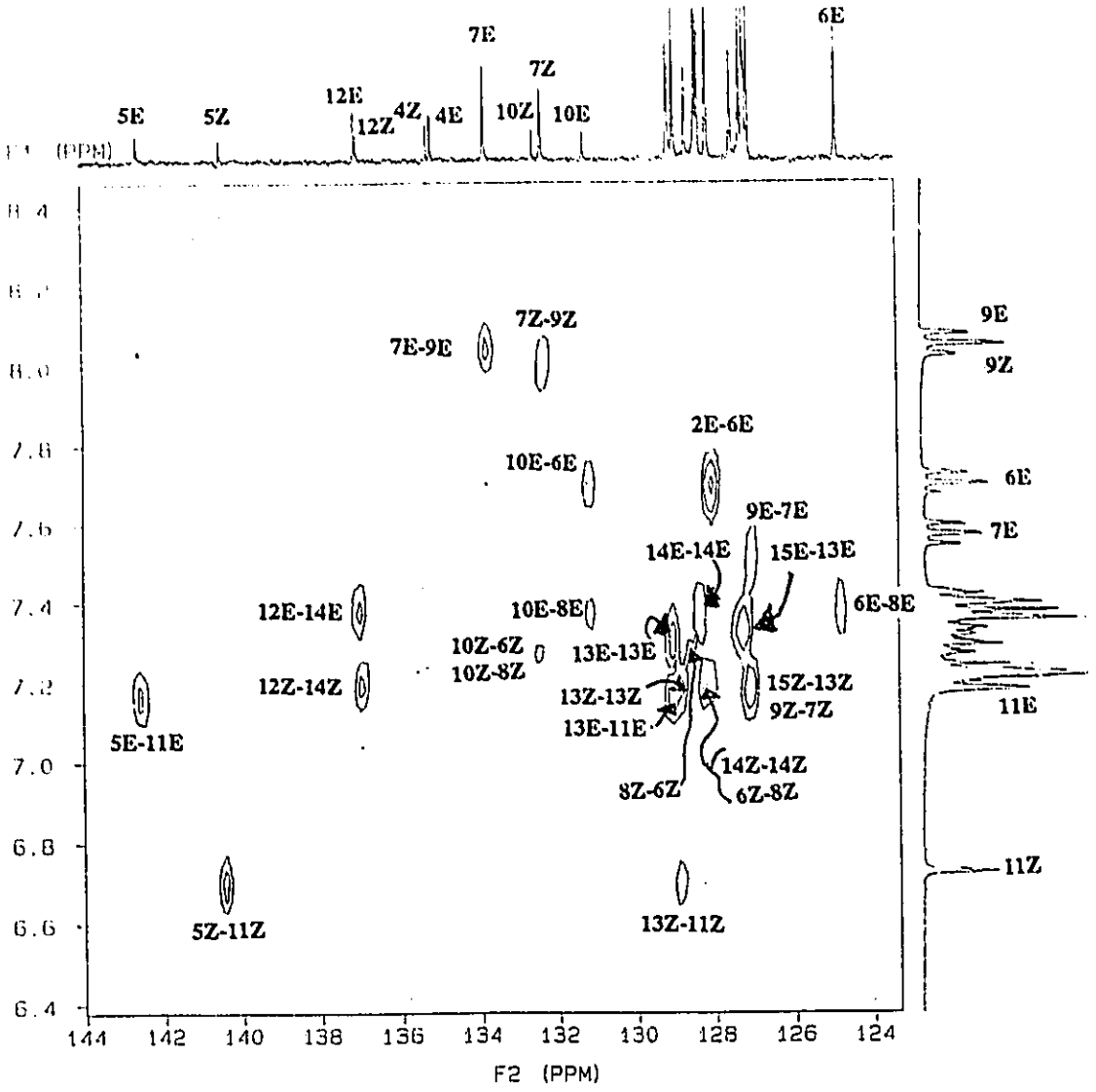


Fig 3: HETCOR of 14E/Z



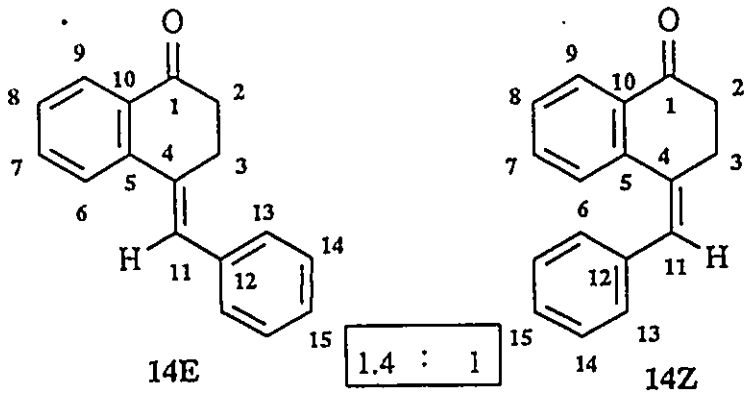
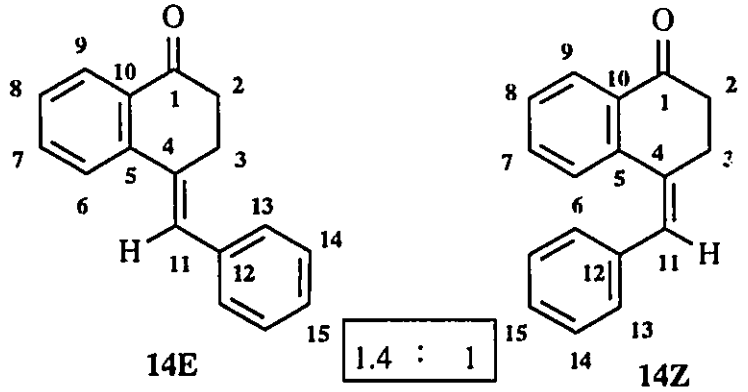


Fig 4: FLOCK (7.5 Hz) of 14E/Z

Table 1: ^{13}C and ^{1}H NMR Assignments and FLOCK Correlations for 14 E/Z

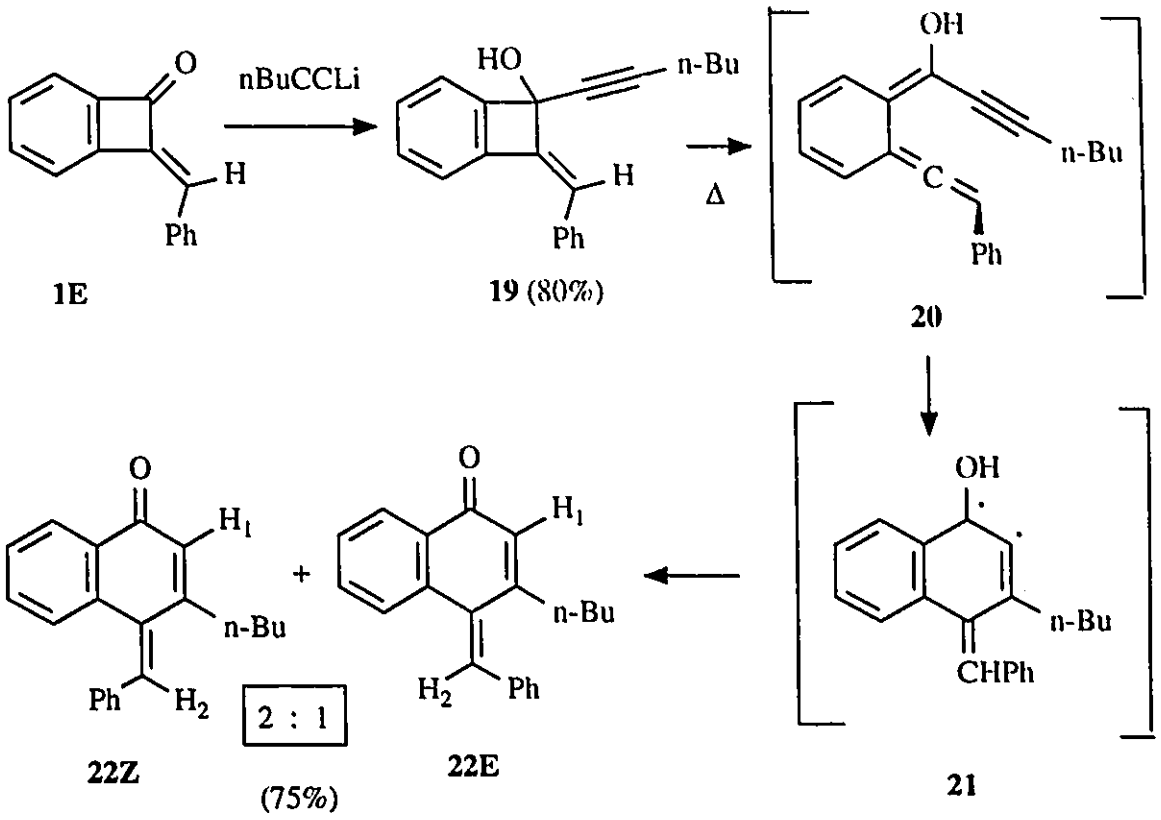
position	^{13}C		^{13}C		C-H correlation	
	E	Z	E[a]	Z[a]	E	Z
1	197.61	197.98				
2	38.84	40.09	2.68t	2.82c	3	3
3	27.19	35.63	3.09t	2.82c	2,11	2,11
4	135.14	135.25			2,3	2,3
5	142.61	140.48			11	11
6	124.85	128.11	7.70d	7.3c	8	8
7	133.79	132.32	7.56t	7.20c	9	9
8	128.10	128.67	7.39c	7.24c	6	6
9	127.08	127.19	8.04d	8.03d	7	7
10	131.24	132.52			6,8	6,8
11	127.50	127.18	7.17s	6.72s	3	3
12	137.05	136.99			14	14
13	129.12	128.97	7.35c	7.20c	11,13	11,13
14	128.40	128.32	7.40c	7.21c	14	14
15	127.28	127.14	7.3c	7.2c	13	13

[a]c = centered at, d = doublet, t = triplet



Alkynyl Adducts

Treatment of **1E** with 1-lithiohexyne at -78°C followed by quenching at room temperature afforded alkynol **19** in 80% yield (Scheme 3). Thermolysis of this adduct was carried out in refluxing decalin for 1.75 h and gave a 2:1 Z:E isomeric mixture of 3-n-butyl-4-benzylidenenaphthoquinonemethides **22** in 75% isolated yield. The identification of these structures rests primarily on the IR absorption at 1640 cm^{-1} which is typical[6] of a p-quinonemethide moiety and an analysis of the ^1H NMR spectum (Fig 5), which showed the two characteristic singlets H_1 and H_2 for each isomer. Irradiation of the methylene protons adjacent to the ring (δ 2.23) in the minor isomer led to NOE enhancement of the singlet at δ 6.43 (H_{1E}) and the aromatic protons at δ 7.3 thus establishing the E isomer as the minor constituent. The formation of **22** is rationalised as involving ring opening to the vinylallene **20** followed by ring closure to the diradical **21**. Intramolecular hydrogen atom transfer yields **22**. The formation of **22** is expected based on the observations by Moore[7] concerning the thermolysis of 4-alkynyl-4-hydroxy-cyclobutenones.


O
nBuCCLi
HO
n-Bu
H
Ph
1E
19 (80%)
Δ
OH
n-Bu
C
Ph
20
21
CHPh
H1
H2
2 : 1
22Z
22E
(75%)

Scheme 3

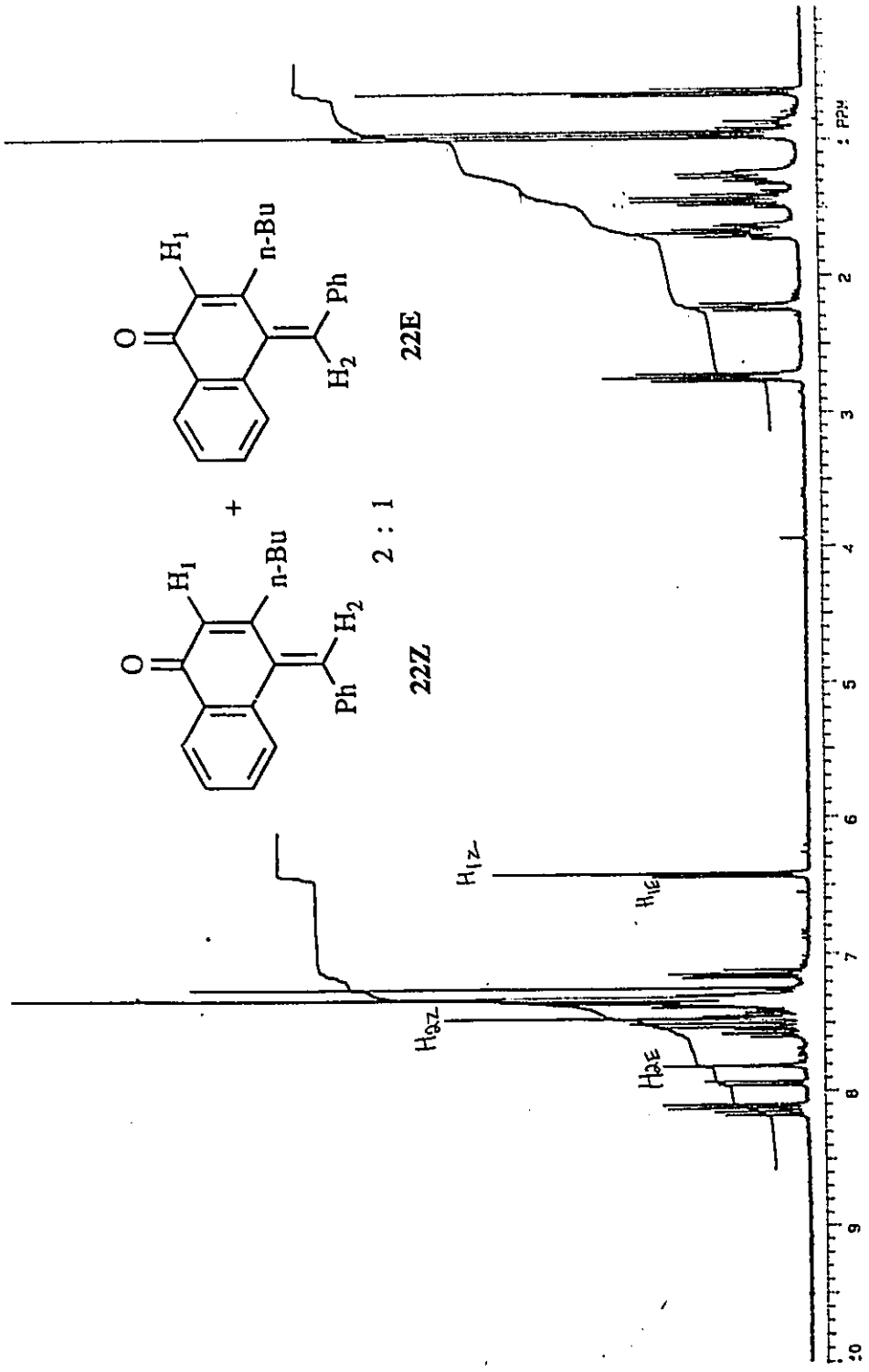


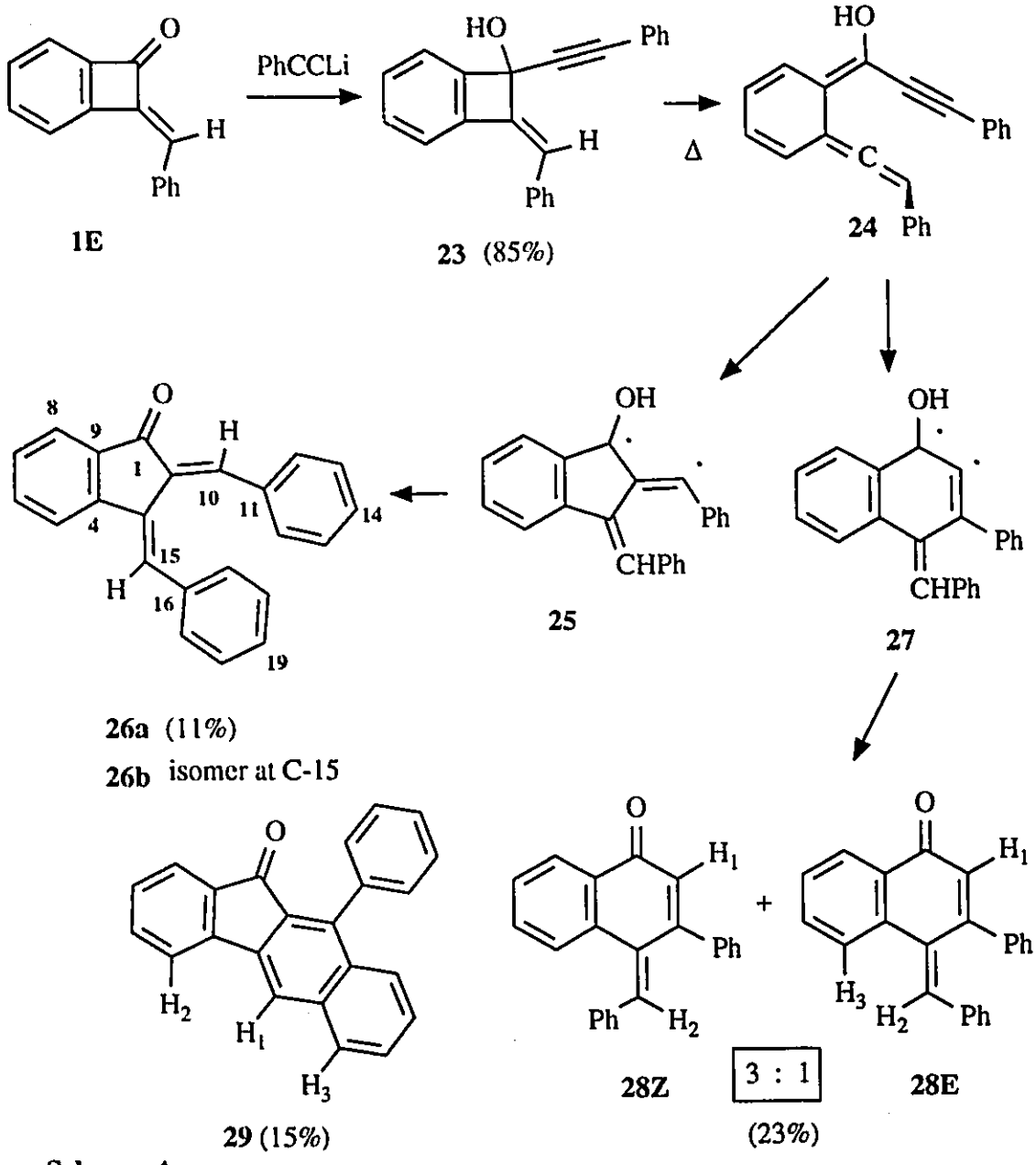
Fig 5: ^{1}H NMR of 22E/Z

The phenylalkynyl alcohol **23** was obtained from the condensation of **1E** with lithium phenylacetylide in 85% yield (Scheme 4). Thermolysis of **23** in refluxing decalin afforded the four isomeric products shown in Scheme 4. One of these, **28**, was shown to be a 3:1 Z:E mixture of 3-phenyl-4-benzylidenenaphthoquinonemethides. Their structure assignment was based on IR and NMR arguments made for the analogous isomeric mixture **22**. In this case, the identification of the E isomer as the minor component was accomplished by inspection of the NOESY (Fig 6), which showed a correlation between the benzylidene hydrogen H_{2E} at δ 7.95 and the nearest hydrogen on the naphthoquinonemethide skeleton H_{3E} at δ 8.10.

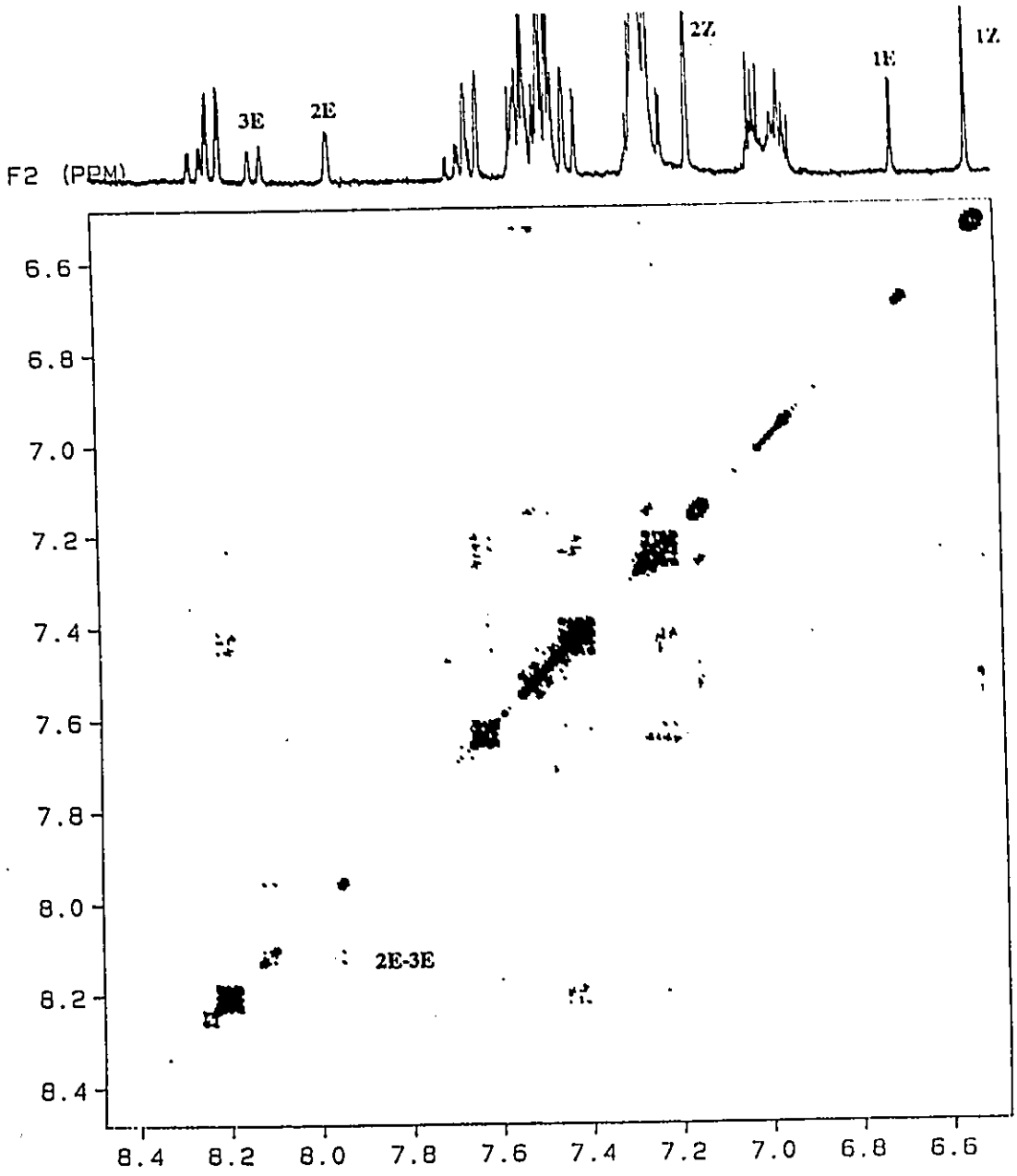
The isomeric pair of 2,3-dibenzyliden-indan-1-ones **26a** and **26b** can be rationalized as arising from an alternate cyclization of **24** to the diradiacal **25** followed by hydrogen transfer. This path becomes competititive with cyclization to **27** since phenyl is a good radical stabilizer.[7] It was possible to isolate **26a** and characterize it by its IR spectrum which showed an absorption at 1703 cm^{-1} characteristic[8] of 2-alkylidene-1-indanones and full assignment of the hydrogen and carbon resonances by means of the same 2-D NMR techniques used for the isomeric mixture **14**.(see Figs 7-9) These results are summarized in Table 2. The stereochemical assignment at the vinyl carbon 15 was unambiguous due to a clear NOE enhancemnt of H-5 upon irradiation of H-15. Irradiation of H-10 only led to enhancement of the ortho phenyl hydrogens H-12. However, the failure to enhance H-17 by irradiating H-10 does not lead to a definitive stereochemical assignment at C-10. Attempts to observe NOE enhancement of H-17 after irradiating H-12 also yielded equivocal results due to the proximity of the shifts for H-12 and H-17. This problem was resolved by addition of the shift reagent $Eu(fod)_3$, which selectively deshielded H-10 by 1.6 ppm and H-8 by 0.6 ppm while the rest of the hydrogens were affected by only 0.1-0.3 ppm (see Fig 10). This is possible only with the assigned stereochemistry at C-10 assuming that the shift reagent coordinated with the carbonyl functionality.[9]

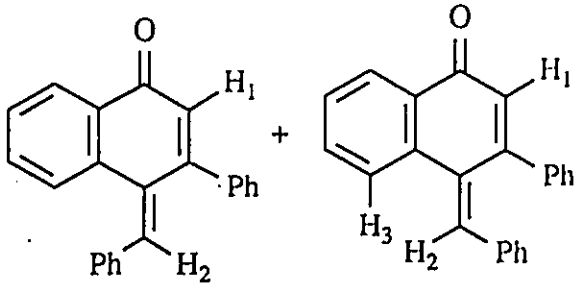
Isolation of the isomer **26b** by chromatography was not possible.

2-Alkylidene-1,3-indanediones have proved to be quite unstable to silica gel[10] and it is possible that **26b** is more sensitive than **26a** and decomposes partially upon attempted purificaiton. Some of the crude fractions suggest that this material may be present since they show an IR absorption at 1704 cm^{-1}, expected for this stucture.



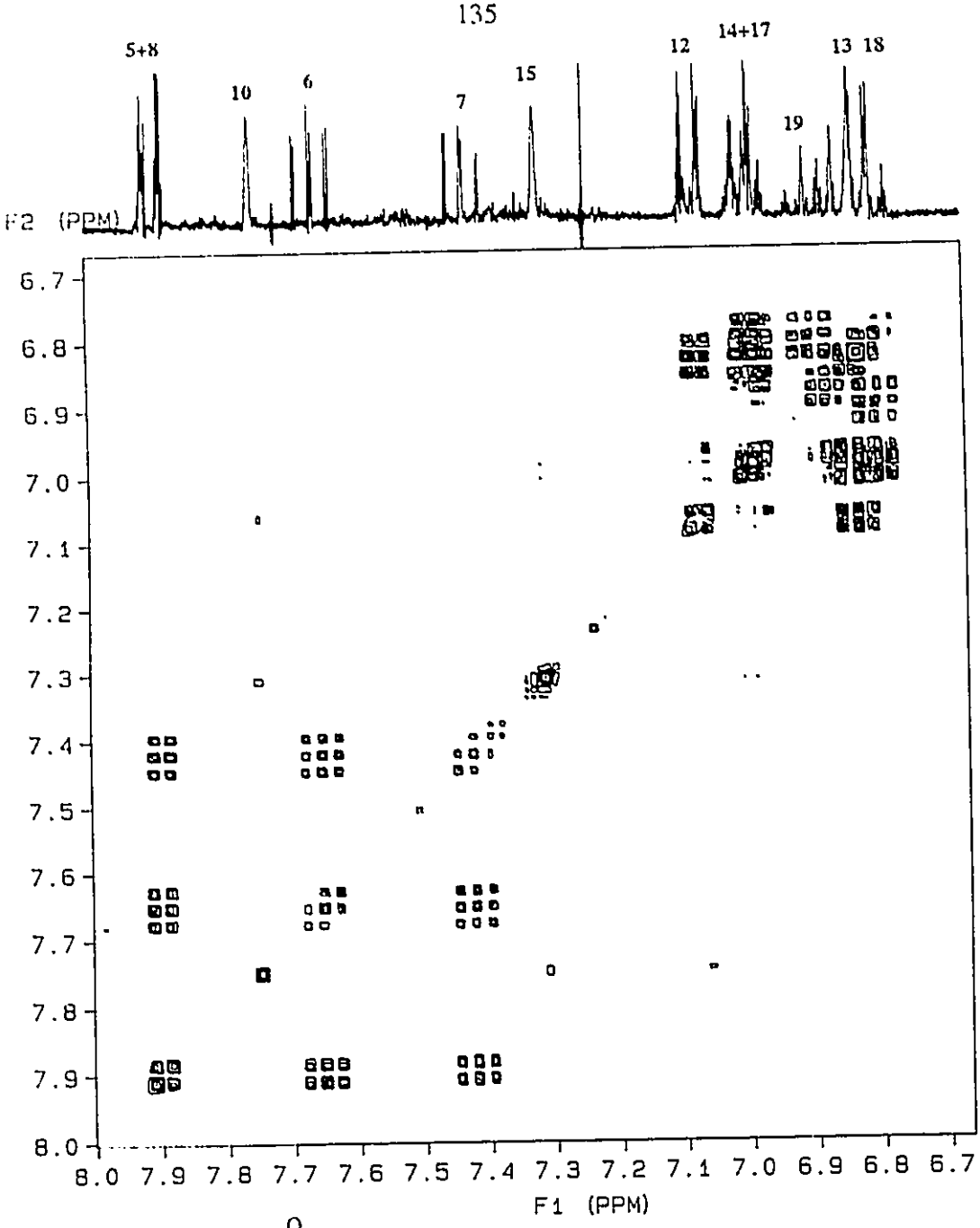
Scheme 4

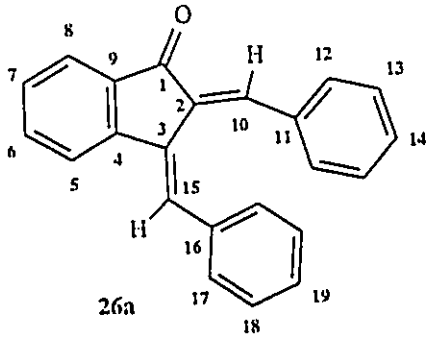




28Z 3 : 1 **28E**

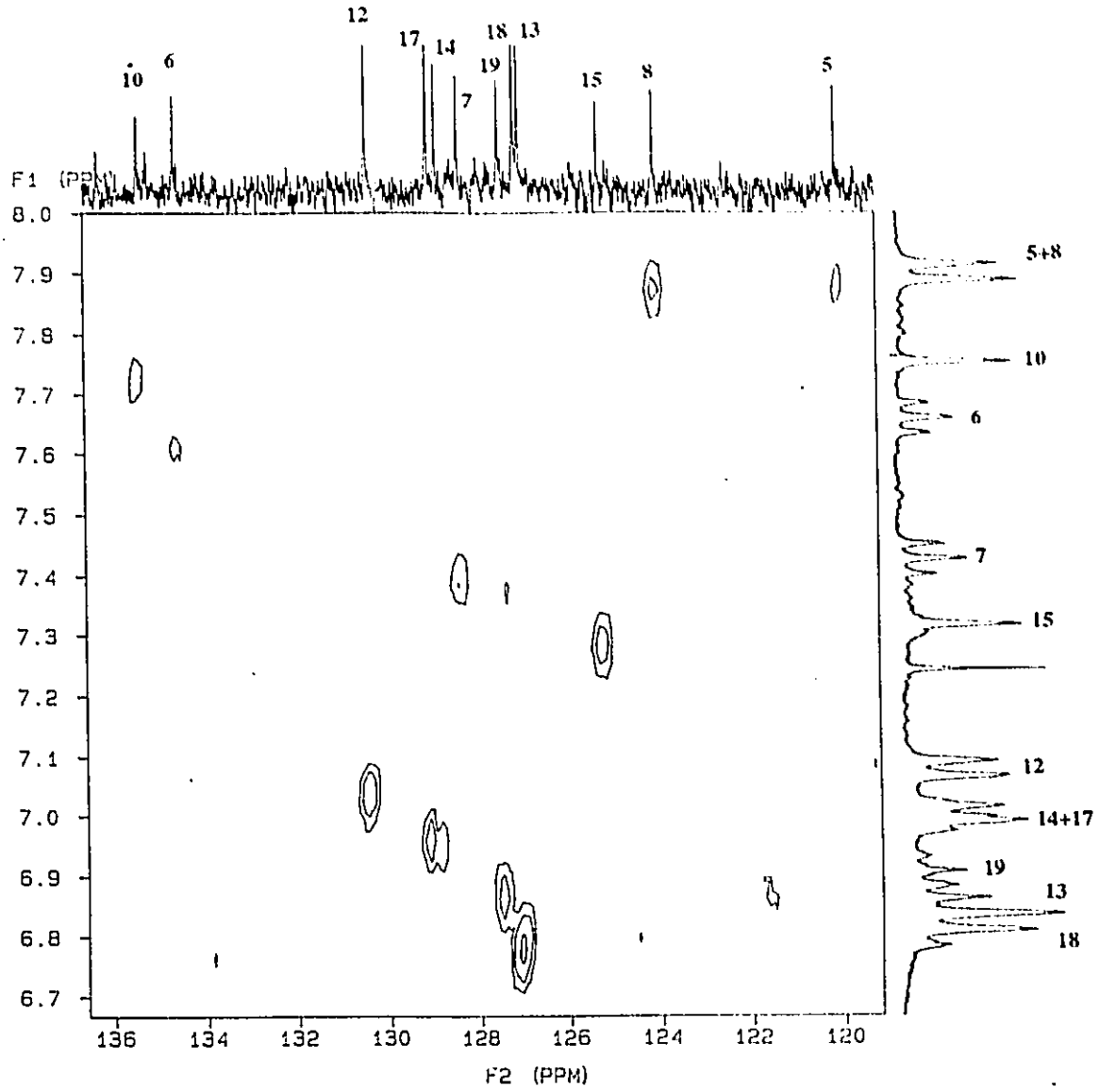
Fig 6: NOESY of 28E/Z

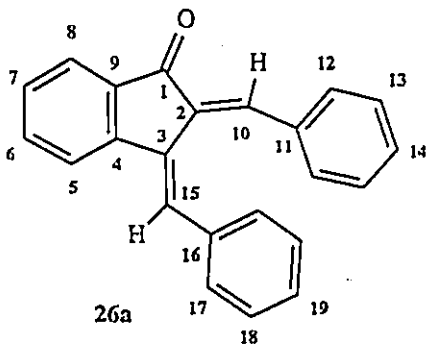




26a

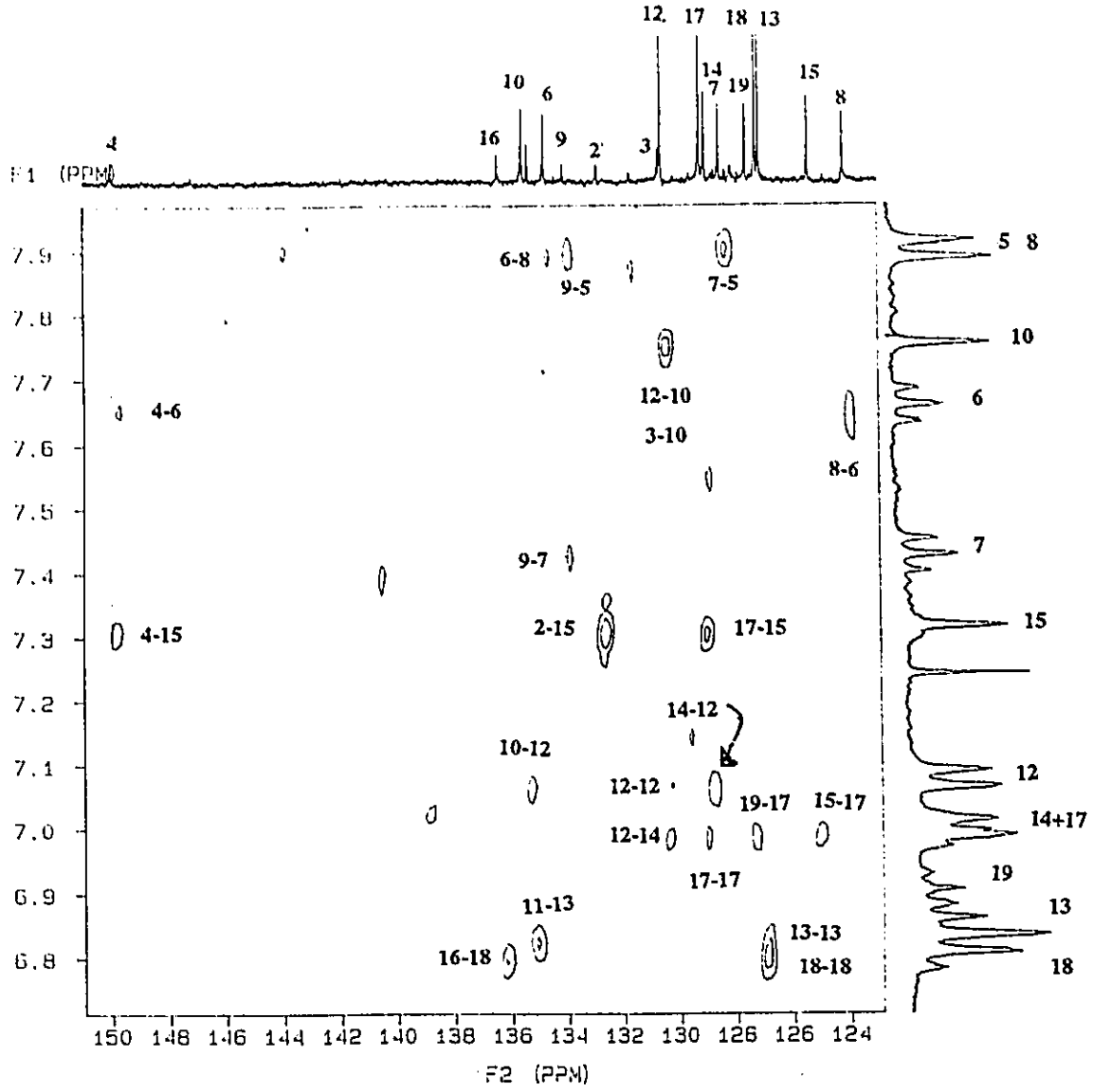
Fig 7: COSY of 26a

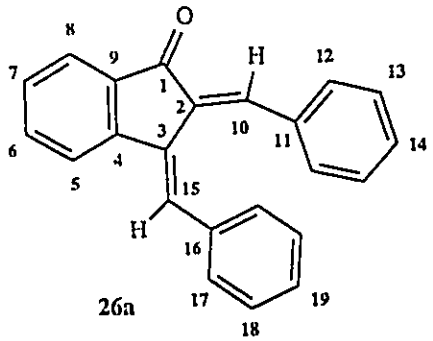




26a

Fig 8: HETCOR of 26a





26a

Fig 9: FLOCK (7.5 Hz) of 26a

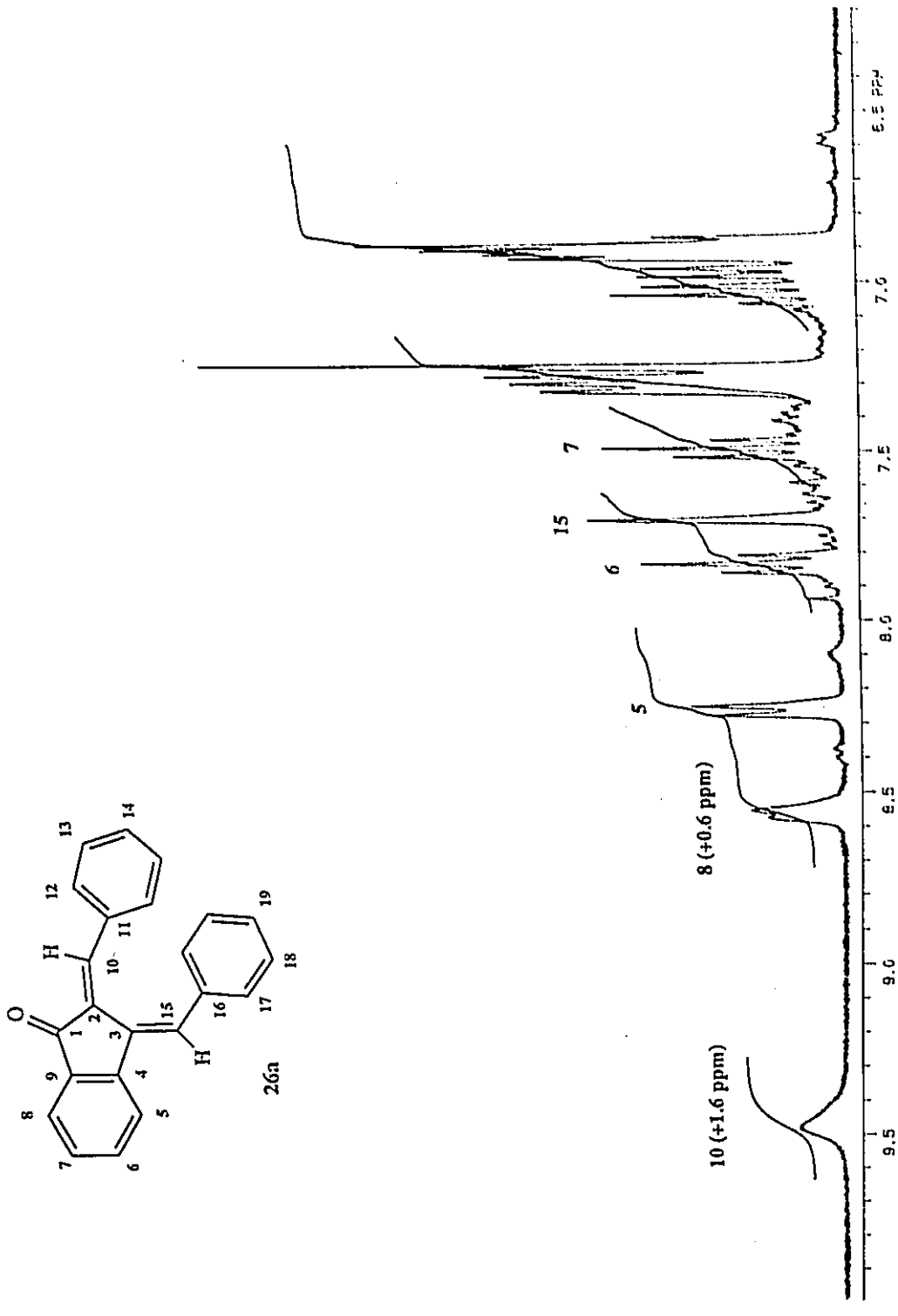
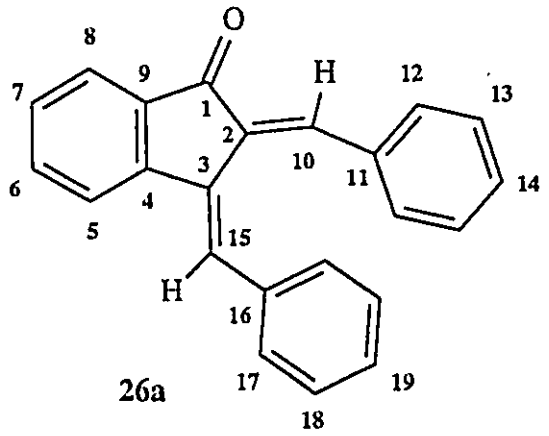


Fig 10: ^{1}H NMR of 26a in the presence of Eu(fod)$_3$

Table 2: ^{13}C and ^{1}H Assignments and FLOCK Correlations for 26a

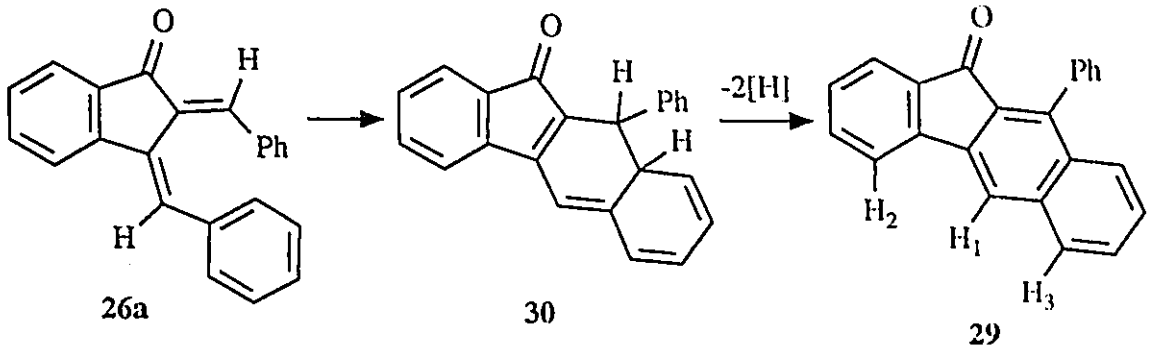
position	^{13}C	$^{1}H^{a}$	C-H corr
1	187.2		
2	132.79		15
3	130.59		10
4	149.98		6,15
5	120.01	7.89d	
6	134.02	7.65t	8
7	128.02	7.42t	5
8	124.08	7.89d	6
9	134.02		5,7
10	135.48	7.74s	12
11	135.28		13
12	130.49	7.08d	10,12,14
13	127.04	6.83c	13
14	128.43	7.00c	12
15	125.31	7.31s	17
16	136.35		18
17	129.43	7.00c	15,17
18	127.15	6.80c	18
19	127.50	6.91t	17

[a]c = centered at, d = doublet, t = triplet

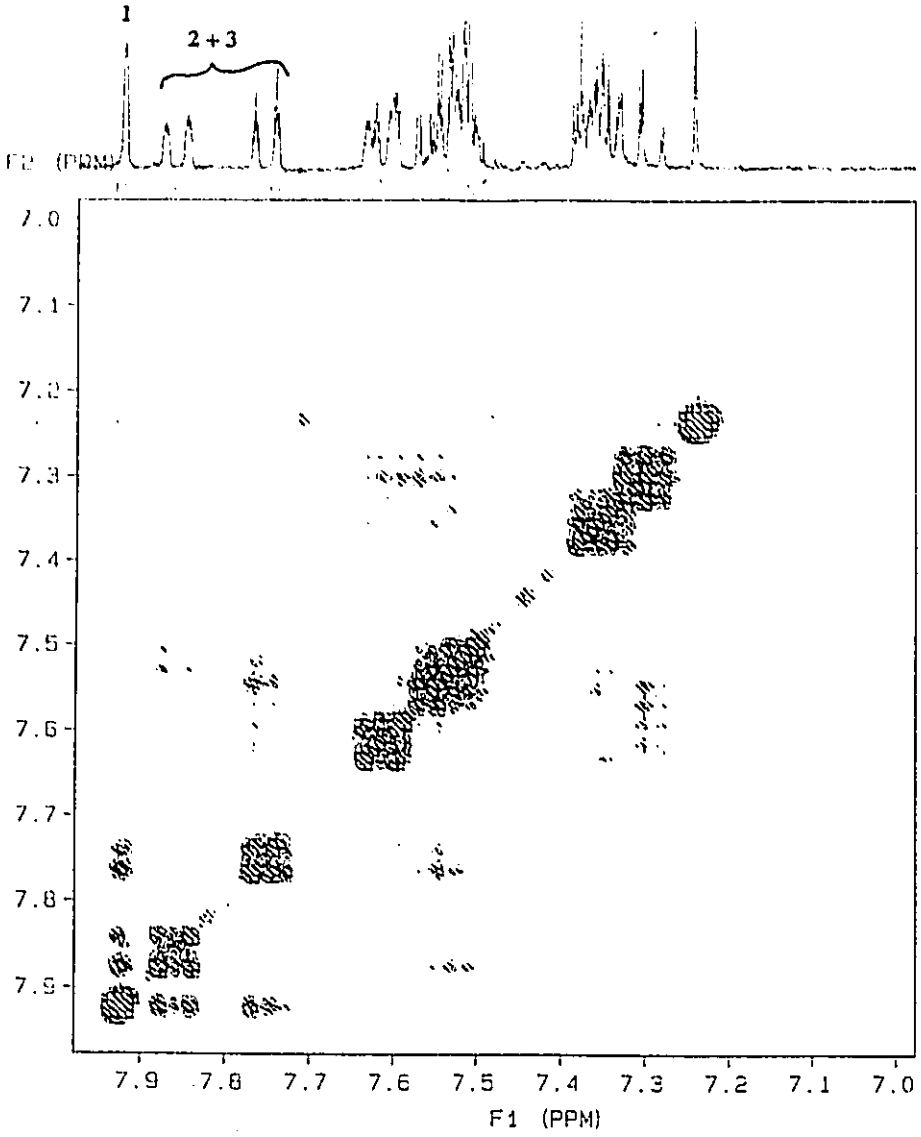


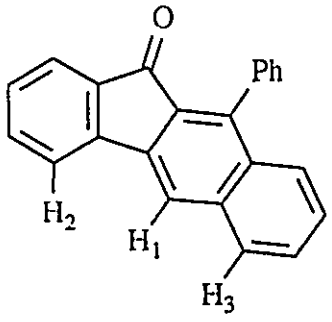
26a

The formation of the tetracyclic product **29** was initially suggested by its mass spectrum showing a strong M^+ at 306 m/e, indicating a loss of H_2 from alcohol **23**. Comparison with the reported[11] mp led to the structural assignment of **29**. A NOESY spectrum fully confirmed the position of the phenyl group adjacent to the carbonyl since strong correlations were observed between the singlet at δ 7.92 corresponding to H_1 and the two doublets at δ 7.86 and δ 7.75 assigned to H_2 and H_3 (Fig 11) The formation of **29** can be rationalized as resulting from a 6π cyclization of **26a** involving both the exocyclic C=C double bonds and 2π electrons of the phenyl group which is part of the 3-benzylidene group followed by *in situ* oxidation to the intermediate **30** to **29** (Scheme 5). Not unexpectedly **26a** undergoes slow conversion to **29** even upon standing in air at room temperature.



Scheme 5





29

Fig 11: NOESY of 29

Conclusion

The above results demonstrate that anthraquinones and naphthoquinones can be generated via a thermolysis-oxidation treatment of benzylidenebenzocyclobutenol derivatives. However, this reaction sequence allows access to only one anthraquinone regioisomer. This significantly detracts from the original synthetic strategy of utilizing benzylidenebenzocyclobutenones as common precursors to both regioisomeric anthraquinones. Consequently, investigations into substituted benzylidenebenzocyclobutenols were not pursued. Nevertheless, the efforts put forth in this direction have demonstrated the interesting thermolytic reactivity of this relatively little studied class of compounds. Specifically, it has been found that suitably substituted benzylidenebenzocyclobutenols will participate in thermolytic behaviour similar to that of the keto analogs, although requiring significantly higher temperatures.

EXPERIMENTAL

General: Same as specified in Chapter 4 with the following additions. Reagent-grade decalin kept over 4A molecular sieves was used without prior distillation. Two-dimensional NMR experiments were run on the Varian XL-300 instrument. The FLOCK pluse sequence was optimized for 7.5 Hz, yielding mainly 3-bond C-H correlations for the compounds under study. For inseperable mixtures, ^{13}C NMR shifts were assigned to each component based on quantitative ^{13}C NMR experiments, using a 90° pulse and a delay of 80 s.

Preparation of 1E: see preparation of **42E** in Chapter 2.

Preparation of 2: see preparation of **61E** in Chapter 4.

Thermolysis of 2: A solution of **2** (66 mg, 0.23 mmol) was refluxed in 10 mL of decalin (190°C) under Ar. After 16 h, a GC sample indicated the disappearance of starting material and formation of **5** (24%) **6** (50%), and **7** (15%). The solvent was removed by washing with hexanes over a plug of silica gel. Chromatography of the residue was unsuccessful in separating the components due to overlapping R_f's in various combinations of hexanes, CH_2Cl_2, ether, ethyl acetate, toluene, and CCl_4. Fractional crystallization using hexanes/CH_2Cl_2 yielded small quantities of sufficiently pure materials in the following order: **anthraquinone (7)** as white needles [^1H NMR δ 8.29 (4H, m), 7.78 (4H, m); IR (CH_2Cl_2, cm^{-1}) 1675; MS (m/e, int) 208 (100, M^+), 180 (97), 152 (77), 76 (54)]; **benzylideneanthrone (6)** as a yellowish solid [mp 128°C (lit.[12] mp 127°C); ^1H NMR δ 8.28 (1H, d, J = 8 Hz), 8.24 (1H, d, J = 8 Hz), 7.64 (1H, td, J = 8, 1.5 Hz), 7.57 (1H, s), 7.54-7.46 (2H, m), 7.40 (1H, td, J = 8, 1 Hz), 7.34-7.25 (5H, m), 7.22 (1H, td, J = 8, 1.5 Hz); IR (CH_2Cl_2, cm^{-1}) 1660, 1602; MS (m/e, int) 282 (83, M^+), 281 (100), 252 (57)]; **benzylanthrone (5)** [identified by comparison of the MS (m/e, int) 284 (22, M^+), 193 (100), 165 (37), 91 (56) (obtained by GC-MS) with the reported[13] cleavage pattern. In other runs compounds **8** and **9** were also obtained in yields of up to 35% and 14%, respectively, as estimated by GC]; **9-benzylanthracene (8)** [identified by GC-MS and comparison of the reported[14] cleavage pattern, MS (m/e, int) 194 (100, M^+), 191

(50)]; and **anthrone (9)** [identified by GC-MS and comparison with an authentic sample, MS (m/e, int) 194 (100, M^+), 165 (83)].

Preparation of 11: Vinylmagnesium bromide (1 M in hexanes, 2.8 mL, 2.8 mmol) was added to a solution of **1E** (308 mg, 1.50 mmol) in 10 mL of THF at -78°C. The solution was stirred at -78°C for 45 min and then allowed to warm to rt over 30 min. Saturated NH_4Cl was then added and the mixture extracted with ether (2 x 20 mL), dried over $MgSO_4$, and evaporated to give **11** (308 mg, 88% yield) as a colorless glassy residue: ^1H NMR δ 2.64 (1H, s), 5.22 (1H, dd, J = 10.5, 1.5 Hz, 5.53 (1HH, dd, J = 17.2, 1.5 Hz), 6.14 (1H, dd, J= 17.5, 10.5 Hz), 6.44 (1H, s), 7.25-7.45 (6H, m), 7.5-7.6 (3H, m); IR (CH_2Cl_2, cm^{-1}) 3579, 1079, 992, 930; MS (m/e, int) 234 (73, M^+), 233 (48), 215 (70), 202 (50), 178 (66), 157 (50), 131 (99), 119 (100); HRMS $C_{17}H_{14}O$ 234.1045 (calcd), 234.1047 (found).

Thermolysis of 11: A solution of **11** (65 mg, 0.28 mmol) in 10 mL of decalin was refluxed (190°C) under N_2 for 30 min. TLC indicated completion of the reaction, and the mixture was washed on a plug of silica (70-230 mech, 12 g) with 150 mL of hexanes. An orange band was eluted out with ether (25 mL), and the residue was chromatographed on a Chromatotron plate (2 mm, 20:1 hexanes-EtOAc) to yield **4-benzylidenetetralone (14)** as a white solid consisting of a 1.4:1 E/Z mixture (50 mg, 75% yield): ^1H and ^{13}C NMR (see Table 1); IR (CH_2Cl_2, cm^{-1}) 1682 (CO); MS (m/e, int) 234 (100, M^+), 191 (40), 91 (60); HRMS $C_{17}H_{14}O$ 234.1045 (calc), 234.1046 (found).

Ozonolysis of 14: A solution of **14** (74 mg, 0.32 mmol) in CH_2Cl_2 (5 mL)/MeOH (0.5 mL) was placed in a gas bubbler and cooled to -78°C. Ozone was bubbled through for 3 min, at which time the solution was deep blue. A solution of thiphenylphosphine (0.92 mg, 0.35 mmol) in 1 mL of CH_2Cl_2 was then added and the mixture stirred at -78°C for 5 min then allowed to warm to rt, evaporated, and purified on a Chromatotron plate (2 mm, 10:1 hexanes/EtOAc) to yield **naphthoquinone 16** (48 mg, 95% yield) as a yellow solid: mp 127-128°C (lit.[15] mp 126°C); ^1H NMR δ 6.95 (2H, s), 7.73 (2H, dd, J = 5.7, 3.4 Hz), 8.06 (2H, dd, J = 5.8, 3.3 Hz); ^{13}C NMR δ 126.39, 131.88, 133.90, 136.64, 184.98; IR

(CH_2Cl_2, cm^{-1}) 1669, 1599; MS (m/e, int) 158 (100, M^+), 130 (47), 104 (64), 102 (59), 76 (61), 50 (39); HRMS $C_{10}H_6O_2$ 158.0368 (calcd), 158.0359 (found).

Preparation of 19: n-BuLi (2.15 M in hexanes, 1.5 mL, 3.2 mmol) was added to a solution of 1-hexyne (0.33 g, 4.0 mmol) in 10 mL of THF at -78°C and the mixture was stirred for 25 min. A solution of **1E** (186 mg, 0.90 mmol) in THF (5 mL), precooled to -78°C, was added via cannula over 15 min, and the resulting mixture was stirred at -78°C for 6 h, quenched with saturated NH_4Cl (5 mL), and then allowed to warm to rt, extracted with ether (25 mL), and dried over $MgSO_4$. The evaporated residue was purified on a Chromatotron plate (2 mm, 1:1 hexanes/CH_2Cl_2) to yield **19** (183 mg, 71% yield) as a colorless oil: ^1H NMR δ 0.87 (t, 3H), 1.3-1.6 (m, 4H), 2.24 (t, 2H), 2.71 (s, 1H, OH), 6.62 (s, 1H, CHPh), 7.25-7.47 (m, 6H), 7.5-7.6 (m, 3H); IR (CH_2Cl_2, cm^{-1}) 3570 (OH), 2233 (C≡C); MS (m/e, int) 288 (10, M^+), 231 (100), 215 (39), 202 (48); HRMS $C_{21}H_{20}O$ 288.1514 (calcd), 288.1523 (found).

Thermolysis of 19: The acetylenic alcohol **19** (47.2 mg, 0.16 mmol) was refluxed in 3 mL of decalin for 1.75 h, when the reaction was judged complete by TLC. The reaction mixture was washed on a silica plug (15 g) with hexanes (400 mL). Elution with ether yielded the **4-benzylidene-3-butyl-1,4-naphthoquinonemethides** (**22**) (35.4 mg, 75% yield) as a brown oil (2:1 Z/E mixture): ^1H NMR δ (**22Z**) 0.95 (3H, t), 1.42 (2H, m), 1.68 (2H, m), 2.73 (2H, t), 6.41 (1H, s), 7.13 (1H, t, J = 7.3 Hz), 7.46 (1H, s), 7.51 (1H, d, J = 8.3 Hz) 8.11 (1H, d, J = 8 Hz); (**22E**) 0.63, (3H, t), 0.85 (2H, m), 1.25 (2H, m), 2.23 (2H, t), 6.43 (1H, s), 7.57 (1H, t, J = 8.3 Hz), 7.80 (1H, s), 7.94 (1H, d, J = 8.2 Hz), 8.16 (1H, d, J = 7 Hz); (overlapping **22E** + **22Z**) 7.25-7.40 (m); ^{13}C NMR δ (**22Z** + 2 double int. of **22E**) 13.89, 22.67, 31.65, 33.09, 125.89, 126.02, 128.17, 128.32, 128.56, 128.74, 128.87(x2), 129.43, 129.95, 132.07, 132.18, 135.51, 136.06, 137.23, 156.17, 185.24; (**22E**) 13.55, 22.14, 31.95, 35.10, 122.66, 126.06, 127.54, 128.23, 128.93, 130.52, 131.71, 132.53, 136.65, 137.41, 139.83, 156.25, 185.24; IR (CH_2Cl_2, cm^{-1}) 1641 (CO); MS (m/e, int) 288 (65, M^+), 207 (38), 181 (100), 105 (30), 91 (43); HRMS $C_{21}H_{20}O$ 288.1514 (calcd), 288.1511 (found).

Preparation of 23: Phenylacetylene (130 µL, 1.22 mmol) was added to a solution of n-BuLi (2.35 M in hexanes, 0.50 mL, 1.18 mmol) at -78°C. The mixture was stirred for 45 min followed by addition of **1E** (125 mg, 0.61 mmol) in 5 mL of THF, precooled to -78°C. The mixture was stirred at -78°C for 1.5 h and then allowed to warm to rt for 30 min. THe resulting brownish solution was poured into a vigorously stirred mixture of ether (40 mL) and saturated NH_4Cl (10 mL) which turned yellowish after a few minutes. The organic phase was separated, dried, evaporated and then purified on a Chromatotron plate (2 mm, 3:1 hexanes/ethyl acetate) to yield **23** (158.3 mg, 85% yield) as a brown oil: ^{1}H NMR δ 2.92 (1H, s, OH), 6.72 (1H, s, CHPh), 7.2-7.6 (14H, m); ^{13}C NMR δ 84.59, 88.23, 119.94, 121.24, 122.16, 122.41, 127.71, 127.98, 128.25, 128.56, 128.62, 130.23, 130.62, 131.93, 136.39, 143.57, 145.89, 151.42; MS (m/e, int) 308 (78, M^+), 307 (94), 231 (100), 202 (41); HRMS $C_{23}H_{16}O$ 308.1201 (calcd), 308.1117 (found).

Thermolysis of 23: A solution of the acetylenic alcohol **23** (169 mg, 0.55 mmol) in 20 mL of decalin was refluxed for 2 h, at which time the reaction was judged to be complete by TLC. The mixture was washed with hexanes (400 mL) over a plug of silica (20g) and then eluted with ether (100 mL), CH_2Cl_2 (100 mL), and EtOAc (100 mL). The combined elutents were chromatographed on a Chromatotron plate (2 mm, 3:1 hexanes/CH_2Cl_2 -> pure CH_2Cl_2). The following fractions were obtained:

26a (18.6 mg, 11% yield): ^{1}H and ^{13}C NMR (see Table 2); IR (CH_2Cl_2, cm^{-1}) 1703, 1615; MS (m/e, int) 308 (100, M^+), 307 (43), 306 (33), 231 (54), 202 (38), 138 (23); HRMS $C_{23}H_{16}O$ 308.1201 (calcd), 308.1210 (found).

28 (38.9 mg, 23% yield) (isolated as 3:1 Z/E mixture): ^{1}H NMR δ (**28Z**, major) 6.53 (1H, d, J = 0.5 Hz), 7.15 (1H, s, br), 7.43 (1H, t, J = 7.9 Hz), 7.63 (1H, d, J = 8.6 Hz), 8.20 (1H, d, J = 8.4 Hz); (**28E**, minor) 6.70 (1H, d, J = 1.5 Hz), 7.67 (1H, t, J = 7.2 Hz), 7.95 (1H, d, J = 1.5 Hz), 8.10 (1H, d, J = 7.5 Hz), 8.25 (1H, d, J = 7.8 Hz); (overlapping peaks for **28Z** and **28E**) , 6.92-7.03 (m), 7.2-7.3 (m), 7.46-7.56 (m); ^{13}C NMR δ (**28Z**, major) 126.10, 126.18, 128.49, 128.53, 128.62, 128.73, 128.79, 129.01, 129.21, 129.36, 130.23, 132.52, 132.93, 135.34, 136.82, 138.45, 141.69, 156.95, 184.98; (**28E**, minor)

122.71, 126.30, 127.41, 127.73, 127.77, 127.86, 128.32, 129.87, 130.75, 132.04, 135.82, 138.58, 139.22, 139.97, 152.99, 185.25; IR (CH_2Cl_2, cm^{-1}) 1641, 1600; MS (m/e, int) 308 (77, M^+), 230 (100), 202 (50), 100 (89); HRMS $C_{23}H_{16}O$ 308.1201 (calcd), 308.1162 (found).

29 (25.4 mg, 15% yield): mp 218-219°C (lit.[11] mp 219°C); ^1H NMR δ 7.31 (td, J = 7.4, 0.95 Hz), 7.35-7.4 (3H, m), 7.49-7.65 (7H, m), 7.75 (1H, dt, J = 7.5, 0.8 Hz), 7.86 (1H, dt, J = 8.1, 0.6 Hz), 7.92 (1H, s); ^{13}C NMR δ 118.67, 120.64, 124.13, 126.76, 127.95, 128.03, 128.54, 128.62, 128.70, 128.96, 129.15, 129.52, 133.77, 134.64, 135.44, 136.27, 136.60, 138.36, 141.18, 144.00, 192.16; IR (CH_2Cl_2, cm^{-1}) 1711 cm^{-1}; MS (m/e, int) 306 (100, M^+), 305 (77), 276 (38), 138 (39); HRMS $C_{23}H_{14}O$ 306.1044 (calcd), 306.1023 (found).

REFERENCES

1. Bradley, J.C.; Durst, T.; Williams, A.J. *J. Org. Chem.* **1992**, 57, 6575.

2. Cauquis, G.; Reverdy, G. *Tetrahedron Lett.* **1967**, 1493.

3. Liebeskind, L.S.; Iyer, S.; Jewell, C.F. *J. Org. Chem.* **1986**, 51, 3065.

4. Reynolds, W.F.; McLean, S.; Perpick-Dumont, M.; Enriquez, R.G. *Mag. Res. Chem.* **1989**, 27, 162.

5. Hickman, D.; Wallace, T.W.; Wardleworth, J.M. *Tetrahedron Lett.* **1991**, 32, 619.

6. Angle, S.R.; Louie, M.S.; Mattson, H.L.; Yang, M.W. *Tetrahedron Lett.* **1989**, 30, 1193.

7. Foland, L.D.; Karlsson, J.O.; Perri, S.T.; Schwaber, R.; Xu, S.L.; Patil, S.; Moore, H.W. *J. Am. Chem. Soc.* **1989**, 111, 975.

8. Mitchell, D.; Liebeskind, L.S.; *J. Am. Chem. Soc.* 112, 291.

9. Fraser, R.R. *Asymmetric Synthesis*, **1983**, 1, 173.

10. Liebeskind, L.S.; Chidambaram,R.; Mitchell, D.; Foster, B.S. *Pure Appl. Chem.* **1988**, **60**, 27.

11. Reid, W.; Claub, G. *Liebigs Ann. Chem.* **1975**, 953.

12. Bergmann, E.D.; Rabinovitz, M.; Glily, S. *Tetrahedron Suppl.* **1966**, 141.

13. Netto-Ferreira, J.C.; Murphy, W.F.; Redmond, R.W.; Scaiano, J.C. *J. Am. Chem. Soc.* **1990**, 112, 4472.

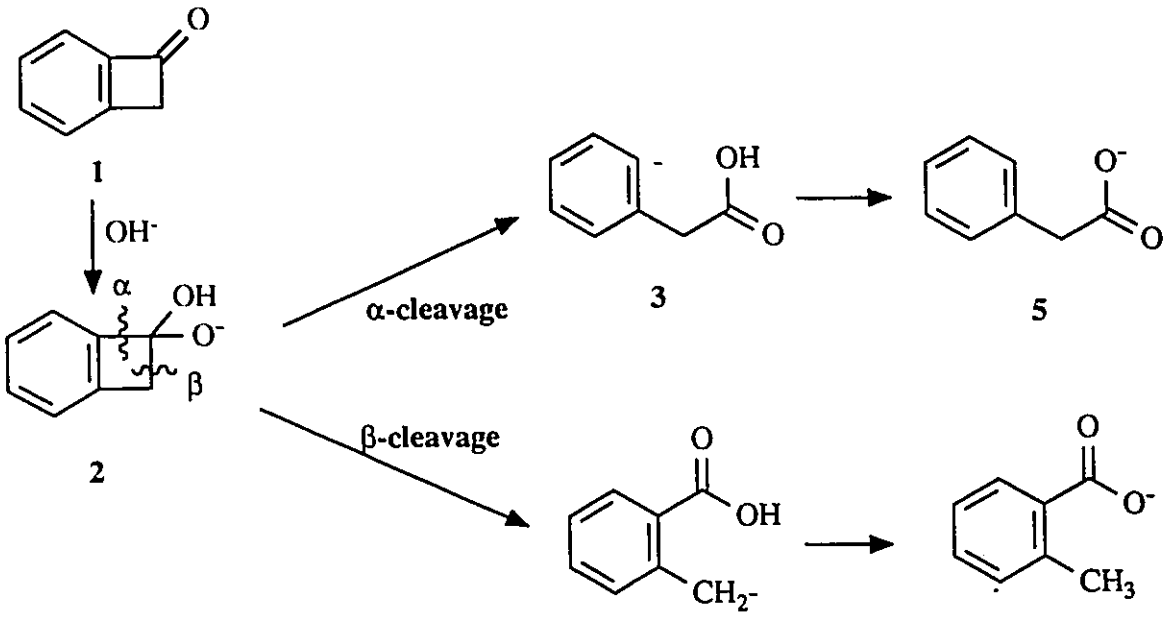
14. Fox, M.A.; Ranade, A.C.; Madany, I. *J. Organometal. Chem.* **1982**, 269.

15. Merk Index, 10th ed. Merk: Rahway, NJ, **1983**, p. 6247.

CHAPTER 6: ANIONIC CLEAVAGE OF BENZYLIDENEBENZOCYCLOBUTENONES AND DERIVATIVES

Introduction

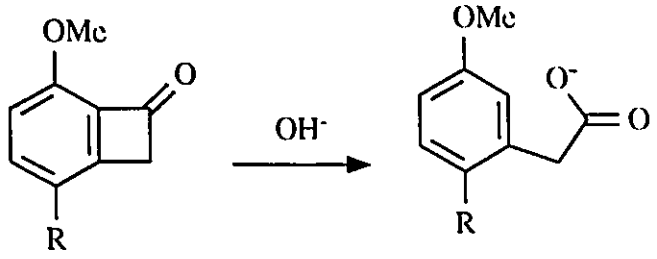
Benzocyclobutenones and their derivatives exhibit some very interesting properties when treated with various bases and nucleophiles. When treated with an aqueous solution of sodium hydroxide, benzocyclobutenone **1** yields phenylacetic acid **5** and o-toluic acid **6** in equal proportions[1] (Scheme 1). Cava's explanation of this behaviour suggested that an intermediate **2** formed which then had an equal probability of cleaving the bond alpha to the aromatic ring yielding **3** or the bond beta to the aromatic ring yielding **4**.



Scheme 1

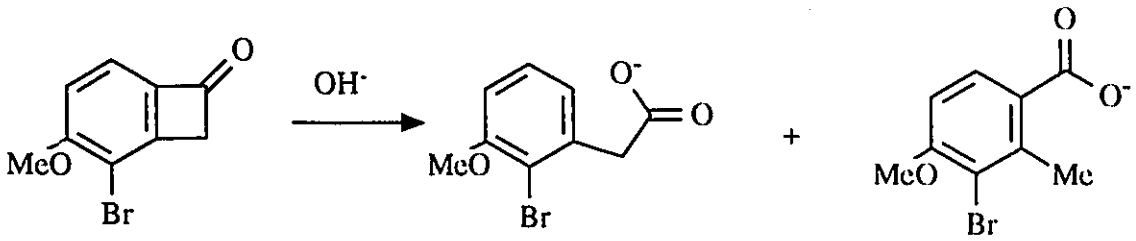
Such a mechanism was supported by further investigations which revealed that groups stabilizing a negative charge on the aromatic ring favour alpha cleavage whereas groups stabilizing an anion at the benzylic position favour beta cleavage. For example, in benzocyclobutenones **7**, a methoxy substituent ortho to the incipient aryl carbanion yielded exclusively the phenylacetic acid derivatives **8** upon treatment with aqueous

sodium hydroxide[2,3] (Scheme 2). A less pronounced effect was observed when the methoxy functionality was para to the incipient aryl carbanion as in **9**. In this case a 2:1 mixture of phenylacetic acid **10** and o-toluic acid **11** was obtained[3] (Scheme 3). On the other hand, if the incipient benzylic carbanion is stabilized, as in the bromo derivative **12**, the resulting cleavage occurrs exclusively beta to the aromatic ring to yield phthalide **15** presumably through the intermediacy of benzyl bromide **13**[4] (Scheme 4). The authors suggest that the alcohol **14** is the precursor of **15** although direct cyclization from benzyl bromide **13** is at least equally probable.



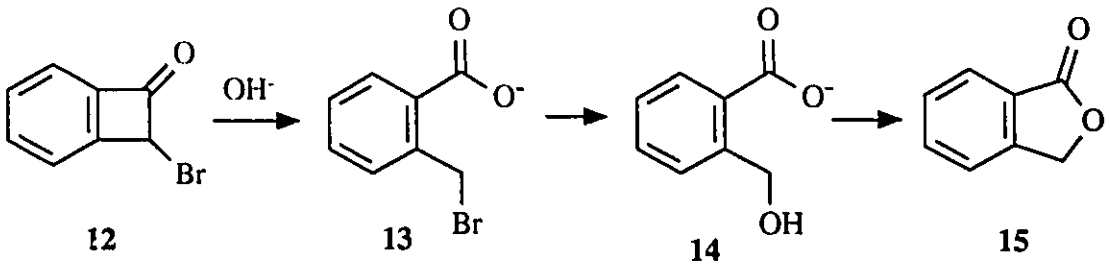
7 (R = H, Br) **8** (R = H, Br)

Scheme 2



9 **10** 2 : 1 **11**

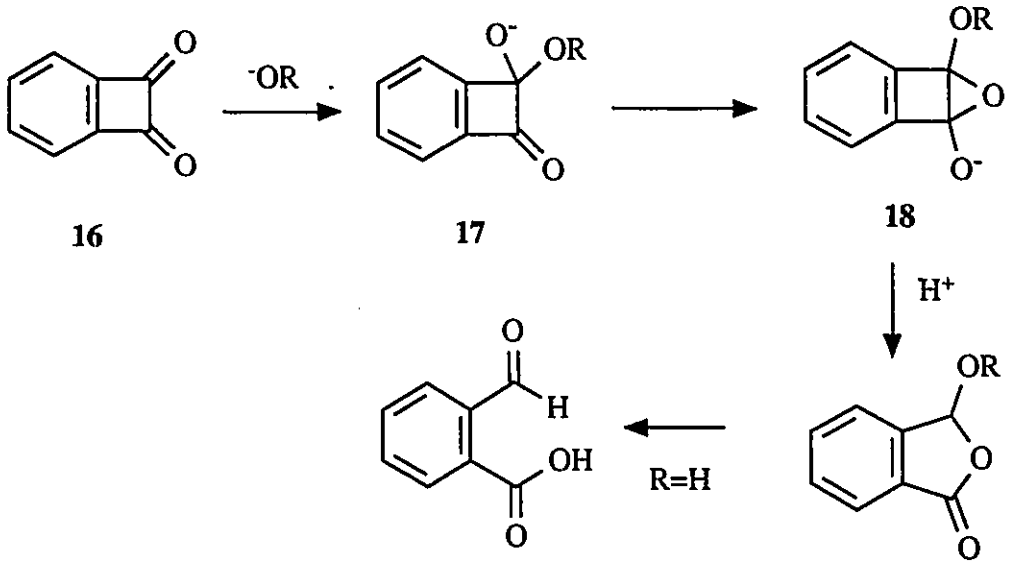
Scheme 3



12 13 14 15

Scheme 4

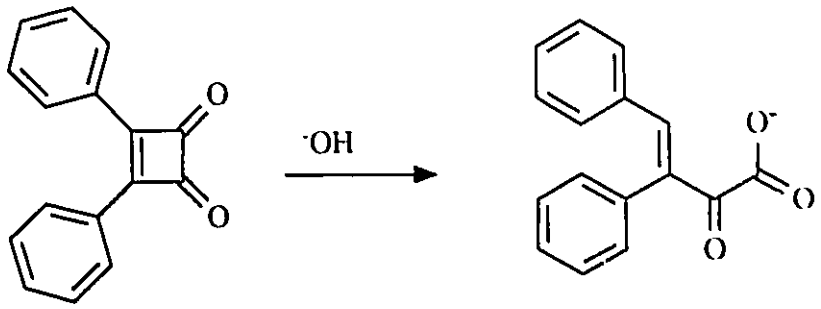
Other benzocyclobutene derivatives usually yield products arising from scission beta to the aromatic ring. For example, benzocyclobutenedione **16** yielded phthalaldehydic acid **20** when treated with methanolic sodium hydroxide[5] (Scheme 5). Treatment with alkoxide generated alkoxy phthalides **19**. These reactions are postulated to occurr via the epoxide intermediate **18** after initial formation of **17**.



16 17 18 19 20

Scheme 5

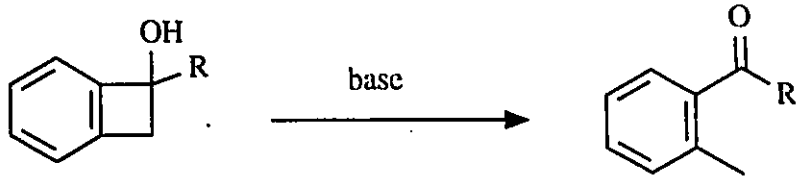
There is one notable exception to this cleavage pattern observed for diphenylcyclobutenedione **21**, which cleaves exclusively alpha to the cyclobutene double bond to **22**[6] (Scheme 6).



21 **22**

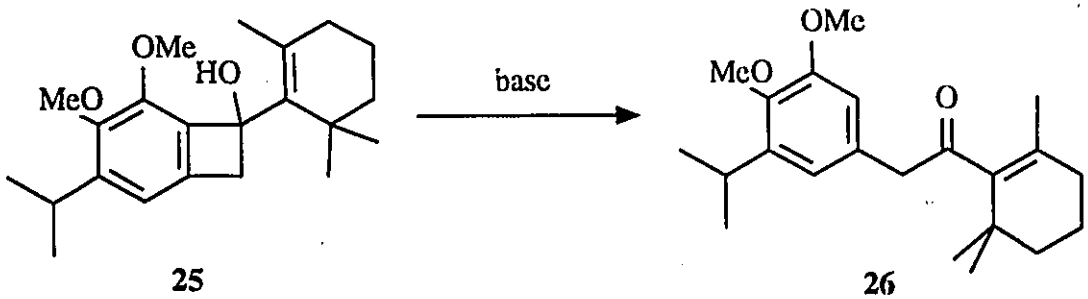
Scheme 6

In the case of benzocyclobutenols **23**, intermediates such as **18** are not possible. Anionic cleavage seems to occur exclusively beta to the aromatic ring to yield **24**[1,7-11] (Scheme 7), except in situations where there is strong stabilization of the incipient aryl carbanion as in **25**[12] (Scheme 8). For this reason, it has frequently been proposed that ring opening is due to an oxy-anionic accelerated electrocyclic ring opening.[10,13-16] There is much precedent for a similar effect in accelerations of [3,3] sigmatropic rearrangements.[17-20]



23 (R=alkyl, aryl, vinyl) **24**

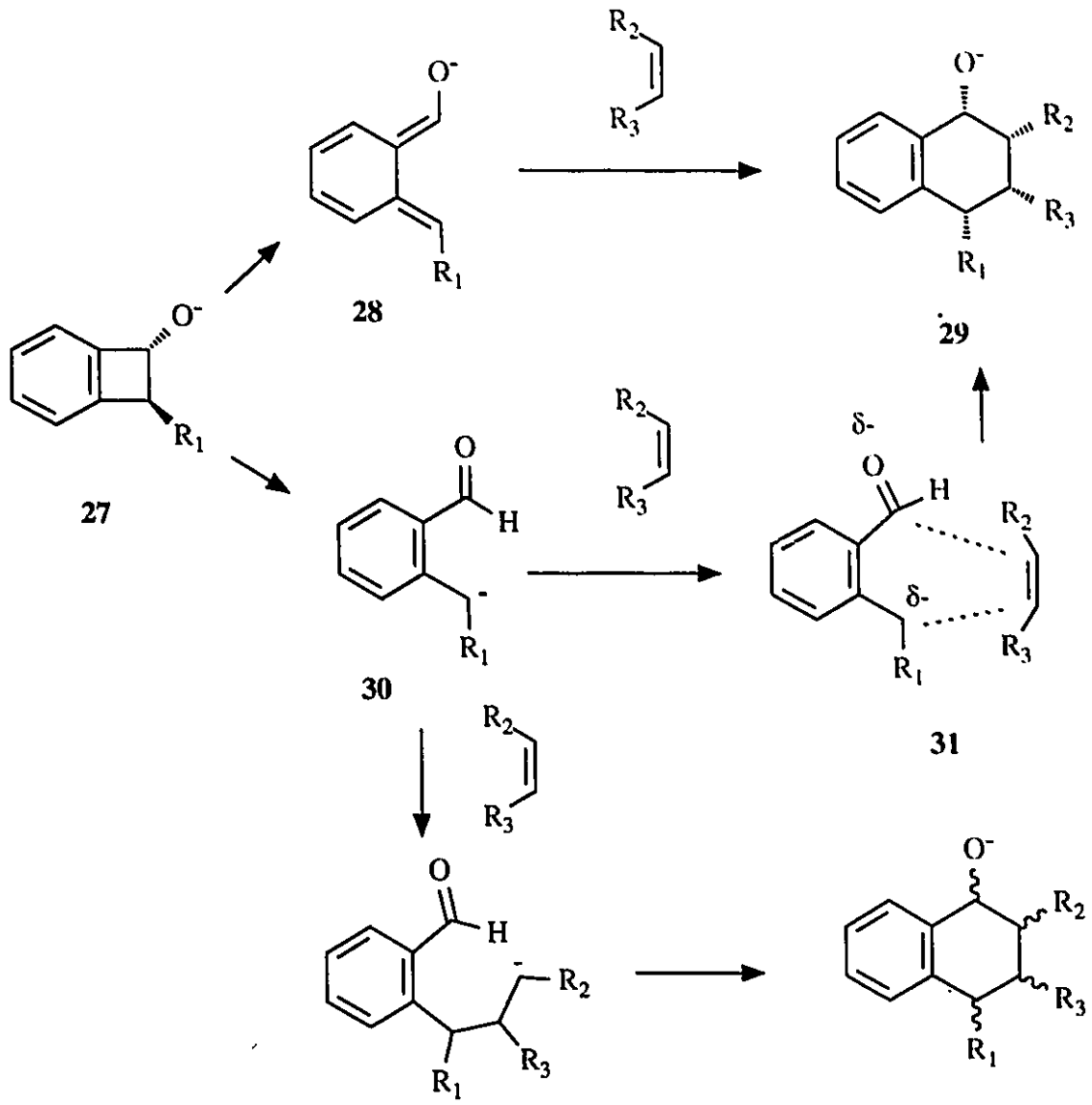
Scheme 7



25 **26**

Scheme 8

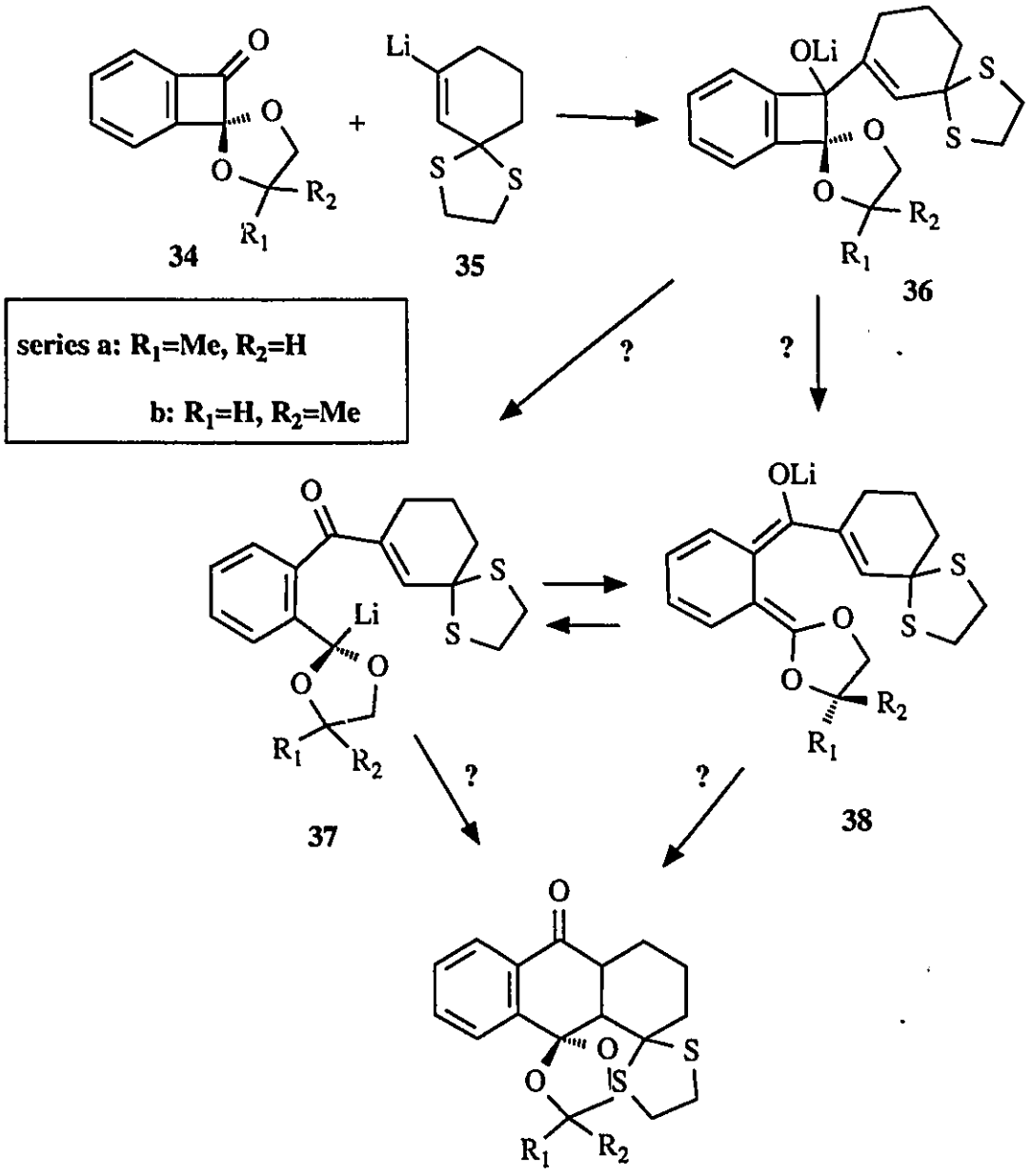
In most cases, discrimination between carbanionic and oxy-anionic promoted electrocyclic ring opening is not possible. However, there have been a few attempts to resolve the issue. One approach by Choy[10] involved trapping the putative o-quinodimethane **28** generated by forming the benzocyclobutenoxide **27** (Scheme 9). Loss of stereochemistry of the dienophile in the product **33** would only be consistent with a purely carbanionic mechanism via **30** and **32**; complete retention of stereochemistry in product **29** would certainly support an electrocyclic pathway but cannot rule out an anionic mechanism since coordination between the diene and dienophile during cyclization such as in transition state **31** could also account for the stereochemical retention. The results were that mainly retention of stereochemistry occurred but some scrambling was also noted. Thus, in this study electrocyclic opening is tentatively proposed as the major pathway.



Scheme 9

In another investigation, Swenton[21] sought to resolve this mechanistic duality by preparing two diastereomeric ketals **34a** and **34b** (Scheme 10). Reacting these ketones with the vinyllithium species **35** afforded benzocyclobutenoxide **36** which then suffered cyclobutene ring opening followed by cylization to the tricyclic ketone **39**. The result was that the same diastereomeric ratio of **39a/39b** was obtained independent of the diastereomer **34** used. A [1,3] sigmatropic rearrangement could then be ruled out since this would have likely yielded different ratios depending on the diastereomer used. The only conclusion which could be made was that o-quinodimethane **38** is likely involved to

lead to scrambled products. However, on the basis of this information it is impossible to tell if the ring opening is concerted or if it involves carbanion intermediate **37**.

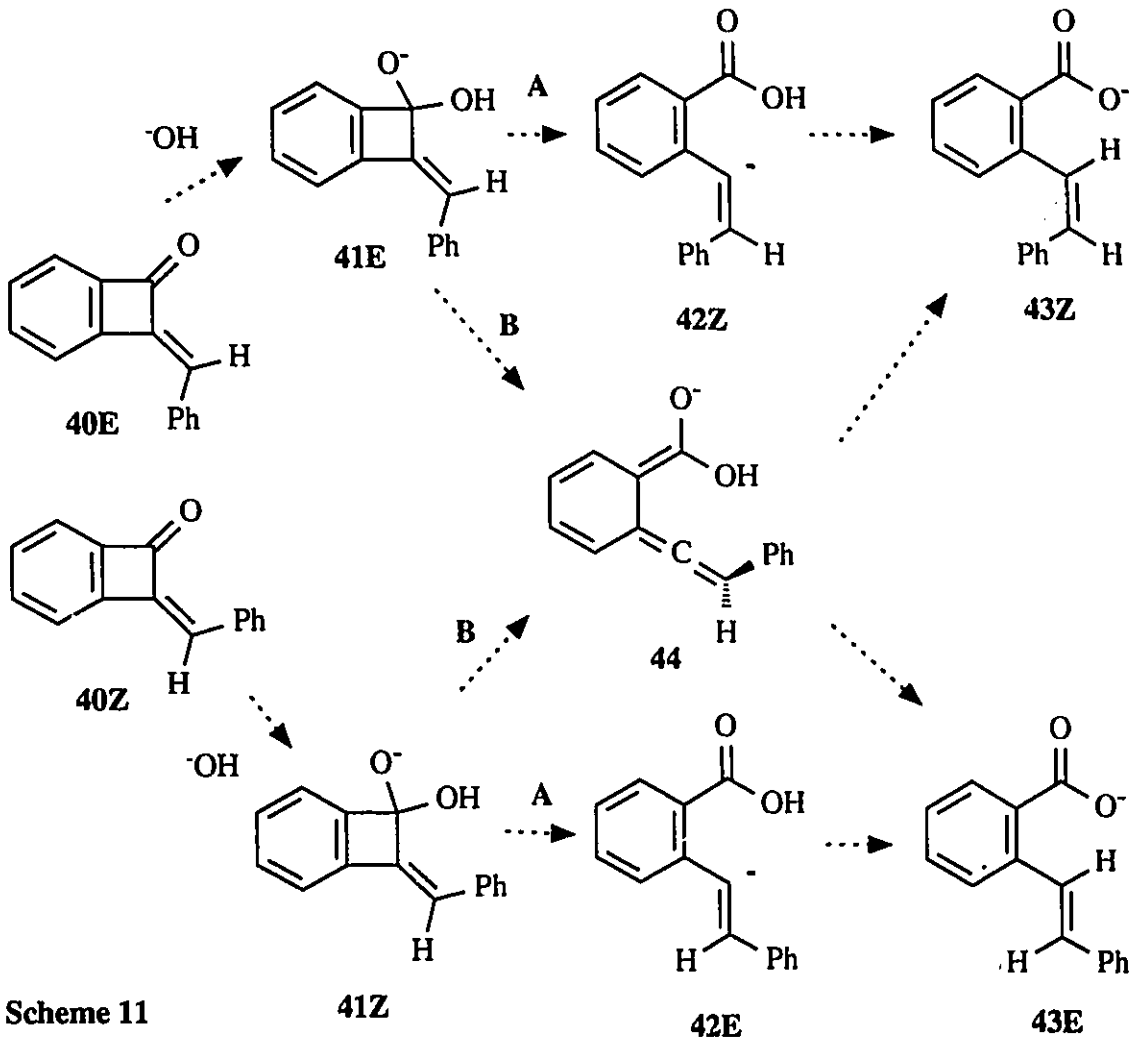


Scheme 10

Proposal for mechanistic investigations

The benzylidenebenzocylobutenones and their derivatives seemed to be ideal candidates as stereochemical probes for discriminating between oxy-anionic promoted

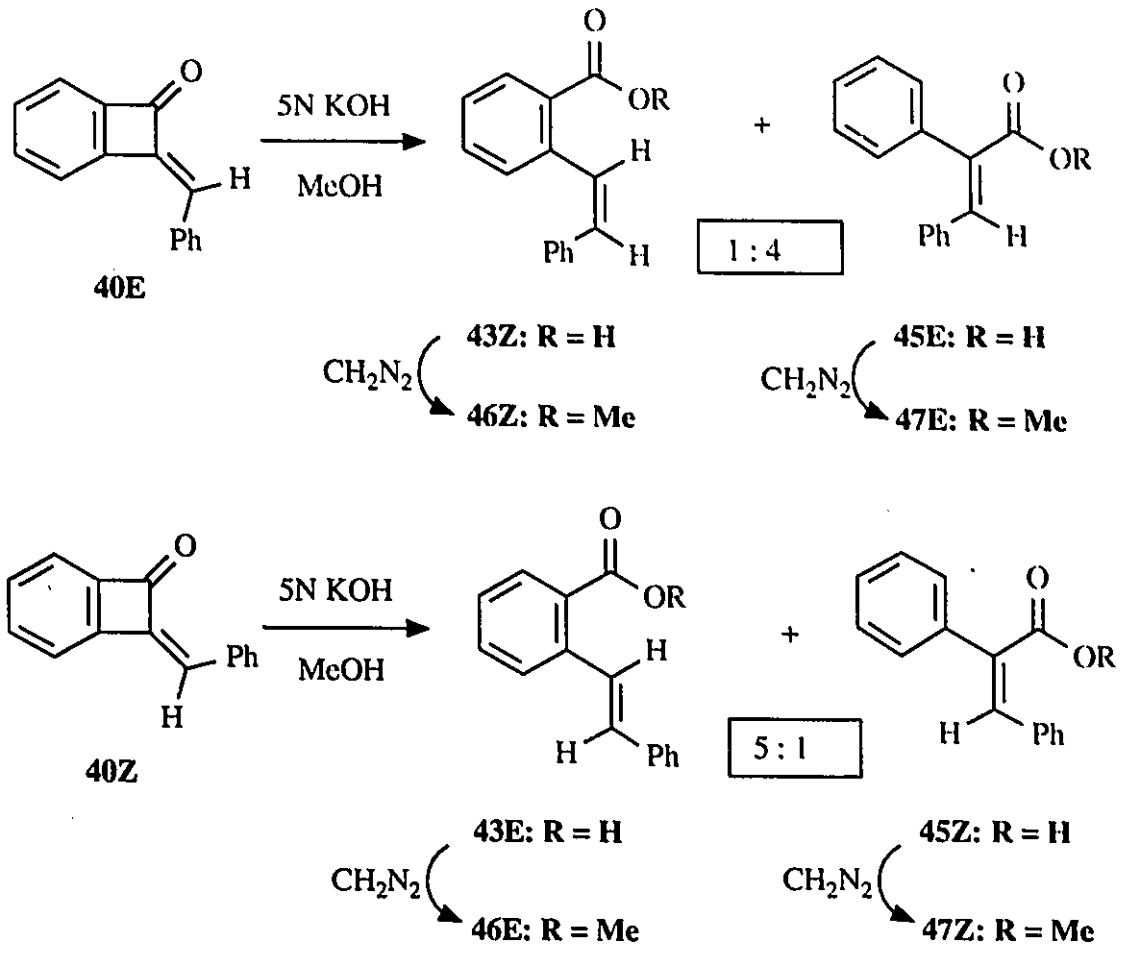
electrocyclic ring opening and a carbanionic mechanism. For example, the hydroxide-mediated cleavage of benzylidenebenzocyclobutenones **40E** and **40Z** beta to the aromatic ring could occur in principle via two possible pathways from the hydroxide adducts **41E** and **41Z** (Scheme 11). A carbanionic mechanism (Path A) would yield the stilbenes **43Z** and **43E** with stereoretention, provided the vinyl anions **42Z** and **42E** do not undergo inversion. Alternatively, via an oxy-anionic promoted electrocyclic ring opening (Path B), both isomers would generate the same vinyl-allene intermediate **44**, which would lead to the same mixture of products regardless of the stereochemistry of the ketone **40**.



Scheme 11

Results

When ketones **40E** and **40Z** were subjected to a methanolic KOH solution, complete stereoretention in the β-cleavage reactions was observed (Scheme 12). This is consistent only with a carbanionic mechanism (i.e. Path A in Scheme 11). These conclusions are based on the following evidence. After **40E** was treated with 5N KOH in methanol at room temperature overnight, a ^{1}H NMR spectrum of the acid quenched mixture indicated complete diappearance of starting material. Two characteristic peaks were discernible from the spectrum: a doublet at δ 6.62 (J = 12.4 Hz, cis) and a singlet at δ 7.95 in a 1 : 4 integration ratio. These were tentatively assigned to acids **43Z** and **45E** respectively. Similar treatment of **40Z** yielded a ^{1}H NMR spectrum again with two characteristic peaks: a doublet at δ 7.02 (J = 16.4 Hz, trans) and a singlet at δ 7.08 in a 5 : 1 integration ratio. These resonances were assigned to acids **43E** and **45Z**, respectively. The absence of common products from the hydroxide cleavage of **40E** and **40Z** strongly supports these assignments, assuming stereoretention during both α- and β-cleavage.

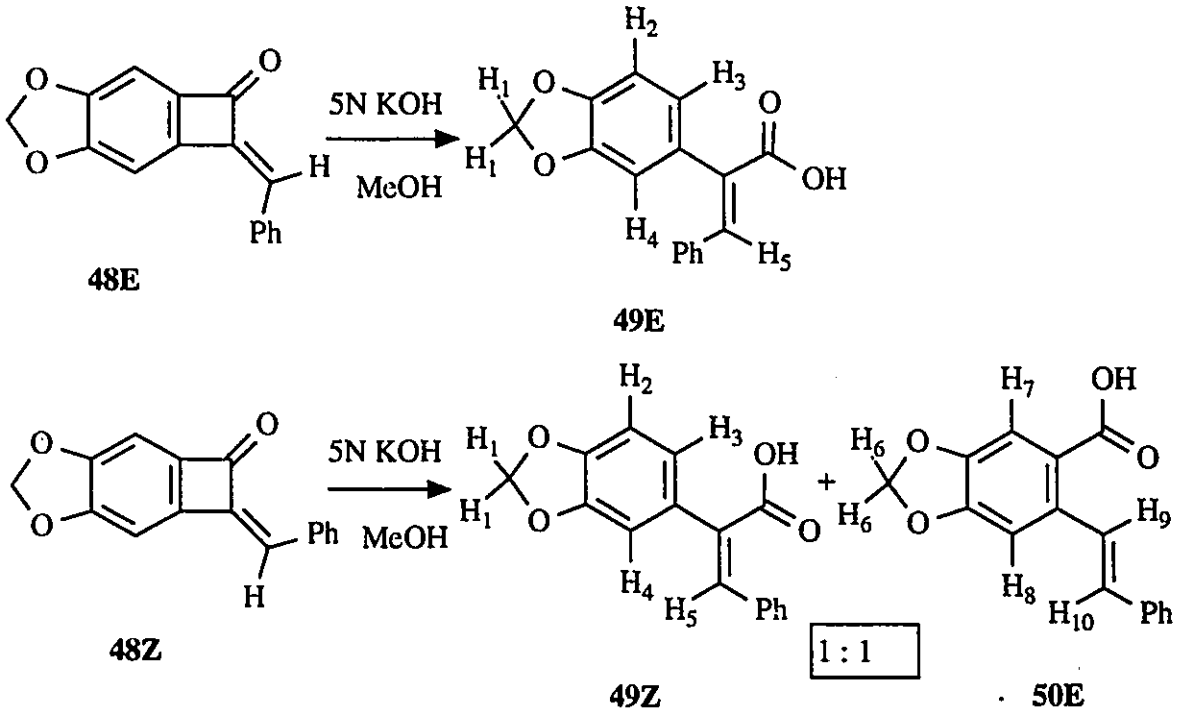


Scheme 12

In an attempt to separate and further characterize the products, the reaction mixtures were treated with diazomethane. As expected, only two methyl ester peaks for each reaction were detected, with their relative integration corresponding exactly to the previously assigned ratios of acids **43** and **45**. The esters from both reaction mixtures proved to be quite difficult to separate chromatographically. However, repeated passes on a Chromatotron plate yielded small amounts of reasonably pure materials for analysis. The following key ^{1}H NMR characteristics were discerned for each isomer: **46E** δ 3.92 (s, 3H, OMe), 7.00 (d, J = 16.1 Hz, 1H, trans vinylic), 7.98 (d, J= 16.2 Hz, 1H, trans vinylic); **46Z** δ 3.87 (s, 3H, OMe), 6.63 (d, J = 12.4 Hz, 1H, cis vinylic); **47E** δ 3.77 (s, 3H, OMe), 7.85 (s, 1H, vinylic); **47Z** δ 3.76 (s, 3H, OMe), 7.02 (s, 1H, vinylic). Furthermore, upon mass spectral analysis, all four esters generated the same M^+ at 238 m/e, with

stereoisomeric pairs yielding identical MS cleavage patterns.

The 4,5-methylenedioxy analog **48E** and **48Z** were next studied (Scheme 13). Treatment of **48E** with 5N KOH in methanol yielded a product which proved to be insoluble in $CDCl_3$, CCl_4 or acetone. However, it was possible to dissolve this product with K_2CO_3 in D_2O. The ^1H NMR spectrum obtained was consistent only with exclusive formation of the potassium salt of **49E**: δ 5.93 (s, 2H, H_1), 6.62 (dd, J = 1.7, 8 Hz, 1H, H_3), 6.66 (dd, J = *ca.* 0.5, 1.2 Hz, 1H, H_3), 6.82 (dd, J = 0.5, 8 Hz, 1H, H_2), 7.04-7.22 (m, 5H), 7.42 (s, 1H, H_5). A similar treatment of **48Z** yielded a ^1H NMR spectrum which is consistent only with formation of a 1 : 1 mixture or acids **49Z** and **50E**: δ 5.96 (s, 4H, H_1+H_6), 6.66 (s, 1H, H_5 or H_7 or H_8), 6.85 (d, J = 8 Hz, 1H, H_2) 6.93 (s, 1H, H_5 or H_7 or H_8), 7.00 (d, J = 16 Hz(trans), 1H, H_9 or H_{10}), 7.10 (dd, J = 1.8, 8 Hz, 1H, H_3), 7.09 (d, J= 1.5 Hz, 1H, H_4), 7.22 (s, 1H, H_5 or H_7 or H_8), 7.3-7.6 (m, 11H).

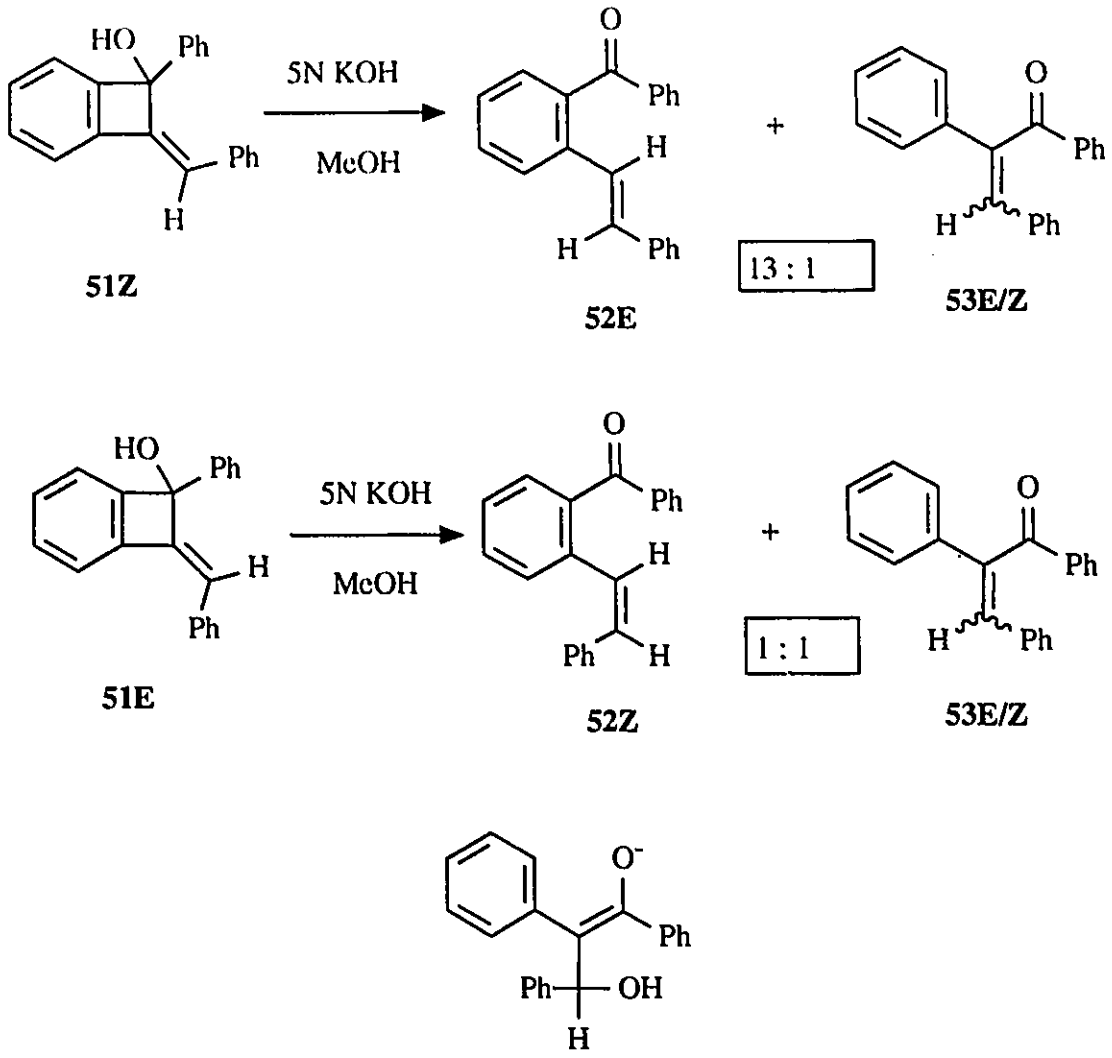


Scheme 13

Thus, for the benzylidenebenzocyclobutenones studied, complete stereoretention during β-cleavage was observed. This indicates that the carbanionic mechanism is taking

place to the exclusion of electrocyclic ring opening. Furthermore, there appears to be a relationship between the stereochemistry of the ketone substrates and site of cleavage, with the Z isomers yielding a greater β/α cleavage ratio. This may perhaps be attributable to the steric interaction between the phenyl ring and the carbonyl functionality in **40Z** and **48Z**, which is absent in **40E** and **48E**. It is also notable that α-cleavage was further favored in the methylenedioxy analogs so that this became the only route for **48E** whereas **48Z** gave a 1:1 mixture of α/β cleavage (**49Z/50E**). This is consistent with the known ability of inductive groups (e.g. OMe) ortho,[2] and to a lesser extent para,[3] to the incipient carbanion on the aromatic ring to direct the α-cleavage of benzocylobutenones.

It was then of interest to study the anionic cleavage of benzylidenebenzocyclobutenols (Scheme 14). The phenyl derivatives **51Z** and **51E** were thus examined. When **51Z** was treated with 5N KOH in methanol, an almost complete conversion to **52E** was observed. This was ascertained by analysis of the resulting ^{1}H NMR spectrum which showed two doublets (J = 16 Hz) at δ 7.04 and 7.18, characteristic of a vinylic trans coupling pattern. The remaining resonances intregrated reasonably well to the expected remaining 14 hydrogens in **52E**. Analysis by GC revealed a single main peak with two small minor peaks. Further analysis by GC-MS indicated that the minor peaks had the same M^+(284 m/e) as the minor component but with a different cleavage pattern. The most reasonable assignment for these minor constituents would be ketones **53E/Z**, resulting from α-cleavage of **51Z**. By comparing the GC integration ratio, the proportion of β/α cleavage (**52E:53E/Z**) can be estimated to be 13:1.



Scheme 14

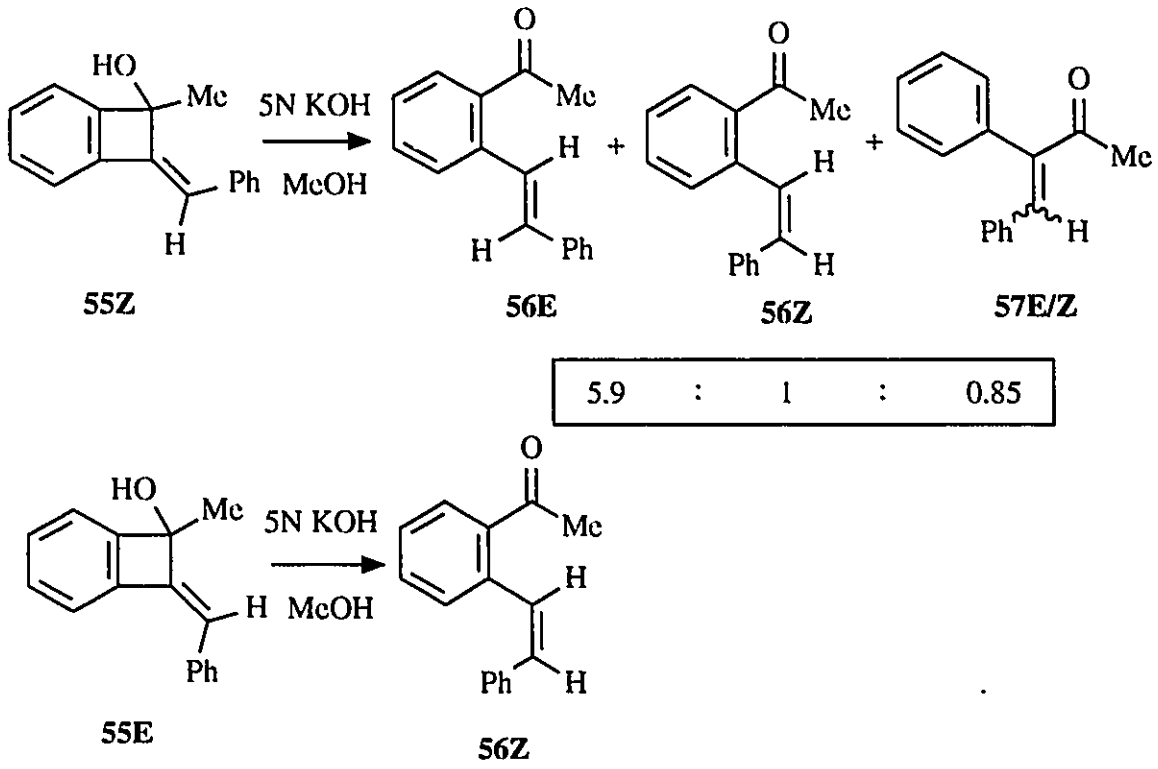
Similar treatment of **51E** yielded identical results. The ^{1}H NMR of the reaction mixture clearly revealed a characteristic cis vinylic coupling of 12.2 Hz with doublets centered at δ 6.48 and 6.60 corresponding to **52Z**. The integration of the remaining hydrogens amounted to roughly twice as much as expected if **52Z** had been the only product, suggesting that α- and β-cleavage occured in about equal proportion. Chromatographic separation allowed isolation of some **52Z**, reasonably pure by ^{1}H NMR. Another fraction corresponded to a mixture of **53E** and **53Z**, in roughly equal proportions. This assignment was based primarily on the ^{13}C NMR, which showed two carbonyl absorptions at δ 199.3 and 197.6 along with other closely paired resonances, indicative of

geometric isomers. No additional information could be gained from the ^{1}H NMR spectrum, which showed only highly overlapping aromatic resonances. The GC of this fraction showed only two close sharp peaks, with retention times and a GC-MS cleavage pattern identical those previously assigned to **53E** and **53Z** as the minor products of the anionic cleavage of **51Z**. Analysis by GC of pure **52Z** revealed a very broad peak with two sharper peaks on either side it. One of these sharp peaks posessed the same retention time as **52E**. In addition, GC-MS analysis of both sharp peaks produced the same cleavage pattern, identical with that of **52E**. These results suggest that **52Z** undergoes partial thermal isomerization to **52E** in the GC. Due to this complication, extensive overlapping of GC peaks corresponding to **52Z** and **53E/Z** occurs, thus preventing quantitative corroboration of the ratio estimated by ^{1}H NMR. However, the GC pattern obtained agrees qualitatively with a simple superposition of peaks corresponding to **52Z** and **53E/Z**.

These results indicate that stereoretention was observed during the β-cleavage of **51E** and **51Z**. This of course supports an entirely carbanionic mechanism for the phenyl derivatives. Furthermore the cleavage of **51E** to **53E/Z** appears to be the first example of the α-cleavage of a benzocyclobutenoxide without carbanionic stabilizing groups on the aromatic ring. This may in part be due to the less acidic nature of a vinyl carbanion (pKa 44[22]) as opposed to a benzylic carbanion (pKa 41[22]). The presence of both **53E** and **53Z** in both cleavage reactions is most likely the result of isomerization following α-cleavage. Conjugated enone such as these have proven to be prone to isomerization[23] and this process may be further accelerated in the basic medium via an intermediate such as **54**.

When the methyl adduct **55Z** was stirred at room temperature in methanolic 5N KOH followed by quenching with dilute HCl, an ^{1}H NMR spectrum revealed four peaks in the high field region, characteristic for the expected products **56E**, **56Z**, **57E** and **57Z** (Scheme 15). Chromatographic separation identified the major component at δ 2.59 as **56E**, characterized by a doublet at δ 6.97 (J = 16.2 Hz, trans vinylic). Another product also isolated with the methyl resonance at 2.51 was identified as **56Z** by its two vinylic

hydrogens with typical cis couplings: δ 6.61 (d, J = 12.1 Hz), 6.89 (d, J = 12.2 Hz). The other two methyl resonances at δ 2.29 and 2.23 (2.7 : 1 integration ratio) are assumed to correspond to products of alpha cleavage **57E/Z**. The product distribution is thus estimated to be 5.9 : 1 : 0.85 (**56E:56Z:57E/Z**).

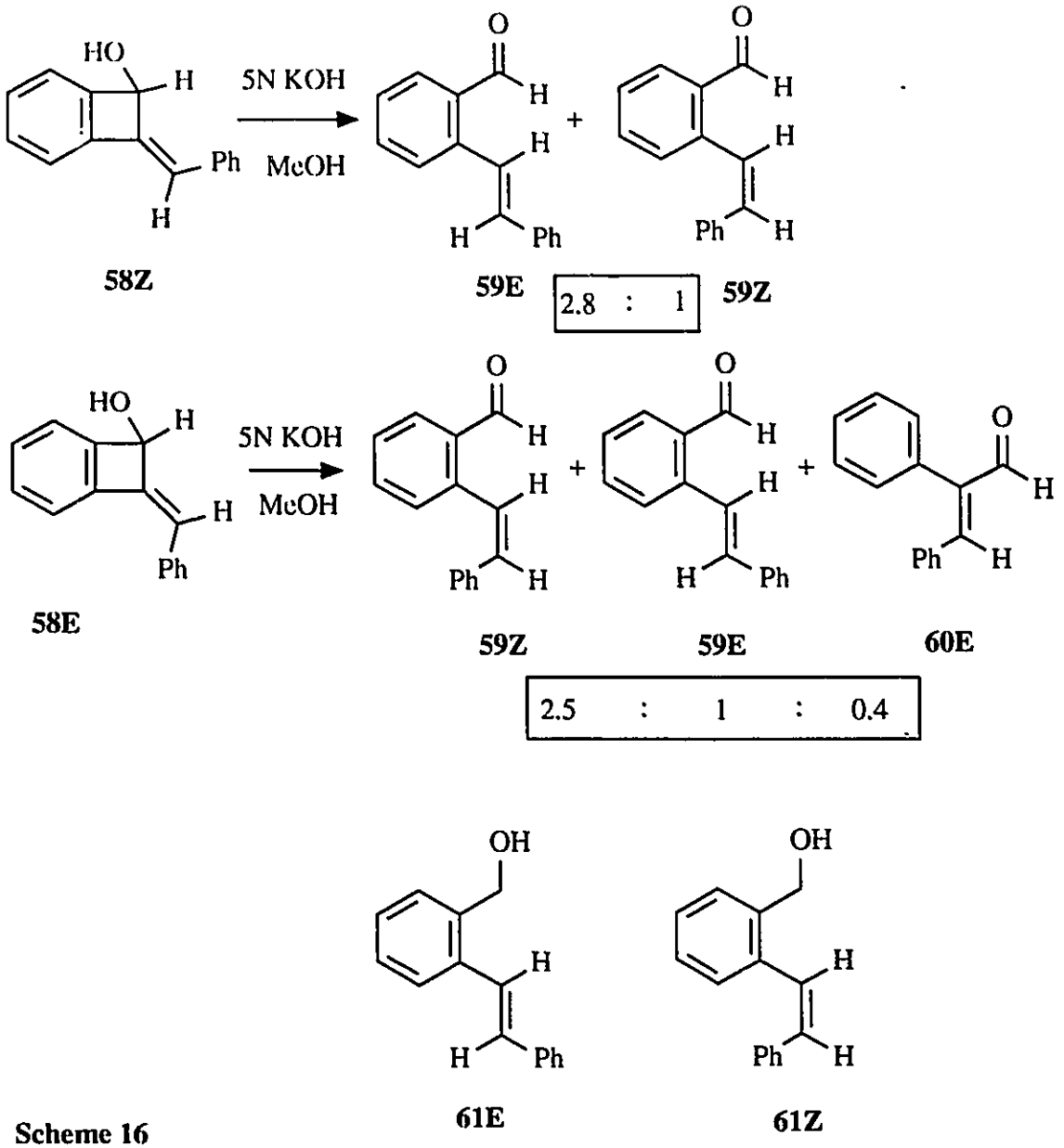


Scheme 15

Investigations into the anionic cleavage of **55E** were severely complicated by the higher temperatures required for the reaction. Even upon stirring at room temperature for three days in methanolic 5N KOH, little conversion of starting material was observed, as judged by GC analysis. Thus it was found necessary to reflux the reaction mixture for 30 min, at which point disappearance of starting material was noted. Inspection of the ^{1}H NMR of this reaction mixture revealed a singlet δ 2.53 corresponding to **56Z**. This assignment was corroborated by GC-MS analysis. No peaks corresponding to the methyl resonances of **56E**, **57E**, or **57Z** were detected. However, this result is not conclusive since it could arise from preferential aldol condensation reactions of these products as

compared to **56Z**. The complex appearance of the ^{1}H NMR is suggestive that such side reactions dominate under the conditions necessary for anionic cleavage of **55E**.

Treatment of the secondary alcohol **58Z** for 3.5 h with 5N methanolic KOH yielded products **59E** and **59Z** in a 2.8 : 1 ratio, resulting from exclusive β-cleavage (Scheme 16). This was readily determined from the integration of the aldehyde peaks in the ^{1}H NMR at δ 10.31 and 10.25 corresponding respectively to **59E** and **59Z**. Chromatographic purification of these aldehydes permitted characterization of **59E** by ^{1}H NMR: δ 7.05 (d, J = 16.3 Hz, trans vinylic) and 8.04 (d, J = 16.2 Hz, trans vinylic). Similarily, for **59Z**: δ 6.82 (d, J = 12.2 Hz, cis vinylic) and 6.97 (d, J = 12.2 Hz, cis vinylic). By treating samples of the reaction mixture with bis(trimethylsilyl)acetamide (BSA), the silylated alcohol **58Z** was resolvable as a sharp peak on the GC, as were **59E** and **59Z**. Samples taken between 10 min and 17h after initiation of the reaction indicated no significant change in the **59E/59Z** ratio. This indicates either the formation of a very rapid equilibrium (<10 min) between **59E** and **59Z** or reflects the actual ratio of the initially formed products. The first hypothesis can be ruled out since a different ratio of **59E** and **59Z** obtained from the cleavage of **58E** also remains constant within 17h. In addition, from the GC data, it was possible to obtain an estimation of the first order rate constant for the ring opening of **58Z** at about 7×10^{-4} s^{-1}.



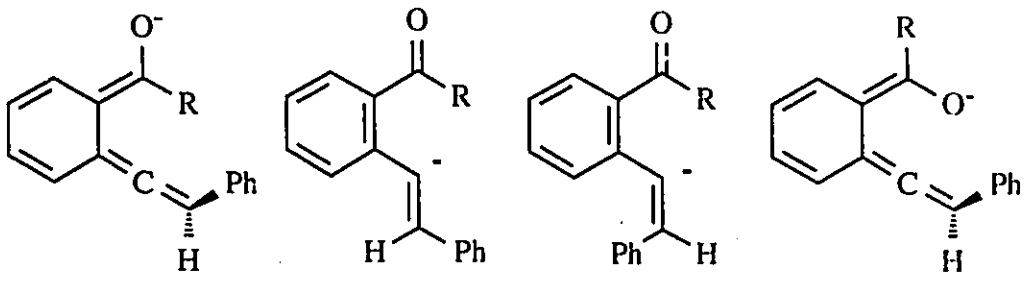
Scheme 16

The stereoisomeric secondary alcohol **58E** was also amenable to GC resolution by treatment with BSA. In this case, monitoring the reaction up to about 40% conversion of starting material (17h) revealed the presence the previously obtained aldehydes **59E** and **59Z** in addition to a new peak. ^{1}H NMR analysis also showed a new aldehyde resonance at δ 9.74, most likely corresponding to the alpha cleavage product **60E**. Integration of the three aldehyde resonances yielded a ratio of 2.5 : 1 : 0.4 (**59Z**:**59E**:**60E**). The GC data at low conversion times also allowed an estimation of the first order rate constant of the ring opening of **58E** at roughly 9 x 10^{-6} s^{-1}. This is about two orders of magnitude slower than

for the stereoisomeric **58Z**. The result is that for **58E** competing side reactions begin to dominate and interfere with product analysis before completion of the ring cleavage. Inspection of the GC-MS indicated the formation of significant quantities of two products with m/e 210, two mass units above that of the aldehydes **59E/Z**. Furthermore these products had identical MS cleavage patterns, strongly implicating the stereoisomeric Cannizzaro products **61E** and **61Z**.

Discussion

For the ketones and phenyl alcohols studied complete stereoretention during β-cleavage was observed, indicating unambiguously that a carbanionic mechanism was taking place exclusively. The situation for the secondary alcohols **58E/Z** and methyl alcohol **55Z** is more ambiguous since the stereochemistry of the benzylidene group was not completely maintained during β-cleavage. However, a purely electrocyclic mechanism via a common intermediate **62** can be ruled out since the E and Z isomers did not produce identical ratios of β-cleavage products. Two mechanisms can be proposed to account for these results. The first is that electrocylic ring opening is competitive with a carbanionic mechanism. The second is that a purely carbanionic mechanism is still taking place but that the initially formed vinyl anion **63E** or **63Z** partially isomerizes before being quenched by the protic solvent.



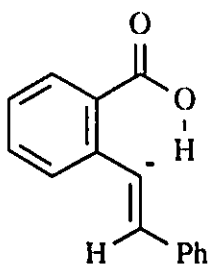
62 **63E** **63Z** **64**

In support of the second hypothesis, it is known that α-styryl anions isomerize readily,[24-26] especially in coordinating solvents[25] such as THF, with inversion barriers[24] estimated at 10-20 kcal/mol. This is thought to arise due the resonance ability of the aryl

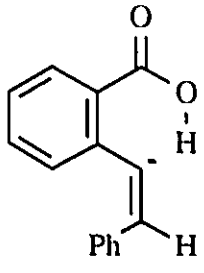
ring since alkyl vinyl anions are generally quite stable to isomerization.[25] In the case of the compounds we have studied the major resonance contributor would actually be an o-quinodimethane intermediate such as **62** or **64**, when the pi-system is coplanar. The observed case of stereoinversion for **63E/Z** was R=H > R=Me > R=Ph,OH. This may be explained on the basis of the decreasing resonance ability of the corresponding functional groups in the following order: CHO > COMe > CO_2R. This order was estimated by assuming that it reflects the increasing pKa values[22] of the following compounds: $CH_2(CHO)_2$ (5) < $CH_2(COMe)_2$ (9) < $CH_2(CO_2Et)_2$ (13). The relative stability of the phenyl substituted vinyl anions **63E** and **63Z** (R = Ph) may partially be a reflection of steric demands imposed by the phenyl ring on the ability of the carbonyl group to reach the coplanarity necessary to form the o-quinodimethane system in **62** and **64**. In the absence of any additional resonance stabilizing groups on the aryl ring, the inversion barrier for α-styryl anions appears to be high enough so that quenching by a protic solvent occurs before isomerization to an almost complete extent. For example, the *t*-butoxide-catalysed deuteration of cis-stilbene was found to be 2500 times faster than isomerization at 146°C.[27] This agrees well the the stereoretention we observed in methanol for the vinyl anions with the least effective resonance stabilizing groups on the aryl ring.

Finally, it could be argued that the stereoretention found during the hydroxide mediated cleavage of the ketones was due to an accelerated intramolecular proton quenching via **65E** and **65Z**, not possible for the other anionic cleavage reactions. In order to test this hypothesis, the ketones **40E** and **40Z** were treated with 3N methanolic NaOMe for 23h at room temperature (Scheme 17). The β-cleavage products **46Z** and **46E** from each reaction, respectively, showed that complete stereoretention of the benzylidene group was still maintained, as evidenced by ^{1}H NMR. This indicated that intramolecular proton quenching was not responsible for the stereoretention observed during the hydroxide mediated β-cleavage reactions. However, it is interesting that methoxide encouraged more α/β cleavage as compared to hydroxide. Specifically,

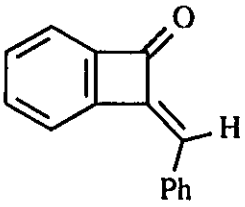
cleavage of **40E** with methoxide yielded a 7:1 α/β ratio (**46Z:47E/Z**) as compared to the 4:1 ratio obtained with hydroxide. Cleavage of **40Z** with methoxide gave a 1:2 α/β ratio (**46E:47E/Z**), whereas hydroxide yielded a 1:5 ratio. Although not readily discernable by ^{1}H NMR due to overlapping resonances, GC and GC-MS analysis indicated subsequent isomerization of the α-cleavage products **47E** and **47Z**. By GC estimation a slow equilibrium favoring **47E** is approached by inspecting the ratios of **47E:47Z** after 23h for the cleavage of **40E** (36:1) and **40Z** (0.8:1). Again, the isomerization of such conjugated enones could reasonably proceed via a Michael addition-elimination sequence with methoxide as the nucleophile.[28]



65E



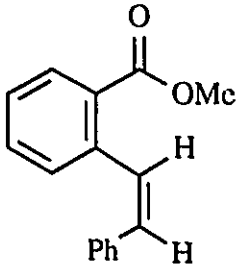
65Z



40E

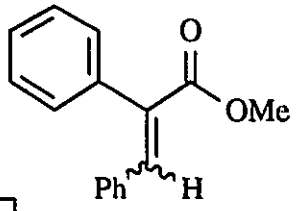
3N NaOMe

MeOH

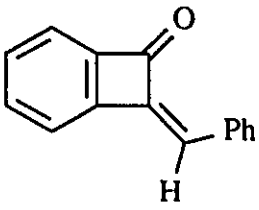


46Z

1 : 7



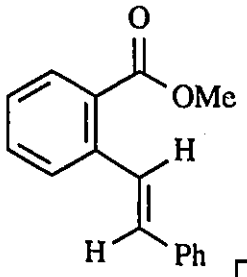
47E/Z



40Z

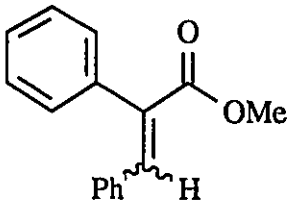
3N NaOMe

MeOH



46E

2 : 1



47E/Z

Scheme 17

Studies in aprotic media

In order to possibly observe directly either vinyl anions such as **63E/Z** or even o-quinodimethanes **62** or **64**, we carried out the anionic cleavage in an aprotic medium and monitored the process by ^{13}C NMR spectroscopy. Thus, one equivalent of MeLi was added to a THF solution of **55Z** at -78°C and ^{13}C NMR spectra of the resulting mixture were taken at increasingly higher temperatures. The initial spectra corresponding to alkoxide **65Z** showed no significant changes up to 0°C (see Fig 1). Upon attaining room temperature, a new spectrum appeared, probably corresponding to alkoxide **65E** (see Fig 2). Even after stirring at room temperature for 16h no further change was observed in the ^{13}C NMR spectrum. Quenching with water (Fig 3) revealed that complete conversion to **55E** had taken place with no direct NMR evidence of an o-quinodimethane intermediate such as **67** or vinyllithiated aldehydes **66Z** and **66E**. In addition, no β-cleavage products such as **56E** and **56Z**, as observed in methanolic solution were observed.

To account for these obsvervations, the following mechanistic scheme was postulated (Scheme 18). The initially formed alkoxide **65Z** is in equilibrium with a small concentration of vinyl anion **66E**. In the absence of a protic quenching agent, **66E** isomerizes via the o-quinodimethane **67** to vinyl anion **66Z**. The equilibrium then shifts by an irreversible cyclization of **66Z** to **65E**. We suggest that a Z-o-quinodimethane **67** is involved since minimal movement of the lithium cation is required during the isomerization process. This would not be the case for an E-o-quinodimethane such as **62**, which would require significant cation displacement for sequential stabilization of the oxy and vinyl anions.

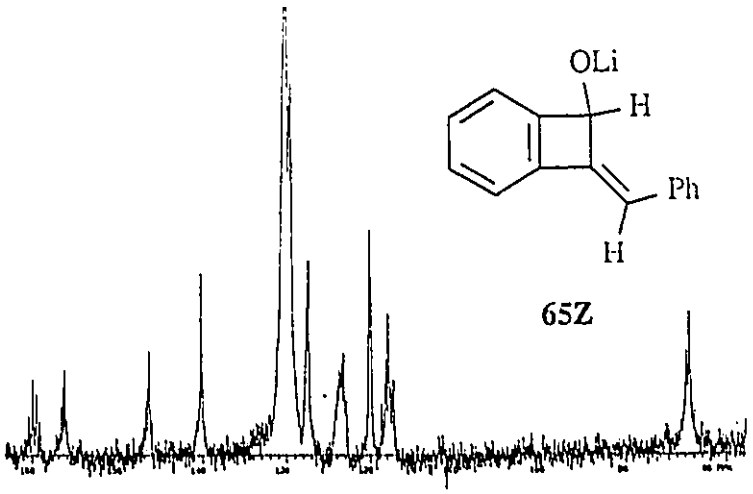


Fig 1: ^{13}C NMR of 65Z (0°C)

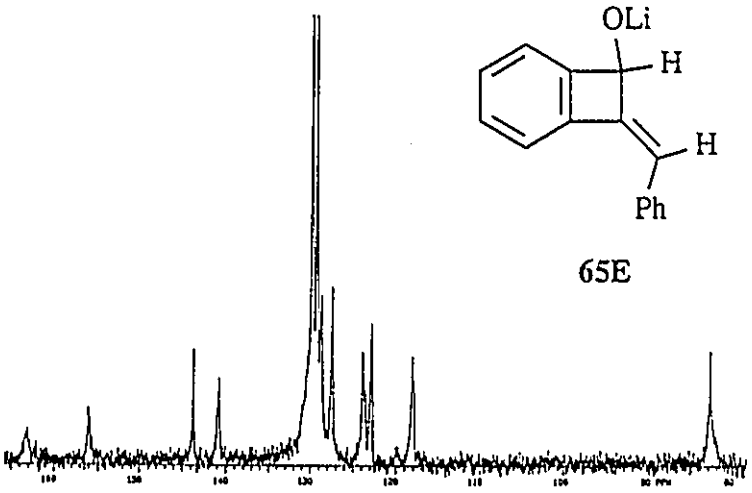


Fig 2: ^{13}C NMR of 65E (rt)

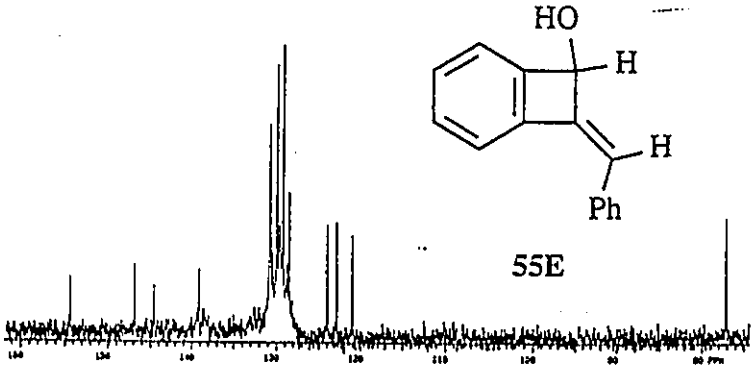
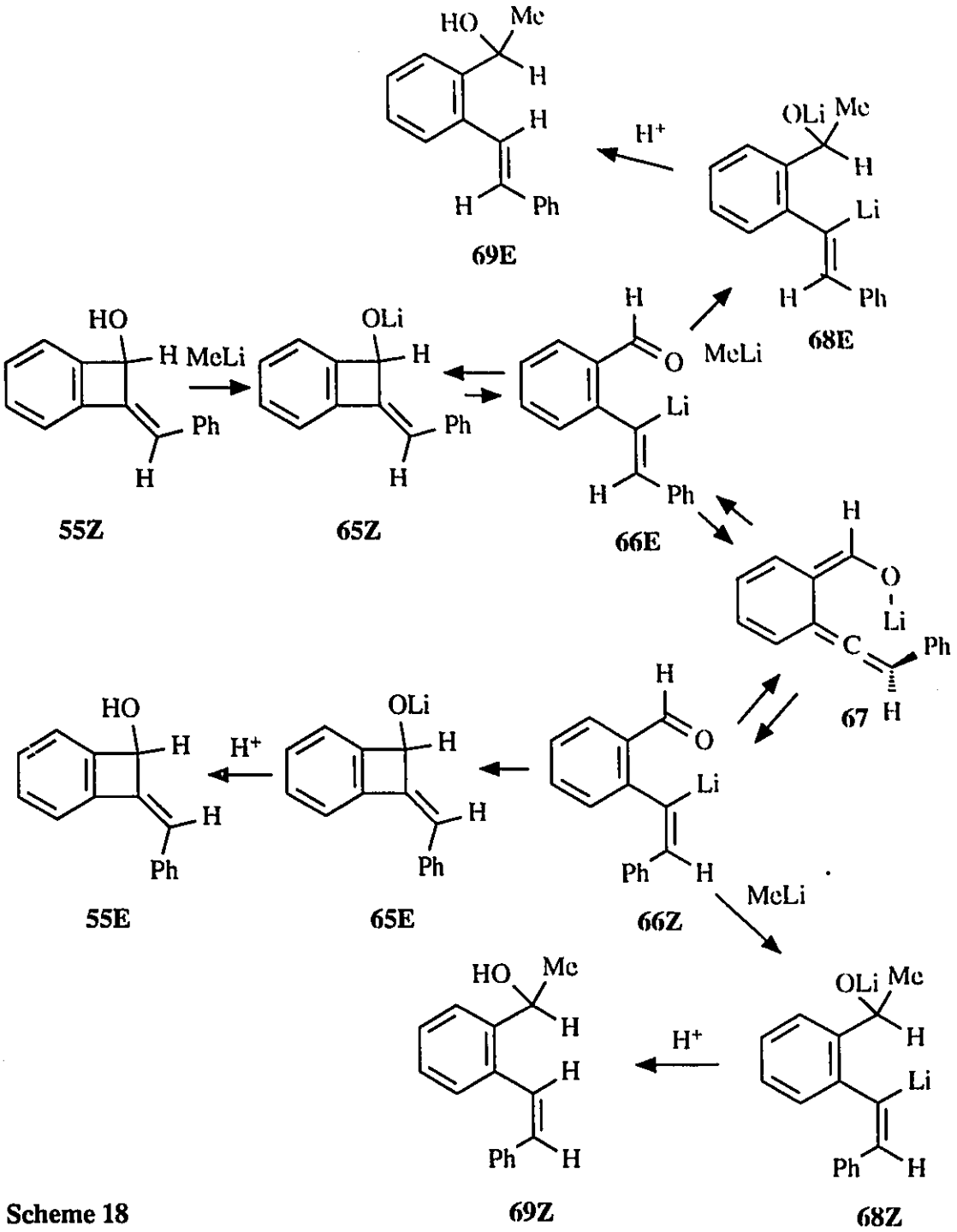


Fig 3: ^{13}C NMR of 55E (after quenching of 65E at rt)


HO
Me
H
H
H
Ph
69E
H+
OLi
Me
H
Li
H
Ph
68E
HO
H
MeLi
Ph
H
55Z
OLi
H
Ph
H
65Z
H
O
MeLi
Li
H
Ph
66E
H
O
Li
C
Ph
H
67
H
O
Li
Ph
H
66Z
OLi
H
H
Ph
65E
HO
H
H+
H
Ph
55E
MeLi
HO
Me
H
H
Ph
H
69Z
H+
OLi
Me
H
Li
Ph
H
68Z

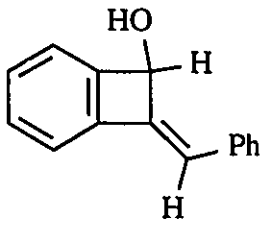
Scheme 18

In order to investigate the validity of this proposed mechanism for the isomerization of **55Z** to **55E** via its lithium salt, a series of experiments were undertaken. These results are summarized in Table 1. The irreversibility of the formation of **65E** was easily demonstrated by treating **55E** with 2 eq. of MeLi at rt for 40 min then quenching with water and recovering the starting material unchanged. The second critical test was to prove the intermediacy of the vinyl carbanion aldehydes **66Z** and **66E**. By treating **55Z** with an excess of MeLi followed by quenching with saturated NH_4Cl solution, it was indeed possible to trap the aldehyde intermediates to yield alcohols **69E** and **69Z**, presumably via the dianions **68E** and **68Z** respectively. These compounds were readily identified by characteristic resonances in their ^1H NMR spectum. For **69E**: δ 1.50 (d, J = 6.4 Hz, 3H, CH_3), 5.27(q, J = 6.4 Hz, 1H, C<u>H</u>(OH)Me), 6.95 (d, J = 16.0 Hz, 1H, trans vinylic); for **69Z**: δ 1.41 (d, J = 6.4 Hz, 3H, CH_3), 5.12 (q, J = 6.4 Hz, 1H, C<u>H</u>(OH)Me), 6.63(d, J = 12.2 Hz, 1H, cis vinylic), 6.74(d, J = 12.3 Hz, 1H, cis vinylic). Furthermore, addition of MeLi to aldehydes **56E** and **56Z** prepared from an alternate route yielded products with identical ^1H NMR resonances.

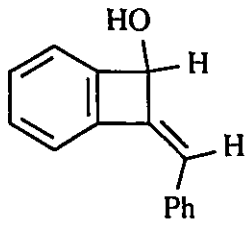
Table 1: Aprotic studies of 55Z*

MeLi (eq.)	conditions	55Z	55E	69E	69Z
1	rt	0	1	-	-
2	rt	0.1	1	1	0.2
10	rt	3.1	1	1	0.2
1	-78°C->rt	0.2	1	-	-
2	-78°C->rt	0.8	1	1.5	trace
5.5	-78°C->rt	6.3	1	1.3	trace
1	0°C	10	1	-	-
2	0°C	12	1	-	-

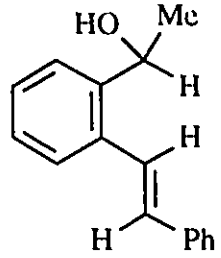
*carried out in THF for 40 min then quenched with NH_4Cl



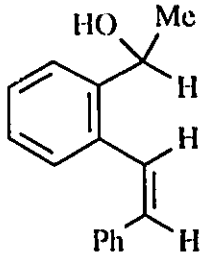
55Z



55E



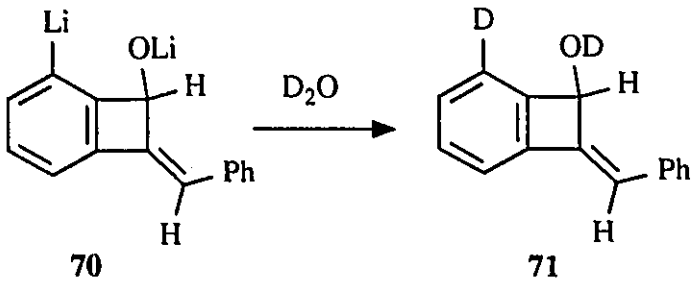
69E



69Z

By varying the amount of MeLi added some rather unexpected results surfaced. With one equivalent of MeLi, complete conversion was observed after 40 min. With 2 equivalents of MeLi, after the same reaction time, a 10:1 ratio of **55E/55Z** was observed along with alcohols **69E** and **69Z**. Hoping to completely shift the equilibrium towards formation of **69E** and **69Z**, 10 eq of MeLi were added and reacted for the same time. Surprisingly, this did not increase the amount of **69E** and **69Z** but rather only *decreased* the extent of the isomerization.

One explanation for the apparent "protection" of the starting material with excess MeLi is the formation of a species which is resistent to cleavage while regenerating the starting material upon quenching with water. One such possibility is ortho metallation of the alkoxide **65Z** to yield species **70** (Scheme 19). This was shown not to be the case by quenching the reaction with D_2O, which would presumably have yielded **71**. Mass spectral analysis (GC-MS) indicated that no deuterium incorporation had taken place.



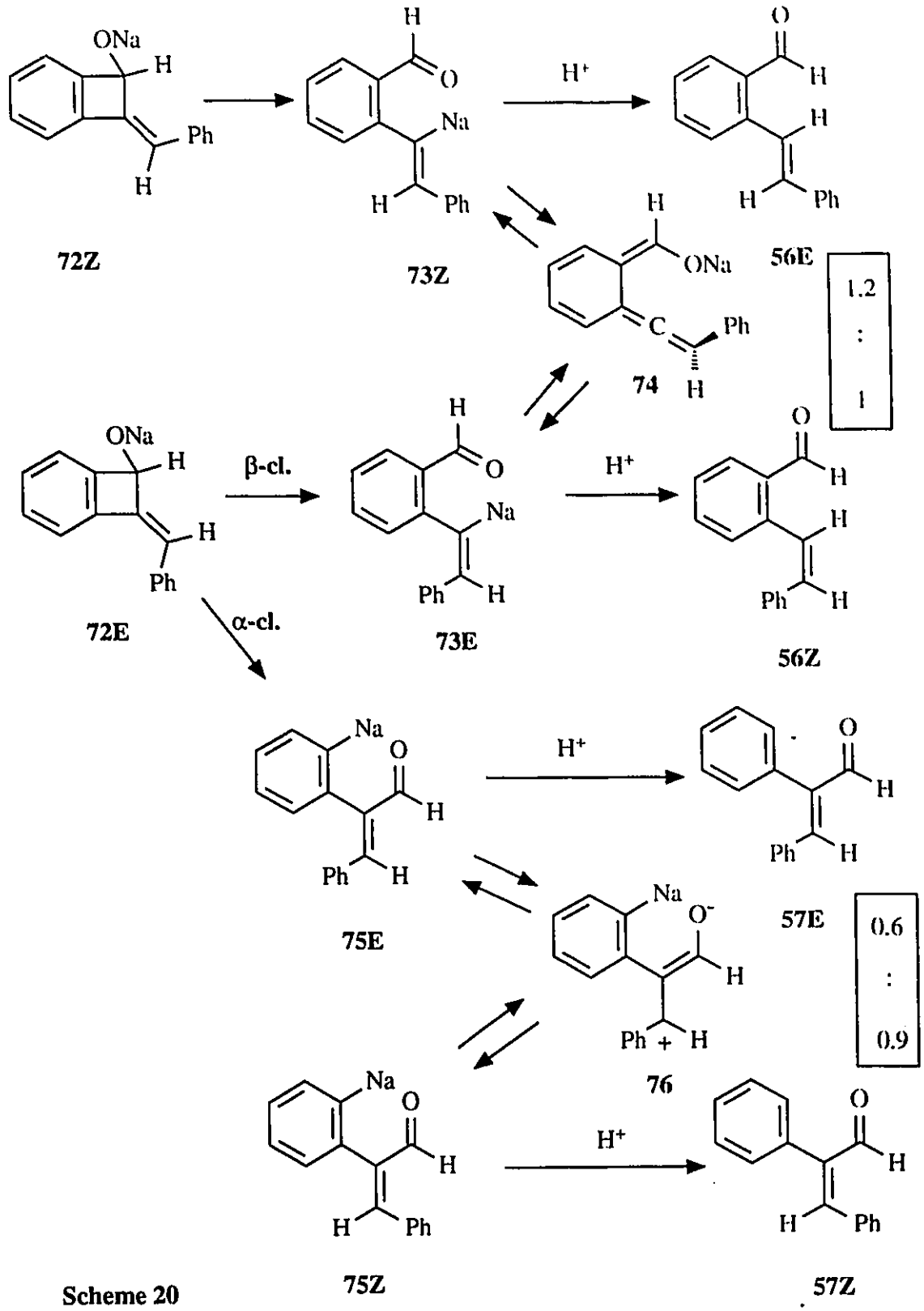
70 **71**

Scheme 19

Next, the temperature dependence of the reaction was studied. When carried out at 0°C for 40 min the isomerization process occured to an extent of only about 10%, in the presence of one or two equivalents of MeLi. This corroborates the findings from the low temperature ^{13}C NMR experiment which suggested that ring opening of **55Z** occurs to a significant extent on this timescale between 0°C and room temperature. In another series of experiments, the addition of MeLi was carried out at -78°C, the mixture stirred for 15 min to allow complete anion formation then allowed to warm to room temperature and stirred for a further 40 min until quenching. Two interesting observations can be made from the results of these experiments. First, in the presence of excess MeLi, the isomerisation was even further suppressed than when carried out at room temperature. For example with 2 eq. MeLi, at room temperature the final **55Z/55E** ratio is 0.1 : 1 whereas with slow warming the ratio becomes 0.8 : 1. This probably reflects the more negative activation entropy of a bimolecular o-metalation reaction as compared to a ring opening reaction, the result being a higher ratio of o-metallation/ring opening as the temperature decreases. The second observation is that the ratio of the trapping products **69E/69Z** is

shifted completely to **69E** under the slow warming protocol. This can again be interpreted as an entropy effect. The negative activation entropy of the cyclization of **66Z** to **65Z** would be expected to hasten this process at lower temperatures thus shortening the lifetime of **66Z** relative **66E**. This would be reflected as a lower proportion of **69Z** at lower temperatures.

This contrasts with the behaviour of the sodium salts of **72E** and **72Z**, prepared by treating the alcohols **55E** and **55Z** with sodium hydride in THF (Scheme 20). Since both **72E** and **72Z** are subject to ring opening at room temperature, the vinyl anions **73E** and **73Z** have a chance to equilibrate via **74** and yield the same 1.2 : 1 ratio of aldehydes **56E/56Z** upon quenching with saturated NH_4Cl two hours later. Inspection of the ^1H NMR of the reaction mixture from **72E** also revealed the presence of two other aldehyde peaks. The resonance at δ 9.73 was previously assigned to **57E**, the expected product of α-cleavage. The new peak at δ 9.99 was then tentatively assigned as its stereoisomer **57Z**. The ratio of **56Z:57Z:57E** could then be estimated as 1 : 0.9 : 0.6 from the integration of the aldehyde resonances. It is tempting to speculate that this isomeric mixture of alpha cleavage products not found to occur in methanol is due to equilibration of **75E** and **75Z** via the intramolecularily stabilized zwitterionic intermediate **76**. It should be noted that the aldehyde products constitute only a minor portion the complex mixture obtained, probably due to extensive side reactions of the vinyl anions involved. The different behaviour of the sodium and lithium salts may be thought to arise due to the looser binding of sodium with the alkoxide oxygen.[29] The result is a less stabilized anion which leads to ring opening at a lower temperature than for the thighter binding more stabilized lithium alkoxide.


ONa
H
Ph
H
72Z
H
O
Na
H
Ph
73Z
H+
O
H
H
H
Ph
56E
H
ONa
C
Ph
H
74
1.2
:
1
ONa
H
H
Ph
72E
β-cl.
H
O
Na
Ph
H
73E
H+
O
H
H
Ph
H
56Z
α-cl.
Na
O
H
Ph
H
75E
H+
O
H
Ph
H
57E
0.6
:
0.9
Na
O
H
Ph + H
76
Na
O
H
H
Ph
75Z
H+
O
H
H
Ph
57Z

Scheme 20

Conclusion

The anionic ring opening of benzylidenebenzocyclobutenols and -ones was found to occur via a carbanionic pathway rather than an oxy-anionic promoted electrocyclic process. This contrasts with the evidence from the work of Choy[10] and Swenton[21] (see Schemes 9 and 10) supporting electrocyclic ring opening of benzocyclobutenonoxides. In the case of Swenton's work, it is possible that the intramolecular Michael addition trap was simply not as effective as the protic solvent used in our study to capture the carbanion before isomerization. However, especially in the light of the work by Choy involving Diels-Alder trapping, it is quite possible that the nature of the substituent at the 2-position of benzylidenebenzocyclobutenols favors one mechanism over the other. If this is the case then it points to a fruitful area of research from both the theoretical and practical perspectives.

EXPERIMENTAL

General: Same as specified in Chapter 5 with the following additions. ^{2}H NMR spectra were taken on the Varian XL-300 spectrometer. Low temperature ^{13}C NMR were taken on the same intrument with THF as an internal reference.

Preparation of 40E: see preparation of **42E** in Chapter 2.

Preparation of 40Z: see preparation of **42Z** in Chapter 2.

Cleavage of 40E with KOH: A solution of **40E** (46.9 mg, 0.23 mmol) in 5 N methanolic KOH was warmed to about 40°C for 1.5 h then stirred at rt for 18h. The reaction mixture was then partitioned between 5 mL of ether and 5 mL of dilute HCl and the aqueous layer was washed 4 times with ether. The organic phases were combined, dried over $MgSO_4$ and evaporated to yield a white solid consisting of a 1:4 mixture of **43Z/45E** (50.6 mg, 0.22 mmol, 96% yield). The salient ^{1}H NMR peaks were at δ 6.62 (d, J = 12.4 Hz, cis coupling in **43Z**) and δ 7.95 (s, CHPh in **45E**). This mixture was dissolved in ether and treated with an ethereal solution of diazomethane until a persistent yellow color appeared. A dilute solution of glacial acetic acid in ether was added until the disappearance of the yellow color, followed by addition of saturated $NaHCO_3$ until the evolution of gas ceased. The aqueous layer was washed 4 times with ether, the organic phases were combined, dried over $MgSO_4$ and evaporated to yield a white solid consisting of a 1:4 mixture of **46Z/47E** (51.2 mg, 0.22 mmol, 96% yield). This ratio was determined by integration of the methoxy resonances for each isomer. Chromatography of the mixture on a Chromatotron plate (5:1 -> 1:1 hexanes/CH_2Cl_2) afforded only partial separation of the esters. The purest fractions were used for spectral analysis.

For **46Z**: ^{1}H NMR δ 3.87 (3H, s, OMe), 6.63 (1H, d, J = 12.4 Hz, cis vinylic), 7.01-7.06 (3H, m), 7.08- 7.14 (m, 3H), 7.18-7.22 (1H, m), 7.26-7.30 (2H, m), 7.96 (1H, m); ^{13}C NMR δ 52.0, 126.9, 127.1, 128.0, 129.2, 129.3, 129.6, 130.4, 130.6, 131.1, 131.9, 136.7, 139.6, 167.5; MS (m/e, int) 238 (100, M^+), 207 (29), 206 (16), 179 (43), 178 (49), 119 (14), 89 (15); HRMS $C_{16}H_{14}O_2$ 238.0994 (calcd), 238.0988 (found).

For **47E**: ^{1}H NMR δ 3.77 (3H, s, OMe), 6,96-7.04 (2H, m), 7.08-7.23 (5H, m),

7.3-7.4 (3H, m), 7.85 (1H, s, CHPh); ^{13}C NMR δ 52.4, 127.8, 128.2, 128.7, 129.1, 129.7, 130.6, 132.4, 134.6, 135.9, 140.5, 168.4; IR (CH_2Cl_2, cm^{-1}) 1709; MS (m/e, int) 238 (100, M^+), 179 (67), 178 (56), 121 (72); HRMS $C_{16}H_{14}O_2$ 238.0994 (calcd), 238.0999 (found).

Cleavage of 40Z with KOH: The same procedure as for **40E** was used yielding a 5:1 mixture of acids **43E/45Z**, as judged by the relative integration of the doublet at δ 7.02 (J = 16.4 Hz, trans vinylic for **43E**) and the singlet at δ 7.08 (CHPh for **45Z**). Treatment with diazomethane yielded a 5:1 mixture of methyl esters **46E/47Z**.

For **46E**: ^{1}H NMR δ 3.92 (3H, s, OMe), 7.0 (1H, d, J = 16.1 Hz, trans vinylic), 7.23-7.39 (4H, m), 7.50 (1H, t, J = 8 Hz), 7.55 (2H, d, J = 8 Hz), 7.71 (1H, d, J = 8 Hz), 7.92 (1H, dd, J = 1.4, 7.9 Hz), 7.98 (1H, d, J = 16.2 Hz, trans vinylic); ^{13}C NMR δ 52.1, 126.8, 126.9, 127.1, 127.4, 127.8, 128.5, 128.6, 130.6, 131.4, 132.1, 137.4, 139.2, 167.8; MS (m/e, int), 238 (90, M^+), 206 (64), 205 (41), 179 (77), 178 (100), 119 (31), 89 (24); HRMS $C_{16}H_{14}O_2$ 238.0994 (calcd), 238.0989 (found).

For **47Z**: ^{1}H NMR δ 3.76 (3H, s, OMe), 7.02 (1H, s, CHPh), 7.2-7.5 (10H, m); ^{13}C NMR δ 52.2, 126.5(x2), 128.2, 128.4, 128.5, 128.7, 131.6, 134.9, 135.7, 136.9, 170.1; MS (m/e, int) 238 (100, M^+), 207 (23), 179 (57), 178 (56), 121 (40); HRMS $C_{16}H_{14}O_2$ 238.0994 (calcd), 238.0974 (found)

Cleavage of 48E with KOH: A solution of **48E** (59.5 mg, 0.24 mmol) in 3 mL of 5 N methanolic KOH was stirred at rt for 22 h. The reaction mixture was then partitioned between 10 mL of 1.5N HCl and 10 mL of ether. The aqueous layer was washed with 20 mL of ether and the combined organic phases were dried over $MgSO_4$ then evaporated to a yellowish solid (62.4 mg), which was insoluble in $CDCl_3$, acetone or CCl_4: IR (KBr, cm^{-1}) 2700-3500 (CO_2H), 1682, 1613. This solid was dissolved in a solution of anhydrous K_2CO_3 in D_2O, which produced the following ^{1}H NMR spectrum, attributable to the potassium salt of **49E**: δ 5.93 (2H, s, -OCH_2O-), 6.62 (1H, dd, J = 1.7, 8 Hz), 6.66 (1H, dd, J= 0.5, 1.2 Hz), 6.82 (1H, dd, J = 0.5, 8 Hz), 7.04-7.22 (5H, m), 7.42 (1H, s).

Cleavage of 48Z with KOH: The same procedure as for **48E** was used to yield a solid also insoluble in common deuterated solvents: IR (KBr, cm^{-1}) 2700-3500 (CO_2H),

1685, 1630, 1606. Treatment with K_2CO_3 in D_2O produced the following ^1H NMR spectrum, attributable to a 1:1 mixture of the potassium salts of **49Z** and **50E**: δ 5.96 (4H, s, -OCH_2O-), 6.66 (1H, s), 6.85 (1H, d, J = 8 Hz), 6.93 (1H, s), 7.00 (1H, d, J = 16 Hz, trans vinylic), 7.10 (1H, dd, J = 1.8, 8 Hz), 7.09 (1H, d, J = 1.5 Hz), 7.22 (1H, s), 7.3-7.6 (11H, m).

Preparation of 51Z: see preparation of **61Z** in Chapter 4.

Preparation of 51E: see preparation of **61E** in Chapter 4.

Cleavage of 51Z with KOH: The same procedure as for **40E** was used except that the mixture was stirred at rt for 3 days. GC analysis of a sample indicated that the reaction was complete within 19 h. The ^1H NMR of the reaction mixture consisted essentially only of **52E**: δ 7.04 (1H, d, J = 16.3 Hz, trans vinylic), 7.18 (1H, d, J = 16 Hz, trans vinylic), 7.1-7.85 (14H, m). Only a trace of **52Z** was detected by ^1H NMR as a faint pair of doublets at δ 6.48 and 6.60. GC analysis revealed a major peak and two minor peaks in a 13:1 integration ratio. The major peak, presumably corresponding to **52E**, yielded the following GC-MS data: 284 (100, M^+), 283 (16), 265 (9), 207 (35), 206 (23), 193 (9), 178 (41), 77 (24), 51 (12). The minor peaks, not resolved by GC-MS, yielded the same cleavage pattern as assigned to **53E/Z** (*vide infra*).

Cleavage of 51E with KOH: Under the same conditions as for **51Z**, the hydroxide-mediated cleavage of **51E** yielded approximately equal amounts of **52Z** and **53E/Z**, with only a trace of **52E**. Using ^1H NMR analysis, this ratio was estimated by comparing the integration ratio of the pair of doublets at δ 6.48 and 6.60, assigned to **52Z**, and the remainder of the aromatic hydrogens. Furthermore, GC analysis of the crude mixture approximated well a simple superpostition of the isolated components. Chromatography of the mixture on a Chromatotron plate (2:1 hexanes/CH_2Cl_2) yielded partial separation of the components for spectral analysis:

For **52Z**: ^1H NMR δ 6.48 (1H, d, J = 12.2 Hz, cis vinylic), 6.60 (1H, d, J = 12.2 Hz, cis vinylic), 7.06-7.18 (5H, m), 7.28-7.33 (3H, m), 7.36-7.44, 3H, m), 7.53 (1H, t, J = 7.3 Hz), 7.74 (2H, d, J = 7.0 Hz); ^{13}C NMR δ 126.7, 127.2, 128.1, 128.3, 128.5, 128.6,

129.0, 130.1, 130.2, 130.3, 131.4, 133.0, 136.6, 136.9, 137.6, 138.6, 197.8; MS (m/e, int) 284 (100, M^+), 283 (14), 265 (9), 207 (46), 206 (37), 193 (15), 178 (58), 77 (42), 51 (12).

For **53E/Z** (isolated as approx. 1:1 mixture): ^{1}H NMR δ 7.05-7.55 (28H, m), 7.82-7.87 (3H, m), 7.95-7.99 (1H, m); ^{13}C NMR δ 126.3, 127.9(x2), 128.1, 128.2(x2), 128.4, 128.7(x2), 128.8(x2), 128.9, 129.6(x2), 129.7, 130.1, 130.3, 132.1, 133.6, 134.7, 135.3, 136.3, 136.4, 137.9, 138.1, 140.1, 140.7, 140.8, 197.6, 199.3; MS (m/e, int) 284 (95, M^+), 283 (23), 207 (10), 206 (23), 179 (29), 178 (42), 167 (21), 105 (100), 77 (54), 51 (13).

Preparation of 55E: To a solution of **40E** (95.7 mg, 0.46 mmol) in 10 mL of THF at -78°C was added MeLi (1.4 M in hexanes, 0.66 mL, 0.92 mmol). The mixture was stirred for 30 min at -78°C, allowed to warm to rt for 10 min then poured into a rapidly stirring mixture of ether and saturated aqueous NH_4Cl. The ether layer was separated, dried with $MgSO_4$ then the solvent was evaporated under reduced pressure. Chromatography on a Chromatotron plate (1:3 hexanes/CH_2Cl_2 -> pure CH_2Cl_2) afforded **55E** (94.3 mg, 0.43 mmol, 91% yield): ^{1}H NMR δ 1.74 (3H, s, CH_3), 2.56 (1H, br s, OH), 6.48 (1H, s, CHPh), 7.2-7.45 (6H, m), 7.5-7.6 (3H, m); ^{13}C NMR δ 23.5, 82.4, 117.8, 120.7, 122.04, 127.3, 127.7, 128.5, 129.6, 129.8, 136.8, 142.4, 148.6, 155.1; MS (m/e, int) 222 (100, M^+), 221 (52), 207 (60), 179 (63), 178 (83); HRMS $C_{16}H_{14}O$ 222.1044 (calcd), 222.1054 (found).

Preparation of 55Z: The same procedure as for **55E** was used with **40Z** to yield **55Z** in 43% yield after chromatography with 1:2 hexanes/CH_2Cl_2 as eluent. The lower yield was due to significant cleavage to **56E** and **56Z**, as evidenced by the ^{1}H NMR of the crude reaction product. For **55Z**: ^{1}H NMR δ 1.74 (3H, s, CH_3), 2.65 (1H, br s, OH), 6.56 (1H, s, CHPh), 7.2-7.45 (7H, m), 7.70 (2H, d, J = 8.2 Hz); ^{13}C NMR δ 22.8, 83.7, 118.5, 118.9, 120.5, 126.9, 128.5, 128.9, 129.0, 129.9, 135.7, 144.1, 148.1, 154.1; MS (m/e, int) 222 (100, M^+), 221 (48), 207 (52), 179 (53), 178 (68); HRMS $C_{16}H_{14}O$ 222.1044 (calcd), 222.1057 (found).

Cleavage of 55Z with KOH: The same treatment as for **40E** was used except that

the solution was stirred at rt for 45 min, at which point the reaction was judged to be essentially complete by GC analysis. After the usual work-up, an ^{1}H NMR of the reaction mixture revealed 4 methyl peaks at δ 2.59 (5.9H), 2.51 (1H), 2.29 (0.62H) and 2.23 (0.23H), corresponding to a ratio of 5.9 : 1 : 0.85 (**56E** : **56Z** : **57E/Z**). GC monitoring of another run of the reaction showed that the product ratio did not significantly change after 3 days at rt. Chromatography on a Chromatotron plate (2:1 hexanes/CH_2Cl_2) afforded partial separation and characterization of the following compounds:

56E: ^{1}H NMR δ 2.60 (3H, s, COMe), 6.96 (1H, d, J = 16.3 Hz, trans vinylic), 7.2-7.4 (4H, m), 7.45-7.55 (3H, m), 7.6-7.75 (3H, m); ^{13}C NMR δ 29.8, 126.8, 127.1, 127.3, 127.4, 127.8, 128.6, 129.0, 131.5, 131.6, 137.2, 137.3(x2), 202.1; IR (CH_2Cl_2, cm^{-1}) 1683; MS (m/e, int) 222 (90, M^+), 221 (37), 207 (36), 179 (71), 178 (100), 145 (56).

56Z: ^{1}H NMR δ 2.52 (3H, s, COMe), 6.61 (1H, d, J = 12.1 Hz, cis vinylic), 6.89 (1H, d, J = 12.2 Hz, cis vinylic), 6.95-7.15 (5H, m), 7.2-7.4 (3H, m), 7.6-7.8 (1H, m); ^{13}C NMR δ 41.9, 127.0, 127.2, 128.1, 129.2(x2), 130.1, 130.4, 131.1, 131.6, 136.6, 137.7, 137.8, 201.0; MS (m/e, int) 222 (100, M^+), 221 (38), 207 (52), 179 (63), 178 (95), 145 (60).

Cleavage of 55E with KOH: Under the same conditions as for **55Z**, little conversion of **55Z** was detected after 3 days at rt, as determined by GC analysis. The reaction mixture was then refluxed for 30 min then worked up following the usual method. The crude ^{1}H NMR revealed a complex mixture with only one significant COMe peak at δ 2.53, corresponding to **56Z**. The GC-MS corroborated this assignment. The mixture was not further analysed.

Preparation of 58Z: To a solution of **40Z** (114.2 mg, 0.55 mmol) in 5 mL of methanol was added $NaBH_4$ (61 mg, 1.6 mmol). The mixture was stirred for 30 min at rt then poured into a rapidly stirring mixture of ether and aqueous 1N HCl. The organic layer was seperated and the aqueous layer was washed twice with ether. The organic phases were combined then evaporated to leave a residue which was passed through a short silica gel plug with ether to yield **58Z** (113.8 mg, 0.55 mmol, 99% yield) as a white

solid: ^{1}H NMR δ 2.35 (1H, d, J = 10.9 Hz, OH), 5.78 (1H, d, J = 10.8 Hz, benzylic), 6.59 (1H, s, CHPh), 7.20-7.42 (7H, m), 7.62 (2H, d, J = 8 Hz); IR (CH_2Cl_2, cm^{-1}) 3577, 1592, 1040; MS (m/e, int) 208 (100, M^+), 207 (43), 179 (64), 178 (74).

Preparation of 58E: The same procedure as for the preparation of **58Z** was used with **40E** to yield **58E** in 97% yield: ^{1}H NMR δ 2.51 (1H, s, OH), 5.49 (1H, s, benzylic), 6.50 (1H, s, CHPh), 7.27-7.45 (6H, m), 7.49-7.6 (3H, m); IR (CH_2Cl_2, cm^{-1}) 3580, 1599, 1044; MS (m/e, int) 208 (100, M^+), 207 (45), 179 (66), 178 (73).

Cleavage of 58Z with KOH: The same treatment as for **40E** was used except that the solution was stirred at rt for 3.5 h, at which point the reaction was judged to be essentially complete by GC analysis. After the usual work-up, an ^{1}H NMR of the reaction mixture revealed only two aldehyde peaks at δ 10.31 and 10.25, corresponding to a 2.8 : 1 mixture of **59E/59Z**. Chromatography of the mixture on a Chromatotron plate (10:1 -> 3:1 hexanes/CH_2Cl_2 afforded partial separation of the aldehydes:

59E: ^{1}H NMR δ 7.05 (1H, d, J = 16.3 Hz, trans vinylic), 7.26-7.46 (4H, m), 7.54-7.61 (3H, m), 7.71 (1H, d, J = 7.8 Hz), 7.83 (1H, dd, J = 1.4, 7.7 Hz), 8.04 (1H, d, J = 16.2 Hz, trans vinylic), 10.31 (1H, s, CHO); ^{13}C NMR δ 126.4, 127.5, 127.7, 128.2, 128.1, 129.2, 130.4, 133.3, 133.4, 133.9, 135.8, 140.9, 192.0; MS (m/e, int) 208 (100, M^+), 207 (41), 179 (67), 178 (75), 165 (34), 89 (22), 77 (21), 76 (25).

59Z: ^{1}H NMR δ 6.82 (1H, d, J = 12.2 Hz, cis vinylic), 6.97 (1H, d, J = 12.2 Hz, cis vinylic), 7.00-7.04 (2H, m), 7.11-7.16 (3H, m), 7.27 (1H, d, J = 7.5 Hz), 7.35-7.50 (2H, m), 7.87 (1H, dd, J = 1.5, 7.7 Hz), 10.23 (1H, s, CHO); ^{13}C NMR δ 124.8, 127.0, 127.2, 127.6, 128.3, 128.8, 132.3, 132.9, 133.7, 134.0, 136.9, 140.0, 192.7; MS (m/e, int) 208 (100, M^+), 207 (41), 179 (59), 178 (67), 165 (31), 89 (21), 77 (18), 76 (23).

In a separate run, GC monitoring was carried out by treating samples worked-up in the usual way with BSA dissolved in CH_2Cl_2 at rt for 5 min. Sampling was carried out after 10 min, 30 min, 90 min, 17h and 8 days. No significant variation of the product ratio was observed in the first four samples. A first-order reaction rate was averaged from the first three samples to 7×10^{-4} s^{-1}. After 8 days, two other major peaks appear (attributable

to the Cannizzaro products **61E** and **61Z**) with identical GC-MS cleavage patterns: 210 (21, M^+), 192 (18), 178 (13), 165 (12), 132 (10), 91 (100), 77 (16).

Cleavage of 58E with KOH: The same conditions were used as for **58Z**. GC monitoring of the course of the reaction using the same sampling protocol as for **58E** yielded a first-order rate constant for the conversion of **58E** at about 9 x 10^{-6} s^{-1} (average of samples at 1.5 and 17h). After 17 h, the major reaction products were shown to be **59E** and **59Z**, as evidenced by GC-MS analysis and the aldehyde resonances in the ^{1}H NMR. In addition, another aldehyde peak at δ 9.74 was found, tentatively assigned to **60E**. Integration of the aldehydic resonances yielded the following product ratio: 2.5 : 1 : 0.4 (**59Z** : **59E** : **60E**).

Cleavage of 40E and 40Z with NaOMe: Both ketones were treated seperately with 3N NaOMe in methanol for 23 h and worked up following the usual procedure. The products **46E**, **46Z**, **47E** and **47Z** were identified by ^{1}H NMR and GC-MS and have been previously characterized.

Aprotic experiments with 55Z:

a) with MeLi: The reactions at rt and 0°C were carried out in THF for 40 min. In the remaining reactions, MeLi was added at -78°C, the solution was stirred for 15 min then allowed to warm to rt and stirred for a further 40 min. The work-up was done by quenching with NH_4Cl followed by the usual ether/water extraction procedure. Product ratios were based on analysis of the ^{1}H NMR spectra of the reaction mixtures. The alcohols **69E** and **69Z** were also prepared by treating aldehydes **56E** and **56Z** (prepared by an alternative route[30]) with MeLi. These alcohols were identified by their characteristic ^{1}H NMR resonances. For **69E**: δ 1.50 (3H, d, J = 6.4 Hz, CH_3), 5.27 (1H, q, J = 6.4 Hz, C<u>H</u>(OH)Me), 6.95 (1H, d, J = 16.0 Hz, trans vinylic); for **69Z**: δ 1.41 (3H, d, J = 6.4 Hz, CH_3), 5.12 (1H, q, J = 6.4 Hz, C<u>H</u>(OH)Me), 6.63 (1H, d, J = 12.2 Hz, cis vinylic), 6.74 (1H, d, J = 12.3 Hz, cis vinylic).

b) with NaH: Both **55E** and **55Z** were treated with excess NaH in THF and stirred at rt for 2 h. The reactions were worked-up according to the usual NH_4Cl/ether

procedure. Analysis of the ^{1}H NMR from either crude reaction mixture showed two aldehyde resonances at δ 10.29 and 10.23, corresponding to **56E** and **56Z**, in a 1.2 : 1 ratio, respectively. The reaction products from **55E** showed two additional aldehyde resonances at δ 9.73 (previously assigned to **57E**) and at δ 9.99, tentatively assigned to **57Z**. This gives a total product ratio for the treatment of **55E** with NaH as: 1.2 : 1 : 0.9 : 0.6 (**56E/56Z/57Z/57E**). These products appeared to be minor components (ca. 10%) of the reaction mixture, which was not further analysed.

REFERENCES

1. Cava, M.P.; Muth, H.K. *J. Am. Chem. Soc.* **1960**, 82, 652.

2. Stevens, R.V.; Bisacchi, G.S. *J. Org. Chem.* **1982**, 47, 2393.

3. Amupitan, J.O.; Stansfield, F. *J. Chem. Soc. Perkin Trans. 1.* **1974**, 1949.

4. Cava, M.P.; Mangold, D.; Muth, K. *J. Org. Chem.* **1964**, 29, 2947.

5. Cava, M.P.; Napier, D.R.; Pohl, R.J. *J. Am. Chem. Soc.* **1963**, 85, 2076.

6. Blomquist, A.T.; LaLancette, E.A. *J. Am. Chem. Soc.* **1962**, 84, 220.

7. Horner, L.; Subramaniam, P.V.; Eiben, K. *Liebigs Ann. Chem.* **1968**, 714, 91.

8. Dhawan, K.L.; Gwoland, B.D.; Durst, T. *J. Org. Chem.* **1980**, 45, 924.

9. Jung, M.E.; Lam, P.Y.; Mansuri, M.M.; Speltz, L.M. *J. Org. Chem.* **1985**, 50, 1087.

10. Choy, W.; Yang, H. *J. Org. Chem.* **1988**, 53, 5796.

11. Hickman, D.; Wallace, T.W.; Wardleworth, J.M. *Tetrahedron Lett.* **1991**, 32, 819.

12. Stevens, R.V.; Bisacchi, G.S. *J. Org. Chem.* **1982**, 47, 2396.

13. Swenton, J.S.; Jackson, D.K.; Manning, M.J.; Raynolds, P.W. *J. Am. Chem. Soc.* **1978**, 100, 6182.

14. Kametani, T.; Tsubuki, M.; Nemoto, H.; Suzuki, K. *J. Am. Chem. Soc.* **1981**, 103, 1256.

15. Hassner, A.; Naidorf-Meir, S.; Gottlieb, H.E. *Tetrahedron Lett.* **1990**, 39, 5669.

16. Comber, R.N.; Swenton, J.S. *J. Am. Chem. Soc.* **1979**, 101, 5411.

17. Evans, D.A.; Golob, A.M. *J. Am. Chem. Soc.* **1975**, 97, 4765.

18. Evans, D.A.; Baillargeon, D.J.; Nelson, J.V. *J. Am. Chem. Soc.* **1978**, 100, 2242.

19. Steigerwald, M.L.; Goddard III, W.A.; Evans, D.A. *J. Am. Chem. Soc.* **1979**, 101, 1994.

20. Evans, D.A.; Nelson, J.V. *J. Am. Chem. Soc.* **1980**, 102, 774.

21. Spangler, L.A.; Swenton, J.S. *J. Org. Chem.* **1984**, 49, 1800.

22. March, J. Advanced Organic Chemistry, 3rd Ed., John Wiley & Sons, New York, **1985**, pp. 220-222.

23. Mittal, S.; Durani, S.; Kapil, R.S. *J. Med. Chem.* **1985**, 28, 492.

24. Koeppl, G.W.; Sagatys, D.S.; Krishnamurthy, G.S.; Miller, S.I. *J. Am. Chem. Soc.* **1967**, 89, 3396.

25. Panek, E.J.; Neff, B.L; Chu, H.; Panek, M.G. *J. Am. Chem. Soc.* **1975**, 97, 3996.

26. Curtin, D.Y.; Crump, J.W. *J. Am. Chem. Soc.* **1958**, 80, 1922.

27. Hunter, D.H.; Cram, D.J. *J. Am. Chem Soc.* **1964**, 86, 5478.

28. Newkome, G.R.; Robinson, J.M. *J. Org. Chem.* **1976**, 41, 2536.

29. O'Brian, D.H.; Russell, C.R.; Hart, A.J. *J. Am. Chem. Soc.* **1976**, 98, 7427.

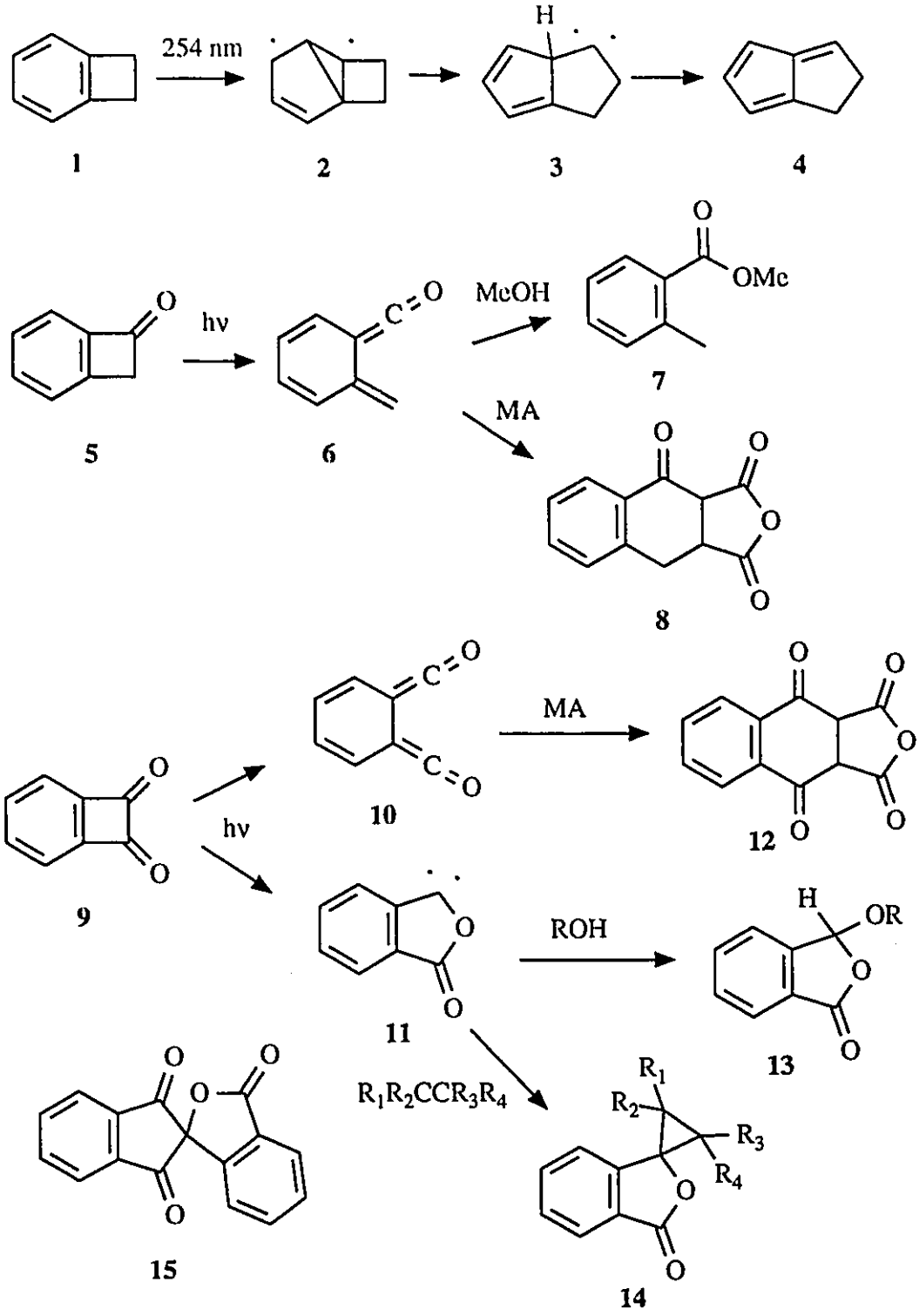
30. Munro, D.P.; Sharp, J.T. *J. Chem. Soc. Perkin Trans. I* **1984**, 849.

CHAPTER 7: PHOTOCHEMICAL INVESTIGATIONS

Introduction

Due to the diversity of photochemical pathways involved for the simple derivatives of benzocyclobutene, it was of interest to study the behaviour of benzylidenebenzocyclobutenones upon irradiation. According to Woodward-Hoffmann rules cyclobutenes and benzocyclobutenes are expected to open photochemically via a concerted disrotatory process.[1] However, this is not observed for even the simplest alkyl derivatives of cyclobutene, where apparantly the forbidden conrotatory process occurs to a large extent.[2-5] Benzocyclobutene **1** does not undergo ring opening upon irradiation but rather produces principally dihydropentalene **4** presumably via diradical and carbene intermediates **2** and **3** (Scheme 1).[6] Benzocyclobutenone **5** produces the expected vinylketene **6**,[7] which can be trapped by methanol to yield ester **7** or by maleic anhydride to Diels-Alder adduct **8**.

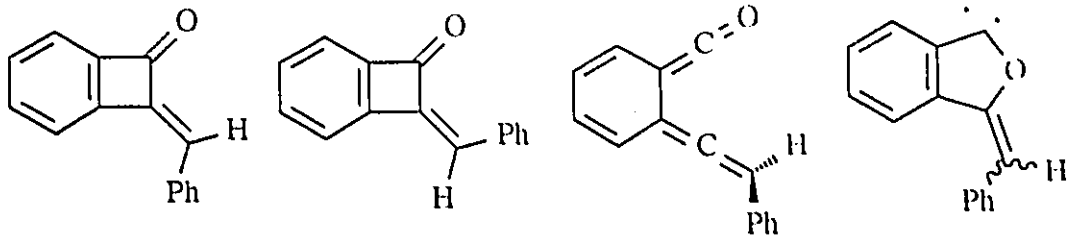
Benzocyclobutenedione **9** gives products of either bis-ketene **10** or oxacarbene **11** intermediates, depending on the trapping agent and temperature.[8-13] With electron withdrawing dienophiles such as maleic anhydride bis-ketene adducts such as **12** are formed, whereas electron donating alkenes and alcohols appear to react with the oxacarbene intermediate to yield **13** and **14**. When **9** is irradiated in the absence of trapping agents, dimer **15** is obtained, which apparently results from adduct formation between bis-ketene **10** and oxacarbene **11**.[13] Finally, low temperature studies in matrices favor the formation of benzyne, which is not observed in the solution photochemistry of **9**.[14-16]



Scheme 1

By analogy with the dione **9**, photochemical ring opening of **16E** or **16Z** might be expected to yield ketene-allene **17** or oxacarbene **18** intermediates. We thus carried out the photolysis of **16** under a variety of conditions in the presence or absence of trapping

agents to determine the photochemical pathways involved.



16E **16Z** **17** **18**

Results

In the absence of trapping agents, irradiation of a 0.03 M solution of **16E** or **16Z** led to rapid isomerization about the C=C double bond.[17-21] The composition of the photostationary state was found to be dependent upon the wavelength of irradiation, corresponding to the different absorbances of each isomer at the respective wavelengths (see Fig 1). After irradiation at 350 nm in $CDCl_3$ or CH_2Cl_2 a 60:40 E/Z photostationary state was obtained, wereas irradiation at 250 nm in $CDCl_3$ led to a 70:30 E/Z mixture.

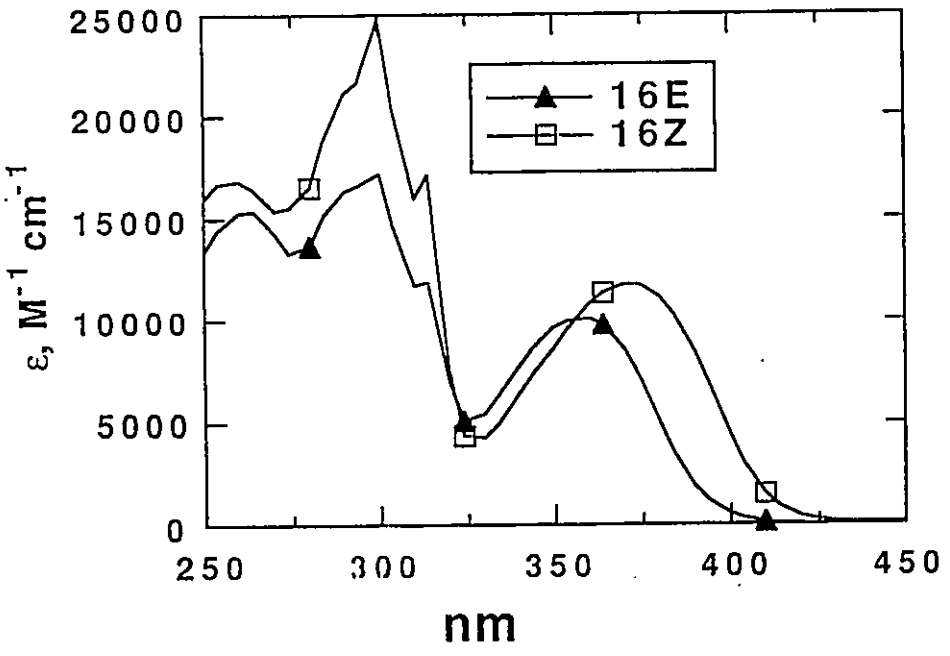


Fig 1: UV spectra of 16E and 16Z in acetonitrile

Continued irradiation of a 0.1 M solution of **16Z** for a few hours at 350 nm led to the appearance of two peaks in the ^{1}H NMR at δ 4.77 and δ 4.63 in about a 4:1 ratio. As will be described shortly, these two resonances signal the formation of dimers **23** and **22**, respectively. ^{1}H NMR monitoring over the course of the irradiation allowed for a quantitative analysis of dimer formation (Fig 2). Although the resonance for **16E** at δ 6.85 was obscured by products, an estimate of starting materials present in the mixture was obtained from the singlet at δ 6.55 corresponding to **16Z** and assuming a 60:40 **16E:16Z** photostationary state. By comparing the combined integration of the resonances corresponding to dimers **23** and **22** with the starting materials **16E** and **16Z**, the percentage of dimer conversion was determined. However, as the irradiation proceeded, secondary photoproducts also accumulated. In order to obtain an estimate for these processes, the combined integrations of **16E**, **16Z**, **22** and **23** were compared to the total integration of the ^{1}H NMR spectrum. The amount of integration which was in excess of that expected from a mixture exclusively composed of the above 4 components was assigned as "other photoproducts". By combining these results, an overall yield of dimers **23** and **23** can be obtained as a function of irradiation time. As is apparent from Fig 2, although longer irradiation times increase the conversion of starting materials to dimers, competing secondary processes have the effect of leveling off the dimer yield to 30-35% within about 4 h.

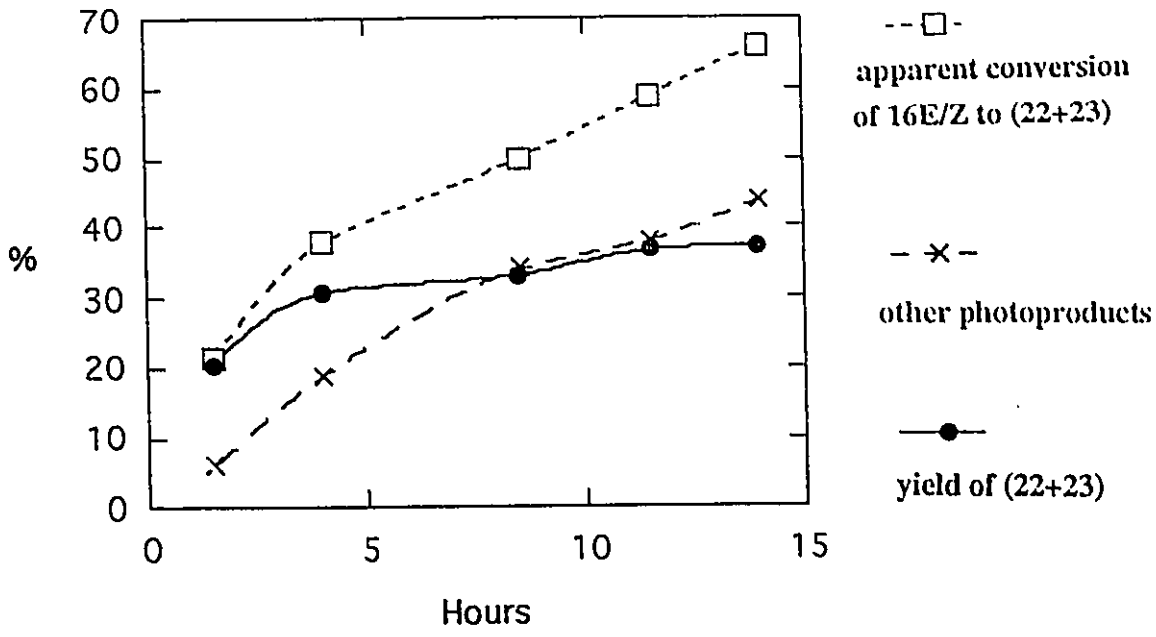
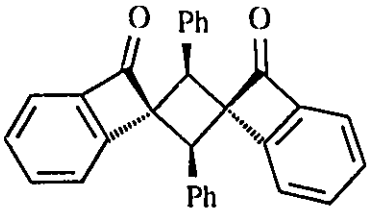


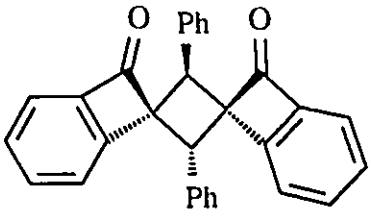
Fig 2: Reaction Profile for the Photodimerization of 16E/Z

Many of the products and starting material from this irradiation experiment showed considerable chromatographic overlap in a number of solvent systems. However, repeated separations with hexanes/CH_2Cl_2 and hexanes/ethyl acetate mixtures yielded small amounts of pure dimers **23** and **22**. The IR spectra of these dimers showed C=O stretching near 1760 cm^{-1} indicating an intact benzocyclobutenone ring system. The most reasonable structures consistent with this observation arise from [2 + 2] photodimerization about the C=C double bonds.[22-26] Ten dimers (**19** to **28**) could potentially result from such a dimerization with the possibility of head-to-head or head-to-tail arrangements and with various syn or anti relationships between the carbonyl functionalities and phenyl groups.



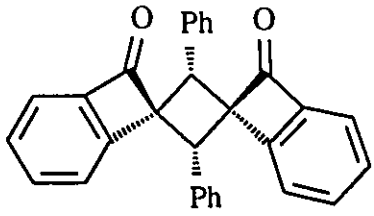
19

ht-syn-syn-syn



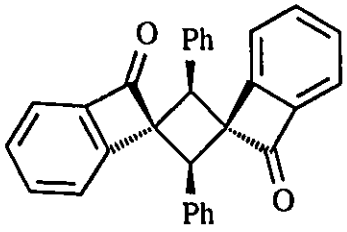
20

ht-syn-syn-anti



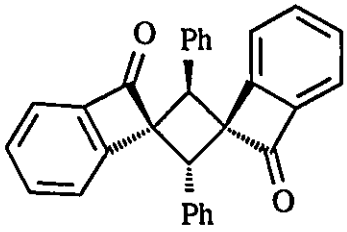
21

ht-anti-anti-anti



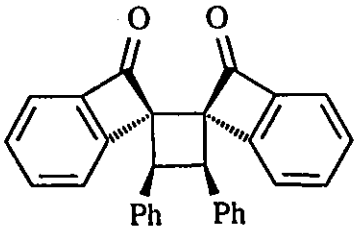
22

ht-syn-anti-anti



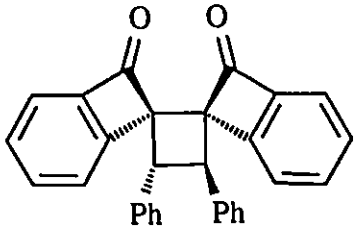
23

ht-syn-anti-syn



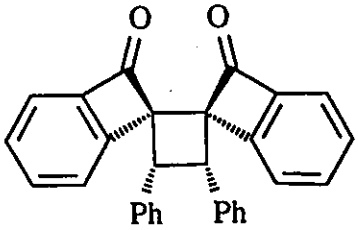
24

hh-syn-syn-syn



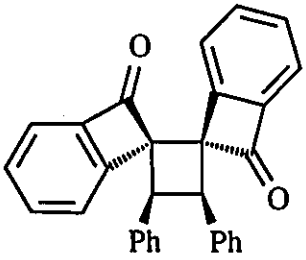
25

hh-syn-syn-anti



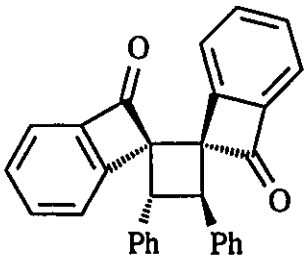
26

hh-syn-anti-syn



27

hh-anti-anti-syn



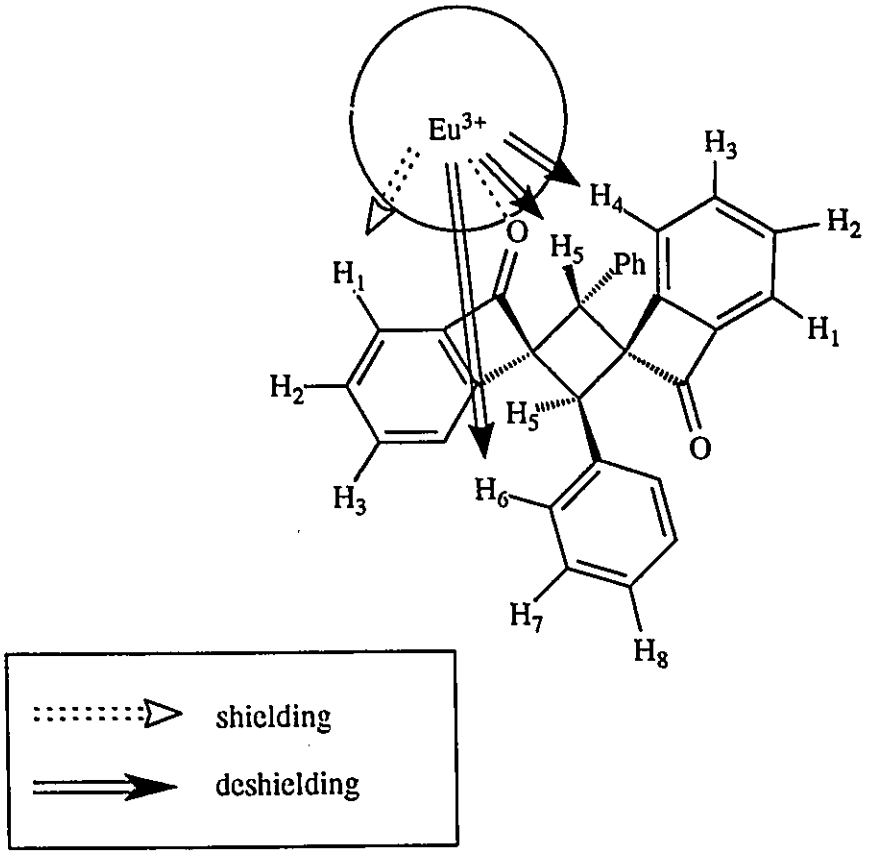
28

hh-anti-anti-anti

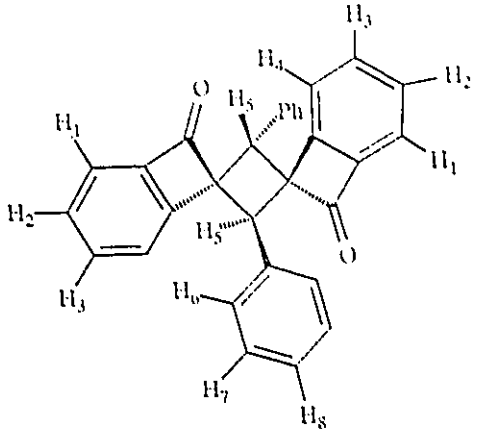
The major dimer was identified as **23** based on the following NMR data. First, the carbon spectrum displayed only 13 lines, consistent only with completely symmetrical structures such as **19**, **21**, **23**, **24**, **26** and **28**. Second, the ^{13}C satellites of the benzylic protons at δ 4.75 (H_5 in Fig 3) showed no coupling > 1 Hz, indicating a head-to-tail arrangement thus narrowing the possibilities to **19**, **21** and **23**. In head-to-head configurations, the two benzylic hydrogens would have a vicienal relationship and the ^{13}C satellites would be expected to show a 3-9 Hz coupling with the adjacent hydrogen attached to a ^{12}C isotope.[25] Finally, irradiation of the benzylic hydrogens (H_5) induced an NOE enhancement of the ortho phenyl hydrogens (H_6) at δ 7.25 as well as the doublet at δ 7.68. Minimization studies revealed that, aside from the ortho phenyl hydrogens, the benzylic hydrogens in **21** were too far removed (> 4 Å) from any other hydrogen to expect a significant NOE effect. This permits the elimination of **21** as a candidate for the major dimer, limiting the possibilities to **19** and **23**.

To distinguish between these two isomers, the shift reagent, $Eu(tfc)_3$, was added incrementally to the major dimer, resulting in the ^1H NMR spectra shown if Fig 4. The shift reagent, a weak Lewis acid,[27] coordinated with the carbonyl oxygen and induced significant downfield shifts of H_4,H_5 and H_6 while causing a upfield shift of H_1 (see Fig 3). The assignments of these resonances were readily deduced from a COSY spectrum taken in the presence of the shift reagent (see Fig 5), coupled with the assignment of H_4 as the lowest field doublet by NOE experiment (*vide supra*). The observation that both H_1 and H_4 were strongly affected by the presence of shift reagent is an excellent indication that the carbonyl functionalities are anti with respect to each other. This thus leaves **23** as the only possible structure for the major dimer.

Fig 3: Anisotropic magnetic effect of shift reagent on dimer 23



Another feature which emerges from Fig 4 is the splitting of the doublets corresponding to H_4, H_6 and H_1 initially to pseudo triplets then to two clearly resolvable doublets for H_4 and H_6 upon incremental addition of shift reagent. This is expected to occur for structure **23** with a chiral shift reagent since the coordination sites at the two carbonyl groups correspond to enantiomerically opposite environments. It is interesting that the singlet assigned to the benzyl hydrogens H_5 is not split even at the maximal concentrations of shift reagent used. This peak, however, does experience significant line broadning. An attempt to resolve these enantiotopic benzyl hydrogens in the presence of shift reagent by aquiring the ^1H NMR spectra at 0°C was not succesful.



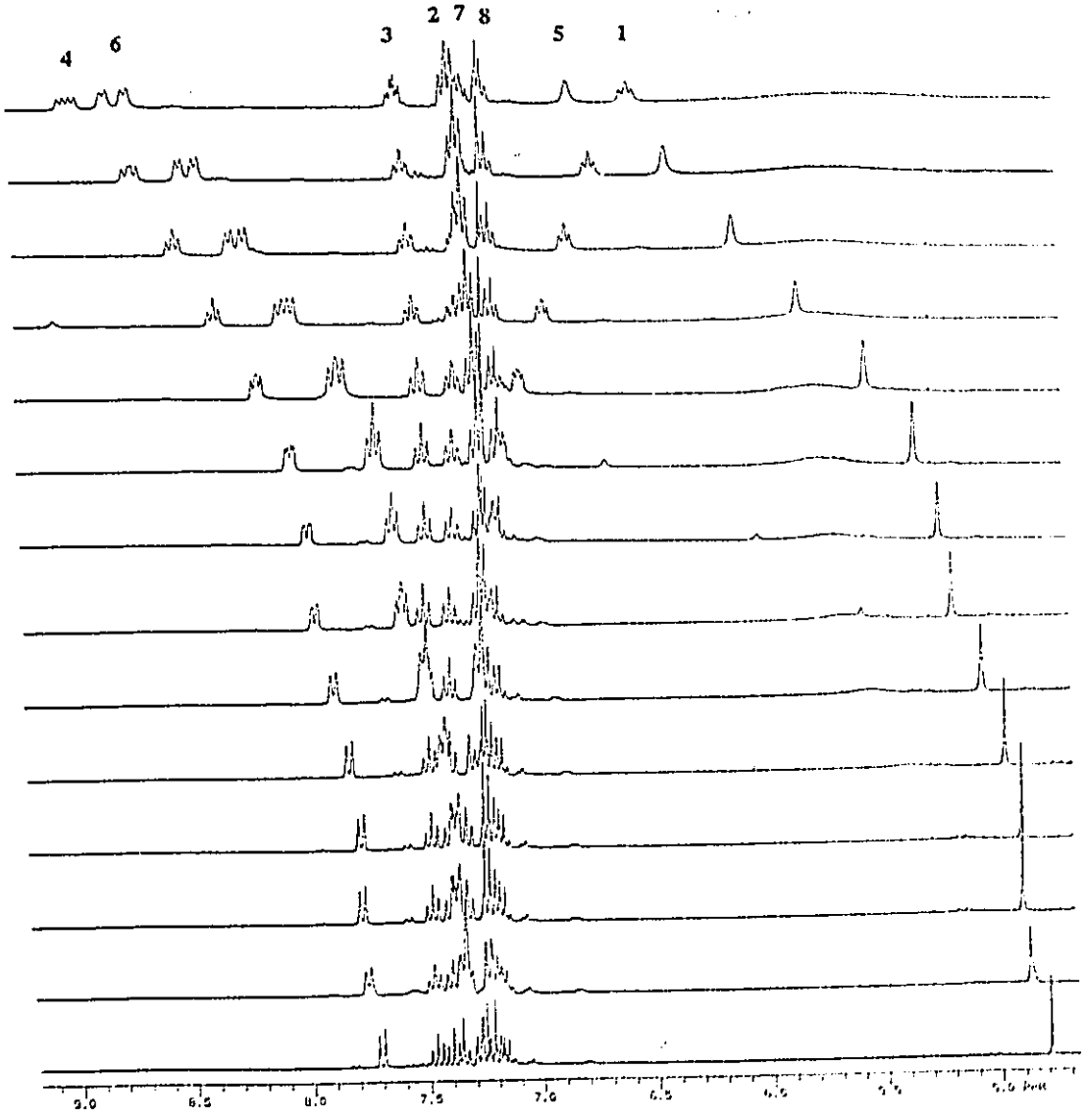
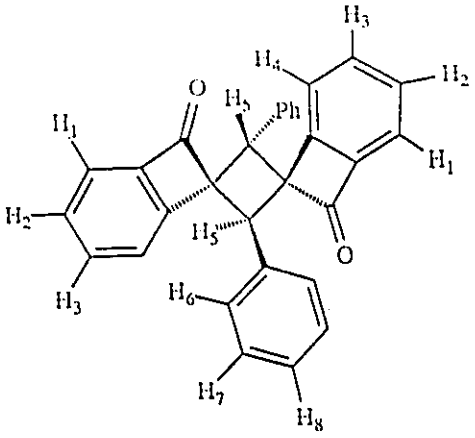


Fig 4: ^{1}H NMR of 23 with incremental addition of Eu(tfc)$_3$



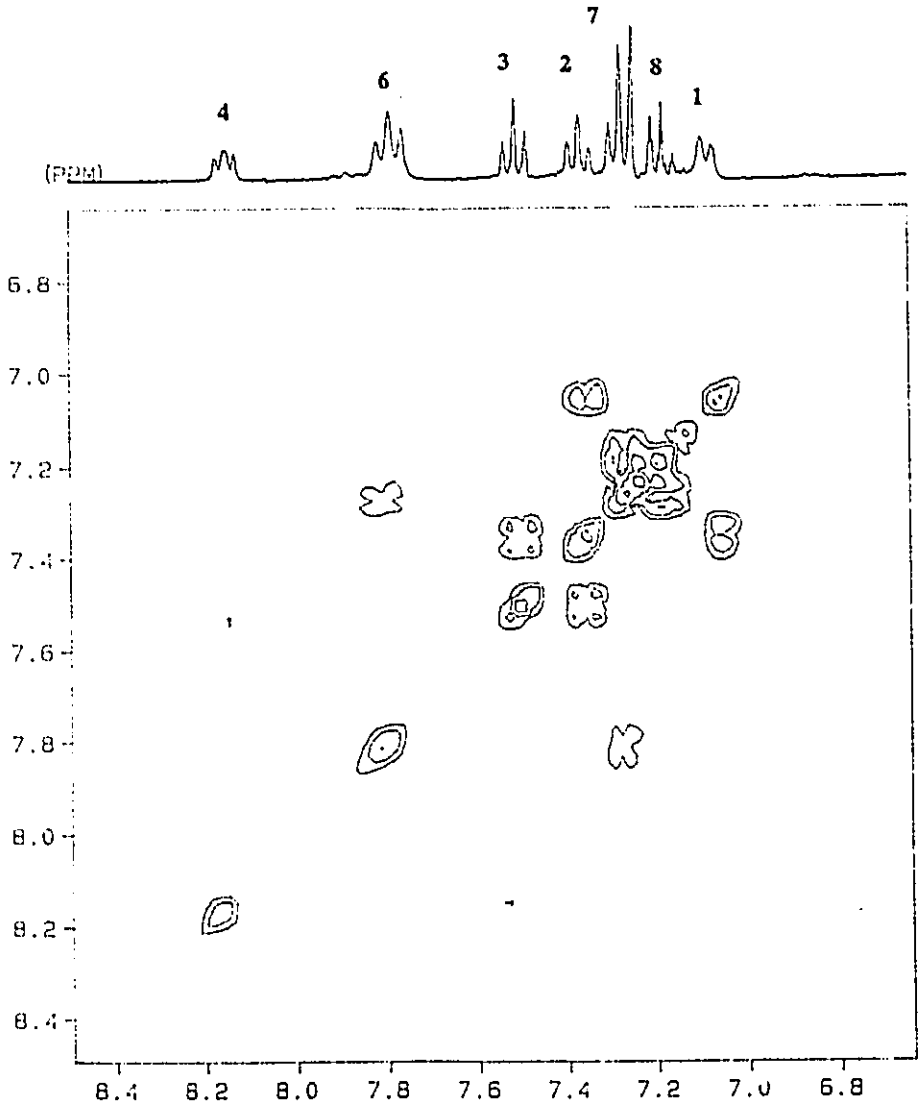
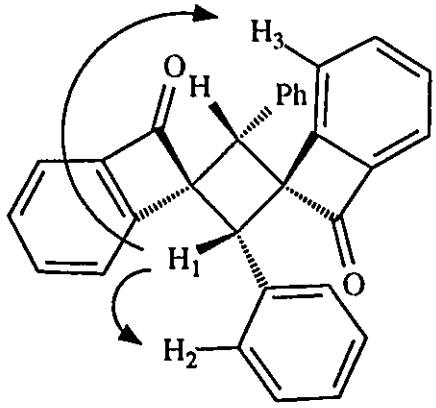
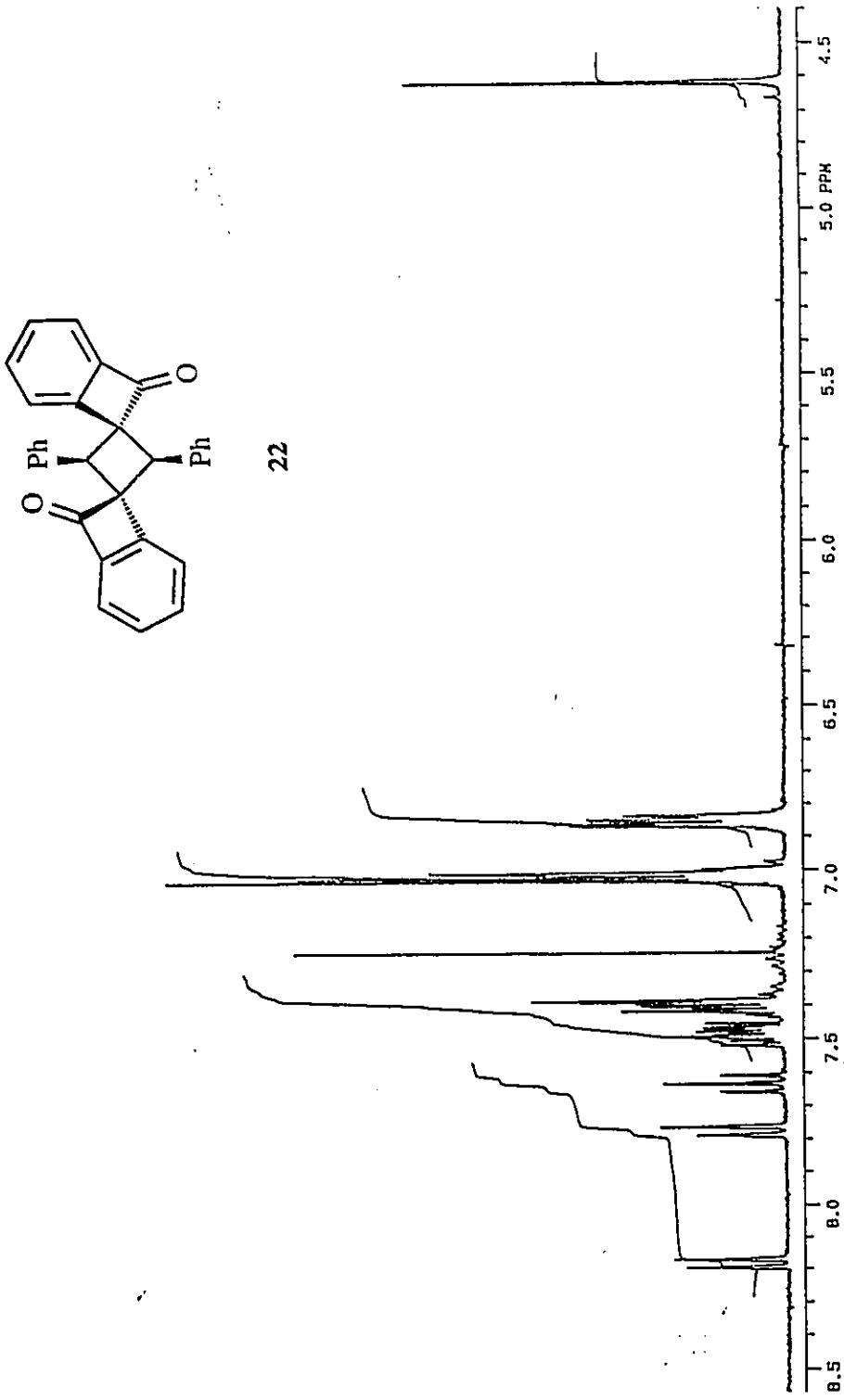


Fig 5: COSY of 23 in the presence of $Eu(tfc)_3$

The minor dimer displayed a single benzylic resonance at δ 4.63, indicating that the benzylic protons were in identical magnetic environments. The benzocyclobutenone aromatic protons, however, did posess different shifts (see Fig 7). Based on ^{13}C satellites which showed no coupling >1 Hz, its structure was identified as belonging too the head-to-tail series. In addition, NOE irradiation of the benzylic hydrogen H_1 at δ 4.61 led to enhancement only of the ortho hydrogens on the phenyl rings (H_2 at δ 6.85) and the doublet at δ 7.78 corresponding to H_3 (see Fig 6). The only structure which is consistent with these observations is **22**. Subsequently, an X-ray crystal determination was obtained for **22**, which fully corroborated the assigned structure (Fig 8).

Fig 6: NOE correlations for dimer 22





22

Fig 7: ^{1}H NMR of dimer 22

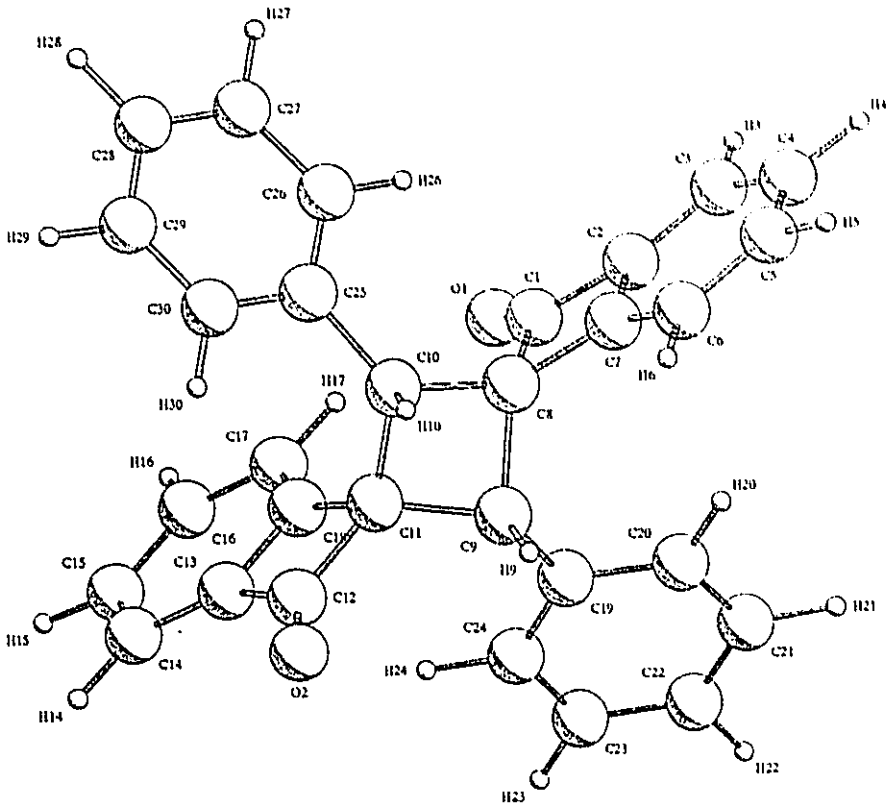


Fig 8: ORTEP diagram of 22

Since the crystal lattice structure of **16E** was revealed to consist nearly perfectly overlapping molecules (see Fig 9), it was hoped that head-to-head dimers would exclusively form upon irradiation in the solid state.[28] However, irradiation at 350 nm of crystalline **16E** for 23h induced no photoreaction as judged by ^{1}H NMR spectroscopy. Apparently, the lattice energy is sufficient to also prevent either dimerization or isomerization to **16Z.**

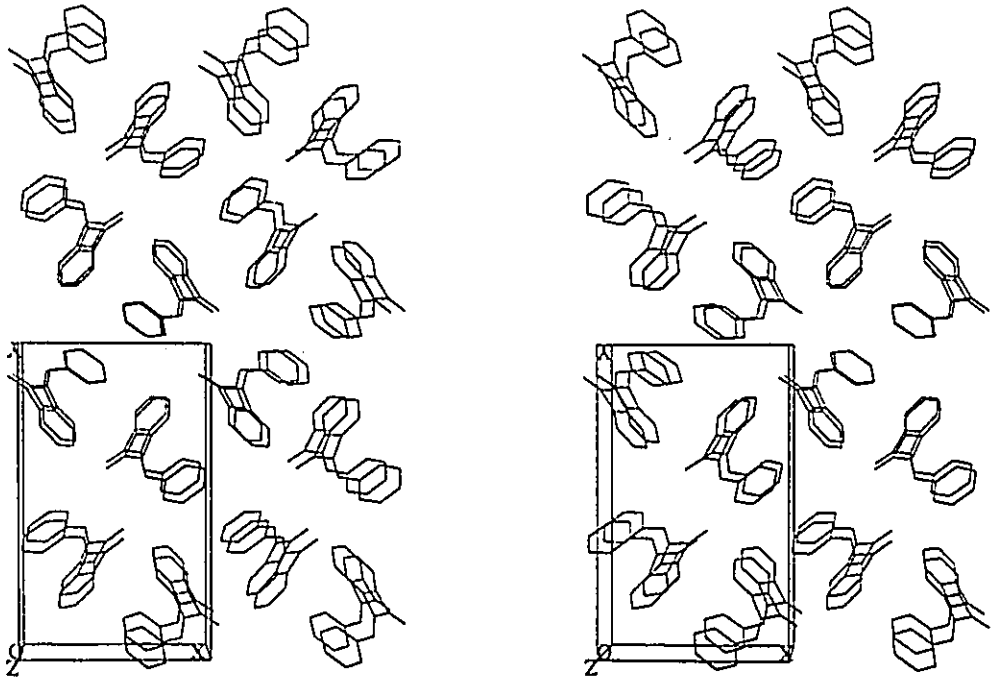
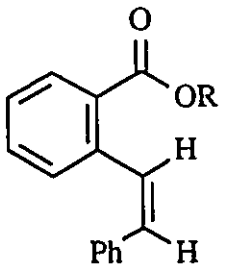


Fig 9: Packing diagram of 16E (stereoscopic view)

Trapping experiments

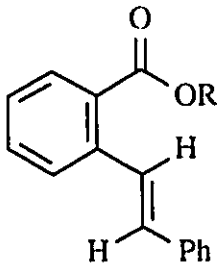
Attempts to trap **17** with maleic anhydride did not lead to any observable trapping products when **16E** was irradiated at 350nm in $CDCl_3$ solution, as juged by ^1H NMR. Instead, isomerisation about the C=C double bond was followed by formation of dimers, although both of these processes were significantly retarded as compared to the control containing **16E** alone.

When **16Z** was irradiated in pure methanol at 350nm, dimer formation occured in preference to trapping in > 10:1 ratio. However, at 250 nm, esters **29** and **30** were obtained in a 1:1 ratio with only traces of dimer formation. These were easily identifiable by the characteristic methyl ester peaks at δ 3.87 and δ 3.91 respectively as well as the cis olefinic coupling of 12.2 Hz (δ 6.63) for **29a** and the trans coupling of 16.3 Hz (δ 6.98) for **30a**. These esters were fully characterized previously (see **46E/Z** in Chapter 6). This wavelength dependence is presumably due to the fact that the dimers posess an absorbtion band at 250 nm but not at 350 nm thus leading to photocycloreversion[25,26] of the dimers regenerating **16E** and **16Z** at the shorter wavelength. Since no peaks corresponding to trapping product **31** could be detected by ^1H NMR, it can be concluded that formation of an oxacarbene intermediate **18** is not a significant photochemical pathway.



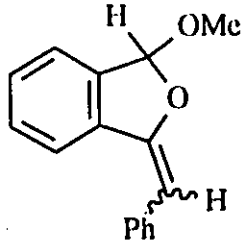
29a: R = Me

29b: R = H



30a: R = Me

30b: R = H



31

Laser Flash Photolysis Studies

In order to further elucidate the mechanisms responsible for the isomerization and dimerization processes laser flash photolysis studies were carried out. It was hoped that some of the intermediates involved in these photoreactions would be detectable in the UV-visible spectral window we had available for observation.

Three possible intermediates can be postulated to be involved in the isomerization process: a singlet or triplet excited state or ketene-allene intermediate **17**. The photodimerization could be expected to proceed via either the singlet or triplet excited states. To probe these possibilities, the following laser flash photolysis experiments were carried out.

Thus, acetonitrile solutions of **16E** and **16Z** (4×10^{-5} M) were irradiated with a 308 nm laser flash. After 1 μs, the spectra shown in Fig 10 were obtained. These spectra repesent the differences in O.D.'s compared to the solution prior to the laser flash. Consequently, the negative peaks observed at shorter wavelengths are due to the depletion of the starting material. Irradiation of either isomer generates a peak centered near 400 nm. Although there appears to be a slight shift in the peak to a longer wavelength after the irradiation of **16Z**, this is simply a consequence of the larger extinction coeffiecient of the depleted starting material at 400 nm compared to **16E** (see Fig 1). In fact transients obtained from both **16E** and **16Z** were shown to have the same lifetime of 36 μs. This is excellent evidence that the same intermediate is being observed from either isomer.

The identity of the 400 nm transient was then probed by adding various potential quenching agents. No observable change in the lifetime of the transient was detected when the flash photolysis was carried out in an oxygen saturated solution. This indicated that the transient did not correspond to a triplet species, which should have been readily quenched by oxygen.[29] However, carrying out the photolysis in the presence of methanol or water led to a significant decrease in the lifetime of this transient. For example, in methanol its lifetime was reduced by about a factor of 10 to 3 μs. Based on the product studies previously described, it is reasonable to assume that the intermediate being

observed is the ketene-allene **17**, yielding adducts **29** and **30** in the presence of a hydroxylic trapping agent.[30]

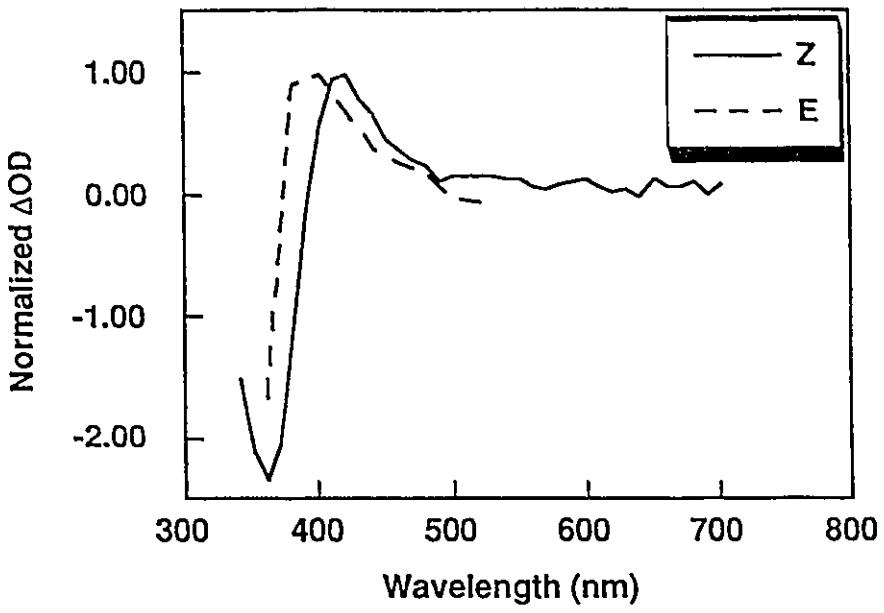


Fig 10: Transient spectra recorded following laser excitation of 16E and 16Z in acetonitrile

A study of the dependence of the lifetime of **17** on the water or methanol concentrations yielded good first-order quenching plots with a rate constant of 6.5 x 10^3 $M^{-1}s^{-1}$ for water and 1.2 x 10^4 $M^{-1}s^{-1}$ for methanol (see Fig 11). Identical water quenching rate constants were obtained from the photolysis of either **16E** or **16Z**, fully confirming that the same intermediate is being observed in both cases. The linear dependence observed from these quenching experiments is highly suggestive that a ketene hydrate type of intermediate such as **32** is not involved. Such intermediates have been postulated to account for the second order dependence often observed in the quenching of ketenes with water.[31] Instead, it is proposed that the reaction between ketene **17** and hydroxylic solvents occurs by a concerted process via transition state **33**.

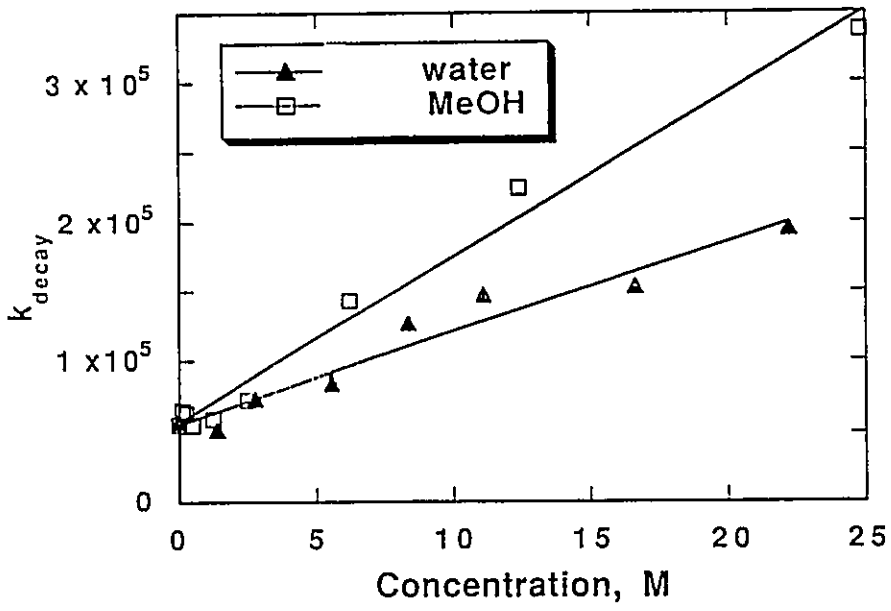
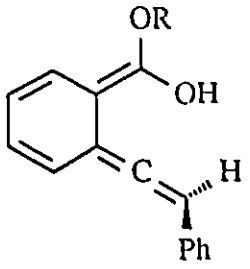
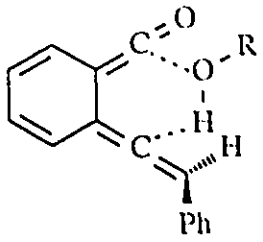


Fig 11: Quenching of 17 by water and methanol (recorded at 410 nm)



32



33

Flash photolysis in the presence of 1% pyridine resulted in quenching of 400 nm absorbance and the appearance of a broad absorbance centered at 440nm, tentativeley assigned as the pyridine ylide **34**.(see Fig 11) Ketenes have previously been characterized by similar ylide formation.[27]

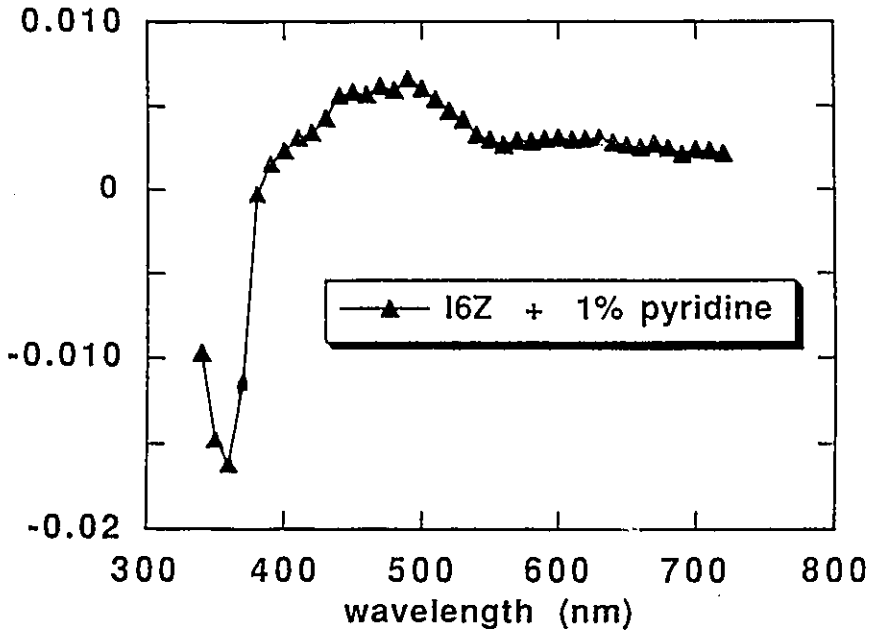
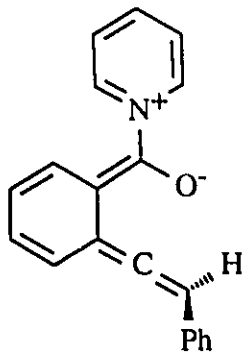


Fig 12: Absorption tentatively assigned to pyridine ylide 34



34

Traces were also taken at various wavelengths to study the isomerization process after flash photolysis of **16E**. (Fig 13) Monitoring at 350 nm (Trace A) showed an initial depletion of staring material followed by a gradual partial recovery towards the baseline. Monitoring at 380 nm (Trace B) revealed a nearly instantaneous (< 50 ns) rise in Δ O.D. followed by a slower growth. Both the recovery at 350 nm and the growth at 380 nm matched exactly the decay of the ketene-allene **17** monitored at 440 nm (Trace C). This is excellent evidence that the ketene-allene **17** recyclizes to **16E** and **16Z**, thus accounting at least partly for the isomerization process.

However, due to significant overlapping of **16E** and **16Z** at 350 nm and interference from mainly **16Z** and **17** at 380 nm, was not possible to estimate the relative ratio of **16E/16Z** being formed from **17** with this information. The nearly instantaneous process at 380 nm should correspond to the formation of ketene-allene **17** and rapid isomerization of **16E** to **16Z** via a singlet or a triplet intermediate. Although it was not possible to quantify the relative contribution of these two events, an upper limit of 50% can be attributed to the isomerization of **16E** to **16Z** via an excited state pathway. After 200 μs, **17** has completely decayed and no longer interferes at 380 nm. Thus, by using the final Δ O.D.'s at 350 nm and 380 nm, it is possible to account for 89% of the depleted **16E** as having been converted to **16Z**.

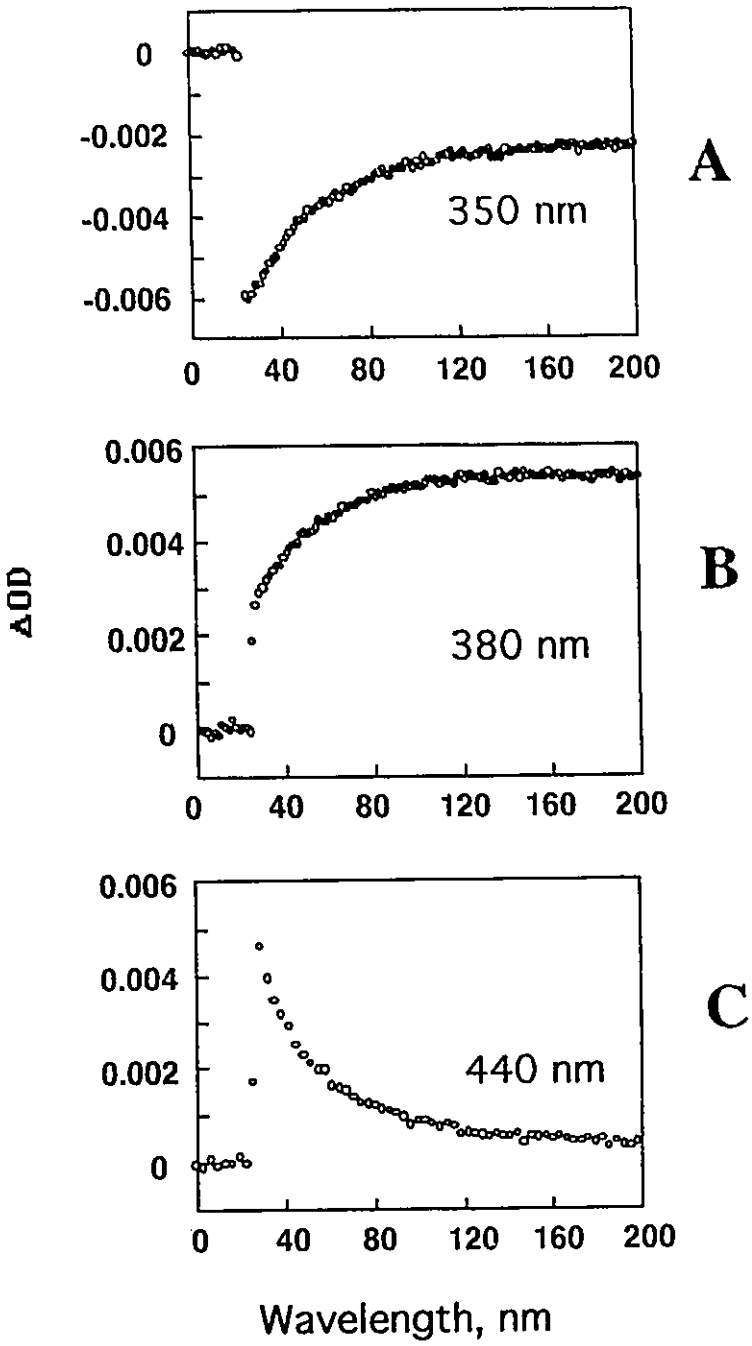
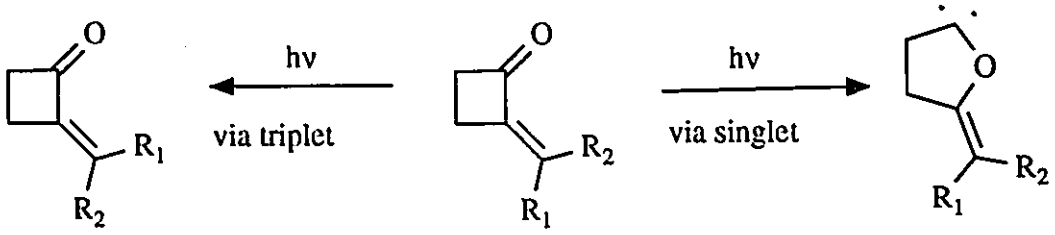


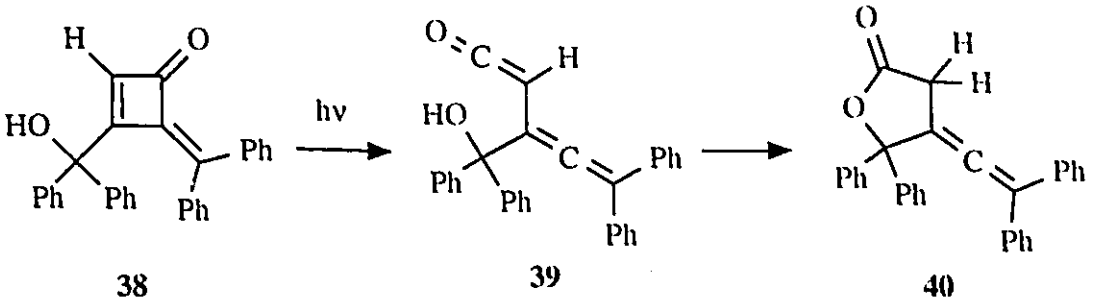
Fig 13: Transient absorbance traces recorded after 308 nm laser excitation of 16E

The nature of the excited state was then investigated. Since no naphtalene triplet was detected after flash photolysis of **16E** at 337 nm in the presence 71 mM naphtalene, a triplet excited state is probably not involved.[31] Therefore, it is likely that a singlet species is responsible for the dimerization and probably for some of the isomerization. The involvement of a singlet is consistent with the accepted mechanism for the isomerization of stilbene.[17-21] However, many substituted stilbenes are known to isomerize by either the singlet or triplet manifolds.[18] In addition, 2-alkylidenecyclobutanes such as **36** have been shown to undergo cis-trans isomerization to **35** via a triplet excited state and ring expansion to oxacarbene **37** via a singlet excited state[32] (Scheme 2). The results obtained in our study are much more in line with those obtained by Toda,[33-35] who found that 4-(diphenylmethylene)-2-cyclobuten-1-one **38** photolyses to yield ketene-allene intermediate **39**, which then cyclize to butanolide **40** (Scheme 3). Apparently, in spite of the additional disruption of aromaticity in forming ketene-allene **17**, this path is favoured over oxacarbene formation during the photolysis of **16E** or **16Z**.



35 **36** **37**

Scheme 2

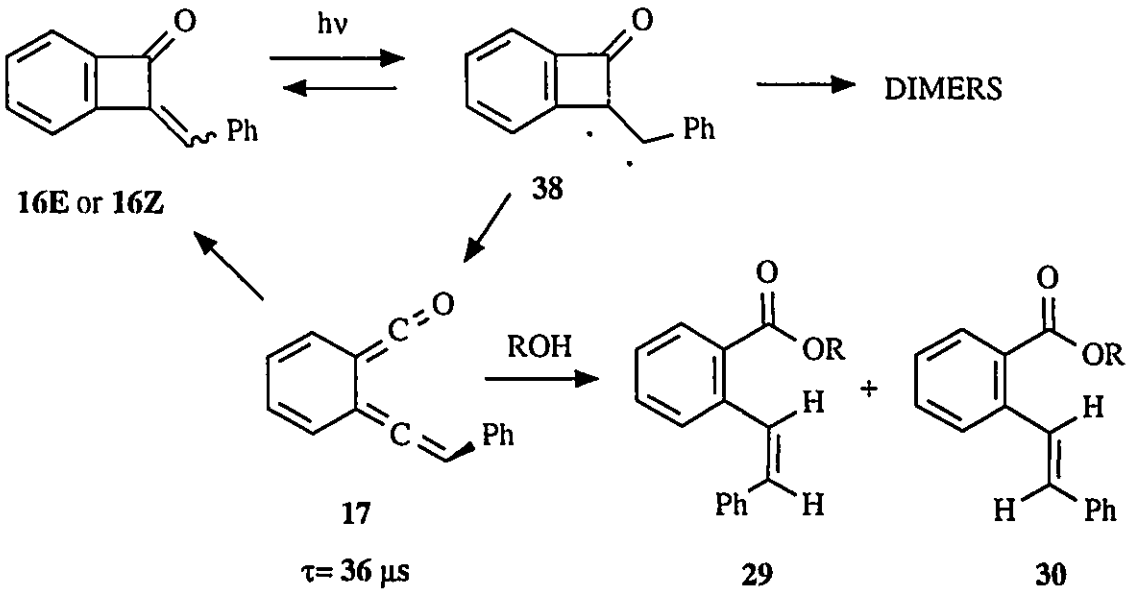


38 **39** **40**

Scheme 3

Conclusion

A summary of our present knowledge of the pathways and intermediates involved in the photochemistry of benzylidenebenzocyclobutenones is shown in Scheme 4. Irradiation of **16E** or **16Z** initially yields an excited singlet state **38** which then either reverts to starting materials, undergoes ring opening to ketene-allene **17** or reacts with a ground state molecule to form dimers. In the absence of trapping agents, **17** recyclizes to both **16E** and **16Z**, thus accounting for a second isomerization process. In the presence of hydroxylic trapping agents, adducts **29** and **30** are formed. Maleic anhydride does not trap **17**, probably in part due to the very short lifetime (36 μs) of this intermediate compared to analogous o-quinodimethanes. For example vinyl-ketene **6** has a lifetime[7] of 170 ms, almost four orders of magnitude longer lived than **17**. Although an exact lifetime for bis-ketene **10** has not been measured, it has been determined to be > 100 μs.[9]



Scheme 4

EXPERIMENTAL

General: Same as specified in Chapter 6 with the following additions. ^{13}C satellites and shift reagent experiments were acquired on the Varian XL-300 instrument.

Laser Flash Photolysis: All samples were examined under flow conditions at concentrations of 4 x 10^{-5} M in acetonitrile and were excited with the 308 nm pulses from a Lumonics EX-510 excimer laser. Air and nitrogen saturated samples showed identical behaviour. The system is controlled by a Macintosh IIci computer operating with LabVIEW 2.2 software; the system is otherwise similar to those described elsewhere.[36-37]

The triplet scavenging experiment[31] was carried in the presence of 71 mM naphtalene in acetonitrile solution. A Molectron UV-24 nitrogen laser emitting at 337 nm was used. Only a peak at 400 nm was observed, corresponding to the ketene-allene **17**.

Product Studies: Steady state irradiations were performed in a photoreactor equiped with nine PRP-254 or 350 nm lamps. The temperature in the reactor was typically between 32-35°C. The samples were nitrogen saturated and contained in quartz tubes for 254 nm irradiation and NMR tubes for 350 nm irradiation. Reactions were traced by ^1H NMR.

Dimerization study: A solution of **16Z** (44 mg, 0.22 mmol) in 2 mL of $CDCl_3$ was introduced into an NMR tube, degassed with a flow of nitrogen for 10 min then irradiated at 350 nm. The course of the reaction was monitored by ^1H NMR (see Fig 2 and text for details). Repeated chromatography with hexanes/CH_2Cl_2 and hexanes/ethyl acetate yielded small amounts of pure dimers **22** and **23**. Crystallization of **22** from methanol afforded crystals suitable for X-ray diffraction.

22 (minor dimer): ^1H NMR δ 4.61 (2H, s, CHPh, ^{13}C satellites: d, J = 134 Hz), 6.86 (4H, m), 7.03 (6H, m), 7.35-7.55 (5H, m), 7.63 (1H, t, J = 7.4 Hz), 7.77 (1H, d, J = 7.5 Hz), 8.18 (1H, d, J = 7.4 Hz); ^{13}C NMR δ 50.6, 76.8, 120.6, 120.9, 122.0, 126.6, 127.5, 128.0, 128.1, 129.9, 130.3, 135.6, 136.0, 136.1, 148.0, 148.7, 156.1, 157.6, 192.8

23 (major dimer): ^1H NMR δ 4.77 (2H, s, CHPh, ^{13}C satellites: d, J = 137 Hz), 7.1-7.3 (10H, m), 7.33 (2H, d, J = 7.5 Hz), 7.39 (2H, t, J = 7.3 Hz), 7.46 (2H, t, J = 7.3

Hz), 7.69 (2H, d, J = 7.3 Hz); ^{13}C NMR δ 54.8, 75.1, 120.7, 124.2, 127.0, 128.3, 128.5, 130.0, 135.8, 136.6, 148.0, 157.2, 191.7; IR (CH_2Cl_2, cm^{-1}) 1764; MS (m/e, int) 412 (60, M^+), 335 (100), UV (MeCN, nm) 244, 210.

Trapping experiments with methanol:

a) at 350 nm: A solution of **16Z** (17.3 mg, 0.084 mmol) in 4 mL of MeOH and a few drops of CH_2Cl_2 to aid dissolution was irradiated at 350 nm in a quartz vessel for 2 h. The solvents were removed and $CDCl_3$ was added to the residue. The ^1H NMR indicated the following ratio (**16E** + **16Z**) 1.3 : (**23** + **22**) 1.0 : (**30a** + **29a**) 0.1.

b) at 250 nm: A solution of **16Z** (100.5 mg, 0.49 mmol) in 20 mL MeOH and 1 mL of CH_2Cl_2 was irradiated in a quartz vessel for 26 h at 250 nm. The solvents were evaporated and the residue dissolved in $CDCl_3$. The ^1H NMR indicated the following ratio (**16E** + **16Z**) 6.0 : (**23** + **22**) 1.0 : (**30a**+**29a**) 9.2. After redissolution in MeOH followed by a further 16 h irradiation the following ^1H NMR ratios were obtained: (**16E** + **16Z**) 1.0 : (**23** + **22**) trace : (**30a**+**29a**) 3.2. Chromatography in 1:1 hexanes/CH_2Cl_2 afforded **30a** and **29a** (mixed in several fractions) in a combined yield of 36%. The ^1H NMR and GC-MS data matched those of compounds **46E** and **46Z** in Chapter 6.

Attempted trapping with maleic anhydride: A solution of **16Z** (25.3 mg, 0.12 mmol) and maleic anhydride (26.5 mg, 0.27 mmol) in 2 mL of $CDCl_3$ was irradiated for 17 h at 350 nm. The ^1H NMR revealed the following ratio: (**16E** + **16Z**) 2 : (**23** + **22**) 1 with only traces of other resonances in the interval δ 4 - 6.5.

REFERENCES

1. Woodward, R.B.; Hoffmann, R. The Conservation of Orbital Symmetry, Verlag Chemie, Weinheim, **1970**.

2 Leigh, W.J.; Zheng, K.; Nguyen, N.; Werstiuk, N.H. Ma, J. *J. Am. Chem. Soc.* **1991**, 113, 4993.

3. Leigh, W.J.; Zheng, K.; Clark, K.B. *Can. J. Chem.* **1990**, 68, 1988.

4. Clark, K.B.; Leigh, W.J. *J. Am. Chem. Soc.* **1987**, 109, 6086.

5. Bernardi, F.; Olivucci, M.; Ragazos, I.N.; Robb, M.A. *J. Am. Chem. Soc.* **1992**, 114, 2752.

6. Turro, N.J.; Zhang, Z.; Trahanovsky, W.S.; Chou, C.-H. *Tetrahedron Lett.* **1988**, 29, 2543.

7. Schiess, P.; Eberle, M.; Huyo-Francotte, M.; Wirz, J. *Tetrahedron Lett.* **1984**, 25, 2201.

8. Croisy-Delcey, M.; Bisagni, E.J. *Heterocyclic Chem.* **1991**, 28, 65.

9. Boate, D.R.; Johnston, L.J.; Kwong, P.C.; Lee-Ruff, E.; Scaiano, J.C. *J. Am. Chem. Soc.* **1990**, 112, 8858.

10. Krohn, K.; Reiger, H.; Broser, E.; Schiess, P.; Chen, S.; Strubin, T. *Liebigs Ann. Chem.* **1988**, 943.

11. Jung, M.E.; Lowe, J.A. *J. Org. Chem.* **1977**, 42, 2371.

12. Mosandl, T.; Wentrup, C. *J. Org. Chem.* **1993**, 58, 747.

13. Staab, H.A.; Ipaktschi, J. *Tetrahedron Lett.* **1966**, 583.

14. Chapman, O.L.; Mattes, K.; McIntosh, C.L.; Pacansky, J.; Calder, G.V.; Orr, G. *J. Am. Chem. Soc.* **1973**, 95, 6134.

15. Kolc, J. *Tetrahedron Lett.* **1972**, 5321.

16. Simon, J.G.G.; Munzel, N.; Schweig, A. *Chem. Phys. Lett.* **1990**, 170, 187.

17. Meier, H. *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1399.

18. Walkeck, D.H. *Chem Rev.* **1991**, 91, 415.

19. Saltiel, J.; D'Agostino, J.; Megarity, D.; Metts, L.; Neuberger, K.R.; Wrighton, M.; Zafiriou, O.C. *Organic Photochemistry*; Chapman, O.L., Ed.; Marcel Dekker:

New York, **1973**; Vol. 3.

20. Hochstrasser, R. M. *Pure Appl. Chem.* **1980**, 52, 2683.

21. Mazzucato, U.; Momicchioli, F. *Chem. Rev.* **1991**, 91, 1679.

22. Lewis, F.D.; Hoyle, C.E.; Johnson, D.E. *J. Am. Chem. Soc.* **1975**, 97, 3267.

23. Chapman, O.L.; Lura, R.D.; Owens, R.M.; Plank, E.D.; Shim, S.C. *Can. J. Chem.* **1972**, 50,1984.

24. Usami, H.; Takagi, K.; Sawaki, Y. *Bull. Chem. Soc. Jpn.* **1991**, 64, 3395.

25. Wolff, T.; Schmidt, F.; Volz, P. *J. Org. Chem.* **1992**, 57, 4255.

26. DeBoer, C.D.; Schlessinger, R.H. *J. Am. Chem. Soc.* **1968**, 90, 803.

27. Fraser, R.R. *Asymmetric Synthesis* **1983**, 1, 173.

28. Venugopalan, P.; Weiss, R.G.; Venkatesan, K. *J. Org. Chem.* **1992**, 57, 276.

29. Turro, N.J. Modern Molecular Photochemistry, The Benjamin/Cummings Publishing Company, Inc. Menlo Park, CA **1978**, p. 354.

30. Barra, M.; Fisher, T.A.; Cernigliaro, G.J.; Sinta, R.; Scaiano, J.C. *J. Am. Chem. Soc.* **1992**, 114, 2630.

31 Netto-Ferreira, J.C.; Avellar, I.G.J.; Scaiano, J.C. *J. Org. Chem.* **1989**, 55, 89.

32. Morton, D.R.; Turro, N.J. *J. Am. Chem. Soc.* **1973**, 95, 3947.

33. Toda, F.; Todo, E. *Chem. Lett.* **1974**, 1279.

34. Toda, F.; Todo. E. *Bull. Chem. Soc. Jpn.* **1976**, 49, 2503.

35. Toda. F.; Todo, Y.; Todo, E. *Bull. Chem. Soc. Jpn.* **1976**, 49, 2645.

36. Scaiano, J.C. *J. Am. Chem. Soc.* **1980**, 102, 7747.

37. Scaiano, J.C.; Tanner, M.; Weir, D. *J. Am. Chem. Soc.* **1985**, 107, 4396.

CHAPTER 8: VISUALIZATION OF COLUMN CHROMATOGRAPHY[1,2]

During the past few decades, preparative organic chemistry has undergone a revolution owing to chromatographic techniques,[3] which have provided extremely versatile and efficient methods of separation and purification of organic compounds. Although advances such as preparative HPLC, automatic fraction collectors and radial chromatography have appeared on the market, perhaps the technique in greatest usage by the average synthetic chemist today is flash chromatography,[4] due to its low cost and ease of operation. The ability to gauge the elution of products would be a significant improvement of this technique. This has been addressed by radial chromatography,[5] where a UV transparent cover allows visualization of compounds capable of quenching the fluorescence of an indicator present in the rotating stationary phase. Limitations of this system include the need for specialized equipment and gel, and a maximum loading of about 1.5 g.

The extension of this methodology to flash chromatography is possible by utilizing columns made of a grade of quartz which is largely transparent to UV radiation at 254nm. The stationary phase is prepared by simply stirring in a small amount of fluorescent indicator[6] into a slurry of adsorbent (e.g. flash quality silica gel) before pouring it into the column. The elution of compounds can be readily followed by UV irradiation. Visualization occurs as purple bands on a green background. This result is due to compounds which quench the green fluorescence of the indicator allowing the purple fluorescence of the quartz to become visible. The fluorescence of the quartz may blur the exact separation between two very close bands therefore taking several fractions at these points during elution may be necessary to monitor the separation. Although fluorescence-free quartz tubes are available, they are about ten times more expensive and they are thus probably not worth the slight increase in convenience.

The column consists simply of a quartz tube adapted on one end to fit a septum, so

that pressure may be applied through a neeedle. Because quartz cannot be directly fused to Pyrex the stopcock is joined by connecting it with with narrowed end of the tube through a short piece of Teflon tubing. The total cost of a 12 mm (inside diameter) quartz column is twice that of a commercial Pyrex column while the corresponding 22 mm column[7] is 4 times the price of the Pyrex equivalent.[8] If a solvent reservoir is desired, it is also possible to purchase a quartz-to-Pyrex connector which can allow one to be fitted at the top of the column. Similarly, for larger columns a ground-glass adaptor can be mounted to insure that a sufficient solvent flow rate is maintained.

In a typical procedure, zinc silicate indicator[6] (7.5 mg/g adsorbent) is added to a slurry of the adsorbent in the solvent system to be used and mixed until homogeneously fluorescent to a 254 nm UV lamp. Although some of the indicator may remain as small clumps this does not seem to appreciably affect performance. The remaining procedure is essentially that of conventional flash chromatography, except that the eluting compounds can be observed as purple bands by irradiating the column with a UV lamp, preferably in a dark room. In many cases, less solvent is needed that in flash chromatography since solvent polarity can be quickly adjusted to yield the shortest elution time while still achieving separation of each band. In general, fractions need only be taken during the elution of each band, which will result in some reduction of TLC plates required and a quicker separation, compared to conventional flash chromatography.

Detection limits of less than 10 mg on a 12 mm inside diameter column are typical, however, this will depend on the activity of individual compounds. In general, the intensity of each band will correspond to how actively it quenches fluorescence on commercial indicating TLC plates. In a similar way, the choice of solvent systems can be decided by viewing a soaked TLC plate and ensuring that fluorescence is not quenched. Typical chromatography solvents such as hexanes, ethyl acetate, chloroform, methylene chloride, acetonitrile, ether and methanol are acceptable but acetone, benzene and toluene are not.

The quartz column offers significant advanatages over currently used preparative

chromatographic methods. First, this technique is applicable to the commonly used commercially available stationary phases. Thus far, both normal and reverse-phase silica as well as alumina have been used successfully. Second, the size of the load is limited only by the size of the quartz tube available. Third, the technique is very economical and requires no other special equipment, except a UV lamp. For these reasons the quartz column should prove to be both an economic and time-saving asset to the synthetic organic chemist.

Acknowledgements. Glassblowers Egon Kristof and John Hopkins are thanked for help in the design and construction of the quartz columns. Ming-de Wang is thanked for extending the application to alumina.

REFERENCES

1. Bradley, J.C.; Durst, T. *Tetrahedron Lett.* **1992**, 33, 7733.

2. After publication of this article, Dr. Zimmerman has pointed out that his group had previously been using a similar method (see Zimmerman, H.E.; Samuel, C.J. *J. Am. Chem. Soc.* **1975**, 97, 4025; Zimmerman, H.E.; Lamers, P.H. *J. Org. Chem.* **1989**, 54, 5788). However, the procedure is described only very succinctly as an introduction to the experimental sections of these papers.

3. Hostettmann, K.; Hostettmann, M.; Marston, A. Preparative Chromatography Techniques, Spinger-Verlag, New York, **1986**.

4. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.

5. see ref 2, p. 12.

6. Activated zinc silicate (available from Sigma) is used, the same material found in commercially available TLC plates. See Barrett, G.C. in Advances in Chromatography (Ed. Giddings, J.C. and Deller, R.A.), vol 11, Marcel Dekker, Inc., New York, **1974**, p. 162.

7. This column is capable of separating about 5 g of material based on the 20-30 : 1 ratio (silica gel:compound) recommended in: Pasto, D.J.; Johnson, C.R. Laboratory text for Organic Chemistry, Prentice-Hall, New Jersey, **1979**, p. 63.

8. T08 commercial quartz tubes were obtained from Heraeus Amersil (650 Jernees Miln Rd., Sayreville, New Jersey, 08872).

CLAIMS TO ORIGINAL RESEARCH

1) A one-pot synthesis of benzylidenebenzocyclobutenones was achieved from (o-bromoaryl)phenylalkynones via a palladium-catalysed tributyltin hydride addition/intramolecular Stille coupling sequence. Some benzylidenebenzocyclobutenols were also prepared in two steps from (o-bromoaryl)phenylalkynols via free-radical addition of tributyltin hydride followed by an intramolecular Stille coupling.

2) A scheme for utilizing benzylidenebenzocyclobutenones as precursors to regioisomeric anthraquinones was investigated. All of the required steps were successfully carried out except for the oxidative removal of the benzylidene group.

3) An unusual rearrangement was observed upon ozonolysis of two benzylidenebenzocyclobutenone ketals and a benzylidenebenzocyclobutenol.

4) Aryl, vinyl and alkynyl benzylidenebenzocyclobutenols were prepared and thermolysed to yield ring expansion products. Ozonolysis of the products from the thermolysis of the aryl and vinyl derivatives yielded anthraquinone and naphthoquinone, respectively.

5) The mechanism for the anionic cleavage of several benzylidenebenzocyclobutenols in methanolic KOH was investigated. The stereochemistry of the benzylidene group was used as a mechanistic probe to distinguish between carbanionic vs. electrocyclic ring opening pathways. The carbanionic mechanism was found to operate for all derivatives studied.

6) The mechanism for the room temperature Z -> E isomerization of lithium

benzylidenebenzocyclobutenoxide in THF was investigated. Trapping of an aldehyde intermediate with excess methyl lithium supports the proposed mechanism of isomerization via a vinyl anion.

7) Two [2+2] photodimers were isolated and characterized from the irradiation of benzylidenebenzocyclobutenones at 350 nm.

8) Laser flash photolysis studies and trapping experiments indicated that the photoisomerization of benzylidenebenzocyclobutenones proceeds via both a singlet excited state and a ketene-allene intermediate. The lifetime of the ketene-allene was measured at 36 μs in dry acetonitrile.

9) A method for visualizing column chromatography by use of a quartz column and addition of a fluorescent indicator to commercial adsorbents was developped and described in detail.

PUBLICATIONS FROM THIS THESIS

"Synthesis of 2-Benzylidenebenzocyclobutenones via an Intramolecular Stille Coupling Reaction" Bradley, J.C.; Durst, T. *J. Org. Chem.* **1991**, 56, 5459.

"Thermolysis of 2-Benzylidenebenzocyclobutenols" Bradley, J.C.; Durst, T.; Williams, A.J. *J. Org. Chem.* **1992**, 57, 6575.

"Visualization of Column Chromatography" Bradley, J.C.; Durst, T. *Tetrahedron Lett.* **1992**, 33, 7733.