SYNTHETIC STUDIES TOWARDS QUASSINOIDS

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

By

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Hyderabad - 500 134

January 1990

TO MY

PARENTS & TEACHERS

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STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Professor M. NAGARAJAN.**

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

M. PULLA REDDY

CERTIFICATE

Certified that the work contained in the thesis entitled **SYNTHETIC STUDIES TOWARDS QUASSINOIDS** has been carried out by **Mr. M. PULLA REDDY**, under my supervision and the same has not been submitted elsewhere for any degree.

M. NAGARAJAN
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

ACKNOWLEDGEMENTS

I wish to express my deep sense of gratitude to Prof. M. Nagarajan for his inspiring and expert guidance through out the tenure of this research. I am indebted to him for giving me the opportunity to do a variety of reactions during this work.

I wish to thank Prof. Goverdhan Mehta for his help and encouragement. Prof. K.D. Sen, Dean and other members of the faculty of the school have been extremely helpful and I wish to thank them all.

It gives me great pleasure to thank all my colleagues and friends for making my stay at University of Hyderabad a very pleasant and a memorable one. I wish to mention particularly Drs. M. Vaman Rao, C. Linga Reddy, and Y. Koteswar Rao, and Messrs. R. Murali and K. Narkunan whose association provided a lively atmosphere in our laboratory.

A special word of appreciation is due to non-teaching staff of the School of Chemistry, technical staff of CIL, Central Workshop and Glass-blowing section.

I would like to express my gratitude and respect to my parents, relatives and other family members and also my in-laws. I would like to thank my family friend, Vasu Dev, whose encouragement and help is unforgettable.

I express my heartfelt appreciation to my wife Vanaja for her patience and understanding and love which added in writing this

thesis in a short time.

I am thankful to P. Venkata Rao for typing the manuscript, P.O. Koshi for typing the schemes and figures, and Dilip Kumar for his assistance in xeroxing the schemes and charts.

Financial assistance from the CSIR and UGC is gratefully acknowledged.

Finally, I wish to express my sincere thanks to the authorities of the University of Hyderabad for providing me the necessary facilities.

M. PULLA REDDY

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Bn	benzyl
Bz	benzoyl
dac	diallyl carbonate
DBU	1,5-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DHP	3,4-dihydro-2H-pyran
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
dppe	1,2-bis(diphenylphosphino)-ethane
EE	ethoxyethyl
Et	ethyl
LDA	lithium diisopropylamide
LiC≡CH.EDA	lithium acetylide-ethylenediamine complex
MCPBA	m-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
MPM	4-methoxyphenylmethyl
Ms	methanesulfonyl
PPTS	pyridinium p-toluenesulfonate
p-TsOH	p-toluenesulfonic acid
Py	pyridine
TBDMS	t-butyldimethylsilyl
TBDMSOTf	t-butyldimethylsilyl trifluoromethanesulonate
TMS	trimethylsilyl

PREFACE

The last decade has witnessed spectacular advances in the isolation and synthesis of quassinoids, a group of highly oxygenated diterpenoids that occur in genera of the Simaroubaceae family. So far, nearly 100 Simaroubaceae family constituents have been isolated and their structures elucidated. Much of the activity in this area has been due in part to the fact that these natural products possess a wide spectrum of biological properties including *in vivo* antileukemic, antiviral, antimalarial, antifeedant, and amoebicidal activity. Despite vigorous synthetic efforts on these cytotoxic substances by numerous synthetic groups worldwide, the total synthesis of only four substances, *viz*., quassin (**1**), castalanolide (**13**), amarolide (**14**), and kleineanone (**14a**) and, very recently, the formal synthesis of bruceantin (**3**) have been achieved. Quassimarin, which is closely related to bruceantin is yet to be synthesized. We too, like many others, were enticed by the quassinoids, bruceantin and quassimarin, to attempt their syntheses.

The present thesis entitled "SYNTHETIC STUDIES TOWARDS QUASSINOIDS" is an account of our synthetic endeavours towards bruceantin (**3**). Two conceptually novel but dissimilar approaches to the BCDE model system and a route to bruceantin itself were concurrently pursued in the quest of this challenging target. The thesis has been organised under four main sections titled, I: Introduction, II: Synthetic Strategies, III: Results and Discussion, and IV: Experimental and Figures.

In Section I, the isolation and biological properties of

quassinoids are discussed. The synthetic approaches developed to-date towards bruceantin and quassimarin are presented.

Section II deals with our retrosynthetic analyses (Scheme 14) towards the BCD and BCE model systems as well as the total synthesis of bruceantin via two different approaches (IMDA and IMPK cyclizations).

Section III, detailing the validity of retrosynthetic analyses of Section II, is further subdivided into (1) IMDA Reaction Approach Towards Total Synthesis of Bruceantin, (2) Model Studies on Bruceantin (IMDA Reaction Approach and Intermolecular Diels-Alder Reaction Approach), (3) Intramolecular Pauson-Khand (IMPK) Reaction Approach, and (4) Summary and Outlook.

Path A of Scheme 14 was examined during model studies in our laboratory. Encouraged by those preliminary results, we started with Wieland-Miescher (WM) ketone so as to include the A ring and also to complete the toal synthesis of bruceantin. Our first objective in this route was to incorporate appropriate functionality present in ring A of **3**. This was successfully achieved via a Shapiro reaction-osmylation sequence (Scheme 16). To incorporate a dienophile moiety, intermediates **140** and **146** were prepared from the ketones **136** and **137**, respectively. After Michael addition of a three carbon malonaldehyde equivalent onto the enones **140** and **146**, vinyl Grignard reaction on the ketone **150**, for generation of a diene unit did not proceed smoothly to give **151**. During the course of this work it was found in our laboratory that the allylic alcohol **152** does not readily undergo dehydration to the corresponding diene.

Anticipation of similar results in dehydration of **151** prompted us to set aside the total synthesis of bruceantin by this route.

Without many changes in the strategy, attempts were made to prepare a suitable Diels-Alder intermediate equivalent to **152** (Scheme 22). In this route, several acids were prepared and esterified with the known diene alcohol **155**. However none of them could be cyclized to give the Diels-Alder adducts.

Simultaneously, two more routes for model systems (BCD and BCE rings) of bruceantin were pursued (Scheme 34). In the first route, diene **155** or its derivatives did not undergo Diels-Alder reaction with different symmetric dienophiles. In the second route, attempts to make a diene similar to **155** were again unsuccessful.

Finally, an entirely different approach (IMPK) towards the synthesis of **3** was sought. Although enough literature is available on IMPK reactions, systems similar to an intermediate shown (path D, Scheme 14) are not known. To begin with, simple model systems (**238**, **251**, **252**, **253**, **254**, and **255**) were chosen. Although intermediate **238** cyclized to give the tricyclic enone **237**, other intermediates (**251**, **252**, **253**, and **255** did not undergo cyclization. In the case of intermediate **254**, it could not be prepared from its precursors **269** or **274**.

Finally, Section IV contains all the relevant experimental details with figures of spectra for selected compounds.

I. INTRODUCTION

Organic synthesis is one of the rapidly expanding areas in fundamental sciences, covering a vast canvas from physical organic chemistry and organic materials on the one hand to complex biological molecules on the other. In the second half of this century, the availability of sophisticated instruments and techniques has contributed to an exponential growth in organic synthesis. In addition to this, the development of new reagents like synthetically equivalent groups, reversed polarity reagents, asymmetric reducing agents, organometallic reagents, ultrasound vibration techniques and cation radical catalysts have also enhanced the growth of organic synthesis. Some of the notable achievements of the past decade include the syntheses of the macrolide antibiotic erythromycin,[1] the platonic hydrocarbon dodecahedrane[2] and, most recently, the marine toxin palytoxin.[3] With the promising selectivity of various types of reagents and sophisticated techniques, no complex molecule (natural or unnatural) seems to be beyond the reach of synthetic practitioners. The study of unnatural molecules has led to the discovery or development of various new reagents and techniques. The other side of the coin, synthesis of natural products, has provided unambiguous proof of structure and has also made available in bulk quantities various medicinally valuable compounds not abundant in Nature.

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1. Woodward, R.B.; et al. J. Am. Chem. Soc. 1981, **103**, 3215.
2. Paquette, L.A.; Ternansky, R.J.; Balogh, D.W.; Kentgen, G. J. Am. Chem. Soc. 1983, **105**, 5446.
3. Kishi, Y.; et al. J. Am. Chem. Soc. 1989, **111**, 7530.

Among the natural products, syntheses of steroids, prostaglandins, anthracyclines, and polycyclopentanoids have been well studied over the past decades. In recent years, natural products having physiological activity as well as complex structures have attracted considerable interest from synthetic chemists.

Synthesis of quassinoids, a group of diterpenoids that occur in genera of the Simaroubaceae family, began only in the early '80s.[4] Many species of the botanical family of Simaroubaceae have been known for a long time to contain bitter substances which are collectively called "quassinoids". The Simaroubaceae trees are indigenous to Ethiopia and their extracts have been used in the treatment of cancer.[5] However, the isolation and structure elucidation of their individual constituents were not accomplished until modern physical techniques of investigation became available. During the past four decades, nearly 100 Simaroubaceae family constituents have been isolated and their structures elucidated. All the Simaroubaceae family constituents are closely related chemically. Those members of the group obtined from the genus Brucea are known as bruceolides.[6]

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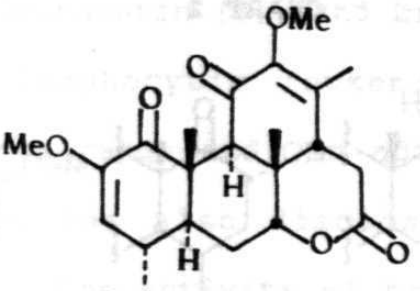
4. (a) Polonsky, J. "Progress in the Chemistry of Organic Natural Products," Herz, W.; Grisbach, H.; Kirby, G.W.; Eds. Springer-Verlag, Berlin, 1973, **30**, 102; (b) Polonsky, J. "Progress in the Chemistry of Natural Products," Herz, W.; Grisbach, H.; Kirby, G.W.; Tamm, Ch. Eds. Springer-Verlag, Berlin, 1985, **47**, 220.

5. Hartwell, J.L. Lloydia 1971, **34**, 231.

6. Polonsky, J.; Baskevitah, Z.; Goudenier, A.; Das, B.C. Experientia 1967, **23**, 424.

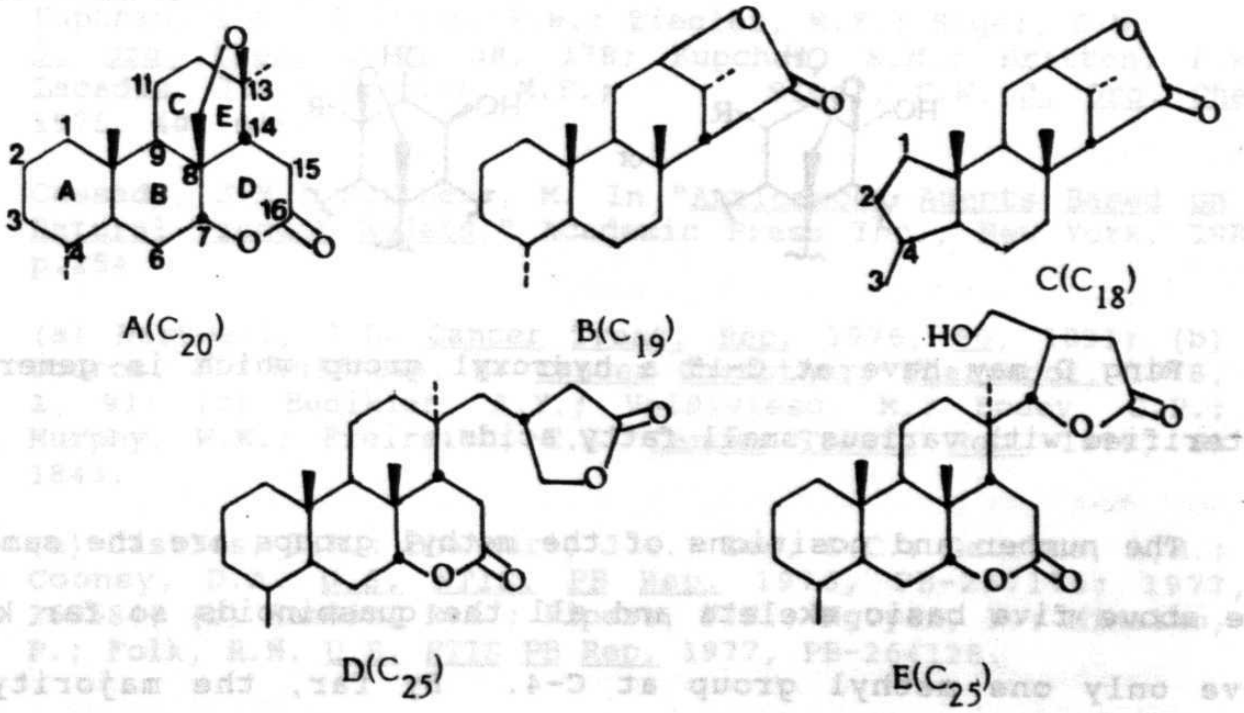
The simplest among the quassinoids is quassin (1) and its structure was established by Valenta and his co-workers in 1962.[7]



Quassin (1)

The quassinoids can be divided into distinct groups according to their basic skeleta. The five skeleta observed are presented in Chart 1.

CHART 1

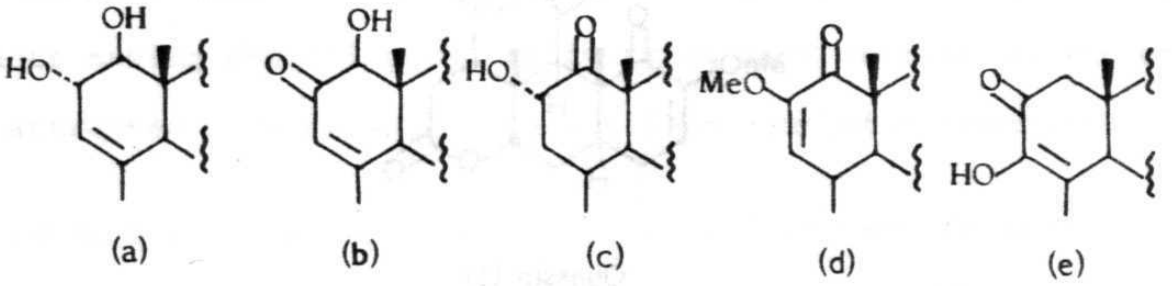


The variations in the structures of quassinoids are principally as follows:

7. Valenta, Z.; Gray, A.H.; Orr, D.E.; Papadopoulos, S.; Podesva, C. Tetrahedron 1962, **18**, 1433.

Ring A may have the structures (a), (b), (c), (d) or (e) as depicted in Chart 2.

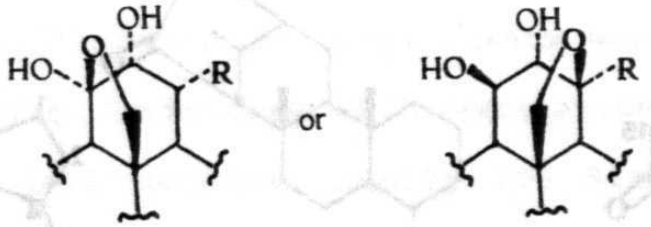
CHART 2



(a) (b) (c) (d) (e)

Ring C may possess at position C-8 either a methyl group or a hydroxymethyl group which forms a hemi-ketal bridge to C-11 or an oxide bridge to C-13 (Ring E, Chart 3).

CHART 3



Ring D may have at C-15 a hydroxyl group which is generally esterified with various small fatty acids.

The number and positions of the methyl groups are the same on the above five basic skeleta and all the quassinoids so far known have only one methyl group at C-4. By far, the majority of quassinoids known have the C_{20} basic skeleton.

I.1 Biological Activity:

Most of the quassinoids are biologically active. In 1973, during the investigation of Brucea antidysenteria, Kupchan and co-

workers isolated eight quassinoids, several of which were subsequently proved to have antitumor and antileukemic properties.[8] Simalikalactone D (**2**), bruceantin (**3**), and bruceantinol (**5**) are most active against P-388 lymphocytic leukemia.[9] Bruceantin shows activity over a wide dose range and, in addition, is active against solid tumors. Kupchan has also disclosed the antineoplastic activity of bruceantin.[8] The activity of bruceantin towards tumors sparked interest in this terpenoid at the National Cancer Institute (NSC 165563) in the USA. It was found that bruceantin is active against L-1210 lymphoid leukemia, Lewis lung carcinoma and B-16 melano carcinoma, resulting in its being selected for clinical trials.[10,11]

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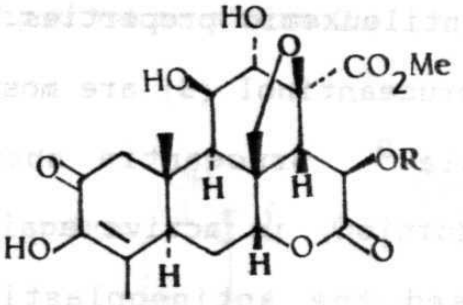
8. Kupchan, S.M.; Britton, R.W.; Ziegler, M.F.; Sigel, C.W. J. Org. Chem. 1973, **38**, 178; Kupchan, S.M.; Britton, R.W.; Lacadie, J.A.; Ziegler, M.F.; Sigel, C.W. J. Org. Chem. 1975, **40**, 648.

9. Cassady, J.M.; Suffness, M. In "Anticancer Agents Based on Natural Product Models," Academic Press Inc., New York, 1980, p.254.

10. (a) Hartwell, J.L. Cancer Treat. Rep. 1976, 60, 1031; (b) Douros, J.; Suffness, M. Cancer Chemother. Pharmacol. 1978, **1**, 91; (c) Bedikian, A.Y.; Valdivieso, M.; Bodey, G.P.; Murphy, W.K.; Freireich, E.J. Cancer Treat. Rep. 1979, **63** 1843.

11. (a) Castles, T.R.; Bhandari, J.C.; Lee, C.C.; Gaurino, A,M.; Cooney, D.A. U.S. NTIS. PB Rep. 1976, PB-257175; 1977, 269584; (b) Hamlin, R.L.; Pipers, F.S.; Nguyen, K.; Mihalko, P.; Folk, R.M. U.S. NTIS PB Rep. 1977, PB-264128.



Bruceantin (3), R = COC(H)=C(Me)CH(Me)$_2$

Bruceantinol (5), R = COC(H)=C(Me)C(Me)$_2$(OAc)

Brucein C (6), R = COC(H)=C(Me)C(Me)$_2$(OH)

Brusatol (7), R = COCH=C(Me)$_2$

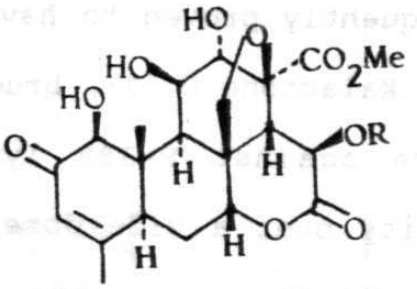
Bruceantarin (8), R = Bz

Brucein A (9), R = COCH$_2$CH(Me)$_2$

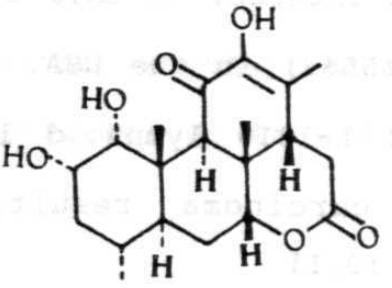
Brucein B (10), R = Ac

Bruceolide (11), R = H

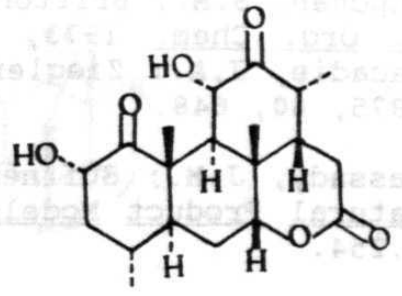
Dihydrobruceantin (12), R = COCH$_2$CH(Me)CH(Me)$_2$



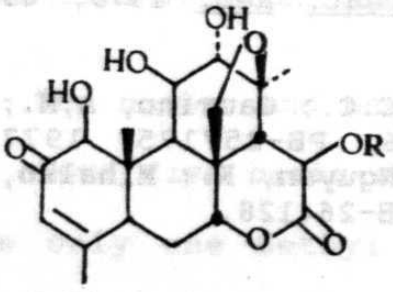
Quassimarin (4)
R = COC(Me)(Et)(OAc)



Castalanolide (13)

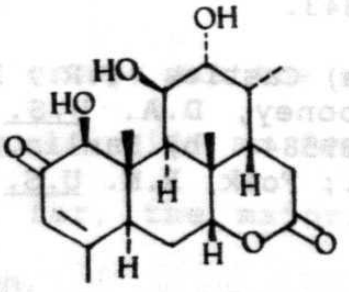


Amarolide (14)



Simalikalactone D(2)

R = COCH(Me)(Et)



Kleineanone (14a)

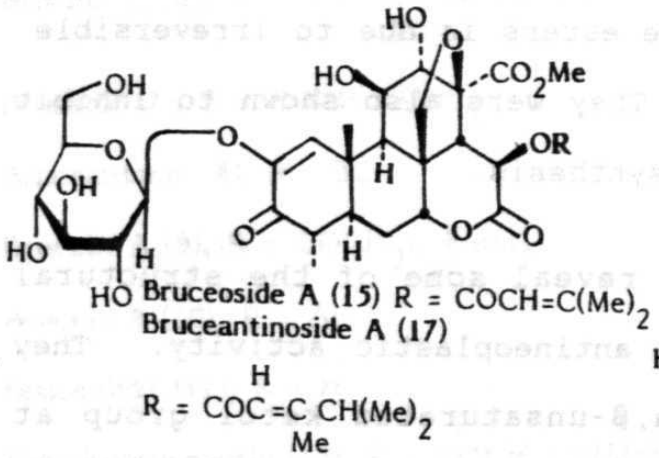
The antileukemic activity of bruceolide derivatives varies with the nature of the ester substituent at C-15. Thus, bruceantin (**3**), bruceantinol (**5**) and brucein C (**6**) which bear α,β-unsaturated esters, demonstrate potent antileukemic activity. Bruceantarin (**8**), which is a benzoate ester, dihydrobruceantin (**12**), and brucein B (**10**) which have saturated esters, and bruceolide (**11**) show only marginal antileukemic activity.[12] The markedly higher antitumor activity of bruceantin (**3**) and bruceantinol (**5**) compared to that of brucein C (**6**) could possibly be attributed to the greater lipophilicity of the side chains of **3** and **5**. Liao[13] has shown that the antitumor activity of bruceolide esters is due to irreversible inhibition of protein synthesis. They were also shown to inhibit DNA polymerase activity and purine synthesis.

Structure-activity[14] studies reveal some of the structural requirements essential for optimal antineoplastic activity. They are (a) ring A with either an α,β-unsaturated ketol group at positions C-1 and C-2 or a diosphenol group at positions C-2 and C-3 (structures (b) and (e) of Chart 2); (b) ring C with an epoxymethano bridge between C-8 and C-11 or between C-8 and C-13 (Chart 3); (c) a free hydroxyl group in ring C at C-12 (Chart 3), in addition to an ester group at C-15.

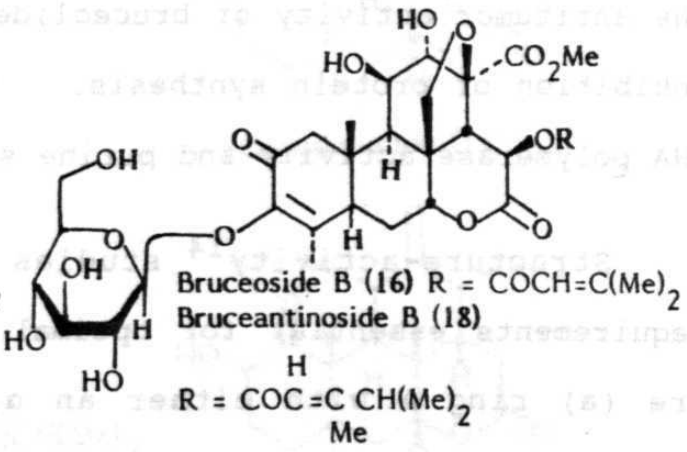
In the early '80s several quassinoid glycosides were isolated.[4]

12. (a) Kupchan, S.M.; Lacadie, J.A.; Howie, G.A.; Sickles, B.R. J. Med. Chem. 1976, **19**, 1130; (b) reference 8.
13. Liao, L.T.; Kupchan, S.M.; Horwitz, S.B. Mol. Pharmacol. 1976, **12**, 167.
14. Wall, M.E.; Wani, M.C. J. Med. Chem. 1978, **21**, 1186.

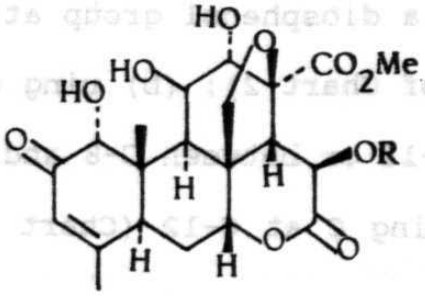
Amongst these, bruceoside A (**15**), bruceoside B (**16**), bruceantinoside (**17**), and bruceantinoside B (**18**) displayed significant antileukemic activity and the latter two were found to be toxic down to the level of 1 mg/kg. Certain quassinoids display <u>in vitro</u> antiviral activity, for example, against the oncogenic Rous sarcoma virus.[15] A number of quassinoids inhibit this transformation at a concentration ranging from 0.15 to 1.00 mcg/ml, without having toxic effects on normal cells. Isobruceine A (**19**) shows the highest percentage of inhibition.[15]



Bruceoside A (15) R = $COCH{=}C(Me)_2$
Bruceantinoside A (17)
R = $COC{=}C\overset{H}{\underset{Me}{}}CH(Me)_2$



Bruceoside B (16) R = $COCH{=}C(Me)_2$
Bruceantinoside B (18)
R = $COC{=}C\overset{H}{\underset{Me}{}}CH(Me)_2$



Isobrucein A (19)

R = $COCH_2CH(Me)_2$

The growth of chloroquine resistant blood parasite <u>Plasmodium falciparum</u> (responsible for malaria) was markedly inhibited <u>in vitro</u>

15. Pierre, A.; Robert-Gero, M.; Tempete, C.; Polonsky, J. <u>Biochem. Biophys. Res. Comm.</u> 1980, **93**, 675.

by certain quassinoids.[16] The most active compound, simalikalactone D(**2**), gave complete inhibition at 0.002 mcg/ml.

Thirteen quassinoids of different structural types displayed significant antifeedant activity against the Mexican Bean beetle.[17] Simalikalactone D (**2**) was found to be the most potent antifeedant. Some of the quassinoids showed significant insecticidal activity.[18]

Bruceantin (**3**), simalikalactone D (**2**) and some other quassinoids displayed activity against the parasite Entamoeba histolytica in Gillin's and Reiner's extensive study.[19] Extracts of many Simarouba species are used to treat fevers, dysentry and amoebiasis in Mexico and China.[4]

Several quassinoids related to brusatol (**7**) are potent inhibitors of induced inflammation and arthritis in rodents. Brusatol is ten times more active than indomethacin. One of the modes of action of quassinoids as anti-inflammatory agents is to stabilize lysosomal membranes, reducing the release of hydrolytic enzymes that cause damage to surrounding tissues.[20]

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16. Trager, W.; Polonsky. J. Am. J. Trop. Med. Hyg. 1981, **30**, 531.
17. Leskinen, V.; Polonsky J.; Bhatnagar, S. J. Chem. Ecol. 1984, **10**, 1497.
18. Odjo, A.; Piart, J.; Polonsky, J.; Roth, M. C.R. Acad. Sci. Paris 1981, **293**, Serie III, 241.
19. Gillin, F.D.; Reiner, D.S.; Suffness, M. Antimicrob. Agents Chemother. 1982, **22**, 342.
20. Hall, I.H.; Lee, K.H.; Imakura, Y.; Okano, M.; Johnson, A. J. Pharm. Sci. 1983, **72**, 1282.

The wide range of biological activity displayed by the quassinoids, along with their complex structural features make them attractive synthetic targets.

I.2 Synthetic Studies:

The highly oxygenated carbon skeleton and wide range of biological activity of quassinoids have attracted considerable interest from synthetic chemists. Bruceantin is a challenging synthetic target owing to the presence of ten asymmetric centres, a high degree of functionalization and promising antitumor activity. Although four tetracyclic quassinoids, quassin (**1**),[21] castalanolide (**13**),[22] amarolide (**14**),[23] and kleineanone (**14a**)[24] have been synthesized, only recently has bruceantin (**3**) been formally synthesized.[25] Quassimarin (**4**) is yet to be synthesized. During the last ten years, many efforts have been focussed on the construction of bruceantin, quassimarin and related quassinoids and considerable progress has been made by several groups around the world.[26]

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21. Vidari, G.; Ferrino, S.; Grieco, P.A. J. Am. Chem. Soc. 1986, **106**, 3539.

22. Grieco, P.A.; Lis, R.; Ferrino, S.; Jaw, J.Y. J. Org. Chem. 1984, **49**, 2342.

23. Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Takahashi, T. Tetrahedron Lett. 1987, **28**, 435.

24. Grieco, P.A.; Nargund, R.P.; Parker, D.T. J. Am. Chem. Soc. 1989, **111**, 6287.

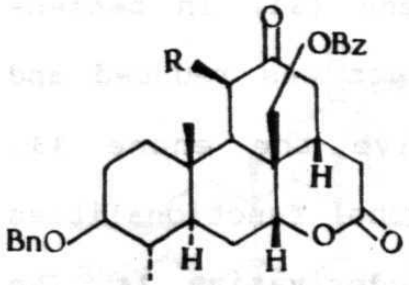
25. Sasaki, M.; Murae, T. Tetrahedron Lett. 1989, **30**, 355.

26. Ref.24 gives a comprehensive bibliography of the synthetic efforts in the bruceantin area.

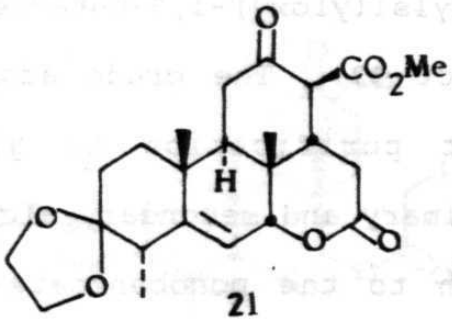
A brief summary of the different approaches employed towards the syntheses of bruceantin and quassimarin is presented in the following pages.

I.2.1. Towards Bruceantin:

So far, three research groups have reported the preparation of four tetracyclic derivatives **20**,[27] **21**,[28] **22**,[29] and **23**[30] and



20 R = OAc



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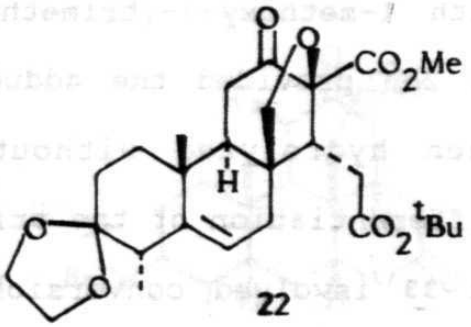

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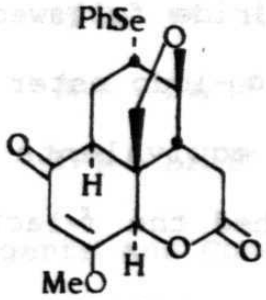

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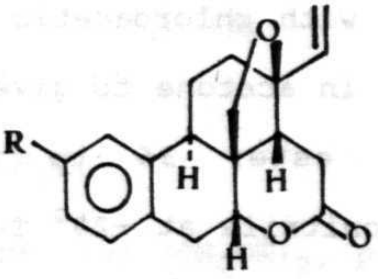
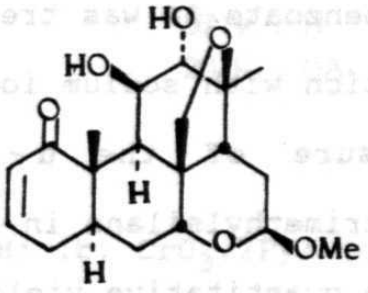


24 R = OMe



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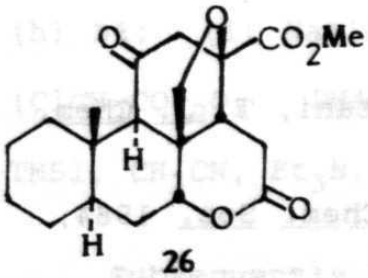

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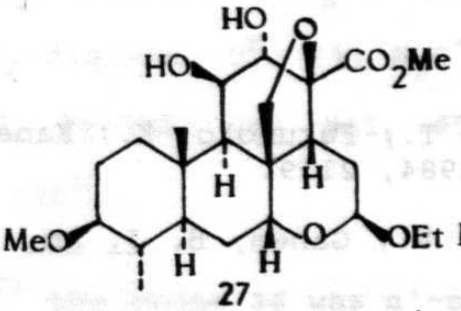
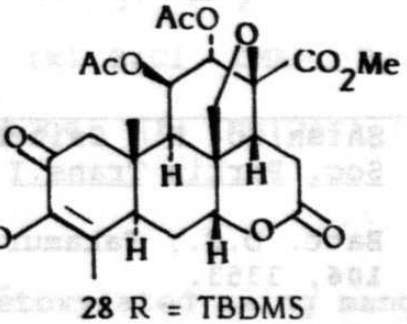


27



28 R = TBDMS

27. Dunlop, N.K.; Sabol, M.R.; Watt, D.S. Tetrahedron Lett. 1984, **25**, 5839.

28. Heathcock, C.H.; Mahaim, C.; Schlecht, M.F.; Utawanit. T. J.Org. Chem. 1984, **49**, 3264.

29. Kerwin, S.M.; Paul, A.G.; Heathcock, C.H. J. Org. Chem. 1987, **52**, 1686.

30. Stevens, R.V.; Vinogradoff, A.P. J. Org. Chem. 1985, **50**, 4056.

five groups the preparation of pentacyclic derivatives **24**,[31] **25**,[32] **26**,[33] **27**,[34] and **28**[35] towards the synthesis of bruceantin.

In 1983, Watt and co-workers[36] reported a synthetic approach for construction of the ABCD ring system of bruceantin. As outlined in Scheme 1, compound **30** was obtained in seven steps from the bicyclic enone **29**. An intermolecular Diels-Alder reaction of **30** with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**31**) in benzene at 25° provided the adduct **32**. The crude adduct was reduced and then hydrolyzed without purification to give the enone **33**. Differentiation of the primary and secondary alcohol functionalities in **33** involved conversion to the monobenzoate derivative **34**. The monobenzoate **34** was treated with chloroacetic anhydride followed by reaction with sodium iodide in acetone to give the α-iodo ester **36**. Exposure of the α-iodo ester **36** to two equivalents of iodotrimethylsilane in acetonitrile at -20° furnished the δ-lactone **37** in quantitative yield.

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31. Shishido, K.; Saitoh, T.; Fukumoto, K.; Kametani, T. J. Chem. Soc. Perkin Trans.I 1984, 2139.

32. Batt. D.G.; Takamura, N.; Ganem, B. J. Am. Chem. Soc. 1984, **106**, 3353.

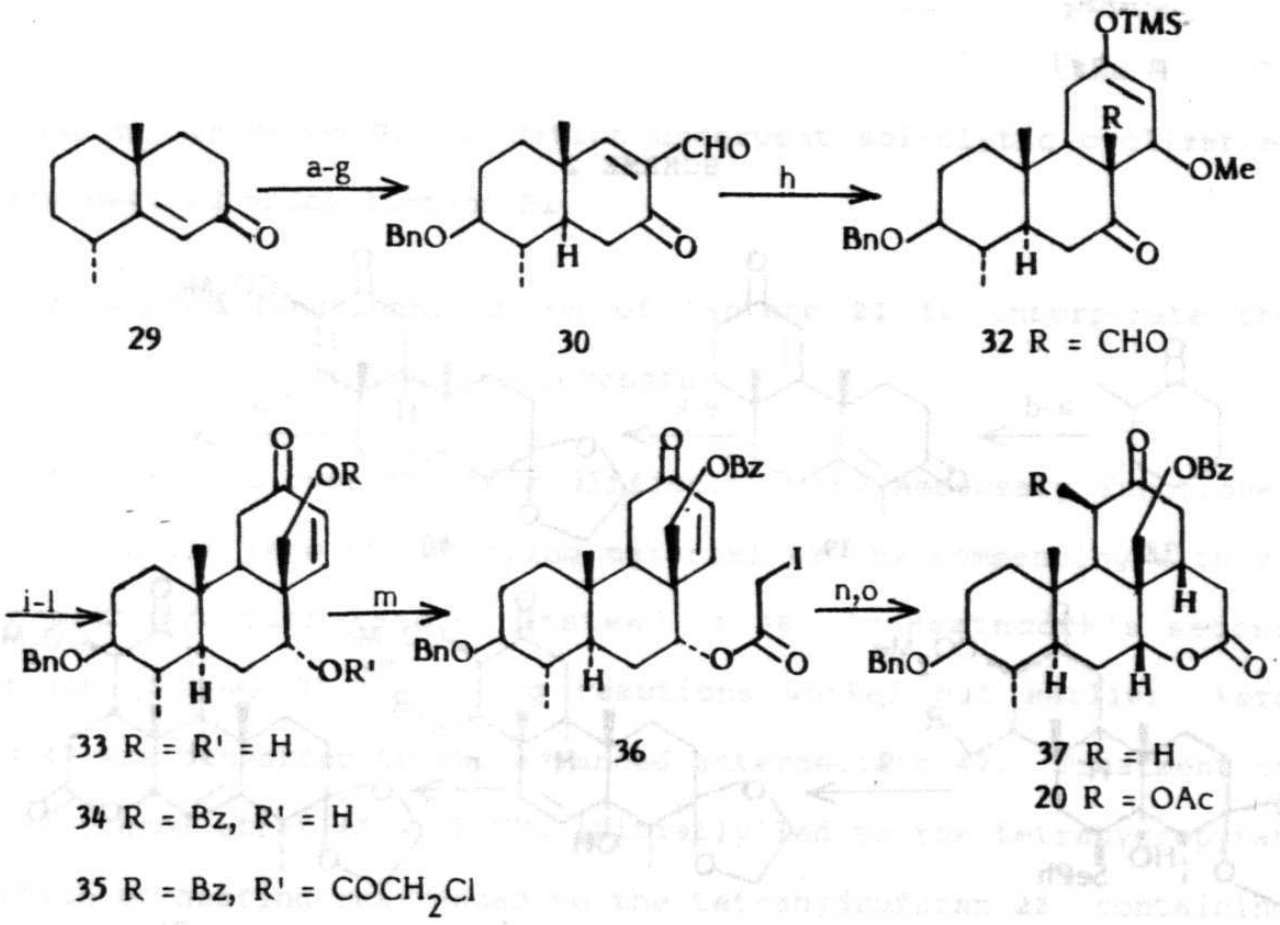
33. Ziegler, F.E.; Klein, S.I.; Pati, U.K.; Wang, T.-F. J. Am. Chem. Soc. 1985, **107**, 2730.

34. Fengjium, K.; Fuchs, P.L. J. Am. Chem. Soc. 1987, **109**, 1122.

35. Sasaki, M.; Murae, T.; Takahashi, T. Tetrahedron Lett. 1988, **29**, 5953.

36. Voyle, M.; Dunlop, N.K.; Watt, D.S. J. Org. Chem. 1983, **48**, 3242.

SCHEME 1



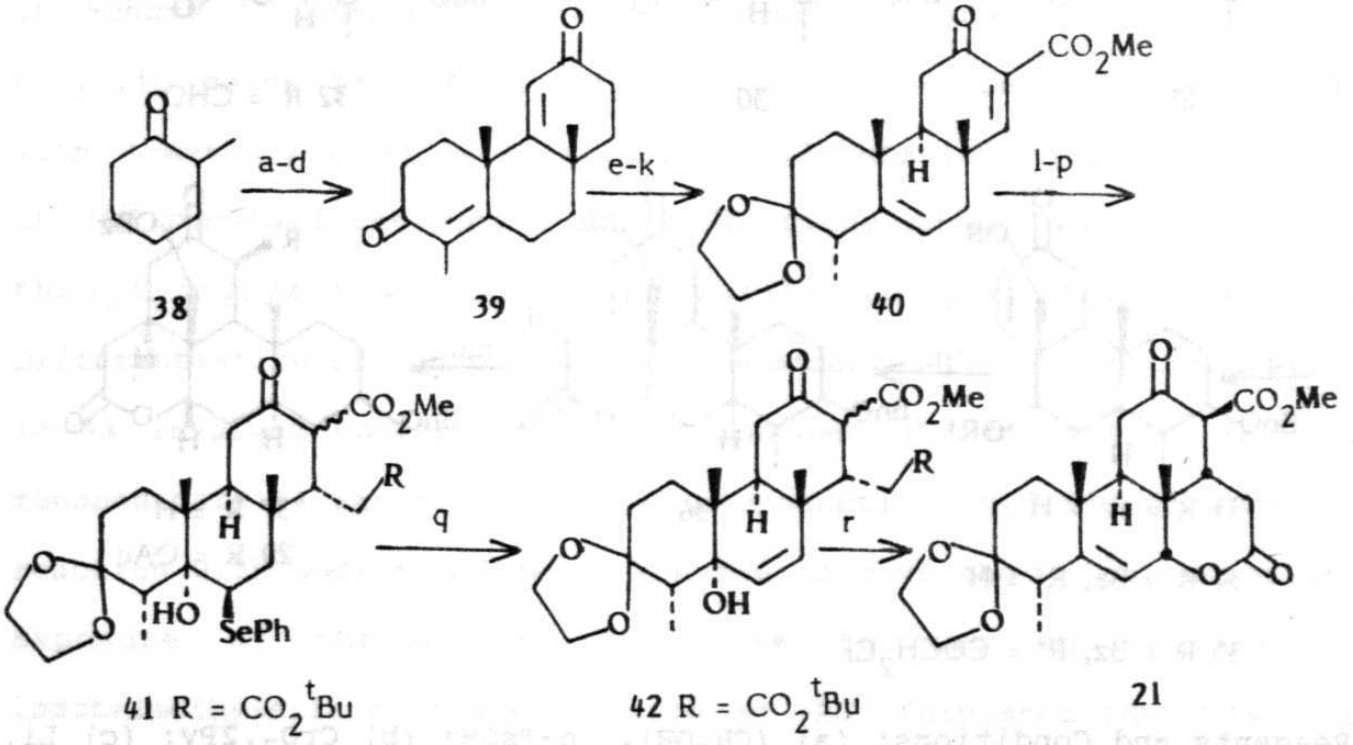
Reagents and Conditions: (a) $(CH_2OH)_2$, p-TsOH; (b) $CrO_3.2Py$; (c) Li, NH_3, EtOH; (d) $PhCH_2Br$, NaH; (e) H_3O^+; (f) $NaOCH_3$, HCO_2Et; (g) DDQ; (h) **31**; (i) $NaAlH_2$-diglyme, 0^o; (j) H_3O^+; (k) BzCl, DMAP, Py; (l) $(ClCH_2CO)_2O$, DMAP, Py-THF; (m) NaI, acetone; (n) $Mn(OAc)_3$; (o) TMSI, CH_3CN, Et_3N, -20^o.

Subsequently,[27] the enone **36** was α'-acetoxylated using manganese(III) acetate and treated with iodotrimethylsilane (2 equiv.) and triethylamine (1 equiv.) in acetonitrile at -20^o to afford **20** in 60% yield.

In 1984, Heathcock and co-workers[28] reported a synthetic approach for construction of the ABCD ring system of bruceantin

(Scheme 2). A two stage annelation of 2-methylcyclohexanone (**38**) with 1-chloro-3-pentanone, followed by allylic oxidation with chromium trioxide gave the tricyclic enone **39**. Selective

SCHEME 2



Reagents and Conditions: (a) 1-chloro-3-pentanone, ß-$NpSO_3H$; (b) NaH-DMSO, 1-chloro-3-pentanone; (c) MeOH-KOH; (d) CrO_3, Ac_2O, HOAc; (e) $(CH_2OH)_2$, ß-$NpSO_3H$; (f) SiO_2, H_2O, CH_2Cl_2; (g) Li-NH_3, t-BuOH; (h) 2M methoxymagnesium methyl carbonate, DMF; (i) CH_2N_2; (j) NaH, PhSeCl; (k) H_2O_2; (l) CH_2=C(OTBDMS)(O^tBu), MeCN, 5-7 kbar, 8-14 days, r.t.; (m) KF, H_2O, THF; (n) MCPBA; (o) PhSeNa, EtOH; (p) CH_2N_2; (q) MCPBA; (r) PCC.

monoketalization of **39**, lithium-ammonia reduction, reaction with Stiles reagent, esterification with diazomethane followed by dehydrogenation using Reich's method yielded the ketoester **40**. In a key step, **40** was reacted in a Michael reaction under high pressure

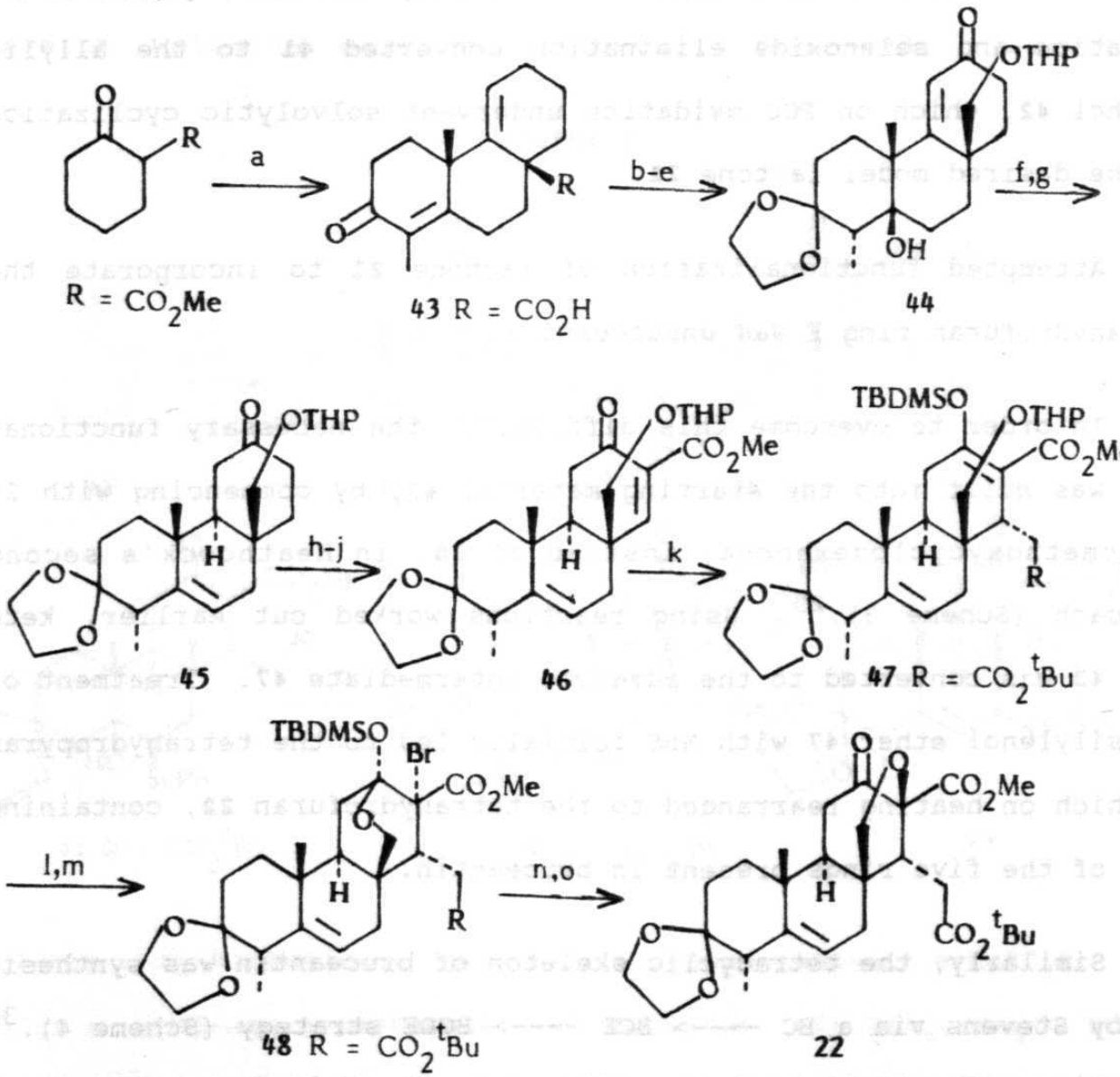
with a silyl ketene acetal to give the Michael addition product which was further transformed to **41** by routine procedures. Oxidation and selenoxide elimination converted **41** to the allylic alcohol **42**, which on PCC oxidation underwent solvolytic cyclization to the desired model lactone **21**.

Attempted functionalization of lactone **21** to incorporate the tetrahydrofuran ring E was unsuccessful.

In order to overcome this difficulty, the necessary functionality was built into the starting material **43**, by commencing with 2-carbomethoxycyclohexanone, instead of **38**, in Heathcock's second approach (Scheme 3).[29] Using reactions worked out earlier, keto acid **43** was converted to the advanced intermediate **47**. Treatment of the silylenol ether **47** with NBS initially led to the tetrahydropyran **48** which on heating rearranged to the tetrahydrofuran **22**, containing four of the five rings present in bruceantin.

Similarly, the tetracyclic skeleton of bruceantin was synthesized by Stevens via a BC ----> BCE ----> BCDE strategy (Scheme 4).[30] Reduction and oxidation of o-vanillin gave the quinone **50**, which was reacted with methyl 3,5-hexadienoate to give the Diels-Alder adduct **51**. The Diels-Alder reaction did not yield the required stereochemistry at C-9 (quassinoid numbering) and an attempted epimerization after synthesizing the BCD rings was unsuccessful. After routine reactions, compound **51** was converted to the hydroxy diester **52**. Reaction of **52** with phenylselenyl chloride in the presence of potassium carbonate gave **53**, after saponification of the

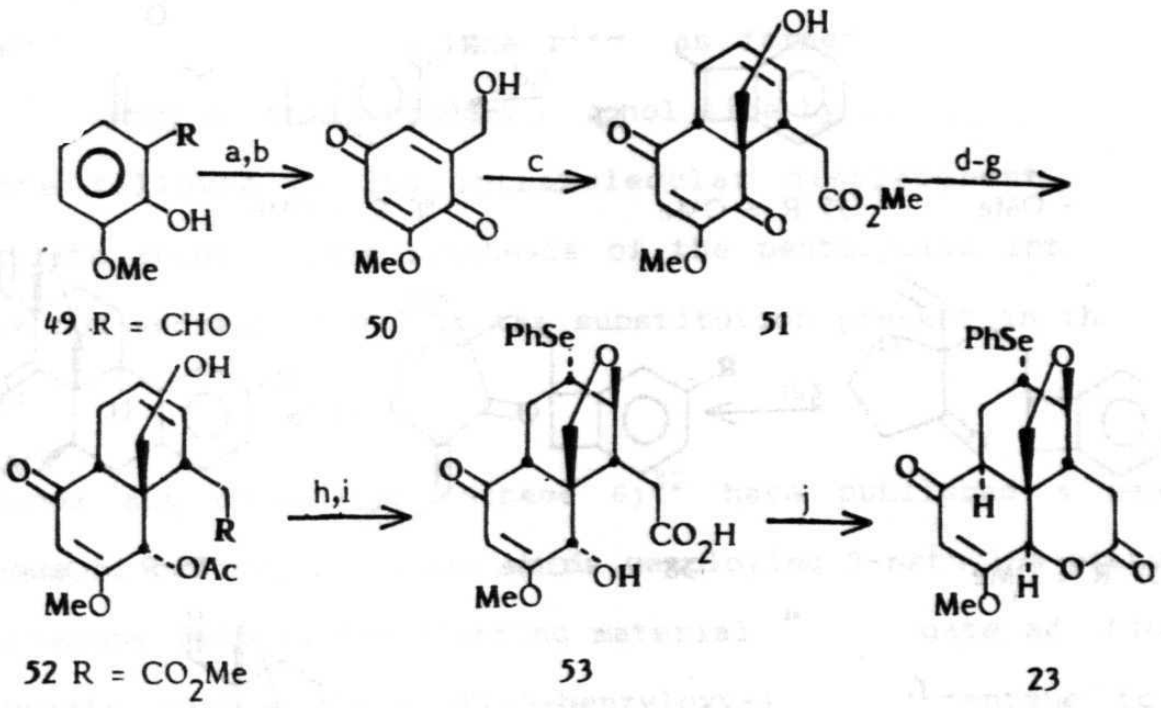
SCHEME 3



Reagents and Conditions: (a) 1-Chloro-3-pentanone, NaOMe, MeOH, reflux; (b) $(CH_2OH)_2$, p-TsOH; (c) LAH; (d) DHP, PPTS; (e) CrO_3-3,5-dimethylpyrazole; (f) DMAP, Ac_2O, Py, reflux; (g) Li-NH_3, t-BuOH; (h) $MeOMgOCO_2Me$, DMF, reflux; (i) CH_2N_2; (j) $SOCl_2$, sym-collidine, CCl_4, reflux; (k) CH_2=C(OTBDMS)(O^tBu); CH_3CN, 7 kbar, 5 days; (l) PPTS, EtOH; (m) NBS, THF, 0^o; (n) DMF, reflux; (o) KF, MeOH, 0^o.

diester functionality with excess sodium hydroxide. Compound **53** was lactonized to the desired tetracyclic BCDE ring system **23**, using a

SCHEME 4

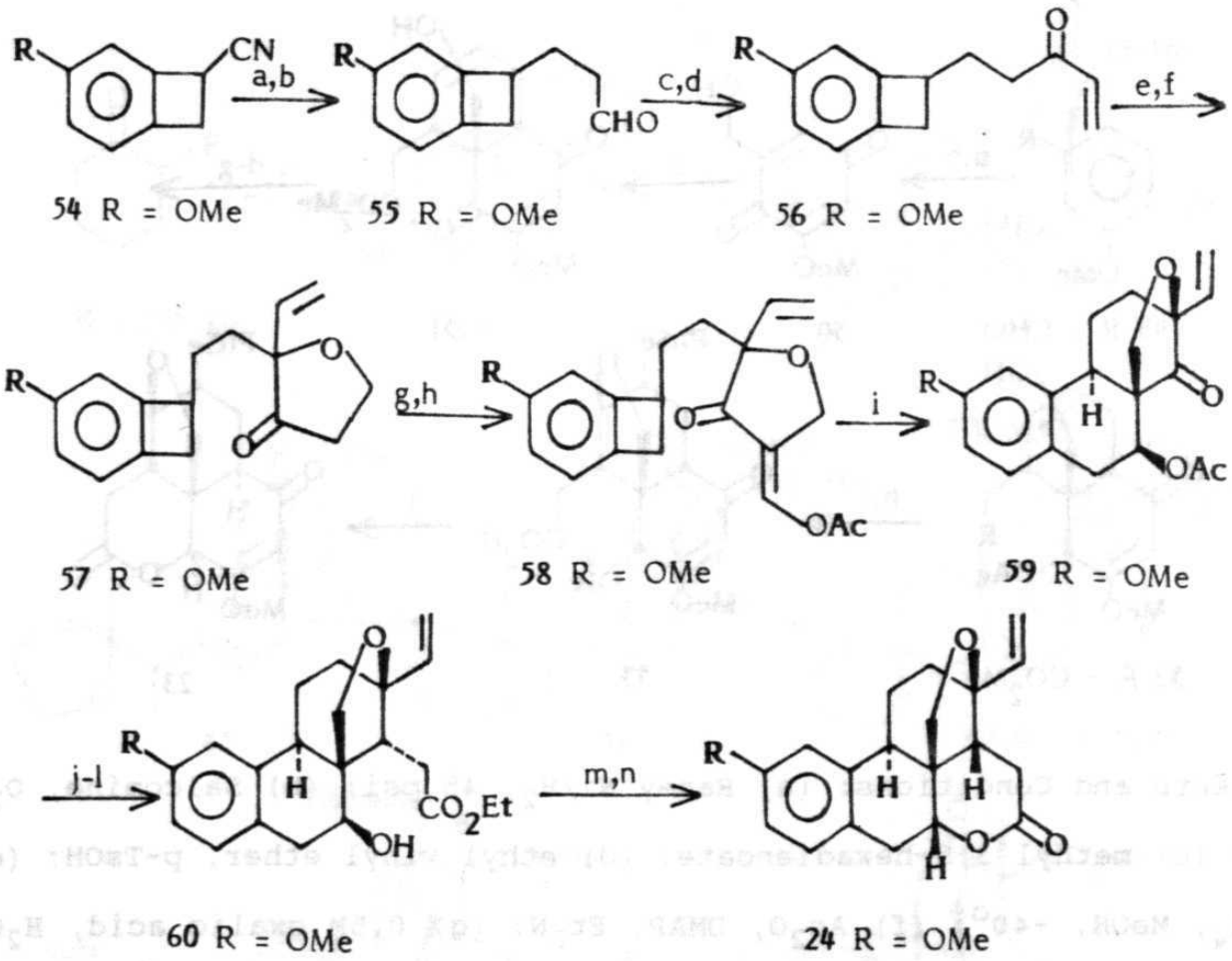


Reagents and Conditions: (a) Raney Ni/H_2, 45 psi; (b) Salcomine, O_2, DMF; (c) methyl 3,5-hexadienoate; (d) ethyl vinyl ether, p-TsOH; (e) $NaBH_4$, MeOH, -40^{o}; (f) Ac_2O, DMAP, Et_3N; (g) 0.5M oxalic acid, H_2O; (h) PhSeCl, CH_2Cl_2, -50^{o}; (i) 1M NaOH; (j) THF-benzene, p-TsOH.

catalytic amount of p-toluenesulfonic acid.

A pentacyclic intermediate towards bruceantin was reported by Kametani and co-workers in 1984.[31] However, it lacks quite a few of the functional groups present in bruceantin (Scheme 5). Aldehyde **55** was prepared from the cyano compound **54** in two steps. The product obtained from the Grignard reaction of **55** with vinylmagnesium bromide was oxidized to the enone **56**. 1,2-Addition of 1-lithio-1-methoxyallene to the enone, followed by treatment with potassium t-butoxide in the presence of 18-crown-6 and then acidic hydrolysis provided the dihydrofuranone **57**. By routine methods, **57** was trans-

SCHEME 5



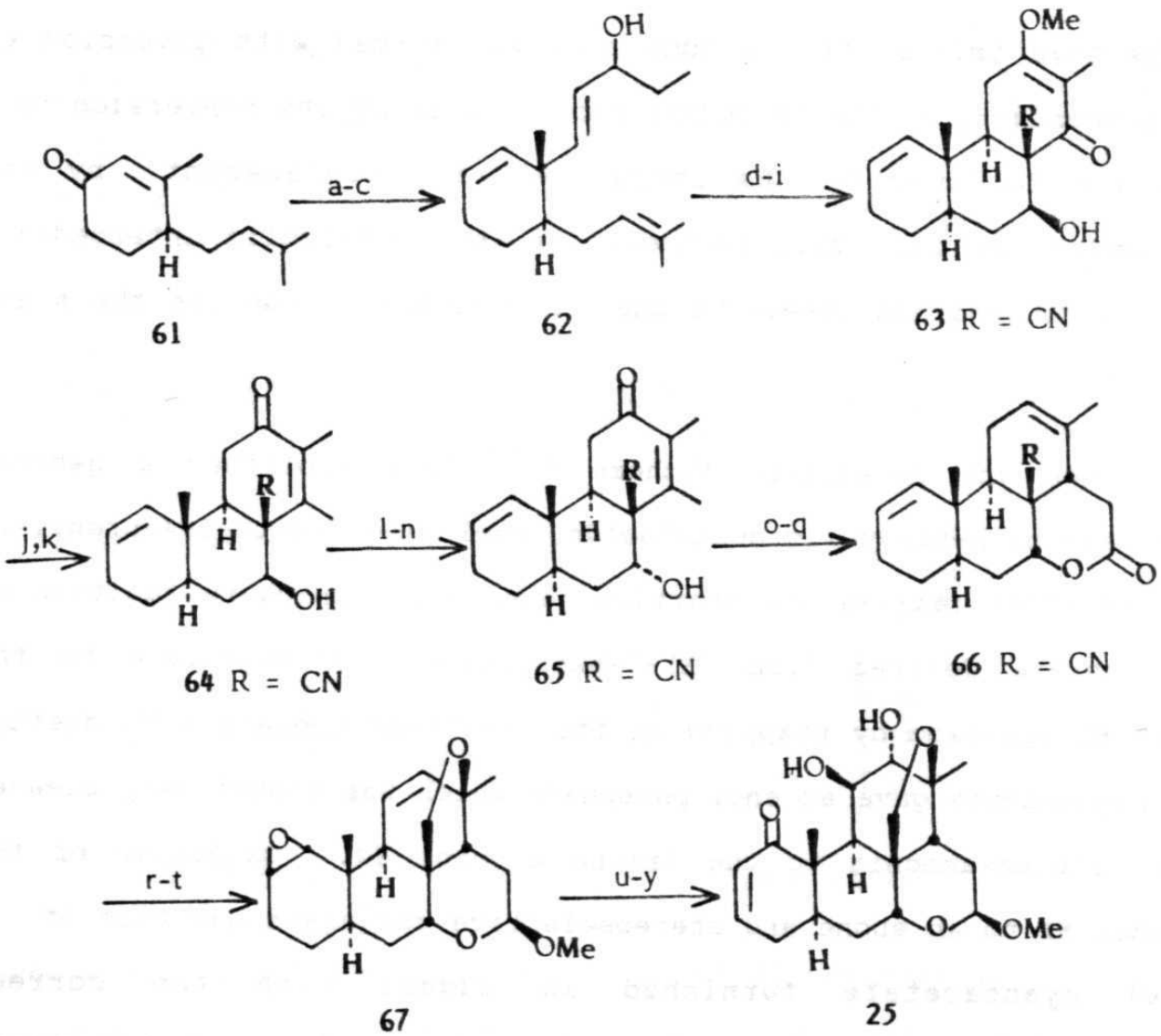
Reagents and Conditions: (a) $NaNH_2$, 3,3-ethylenedioxypropyl bromide; (b) AcOH, H_2O; (c) CH_2=CHMgBr, THF; (d) PDC, CH_2Cl_2; (e) LiC(OMe)=C=CH_2, THF; (f) t-BuOK, t-BuOH, 18-crown-6; (g) NaH, HCO_2Et; (h) Ac_2O, DMAP, Py, r.t.; (i) o-xylene, 180°; (j) NaOH, H_2O, MeOH, CH_2Cl_2; (k) NaH, triethyl phosphonoacetate; (l) Te, $NaBH_4$; (m) KOH, EtOH; (n) triethylamine, MsCl, DMAP.

formed to the α-acetoxymethylene derivative **58**, which was subjected to an IMDA reaction via the intermediacy of an ortho-xylylene, with the α-acetoxymethylene unit serving as the dienophile, leading to the tetracyclic intermediate **59** as the major isomer. A two carbon Wittig reaction on the carbonyl group of **59**, followed by selective

reduction of the conjugated double bond using sodium hydrotelluride gave the hydroxy ester **60** as the only product. After several ineffective trials, the lactone ring was formed with inversion of stereochemistry at the secondary alcohol site by its conversion to a mesylate followed by its intramolecular displacement by the carboxylate anion. This synthesis of the pentacyclic intermediate **24** does not address itself to the substitution present in the A and C rings.

Ganem and co-workers (Scheme 6)[32] have published a general synthesis of pentacyclic quassinoids, employing 3-methyl-4-prenyl-2-cyclohexenone (**61**) as the starting material. Conjugate addition of the cuprate derived from (E)-3-benzyloxy-1-iodo-1-pentene to the enone **61** followed by trapping of the resulting enolate with diethyl chlorophosphate gave an enol phosphate which was reductively cleaved with lithium-ammonia to the triene alcohol **62**. Oxidation of the alcohol **62** to an enone and stereoselective conjugate addition of ethyl cyanoacetate furnished an adduct with the correct configuration at C-9 (<u>vide infra</u>) for the quassinoids. The prenyl double bond was selectively cleaved with ozone and the resulting aldehyde reacted with sodium bicarbonate to form the B ring in an intramolecular aldol reaction. Treatment of the aldol product with a stronger base (LiOEt, EtOH) generated the C ring through a Dieckmann cyclization. Methyllithium addition followed by hydrolysis converted **63** to **64**. The stereochemistry of the secondary alcohol **64** was inverted through a sequence of oxidation, reduction, and allylic alcohol oxidation, leading to **65**. The lactone D ring was annulated making use of the enhanced acidity of the β-methyl

SCHEME 6



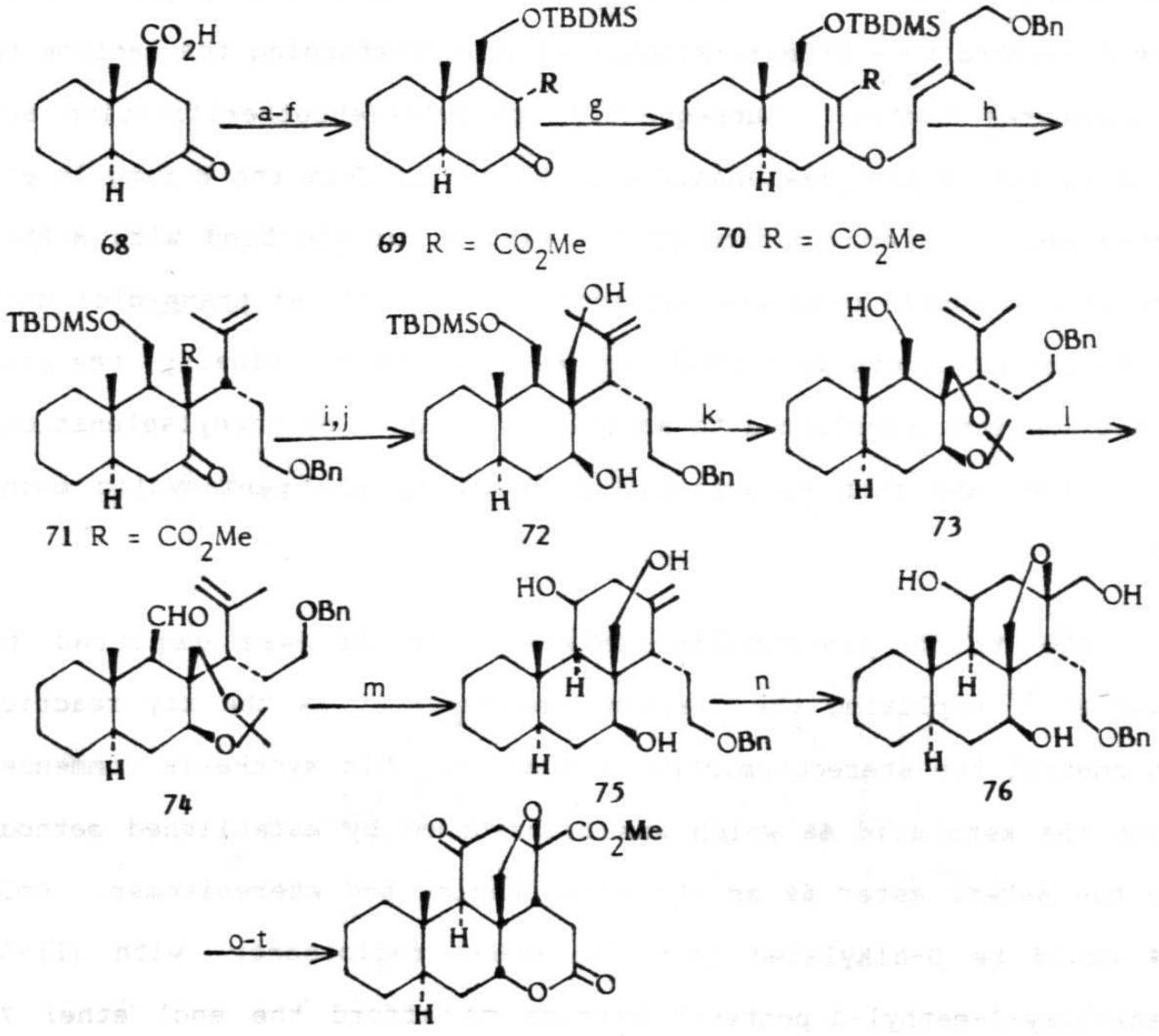
Reagents and Conditions: (a) (E)-IHC=CHCH(OBn)(Et), n-BuLi, $CuI.PBu_3$; (b) $(EtO)_2POCl$-triethylamine; (c) Li-NH_3; (d) oxidation; (e) Michael addition of $CH_2(CN)CO_2Et$; (f) O_3; (g) $NaHCO_3$; (h) LiOEt-EtOH; (i) $HC(OMe)_3$, H^+; (j) MeLi; (k) H^+; (l) oxidation; (m) DIBAL; (n) MnO_2; (o) 1,1-carbodiimidazole, KH; (p) $TsNHNH_2$; (q) $NaBH_3(CN)$-HOAc, 60^o; (r) DIBAL; (s) PhSeCl - H_2O_2; (t) selective monoepoxidation; (u) osmylation; (v) selective oxidation at C-11 carbon; (w) reduction of C-11 keto group with Bu_4NBH_4; (x) PhSeNa, H_2O_2; (y) allylic oxidation.

group of the enone **65** and that moiety was reductively rearranged to the single diene **66** via its tosylhydrazone. The nitrile group in **66** was converted to a primary alcohol after transforming the lactone to a protected lactol. Subsequently, phenylselenoetherification and elimination of phenylselenenic acid served to form the E ring in **67**. After selective epoxidation of the ring A double bond with MCPBA, the ring C double bond was converted to the desired trans-diol unit using the procedure described earlier by Fuchs.[37] Finally, the ring A epoxide was transformed to an allylic alcohol by phenylselenation-oxidation, and then selectively oxidized to the pentacyclic enone **25**.

The third pentacyclic intermediate **26** was reported by Ziegler,[33] employing the Claisen rearrangement as the key reaction to control the stereochemistry (Scheme 7). His synthesis commences with the keto acid **68** which was transformed by established methods to the β-keto ester **69** as the major regio- and stereoisomer. Only **69** could be O-alkylated (not its other regioisomer) with (E)-5-benzyloxy-2-methyl-2-pentenyl bromide to afford the enol ether **70** which on Claisen rearrangement gave the keto ester **71**. At this juncture, the stereochemistry was assigned on the basis of a working hypothesis, which was proved after the assembly of the rings C, D and E. As direct reduction of **71** did not give the diol **72**, sequential reduction was carried out by differentiating the ester and keto group in **71**. Selective reduction of the keto group of **71** with DIBAL, protection of the thus formed alcohol as the TBDMS ether

37. Dailey, O.D. Jr., Fuchs, P.L. J. Org. Chem. 1980, **45**, 216.

SCHEME 7



Reagents and Conditions: (a) CH_2N_2; (b) $CH(OEt)_3$, MeOH, p-TsOH; (c) LAH; (d) H_3O^+; (e) TBDMSCl, triethylamine, DMAP; (f) sodium hexamethyldisilazide, methyl cyanoformate; (g) t-BuOK, 5-(benzyloxy)-1-bromo-2-methyl-2(E)-hexene, NaI; (h) n-nonane, 150°, 40h; (i) DIBAL; (j) TBDMSOTf, LAH; (k) $Me_2C(OMe)_2$, p-TsOH; (l) PDC; (m) 0.1M $SnCl_4$ in CH_2Cl_2; (n) MCPBA; (o) 10% Pd-C, H_2; (p) CrO_3; (q) CH_2N_2; (r) $LiAl(t\text{-}BuO)_3H$; (s) MsCl, triethylamine; (t) K_2CO_3, MeOH, reflux.

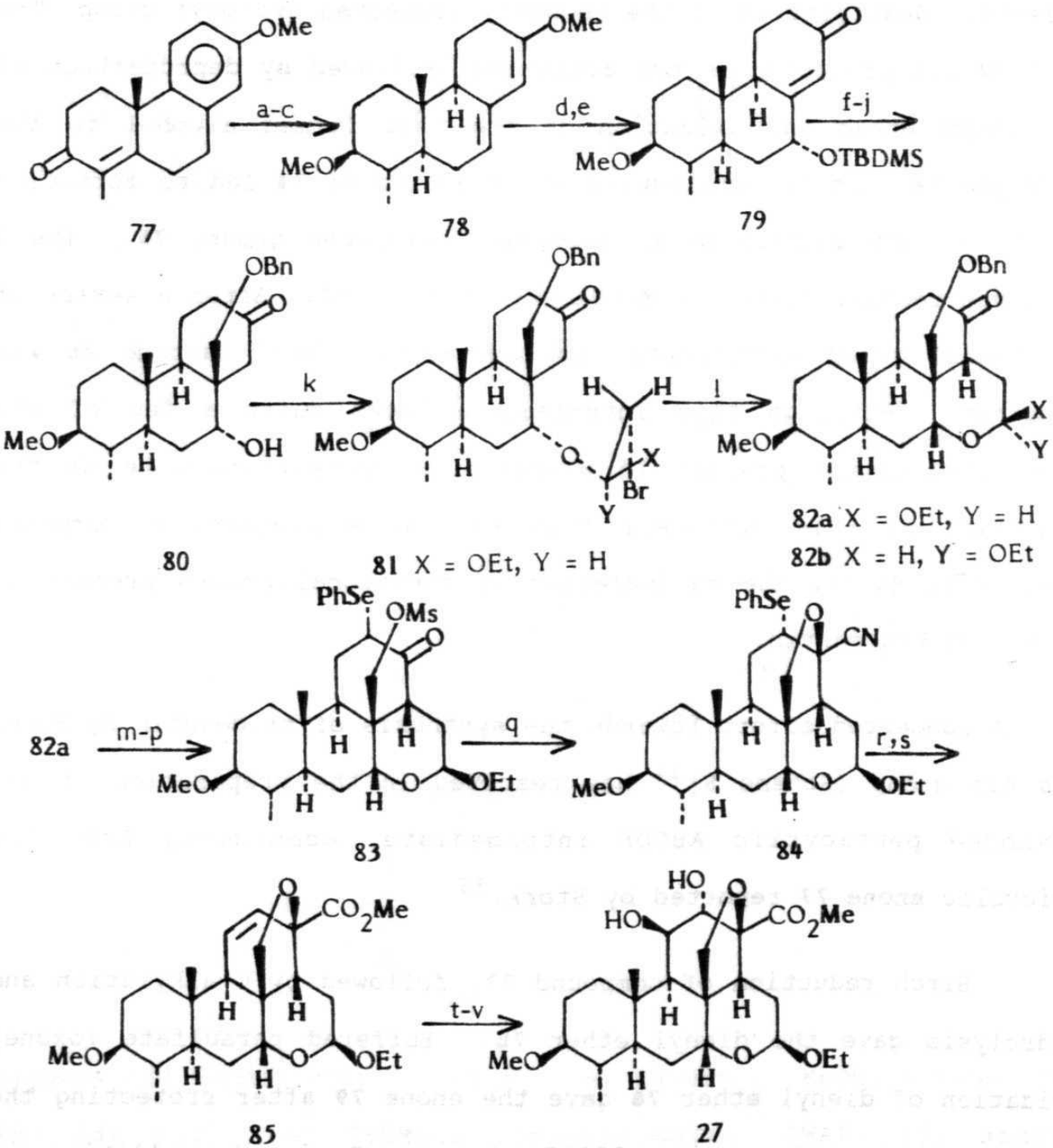
followed by reduction of the ester with LAH gave the diol **72**, with selective desilylation of the recently protected hydroxyl group. The diol **72** was protected as the acetonide, followed by deprotection of the TBDMS ether and oxidation of the thus formed alcohol to the aldehyde **74**. An intramolecular ene reaction of **74** led to formation of the C ring containing an exocyclic methylene group, **75**. The E ring was readily formed by MCPBA oxidation of **75**. After a series of functional group adjustments, the pentacyclic keto lactone **26** was obtained. Although this intermediate lacks quite a few of the functional groups present in bruceantin, the authors note at the beginning of this synthesis that they have prepared a compound similar to **68** for the manipulation of functional groups present in ring A of bruceantin.

A concerted effort towards the synthesis of bruceantin by Fuchs and his group (Scheme 8)[34] has resulted in the preparation of an advanced pentacyclic ABCDE intermediate, commencing from the tricyclic enone **77** reported by Stork.[38]

Birch reduction of compound **77**, followed by O-alkylation and hydrolysis gave the dienyl ether **78**. Buffered persulfate (oxone) oxidation of dienyl ether **78** gave the enone **79** after protecting the generated alcohol as its TBDMS ether. Conjugate addition of hydrogen cyanide to the enone **79**, followed by reduction of cyanide and protection as a benzyl ether afforded **80**, which contains suitable functionality for the E ring formation. To set up the D

38. Stork, G.; Meisels, A.; Davies, J.E. J. Am. Chem. Soc. 1963, **85**, 3419.

SCHEME 8



Reagents and Conditions: (a) Li-NH_3; (b) NaH, MeI; (c) HOAc, (d) $2KHSO_5.K_2SO_4.KHSO_4$; (e) TBDMSCl; (f) Et_2AlCN; (g) TBDMSOTf; (h) (i) DIBAL, HOAc; (ii) DIBAL; (i) BnBr, (j) H^+, n-Bu_4NF; (k) $BrCH_2CH(Br)OEt$; (l) t-BuOK; (m) TBDMSOTf; (n) Li-NH_3; (o) MsCl; (p) PhSeCl; (q) KCN, 18-crown-6; (r) H_2O_2; (s) (i) KOH-H_2O_2; (ii) KOH, 100°; (iii) MeI; (t) OsO_4; (u) Swern oxidation; (v) Bu_4NBH_4.

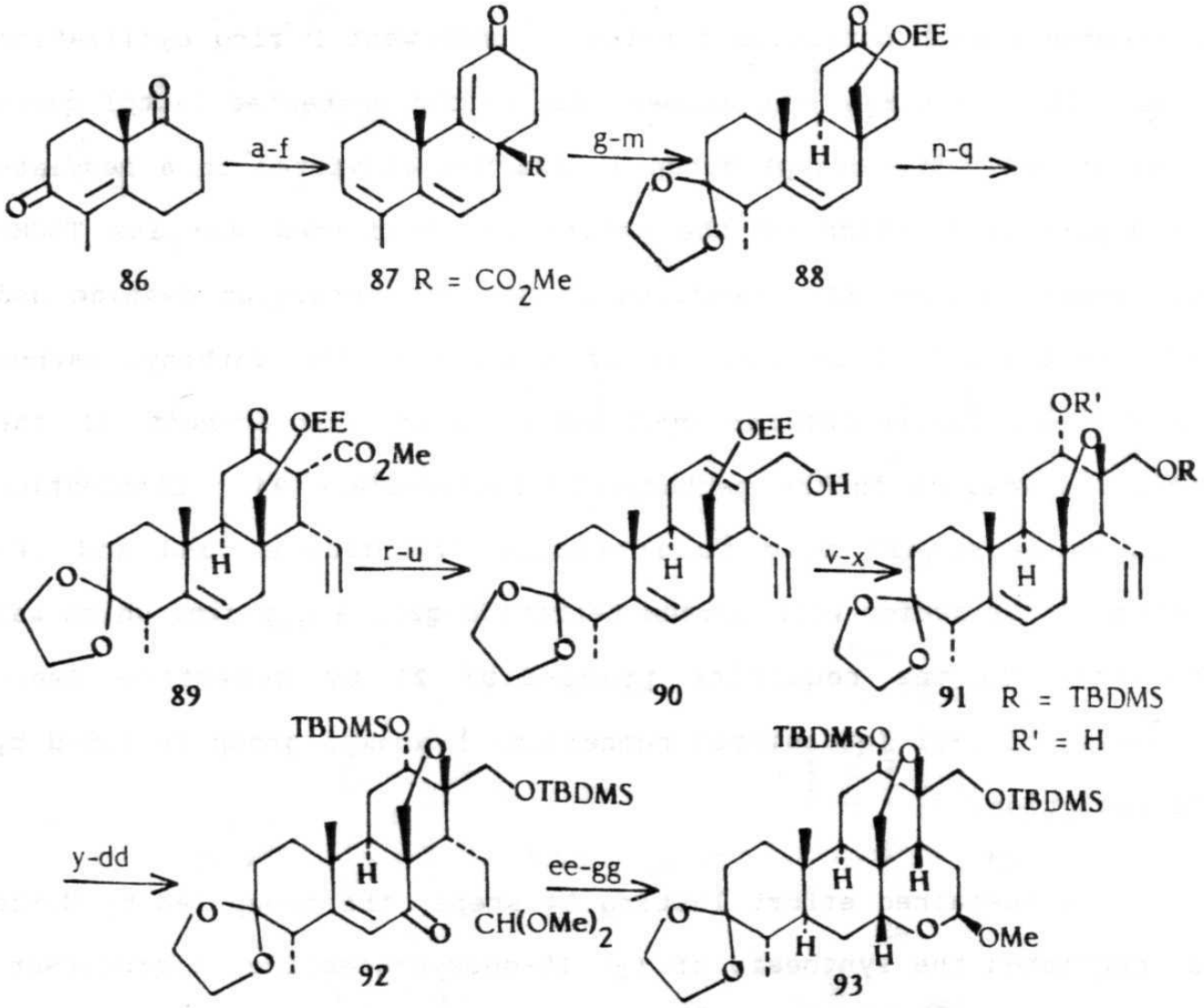
ring, the free secondary alcohol group in **80** was reacted with 1,2-dibromoethyl ethyl ether to give **81** as a mixture of isomers, which on treatment with potassium t-butoxide underwent D ring cyclization to **82**. At this stage, the isomers due to the protected lactol could be separated. The benzyl group in **82a** was converted to a mesylate and α-phenylselenation of the ketone was performed via its TBDMS enol ether to give **83**. Reaction of **83** with potassium cyanide and 18-crown-6 resulted in addition of cyanide to the carbonyl carbon followed by intramolecular cyclization with displacement of the mesylate, leading to the pentacyclic intermediate **84**. Elimination of phenylselenenic acid to introduce the double bond and its subsequent oxidation with osmium tetroxide gave a cis-diol which was converted to the requisite trans-diol **27** by selective Swern oxidation of C-11 (quassinoid numbering) hydroxyl group followed by its reduction.

In a sustained effort lasting 54 steps, the group led by Murae has published the synthesis of (±) 15-deoxybruceolide, a precursor for bruceantin.[35] Recently,[25] they have reported the conversion of the TBDMS ether of 15-deoxybruceolide derived from naturally occurring brusatol into bruceantin. Therefore, the first total synthesis of bruceantin has now been formally achieved.

The readily available homologue **86** of Wieland-Miescher ketone (Scheme 9) was converted through routine methods to the tricyclic keto ester **87**.[39] The A ring was selectively functionalized by

39. Murae, T.; Sasaki, M.; Konosu, T.; Matsuo, H.; Takahashi, T. Tetrahedron Lett. 1986, **27**, 3411.

SCHEME 9



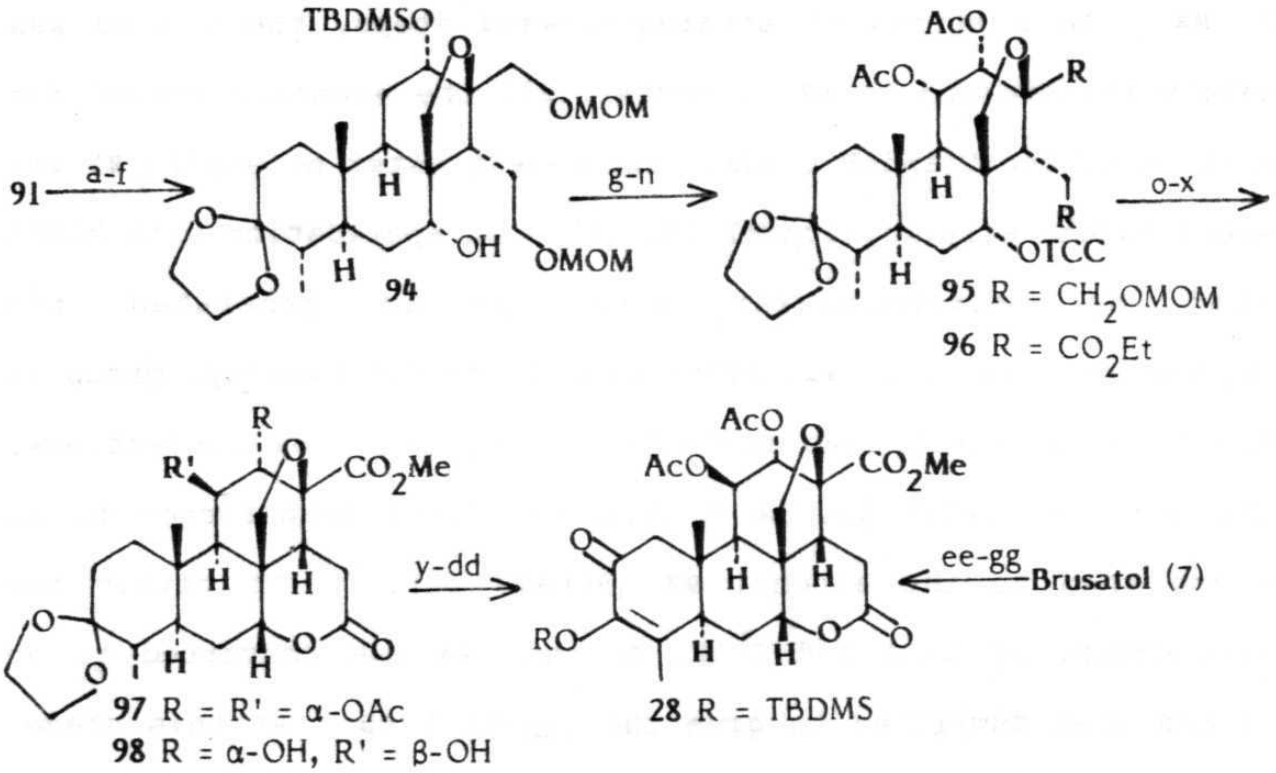
Reagents and Conditions: (a) $(CH_2OH)_2$, H^+; (b) $NaBH_4$; (c) HCl-AcOH; (d) $(MeO)_2CO$, NaH-KH; (e) $MeCOCH=CH_2$, NaOMe; (f) aldol condensation; (g) as in (a); (h) MCPBA; (i) $BF_3.Et_2O$; (j) as in (a); (k) LAH, H^+; (l) $CH_2=CHOEt$, H^+; (m) NaHTe/EtOH; (n) as in (d); (o) NaH, PhSeCl; (p) H_2O_2; (q) cuprate addition; (r) as in (b); (s) $MsCl-Et_3N$; (t) DBU; (u) DIBAL; (v) epoxidation; (w) H^+; (x) TBDMSCl, DMF, imidazole; (y) TBDMSCl, KH/THF-DMF; (z) hydroboration-oxidation; (aa) CrO_3-2Py; (bb) $HC(OMe)_3$, PPTS; (cc) CrO_3, dimethylpyridine; (dd) $Li-NH_3$; (ee) $LiBH(Et)_3$; (ff) as in (w); (gg) Bu_4NF.

oxidation and rearrangement to a ketone which was protected as a ketal, **88**. In a series of straightforward steps, the C ring was adequately transformed to **89** to install all the elements needed for elaboration of the D and E rings. The β-keto ester moiety in **89** was converted to the allylic alcohol **90**, which on epoxidation with MCPBA followed by intramolecular ring opening generated the tetrahydrofuran ring E in **91**. After protecting the hydroxyl group in **91**, the terminal olefin was converted to an ether by conventional methods and the olefin in the B ring was first transformed to an enone and then to the alcohol **94** (Scheme 10).[35] To obtain the hydroxyl groups at C-11 and C-12, alcohol **94** was converted to an olefin and then osmylated to give the cis-diol **95**. At this stage, attention was focussed on ring D formation. After protecting the cis-diol in the diacetate form, the ethers of primary alcohols were deprotected with selective reagents (to avoid the deprotection of the ketal in ring A) and the alcohols oxidized to give the diester **96**. The trichloroethoxy carbonate (TCC) was selectively deprotected and lactonized to form the D ring, **97**. The cis-diester in the C ring was deprotected and converted to trans-diol **98**, by employing the procedure reported by Fuchs.[37] After protecting the trans-diol in the acetate form, the ketal group in ring A was converted into the diosphenol derivative by straightforward procedures to give **28**.

The intermediate **28** was also obtained from brusatol by removing the hydroxyl group at C-15 followed by protecting the ring A hydroxyl group and the trans-diol unit in ring C.

To complete the formal total synthesis, the ring D lactone in **28** was converted to the vinyl ether **99** by a reduction-elimination

SCHEME 10

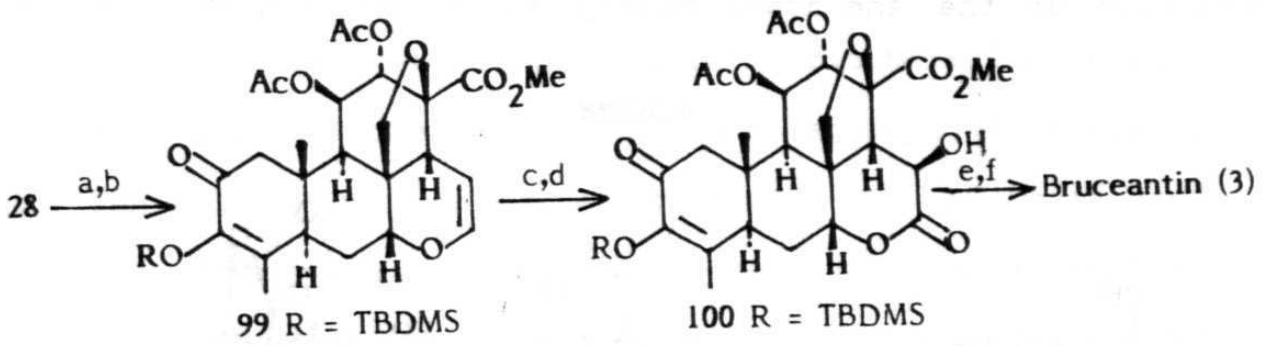


Reagents and Conditions: (a) MOMCl, KH/THF-DMF; (b) BH_3.THF, NaOH, H_2O_2; (c) MOMel, $(ipr)_2NEt$; (d) CrO_3.2py; (e) Li-NH_3; (f) $LiEt_3BH$, LiBr; (g) Ac_2O, DMAP, Py; (h)Bu_4Nf; (i) as in (d); (j) $TsNHNH_2$, p-TsOH; (k) MeLi; (l) TCCCl, DMAP, Py; (m) OsO_4; (n) as in (g); (o) $(CH_2SH)_2$, $BF_3.Et_2O$; (p) NBS, aq.CH_3CN; (q) Swern oxidation; (r) Jones oxidation; (s) CH_2N_2; (t) $(CH_2OH)_2$, p-TsOH; (u) Zn/AcOH; (v) KOMe/MeOH; (w) as in (q); (x) Bu_4NBH_4; (y) as in (g); (z) HCl; (aa) TMSOTf, Et_3N; (bb) MCPBA; (cc) Bi_2O_3; (dd) TBDMSCl, DMF, imidazole; (ee) PhOCSCl, DMAP, Py; (ff) Bu_3SnH, azoisobutyronitrile; (gg) as in (g).

process (Scheme 10a).[25] The double bond present in the D ring of **99** was selectively epoxidized in a two phase system and opened up to give the bruceolide derivative **100** after oxidizing the lactol. The D ring hydroxyl group in **100** was esterified with the appropriate side chain and subsequently the TBDMS ether and acetates were hydrolyzed to give bruceantin (**3**), thus constituting its formal

total synthesis.

SCHEME 10a



Reagents and Conditions: (a) 1 Equiv. $NaBH_4$; (b) $POCl_3$, Py; (c) MCPBA, CH_2Cl_2-aq.$NaHCO_3$; (d) AgO, CH_3CN; (e) (E)-3,4-dimethyl-2-pentenoic acid, DCC, DMAP; (f) 1.5M H_2SO_4, MeOH.

I.2.2 Towards Quassimarin:

Quassimarin, which differs from bruceantin in the A ring substitution pattern as well as in the C and D rings, has also attracted the attention of synthetic chemists. So far, the syntheses of two tetracyclic intermediates **107**[40] and **116**,[41] and one pentacyclic intermediate **124**[42] have appeared in the literature. A brief summary of the approaches towards the above tetracyclic and pentacyclic intermediates is presented in the following pages.

The construction of a simple BCDE model system has been

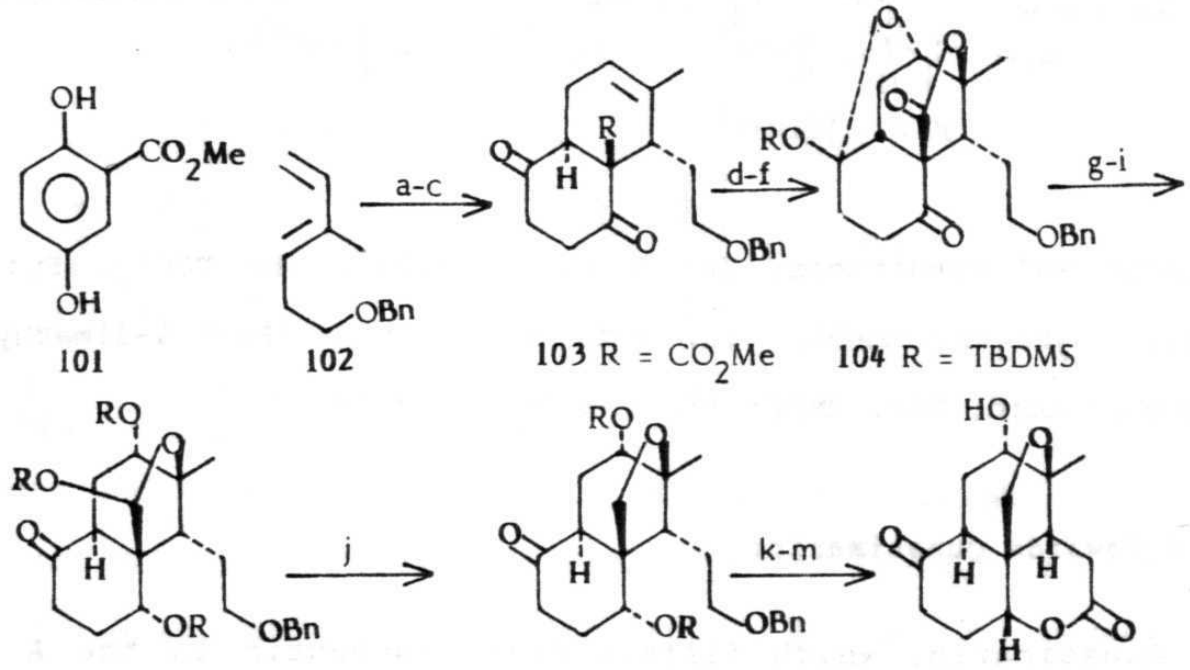
40. Kraus, G.A.; Taschner, M.; Shimagaki, M. J. Org. Chem. 1982, **47**, 4271.

41. Shishido, K.; Takahashi, K.; Fukumoto, K, Kametani, T.; Honda, T. J. Org. Chem. 1987, **52**, 5704.

42. Grieco, P.A. Inanaga, J.; Sham, H.L.; Sasaki, S.; Kim, H. J. Chem. Soc., Chem. Commun. 1987, 1044.

reported by Kraus (Scheme 11).[40] Diels-Alder reaction of 2-carbomethoxy-1,4-benzoquinone and the diene **102** gave, after reduction of the ene-dione moiety and epimerization, the product

SCHEME 11



Reagents and Conditions: (a) Ag_2O; (b) Zn/HOAc; (c) Al_2O_3; (d) MCPBA; (e) $HClO_4$, aq.acetone; (f) TBDMSCl, DMF, imidazole, 50^{o}; (g) DIBAL; (h) $(n\text{-}Bu)_4NF$; (i) triethylamine, Ac_2O, DMAP; (j) Et_3SiH, $BF_3.Et_2O$; (k) H_2/Pd/C; (l) Jones oxidation; (m) aq.methanol, K_2CO_3.

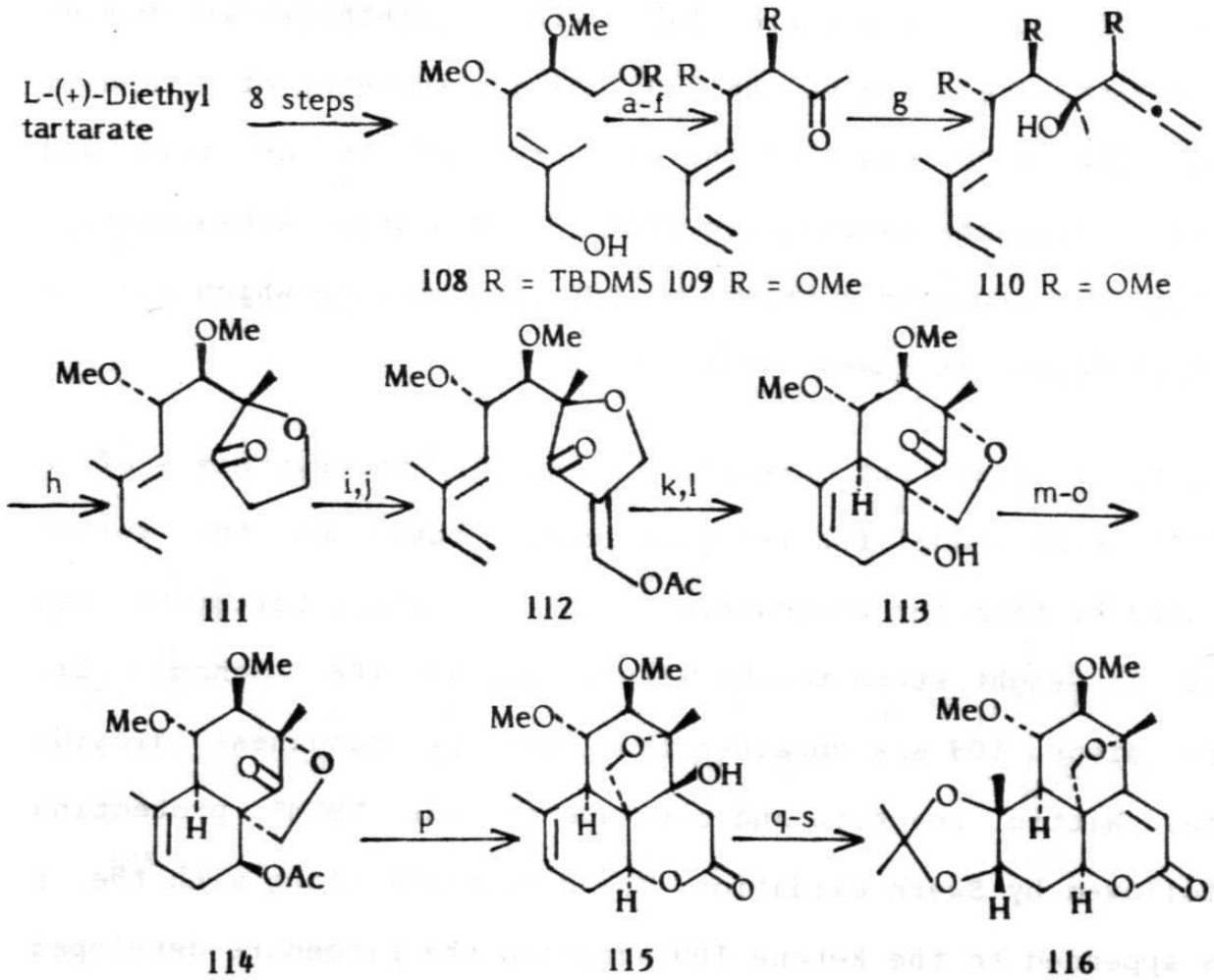
103. The double bond was epoxidized with MCPBA and lactonization occurred on treatment of the epoxide with acid. The two carbonyls were differentiated by intramolecular hemi-acetal formation and protection as the corresponding TBDMS acetal **104.** Reduction with DIBAL and deprotection with tetra-n-butylammonium fluoride gave the keto-diol hemi-acetal, which was converted to its triacetate, **105.**

The hemi-acetal was deoxygenated to the tetrahydrofuran ring E by reduction of the triacetate **105** with triethylsilane/boron-trifluoride-etherate to give **106**. By doing a sequence of standard reactions, the side chain of **106** was converted to an acid and lactonized to give the tetracyclic BCDE intermediate. Subsequently, Kraus[43] has also reported a tricyclic ACE intermediate which can be further transformed to quassimarin.

In 1987, Kametani and co-workers[41] reported the synthesis of a tetracyclic BCDE model for (-) quassimarin, based on the format earlier used by them for bruceantin.[31] L-(+)-Diethyl tartarate was converted in eight steps to the allylic alcohol **108** (Scheme 12). The keto diene **109** was obtained from **108** by manganese dioxide oxidation, Wittig reaction and cleavage of the TBDMS protecting group followed by Swern oxidation. The dienophile along with the E ring was appended to the ketone **109** adopting the procedure developed earlier[31] for the bruceantin model system leading to the IMDA reaction precursor **112**. Heating **112** in toluene gave **113**, comprising the BCE rings of quassimarin. **113** has the wrong stereochemistry at C-7. Therefore, after deprotecting the acetate group in **113**, a mild oxidation- reduction sequence gave **114** on protection of the epimerized alcohol. On subjecting the acetate **114** to an intramolecular Claisen condensation, the tetracyclic lactone **115** was obtained. Hydroxy lactone **115** was dehydrated and osmylated to give the acetonide lactone **116** after protection of the diol unit. Tetracyclic **116** is epimeric with the natural series at C-9.

43. Kraus, G.A.; Krolski, M.E. J. Org. Chem. 1986, 51, 3347.

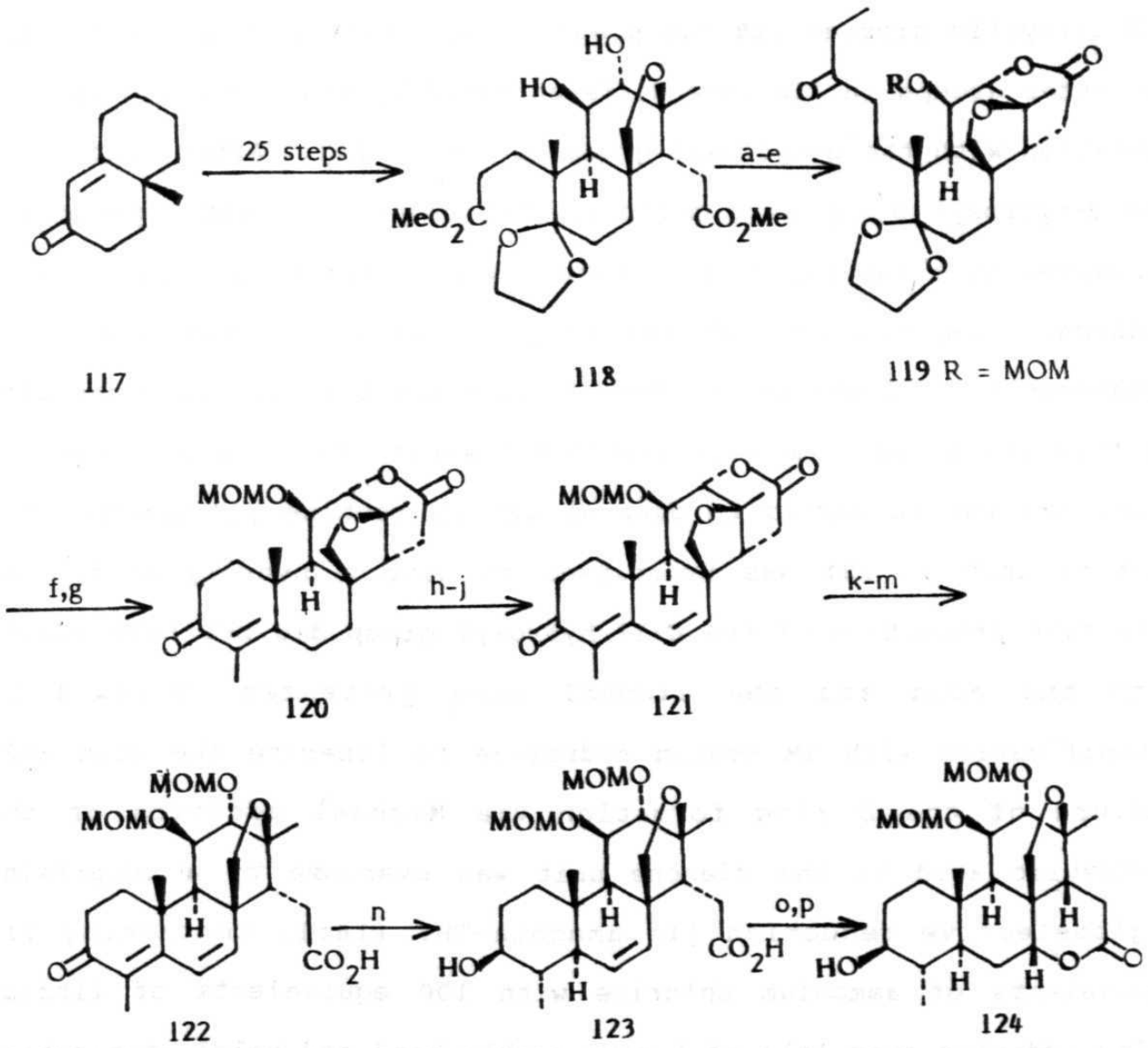
SCHEME 12



Reagents and Conditions: (a) MnO_2; (b) $Ph_3P{=}CH_2$; (c) $(n\text{-}Bu)_4NF$; (d) Swern oxidation; (e) MeMgBr; (f) as in (d); (g) $Li(MeO)C{=}C{=}CH_2$; (h) t-BuOK, 18-crown-6; (i) HCO_2Et, NaH; (j) Ac_2O, Py, DMAP; (k) toluene, reflux; (l) LiOH, MeOH, H_2O, CH_2Cl_2; (m) as in (d); (n) $LiBH(Et)_3$; (o) Ac_2O, Py, DMAP; (p) LDA; (q) $SOCl_2$, Py; (r) OsO_4, NMO; (s) $(MeO)_2CMe_2$, PPTS.

As part of a continuous synthetic effort on quassinoids, Grieco has published the synthesis of the pentacyclic lactone **124** possessing nine of the eleven stereocentres present in quassimarin.[42] The synthesis of **124** constitutes the farthest advance reported to-date

SCHEME 13



117 118 119 R = MOM

120 121

122 123 124

Reagents and Conditions: (a) p-TsOH; (b) MOMCl, diisopropylethylamine; (c) DIBAL; (d) EtMgBr, -78°; (e) Collin's oxidation; (f) p-TsOH, acetone, $CaCl_2$; (g) t-BuOK, toluene; then p-TsOH, acetone, $CaCl_2$; (h) TMSI, HMDS; (i) NBS, -78°; (j) DBU; (k) 1M NaOH, MeOH; (l) as in (b); (m) as in (k); (n) NH_4Cl, NH_3, THF, Li; (o) Me_3CCO_2Tl, Br_2; (p) Bu_3SnH, azoisobutyronitrile.

towards quassimarin. Synthesis of the pentacyclic lactone **124** was published in two parts. Starting from the known octalone **117**, the BCE tricyclic diester **118** was prepared in twenty five steps.[44] The two ester groups in **118** were differentiated by regiospecific lactone formation with the α-hydroxyl group of the C ring. After protecting the β-hydroxyl group as a methoxymethyl ether, the ester group was converted to a two carbon homologated ketone **119** by straightforward methods. Deprotection of the ethylene ketal in **119** and aldol condensation followed by dehydration gave the pentacyclic enone **120**. At this stage, efforts were directed towards the D ring formation. Enone **120** was converted to dienone **121** by routine processes. The lactone unit in **121** was hydrolysed to give a hydroxy acid. As selective protection of the C-12 hydroxyl group did not take place, both the acid and the alcohol were protected followed by saponification with 1M sodium hydroxide to liberate the acid **122**. Failure of the D ring formation via Michael addition of the carboxylic acid to the dienone unit was overcome by a surprising regioselective reduction [in ammonia-THF (16:1) containing 110 equivalents of ammonium chloride with 100 equivalents of lithium (slow addition over 1h)] of A ring double bond and halolactonization using thallium pivalate-bromine followed by debromination to give the required pentacyclic ring system **124**.

As outlined above, although considerable progress has been made in the past decade towards the synthesis of quassinoids, important compounds like bruceantin and quassimarin are yet to be synthesized.

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44. Grieco, P.A.; Sham, H.L.; Inanaga, J.; Kim, H.; Tuthil, P.A. J. Chem. Soc., Chem. Commun. 1984, 1345.

The next section of this thesis deals with the work undertaken to synthesize bruceantin as well as its various model systems.

II. SYNTHETIC STRATEGIES

The structural complexity and the dense functionality present in quassinoids call for a synthetic strategy which can accommodate the two above mentioned features. Amongst the quassinoids, bruceantin was chosen as the target molecule for two reasons. First, it has significant antineoplastic properties and secondly, its structural complexity is such that any successful synthesis of bruceantin can be readily adapted to that of its less complicated congeners.

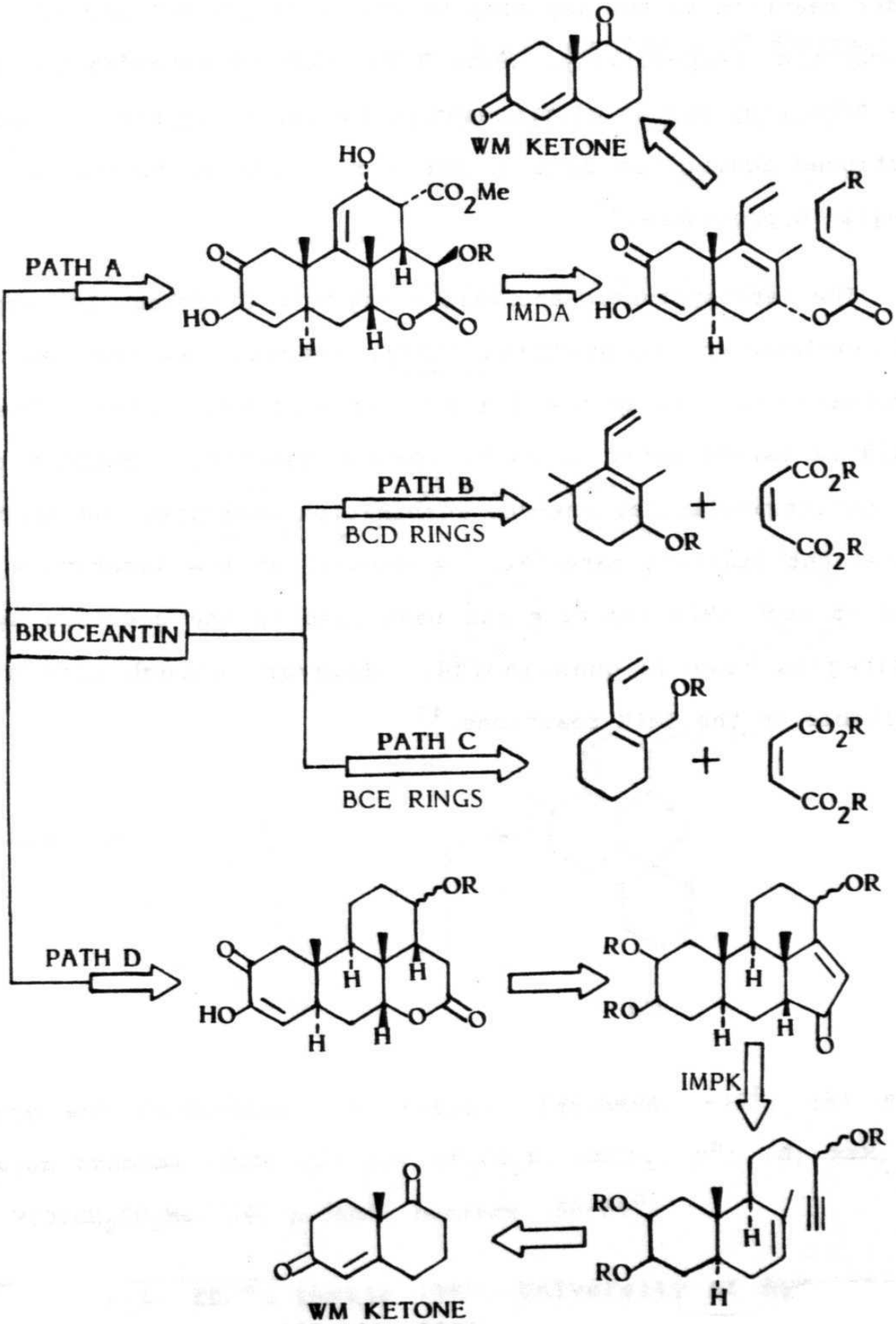
Strategies for the model as well as total synthesis of bruceantin are delineated through retrosynthetic analyses (Scheme 14). Path A of the retrosynthetic scheme (Scheme 14) involves as the key step an IMDA reaction to simultaneously set up the C and D rings. The tetrahydrofuran E ring would be formed last, using the Barton reaction or one of its variants.[45] Further analysis of the intramolecular diene-dienophile combination ultimately leads to WM ketone[#] as a suitable starting material. As the optically active form of WM ketone necessary for the synthesis of bruceantin is also readily available,[46] this route has the added advantage of being an enantiospecific synthesis as well.

[#] Chemical Abstracts Nomenclature: 8a-methyl-3,4,8,8a-tetrahydro 1,6(2H,7H)-naphthalenedione.

45. Barton, D.H.R.; Beaton, J. M.; Geller, L.E.; Pechet, M.M. J. Am. Chem. Soc. 1960, **82**, 2640; 1961, **83**, 4076.

46. Schacher, P.B.; Furst, A. Org. Syn. 1985, **63**, 37.

SCHEME 14


WM KETONE
HO
CO2Me
OR
PATH A
IMDA
R
PATH B
BCD RINGS
CO2R
CO2R
BRUCEANTIN
PATH C
BCE RINGS
PATH D
RO
RO
IMPK
WM KETONE

Paths B and C of Scheme 14 involve an intermolecular Diels-Alder reaction as the key step to construct the BCD and BCE rings of bruceantin, respectively. Path B can also be extended to construct the BCDE ring system of bruceantin, by using the Barton reaction as mentioned above. In path C, the E ring can be formed by applying Ziegler's procedure.[33]

The retrosynthetic analysis along path D (Scheme 14) employs an intramolecular Pauson-Khand (IMPK) reaction as the key step to simultaneously set up the C and D rings of bruceantin. The E ring would be formed later using the Barton reaction. Further analysis of the intramolecular ene-yne combination indicates WM ketone as a convenient starting material. A perusal of the literature reveals that no such IMPK reaction has been used in the previous synthetic strategies towards quassinoids. However, enough literature is available on the IMPK reactions.[47]

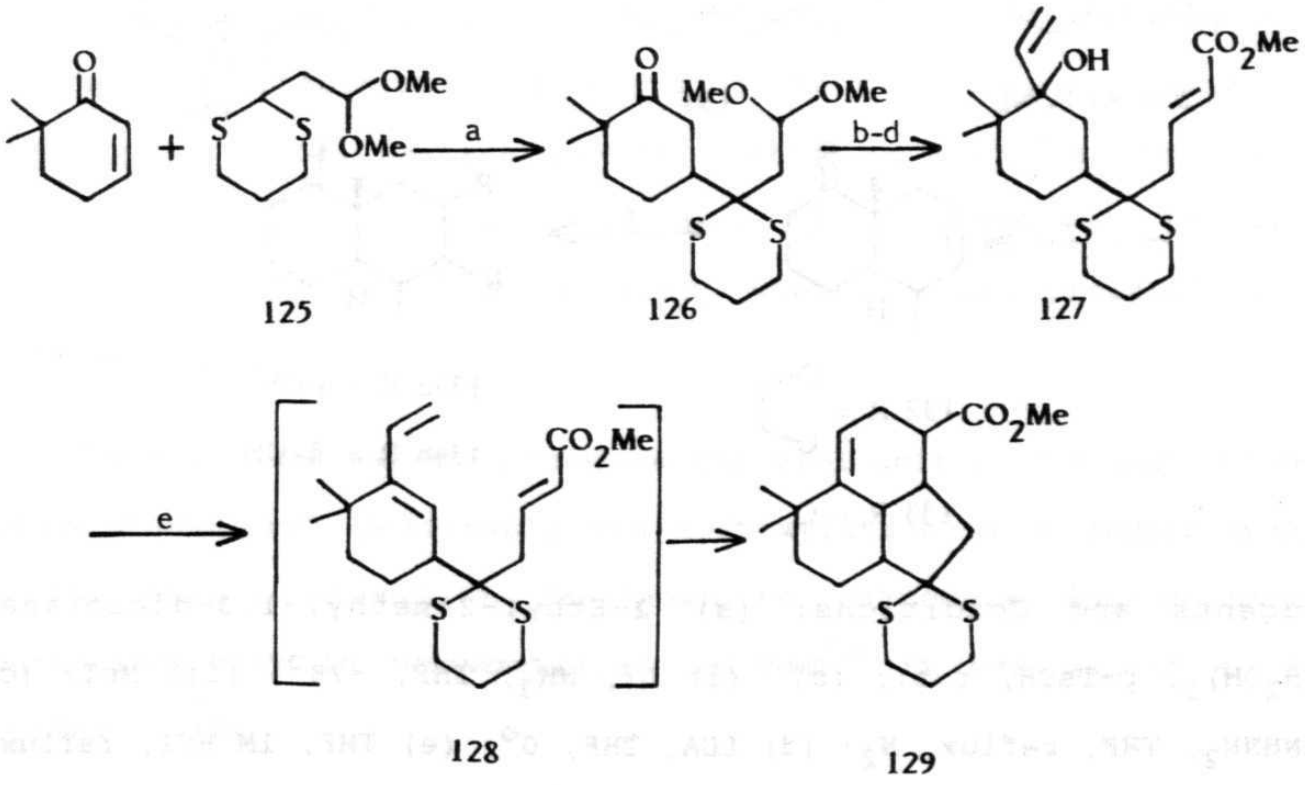
47. Pauson, P.L. Tetrahedron 1985, **41**, 5855.

III. RESULTS AND DISCUSSION

III.1 IMDA Reaction Approach Towards Total Synthesis of Bruceantin:

Path A in Scheme 14 was examined during the course of model studies in our laboratory (Scheme 15).[48] Starting from 6,6-dimethyl-2-cyclohexenone, the IMDA reaction precursor **127** was prepared in four steps. The dehydration-cum-IMDA reaction of **127**

SCHEME 15



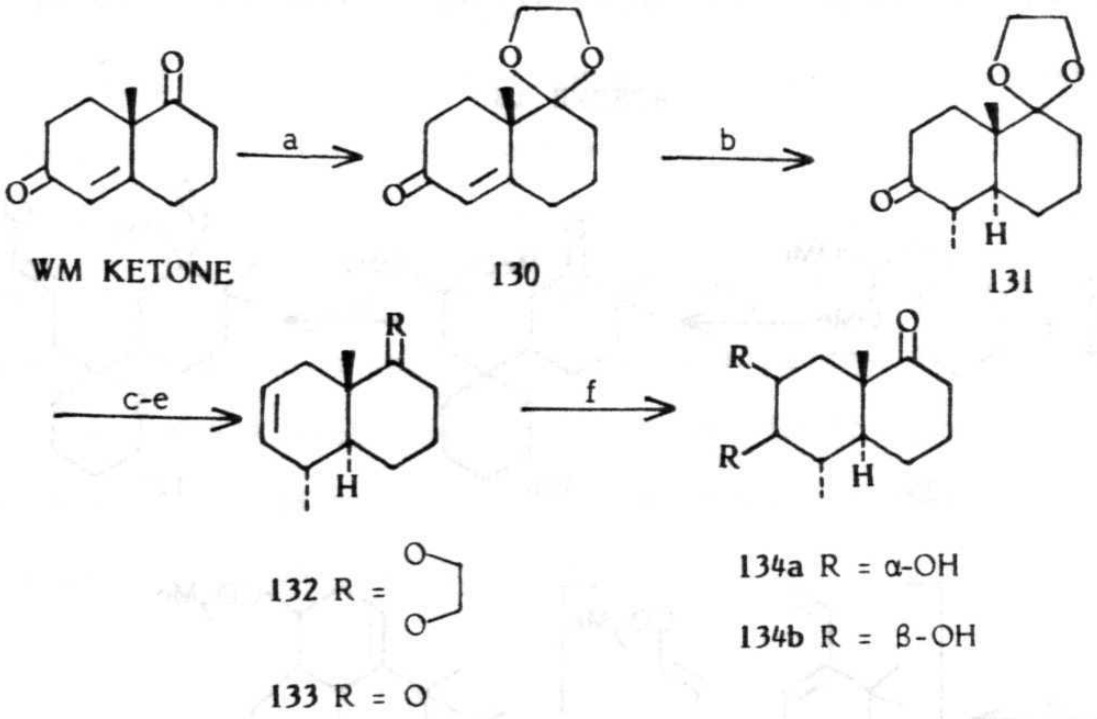
Reagents and Conditions: (a) n-BuLi, THF-HMPA, -78°; (b) vinyl-magnesium bromide, THF; (c) 50% CF_3CO_2H, $CHCl_3$, 0°; (d) NaH, THF, $(EtO)_2P(O)CH_2CO_2Me$; (e) p-TsOH, benzene, 50-60°.

48. Reddy, C.L. Ph.D. thesis 1987, University of Hyderabad, Hyderabad.

proceeded smoothly to give the tricyclic BCD ring system **129**, presumably via **128**, which was not isolateld.

Encouraged by these results, we started with WM ketone[46] so as to include the A ring and also to complete the total synthesis of bruceantin. To begin with, the racemic form of WM ketone was used.

SCHEME 16



Reagents and Conditions: (a) 2-Ethyl-2-methyl-1,3-dioxolane, $(CH_2OH)_2$, p-TsOH, r.t.; (b) (i) Li, NH_3, THF, -78^{o}; (ii) MeI; (c) $TsNHNH_2$, THF, reflux, N_2; (d) LDA, THF, 0^{o}; (e) THF, 1M HCl, reflux, 1h; (f) OsO_4, NMO, water, acetone, t-butanol, r.t., N_2.

Our first objective was to incorporate the functionality present in the A ring of bruceantin into the cyclohexenone moiety of WM ketone. These include a methyl group at C-5 (WM ketone numbering) and a diol unit at C-6, C-7. The stereochemistry at these centres is immaterial as they are present in bruceantin as a

diosphenol unit.

Towards this end, the monoketal **130** was prepared from WM ketone according to the literature procedure[49] using 2-ethyl-2-methyl-1,3-dioxolane as the trans-ketalizing agent (Scheme 16). Generation of the trans ring fusion and α-methylation to ketal-ketone **131** was accomplished by metal ammonia reduction followed by quenching with iodomethane. Optimum yields (57.7%) of **131** were obtained by the addition of lithium metal to a solution of the ketal-ketone **130** (10 mmol) in THF (20 ml) and dry ammonia (200 ml) followed by quenching with iodomethane. Yields were reduced when the reaction was scaled up. The stereochemistry of ring fusion and of the newly introduced methyl group in **131** was assigned by analogy to a similar example in the literature.[50] The spectral data (IR and PMR) of **131** were identical to that reported earlier, where it was prepared by a different route.[51]

The next task was to introduce the diol unit at C-6 and C-7 (WM ketone numbering), preferably via hydroxylation of a double bond. As the Shapiro reaction is known to introduce double bonds regioselectively in unsymmetrical ketones[52] it was sought to be applied to **131**.

The p-tosylhydrazone of **131** was prepared by a modified procedure[51] by refluxing a mixture of **131** and p-tosylhydrazide in

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49. Bauduin, G.; Pietrasanta, G. Tetrahedron 1973, **23**, 4225.

50. Majetich, G.; Grieco, P.A.; Nishizawa, M. J. Org. Chem. 1977, **42**, 2327.

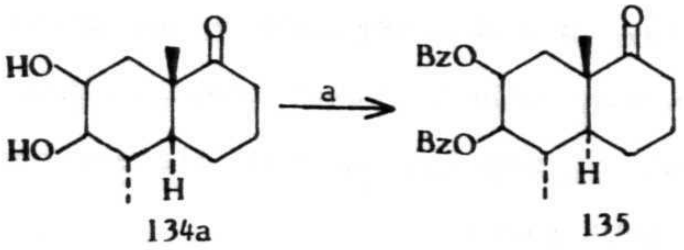
51. Banerjee, A.K; Boente, M.I.P. Heterocycles 1985, **23**, 5.

THF. The IR spectrum of the crude derivative showed the absence of carbonyl band and the presence of characteristic hydrazone bands (3200, 700, and 660 cm^{-1}). The crude p-tosylhydrazone of **131** on reaction with LDA in THF at 0^{o} gave the olefin **132**[52] in 75% yield (from the ketone **131**). The structure of **132** was established from the absence of a carbonyl band in its IR spectrum and presence of a signal at δ 5.64-5.22 (m, 2H, olefinic proton) in the PMR spectrum in addition to other prominent peaks. Hydrolysis of **132** using 1M HCl gave the ketone **133** quantitatively. Ketone **133** was characterized from its spectral data (IR, PMR, and CMR). In the IR spectrum, presence of a carbonyl band (1710 cm^{-1}) and in the PMR spectrum absence of ethylene ketal signals at δ 3.87 (br s, 4H) and presence of other characteristic signals are fully in agreement with the structure of **133**. Finally, a 12 line CMR spectrum with the carbonyl carbon at 215 ppm is in support of the structure of **133**. cis-Hydroxylation of **133** using osmium tetroxide and 4-methylmorpholine N-oxide[53] yielded a stereoisomeric mixture of two cis-diols **134a** and **134b** in a ratio of 1:4.8, which were easily separable on a silica gel column. Besides satisfactory elemental analysis, the major stereoisomer **134b** has bands in the IR spectrum at 3425, 3325, and 1710 cm^{-1} for the diol and carbonyl moieties, respectively. The PMR spectrum of **134b** has signals at δ 4.18-4.00 (m, 1H) and 3.20-2.94 (m, 1H) due to the hydroxyl methine protons. Similarly, the minor isomer **134a** was also characterized from its spectral data (IR and PMR).

52. Shapiro, R.H. Org. React. 1976, **23**, 405.

53. Van Rheenen, V.; Kelly, R.C.; Cha, D.Y. Tetrahedron Lett. 1976, **17**, 1973.

In order to assign the stereochemistry of the cis-diol unit in **134a** and **134b**, **134b** was converted to its dibenzoate **135** by using the standard procedure (Eq.1). The PMR spectrum (Fig.1) of **135** showed two benzoate methine protons at δ 5.76 (dt appearing as a quartet, J = 4,8 Hz) and δ 4.87 (dd, J = 4,12 Hz). Irradiation of the signal



134a 135 Eq.1

(a) PhCOCl, pyridine, DMAP, r.t., 10h.

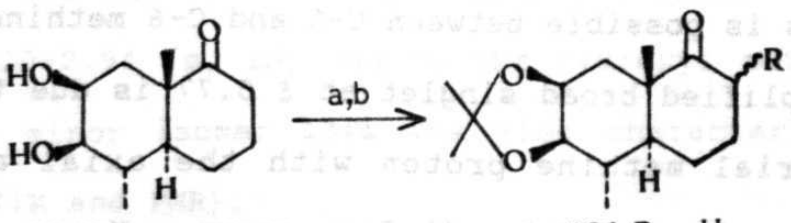
at δ 5.76 simplified the signal at δ 4.87 to a doublet at δ 4.86 (J = 11 Hz). Similarly, irradiation of the signal at δ 4.87 simplified the signal at δ 5.76 to a broad singlet at δ 5.77.

In the absence of complicating factors, equatorial protons in the cyclohexane ring give rise to resonances downfield from their axial counterparts.[54] Also, in the chair form of six-membered rings $J_{axial, axial}$ is usually in the range of 8-13 Hz and $J_{axial, equatorial}$ in the range of 2-6 Hz. The above decoupling studies therefore reveal that the doublet at δ 4.86 with coupling constant of 11 Hz is due to the axial orientation of two adjacent methine protons. This is possible between C-5 and C-6 methine protons only. Also, the simplified broad singlet at δ 5.77 is due to the coupling of an equatorial methine proton with the axial and equatorial protons of the adjacent C-8 methylene group. Hence, the decoupling

54. Jackmann, L.M.; Sternhell, S. "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd Edn., Pergaman, Oxford, 1969, p.238.

studies indicate that the doublet of doublet resonating at high field (δ 4.87) is due to the axial C-6 benzoate methine proton. This automatically fixes the assignment of C-7 benzoate methine proton as that at δ 5.76 and in the equatorial position, because **135** is derived from a cis-diol. The major diol **134b** therefore has the stereochemistry 6β, 7β and consequently the minor diol **134a** is 6α, 7α. Having thus successfully functionalized the A ring, attention was next focussed on setting up the diene-dienoplile combination required for the IMDA raction.

The diol unit in **134b** was protected in its acetonide form by using acetone and a catalytic amount of sulfuric acid in the presence of anhydrous copper sulfate to give **136** (Eq.2). Spectral information in support of **136** include the absence of hydroxyl band and the presence of ether bands (1240, 1225, and 1060 cm^{-1}) in the IR spectrum and signals at δ 4.25 (dt, 1H, H-7, J = 2,6 Hz), 3.41 (dd, 1H, H-6, J = 6,9 Hz), 1.44 (s, 3H, 8a-CH_3), 1.32 (s, 6H, acetonide CH_3), 0.98 (d, 3H, 5-CH_3, J = 7 Hz) in the PMR spectrum. Finally, appearance of the carbonyl carbon at 214.5 ppm along with other 13 lines in the CMR spectrum (Fig.2) supported the structural assignment of **136**.



Eq.2

134b

136 R = H

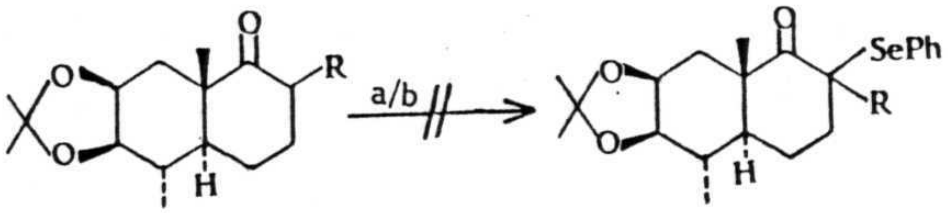
137 R = Me

(a) Acetone, $CuSO_4$, H_2SO_4, r.t.; (b) LDA, THF, -15° (ice-salt), MeI.

At this stage, the methyl group required for the formation of the E ring was introduced by alkylating the ketone **136**. Conditions for optimum yield (95%) of **137** consisted in forming the enolate of **136** using LDA at -15^{o} (ice-salt bath) followed by quenching with iodomethane to give the C-alkylated product (Eq.2). The gross structure of the methylated ketone **137** was obtained from its PMR (Fig.3) and CMR (Fig.2a) spectra. In the PMR spectrum, the doublet due to the newly introduced methyl group merged with the existing doublet due to the C-5 methyl group, giving rise to a triplet at δ 0.96. The other prominent signals present in **136** were also present in **137**. The CMR spectrum of **137** showed a 15 line pattern with the carbonyl carbon at 214.6 ppm and the newly introduced methyl at 41.2 ppm. The stereochemistry of the C-2 methyl was not worked out as it gets destroyed subsequently in the course of enone formation (see below).

In keeping with the model study (Scheme 15), the ketones **136** and **137** were sought to be converted to the corresponding enones, so that the requisite side chains, to be subsequently transformed to the dienophile, could be introduced via a conjugate addition. The conversion of a ketone to an enone is a well studied transformation in synthetic organic chemistry and many methods are available for this purpose. Some of the procedures used in this work are discussed in the following paragraphs. They include: (i) selenation/oxidation/elimination, (ii) sulfenation/oxidation/elimination, (iii) trimethylsilyl enol ether formation/oxidation, and (iv) halogenation/elimination.

To obtain the corresponding enones from the ketone 136 and 137, attempts were made initially to α-phenylselenate them (Eq.3). Both the ketones as well as their enolates did not react with phenylselenyl chloride or phenylselenyl bromide at room temperature or at -20°. α-Bromination of ketone 136 using NBS was also unsuccessful.



136 R = H 138a R = H

137 R = Me 138b R = Me

Eq.3

(a) PhSeCl, EtOAc, r.t.; (b) LDA, PhSeBr, -20°.

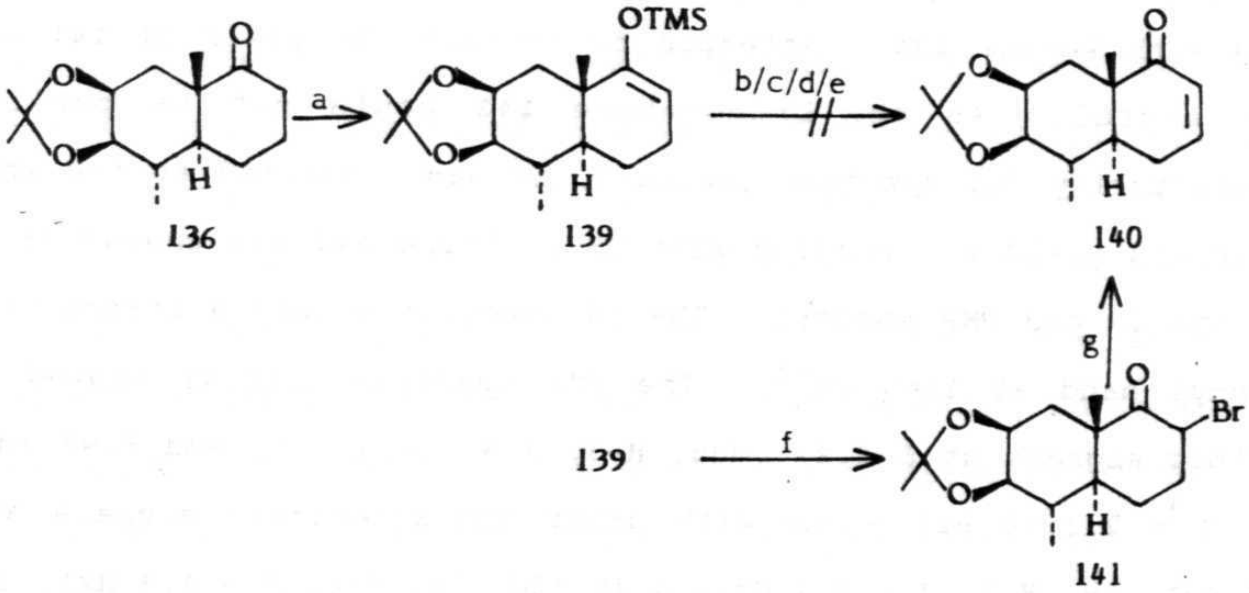
Tsuji[55] has reported the preparation of α,β-unsaturated carbonyl compounds from silyl enol ethers. To apply this methodology, ketone 136 was converted to the enol ether 139 using the procedure of Yamaguchi[56] with a modification in the workup (Scheme 17). Characterization of 139 was straightforward as the IR spectrum showed absence of the carbonyl band and presence of other characteristic bands (1640, 1380, 1240, 1220 and 1050 cm^{-1}). In the PMR spectrum, signals at δ 4.50 (t, 1H, H-2) and 0.18 (s, 9H, $-Si(CH_3)_3$) along with other characteristic signals are in support of the structure of 139. Enol ether 139 was subjected to

55. Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. Tetrahedron 1986, 42, 2971.

56. Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. Bull. Chem. Soc. Jpn. 1981, 54, 3229.

Tsuji's conditions for enone formation. Under both conditions (b and c of Scheme 17) no trace of enone was obtained; instead, only the saturated ketone **136** was isolated after usual workup. Trimethylsilyl enol ethers are also known to give α,β-unsaturated

SCHEME 17



Reagents and Conditions: (a) DBU, TMSCl, CH_2Cl_2, 40°, 24h; (b) dppe, diallyl carbonate, $Pd(OAc)_2$, CH_3CN, reflux; (c) dppe, allyl methyl carbonate, $Pd(OAc)_2$, CH_3CN, reflux; (d) $Pd(OAc)_2$, CH_3CN, reflux; (e) NBS, CCl_4, reflux; (f) NBS, THF, 0°; (g) DBU, benzene, reflux.

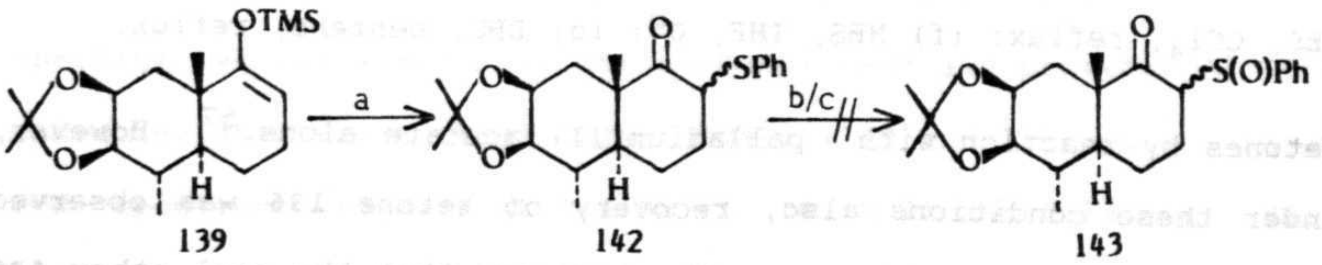
ketones by reaction with palladium(II) acetate alone.[57] However, under these conditions also, recovery of ketone **136** was observed after usual workup. These results indicate that the enol ether **139** is not undergoing any reaction, but getting hydrolyzed during water workup to give the ketone **136**.

Trimethylsilyl enol ethers are also known to give α-bromo-

57. Ito, Y.; Hirao, T.; Saelgusa, T. J. Org. Chem., 1978, **43**, 1011.

ketones with N-bromosuccinimide.[58] Under these conditions, enol ether **139** gave a complex mixture, which showed hydroxyl bands in the IR spectrum. This could be due to hydrolysis of the isopropylidene group in **139**. However, no attempt was made to purify this complex mixture. When a solution of the enol ether **139** in THF was reacted with NBS at 0^{o}, bromoketone **141** was obtained in low yield (31%) along with ketone **136**. Attempts to improve the yield of **141** were unsuccessful. As the bromoketone **141** could not be purified satisfactorily for spectral analysis, it was converted to the enone **140** in 67% yield by treating with DBU. Enone **140** was characterized from its IR and PMR spectra. The IR spectrum showed a strong enone carbonyl band at 1665 cm^{-1}. The PMR spectrum (Fig.4) showed two olefinic signals at δ 6.87 (ddd, H-3, J = 3,6,10 Hz) and 5.90 (ddd, H-2, J = 2,3,10 Hz) along with other characteristic signals at δ 4.28 (dt, 1H, H-7, J = 2,4 Hz), 3.48 (dd, 1H, H-6, J = 4,8 Hz), 1.59 (s, 2H, H-4), 1.50 and 1.35 (two singlets, 3H each, acetonide CH_3),

SCHEME 18



Reagents and Conditions: (a) PhSCl, CH_2Cl_2, -78^{o}; (b) $(n\text{-}Bu)_4NIO_4$, $CHCl_3$, reflux, (c) MCPBA, CH_2Cl_2, 0^{o}.

58. Blanco, L.; Amice, P.; Conia, J.M. Synthesis 1976, 194.

1.23 (s, 3H, 8a-CH_3), and 1.03 (d, 3H, 5-CH_3, J = 6 Hz).

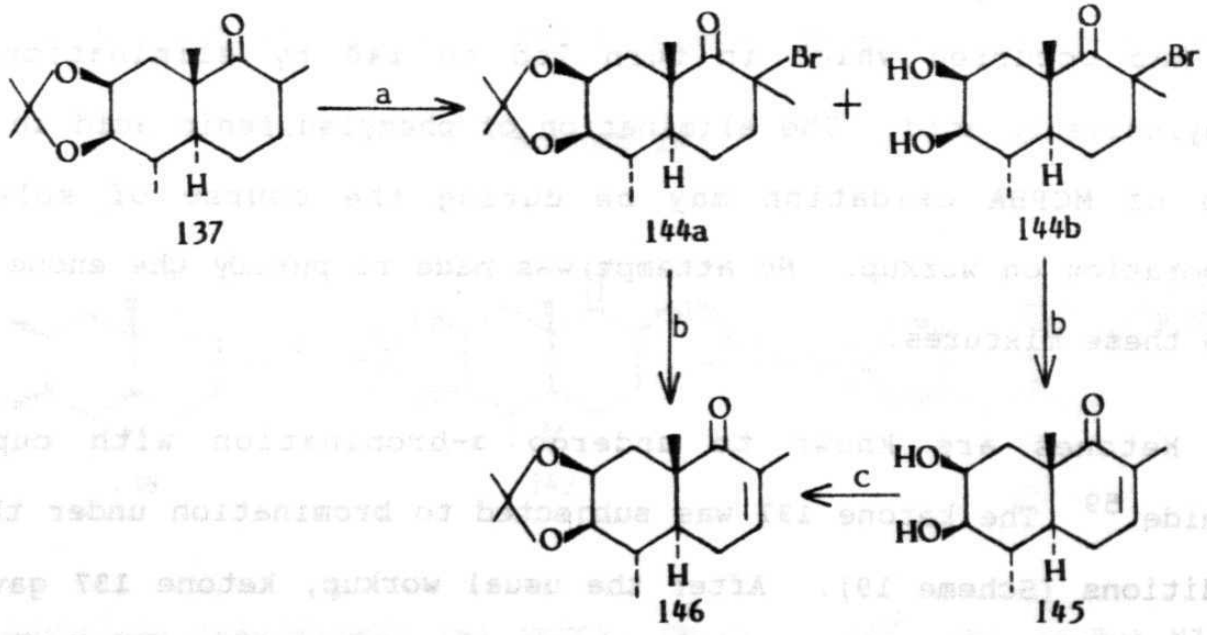
As the yield of **141** could not be improved, other methods were sought to achieve the same transformation (Scheme 18). Enol ether **139** was converted to the α-phenylsulfenyl ketone **142** in 91% yield. The gross structure of **142** was once again indicated by its IR and PMR spectral data summarized in the experimental section. In particular, the presence of aromatic protons at δ 7.46-7.14 (m, 5H) proved incisive. The stereochemistry of the phenylsulfenyl group was not established, as it gets destroyed during the enone formation. Attempts were made to oxidize the sulfide to sulfoxide, so as to eliminate phenylsulfenic acid to obtain the enone **140**. Oxidation of **142** with MCPBA or tetra-n-butylammonium periodate gave a complex mixture after usual workup. The IR spectrum of the crude mixture showed two carbonyl bands (1710 and 1680 cm^{-1}). This indicates that partial oxidation of the sulfide **142** to the sulfoxide **143** had occurred which in turn led to **140** by elimination of phenylsulfenic acid. The elimination of phenylsulfenic acid in the case of MCPBA oxidation may be during the course of solvent evaporation on workup. No attempt was made to purify the enone **140** from these mixtures.

Ketones are known to undergo α-bromination with cupric bromide.[59] The ketone **137** was subjected to bromination under these conditions (Scheme 19). After the usual workup, ketone **137** gave a mixture of two major bromo compounds. The IR spectrum of the crude α-brominated compounds showed hydroxyl band (3450 cm^{-1}) as well as

59. King, L.C.; Ostrum, G.K. J. Org. Chem. 1964, **29**, 3459.

bands due to gem-dimethyl group of the isopropylidene unit (1390 and 1380 cm^{-1}). The presence of a strong hydroxyl band could be due to hydrolysis of the isopropylidene unit by the hydrogen bromide evolved during bromination. Without separation of the bromodiol **144b** and the bromoacetonide **144a**, the crude mixture was subjected to dehydrobromination using DBU. The IR spectrum of the crude compound showed a sharp band due to enone carbonyl at 1665 cm^{-1} and also the hydroxyl band at 3400 cm^{-1}. Both the enones **145** and **146** could be easily separated on a silica gel column. The structure of **146** was in accordance with its spectral characteristics (IR, PMR (Fig.5), and MS). The IR spectrum showed a sharp enone carbonyl band at 1665 cm^{-1}. In the PMR spectrum, the olefinic proton appeared as a multiplet at δ 6.60-6.42. Finally, the mass spectrum with peaks at 264 (M^+) and 249 ($M-CH_3$) is in support of the structure of **146**. The

SCHEME 19

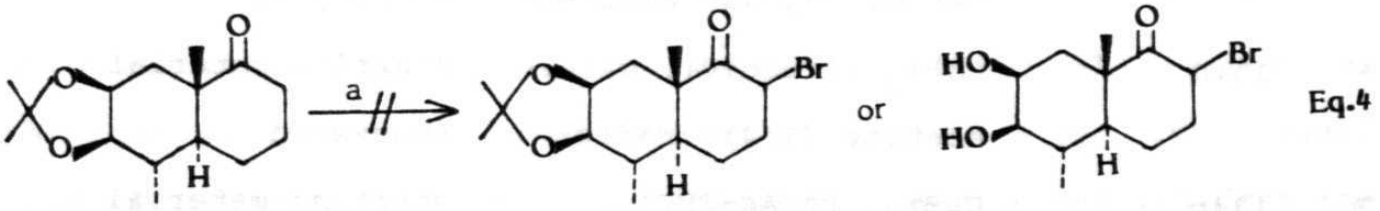


Reagents and Conditions: (a) $CuBr_2$, EtOAc-$CHCl_3$, reflux; (b) DBU, benzene, reflux; (c) acetone, $CuSO_4$, H_2SO_4, r.t.

diol-enone **145** could be easily reprotected as its acetonide by

applying the previously used methodology. The spectral data of this enone was identical to that of the enone **146** obtained from the dehydrobromination method. The overall yield of enone **146** obtained from the ketone **137** by this method was 72%.

Encouraged by these results, attempts were made to convert the ketone **136** to the enone **140** under similar conditions (Eq.4). Surprisingly, bromination of **136** with cupric bromide under identical conditions gave a complex mixture. The complex mixture may be due to mono- and dibromination along with hydrolysis of the acetonide group present in **136**. To avoid excess bromination, one equivalent of cupric bromide was used. Also, to prevent hydrolysis of the acetonide functionality, various modifications were tried (Table 1).



136 141 147

(a) $CuBr_2$, EtOAc-$CHCl_3$, reflux.

To quench the <u>in situ</u> formed hydrogen bromide an equivalent amount of potassium carbonate was added. Surprisingly, cupric bromide did not react with the ketone **136** in the presence of potassium carbonate. Similarly, in the presence of propylene oxide as the acid scavenger, the starting ketone was recovered unchanged. Cupric bromide also did not undergo any reduction as in the earlier reaction. However, when the reaction was performed in aq. acetone or in ethyl acetate-chloroform (entries 4 and 5 of Table 1) the aceto-

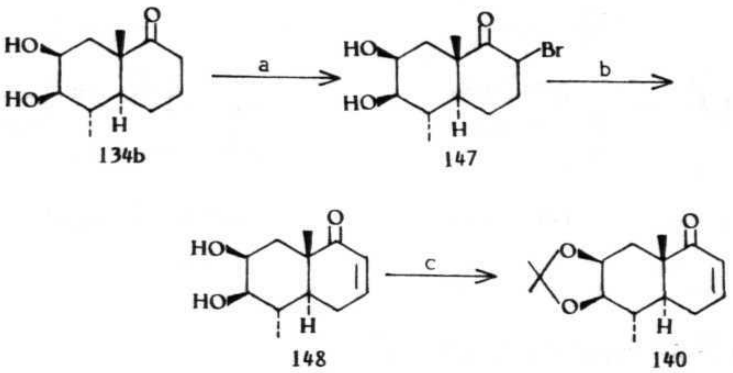
Table 1

S.No.	Substrate	Reaction Conditions	Result
1	**136**	$CuBr_2$, EtOAc-$CHCl_3$, reflux	complex mixture
2	**136**	$CuBr_2$, K_2CO_3, EtOAc-$CHCl_3$, reflux	starting material recovered
3	**136**	$CuBr_2$, propylene oxide, EtOAc-$CHCl_3$, reflux	starting material recovered
4	**136**	$CuBr_2$, water-acetone (1:2), reflux	acetonide group hydrolysed
5	**136**	$CuBr_2$, EtOAc-$CHCl_3$, reflux, N_2 gas bubbled	acetonide group hydrolysed
6	**134b**	$CuBr_2$ (2 equiv), water-acetone (1:2), reflux	starting material recovered
7	**134b**	$CuBr_2$, EtOAc-$CHCl_3$, reflux, N_2 gas stream	starting material recovered

nide group was cleaved. Under similar conditions, ketone **134b** did not undergo bromination (entries 6 and 7).

Fortunately, diol-ketone **134b** reacted with cupric bromide under normal conditions to give the crude bromo compound **147** (Scheme 20). The IR spectrum of crude **147** showed all the required bands (3400, 1720, 1450, 1040, and 710 cm^{-1}). Without further characterization, **147** was converted to the enone **148** using DBU. The structure of enone **148** is in accordance with its spectral data (IR and PMR) summarized in the experimental section.

SCHEME 20



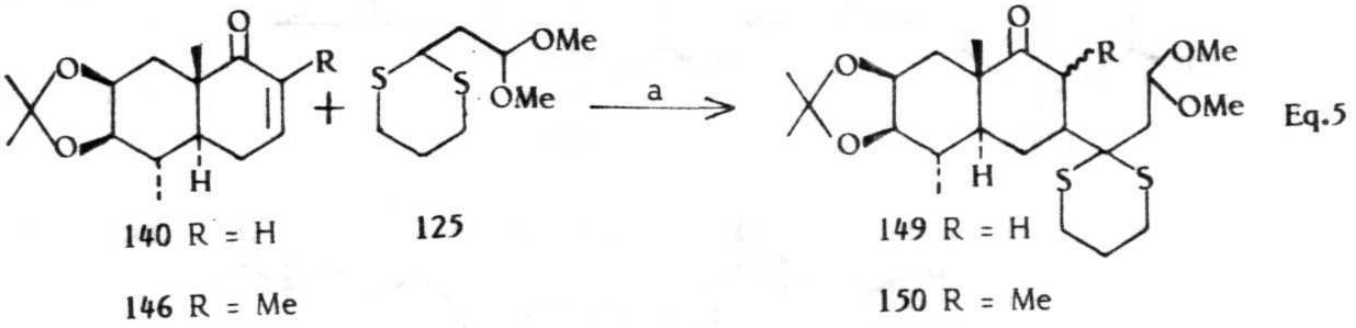
Reagents and Conditions: (a) $CuBr_2$ (2 equiv), EtOAc-$CHCl_3$, reflux; (b) DBU, benzene, reflux; (c) acetone, H_2SO_4, $CuSO_4$, r.t.

The diol unit of **148** could be readily protected in its acetonide form. Once again, the spectral data of this enone was identical with those of prepared earlier (Scheme 17). The overall yield of the enone **140** obtained by this methodology was 46% from the keto-diol **134b**.

At this stage, a differentially protected malonaldehyde derivative **125** was added in a Michael fashion to the enones **140** and **146** with a modification of Heathcock's procedure (Eq.5).[60] Although Heathcock's procedure worked for various cyclohexenones in our laboratory, enones **140** and **146** did not undergo Michael addition under these conditions. Assuming that the temperature (-78°) was too low for these enones, attempts were made at various

60. Rosen, T.; Tachner, M.J.; Thomas, J.A.; Heathcock, C.H. J. Org. Chem. 1985, **50**, 1190.

temperatures. The Michael addition did not take place at -78° or at -20° but at 0° Michael adducts were obtained in good yields.



Eq.5

140 R = H

146 R = Me

125

149 R = H

150 R = Me

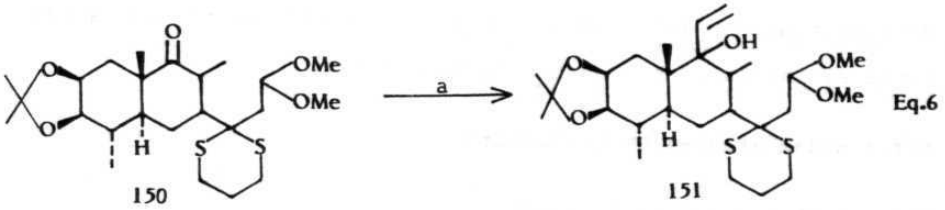
(a) n-BuLi, THF-HMPA (3:1), 0°, 7h.

In the case of enone **140**, attempts to trap the intermediate enolate by adding iodomethane so as to obtain **150** were unsuccessful.

The structures of **149** and **150** rest on their spectral data (IR and PMR). In the IR spectrum of **149**, a band at 1720 cm^{-1} confirmed the presence of a saturated carbonyl group. The PMR spectrum displayed characteristic signals at δ 4.62 (t, acetal proton), 1.46, 1.30, and 1.20 (s, 3H each, methyls of acetonide and C-8a), and 1.04 (d, 3H, 5-CH_3). The absence of the signals at δ 6.87 (ddd, 1H), and 5.90 (ddd, 1H) which are present in **140** gave a clear indication about the course of the addition reaction. Since the adduct was unstable, no attempt was made to obtain elemental analysis. Similarly, the structure of **150** was also in accordance with its spectral data (IR and PMR).

To generate a dienophile unit in **150**, attempts were made to add vinylmagnesium bromide to the carbonyl carbon (Eq.6). At room temperature, no addition of the Grigrand reagent to the ketone **150**

could be observed. In refluxing THF, Grignard reaction with a large



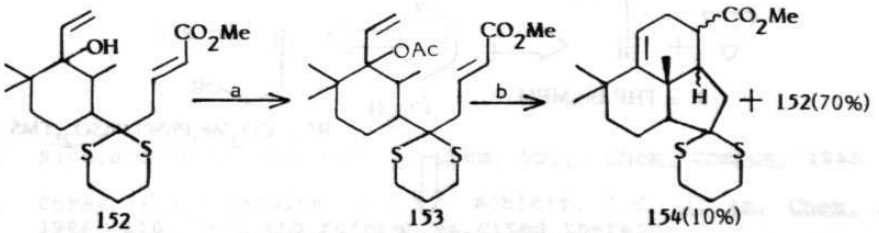
150 151 Eq.6

(a) vinylmagnesium bromide (10 fold excess), THF, reflux, 24h.

excess (10 fold) of vinylmagnesium bromide gave a crude product after usual workup, whose IR spectrum showed a strong hydroxyl band (3400 cm^{-1}) and a weak carbonyl band (1700 cm^{-1}). But the tlc of the product showed a complex mixture. Because of its complexity, no further attempt was made to purify the mixture and characterize the allylic alcohol **151**.

During the course of this work, it was found in our laboratory[48] that the allylic alcohol **152** does not undergo dehydration readily (Scheme 21). Similar results were anticipated with the allylic alcohol **151** as well. Sluggishness in the addition

SCHEME 21



152 153 154(10%)

Reagents and Conditions: (a) AcCl, DMAP, CH_2Cl_2, r.t; (b) Ph_3P, $Pd(OAc)_2$, toluene, reflux.

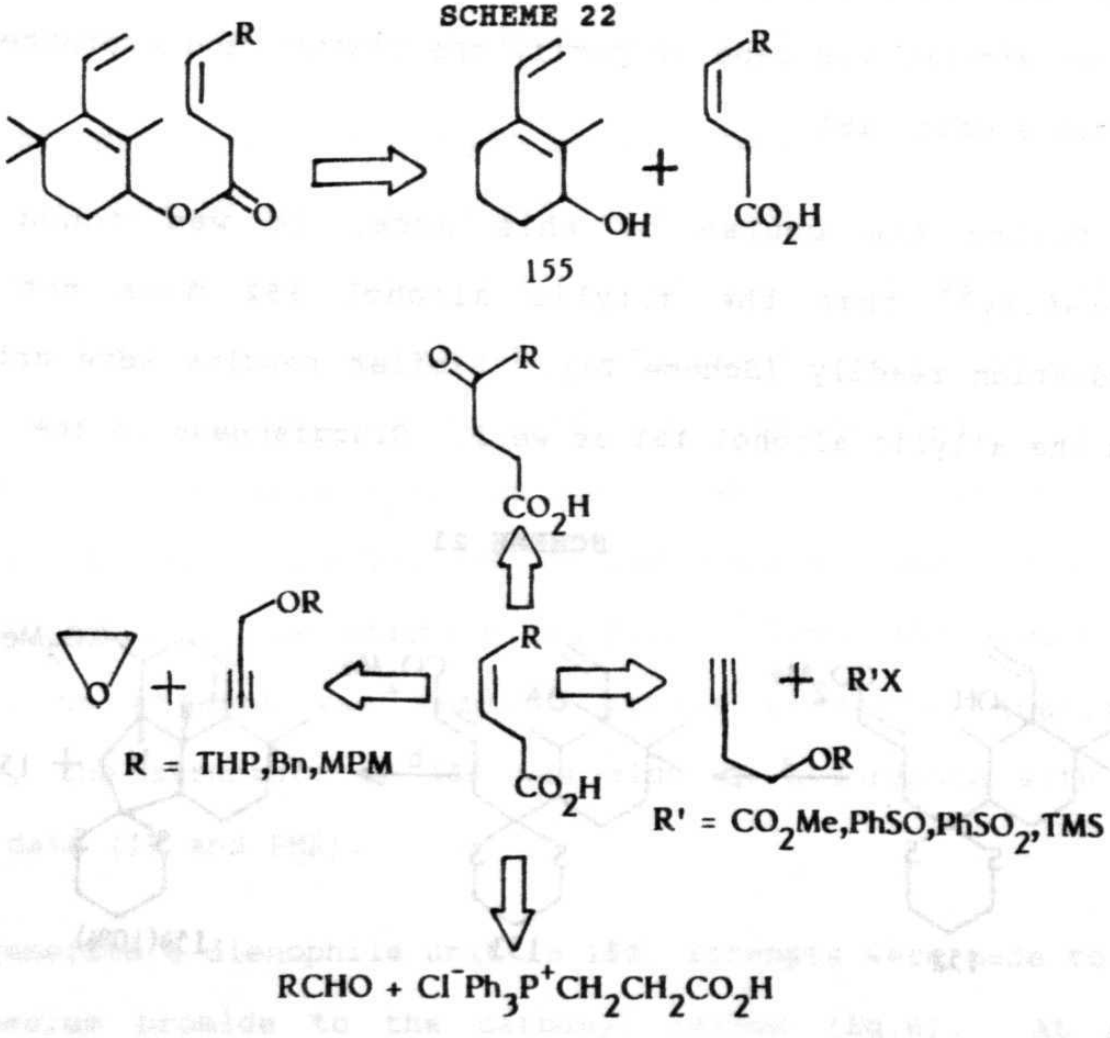
of vinylmagnesium bromide to ketone **150** and anticipation of difficulties in dehydration of **151** prompted us to set aside the total synthesis of bruceantin by this route.

III.2 Model Studies On Bruceantin

III.2.1 IMDA Reaction Approach:

Without many changes in the strategy, attempts were made to prepare a suitable Diels-Alder intermediate equivalent to **152** (Scheme 22). As shown in Scheme 22, the IMDA reaction precursor can be prepared from the diene alcohol **155** and a five carbon acid con-

SCHEME 22

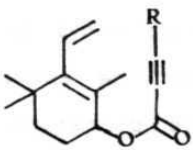


taining the dienophile unit. As a perusal of literature revealed that the diene alcohol **155** was easily prepared from α-ionone in four

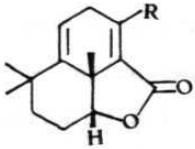
steps,[61] attempts were made to prepare the requisite acid unit.

At this juncture, it is appropriate to examine in brief the reactivity of diene unit in alcohol **155** with various dienophiles. In the main, alcohol **155** was esterified with different α,β-unsaturated acids for the synthesis of forskolin[62] and its precursors (Chart 4). Ester **156a** underwent IMDA reaction under mild conditions (0.44M chloroform solution, 23°, 30h) to give the tricyclic compound **157a** in good yield (72%).[62] Similarly, thermolysis of **156b**[61] (benzene, sealed tube, 140°, 24h) gave the tricyclic compound **157b** in 92% yield. However, esters **158a-c**[63] required longer times (3 to

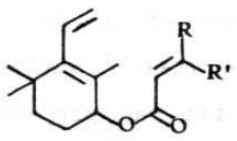
CHART 4



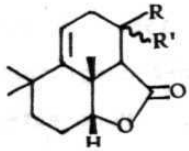
156a R = Ts
156b R = TMS



157a R = Ts
157b R = TMS



158a R = Me, R' = CHO
158b R = H, R' = CO_2Et
158c R = CO_2Et, R' = H



159a R = Me, R' = CHO
159b R = H, R' = CO_2Et
159c R = CO_2Et, R' = H

61. Nicolaou, K.C.; Li, W.S. J. Chem. Soc., Chem. Commun. 1985, 421.

62. Corey, E.J.; Jardine, P.D.S.; Rohloff, J.C. J. Am. Chem. Soc. 1988, **110**, 3672 and references cited therein.

63. Ziegler, F.E.; Jaynes, B.H.; Saindane, M.T. Tetrahedron Lett. 1985, **26**, 3307; Jenkins, P.R.; Menear, K.A.; Barraclough, P.; Nobbs, M.S. J. Chem. Soc., Chem. Commun. 1984, 1423.

6 days) at higher temperature (140-160°) for IMDA reaction and the yields were also lower [**159a** (47%), **159b** (56%), and **159c** (48%)].

The above results indicate that the presence of sulfones or silanes in the dienophile increases the feasibility as well as the yield of the IMDA reaction. Also, the presence of carbonyl functionality on the dienophile favours the IMDA reaction but under vigorous conditions and with lower yields. Moreover, the triple bond in **156a-b** seems to be a better dienophile than the double bond in **158a-c**.

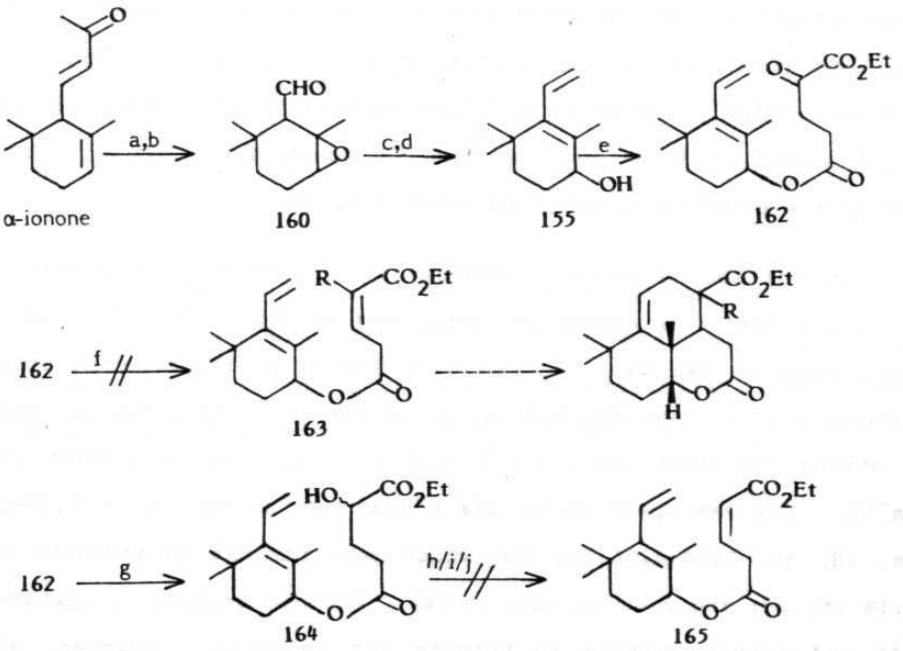
Initially, attempts were focussed on the synthesis of a five carbon unit with an appropriate functionality suitable for generation of the double bond after esterifying with the diene alcohol **155**. A perusal of the literature showed that ethyl 5-hydrogen-2-oxoglutarate (**161**)[64] would be suitable for the above purpose. Mono-ester **161** was prepared via literature procedure. Diene alcohol **155** was prepared from α-ionone by following Nicolaou's route (Scheme 23).[61]

Epoxidation of the isolated double bond in α-ionone, followed by ozonolysis gave the epoxy aldehyde **160**. Treatment of **160** with DBU converted the epoxide to an allylic alcohol. The aldehyde unit was subjected to methylene Wittig reaction to give the diene alcohol **155**. Structure of the alcohol **155** is in accordance with the spectral data (IR and PMR) summarized in the experimental section.

64. Domagala, J.M. Tetrahedron Lett. 1980, **21**, 4997.

The alcohol **155** was esterified with the keto acid **161** by following Nicolaou's esterification procedure to give the ester **162**.

SCHEME 23



Reagents and Conditions: (a) MCPBA, CH_2Cl_2, -78 to 0°, 12h; (b) O_3, CH_2Cl_2-MeOH, -78°, Me_2S; (c) DBU, 0-25°; (d) $MeP^+Ph_3I^-$, n-BuLi, THF, 0°; (e) **161**, DCC, DMAP, CH_2Cl_2, 0-25°; (f) isopropenyl acetate, p-TsOH, r.t.; (g) $NaBH_4$, EtOH, 0-20°; (h) $CuSO_4$, benzene, reflux; (i) p-TsOH, C_6H_6, reflux; (j) pyridine, $POCl_3$, 0-20°.

The IR spectrum of **162** showed two carbonyl bands at 1800 and 1725 cm^{-1}. The PMR spectrum showed vinylic protons at δ 6.20 (dd, 1H, J = 11,18 Hz), 5.30 (m, 2H), and 5.04 (dd, 1H, J = 3,18 Hz), ethyl ester

signals at δ 4.34 (q, 2H), 1.40 (t, 3H) and methyl signals at δ 1.68, 1.02, and 1.00, each integrating for three protons.

To generate a double bond in the side chain of **162**, two methods were attempted. In the first method, attempts were made to convert the keto group into an enol acetate by treating **162** with isopropenyl acetate in the presence of p-toluenesulfonic acid. However, after usual workup, tlc as well as the IR spectrum of crude compound showed the presence of starting keto ester **162**.

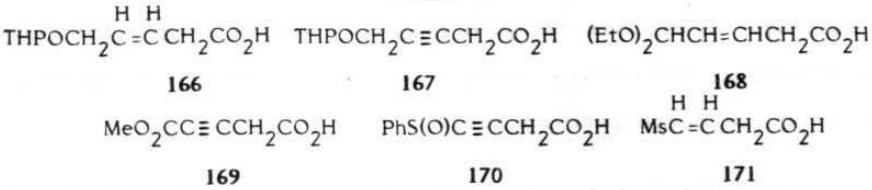
In the second method, attempts were made to reduce the keto group and then dehydrate the resulting alcohol. Reduction of the keto group in **162** was achieved with sodium borohydride in ethanol between 0-5^{o} to give the hydroxy ester **164** whose IR spectrum showed a strong O-H band (3400 cm^{-1}) and a single carbonyl band (1710 cm^{-1}). The PMR spectrum of **164** showed two signals at δ 3.00-2.76 (m, 2H) and 2.60-2.34 (m, 2H) which were present as triplets at δ 3.18 (t, 2H) and 2.68 (t, 2H) in **162**. For dehydration, a mixture of **164** and copper sulfate in benzene was refluxed. However, after usual workup, only the starting alcohol was recovered. Other methods of dehydration like refluxing in benzene with p-toluenesulfonic acid or phosphorous oxychloride/pyridine between 0-20^{o} did not lead to the formation of **165**. Instead, an intractabl mixture resulted.

As the double bond could not be readily generated after esterifying with the diene alcohol **155**, attempts were made to prepare an acid with the double bond, suitable for IMDA reaction. To begin with, attempts were focussed on the preparation of the

acids **166**, **167**, **168**, **169**, **170**, and **171** (Chart 5).

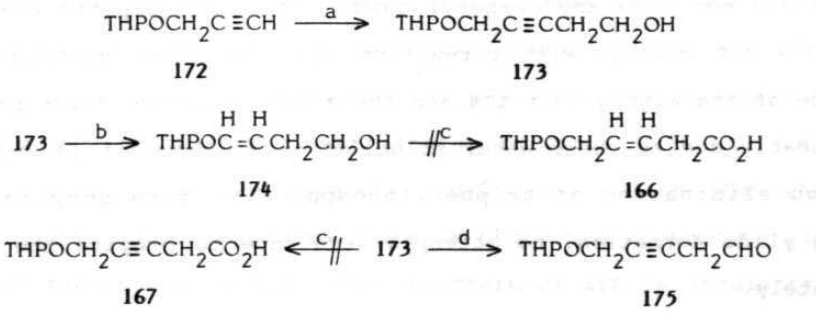
To synthesize acids **166** and **167**, alcohol **173** was prepared from

CHART 5



the THP ether **172** by following the literature procedure (Scheme 24).[65] Again, its partial hydrogenation was performed, via literature procedure, to give **174**.[65] Surprisingly, standard procedures like PDC/DMF or silver(II) oxide/DMSO oxidations did not

SCHEME 24



Reagents and Conditions: (a) $NaNH_2$, ethylene oxide, THF, -40^{o}; (b) Lindlar catalyst, benzene, 28 psi H_2, 1h, (c) PDC, DMF, r.t. 15h; (d) AgO, DMSO, 90^{o}, 16h.

65. Borch, R.F.; Evans, A.J.; Wide, J.J. J. Am. Chem. Soc. 1977, **99**, 1612.

work on **173** to give the acid **167** even after prolonged reaction times. Although silver(II) oxide oxidation proceeded to the aldehyde **175**, further oxidation did not take place even with excess of the oxide. Similarly, alcohol **174** also did not react with PDC under standard conditions to give the acid **166**. In all the three cases, starting materials were recovered during unsuccessful oxidation to the corresponding acids.

The acetal acid **168** was sought to be prepared from 2,2-diethoxyacetaldehye via a Wittig reaction. The salt **176** is known to undergo Wittig reaction under specific conditions.[66] Under identical conditions, a solution of the Wittig salt **176** and 2,2-diethoxyacetaldehyde in THF-DMSO (1:1) was added to sodium hydride at 0^{o} (Eq.7). After usual workup, the IR spectrum of the crude substance did not show any carbonyl band. It is anticipated that the salt did not undergo Wittig reaction with the above acetaldehyde. Absence of the Wittig salt **176** and the aldehyde in the crude product is probably due to their water solubility. As the salt is known to undergo elimination of triphenylphosphine to form acrylic acid during ylide formation, no attempts were made to prepare the ylide separately.

$$(EtO)_2CHCHO + Cl^{-}Ph_3P^{+}CH_2CH_2CO_2H \xrightarrow{a} (EtO)_2CHCH{=}CHCH_2CO_2H \qquad \textbf{Eq.7}$$

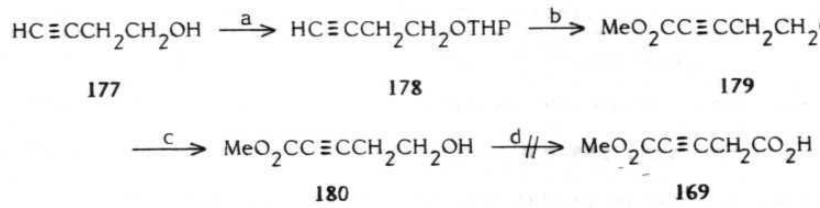
176 **168**

(a) NaH, THF-DMSO (1:1), 0-25^{o}, 15h.

66. Corey, H.S. Jr.; McCormick, J.R.D.; Swensen, W.E. J. Am. Chem. Soc. 1964, **86**, 1884.

Attempted synthesis of the acid **169** commenced with 3-butyn-1-ol **177**[67] which was converted to its THP ether **178** by applying the reported procedure (Scheme 25).[68] The anion of **178** was quenched

SCHEME 25



177 178 179 180 169

Reagents and Conditions: (a) Dihydropyran, p-TsOH, CH_2Cl_2, r.t.; (b) n-BuLi, $ClCO_2Me$, THF, -78°; (c) 1M HCl, THF, r.t., 2h; (d) chromic acid, acetone-water, 0-10°.

with methyl chloroformate to give the ester **179**. The structure of **179** was based on its IR and PMR spectra. Absence of acetylenic C-H band (3300 cm^{-1}) and presence of strong bands at 2190 and 1720 cm^{-1} are in support of the structure of **179**. The PMR spectrum showed signals at δ 4.62 (br s, 1H, acetal proton), 3.76 (s, 3H, ester methyl) along with other signals. Hydrolysis of the THP ether in **179** could be easily performed with 1M hydrochloric acid to give the alcohol **180** in high yield. The structure of **180** is straightforward from its spectral data (IR and PMR). A strong O-H band at 3400 cm^{-1} along with the previously existing characteristic bands in the IR spectrum and a simplified PMR spectrum with three characteristic

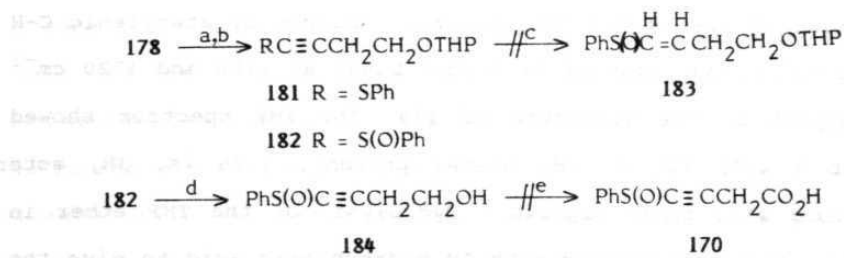
67. Gerand, F.; Miginiac, Ph. Syn. Commun. 1976, **6**, 461.
68. Negishi, E.; Chiu, K.-W. J. Org. Chem. 1976, **41**, 3484.

peaks at δ 3.82 (t, 2H, $-\underline{CH_2}OH$), 3.78 (s, 3H, $-CO_2CH_3$), and 2.62 (t, 2H, $-\underline{CH_2}CH_2OH$) are in support of the structure of **180**. The overall yield of the hydroxy ester **180** is 33% from the alcohol **177**. The corresponding ethyl ester was prepared from alcohol **177** in two steps, with an overall yield of 21% by Jones.[69]

In view of the cyclization of **180** to a six-membered lactone upon partial hydrogenation,[70] no attempt was made to hydrogenate the hydroxy ester **180**. While PDC oxidation of the hydroxy ester **180** in DMF to prepare the acid **169** gave back the starting material, chromic acid or silver(II) oxide oxidations gave a complex mixture.

Keeping the activation of the dienophile in mind, and to circumvent the cyclization of **180** upon partial hydrogenation, phenylsulfinyl and phenylsulfonyl groups were chosen as alternatives

SCHEME 26



Reagents and Conditions: (a) n-BuLi, THF, PhSSPh, -20^{o}; (b) MCPBA, CH_2Cl_2, 0^{o}, 1h; (c) Lindlar catalyst, 40 psi H_2, 2h; (d) 1M HCl, THF, r.t., 10h; (e) chromic acid, acetone-water, 10^{o}, 2h.

69. Jones, E.R.H.; Shen, T.Y.; Whiting, M.C. J. Chem. Soc. 1950, 2

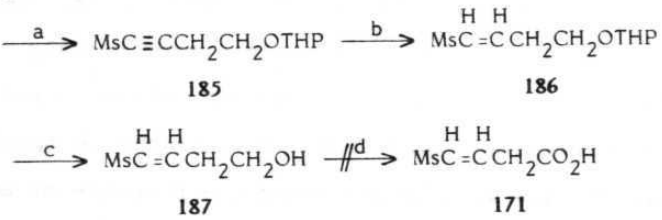
70. Haynes, L.J.; Jones, E.R.H. J. Chem. Soc. 1946, 954.

to the carbomethoxy group present in **180**. Initially, attempts were made to prepare the acid **170**, starting from the acetylenic ether **178** (Scheme 26).

The anion of **178** was reacted with diphenyl disulfide to give the thio compound **181**. The structure of **181** was supported by its IR and PMR data, summarized in the experimental section. In particular, the absence of an acetylenic C-H band in the IR spectrum and presence of phenyl protons at δ 7.56-7.16 (m, 5H) in the PMR spectrum proved the structure of **181** unambiguously. Oxidation of **181** with MCPBA gave the sulfoxide **182** almost quantitatively. A strong acetylenic C-C band (2190 cm^{-1}) in the IR spectrum which was very weak in **180** clearly indicated the presence of sulfoxide group on the acetylenic carbon. A band at 1080 cm^{-1} due to S=O was also present in support of the structure of **182**. With Lindlar catalyst, **182** could not be hydrogenated to give **183**. Only the starting material was recovered unchanged. This may be due to poisoning of the catalyst by sulfur. Hydrolysis of the THP ether group in **182** was achieved with 1M hydrochloric acid in THF. Once again, the structure of alcohol **184** is in accordance with its spectral data (IR and PMR). Hydroxyl absorption at 3400 cm^{-1} and acetylenic C-C band at 2190 cm^{-1} in its IR spectrum, and aromatic protons at δ 7.88-7.44 (m, 5H), and methylene protons at δ 3.76 (t, 2H), 2.66 (t, 2H) in the PMR spectrum were fully in agreement with the structure. Under Jones oxidation conditions, alcohol **184** could not be oxidized to the acid **170**. After usual workup, only a small amount of starting alcohol was recovered.

Similarly, attempts were made to prepare the acid **171**, starting from the ether **178** (Scheme 27). The anion of the acetylenic ether **178** was reacted with methanesulfonyl chloride to give the sulfone **185**, whose structure was fully secured by a strong acetylenic band at 2200 cm^{-1} in its IR spectrum and the presence of a methyl signal at δ 3.18 (s, 3H) in its PMR spectrum. Unlike sulfoxide **182**, **185**

SCHEME 27



Reagents and Conditions: (a) n-BuLi, THF, -15°, MsCl; (b) Lindlar catalyst, benzene, 40 psi H_2, 1.5h; (c) 5M HCl, THF, r.t., 10h; (d) chromic acid, acetone-water, 10°, 0.5h.

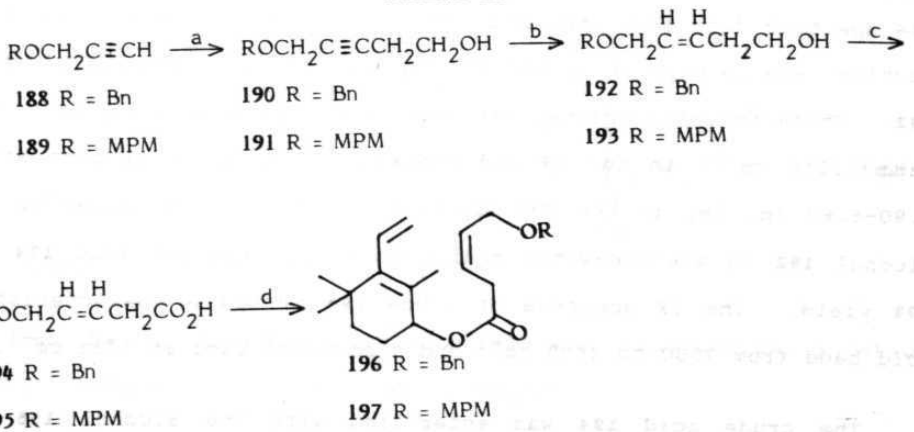
could be readily partially hydrogenated with Lindlar catalyst to give the cis-olefin **186**. The structure of **186** follows from its spectral data. The acetylenic C-C band was absent in the IR spectrum and two olefinic protons at δ 6.56-6.24 (m, 2H) were present in the PMR spectrum. Hydrolysis of THP ether in **186** was achieved with 5M hydrochloric acid. A hydroxyl band at 3450 cm^{-1} in the IR spectrum and a simplified PMR spectrum with olefinic signals at δ 6.58-6.34 (m, 2H) and a methyl signal at δ 3.02 (s, 3H) are in support of the structure of the alcohol **187**. Once again, alcohol **187** could not be oxidized to the acid **171** using chromic acid. After

usual workup, the crude residue showed neither the acid **171** nor the starting alcohol **187**.

When the attempts to make activated dienophile acids failed, attention was directed to prepare unactivated dienophile acids, and activate them after esterification with the diene alcohol **155**.

The alcohol **190** was synthesized starting from the ether **188** by applying the procedure[65] used for the preparation of alcohol **173** with a modification (Scheme 28). The ether **188** was obtained from propargyl alcohol by following the literature procedure.[71] Acetylenic ether **188** was reacted with ethylmagnesium bromide and

SCHEME 28



Reagents and Conditions: (a) EtMgBr, ethylene oxide, THF-Et_2O, -20°; (b) Lindlar catalyst, 40 psi H_2, benzene, (c) chromic acid, acetone-water, 5-10°, 0.5h; (d) **155**, DCC, DMAP, CH_2Cl_2, 0-25°, 12h.

then quenched with ethylene oxide to give the alcohol **190** in 61%

71. Vontanyan, R.S.; Kazaryan, Zh.V.; Kucherov, V.F. Arm. Khim. Zh. 1974, **27**, 295.

yield with 64% conversion of **188**. The structure of alcohol **190** was fully in accordance with its spectral data (IR, PMR, and CMR). Absence of the acetylenic C-H band and presence of a strong O-H band (3375 cm^{-1}) and a weak acetylenic C-C band (2210 cm^{-1}) are among the characteristic bands in the IR spectrum. The PMR spectrum of **190** consists of signals at δ 7.33 (s, 5H, Ph), 4.57 (s, 2H, $Ph\underline{CH_2}$-), 4.16 (br s, 2H, $-OCH_2C{\equiv}C-$), 3.72 (t, 2H, $-\underline{CH_2}OH$) and 3.61-3.37 (m, 2H, $-\underline{CH_2}CH_2OH$). Also, a ten line CMR spectrum is in support of the structure of alcohol **190**. Partial hydrogenation of acetylenic alcohol **190** could be achieved with Lindlar catalyst in a Paar hydrogenation flask at 40 psi. It is important to note that the benzyl ether was unaffected under these hydrogenation conditions. The spectral data (IR, PMR, and CMR) summarized in the experimental section are in support of the structure of the hydrogenated alcohol **192**. Characteristic changes are absence of the weak acetylenic C-C band (2210 cm^{-1}) in the IR and presence of olefinic protons at δ 6.80-6.60 (m, 2H) in the PMR spectrum. Chromic acid oxidation of alcohol **192** in acetone-water medium gave the required acid **194** in 49% yield. The IR spectrum of crude **194** showed a characteristic acid band from 3500 to 2600 cm^{-1} and a carbonyl band at 1725 cm^{-1}.

The crude acid **194** was esterified with the alcohol **155** by applying the previous methodology (Scheme 23) to give the ester **196**. The IR spectrum of **196** showed a strong carbonyl band at 1725 cm^{-1}. In the PMR spectrum all the proton signals of alcohol **155** and the acid **194** were retained without much changes in the chemical shift. The ester **196** also gave satisfactory elemental analysis.

Following the same sequence delineated above, the p-

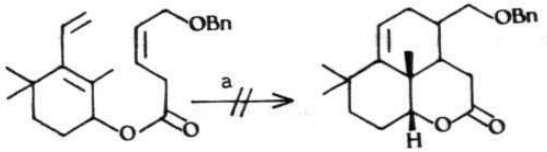
methoxybenzyl ether **189** was converted to the ester **197**. The starting material, the propargyl ether **189**, was prepared from propargyl bromide in 91% yield (Eq.8).

$$HC{\equiv}CCH_2Br + p\text{-}MeOC_6H_4CH_2OH \xrightarrow{a} HC{\equiv}CCH_2OMPM \qquad \textbf{Eq.8}$$

189

(a) NaH, THF, 60°, 1h.

Initially, the IMDA reaction was attempted on the ester **196** (Eq.9). As both the diene and dienophile are unactivated towards IMDA reaction, thermolysis of **196** was performed at high temperature (230°, xylene, sealed tube, 10h). After usual workup, only partial decomposition of the starting ester was noticed. However, no IMDA adduct **198** was found.



Eq.9

196 **198**

(a) xylene, 230°, sealed tube, 10h.

As the thermal IMDA reaction of **196** was unsuccessful, a cation radical induced IMDA reaction was attempted.

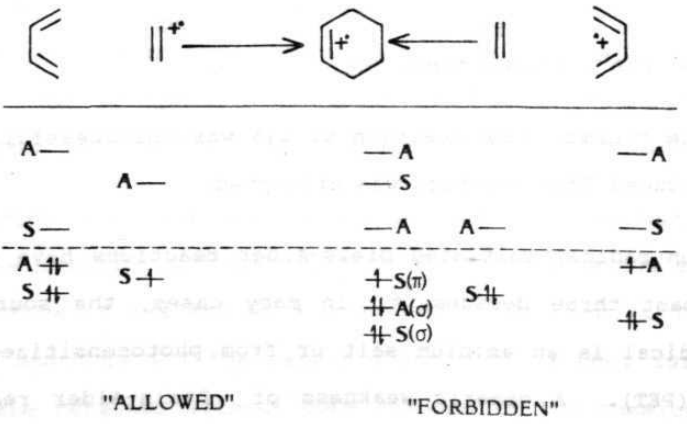
Cation radical initiated Diels-Alder reactions have been known for the past three decades.[72] In many cases, the source of the cation radical is an aminium salt or from photosensitized electron transfer (PET). A generic weakness of Diels-Alder reactions is that they are typically not efficient unless the dienophile is

72. Bauld, N.L. Tetrahedron 1989, **45**, 5307.

substantially electron deficient or vice versa with respect to its counter part, the diene. Ionization to the cation radical state is an effective and direct remedy for the absence of electron deficiency in the dienophile unit.

Bauld and co-workers[73] in their early studies on the cation radical Diels-Alder reaction developed theoretical insights into important details of the reaction path, such as concerted versus stepwise nature of the reaction and the preferred reaction stereochemistry. According to their orbital correlation diagrams, two distinct pathways exist for the cation radical Diels-Alder reactions. The mechanism involving the cation radical component in the dienophilic role is classified as a [4+1] cycloaddition and is formally symmetry allowed (Scheme 29). The alternate mode, involving the cation radical in the dienic role, classified as a

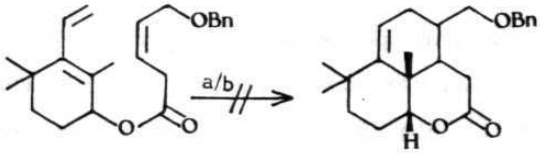
SCHEME 29



73. Bauld, N.L.; Bellville, D.J.; Chelsky, R.; Green, G. J. Am. Chem. Soc. 1983, **105**, 2378.

[3+2] cycloaddition, is formally symmetry forbidden. In any case, both types of Diels-Alder cycloadditions, normal and role reversed, have been identified and both are extremely rapid.

The general nature of the cation radical Diels-Alder reaction prompted us to apply it to the ester **196**. Initially, tris(4-bromophenyl)aminium hexachloroantimonate was used as a cation radical source. Recently, Bauld[74] reported an intermolecuar Diels-Alder reaction using the above mentioned cation radical source. Ester **196** was subjected to the IMDA reaction under identical conditions (Eq.10). After usual workup, tlc of the crude reaction



Eq.10

196 198

(a) $(p\text{-}BrC_6H_4)_3N^+SbCl_6^-$, CH_2Cl_2, 0^o, 0.5h; (b) DCN, CH_3CN, h , r.t., 8h.

mixture showed a complex mixture. No attempts were made to isolate any product.

The relative mildness of the PET conditions is known to make possible a cleaner and more efficient Diels-Alder cycloaddition of a number of simple hydrocarbon dienes.[72] As an alternative cation radical source instead of the above mentioned aminium salt, PET method was used with 1,4-dicyanonaphthalene (DCN) as a sensitizer. A solution of the ester **196** (0.007M) in acetonitrile was irradiated

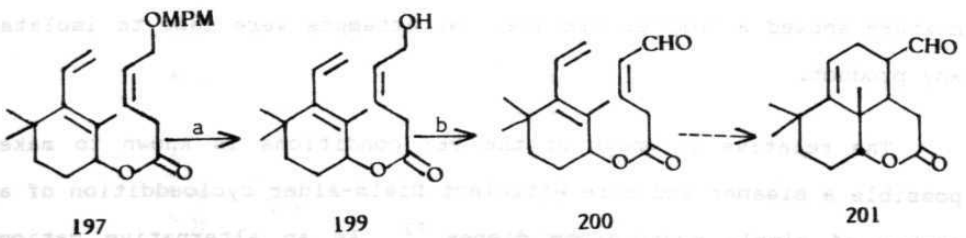
74. Harirchian, B.; Bauld, N.L. J. Am. Chem. Soc. 1989, **111**, 1826.

for 8h without removal of air from the solvent. The irradiation was carried out in an immersion well type photoreactor using a 125-W mercury vapour lamp, surrounded by a Pyrex water jacket. After evaporation of the solvent, chromatography of the crude mixture gave back the starting ester **196**. No cyclized product **198** was obtined.

It is likely that under these conditions, the cation radical may be forming from the diene unit (symmetry forbidden), which in turn may not be reactive towards the dienophile. Work is under way to generate a cation radical from the dienophile unit (symmetry allowed).

To activate the dienophile unit present in ester **197**, it was planned to cleave the MPM ether and to oxidize the thus formed alcohol (Scheme 30). DDQ is known to cleave MPM ethers.[75] Using this reagent, MPM ether **197** was cleaved to give the alcohol **199**. Conditions for optimum yield (60%) of **199** were addition of 1.2

SCHEME 30



197 **199** **200** **201**

Reagents and Conditions: (a) DDQ, wet dichloromethane, r.t., 1h; (b) PCC, NaOAc, CH_2Cl_2, r.t., 1h.

75. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. Tetrahedron Lett. 1982, **23**, 885.

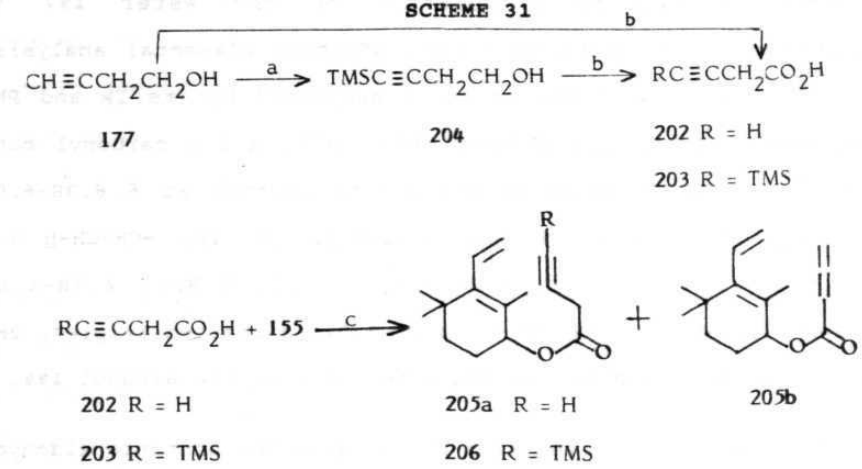
equivalents of DDQ to a solution of the ester **197** in dichloromethane. In addition to satisfactory elemental analysis, the structure of alcohol **199** is fully supported by its IR and PMR spectral data. A strong O-H band (3400 cm^{-1}) and a carbonyl band (1725 cm^{-1}) in the IR spectrum and proton signals at δ 6.38-6.00 (dd, 1H, -$\underline{CH}$=CH_2, J = 12,18 Hz), 5.92-5.68 (m, 2H, -CH=CH-$\underline{H}$ and -CHO-), 5.16-4.86 (dd, 1H, -CH=$\underline{CH}$-H, J = 3,18 Hz), 4.38-4.08 (distorted triplet, 2H, -$OCOCH_2$-), 3.26-3.04 (distorted triplet, 2H, -$\underline{CH_2}$OH) in the PMR spectrum are characteristic of the alcohol **199**.

Alcohol **199** was oxidized with PCC to give the unstable aldehyde **200** in poor yield (16%). The IR spectrum of this compound showed two well separated carbonyl bands (1720 and 1680 cm^{-1}) due to ester and aldehyde carbonyls. However, a satisfactory PMR spectrum of this compound could not be obtained because of some minor impurities present in and also because of its instability. Other mild oxidation methods, like manganese dioxide oxidation or Swern oxidation did not improve the yield of the aldehyde **200**. The IMDA reaction of **200** could not be carried out because of its instability and poor yield of formation.

To study the IMDA reaction with the dienophile unit being a four carbon acetylene, acids **202** and **203** were prepared (Scheme 31). While acid **202** was prepared by following the literature procedure,[76] acid **203** was prepared from the TMS alcohol **204** by chromic acid oxidation in 54% yield (Scheme 31). The structure of acid **203**

76. Heilbron, S.I.; Jones, E.R.H.; Sondheimer, F. J. Chem. Soc. 1949, 604.

SCHEME 31



Reagents and Conditions: (a) (i) EtMgBr, THF-Et_2O, TMSCl, -20°; (ii) H^+; (b) chromic acid, acetone-water, 5-10°, 0.5h; (c) DCC, DMAP, CH_2Cl_2, 0-25°, 12-15h.

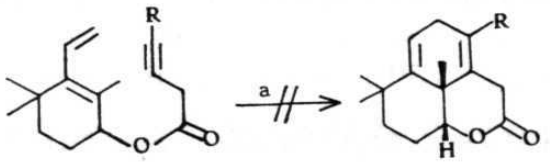
was fully in agreement with its spectral data (IR and PMR).

Acids **202** and **203** were esterified with the alcohol **155** by using the previous methodology to give the esters **205a** and **206**. Acid **202** gave the allenic ester **205b** as a minor product. The structure of both the isomeric esters **205a** and **205b** are in accordance with their IR and PMR spectral data. Ester **205a** showed a strong acetylenic C-C band (2150 cm^{-1}) and a carbonyl band (1720 cm^{-1}) in the IR spectrum. Proton signals at δ 6.18 (dd, 1H, -$\underline{CH}$=CH_2, J = 12,18 Hz), 5.01 (dd, 1H, -CH=$\underline{CH}$-H, J = 3,18 Hz), 3.48 (s, 2H, -CH_2COO-), 2.28 (s, 2H, -C≡CH) are among the characteristic signals in the PMR spectrum. In the case of allenic ester **205b**, presence of two strong allenic C-C bands (1970 and 1940 cm^{-1}) in the IR spectrum, and absence of the

methylene signal at δ 3.48 (s, 2H) and presence of two signals at δ 5.40-4.90 (m, 4H, out of which two are from terminal allenic protons) and δ 3.32 (s, 1H, -CHCOO-) in the PMR spectrum are strongly in support of its structure.

Similarly, ester **206** was fully characterized by its IR and PMR spectral data.

Initially, ester **205a** was subjected to IMDA reaction under normal conditions (benzene, 140°, sealed tube) for one day (Eq.11). Under these conditions, the starting material was recovered unchanged. Thermolysis of **205a** at 180° also gave back the starting material. When the thermolysis of **205a** was performed under vigorous conditions (xylene, 220°, sealed tube, 24h), some of the starting ester decomposed, without formation of the IMDA adduct **207**.



Eq. 11

205a R = H

206 R = TMS

207 R = H or TMS

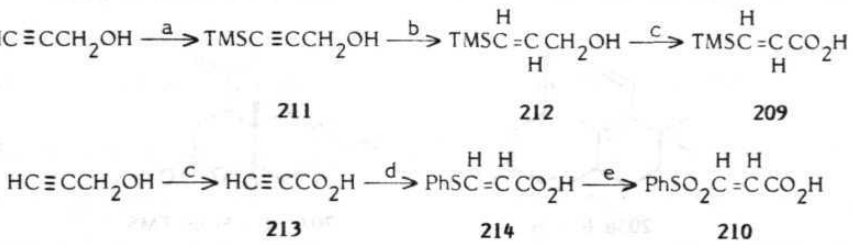
(a) xylene, sealed tube, 220°, 24h.

Next, our attention was focussed on the IMDA reaction of ester **206**. Nikolaou,[61] in his synthesis of a forskolin precursor, reported that substitution of a silicon atom on the dienophile unit could enhance its reactivity in the Diels-Alder reaction. Based on this, when the ester **206** was subjected to thermolysis (benzene, 180°, sealed tube, 28h), only the starting compound was recovered

without any IMDA adduct formation. This indicates that mere silico ativation of the dienophile is insufficient. Under more vigorou thermolysis conditions (xylene, 220°, sealed tube, 17h), some of th starting ester decomposed without any IMDA adduct formation.

It is known from the literature[77] that five-membered lactone can be homologated to six-membered lactones. As the attempts t form six-membered lactones via IMDA reaction were unsuccessful studies were diverted towards the formation of five-membere lactones. The advantage in this methodology is that both termin of the dienophile can be activated. Three α,β-unsaturated acid (**208**, **209**, and **210**) having on the β-carbon an unreactive substituen

SCHEME 32

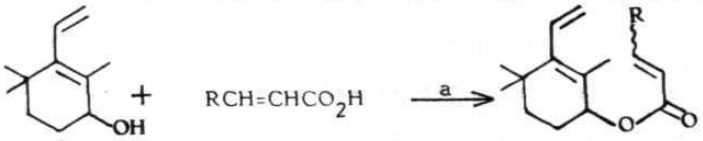


Reagents and Conditions: (a) (i) EtMgBr, THF-Et_2O, TMSCl, -20°; (ii) H^+; (b) LAH, THF, r.t., 24h; (c) chromic acid, acetone-water, 5-10°, 0.5h; (d) NaOEt-EtOH, PhSH, r.t.; (e) H_2O_2, AcOH, 80°, 1h.

77. Davidson, A.H.; Floyd, C.D.; Lewis, C.N.; Myers, P.L. J. Chem. Soc., Chem. Commun. 1988, 1417.

towards lactone homologation were chosen for esterification with alcohol **155**. While crotonic acid (**208**) was commercially available, acids **209**[78] and **210**[79] were prepared according to the literature procedures (Scheme 32).

The acids **208**, **209**, and **210** were esterified with the alcohol **155** to give the esters **215**, **216** and **217**, respectively (Eq.12). The



Eq. 12

155

208 R = Me(E)
209 R = TMS(E)
210 R = SO_2Ph(Z)

215 R = Me(E)
216 R = TMS(E)
217a R = SO_2Ph(E)
217b R = SO_2Ph(Z)

(a) DCC, DMAP, CH_2Cl_2, 0-25°, 12-15h.

structure of crotonate **215** is in accordance with its IR and PMR spectral data which are summarized in the experimental section. Once again, the structure of ester **216** is in consonance with its IR and PMR spectral data. The IR spectrum showed a strong carbonyl band at 1720 cm^{-1} and the PMR spectrum showed signals at δ 7.29 and 6.27 (two doublets, dienophile protons, J = 19 Hz), 6.16 and 5.01 (two doublet of doublets, vinyl protons) along with other signals.

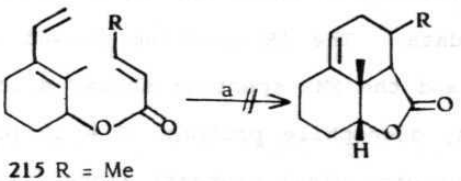
The acid **210** on esterification with **155** gave a mixture of cis- and trans-isomers in about 1:1 ratio. These could be readily separated on a silica gel column. The structures of **217a** and **217b**

78. Cunico, R.F.; Lee, H.M. J. Am. Chem. Soc. 1977, **99**, 7613.
79. Hogeveen, H. Recuil. Trans. Chim. 1964, **83**, 813.

are readily evident from their PMR spectral data. The dienophile protons of the trans-isomer **217a** appear at δ 7.31 and 6.81 (each one doublet, J = 16 Hz). In the case of the cis-isomer **217b**, the dienophile protons coincidentally appear as a singlet at δ 6.51. Both the esters **217a** and **217b** gave satisfactory elemental analysis.

To begin with, crotonate **215** was subjected to thermolysis (toluene, 180°, sealed tube) (Eq.13). Under these conditions, after two days, only starting material was recovered. When ester **217a** was subjected to IMDA reaction under normal conditions (benzene, 120°, sealed tube, 40h), no IMDA adduct formed. Instead, some of the ester decomposed to give a carboxylic acid which was not characterized.

Similarly, ester **216** also did not undergo IMDA reaction under normal (benzene, 140°, sealed tube, 27h) or vigorous conditions (xylene, 200°, sealed tube, 20h). While in the former the starting material was recovered, in the latter reaction, partial decomposi-



Eq.13

215 R = Me

216 R = TMS

217a R = SO_2Ph

(a) benzene/toluene/xylene, 120-180°, sealed tube, 1-2 days.

tion to a carboxylic acid occurred.

Although examples are known in the literature of the activation

of dienophile by sulfones and silanes,[62,63] in the case of **216** and **217a** no adducts were formed. It is likely that our activated dienophiles (i.e. **216** and **217a**) are not active enough to undergo the IMDA reaction.

III.2.2 Intermolecular Diels-Alder Reaction Approaches:

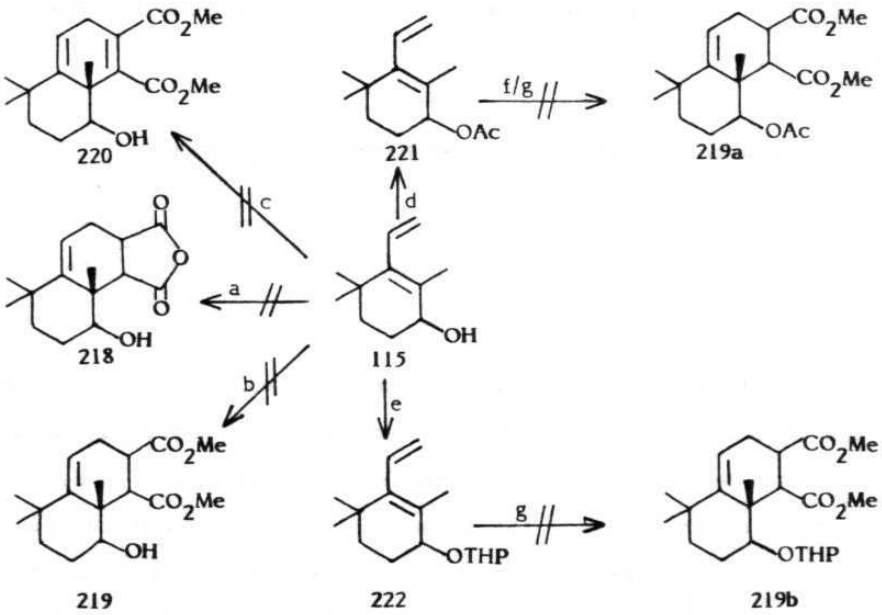
Simultaneously, two intermolecular Diels-Alder routes, discussed in the following pages, were pursued to construct the BCD and BCE ring systems of bruceantin.

As outlined in path B of Scheme 14, studies were concentrated on the intermolecular Diels-Alder reaction between the diene alcohol **155** or its derivatives, and symmetric dienophiles. A perusal of literature on the alcohol **155** revealed that it had not been used in intermolecular Diels-Alder reactions. However, an analogue of **155**, 1,3,3-trimethyl-2-ethenylcyclohexene was used in a Diels-Alder reaction by Ley in his synthesis of warburganal.[80]

A mixture of alcohol **155** and maleic anhydride in benzene was heated in a sealed tube at 150^{o} for 18h (Scheme 33). After usual workup, the IR spectrum of the crude product showed no hydroxyl band and the tlc showed a complex mixture. Absence of hydroxyl group in the crude reaction mixture may be due to esterification with maleic anhydride. However, when the Diels-Alder reaction was performed

80. Hollinshead, D.M.; Howell, S.C.; Ley, S.V.; Mahon, M.; Ratcliffe, N.M.; Worthington, P.A. J. Chem. Soc., Perkin Trans.1 1983, 1579.

SCHEME 33



Reagents and Conditions: (a) Maleic anhydride, benzene, sealed tube, 150°, 18h; (b) dimethyl maleate, toluene, sealed tube, 150°, 5 days; (c) dimethyl acetylenedicarboxylate, toluene, sealed tube, 150°, 2 days; (d) AcOH, DCC, DMAP, CH_2Cl_2, 0-25°, 12h; (e) dihydropyran, p-TsOH, CH_2Cl_2, r.t., 12h; (f) dimethyl maleate, ultrasound, MeOH, r.t., 3h; (g) toluene, sealed tube, 190°, 20h.

with the alcohol **155** and dimethyl maleate at 150° in a sealed tube, no adduct was formed even after five days. Both the starting materials were intact after usual workup. A similar result was observed with dimethyl acetylenedicarboxylate under normal conditions (toluene, 150°, sealed tube, 2 days).

To study the reactivity of its derivatives, the alcohol **155** was converted to the acetate **221** and to the THP ether **222** (Scheme 33). Alcohol **155** was esterified with acetic acid to give the required acetate **221**. The structure of **221** is in accordance with its spectral data (IR and PMR). A strong carbonyl band (1725 cm^{-1}) in the IR spectrum and a proton signal at δ 1.92 (s, 3H) in the PMR spectrum are in support of the structure of **221**.

A mixture of the acetate **221** and dimethyl maleate was subjected to Diels-Alder reaction under normal conditions (benzene, 150°, sealed tube, 20h). Evaporation of the solvent afforded only starting materials as indicated by tlc and IR.

Recently, Snyder reported that ultrasonic vibrations enhance the rate of Diels-Alder reactions.[81] However, under these conditions also, acetate **221** and dimethyl maleate did not undergo any Diels-Alder reaction.

In a continuing effort on Diels-Alder reactions and to see the effect of functionality on C-1 of **155**, it was protected as its THP ether (Scheme 33). The ether **222** was readily formed from the alcohol **155** and dihydropyran in acidic medium. The structure of ether **222** is fully in agreement with its IR and PMR spectral data. Absence of O-H band in the IR and presence of proton signals at δ 5.14-4.86 (m, 2H, terminal olefinic and -CHOTHP), 4.80-4.62 (m, 1H, -OCHO-) in the PMR spectrum are in support of the structure of **222**. Once again, efforts on the Diels-Alder reaction between the ether **222** and dimethyl maleate under normal conditions (toluene, 190°,

81. Lee, J.; Snyder, J.K. J. Am. Chem. Soc. 1989 **111**, 1522.

sealed tube, 20h) were futile.

As the intermolecular Diels-Alder reactions of the dienes **155**, **221**, and **222** are not known, reactivity of these dienes towards Diels-Alder reactions is yet to be understood.

As mentioned earlier at the beginning of this section, 1,3,3-trimethyl-2-ethenylcyclohexene readily undergoes Diels-Alder reactions. In our synthetic studies towards BCE model studies on bruceantin, efforts were made to prepare a similar diene, with a substituent on the allylic methyl group, as shown in path C of Scheme 14.

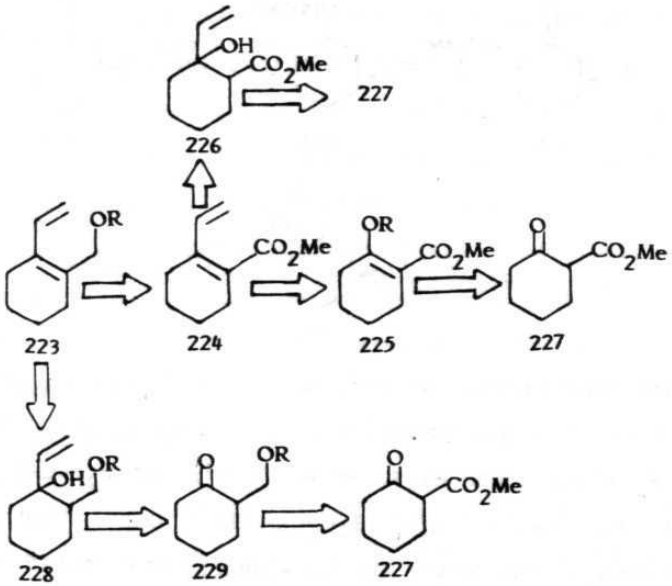
Further retrosynthetic analysis of the diene component in path C of Scheme 14 indicates that it can be derived from 2-carboalkoxy-cyclohexanone or 2-(benzyloxymethyl)cyclohexanone (Scheme 34). The former cyclohexanone (alkoxy=OEt) is commercially available, and a survey of literature for the latter revealed that it was prepared from the TMS enol ether of cyclohexanone by reaction with dibenzyloxymethane.[82]

Weiler[83] reported the stereoselective syntheses of β-substituted α, β-unsaturated esters by the coupling of lithium dialkylcuprate with the enol phosphates of β-keto esters. Extending this to vinylcuprates, attempts were made to prepare the diene ester **224** (Scheme 35). In the first approach towards the synthesis of BCE rings of bruceantin, 2-carbomethoxycyclohexanone (**227**) was prepared

82. Murata, S.; Suzuki, M.; Noyori, R. Tetrahedron Lett., 1980, 2527.

83. Sam, F.-W.; Weiler, L. Can. J. Chem. 1979, **57**, 1431.

SCHEME 34



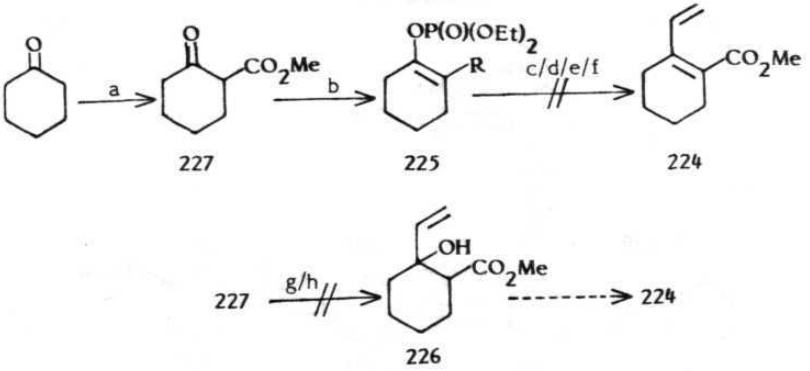
from cyclohexanone according to the literature procedure.[84] The enol phosphate **225** of the keto ester **227** was prepared by following Weiler's procedure.[83] The spectral data (IR and PMR) of **225** are identical to that reported.

Lithium divinylcuprate, prepared *in situ* from vinyllithium (obtained from tetravinyltin and phenyllithium via literature procedure[85]) and CuI was reacted with the enol phosphate **225** at -20° for 2h. After usual workup, no trace of the diene ester **224** was found. Instead, some of the keto ester **227** and some alcohol (not characterized, may be the enol form of ester **227**) were isolated.

84. Deslongchamps, P.; Ruest, L. *Syn. Commun.* 1976, **6**, 169.

85. Seyferth, D.; Weiner, M.A. *Chem. Ind* (*London*). 1959, 402.

SCHEME 35



Reagents and Conditions: (a) NaH, KH(cat.), $MeOCO_2Me$, THF; (b) NaH, ether, diethyl chlorophosphate, 0°; (c) H_2C=CHLi, CuI, ether, -63 to -20°; (d) H_2C=CHLi, CuBr.Me_2S, ether, -78°; (e) H_2C=CHLi, CuI.PBu_3, THF, -78 to -20°; (f) H_2C=CHMgBr, CuI, THF, 0°; (g) H_2C=CHMgBr/$CeCl_3$, THF, -78°; (h) H_2C=CHMgBr, THF, 0-25°.

Formation of **227** may be due to hydrolysis of the enol phosphate **225** during workup.

To overcome the purity and solubility problems associated with copper(I) iodide, the easily purified copper(I) iodide.tri-n-butylphosphine or copper(I) bromide.dimethyl sulfide complexes were used for lithium divinylcuprate formation and the thus formed cuprate was reacted with the enol phosphate **225** at different temperatures (-78°, -40°, and -20°). Under these conditions also, no diene ester **224** was obtained.

It may be mentioned that Weiler has no example of an alkenylcuprate coupling with an enol phosphate.[83]

In the second approach towards the diene ester **224**, attempts were made to add a vinyl moiety to the keto group of **227** followed by dehydration. As Grignard reagents are basic enough to react with the α-proton of β-keto ester **227**, vinylmagnesium bromide was converted to the less basic (towards α-proton) and reactive enough (towards keto group) cerium reagent according to Imamoto's procedure.[86] Surprisingly, under identical conditions, keto ester **227** did not give any hydroxy ester **226**. After usual workup, only the starting keto ester **227** was recovered. The same reaction at different temperatures (-78 to -20°, -78 to 25°, and 0°) also did not give any trace of **226**.

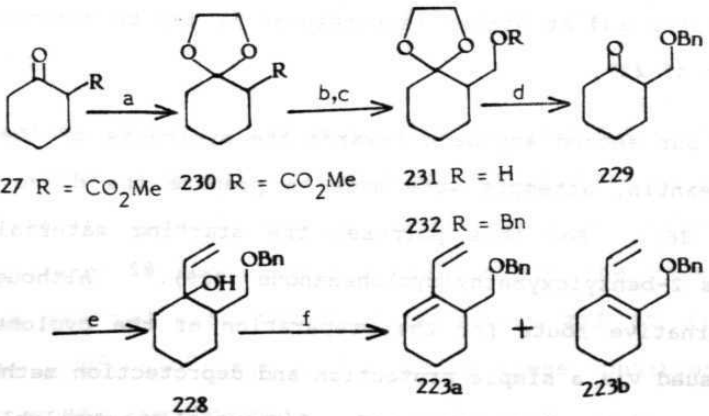
Imamoto, in his report did not use any β-keto ester for the study of the cerium reagents. It is likely that our transmetallated Grignard reagent may not be reactive towards the keto group at lower temperatures and at higher temperatures it may be reacting with the α-proton of **227**.

In our second approach towards the synthesis of the BCE rings of bruceantin, attempts were made to prepare the diene ether **223b** (Scheme 36). For this purpose, the starting material could be Noyori's 2-benzyloxymethylcyclohexanone (**229**).[82] Although lengthy, an alternative route for the preparation of the cyclohexanone **229** was pursued via a simple protection and deprotection method from the readily available keto ester **227**. Commercially available 2-carbethoxycyclohexanone can also be used as starting material.

86. Imamoto, T.; Takiyama, N.; Nakamura, K. Tetrahedron Lett. 1985, **26**, 4763.

Keto ester **227** was reacted with ethylene glycol and p-toluenesulfonic acid in refluxing benzene with continuous removal of water to give the selectively protected ketal-ester **230** in 84% yield. The structure of **230** is in full agreement with its spectral data (IR and PMR). Presence of a strong carbonyl band (1730 cm^{-1}) and a C-O band (1160 cm^{-1}) in the IR spectrum and proton signals at δ 3.92 (br s, 4H, $-OCH_2CH_2O-$), 3.66 (s, 3H, $-CO_2CH_3$) and 2.66 (t, 1H, $-\underline{CH}CO_2CH_3$) in the PMR spectrum are in support of the structure of **230**. LAH reduction of the ester group of **230** at room temperature cleanly gave the hydroxy ketal **231** in 90% yield. Absence of the carbonyl band and presence of a broad hydroxyl band (3400 cm^{-1}) in the IR and proton signals at δ 4.00 (s, 4H, $-OCH_2CH_2O-$), 3.80-3.66 (m, 2H, $-\underline{CH_2}OH$), and 2.90-2.70 (m, 1H, $-\underline{CH}CH_2OH$) in the PMR spectrum

SCHEME 36



Reagents and Conditions: (a) $(CH_2OH)_2$, benzene, p-TsOH; (b) LAH, THF, r.t., 14h; (c) NaH, $PhCH_2Br$, r.t., 14h; (d) p-TsOH, acetone, 25°, 15h; (e) H_2C=CHMgBr, THF, 0-25°, 15h; (f) anhydrous $CuSO_4$, xylene, 150°, 1h.

are among the characteristic spectral features of **231**.

Hydroxy ketal **231** was protected as its benzyl ether using sodium hydride as the base. The IR spectrum of the benzyl ether **232** showed absence of the hydroxyl band and presence of two strong aromatic bands (740 and 700 cm^{-1}). In the PMR spectrum, signals at δ 7.30 (s, 5H, Ph), 4.50 (narrow doublet, 2H, Ph$\underline{CH_2}$-), 3.98-3.80 (m, 4H, -OCH_2CH_2O-), 3.72 (dd, 1H, -$\underline{CH_2}$OBn, J = 4,10 Hz), 3.30 (dd appearing as triplet, 1H, -$\underline{CH_2}$OBn, J = 9 Hz) are characteristic of the structure of **232**.

Transketalization of the ketal group from **232** to acetone was effected by adding a catalytic amount of p-toluenesulfonic acid to give the ketone **229** in 90% yield. IR [3050, 1710, 1100, 740, and 700 cm^{-1}] and PMR [δ 7.28 (s, 5H, Ph), 4.02-3.57 (m, 2H, H-2 and -$\underline{CH_2}$OBn), 3.38 (dd, 1H, -$\underline{CH_2}$OBn, J = 7,12 Hz)] spectra are in support of the structure of **229**. The overall yield of the ketone **229** is 57% from the keto ester **227**. Although the yield in Noyori's method is high (87%), the present methodology is simple and convenient for any scale.

The ketone **229** was reacted with vinylmagnesium bromide to give the allylic alcohol **228** in 70% yield. A sharp hydroxyl band at 3450 $cm,^{-1}$ present in the IR spectrum of **228** is characteristic of a tertiary alcoholic group. The PMR spectrum consists of characteristic signals at δ 7.28 (m, 5H, Ph), 5.88 (dd, 1H, -$\underline{CH}$=CH_2, J = 10,18 Hz), 5.23 (ddd, 2H, -CH=$\underline{CH_2}$), 4.44 (s, 2H, Ph$\underline{CH_2}$-), 3.80 (dd, 1H, -$\underline{CH_2}$OBn, J = 3,9 Hz), 3.41 (dd, 1H, -$\underline{CH_2}$OBn, J = 3,9 Hz).

No attempts were made to establish the stereochemistry present

in the compounds **228**, **229** and **230** to **232** as it would be destroyed in the next step of the sequence.

To generate a diene unit present in **223b**, the allylic alcohol **228** was heated in xylene at 150^{o} with anhydrous copper sulfate. After workup, the IR spectrum of the crude compound showed no hydroxyl band and presence of some characteristic bands (2950, 1610, 1460, 1100, 740, and 700 cm^{-1}). The PMR spectrum of a purified sample showed signals at δ 7.28 (br s), 6.05 (dd, J = 10,18 Hz), 5.74 (t, J = 4 Hz), 5.20-4.72 (m), 4.46 (two narrow singlets), 3.62-3.16 (m), 2.26-1.36 (m). This indicates that the dienes **223a** and **223b** are formed in a ratio of 5.5:4.5 by integration of signals characteristic of them (δ 5.74 and δ 4.46, respectively). With other dehydrating reagents, like p-toluenesulfonic acid in refluxing benzene or phosphorous oxychloride/pyridine, similar mixtures were obtained. Since the two regioisomers were inseparable on tlc, no attempt was made to separate them and proceed further. This clearly indicates that the dehydration is not regiospecific.

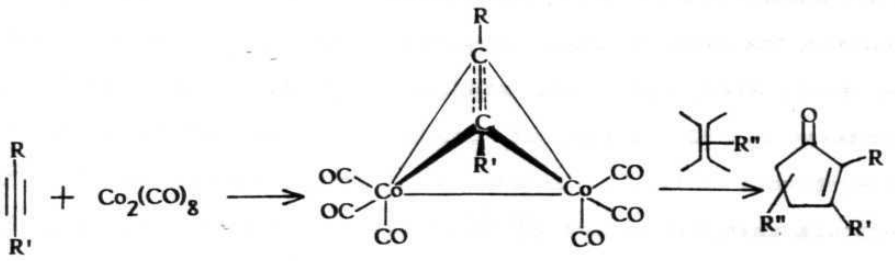
III.2.3 Intramolecular Pauson-Khand Reaction Approach:

As the efforts on inter- and intramolecular Diels-Alder reactions were unsuccessful, an entirely different approach towards bruceantin synthesis was pursued. An IMPK reaction approach, as mentioned in Section II, was considered for bruceantin synthesis. The results of this approach are discussed below.

Before embarking on the IMPK approach towards bruceantin, it is appropriate to examine the scope and limitations of the Pauson-Khand

reaction. The Pauson-Khand reaction (the formation of cyclopentenones in a single step from an alkyne, via its hexacarbonyl dicobalt complex, an alkene, and carbon monoxide, present as a ligand in the complex) has become a popular reaction due in large measure to the high degree of stereo- and regiochemical control (Scheme 37).[47,87] Magnus has extensively studied the stereochemical outcome of ene-yne

SCHEME 37



cyclizations leading to bicyclo[3.3.0]octenones.[88]

IMPK reactions become possible when the multiple bonds are separated by three or more atoms. So far, a variety of IMPK reactions have been studied world-wide.[88] Most of them are without any rings attached to ene-yne chains. The IMPK reactions with only a five-membered ring being part of the ene-yne chain are known (Chart 6).[89] However, no examples are known with cyclohexenes.

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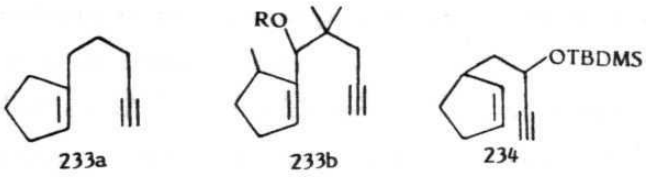
87. For original references to the Pauson-Khand reaction see: Khand, I.U.; Knox, G.R.; Pauson, P.L.; Watts, W.E. J. Chem. Soc. Perkin Trans.1 1973, 975 and Khand, I.U.; Knox, G.R.; Pauson, P.L.; Watts, W.E.; Foreman, M.I.; ibid. 1973, 977.

88. Magnus, P.; Becker, D.P. J. Am. Chem. Soc. 1987, **109**, 7495 and references cited therein.

89. (a) Knudsen, M.J.; Schore, N.E. J. Org. Chem. 1984, **49**, 5025. (b) Schore, N.E.; Rowley, E.G. J. Am. Chem. Soc. 1988, **110**, 5224

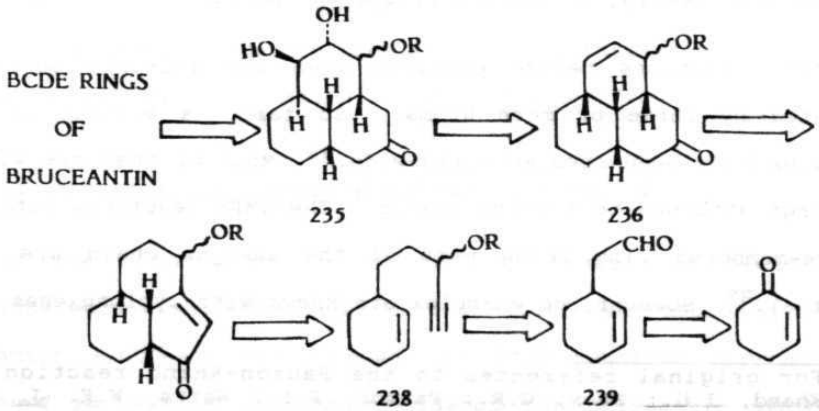
CHART 6



233a 233b 234

As the examples related to our methodology (path D, Scheme 14) are not known, initially studies were concentrated on model systems. To obtain the IMPK reaction precursor readily, the rings A and E were eliminated and model studies were directed towards the synthesis of BCD rings of bruceantin, as outlined in the retrosynthetic analysis, Scheme 38. It is noteworthy from the literature that the attack of hexacarbonyl dicobalt complex on the

SCHEME 38



double bond is facially selective.[90] Based on this, a mechanistic hypothesis to rationalize and predict the stereochemical outcome of the IMPK reaction on the ene-yne **238** leads to the intermediate **237**.

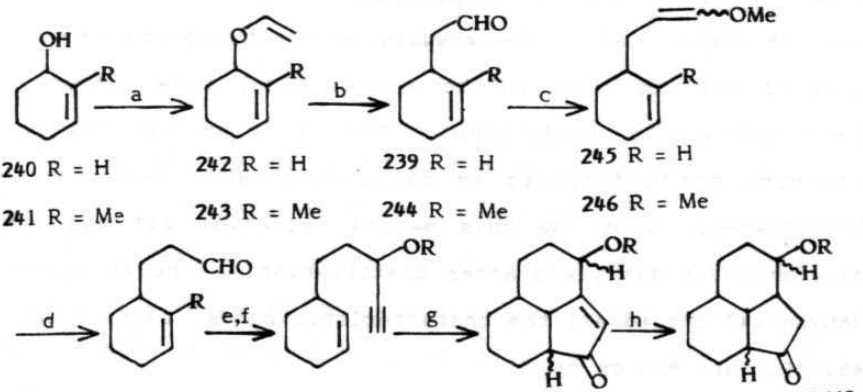
90. Khand, I.U.; Pauson, P.L. J. Chem. Soc., Perkin Trans.1 1976, 30.

Although the stereochemistry of the ring fusion in the intermediate **237** is not known a priori epimerization could be done at a later stage, if needed.

With this background on the IMPK reaction, studies towards a BCD model system were started from readily available 2-cyclohexenone (Scheme 39).

2-Cyclohexenone was reduced with sodium borohydride to give 2-cyclohexenol (**240**). At this stage, the stereochemistry of the hydroxy methine carbon establishes the stereochemistry of the side chain, as the Claisen rearrangement proceeds stereospecifically.

SCHEME 39



240 R = H **241** R = Me

242 R = H **243** R = Me

239 R = H **244** R = Me

245 R = H **246** R = Me

247 R = H **248** R = Me

249 R = H **238** R = TBDMS

237 R = TBDMS **250** R = TBDMS

Reagents and Conditions: (a) $C_2H_5OCH{=}CH_2$, $Hg(OAc)_2$, reflux, 18h; (b) 190°, sealed tube, 0.5h; (c) t-AmONa, $CH_3OCH_2P^+(Ph)_3Cl^-$, ether, 0°, 0.5h; (d) 50% CF_3CO_2H, $CHCl_3$-H_2O, 1h; (e) LiC≡CH.EDA, THF, 0-25°, 6h; (f) DMF, imidazole, TBDMSCl, r.t., 18h; (g) $Co_2(CO)_8$, benzene, CO, reflux, 18h; (h) Pd/C, ethyl acetate, r.t., 10 psi H_2.

However, work was started with the racemic alcohols **240** and **241**. The vinyl ether **242** and its Claisen rearrangement product **239** were prepared via a literature procedure.[91] The IR spectra of **242** and **239** were identical to that reported. The homologated aldehyde **247** was prepared via a methoxymethylene Wittig reaction. Enol ether **245** was obtained in 92% yield by adding the aldehyde **239** to the in situ prepared ylide from methoxymethyltriphenylphosphonium chloride. The IR spectrum of **245** showed absence of aldehyde C-H and C=O absorptions and presence of typical strong vinyl ether absorptions at 1625, 1605, and 1185 cm^{-1}.

Hydrolysis of enol ether **245** by the standard procedure[92] (ether, 35-70% perchloric acid, 0-25°) gave the aldehyde **247** in about 30% yield. Also, the results were not reproducible. Lower yields of **247** could be due to a self aldol type reaction under acidic hydrolysis conditions. This problem was overcome by performing the hydrolysis in chloroform-water medium with 50% trifluoroacetic acid. By this method, aldehyde **247** was obtained consistently in 93% yield after distillation. The IR spectrum of aldehyde **247** showed all the characteristic bands (2925, 2700, 1720, 1445, 880, and 800 cm^{-1}).

At this stage, the acetylenic group required for the IMPK reaction was introduced by adding commercially available lithium acetylide-ethylenediamine complex to the aldehyde **247** under

91. Burstahler, A.W.; Nordin, I.C. J. Am. Chem. Soc. 1961, **83**, 198.

92. Danishefsky, S.; Nagasawa, K.; Wang, N. J. Org. Chem. 1975, **40**, 1989.

literature conditions.[93] After workup, the propargylic alcohol 249 was obtained in low yield (16%) along with some uncharacterized products.

The gross structure of alcohol 249 was based on its IR and PMR spectral data. In the IR spectrum, absorptions at 3350, 3300, 2950, 1170, and 1120 cm^{-1} are strongly in support of the structure of 249. In the PMR spectrum, signals at δ 5.88-5.40 (m, 2H), 4.40 (dt, 1H, J = 2,6 Hz), 2.5 (d, 1H, J = 2 Hz) are due to olefin, hydroxy methine and acetylenic protons, respectively. The stereochemistry of the hydroxyl group was not established, as it gets destroyed in the later stage of the synthesis.

Before performing the IMPK reaction, the hydroxy ene-yne 249 was converted to its TBDMS ether by a standard procedure. Formation of TBDMS ether 238 was confirmed by its IR spectrum (3300, 2925, 1250, 1100, 840, and 780 cm^{-1}).

Ene-yne 238 was subjected to the IMPK reaction by following the standard Pauson-Khand reaction conditions.[94] After workup and purification over a silica gel column, the cyclized product 237 was obtained in 45.5% yield as a colourless oil. The IR spectrum of 237 showed bands at 2925, 1700, 1260, 1140, 1100, 840, and 780 cm^{-1}. The PMR spectrum (Fig.6) showed two broad singlets at δ 6.00 and 5.77 (together integrating for one olefinic proton), one broad singlet at δ 4.74 and one triplet at δ 4.46 (together integrating

93. Schmidt, C. Can. J. Chem. 1976, 54, 2310.

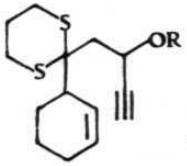
94. Magnus, P.; Exon, C.; Albaugh-Robertson, P. Tetrahedron 41, 5861.

for one -CHO- proton), two narrow singlets at δ 0.93 and 0.90 (together integrating for nine t-butyl protons), and a broad singlet at δ 0.10 (6H, $-Si(CH_3)_2$). The above signals appearing as pairs indicates that the tricyclic enone 237 is a mixture of stereoisomers. This is the first example of the generation of a tertiary carbon at a multiple ring fusion via this methodology.

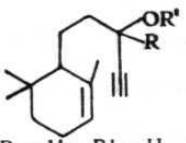
To further confirm the structure of 237 and also to form a six-membered lactone via Baeyer-Williger oxidation, the enone 237 was reduced with hydrogen and palladium-on-carbon to give the low melting saturated ketone 250 in 80% yield. Tlc of the crude hydrogenated product showed a UV inactive spot (enone 237 is UV active) which is an indication of enone double bond reduction. The IR spectrum of 250 showed a strong carbonyl band at 1730 cm^{-1} along with other characteristic bands (1250, 1085, 840, and 770 cm^{-1}). The PMR spectrum of 250 showed absence of olefinic signals and presence of signals at δ 4.04-3.88 (m, 1H, -CHOSi-), 0.92 and 0.88 (two singlets, together integrating for nine protons, t-Bu), and 0.07 (s, 6H, $-Si(CH_3)_2$) in support of its structure. Here also, appearance of t-butyl group in the form of a pair indicates that the ketone 250 is a stereoisomeric mixture. Finally, the mass spectrum with peaks at 308 (M^+), 293 ($M-CH_3$) and 251 (M - t-Bu) is in support of the structure of 250.

Successful synthesis of our pretarget in the BCD model system of bruceantin encouraged us to look for some more IMPK reaction precursors suitable for epimerization at the C-9 center (quassinoid numbering) so that the stereochemistry at that atom could be varied if necessary and also for further elaboration towards the total

synthesis of bruceantin. Some of the readily preparable precursors identified for this purpose were:

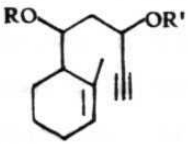


251 R = TBDMS

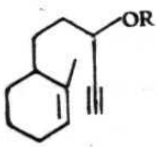


252 R = Me, R' = H

253 R = H, R' = TBDMS



254 R = Bn, R' = TBDMS

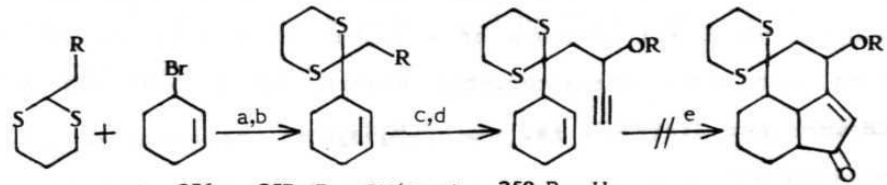


255 R = TBDMS

While precursor **251** contains the requisite functionality for epimerization of the C-9 center as well as for amplifying the C ring, precursors **252**, **253**, and **255** possess a vinylic methyl group suitable for elaboration of the tetrahydrofuran E ring. Precursor **254** combines both features.

Synthesis of precursor **251** commenced with 3-bromocyclohexene (**256**), Scheme 40. The three carbon appendage in **257** was introduced in 37% yield via an alkylation reaction of the differentially

SCHEME 40



125 R = $CH(OMe)_2$ **256** **257** R = $CH(OMe)_2$ **258** R = CHO **259** R = H **251** R = TBDMS **260** R = TBDMS

Reagents and Conditions: (a) n-BuLi, THF, -20° for 4h, -40 to 25° for 2h; (b) 50% CF_3CO_2H, $CHCl_3$-H_2O, 0-25°, 4h; (c) LiC≡CH.EDA, THF, 0-25°, 12h; (d) TBDMSCl, DMF, imidazole, r.t., 18h; (e) $Co_2(CO)_8$, CO, benzene, reflux, 24h.

protected malonaldehyde derivative **125** with 3-bromocyclohexene (**256**). The structure of **257** is based on its IR and PMR spectral data. The IR spectrum showed absorptions at 2925, 1430, 1180, 1120(s), 1070(s), 900, and 820 cm^{-1}. The PMR spectrum showed the absence of dithioacetal proton (which is present in **125** at 4.64) and the presence of characteristic signals at δ 6.08-5.84 (m, 2H, -CH=CH-), 4.08 (t, 1H, acetal proton), 3.34 (s, 6H, $-OCH_3$) and 2.96-2.68 (m, 4H, $-SCH_2CH_2S-$). It was noticed in many examples in our laboratory that the acetal proton and $-SCH_2-$ protons appear in the above mentioned region.

Selective hydrolysis of the dimethylacetal protecting group in **257** could be readily achieved by treating with 50% trifluoroacetic acid in chloroform-water medium. Thus, aldehyde **258** was obtained in almost quantitative yield. Spectral data in support of the structure of **258** include IR and PMR. While bands at 2725 and 1710 cm^{-1} (due to aldehyde C-H and C=O) are the characteristic features of the IR spectrum, the PMR spectrum showed absence of the acetal methyl singlet and presence of a signal at δ 9.85 (t, 1H, -CHO) along with other characteristic signals at δ 5.94 (br s, 2H, -CH=CH-) and 3.00-2.72 (m, 4H, $-SCH_2CH_2S-$).

The acetylenic unit in **259** required for IMPK reaction was introduced via nucleophilic addition of lithium acetylide-ethylenediamine complex to the aldehyde **258**. The structure of **259** was confirmed based upon its IR and PMR data. Absence of carbonyl band and presence of absorptions at 3400, 3300, 2120, 1075, 1050, 950, and 810 cm^{-1} are characteristic of the IR spectrum of **259**. Similarly, in the PMR spectrum, signals at δ 6.02-5.72 (m, 2H,

-CH=CH-), 4.98-4.68 (m, 1H, -CH(OH)-), 2.98-2.62 (m, 4H, $-SCH_2CH_2S-$) 2.40 (d, 1H, -C≡CH) are among the salient signals of **259**.

The alcohol **259** was protected as its TBDMS ether. Spectral data (IR and PMR), summarized in the experimental section are in support of the structure of the ether **251**. Especially, absence of the O-H band in the IR and presence of signals at δ 0.90 (s, 9H, t-Bu), 0.18 (s, 3H, $-SiCH_3$), 0.14 (s, 3H, $-SiCH_3$) in the PMR are significant.

With the successful preparation of the functionalised IMPK reaction precursor, studies were focussed on its cyclization to give the tricyclic compound **260**. Ene-yne **251** was subjected to the IMPK reaction by employing the previous methodology (Scheme 39). Surprisingly, IR spectrum of the crude reaction mixture showed no indication of enone **260** and tlc also showed a complex mixture.

This could probably due to sulfur poisoning the cobalt carbonyl, thus preventing its complexation with the triple bond. However, no attempts were made to deprotect the thioketal for studying the IMPK reaction.

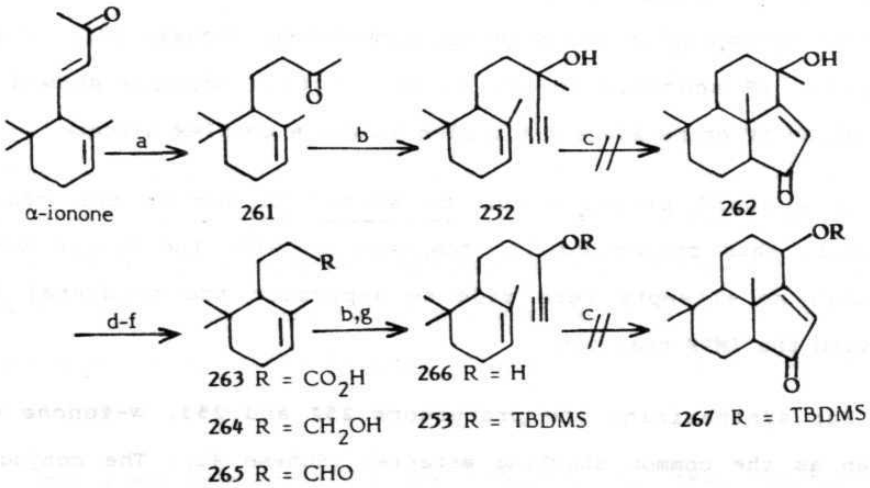
For synthesizing the precursors **252** and **253**, α-ionone was chosen as the common starting material (Scheme 41). The conjugate reduction of α-ionone was selectively achieved via the reported lithium-ethylamine method.[95] Spectral data (IR and PMR) of dihydroionone **261** were identical to that reported.[96] The hydroxy

95. Dorota, S.-H. Rocz. Chem. 1976, **50**, 265.

96. Takeda, R.; Naoki, H.; Iwashita, T.; Mizukawa, K.; Hirose, Y.; Isida, T.; Inone, M. Bull. Chem. Soc. Jpn. 1983, **56**, 1125.

ene-yne **252** was prepared in 50% yield (based on recovered **261**) by following the previous methodology (Scheme 39). The structure of alcohol **252** is in accordance with its IR and PMR spectral data. The IR spectrum showed characteristic absorptions of hydroxyl group (3400 cm^{-1}) and terminal acetylene group (3300 and 2105(w) cm^{-1}). The PMR spectrum showed signals at δ 5.37-5.19 (m, 1H, olefinic proton), 2.42 (s, 1H, $-C\equiv CH$), 1.66 (br s, 3H, allylic CH_3), 1.48 (s, 3H, $-CH_3$), 0.93 (s, 3H, $-CH_3$), 0.87 (s, 3H, $-CH_3$). The t-hydroxy ene-yne **252** could not be readily protected as its TBDMS ether under normal conditions (TBDMSCl, DMF, imidazole, room temperature). Without concentrating much on the ether formation, hydroxy ene-yne **252** was subjected to IMPK cyclization conditions (Scheme 39). After

SCHEME 41



Reagents and Conditions: (a) Li, $EtNH_2$, THF, -20°, 5h; (b) $LiC\equiv C.EDA$, $0-25^{\circ}$, 18h; (c) $Co_2(CO)_8$, C_6H_6, reflux, 18h; (d) NaOCl, MeOH-water, $0-25^{\circ}$, 12h; (e) LAH, THF, r.t., 12h; (f) PDC, CH_2Cl_2, r.t., 4h; (g) TBDMSCl, DMF, imidazole, r.t., 24h.

workup, the IR spectrum of the crude product showed absence of the acetylenic band and presence of broad carbonyl band (1720-1670 cm^{-1}). However, tlc showed a complex mixture whose purification was not attempted.

The acid **263** was obtained from dihydroionone **261** via the haloform reaction.[97] LAH reduction of the acid **263** in THF gave the reported alcohol **264**.[98] PDC oxidation of the alcohol **264** in dichloromethane provided the aldehyde **265**. The structure of the aldehyde **265** is in accordance with its spectral data (IR and PMR). The IR spectrum showed aldehyde absorptions at 2700 and 1720 cm^{-1} and the PMR spectrum showed signals at δ 9.72 (t, 1H, -CHO), 5.38 (br s, 1H, olefinic proton), 2.60-2.32 (distorted triplet, 2H, $-CH_2CHO$), and 1.64 (br s, 3H, allylic CH_3).

The acetylenic unit in the hydroxy ene-yne **266** was introduced by nucleophilic addition of lithium acetylide-ethylenediamine complex to the aldehyde **265**. After workup and purification, hydroxy ene-yne **266** was obtained in 30% yield. The structure of hydroxy ene-yne **266** was fully in agreement with its spectral data [IR: 3375 and 3300 cm^{-1}; PMR : δ 5.30 (br s, 1H, olefinic proton), 2.45 (d, 1H, -C≡CH), 1.66 (br s, 3H, allylic CH_3), 0.92 (s, 3H), 0.86 (s, 3H)]. Unlike the alcohol **252**, alcohol **266** could be protected as its TBDMS ether **253** under normal conditions. Once again, the structure of the ene-yne **253** is supported by its spectral data (IR and PMR)

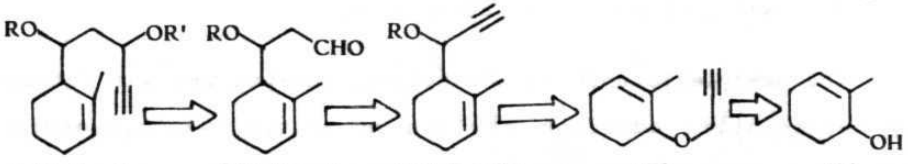
97. Royals, E.E. J. Am. Chem. Soc. 1947, **69**, 841.

98. Buchecker, R.; Egli, R.; Helen, R.-W.; Tscharner, C.; Eugster, C.H.; Uhde, G.; Ohloff, G. Helv. Chim. Acta. 1973, **56**, 2548.

summarized in the experimental section. In particular, absorptions at 3300(s), 1260, 1100, 840, and 780 cm^{-1} in the IR spectrum and signals at δ 5.28 (br s, 1H, olefinic proton), 2.37 (d, 1H,-C≡CH), 0.92 (s, 9H, t-Bu), 0.14 (s, 3H, $-SiCH_3$), and 0.12 (s, 3H, $-SiCH_3$) in the PMR spectrum are strongly in support of the structure of **253**. Ene-yne **253** was subjected to IMPK reaction under the usual conditions (Scheme 39). After workup, the IR spectrum of the crude reaction mixture showed neither the characteristic bands of the cyclized product **267** nor the starting ene-yne **253**.

The precursor **254**, shown retrosynthetically in Scheme 42, can be synthesized via a crucial Wittig rearrangement.

SCHEME 42



254 R = Bn, R' = TBDMS **268** R = Bn **269** R = Bn **270** **241**

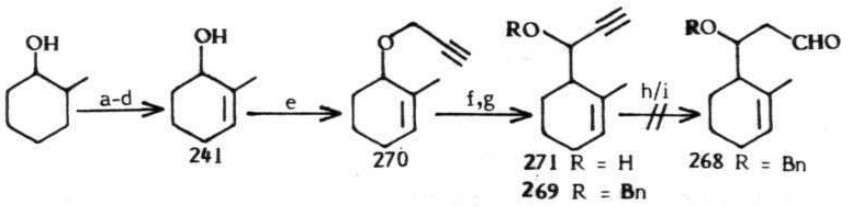
The intermediate ene-yne **254** can be synthesized from the aldehyde **268** as described earlier. Further analysis of the intermediate aldehyde **268** shows that it can be obtained via hydroboration-oxidation of the propargylic ether **269**, which in turn can be derived from the Wittig rearrangement of the propargyl ether **270**.

The starting material for synthesis of the intermediate **254**, 2-methyl-2-cyclohexenol (**41**), was prepared from 2-methyl-2-cyclohexenone as per the literature procedure (Scheme 43).[99] 2-

99. Dauben, W.G.; Berezin, G.H. J. Am. Chem. Soc. 1963, **85**, 468.

Methyl-2-cyclohexenone was prepared in an improved yield from 2-methylcyclohexanol via an oxidation, chlorination, and dehydrochlorination sequence.[100] LAH reduction of 2-methyl-2-cyclohexenone gave the alcohol **241** in 92% yield.[99] The alcohol **241** was converted to the propargyl ether **270** using sodium hydride and

SCHEME 43

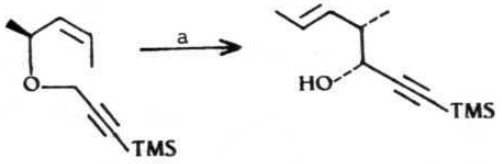


Reagents and Conditions: (a) $Na_2Cr_2O_7$, H_2SO_4, AcOH, benzene-water, 0-10°; (b) SO_2Cl_2, CCl_4, r.t., 4h; (c) sym-collidine, 145-150°, 15 min; (d) LAH, THF, r.t., 4h; (e) NaH, propargyl bromide, THF, r.t., 10h; (f) n-BuLi, THF, 0°, 2h; (g) NaH, $PhCH_2Br$, THF, $(n\text{-}Bu)_4NI$(cat.), 12h; (h) catecholborane, THF, r.t. to reflux; (i) dicylohexylborane, THF, r.t.,12h then $NaOAc\text{-}H_2O_2$.

propargyl bromide. Formation of ether **270** was based on its spectral data (IR, PMR, and CMR). The IR spectrum showed characteristic absorptions at 3300, 2120, and 1040 cm^{-1} and the PMR spectrum displayed signals at δ 5.58 (br s, 1H, olefinic proton), 4.20 (d, 2H, $-OCH_2-$), 3.84 (br s, 1H, -CHO-), and 3.40 (t, 1H, $-C\equiv CH$) among others. Finally, a ten line CMR spectrum is clearly indicative of propargyl ether formation.

100. Warnhoff, E.W.; Martin, D.G.; Johnson, W.S. Org. Syn. Coll. Vol. IV, p. 162.

Nakai,[101] in his study of Wittig rearrangements, reported that allyl propargyl ethers readily undergo a [2,3] Wittig rearrangement in the presence of base to give propargyl alcohols (Eq.14). Based on this, propargyl ether **270** was subjected to [2,3] Wittig re-



Eq.14

(a) n-BuLi, THF, -85°, 6h.

arrangement under identical conditions with two equivalents of base. Surprisingly, only 25% of the starting material rearranged to give the low melting alchol **271**. The major component was the recovered ether **270**. The structure of the rearranged product **271** was based on its spectral data (IR, PMR, and CMR). The IR spectrum showed characteristic absorptions at 3400, 3300 and 2100(w) cm^{-1} and the PMR spectrum showed signals at δ 5.64-5.38 (m, 1H, olefinic proton), 4.62 (br s, 1H, -CH(OH)-), 2.22 and 1.98 (two narrow doublets, 1H, -C≡CH, J = 2 Hz). A 19 line CMR spectrum with most of them present as pairs, indicates that alcohol **271** is a diastereomeric mixture. However, no attempts were made to separate them, as tlc showed a single spot.

It is likely that the temperature (-85°) may be too low for the substrate (dianon of **270**) to attain the required transition state

101. Sayo, N.; Ajuma, K.; Mikami, K.; Nakai, T. Tetrahedron Lett. 1984, 565.

for the [2,3] rearrangement. Keeping this in mind, the same reaction was repeated at different temperatures (Table 2). Table 2 indicates that with increasing temperature, the conversion of **270**

TABLE 2

Wittig rearrangement of **270** to **271**

S.No.	Reaction Conditions	Reaction temperature (^{o})	% of conversion of **270** to **271**	Yield of **271**(%)
1	2 equiv. n BuLi, THF, 5h.	-78	25	21
2	-do-	-63	61	36
3	2 equiv. n BuLi, THF-HMPA (2:1)	-63	No conversion	--
4	2 equiv. n-BuLi, THF, 5h.	-41	49	70
5	-do-	0-25	100	57
6	-do-	0	100	70

to **271** increases. Above 0^{o} (entry 5, Table 2), conversion was complete, but the yield was low. Optimum yields (70%) of **271** with 100% conversion of **270** to **271** were observed at 0^{o} (entry 6). It was noticed that a mixture of solvents (entry 3) did not lead to rearrangement of **270**.

Conversion of propargylic alcohol **271** to its benzyl ether **269** was straightforward. Conditions for optimum yield (73%) of **269** were generation of the anion of **271** in refluxing THF for 5 min using sodium hydride, followed by quenching with benzyl bromide using a catalytic amount of tetra-n-butylammonium iodide. The structure of

269 was in accordance with the spectral data (IR, PMR, and CMR) summarized in the experimental section. Characteristic features of the spectral data include presence of bands at 3275, 1600(w), 740 and 700 cm^{-1} in the IR and signals at δ 7.32 (s, 5H, Ph), 5.54 (br s, 1H, olefinic proton), 4.96-4.26 (m, 3H) and 2.28 (two narrow doublets appearing as a triplet, 1H, -C≡CH) in the PMR spectrum. Once again, a 24 line CMR spectrum with most signals in pairs is an indication that **269** is a diastereomeric mixture.

With the successful completion of pretarget **269** towards the IMPK reaction precursor **254**, the stage was set for the selective hydroboration-oxidation of the triple bond to obtain the aldehyde **268**. Catecholborane is known to selectively hydroborate the triple bonds to give vinyl boranes.[102] Oxidation of vinyl boranes to aldehydes is also known.[102]

Catecholborane (neat) was prepared according to Brown's procedure and used for selective hydroboration-oxidation of **269**. Surprisingly, after usual workup, starting ene-yne **269** was recovered unchanged. Reasons for the failure of catecholborane towards hydroboration of **269** are yet to be understood.

As an alternative for catecholborane, dicyclohexylborane was prepared <u>in situ</u> in the form of a solid suspension in THF and used for selective hydroboration-oxidation of the ene-yne **269** under reported conditions.[103] Unfortunately, with this reagent also no

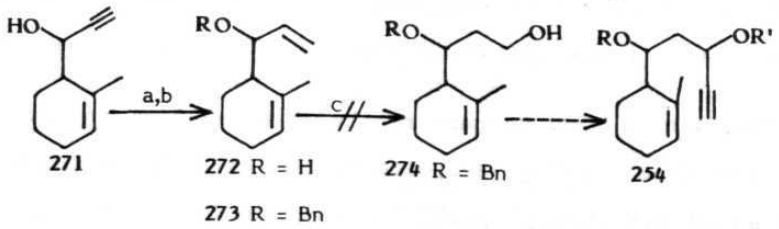
102. Brown, H.C. " <u>Organic Syntheses via Boranes</u>", Wiley-Interscience publication, New York, 1975, p.63.

103. Ref. 102, p. 178.

reaction occurred. It is likely that the ene-yne **269** is not undergoing hydroboration-oxidation under these conditions. However, no further attempts were made by varying the conditions.

In the continuing quest for the IMPK reaction precursor **254**, propargylic alcohol **271** was reduced with LAH to give the allylic alcohol **272** (Scheme 44). Spectral data (IR and PMR) are fully in

SCHEME 44



Reagents and Conditions: (a) LAH, THF, reflux, 1h; (b) NaH, THF, $PhCH_2Br$, $(n\text{-}Bu)_4NI$, r.t., 12h; (c) dicyclohexylborane, THF, 0-25°, 4h.

agreement with the structure of alcohol **272**. Absence of acetylenic bands and presence of a hydroxyl band (3350 cm^{-1}) in the IR, and signals at δ 6.08-5.76 (m, 1H, $-\underline{CH}=CH_2$), 5.54 (br s, 1H, -CH=C-), 5.42-5.06 (m, 2H, $-CH=\underline{CH_2}$) and 4.58-4.36 (m, 1H, -CH(OH)-) in the PMR spectrum are among the notable characteristics of the spectra of **272**. The unresolved multiple pattern of vinylic proton signals in the PMR spectrum may be due to the diastereomeric mixture of **272**. The alcohol **272** was protected in its benzyl ether form by following previous methodology to give the diene **273**. The structure of **273** was again confirmed from its spectral data (IR and PMR) given in the

experimental section.

With a view to effect selective hydroboration-oxidation of the diene **273**, *in situ* prepared dicyclohexylborane was used as the hydroborating agent. After adding the diene **273** to the *in situ* prepared slurry of dicylohexylborane, the reaction mixture was stirred for four hours at room temperature and quenched by adding 3M sodium hydroxide and 33% hydrogen peroxide. After usual workup, only the starting diene was recovered back.

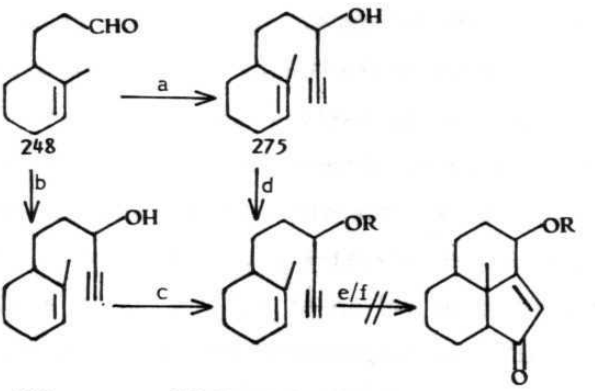
As enough literature is available on similar systems, the above unusual results in these hydroborations are yet to be understood.

Finally, with a view to perform the IMPK reaction on precursor **255**, starting from 2-methyl-2-cyclohexenol (**241**) the aldehyde **248** was obtained in 71% overall yield as shown in Scheme 39. All the compounds **243**, **244**, **246**, and **248** were characterized by their spectral data (IR, PMR, and CMR), summarized in the experimental section. In the case of enol ether **246**, both PMR and CMR spectra showed a mixture of *cis*- and *trans*-isomers in a ratio of about 1:1.

The aldehyde **248** was reacted with lithium acetylide-ethylenediamine complex to give the required propargylic alcohol **275** (11%) along with some unidentified products (Scheme 45). The structure of **275** was readily confirmed from its IR and PMR spectral data. The presence of bands in the IR spectrum at 3350, 3300, and 1020 cm^{-1} and signals in the PMR spectrum at δ 5.54-5.34 (m, 1H, olefinic proton), 4.46-4.24 (m, 1H, -CH(OH)-), 2.47 (d, 1H, -C≡CH, J = 3 Hz), and 1.66 (br s, 3H, allylic CH_3) are in keeping with the assigned structure. To minimize the side products and to improve

the yield of **275**, aldehyde **248** was reacted with <u>in situ</u> prepared lithium acetylide. After workup, alcohol **275** was obtained in 39% yield. When the alcohol **275** was silylated with TBDMSCl, only 50% of

SCHEME 45



275 **255** R = TBDMS **276** R = TBDMS

Reagents and Conditions: (a) LiC≡CH.EDA, THF, 0-25°, 6h; (b) LiC≡C, THF, -70 to -10°, 1h; (c) NaH, THF, TBDMSCl, r.t., 12h; (d) TBDMSCl, DMF, imidazole; (e) $Co_2(CO)_8$, CO, C_6H_6, reflux, 24h; (f) (i) $Co_2(CO)_8$, CO, r.t., 3h; (ii) SiO_2, oxygen flow, 50° for 3h, 25° for 12h.

the alcohol was converted to the ether **255** in 75% yield. Routine spectral analysis (IR and PMR) of **255** confirmed its structure.

To improve the yield of **255** and to minimize the recovery of **275**, it was treated with sodium hydride and then quenched with TBDMS chloride. After usual workup, ether **255** was obtained in 82% yield with no trace of the starting alcohol.

The ene-yne **255** was subjected to Pauson-Khand cyclization under

normal conditions ($Co_2(CO)_8$, CO, benzene, reflux, 24h). After workup, the IR spectrum of the crude mixture did not show any enone band and tlc showed an intractable mixture.

Smit[104] has reported a mild and general method for IMPK cyclizations of dicobalt hexacarbonyl complexes of allyl propargyl ethers in an adsorbed state under oxygen atmosphere to the corresponding pentenone derivatives in moderate to high yields. This report prompted us to attempt the cyclization of the ene-yne **255** in an adsorbed state. The dicobalt hexacarbonyl complex of the ene-yne **255** was adsorbed on silica gel (100-200 mesh) and rotated in a Kugelrohr distillation set up at 50° for 5h in a slow stream of oxygen and then at room temperature for 10h. In this case also, only the starting material was recovered.

The above results of IMPK reaction (summarized in Table 3) indicate that the IMPK reaction proceeds smoothly if there is no substitution on the olefin moiety of cyclohexene (entry 1, Table 3). In the case of the ene-yne **251**, failure of cyclization may be due to the effect of sulfur atom as mentioned earlier (entry 2). Although the reaction of ene-yne **252** (entry 3) indicated the presence of cyclized product **262** (by IR), it could not be purified due to its miniscule quantity in the crude mixture. Similar effect of methyl group on the olefin moiety was also observed by Shore[89] during the cyclization of an ene-yne similar to **233a**.

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104. Simonian, S.O.; Smit, N.A.; Gybin, A.S.; Shashkov, A.S.; Mikaelian, G.S.; Tarasov, V.A.; Ibragimov, I.I.; Caple, R.; Froen, D.E. Tetrahedron Lett., 1986, 27, 1245.

TABLE 3

S.No.	Substrate	Conitions	Inference
1	**238**	A	product formed in 45.5% yield
2	**251**	A	complex mixture
3	**252**	A	trace amount of product as indicated by the IR spectrum.
4	**253**	A	complex mixture
5	**255**	A	complex mixture
6	**255**	B	starting material recovered

(A) $Co_2(CO)_8$, CO, benzene reflux, 18-24h.

(B) hexacarbonyl dicobalt complex of the ene-yne **255** was adsobred on silica gel and stirred at 50^{o} in oxygen flow for 4h and at room temperature for 10h.

III.3 SUMMARY AND OUTLOOK:

During the course of this work, various inter- and intramolecular Diels-Alder reactions as well as IMPK reactions have been studied. As mentioned earlier, although reported esters of the diene alcohol **155** (**156**, **157**, and **158**) underwent IMDA reaction, in our experiments both mono-activated and non-activated dienophiles did not participate in the IMDA reaction. It is likely that our activated dienophiles (e.g. **216**, **217**) are not reactive enough to undergo the IMDA reaction. In the case of ester **196** efforts are underway to generate a cation radical from the dienophile unit (symmetry allowed) to achieve a Diels-Alder cyclization.

During the course of IMPK reactions, a new method for generation of an acenaphthylene type tricyclic system, present in quassinoids has been conceived (Scheme 39). Althouh the angular C-9 methyl (quassinoid numbering) could not be introduced via this method, it could be possible via migration of the double bond of the cyclopentenone to the tetra-substituted position, followed by methylcuprate addition. Efforts are currently underway to apply this route for the total synthesis of bruceantin starting with appropriate functionality present in the A ring.

IV. EXPERIMENTAL AND FIGURES

IV.1 Experimental:

Melting Points:

Melting points were determined using a Buchi 510 capillary point apparatus and are uncorrected.

Boiling Points:

Boiling points refer to bath temperatures (short path distillations) or oven temperatures (Buchi Kugelrohr-GKR 50 apparatus).

Chromatography:

Analytical thin layer chromatography (TLC) was performed on glass plates (3 x 8 or 5 x 10 cm) coated with Acme's silica gel G or GF_{254} containing 13% calcium sulfate as binder. Visualization of the spots was achieved by exposure to iodine or UV light. Column chromatography was effected using Acme's silica gel (100-200 mesh) employing appropriate solvent systems.

Infrared (IR) Spectra:

Infrared spectra were determined on Perkin-Elmer models 1310 or 297 recording spectrophotometers. All spectra were calibrated against a polystyrene absorption at 1601 cm^{-1}. Solid samples were prepared as KBr wafers and liquid samples as a film between NaCl plates.

Nuclear Magnetic Resonance Spectra:

Proton magnetic resonance (PMR) spectra (100 MHz) and carbon-13

magnetic resonance (CMR) spectra (25 MHz) were recorded on a JEOL FX-100 spectrometer. PMR and CMR samples were made in chloroform-d solvent. Spectral assignments for PMR are as follows (1) chemical shift on the δ scale (tetramethylsilane = δ 0.00); (2) multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of a doublet, dt = doublet of a triplet, ddd = doublet of a doublet of a doublet, (3) number of hydrogens integrated for by the signals, (4) assignment of the signal (wherever possible), and (5) coupling constant in Hertz (Hz). Decoupling experiments were carried out by irradiating the frequency, of the signal concerned with high power (6-8 watts) and observing the affected signals. For CMR spectral data values are in ppm scale (tetramethylsilane = 0.00 ppm).

Elemental Analysis:

Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyser.

Mass Spectra:

Mass measurements were carried out on Jeol, JMS DX-303 mass spectrometer.

General:

Hydrogenations were carried out in a Paar hydrogenation apparatus in 250 ml pressure bottles. As a routine practice, all reactions were monitered by tlc using appropriate solvent systems for development. Moisture sensitive reactions were carried out by using standard syringe septum techniques under inert atmosphere (nitrogen or argon). Hexane refers to the petroleum ether fraction boiling between 60-80^{o}. All dry solvents were distilled from

appropriate drying agents just before use.

All solvent extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated on a Buchi-EL rotary evaporator or on a water bath at reduced pressure unless otherwise mentioned. All yields reported are isolated yields of material judged homogeneous by tlc and other spectroscopic techniques and for crystalline solids, material having the indicated melting point.

The chromic acid used for oxidations refers to a solution made by diluting a mixture of chromium trioxide (10 g) and concentrated sulfuric acid (16 g) to 50 ml with water.

1,1-Ethylenedioxy-8aβ-methyl-1,2,3,4,8,8a-hexahydro-6(7H)-naphthalenone (130):[49]

A mixture of WM ketone (5.00 g, 28.09 mmol), 2-ethyl-2-methyl-1,3-dioxolane (18.89 g, 163 mmol) containing 2% ethylene glycol and p-TsOH (0.100 g) was stirred at room temperature for 30h. After neutralization with triethylamine (0.5 ml), the reaction mixture was diluted with benzene (50 ml). The organic layer was washed with water, dried, and evaporated to give the crude product. Purification over a column of silica gel gave the required monoketal **130** (5.25 g, 84%) as a colourless solid.

m.p. : 64-65^{o} (hexane-ether) (Lit.[49] 65-66^{o} (hexane-ether))

IR(KBr) : 2950, 2875, 1660, 1610, 1230, 1110, 1070, 940, 860.

1,1-Ethylenedioxy-5α,8aβ-dimethyl-1,2,3,4,4a,5,8,8a-octahydro-6(7H)-naphthalenone (131):[51]

Dry ammonia (about 200 ml) was passed into the solution of the

monoketal **130** (2.122 g, 9.56 mmol) in THF (20 ml) at -78°. To this mixture, lithium (0.468 g, 66.9 mmol) was added slowly in small pieces and the contents were stirred for 1.5h at the same temperature. The reaction was quenched with iodomethane (5.95 ml, 95.6 mmol) and the ammonia allowed to evaporate over a period of 8h. Water (50 ml) was added and the compound was extracted into ether (3 x 50 ml) and the organic extract was dried and evaporated. The crude compound on chromatographic purification on silica gel (5% ethyl acetate in hexane as eluant) gave **131** (1.312 g, 57.7%) as a colourless oil.

IR (neat): 2950, 1700, 1440, 1180, 1120, 1030, 850

PMR : δ 3.94-3.81 (m, 4H, $-OCH_2CH_2O-$), 2.44-1.40 (m, 12H), 1.24 (s, 3H, 8a-CH_3), 0.97 (d, 3H, 5-CH_3, J = 6).

1,1-Ethylenedioxy-5α,8aβ-dimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (132):[51]

A solution of the ketone **131** (1.865 g, 7.836 mmol) and p-toluenesulfonylhydrazide (1.749 g, 9.39 mmol) in THF (60 ml) was refluxed overnight in a nitrogen atmosphere. The reaction mixture was cooled and poured into water and extracted with dichloromethane (2 x 50 ml). The organic layer was dried and evaporated to give the crude p-toluenesulfonylhydrazone (3.100 g, 97%) of **131**. The IR spectrum of this compound showed no carbonyl band.

To a stirred solution of lithium diisopropylamide (34.0 mmol, prepared from 42.5 mmol of diisopropylamine and 34 mmol of 1.2M n-butyllithium in hexane) in THF (40 ml) at 0° was added a solution of the above crude p-toluenesulfonylhydrazone (3.100 g) in THF (10 ml)

and the stirring was continued for another 1h before quenching with water. Workup as usual with dichloromethane (2 x 20 ml) gave the crude olefin **132**. Upon chromatographic purification over a column of silica gel, eluting with 5% ethyl acetate in hexane, the pure olefin **132** (1.306 g, 75%) was obtained.

IR (neat): 3025, 2950, 2890, 1470, 1380, 1190, 1130, 1090, 1060

PMR : δ 5.64-5.22 (m, 2H, -CH=CH-), 3.87 (br s, 4H, $-OCH_2CH_2O-$) 2.40-1.06 (m, 10H), 0.97 (br s, 3H, 5-CH_3), 0.93 (s, 3H, 8a-CH_3).

5α,8aβ-Dimethyl-3,4,4a,5,8,8a-hexahydro-1(2H)-naphthalenone (133):

To a stirred solution of the ketal **132** (2.144 g, 9.66 mmol) in THF (50 ml) was added 1M HCl (8 ml) and the mixture refluxed for 1h. After dilution with water and extraction with dichloromethane (2 x 50 ml), the organic extract was dried and evaporated to give the crude compound, which was chromatographed over a column of silica gel to give the pure ketone **133** (1.70 g, 99%) as a low melting solid.

IR(neat) : 2950, 2875, 1710, 1450, 1430, 970, 825, 700

PMR : δ 5.70-5.22 (m, 2H, -CH=CH-), 2.82-1.18 (m, 10H), 1.10 (s, 3H, 8a-CH_3), 1.02 (d, 3H, 5-CH_3, J = 6)

CMR : 215.19, 131.48, 123.71, 48.53, 47.00, 37.47, 32.94, 32.83, 25.41, 24.18, 19.24, 16.70.

Preparation of the diols 134a and 134b:

To a solution of the olefinic ketone **133** (0.534 g, 3 mmol) in acetone (0.60 ml) were added water (1.50 ml), t-BuOH (0.24 ml), N-methylmorpholine-N-oxide.dihydrate (0.487 g), and osmium tetroxide

(0.005 g), respectively, and the contents stirred for 7h at room temperature under nitrogen atmosphere. A slurry of sodium hydrosulfite (0.030 g), magnesium silicate or magnesol (0.50 g), and water (3 ml) was added to the reaction mixture and the magnesol was filtered. The filtrate was saturated with NaCl and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were dried and evaporated to give the crude compound. Chromatographic purification over a column of silica gel gave the ß-isomer **134b** as the major component first followed by the α-isomer **134a** as the minor component.

5α,8aβ-Dimethyl-6α,7α-dihydroxy-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (134a):

Yield : 0.084 g (13%)

m.p. : 118° (hexane-ethyl acetate)

IR(KBr) : 3450, 3400, 2960, 1710, 1380, 1250, 1170, 980

PMR : δ 3.81-3.61 (m, 1H, 7-C<u>H</u>OH), 3.00-2.80 (m, 1H, 6-C<u>H</u>OH), 2.64-1.32 (m, 10H), 1.10 (s, 3H, 8a-CH_3), 0.98 (d, 3H, 5-CH_3, J = 6).

5α,8aβ-Dimethyl-6β,7β-dihydroxy-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (134b):

Yield : 0.401 g (63%)

IR (KBr) : 3425, 3325, 2950, 1710, 1435, 1250, 1105, 1050, 960

PMR : δ 4.18-4.00 (m, 1H, 7-C<u>H</u>OH), 3.20-2.94 (m, 1H, 6-C<u>H</u>OH), 2.78-1.48 (m, 10H), 1.38 (s, 3H, 8a-CH_3), 1.04 (d, 3H, 5-CH_3, J = 7).

Analysis : $C_{12}H_{20}O_3$: Calcd. : C, 67.89; H, 9.497

Found : C, 67.68; H, 9.530

1(2H)-Oxo-5α,8aβ-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-6β,7β-naphthalenediol dibenzoate (135):

To a solution of the diol **134b** (0.020 g, 0.094 mmol) in pyridine (2 ml) containing DMAP (0.005 g) was added benzoyl chloride (0.044 ml) and the reaction mixture stirred at room temperature overnight. After pouring into ice-water, the contents were extracted with ether (2 x 30 ml), the organic layer washed with water, dried and evaporated to give the crude compound, which was crystallized from hexane-ether to give the ester **135** (0.038 g, 95%) as a colourless solid.

m.p. : 105° (hexane-ether)

IR(KBr) : 3000, 1720, 1270, 1110, 705

PMR (Fig.1) : δ 8.02-6.96 (m, 10H, Ph), 5.76 (dt appearing as a quartet, 1H, H-7, J = 4,8), 4.87 (dd, 1H, H-6, J = 4,12), 2.96-1.52 (m, 10H), 1.48 (s, 3H, 8a-CH_3), 0.98 (d, 3H, 5-CH_3, J = 6).

5α,8aβ-Dimethyl-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (136):

A mixture of the diol **134b** (0.20 g, 0.943 mmol), acetone (5 ml) and anhydrous $CuSO_4$ (5.0 g) containing a trace amount of conc. H_2SO_4 was stirred at room temperature for 12h under nitrogen. The reaction mixture was quenched by adding solid $NaHCO_3$ (0.5 g) and filtered. The inorganic salts were repeatedly washed with ethyl acetate and the combined filtrates were evaporated to give an oily material, which was crystallized from hexane to give the ketone **136** (0.221 g, 93%).

m.p. : 90° (hexane)

IR : 2950, 2875, 1710, 1460, 1390, 1380, 1240, 1225, 1060

PMR : δ 4.25 (dt, 1H, H-7, J = 6,2), 3.41 (dd, 1H, H-6, J = 6,9), 2.70-1.50 (m, 10H), 1.44 (s, 3H, 8a-CH_3), 1.32 (s, 6H, acetonide CH_3), 0.98 (d, 3H, 5-CH_3, J = 7)

CMR (Fig.2) : 214.5, 107.5, 81.1, 73.1, 47.5, 47.1, 36.5, 34.4, 32,7, 28.6, 26.0, 23.2, 18.4, 15.7.

2,5α,8aβ-Trimethyl-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (137):

A solution of diisopropylamine (0.11 ml, 0.8 mmol in THF (1 ml) was cooled to -5 to -10°. n-Butyllithium (0.5 ml, 0.6 mmol, 1.2M in hexane) was injected and the contents stirred at the same temperature for 30 min. A solution of the ketone **136** (0.10 g, 0.4 mmol) in THF (2 ml) was injected slowly. After stirring for another 1h at the same temperature iodomethane (0.7 ml, 1.2 mmol) was injected and the reaction mixture allowed to reach room temperature. The reaction mixture was poured into water and after usual workup with ethyl acetate (3 x 25 ml) the residue was charged over a silica gel (25 g) column and eluted with 5% ethyl acetate in hexane to furnish the methylated ketone **137** (0.100 g, 95%) as a colourless liquid.

IR (neat): 3000, 2950, 2875, 1720, 1390, 1380, 1250, 1220, 1060

PMR (Fig.3) : δ 4.34 (dt, 1H, H-7, J = 4,2), 3.48 (dd, 1H, H-6, J = 4,10), 2.86-1.54 (m, 9H), 1.46 (s, 6H, acetonide CH_3), 1.34 (s, 3H, 8a-CH_3), 1.08 (two doublets appea- ring as a triplet, 6H, 5-CH_3 and 2-CH_3)

CMR (Fig.2a) : 214.6, 107.5, 81.1, 73.0, 47.6, 47.2, 41.2, 36.6, 34.5, 32.7, 28.6, 26.0, 23.3, 18.6, 15.8.

1-Trimethylsilyloxy-5α,8aβ-dimethyl-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydronaphthalene (139):

To a stirred solution of the ketone **136** (0.073 g, 0.29 mmol) and TMSCl (0.044 ml, 0.347 mmol) in dichloromethane (2 ml) was added DBU (0.056 ml, 0.375 mmol) and the contents refluxed for 24h. After removal of the solvent under vacuum, the compound was taken into hexane. Removal of the solvent gave reasonably pure enol ether **139** (0.082 g. 87%). However, chromatographic purification over a column of silica gel led to partial hydrolysis of the enol ether.

IR(neat) : 2950, 1640, 1390, 1380, 1240, 1220, 1050, 850

PMR : δ 4.50 (t, 1H, H-2, J = 4), 4.22 (dt, 1H, H-7, J = 5,2), 3.46 (dd, 1H, H-6, J = 5,10), 2.46-1.48 (m, 8H), 1.46 (s, 3H, acetonide CH_3), 1.32 (s, 3H, acetonide CH_3), 1.18 (s, 3H, 8a-CH_3), 0.96 (d, 3H, 5-CH_3, J = 6), 0.18 (s, 9H, $-Si(CH_3)_3$).

2-Bromo-5α,8aβ-dimethyl-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (141):

A mixture of the enol ether **139** (0.023 g, 0.071 mmol) and NBS (0.014 g, 0.078 mmol) in THF (2 ml) was stirred at 0^{o} for 15 min and quenched by adding saturated $NaHCO_3$. The compound was extracted into dichloromethane (2 x 20 ml) and the organic layer was dried and evaporated to give the crude bromo compound. Chromatographic purification over a column of silica gel gave the required bromo ketone **141** [0.006 g, 31%, based on the ketone **136** recovered

(0.004 g)] as a syrup.

IR(neat) : 2950, 2875, 1725, 1380, 1390, 1225, 1060.

5α,8aβ-Dimethyl-6β,7β-O-methylethylidene-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (140):

Method 1:

To a stirred solution of the bromo ketone **141** (0.006 g, 0.018 mmol) in benzene (1 ml) was added DBU (0.004 ml, 0.029 mmol) and refluxed for 0.5h. After usual workup with dichloromethane, crude compound was purified over a column of silica gel (eluant: 3-5% ethyl acetate in hexane) to give the enone **140** (0.003 g, 67%).

Method 2:

A mixture of the enone **148** (0.069 g, 0.329 mmol), anhydrous acetone (5 ml) and $CuSO_4$ (1.00 g), containing a trace amount of conc. H_2SO_4 was stirred under nitrogen for 6h at room temperature. After neutralization with solid $NaHCO_3$ (0.200 g), the mixture filtered and the inorganic salts washed with ethyl acetate. The combined organic layers were evaporated to give the crude isopropylidene derivative **140**. Chromatographic purification over a column of silica gel gave **140** (0.060 g, 73%) as a solid.

m.p. : 109-110^{o} (hexane-ethyl acetate)

IR (KBr) : 3000, 2950, 2900, 1665, 1460, 1380, 1375, 1240, 1060.

PMR (Fig.4) : δ 6.88 (ddd, 1H, H-2, J = 3,6,10), 5.90 (ddd, 1H, H-3, J = 2,3,10), 4.28 (dt, 1H, H-7, J = 2,4), 3.48 (dd, 1H, H-6, J = 4,8), 2.58-1.68 (m, 6H), 1.59 (br s, 2H, H-4), 1.50 (s, 3H, acetonide CH_3), 1.35 (s, 3H, acetonide CH_3), 1.23 (s, 3H, 8a-CH_3), 1.03 (d,

3H, 5-CH_3, J = 6).

2-Phenylsulfenyl-5α,8aβ-dimethyl-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (142):

The enol ether **139** (0.061 g, 0.18 mmol) was dissolved in dichloromethane (4 ml) and cooled to -78° under nitrogen. To this solution was added phenylsulfenyl chloride (0.030 g, 0.21 mmol) in dichloromethane (2 ml) and the solution stirred at the same temperature for 15 min. The reaction was quenched with water and worked up as usual with dichloromethane (2 x 15 ml). The crude compound was purified over a column of silica gel to give the pure -phenylsulfenyl ketone **142** (0.062 g, 91%) as an oil.

IR (neat): 2950, 1720, 1600, 1390, 1380, 1230, 1060, 740, 690

PMR : δ 7.46-7.14 (m, 5H, Ph), 4.36-4.08 (m, 1H, H-7), 3.52-3.28 (m, 1H, H-6), 2.40-1.52 (m, 9H), 1.44 (s, 3H, acetonide CH_3), 1.36 (s, 3H, acetonide CH_3), 1.30 (s, 3H, 8a-CH_3), 0.96 (d, 3H, 5-CH_3, J = 6).

Preparation of enones 145 and 146 from the ketone 137:

(i) Bromination of 137 with $CuBr_2$:

Copper(II) bromide (0.178 g, 0.8 mmol) was placed in a 25 ml two necked RB flask and ethyl acetate (2 ml) was added and brought to reflux. The compound **137** (0.100 g, 0.376 mmol) in chloroform (2 ml) was injected and the refluxing continued for 3h. At this time all the black copper(II) bromide became green to ambar copper(I) bromide. Reaction mixture was brought to room temperature and filtered the inorganic salt. Evaporation of the solvent gave two major brominated components (0.112 g) as indicated on tlc. As

the products were unstable, no attempt was made to purify them.

(ii) Dehydrobromination:

The above crude mixture of bromo compounds were dissolved in benzene (5 ml) and DBU (0.149 ml, 1.0 mmol) was added and refluxed for 8h. After cooling to room temperature, the reaction mixture was poured into water, extracted with ethyl acetate (4 x 25 ml) and worked up as usual. The crude residue was charged on a silica gel (25 g) column and, first eluted with 5-10% ethyl acetate in hexane to give the enone **146** (0.058 g, 56% from ketone **137**) as a colourless solid with isopropylidene group intact. Further elution of the column with 20% ethyl acetate in hexane furnished the dihydroxy enone **145** (0.019 g, 19% from ketone **137**) as a colourless syrup.

2,5α,8aβ-Trimelthyl-6β,7β-O-methylethylidene-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (146):

m.p. : 112-113° (hexane-ethyl acetate)

IR (KBr) : 2980, 2950, 1665, 1440, 1360, 1100, 1060, 1000, 710

PMR (Fig.5) : δ 6.68-6.50 (m, 1H, H-3), 4.28 (dt, 1H, H-7, J = 2,4), 3.42 (dd, 1H, H-6, J = 4,8), 2.48-1.44 (m, 9H), 1.74 (br s, 2H, H-4), 1.46 (s, 3H, 2-CH_3), 1.32 (s, 6H, acetonide CH_3), 1.15 (s, 3H, 8a-CH_3), 0.98 (d, 3H, 5-CH_3, J = 6).

2,5α,8aβ-Trimethyl-6β,7β-dihydroxy-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (145):

IR (neat): 3400, 2950, 1665, 1460, 1375, 1240, 1040.

Preparation of the enone 146 from 145:

A mixture of the enone **145** (0.019 g, 0.085 mmol), acetone (3 ml), and anhydrous $CuSO_4$ containing a trace amount of conc. H_2SO_4

was stirred at room temperature for 8h under nitrogen atmosphere and worked up according to the procedure given for the ketone **136** to give the crude enone **146**. The crude compound was loaded onto a silica gel (15 g) column and eluted with 5-10% ethyl acetate in hexane to furnish the enone **146** (0.018 g, 80%) as a colourless solid. Spectral data of this compound was identical to the previous enone.

2-Bromo-5α,8aβ-dimethyl-6β,7β-dihydroxy-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (147):

Copper(II) bromide (0.316 g, 1.42 mmol) was placed in a 25 ml two necked RB flask and ethyl acetate (3 ml) was added and the contents brought to reflux. The compound **134b** (0.150 g, 0.70 mmol) in chloroform (3 ml) was injected and brominated as described earlier to give the crude brominated product **147** (0.130 g).

IR (neat): 3400, 2950, 1720, 1450, 1040, 960, 830, 740, 710.

5α,8aβ-Dimethyl-6β,7β-dihydroxy-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (148):

The above crude bromo ketone **147** (0.130 g) and DBU (0.204 g, 1.34 mmol) in benzene (10 ml) was refluxed for 5h, cooled to room temperature and poured into water. Extraction into ethyl acetate (5 x 25 ml) and workup as usual gave the crude compound. Chromatographic purification over a column of silica gel furnished the pure enone **148** (0.069 g, 46.3% from ketone **134b**) as a syrup.

IR (neat): 3400, 2930, 1665, 1450, 1380, 1250, 1040, 1020

PMR : δ 6.98-6.72 (m, 1H, H-3), 5.96-5.76 (m, 1H, H-2), 4.18-4.00 (m, 1H, H-7), 3.22-3.00 (m, 1H, H-6), 2.64-1.34 (m,

6H), 1.36 (s, 3H, 8a-CH_3), 1.00 (d, 3H, 5-CH_3, J = 6).

3-[2-(2,2-Dimethoxyethyl)-1,3-dithiano]-5α,8aβ-dimethyl-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (149):

The dithiane **125** (0.100 g, 0.48 mmol) was placed in a 25 ml two necked RB flask and flushed with nitrogen. Dry THF (2 ml) was introduced and the solution cooled to 0^{o}. n-Butyllithium (0.36 ml, 1.2M in hexane, 0.38 mmol) was slowly added to the dithiane solution and stirred at the same temperature for 2h. HMPA (1 ml) was added to the reaction mixture and stirred for another 30 min at the same temperature. The enone **140** (0.060 g, 0.24 mmol) in THF (1 ml) was added to the reaction mixture and stirred for 6h before quenching with saturated NH_4Cl. Workup as usual with ethyl acetate (2 x 25 ml), gave a crude product which was purifed by chromatography on silica gel (25 g). Elution with 5% ethyl acetate in hexane gave the pure ketone **149** (0.060 g, 54.6%) as a pale yellow oil.

IR (neat): 2950, 2850, 1720, 1390, 1380, 1250, 1230, 1130, 1060

PMR : δ 4.62 (t, 1H, -OCHO-), 4.30-4.08 (m, 1H, H-7), 3.56-3.34 (m, 1H, H-6), 3.32 (s, 6H, -OCH_3), 2.98-2.40 (m, 4H, -SCH_2-), 3.32 (d, 2H, -$\underline{CH_2}CH(OMe)_2$), 2.24-1.52 (m, 9H), 1.46 (s, 3H, acetonide CH_3), 1.30 (s, 3H, acetonide CH_3), 1.20 (s, 3H, 8a-CH_3), 1.04 (d, 3H, 5-CH_3).

2,5α,8aβ-Trimethyl-3-[2-(2,2-dimethoxyethyl)-1,3-dithiano]-6β,7β-O-methylethylidene-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (150):

Following the above procedure the enone **146** (0.050 g, 0.189 mmol) was reacted with the dithiane **125** (0.079 g, 0.378 mmol) to give the ketone **150** (0.048 g, 54%).

IR(neat): 2950, 1710, 1460, 1380, 1210, 1130, 1060, 900, 750

PMR : δ 4.61 (t, 1H, -OCHO-), 4.34-4.10 (m, 1H, H-7), 3.68-3.42 (m, 1H, H-6), 3.32 (s, 6H, $-OCH_3$), 2.98-2.52 (m, 4H, $-SCH_2-$), 2.40 (d, 2H, $-\underline{CH_2}CH(OMe)_2$), 2.32-1.72 (m, 9H), 1.46 (s, 3H, acetonide CH_3), 1.36 (s, 3H, acetonide CH_3), 1.28 (s, 3H, 8a-CH_3), 1.08 (two doublets appearing as a broad triplet, 6H, 5-CH_3 and 2-CH_3).

Attempted addition of vinylmagnesium bromide to the ketone 150:

To a solution of vinylmagnesium bromide [prepared from Mg (0.021 g, 0.90 mg-atom) and vinyl bromide (1.0 ml, approximately 1.5M in THF)] in THF (1 ml) was added a solution of the ketone **150** (0.044 g, 0.09 mmol) in THF (2 ml) and stirred at room temperature for 2h, then at reflux for 12h. The reaction was quenched by adding saturated NH_4Cl and worked up as usual with ethyl acetate (2 x 20 ml) to give a crude mixture. The IR spectrum of the mixture showed a strong O-H band (3400 cm^{-1}) and a weak carbonyl band (1700 cm^{-1}). However, tlc showed a complex mixture and no purification was attempted.

2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-ol (155):[61]

Starting from 10.0 g (52 mmol) of α-ionone, alcohol **155** was prepared in four steps in 41% overall yield (3.56 g) according to the literature procedure. The only difference was that instead of methyltriphenylphosphonium chloride, methyltriphenylphosphonium

iodide was used in the last step.

IR (neat): 3350, 2925, 1610, 1440, 1030, 1000, 960, 920, 900, 880

PMR : δ 6.16 (dd, 1H, $-\underline{CH}=CH_2$, J = 12,18), 5.36-5.18 (m, 2H, $-CH_2=\underline{CH}-H$ and H-1), 4.99 (dd, 1H, $-CH=CH-\underline{H}$, J = 2,18), 1.71 (br s, 3H, allylic CH_3), 1.68-1.20 (m, 4H), 1.03 (s, 3H, 4-CH_3), 0.99 (s, 3H, 4-CH_3).

5-Ethyl hydrogen-2-ketoglutarate (161):[64]

This compound was prepared as reported in the literature in 41% yield.

IR(neat) : 3250, 3000, 2650, 1810, 1725, 1280, 1180, 1050

PMR : δ 4.24 (q, 2H, $-CO_2\underline{CH_2}CH_3$), 3.18 and 2.72 (t, each 2H, $-CH_2CH_2-$), 1.32 (t, 3H, $-CO_2CH_2\underline{CH_3}$).

General procedure for preparation of the esters 162, 196, 197, 205, 206, 215, 216, 217, and 221:

In a 50 ml two necked RB flask was placed the alcohol **155** (1 equiv.), the acid (1.5 equiv., 1.1 equiv. in the case of the acids **194** and **195**) and dichloromethane (10 ml/mmol). The solution was cooled to 0^{o} and DCC (1.5 equiv.) was added followed by DMAP (0.1 equiv.). The reaction mixture was allowed to reach room temperature. Dicyclohexylurea started precipitating out as the esterification proceeded. The progress of the reaction was monitored by tlc; it was over in 12-15h. The reaction mixture was poured into water and extracted with dichloromethane and the combined organic extract was dried and evaporated. The residue was loaded onto a silica gel (15 to 20 g) column. Elution with 2-3% ethyl acetate in hexane afforded the esters as pure, colourless

liquids. The acid **210** gave a mixture of cis- and trans- esters as crystalline solids.

Ethyl 2-oxo-5-(2,4,4-trimethyl-3-ethenyl-2-cyclohexen-1-yl)glutarate (162):

Yield : 56% (based on the starting alcohol recovered)

IR (neat): 2950, 1800, 1725, 1390, 1380, 1260, 1210, 1080, 1040

PMR : δ 6.20 (dd, 1H, $-\underline{CH}=CH_2$, J = 11,18), 5.30 (m, 2H, $-CH=CH-\underline{H}$ and -CHOCO-) 5.04 (dd, 1H, $-CH=CH-\underline{H}$, J = 3,18), 4.34 (q, 2H, $-CO_2\underline{CH_2}CH_3$), 3.18 and 2.68 (t, each 2H, $-CH_2\underline{CH_2}-$), 2.00-1.20 (m, 4H), 1.68 (s, 3H, 2-CH_3), 1.40 (t, 3H, $-CO_2CH_2\underline{CH_3}$), 1.02 (s, 3H, 4-$CH_3$), 1.00 (s, 3H, 4-$CH_3$).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 5-benzyloxy-(3Z)-pentenoate (196):

Yield : 63%

IR (neat): 2950, 1725, 1460, 1170, 1100, 990, 960, 920, 740, 700

PMR : δ 7.26 (s, 5H, Ph), 6.34-5.94 (dd, 1H, $-\underline{CH}=CH_2$, J = 12,18), 5.84-4.84 (m, 5H, $-CH=\underline{CH_2}$, H-1, and $-\underline{CH}=\underline{CH}-$), 4.46 (s, 2H, $Ph\underline{CH_2}-$), 4.02 (br t, 1H, $-\underline{CH_2}OBn$), 3.44 (distorted triplet, 1H, $\underline{CH_2}OBn$), 3.08 (br d, 1H, $-OCOCH-\underline{H}$), 2.42-2.18 (distorted triplet, 1H, $-OCO\underline{CH}-H$), 1.92-1.00 (m, 4H, $-CH_2CH_2-$), 1.62 (br s, 3H, allylic CH_3), 1.02 (s, 3H, 4-CH_3), 0.96 (s, 3H, 4-CH_3).

Analysis : $C_{22}H_{30}O_3$: Calcd. : C, 77.920; H, 8.530

Found : C, 77.730; H, 9.080

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 5-(4-methoxybenzyl-oxy)-(3Z)-pentenoate (197):

Yield : 84%

IR (neat): 2925, 2850, 1720, 1605, 1450, 1240, 1160, 960, 920, 830

PMR : δ 7.32-6.72 (m, 4H, aromatic protons), 6.34-5.94 (dd, 1H, $-\underline{CH}=CH_2$, J = 11,18), 5.84-5.66 (m, 2H, -CH=CH-), 5.38-5.14 (m, 2H, $-CH=\underline{CH}-H$ and H-1), 5.12-4.84 (dd, 1H, $-CH=CH-\underline{H}$, J = 3,18), 4.39 (s, 2H, $-Ph\underline{CH_2}-$), 4.06-3.94 (m, 2H, H-5), 3.76 (s, 3H, $-OCH_3$), 3.16-3.00 (m, 2H, $-OCOCH_2-$), 1.92-1.14 (m, 4H, $-CH_2CH_2-$), 1.62 (br s, 3H, allylic CH_3), 1.00 (s, 3H, 4-CH_3), 0.96 (s, 3H, 4-CH_3).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 3-butynoate (205a):

Yield : 27.5%

IR (neat): 3300, 2950, 2150, 1720, 1160, 960, 920

PMR : δ 6.18 (dd, 1H, $-\underline{CH}=CH_2$, J = 12,18), 5.46-5.16 (m, 2H, $-CH=CH-\underline{H}$ and H-1), 5.01 (dd, 1H, $-CH=CH-\underline{H}$, J = 3,18), 3.48 (s, 2H, $-\underline{CH_2}COO-$), 2.28 (s, 1H, $-C\equiv CH$), 2.10-1.18 (m, 4H, $-CH_2CH_2-$), 1.69 (br s, 3H, allylic CH_3), 1.04 (s, 3H, 4-CH_3), 1.00 (s, 3H, 4-CH_3).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 2,3-butadienoate (205b):

Yield : 25%

IR (neat): 2925, 1970, 1940, 1720, 1120, 980, 850

PMR : δ 6.18 (dd, 1H, $-\underline{CH}=CH_2$, J = 11,16), 5.66 (t, 1H, H-1), 5.40-4.9 (m, 4H, $-CH=\underline{CH_2}$ and $=C=CH_2$), 3.32 (s, 1H,

-OCOCH=), 2.00-1.10 (m, 4H, $-CH_2CH_2-$), 1.67 (br s, 3H, allylic CH_3), 1.04 (s, 3H, 4-CH_3), 1.00 (s, 3H, 4-CH_3).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 4-trimethylsilyl-3-butynoate (206):

Yield : 46%

IR (neat): 2925, 2875, 2190, 1725, 1255, 1160, 850

PMR : δ 6.18 (dd, 1H, $-\underline{CH}=CH_2$, J = 12,18), 5.38-5.13 (m, 2H, -CH=CH-H and H-1), 5.00 (dd, 1H, -CH=CH-H, J = 3,18), 3.30 (s, 2H, $-CH_2COO-$), 1.98-1.08 (m, 4H, $-CH_2CH_2-$), 1.67 (br s, 3H, allylic CH_3), 1.04 (s, 3H, 4-CH_3), 1.00 (s, 3H, 4-CH_3), 0.16 (s, 9H, $-Si(CH_3)_3$).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl)-(2E)-butenoate (215):

Yield : 53% (based on the recovered alcohol)

IR (neat): 2950, 1705, 1450, 1390, 1380, 1180, 1000, 970, 920

PMR : δ 7.02 (dt, 1H, $=\underline{CH}CH_3$, J = 6,18), 6.20 (dd, 1H, $-\underline{CH}=CH_2$, J = 10,18), 5.66 (dd, 1H, $-CO\underline{CH}=CH-$, J = 18,2), 5.40-5.20 (m, 2H, -CH=CH-H and -CHOCO-), 5.02 (dd, 1H, -CH=CH-H, J = 3,18), 1.86 (dd, 3H, $=CH\underline{CH_3}$, J = 6,2), 1.68 (s, 3H, 2-CH_3), 1.64-1.10 (m, 4H), 1.04 (s, 3H, 4-CH_3), 1.00 (s, 3H, 4-CH_3).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) (E)-3-trimethylsilyl-propenoate (216):

Yield : 77%

IR (neat): 2975, 1720, 1230, 1170, 1000, 870, 840

PMR : δ 7.29 (d, 1H, $-COCH=\underline{CH}-$, J = 19), 6.27 (d, 1H,

-CO<u>CH</u>=CH-, J = 19), 6.16 (dd, 1H, -<u>CH</u>=CH_2, J = 12,18), 5.32 (m, 2H, CH=CH-<u>H</u> and H-1), 5.01 (dd, 1H, -CH=<u>CH</u>-H, J = 3,18), 2.04-1.24 (m, 4H, -CH_2CH_2-), 1.70 (br s, 3H, allylic CH_3), 1.06 (s, 3H, 4-CH_3), 1.02 (s, 3H, 4-CH_3), 0.18 (s, 9H, -$Si(CH_3)_3$).

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) (E)-3-phenylsulfonyl-propenoate (217a):

Yield : 31%

m.p. : 86° (hexane-ether)

IR (KBr) : 3060, 2960, 1720, 1325, 1290, 1230, 1150, 1090, 830, 740, 690

PMR : δ 8.00-7.46 (m, 5H, Ph), 7.31 (d, 1H, -<u>CH</u>=CHSO_2Ph, J = 16), 6.81 (d, 1H, -CH=<u>CH</u>SO_2Ph, J =16), 6.13 (dd, 1H, -<u>CH</u>=CH_2, J = 12,18), 5.40-5.18 (m, 2H, -CH=CH-<u>H</u> and H-1), 5.00 (dd, 1H, -CH=<u>CH</u>-H, J = 3,18), 2.02-1.12 (m, 4H, -CH_2CH_2-), 1.64 (br s, 3H, allylic CH_3), 1.03 (s, 3H, 4-CH_3), 0.98 (s, 3H, 4-CH_3).

Analysis : $C_{20}H_{24}O_4S$: Calcd. : C, 66.638; H, 6.711

Found : C, 66.600; H, 6.740

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) (Z)-3-phenylsulfonyl-propenoate (217b):

Yield : 35%

m.p. : 96° (hexane-ether)

IR (KBr) : 3050, 2960, 1720, 1620, 1320, 1225, 1150, 870, 770, 740, 700, 690

PMR : δ 8.09-7.43 (m, 5H, Ph), 6.51 (s, 2H, -CH=CHSO$_2$Ph), 6.18 (dd, 1H, -CH=CH$_2$, J = 11,18), 5.19-5.21 (m, 2H, -CH=CH-H and H-1), 5.03 (dd, 1H, -CH=CH-H, J = 3,18), 2.09-1.17 (m, 4H, -CH$_2$CH$_2$-), 1.76 (br s, 3H, allylic CH$_3$), 1.06 (s, 3H, 4-CH$_3$), 1.03 (s, 3H, 4-CH$_3$).

Analysis : $C_{20}H_{24}O_4S$: Calcd. : C, 66.638; H, 6.711
Found : C , 66.137; H, 6.617

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) acetate (221):

Yield : 70%

IR (neat): 2925, 1875, 1725, 1240, 1020, 960, 920

PMR : δ 6.16 (dd, 1H, -CH=CH$_2$, J = 10,18), 5.36-5.20 (m, 2H, -CH=CH-H and -CHOAc), 5.00 (dd, 1H, -CH=CH-H, J = 3,18), 1.92 (s, 3H, -OCOCH$_3$), 1.70 (br s, 3H, allylic CH$_3$), 1.68-1.25 (m, 4H), 1.03 (s, 3H, 4-CH$_3$), 0.99 (s, 3H, 4-CH$_3$).

Attempted preparation of the enol acetate of ketone 162:

A mixture of the ketone **162** (0.025 g, 0.078 mmol) and isopropenyl acetate (2 ml) containing trace amount of p-TsOH was stirred at room temperature for 10h. Tlc of the reaction mixture did not show any new spot. The reaction was stirred for another 14h. After diluting with water, the compound was extracted into dichloromethane (2 x 15 ml) and the organic layer was dried and evaporated to give back the starting ketone **162** (0.015 g).

Ethyl 2-hydroxy-5-(2,4,4-trimethyl-3-ethenyl-2-cyclohexen-1-yl)glutarate (163):

To a solution of the keto ester **162** (0.010 g, 0.03 mmol) in ethanol (1 ml) at 0-5° was added $NaBH_4$ and the mixture stirred for 30 min before quenching with water. The product was extracted into ethyl acetate (2 x 20 ml) and the organic layers dried and evaporated to give the crude alcohol. Purification by chromatography on silica gel (15 g) column using 50-60% ethyl acetate in hexane as eluant gave the pure alcohol **163** (0.008 g, 80%) as a syrup.

IR (neat): 3400, 2950, 1710, 1390, 1380, 1160, 1030, 1000, 970

PMR : δ 6.20 (dd, 1H, -$\underline{CH}$=CH_2, J = 12,18), 5.28 (m, 2H, -CH=CH-$\underline{H}$ and -CHOCO-), 5.02 (dd, 1H, -CH=$\underline{CH}$-H, J = 3, 18), 4.38-4.04 (m, 3H -$CO_2\underline{CH_2}CH_3$ and -$\underline{CH}$OH), 3.00-2.76 (m, 2H, -HOCH$\underline{CH_2}CH_2$-), 2.60-2.34 (m, 2H, -HOCHC$H_2\underline{CH_2}$-), 1.66 (s, 3H, 2-CH_3), 2.20-1.14 (m, 5H), 1.30 (t, 3H, -$CO_2CH_2\underline{CH_3}$), 1.04 (s, 3H, 4-CH_3), 1.00 (s, 3H, 4-CH_3).

Attempted dehydration of the alcohol 163:

A mixture of the alcohol **163** (0.016 g, 0.05 mmol) and $CuSO_4$ (0.10 g) in benzene (3 ml) was refluxed for 2h, cooled to room temperature and filtered. Evaporation of the filtrate gave only starting material (0.014 g).

When p-TsOH was used as the dehydrating agent, an intractable mixture resulted. A similar result was observed with $POCl_3$/pyridine also.

5-(2-Tetrahydropyranyloxy)-3-pentyn-1-ol (173):[65]

According to literature procedure, alcohol **173** (7.0 g, 28%,

based on recovered starting ether, 11.0 g) was prepared, starting from 2-propynyl (2-tetrahydropyranyl) ether (28.0 g, 0.2 mol) and about 20 g (0.45 mol) of ethylene oxide in THF (50 ml).

b.p. : 116-120°/0.75 mm (Lit.[65] 116-120°/0.7 mm)

IR (neat): 3380, 2920, 2250, 1460, 1120, 1040

PMR : δ 4.76 (br s, 1H, -OCHO-), 4.22 (t, 2H, -$\underline{CH_2}$OH), 3.90-3.36 (m, 4H, ring protons), 2.58-2.16 (m, 2H, -$OCH_2C\underline{\equiv}C$-), 1.84-1.16 (m, 6H).

5-(2-Tetrahydropyranyloxy)-(3Z)-penten-1-ol (174):[65]

According to the literature procedure, acetylenic alcohol **173** (1.0 g, 5.43 mmol) in benzene (5 ml) was hydrogenated in a Paar hydrogenation apparatus at 28 psi with Lindlanr catalyst (0.1 g) to give the product **174** (0.97 g, 96%).

b.p. : 120° (bath temperature)/0.35 mm (Lit.[65] 94-96°/0.35 mm)

IR (neat): 3450, 2950, 1460, 1120, 1040

PMR : δ 5.80-5.52 (m, 2H, -CH=CH-), 4.62 (s, H, -OCHO-), 4.14 (dd, 2H, -$O\underline{CH_2}$CH=CH-), 3.64 (t, 2H, -$\underline{CH_2}$OH), 2.38 (q, 2H, -$\underline{CH_2}CH_2$OH), 2.00-1.30 (m, 9H).

Attempted preparation of 5-(2-tetrahydropyranyloxy)-3-pentynoic acid (167):

Method i: By oxidizing the alcohol 173 with PDC:

A solution of the alcohol **173** (0.184 g, 1 mmol) in DMF (5 ml) at room temperature was treated with PDC (1.316 g, 3.5 mmol) and the mixture stirred for 10h. After usual workup and purification of the crude compound over a column of silica gel (15 g), only the starting material (0.150 g) was recovered.

Method ii: By oxidizing 175 with AgO:

5-(2-Tetrahydropyranyloxy)-3-pentyn-1-al (175):

A mixture of the alcohol **173** (0.184 g, 1 mmol), AgO (0.372 g, 3 mmol) and DMSO (5 ml) was maintained at 80° for 16h and filtered Water was added and the compound was extracted with ether (3 x 25 ml). After usual workup, the crude compound was loaded onto a silica gel (15 g) column and eluted with 2-3% ethyl acetate in hexane to give the aldehyde **175** (0.027 g, 20%, based on recovered alcohol) as a colourless oil. Further elution of the column with 10% ethyl acetate in hexane gave the starting alcohol **173** (0.050 g).

IR (neat): 2960, 2760, 2220, 1740, 1140, 1050

PMR : δ 9.06 (s, 1H, -CHO), 4.74 (s, 1H, -OCHO-), 4.12 (br s, 2H, -$\underline{CH_2}$CHO), 4.22-3.30 (m, 4H), 2.50 (q, 2H), 2.10-1.30 (m, 4H).

Further oxidation of the aldehyde **175** (0.027 g, 0.148 mmol) using AgO (0.372 g, 3.0 mmol) in DMSO did not lead to the acid **167**.

Attempted preparation of 5,5-diethoxy-3-pentenoic acid (168):

To a suspension of NaH (0.240 g, 10 mmol) in THF (5 ml) at 0° was added a solution of diethoxyacetaldehyde (0.528 g, 4 mmol) and 2-carboxyethyltriphenylphosphonium chloride (1.483 g, 4 mmol) in THF (4 ml) and DMSO (4 ml). The mixture was stirred for 30 min at 0° and at room temperature for 15h before quenching with water (25 ml). The product was extracted with dichloromethane (3 x 30 ml) and worked up as usual to give an oil. The IR spectrum of the crude material showed no carbonyl band, and tlc indicated a complex mixture. No attempt was made to purify this mixture.

3-Butyn-1-ol (177):[67]

3-Butyn-1-ol (4.00 g, 51%) was prepared from 3-bromopropyne (10.0 ml, 133 mmol), paraformaldehyde (3.28 g, excess), small pieces of aluminium foil (1.12 g), and mercuric chloride (0.01 g).

b.p. : 126° (Lit.[67] 128-129°).

1-(2-Tetrahydropyranyloxy)-3-butyne (178):

In a 50 ml two necked RB flask was placed 3-butyn-1-ol (4.0 g, 57 mmol), dichloromethane (20 ml), and p-TsOH (0.050 g) at room temperature under nitrogen. 2,3-Dihydropyran (5.04 g, 60 mmol) was introduced slowly. Initially, the reaction mixture became exothermic, and it was brought to room temperature by cooling in a water bath. After stirring for 8h, the reaction was quenched by pouring into saturated $NaHCO_3$ solution. The compound was extracted into dichloromethane (2 x 50 ml) and the combined organic layers were dried, evaporated and the residue was loaded onto a column of silica gel (25 g). Elution with 2% ethyl acetate in hexane afforded **178** (4.70 g, 54%) as a colourless oil.

IR (neat): 3300, 2950, 2150, 1130, 1040

PMR : δ 4.64 (br s, 1H, -OCHO-), 4.00-3.36 (m, 4H, -$\underline{CH_2}\underline{CH_2}$OTHP), 2.50 (dt, 2H, -$\underline{CH_2}$OTHP), 1.98 (t, 1H, -C≡CH), 1.80-1.40 (m, 6H).

Methyl 5-(2-tetrahydropyranyloxy)-2-pentynoate (179):

To a solution of the acetylenic ether **178** (0.865 g, 5.62 mmol) in THF (4 ml) at -15° was added n-butyllithium (3.75 ml of 1.3M in hexane, 5.62 mmol) and the mixture stirred for 2h. It was then

cooled to -78° and methyl chloroformate (0.46 ml, 6 mmol) was added slowly. After stirring at -78° for another 5h, the reaction was quenched by adding saturated NH_4Cl. The product was extracted with dichloromethane (3 x 25 ml) and workedup as usual. The crude compound was purified on a column of silica gel (25 g) eluting with 5-7% ethyl acetate in hexane to afford pure ester **179** (0.690 g, 59%) as a colourless oil.

IR(neat) : 2950, 2190(s), 1720, 1440, 1260, 1080, 1040

PMR : δ 4.62 (br s, 1H, -OCHO-), 3.76 (s, 3H, $-CO_2CH_3$), 4.00-3.36 (m, 4H), 2.64 (t, 2H, $-\underline{CH_2}$OTHP), 1.80-1.30 (m, 6H).

Methyl 5-hydroxy-2-pentynoate (180):

To a solution of the ether **179** (0.600 g, 2.83 mmol) in THF (12 ml) was added 1M HCl (5 ml) and the contents stirred for 2h. After neutralizing the reaction with saturated $NaHCO_3$, the product was extracted into dichloromethane (3 x 25 ml) and the combined organic extracts were dried and evaporated. The crude compound was chromatographically purified over a column of silica gel (20 g). Elution with 7-10% ethyl acetate in hexane afforded pure **180** (0.320 g, 88%) as a colourless oil.

IR (neat): 3400, 2950, 2250 (strong), 1710, 1440, 1260, 1080, 1060

PMR : δ 3.82 (t, 2H, $-\underline{CH_2}$OH), 3.78 (s, 3H, $-CO_2CH_3$), 2.62 (t, 2H, $-\underline{CH_2}CH_2OH$).

Attempted preparation of 4-carbomethoxy-3-butynoic acid (169):

To a solution of the alcohol **180** (0.070 g, 0.547 mmol) in DMF (1 ml) was added PDC (0.720 g, 1.915 mmol) and the solution stirred for 6h at room temperature. Water was added and the mixture was

extracted into ether (3 x 25 ml) and the combined organic layers were dried and evaporated. The crude residue was loaded onto a column of silica gel (15 g). Elution with 5-10% ethyl acetate in hexane led to the recovery of starting material (0.040 g).

When AgO was used as the oxidizing agent in THF, a complex mixture resulted. Chromic acid oxidation of the above alcohol also did not give any of the required product.

1-(2-Tetrahydropyranyloxy)-4-phenylsulfenyl-3-butyne (181):

To a stirred solution of the acetylenic compound **178** (0.077 g, 0.5 mmol) in THF (3 ml) at -20^{o} (CCl_4/N_2) was added a solution of n-butyllithium (0.36 ml, 1.4M in hexane, 0.5 mmol) and the stirring continued for 45 min at -20^{o}. A solution of diphenyl disulfide (0.109 g, 0.5 mmol) in THF (2 ml) was injected and the reaction mixture allowed to reach room temperature (ca. 3h). The reaction was quenched by adding water and the compound extracted with dichloromethane (3 x 25 ml). The combined organic layers were dried and evaporated to leave a residue which on chromatographic purification on a column of silica gel (20 g) using 2-3% ethyl acetate in hexane as eluant afforded the sulfide **181** (0.092 g, 70%) as a pale yellow oil.

IR (neat): 3050, 2940, 1580, 1480, 1440, 1120, 1070, 1030, 980, 960, 750, 680

PMR : δ 7.56-7.16 (m, 5H, Ph), 4.70 (br s, 1H, -OCHO-), 4.08-3.20 (m, 4H), 2.76 (dd, 2H, -$\underline{CH_2}$CHOTHP), 1.88-1.36 (m, 6H).

1-(2-Tetrahydropyranyloxy)-4-phenylsulfinyl-3-butyne (182):

To a solution of the sulfide **181** (0.087 g, 0.33 mmol) in dichloromethane (5 ml) at 0° was added MCPBA (0.100 g, 85%, 4.95 mmol) and the mixture stirred for 1h. Tlc of the reaction mixture showed no starting material. After usual workup with dichloromethane (2 x 25 ml) the crude sulfoxide **182** (0.092 g, 100%) was obtained as a syrup.

IR (neat): 3050, 2940, 2190(s), 1440, 1120, 1080, 1060, 1030, 960, 750, 680.

4-Phenylsulfinyl-3-butyn-1-ol (184):

A mixture of the crude ether **182** (0.092 g, 0.33 mmol) and 3M HCl (3 ml) in THF (5 ml) was stirred at room temperature for 10h and diluted with water. The crude product mixture was extracted with ethyl acetate (3 x 25 ml) and the combined organic extracts were washed with saturated $NaHCO_3$, dried, and evaporated to give the crude **184**. Purification by chromatography on a silica gel (15 g) column and elution with 40-50% ethyl acetate in hexane afforded the alcohol **184** (0.040 g, 62%) as a pale yellow syrup.

IR (neat): 3400, 3060, 2890, 2190(s), 1470, 1450, 1070, 1060, 1000(br), 880, 750, 670

PMR : δ 7.88-7.44 (m, 5H, Ph), 3.76 (t, 2H, $-\underline{CH_2}OH$), 2.66 (t, 2H, $-\underline{CH_2}CH_2OH$).

Attempted preparation of 4-phenylsulfinyl-3-butynoic acid (170):

To a solution of the alcohol **184** (0.040 g, 0.206 mmol) in acetone (1 ml) at 10° was added chromic acid (0.13 ml). The

reaction mixture was allowed to reach room temperature and then stirred for 2h. After dilution with water and saturation with NaCl, the mixture was extracted with ethyl acetate (3 x 20 ml) and the combined organic extracts were dried and evaporated. The crude residue did not show the presence of acid **170**. Only a trace amount of starting material was recovered.

1-(2-Tetrahydropyranyloxy)-4-methanesufonyl-3-butyne (185):

The acetylenic ether **178** (0.308 g, 2 mmol) in THF (3 ml) was cooled to -15° (ice-salt). n-Butyllithium (0.87 ml, 2.3M in hexane, 2 mmol) was added dropwise and the mixture stirred at the same temperature for 45 min. It was then cooled to -78° and methanesulfonyl chloride (0.17 ml, 2.2 mmol) was injected and stirring continued at this temperature for 2h. The reaction was quenched by adding water at -78° and the contents allowed to reach room temperature. The compound was extracted into ether (2 x 25 ml), worked up as usual, and the crude compound was loaded onto a column of silica gel (25 g) and eluted with 2-3% ethyl acetate in hexane to give the starting ether **178** (0.175 g). Further elution of the column with 10-15% ethyl acetate in hexane afforded the required product **185** (0.088 g, 45% based on recoverd **178**) as a colourless oil.

IR (neat): 2950, 2200(s), 1320, 1145, 1060, 1025, 960, 900, 760

PMR δ 4.64 (br s, 1H, -OCHO-), 4.04-3.36 (m, 2H, -$\underline{CH_2}$OTHP), 3.18 (s, 3H, -SO_2CH_3), 2.74 (t, 2H, -C≡CCH_2-), 1.90-1.32 (m, 8H).

1-(2-Tetrahydropyranyloxy)-4-methanesulfonyl-(3Z)-butene (186):

A mixture of the acetylenic sulfone **185** (0.050 g, 0.216 mmol), Lindlar catalyst (0.010 g) and benzene (2 ml) was hydrogenated in a

Paar apparatus at 40 psi for 1.5h. The catalyst was filtered and the solvent evaporated. The residue was purified over a column of silica gel (15 g) by eluting with 10-15% ethyl acetate in hexane to give **186** (0.035 g, 70%) as a colourless syrup.

IR (neat): 2950, 2850, 1600(w), 1300, 1130, 1025, 960, 780

PMR : δ 6.56-6.24 (m, 2H, -CH=CH-), 4.55 (br s, 1H, -OCHO-) 4.00-3.64 (m, 4H, $-\underline{CH_2}OTHP$), 2.98 (s, 3H, $-SO_2CH_3$), 2.94 (t, 2H, $-\underline{CH_2}CH=CH-$, J = 8), 2.08-1.92 (m, 6H).

4-Methanesulfonyl-(3Z)-buten-1-ol (187):

A mixture of the ether **186** (0.035 g, 0.15 mmol) and 5M HCl (2 ml) in THF (2 ml) was stirred at room temperature for 10h and quenched with saturated $NaHCO_3$. After extraction with ethyl acetate (3 x 25 ml), the combined organic layers were dried and evaporated. The crude product was charged on a silica gel (15 g) column and eluted with 20% ethyl acetate in hexane to give the syrupy alcohol **187** (0.014 g, 62%).

IR (neat): 3450, 2950, 1620, 1280, 1120, 1040, 960, 780

PMR : δ 6.58-6.34 (m, 2H, -CH=CH-), 3.80 (t, 2H, $-\underline{CH_2}OH$, J = 6), 3.02 (s, 2H, $-SO_2CH_3$), 2.94 (t, 2H, $-\underline{CH_2}CH=CH-$, J = 6).

Attempted preparation of 4-methanesulfonyl-(3Z)-butenoic acid (171):

To a stirred solution of the alcohol **187** (0.014 g, 0.09 mmol) in acetone (1 ml) was added chromic acid (0.06 ml) at 5-10°. The reaction mixture was stirred at the same temperature for 30 min. After dilution with water (2 ml) and saturation with NaCl, the

mixture was extracted into ethyl acetate (5 x 15 ml). The organic layer was dried and evaporated. The residue did not show any required product by tlc as well as by IR analysis. No starting material was recovered as well.

Benzyl 2-propynyl ether (188):[71]

Starting from 2-propyn-1-ol (4.70 g) and benzyl bromide (14.36 g, 1 equiv.), the ether **188** (11.00 g, 90%) was prepared by following the literature procedure.

b.p. : 90^{o}/4 mm (Lit.[71] 43^{o}/0.4 mm).

(4-Methoxybenzyl) 2-propynyl ether (189):

To a stirred suspension of mineral oil free NaH (2.667 g, 45% suspension in mineral oil, 50 mmol) in THF (15 ml) was injected a solution of 4-methoxybenzyl alcohol (6.24 ml, 50 mmol) in THF (10 ml) and heated at 60^{o} for 1h. After cooling to room temperature, 3-bromo-1-propyne (4.46 ml, 50 mmol) was slowly injected. After stirring for 2h at room temperature, the reaction was quenched by adding water. The compound was extracted into ether (2 x 30 ml) and the organic extract was dried, evaporated, and distilled under reduced pressure to give the pure colourless ether **189** (8.0 g, 91%).

b.p. : 150^{o} (bath temperature)/1 mm

IR(neat) : 3275, 2850, 2125, 1250, 1075, 810

PMR : δ 7.34-6.70 (m, 4H, aromatic protons), 4.48 (br s, 2H, $-\underline{CH_2}OCH_2C\equiv C-$), 4.08 (br s, 2H, $-OCH_2C\equiv C-$), 3.70 (br s, 3H, $-OCH_3$), 2.44 (s, 1H, $-C\equiv CH$)

CMR : 159.24, 129.54, 129.19, 113.59, 79.65, 74.48, 70.77,

56.30, 54.77.

General procedure for preparation of the alcohols 190 and 191:

Ethylmagnesium bromide (prepared from an equal ratio of Mg and bromoethane) in ether (50 ml) was cooled to 5^{o}. A solution of the acetylenic ether (1 equiv.) in THF (10 ml) was slowly added to the Grignard reagent. The reaction mixture was stirred for 3-4h at room temperature and the water circulating condenser was replaced with a liquid nitrogen condenser. After cooling to -20^{o}, a solution of ethylene oxide (large excess) in THF (40 ml) was transferred with a double-ended needle. The contents were stirred at the same temperature for another 1h and then allowed to reach room temperature. After stirring at room temperature for further 2h, the reaction was quenched with saturated NH_4Cl. Usual workup with ether gave the crude product, which was loaded onto a silica gel (50 g) column. Elution with 3-5% ethyl acetate in hexane gave some unreacted ether. Further elution of the column with 15-20% ethyl acetate in hexane gave the required alcohol.

5-Benzyloxy-3-pentyn-1-ol (190):

Starting from the ether **188** (7.30 g, 50 mmol), the alcohol **190** (3.7 g, 61%, based on recovered starting material (2.60 g)) was obtained as a colourless liquid.

b.p. : 190^{o} (bath temperature)/0.5 mm

IR(neat) : 3375, 2850, 2210(w), 1050, 740, 690

PMR : δ 7.33 (s, 5H, Ph), 4.57 (s, 2H, $Ph\underline{CH_2}$-), 4.16 (br s, 2H, $-OCH_2C{\equiv}C-$), 3.72 (t, 2H, $-\underline{CH_2}OH$), 3.25 (br s, 1H,

$-CH_2O\underline{H}$), 3.61-3.37 (m, 2H, $-\underline{CH_2}CH_2OH$)

CMR : 137.48, 128.52, 128.2, 127.99, 84.36, 77.4, 71.69, 70.88, 57.77, 22.96.

5-(4-Methoxybenzyloxy)-3-pentyn-1-ol (191):

Starting from the ether **189** (4.40 g, 25 mmol), the alcohol **192** (2.445 g, 63.5%, based on recovered ether (1.315 g)) was obtained as a colourless liquid.

b.p. : 210° (bath temperature)/0.5 mm

IR(neat) : 3400, 2950, 2250(w), 1610, 1245, 1080, 1030, 810

PMR : δ 7.36-6.76 (m, 4H, aromatic protons), 4.50 (s, 2H, benzylic CH_2), 4.12 (t, 2H, $-OCH_2C\equiv C-$, J = 2), 3.78 (s, 3H, $-OCH_3$), 3.72 (t, 2H, $-\underline{CH_2}OH$, J = 6), 2.48 (t, 2H, $-\underline{CH_2}CH_2OH$, J = 6).

CMR : 159.24, 129.59, 129.30, 113.59, 83.54, 77.12, 70.88, 60.49, 57.06, 54.82, 22.59.

Analysis : $C_{13}H_{18}O_3$: Calcd. : C, 70.887; H, 7.323

Found : C, 70.552; H, 7.284

General procedure for hydrogenation of the alcohols 190 and 191:

A solution of the alcohol in benzene (10 ml) was taken in a 250 ml Parr hydrogenation flask and Lindlar catalyst (0.030 g) was added. Hydrogenation was carried out at 40 psi for 3h. The catalyst was filtered off and the solvent was evaporated. Distillation of the crude product under reduced pressure gave the pure, colourless partially hydrogenated alcohol.

5-Benzyloxy-(Z)-3-penten-1-ol (192):

The alcohol **190** (0.400 g, 2.12 mmol) upon hydrogenation gave

the alcohol **192** (0.350 g, 87%) after distillation.

b.p. : 250° (bath temperature)/0.10 mm

IR(neat) : 3400, 2950, 2875, 1100, 1060, 980, 910, 740, 700

PMR : δ 7.32 (s, 5H, Ph), 6.80-6.60 (m, 2H, -CH=CH-), 4.46 (s, 2H, $PhC\underline{H}_2$-), 4.08-3.80 (m, 2H, $BnOC\underline{H}_2$-), 3.78-3.72 (m, 2H, $-\underline{CH}_2OH$), 2.40-2.16 (m, 2H, $-\underline{CH}_2CH_2OH$).

5-(4-Methoxybenzyloxy)-(Z)-3-penten-1-ol:

The alcohol **191** (0.860 g, 3.91 mmol) was hydrogenated to give the product **193** (0.80 g, 92%) after distillation.

b.p. : 220° (bath temperature)/0.10 mm

IR(neat) : 3380, 2850, 1240, 1170, 1030, 810

PMR : δ 7.36-6.76 (m, 4H, aromatic protons), 5.88-5.56 (m, 2H, -CH=CH-), 4.45 (s, 2H, benzylic CH_2), 4.03 (d, 2H, $-OC\underline{H}_2CH=CH-$), 3.80 (s, 3H, $-OCH_3$), 3.64 (t, 2H, $-\underline{CH}_2OH$), 2.27-2.18 (m, 2H, $-\underline{CH}_2CH_2OH$)

CMR : 158.77, 129.71, 129.54, 129.00, 127.77, 114.20, 71.24, 64.77, 60.88, 54.53, 20.47.

Analysis : $C_{13}H_{20}O_3$: Calcd. : C, 70.246; H, 8.161

Found : C, 69.895; H, 8.070

General procedure for oxidation of the alcohols 192 and 193:

To a stirred solution of the alcohol in acetone at 5-10° was slowly added a solution of chromic acid. The reaction mixture was stirred for 30-45 min and diluted by adding water. The aqueous layer was saturated with NaCl and the compound was repeatedly extracted with ether. The combined organic layers were dried and

the solvent evaporated. The crude product was dissolved in ether and extracted with saturated $NaHCO_3$. The combined aqueous layers were washed with ether, and acidified with conc. HCl, saturated with NaCl, and extracted into ether. The combined ether extract was dried and evaporated to give the acid as a syrup. The crude acid was used for the next step without further purification.

5-Benzyloxy-(3Z)-pentenoic acid (194):

Yield : 48.7%

IR(neat) : 3500-2600(br), 3030, 2950, 1725, 1120, 740, 700.

5-(4-Methoxybenzyloxy)-(3Z)-pentenoic acid (195):

Yield : 58%

IR(neat) : 3500-2600(br), 3000, 1725, 1260, 820.

Attempted IMDA reaction of the ester 196:

Method i:

A solution of the ester **196** (0.073 g, 0.206 mmol) in xylene (1 ml) was heated in a sealed tube for 10h at 230^{o} under nitrogen atmosphere. The reaction mixture was cooled to room temperature and the solvent evaporated. Tlc of the reaction mixture showed mainly starting ester and some decomposed material. Recovery of the ester was 0.050 g.

Method ii:

To a stirred solution of the ester **196** (0.010 g, 0.028 mmol) in dichloromethane (1 ml) at 0^{o} was added a solution of tris(4-bromophenyl)aminium hexachloroantimonate (0.005 g, 0.006 mmol) in dichloromethane (0.5 ml) was added and stirring continued for 30

min. The reaction was quenched with NaOMe/MeOH (1 ml) and worked up as usual with dichloromethane to give the crude material. Tlc of this material showed a complex mixture, from which no single product could be isolated.

Method iii:

The ester **196** (0.026 g, 0.073 mmol) and DCN (0.020 g, 0.112 mmol) were dissolved in acetonitrile (1 ml), and the reaction mixture irradiated for 8h without removal of air from the solvent system. After the irradiation was stopped, solvent was removed under vacuum and the crude product was chromatographed over silica gel column with 5% ethyl acetate in hexane as eluant, which gave back the starting material (0.010 g). No IMDA adduct has formed.

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 5-hydroxy-(3Z)-pentenoate (199):

To a stirred solution of the ester **197** (0.044 g, 0.115 mmol) in dichloromethane (10 ml) at room temperature was added DDQ (0.031 g, 0.138 mmol). The reaction mixture initially became green and then changed to light yellow slowly. After stirring for 1h, the precipitate was filtered and the solvent evaporated. The crude compound was loaded onto a silica gel (15 g) column and eluted with 12-15% ethyl acetate in hexane to afford the required alcohol **199** (0.018 g, 60%).

IR (neat): 3400, 2950, 1725, 1450, 1140, 1025, 1000, 960, 930

PMR : δ 6.38-6.00 (dd, 1H, -$\underline{CH}$=CH_2, J = 12,18), 5.92-5.68 (m, 2H, -CH=CH-), 5.42-5.16 (m, 2H, -CH=$\underline{CH}$-H- and H-1), 5.16-4.86 (dd, 1H, -CH=CH-$\underline{H}$), 4.38-4.08 (distorted

triplet, 2H, $-OCOCH_2-$), 3.26-3.04 (distorted triplet, 2H, $-\underline{CH_2}OH$), 2.12-1.00 (m, 4H, $-CH_2CH_2-$), 1.68 (br s, 3H, allylic CH_3), 1.06 (s, 3H, $4-CH_3$), 1.02 (s, 3H, $4-CH_3$).

Analysis : $C_{16}H_{24}O_3$: Calcd. : C, 72.788; H, 9.163

Found : C, 72.563; H, 9.101

(2,4,4-Trimethyl-3-ethenyl-2-cyclohexen-1-yl) 5-oxo-(3Z)-pentenoate (200):

To a stirred solution of the alcohol **199** (0.018 g, 0.047 mmol) in dichloromethane (2 ml) at room temperature was added PCC (0.030 g, 0.094 mmol) and NaOAc (0.005 g). The reaction mixture was stirred for 1h and then diluted with ether. The chromium impurities were filtered and the filtrate evaporated. Purification of the crude product over a column of silica gel (10 g, eluant: 2-3% ethyl acetate in hexane) gave the aldehyde **200** (0.003 g, 16%). The IR spectrum of this compound showed two well separated C=O bands (1720, 1680 cm^{-1}). However, the PMR spectrum of this compound could not be obtained because of its unstability.

Other methods of oxidation like Swern oxidation, MnO_2 oxidation or PDC oxidation did not improve the yield of **200**.

4-Trimethylsilyl-3-butyn-1-ol (204):[105]

According to literature, alcohol **177** (0.896 g, 12.8 mmol) was reacted with n-butyllithium (20 ml, 1.28M in hexane, 25.6 mmol)

105. Shostakovski, M.F.; Atavin, A.S.; Egorov, N.V. Zh. Obshch. Khim. 1965, **35**, 809.

followed by TMSCl (2.920 g, 26.88 mmol) to give the crude C-silylated **204** (1.75 g, 96%).

3-Butynoic acid (202):[76]

The alcohol **177** (4.0 g, 57 mmol) was oxidized with chromic acid (37 ml) following literature procedure to give the acid **202** (1.40 g, 36%).

m.p. : 79-80° (hexane) (Lit.[76] 82-83°).

4-Trimethylsilyl-3-butynoic acid (203):

To a stirred solution of the above crude alcohol **204** (1.90 g, 13.4 mmol) in acetone (8 ml) between 0-10° was slowly added chromic acid (8.8 ml) and the contents stirred for 15 min. Usual workup with ether (3 x 20 ml) and evaporation of the solvent gave the acid **203** (0.640 g, 31%) as a syrup.

IR(neat) : 3500-2600(br), 2100(s), 1725

PMR : δ 3.36 (s, 2H, $-CH_2CO-$), 0.18 (s, 9H, $-Si(CH_3)_3$).

Attempted IMDA reaction of the ester 205a:

A solution of the ester **205a** (0.035 g, 0.151 mmol) in benzene (1 ml) was heated in a sealed tube at 140° for 24h and cooled to room temperature. Evaporation of the solvent gave only starting material.

The same experiment was repeated at 160-180° in a sealed tube for 24h. Again, only starting material was recovered. However, when the experiment was carried out at 220° with xylene as solvent, partial decomposition of the ester resulted after 24h. No IMDA adduct could be obtained.

Attempted IMDA reaction of the ester 206:

A solution of the ester **206** (0.047 g, 0.15 mmol) in benzene (1 ml) was heated in a sealed tube at 180° for 24h. The solvent was evaporated after cooling to room temperature. The IR spectrum and tlc of the crude material showed the presence of starting material only. Recovery was 0.047 g.

The same experiment at 225° with xylene as the solvent led to decomposition of the starting material.

(E)-3-Trimethylsilylpropenoic acid (209):[78]

Propargyl alcohol (1.00 g, 17.85 mmol) was C-silylated using TMSCl, reduced with LAH, and then oxidized with chromic acid by following literature procedure to give the acid **209** (0.410 g, 16% overall yield as a syrup.

(Z)-3-Phenylsulfonylpropenoic acid (210):[79]

According to the literature procedure, propiolic acid (1.00 g, 14.29 mmol) was reacted with thiophenol and then oxidized using H_2O_2 to give the acid **210** (1.23 g, 48%) in two steps.

m.p. : 165-166° (ether) (Lit.[79] 164-166° (xylene)).

Attempted IMDA reaction of the ester 215:

A solution of the ester **215** (0.045 g, 0.19 mmol) in toluene (1 ml) was heated at 180° in a sealed tube for two days. After evaporation of the solvent, tlc as well as the IR spectrum of the residue showed only starting material. No other product was formed.

Attempted IMDA reaction of the ester 216:

A solution of the ester **216** (0.110 g, 0.377 mmol) in benzene

(1.5 ml) was heated in a sealed tube at 140° for 27h, cooled to room temperature and the solvent evaporated. The IR spectrum and tlc of the crude material showed only the presence of starting material.

The same experiment was performed at 200° with xylene as the solvent for 20h. In this case also, no IMDA adduct could be isolated from the crude material. Recovery of the ester **216** was 0.050 g.

Attempted IMDA reaction of the ester 217a:

A solution of the ester **217a** (0.008 g, 0.022 mmol) in benzene (0.5 ml) was heated in a sealed tube between 120-140° for 40h and cooled to room temperature. Evaporation of the solvent and purification of the crude material on a column of silica gel (10 g) gave the starting material (0.005 g) as the major component. Some of the ester decomposed to give a carboxylic acid which was not characterized.

Attempted Diels-Alder reactions of the diene alcohol 155:

(i) With maleic anhydride:

A mixture of the diene alcohol **155** (0.083 g, 0.50 mmol) and maleic anhydride (0.049 g, 0.50 mmol) in benzene (1 ml) was heated at 150° in a sealed tube under nitrogen atmosphere for 18h and cooled to room temperature. The solvent was removed to give a crude mixture. The IR spectrum of this mixture showed no hydroxyl band and tlc showed an intractable mixture of products.

(ii) With dimethyl maleate:

A mixture of the diene alcohol **155** (0.050 g, 0.33 mmol) and dimethyl maleate (0.04 ml, 0.33 mmol) in toluene (1 ml) was heated

at 150° under nitrogen atmosphere in a sealed tube for 5 days and the solvent evaporated. Tlc and the IR spectrum of this mixture showed that no reaction had occurred.

(iii) With dimethyl acetylenedicarboxylate:

A mixture of the diene alcohol **155** (0.042 g, 0.25 mmol) and dimethyl acetylenedicarboxylate (0.03 ml, 0.25 mmol) in toluene (1 ml) was heated at 150° in a sealed tube for 2 days. The reaction mixture was cooled to room temperature and the solvent evaporated. Tlc and the IR anlysis of the crude mixture showed that no reaction had taken place.

Attempted Diels-Alder reaction between the diene acetate 221 and dimethyl maleate:

Method i: In sealed tube:

A mixture of the diene acetate **221** (0.026 g, 0.125 mmol) and dimethyl maleate (0.022 g, 1 equiv.) in benzene (1 ml) was heated at 150° in a sealed tube for 20h. Evaporation of the solvent at room temperature afforded only the starting materials as indicated by tlc and IR.

Method ii: With Sonicator:

A solution of the diene acetate **221** (0.018 g, 0.087 mmol) and dimethyl maleate (0.013 g, 0.087 mmol) in methanol (0.5 ml) was placed in a conical reaction vial under nitrogen atmosphere and dipped in an ultrasonic cleaning bath for 3h. The temperature was maintained below 45°. Evaporation of the solvent afforded only the starting materials as indicated by tlc and IR.

1-(2-Tetrahydropyranyloxy)-2,4,4-trimethyl-3-ethenyl-2-cyclohexene (222):

A mixture of the alcohol **155** (0.083 g, 0.5 mmol) and dihydropyran (0.050 g, 0.6 mmol) in dichloromethane (5 ml) containing p-TsOH (0.005 g) was stirred at room temperature for 10h. After neutralization with saturated $NaHCO_3$, the product was extracted into dichloromethane (2 x 25 ml) and the combined organic layers were dried and evaporated. Purification on a silica gel (15 g) column using 2-3% ethyl acetate in hexane as eluant afforded the required ether **222** (0.045 g, 36%) as a colourless oil.

IR (neat): 2950, 2860, 1130, 1080, 1020, 980, 920, 880

PMR : δ 6.20 (dd, 1H, $-\underline{CH}=CH_2$, J = 10,18), 5.26 (dd, 1H, $-CH=\underline{CH_2}$, J = 3,18), 5.14-4.86 (m, 2H, $-CH=CH-\underline{H}$ and $-\underline{CH}$OTHP), 4.80-4.62 (m, 1H, -OCHO-), 4.12-3.36 (m, 4H), 2.00-1.20 (m, 8H), 1.74 (br s, 3H, allylic CH_3), 1.06 (s, 3H, 4-CH_3), 1.00 (s, 3H, 4-CH_3).

Attempted Diels-Alder reaction between the diene 222 and dimethyl maleate:

A mixture of the diene **222** (0.022 g, 0.088 mmol) and dimethyl maleate (0.011 ml, 1 equiv.) in benzene (1 ml) was heated at 110° in a sealed tube for 20h. The mixture was cooled to room temperature and the solvent evaporated. Tlc and the IR of the crude mixture showed only the presence of starting materials. Recovery of the diene was 0.015 g. The same reaction was attempted in toluene at 150° for 20h and then at 185° for 20h. However, only the starting material was recovered in each case.

2-Carbomethoxycyclohexanone (227):[84]

According to the literature procedure, cyclohexanone (15.6 g, 160 mmol) was reacted with mineral oil free NaH (12.24 g, 40%, 200 mmol) and KH (0.612 g) and then with dimethyl carbonate (36.04 g, 515 mmol) to give 2-carbomethoxycyclohexanone (20.4 g, 82%).

b.p. : 70^{o}/0.8 mm (Lit.[84] 68^{o}/0.8 mm)
IR (neat): 2940, 1745, 1715, 1655, 1615, 1300, 1260, 1220.

Diethyl (2-carbomethoxy-1-cyclohexenyl)-phosphate (225):[83]

This compound was prepared according to the literature procedure, from the ketone **227** (0.78 g, 5 mmol) and diethyl chlorophosphate (0.80 ml, 5.5 mmol). The crude product was distilled to give the colourless product **225** (0.92 g, 63%).

b.p. : 150^{o}/0.5 mm (Lit.[83] 155^{o}/0.5 mm)
IR (neat): 1720, 1660, 1030.

Vinyllithium:[85]

A solution of vinyllithium in ether (0.8M) was prepared from tetravinyltin (1.134 g, 5 mmol) and phenyllithium (1.680 g, 20 mmol, 0.86M solution in ether), following the literature procedure.

Attempted preparation of methyl 2-ethenyl-1-cyclohexenecarboxylate (224):

To a stirred solution of $CuI.P(n\text{-}Bu)_3$ (0.556 g, 1.4 mmol) in ether (5 ml) at -78^{o} was added a 0.8M solution of vinyllithium (3.5 ml, 2.8 mmol) in ether. After stirring for 15 min, the enol phosphate **225** (0.204 g, 0.7 mmol) in ether (5 ml) was injected and the reaction continued for 2h. After quenching with saturated

NH_4Cl, the product was extracted into ether (3 x 25 ml) and the combined organic layers were dried and evaporated to give an oil. Spectral analysis (IR) showed that none of the required product had formed. The same experiment was tried using $CuBr.Me_2S$ complex, as well as with vinylmagnesium bromide/CuI. However, no required product was observed in either case.

Attempted preparation of 1-ethenyl-2-carbomethoxycyclohexanol (226):

Cerium chloride ($CeCl_3.7H_2O$, 1.49 g, 4.0 mmol) was placed in a 50 ml two-necked RB flask and heated to 140° in vacuo (0.1 mm) for 2h and cooled to room temperature. Dry THF (5 ml) was added with stirring under nitrogen and stirring continued for another 2h. To the resultant suspension cooled to -78° was added a solution of vinylmagnesium bromide [prepared from 0.085 g of Mg and vinyl bromide (3 ml of 2.0M solution in THF)] in THF. After stirring this solution at -78° for 1.5h, a solution of the keto ester **227** (0.468 g, 3 mmol) in THF (3 ml) was injected and the reaction mixture was stirred for 2h prior to quenching with 4% AcOH at 0°. The compound was extracted into ether (3 x 20 ml) and the combined organic layer was dried and evaporated to give back the starting material (0.400 g). The same experiment was carried out without using cerium chloride. This time also only the starting material was recovered.

1,1-Ethylenedioxy-2-carbomethoxycyclohexane (230):

A mixture of 2-carbomethoxycyclohexanone (1.560 g, 10 mmol), ethylene glycol (0.806 g, 13 mmol), and p-TsOH (0.010 g) in benzene (50 ml) was refluxed for 15h with azeotropic removal of water using a Dean-Stark apparatus. After cooling to room temperature, the mixture was quenched by adding aq.$NaHCO_3$ and the compound was

extracted into ether (3 x 30 ml). The combined organic layers were dried, evaporated and the residue loaded onto a silica gel column. Elution with 3-5% ethyl acetate in hexane gave the required ketal **230** (1.675 g, 84%) as a colourless oil.

IR (neat): 2950, 1730, 1440, 1160, 1090, 1040, 930

PMR : δ 3.92 (br s, 4H, $-OCH_2CH_2O-$), 3.66 (s, 3H, $-CO_2CH_3$), 2.66 (t, 1H, $-\underline{CH}CO_2CH_3$), 2.00-1.20 (m, 8H).

1,1-Ethylenedioxy-2-hydroxymethylcyclohexane (231):

To a stirred suspension of LAH (0.370 g, excess) in dry ether (50 ml) was slowly added a solution of the ester **230** (1.297 g, 6.485 mmol) in ether (10 ml). The reaction mixture was stirred for 14h at room temperature, cooled to 0^o, and quenched by adding saturated Na_2SO_4. The inorganic salts were filtered and the precipitate was washed thoroughly with ethyl acetate. Evaporation of the combined filtrates after drying and purification by silica gel chromatography (5-10% ethyl acetate in hexane as eluant) gave the desired product **231** as a colourless liquid (1.042 g, 90%).

IR (neat): 3400, 2950, 2875, 1450, 1220, 1160, 1080, 930, 870

PMR : δ 4.00 (s, 4H, $-OCH_2CH_2O-$), 3.80-3.66 (m, 2H, $-\underline{CH_2}OH$), 2.90-2.70 (m, 1H, $-\underline{CH}CH_2OH$), 2.00-1.20 (m, 8H).

1,1-Ethylenedioxy-2-benzyloxymethylcyclohexane (232):

To a stirred suspension of mineral oil free NaH (0.423 g, 7.06 mmol, 40%) in THF (15 ml) was added a solution of the alcohol **231** (1.042 g, 6.06 mmol) in THF (5 ml). The reaction mixture was warmed to 60^o for 15 min and allowed to stirr at room temperature for 30 min. Benzyl bromide (0.83 ml, 7 mmol) was added to the

reaction mixture and the stirring continued for 14h. After usual workup with ether (3 x 30 ml), chromatographic purification of the crude product over a column of silica gel (25 g) gave the required ether **232** (1.317 g, 83%).

IR (neat): 2950,2875, 1460, 1380, 1100, 740, 700

PMR : δ 7.30 (s, 5H, Ph), 4.50 (narrow doublet, 2H, $Ph\underline{CH_2}$-), 3.98-3.80 (m, 4H, $-OCH_2CH_2O-$), 3.72 (dd, 1H, $-\underline{CH_2}OBn$, J = 4,10), 3.30 (dd appearing as a triplet, 1H, $-\underline{CH_2}OBn$, J = 10), 2.14-1.84 (m, 1H, H-2), 1.80-1.20 (m, 8H).

2-Benzyloxymethylcyclohexanone (229):

A mixture of the acetal **232** (1.317 g, 5.02 mmol), acetone (25 ml), and p-TsOH (0.010 g) was stirred at room temperature for 15h. Solid $NaHCO_3$ (2.0 g) was added and the reaction mixture was filtered, evaporated, and loaded onto a column of silica gel (20 g). Elution with 5% ethyl acetate in hexane afforded the required product **229** (0.986 g, 90%) as a colourless oil.

IR (neat): 3050, 2950, 2900, 1710, 1440, 1380, 1100, 740, 700

PMR : δ 7.28 (s, 5H, Ph), 4.49 (s, 2H, $Ph\underline{CH_2}$-), 4.02-3.57 (m, 2H, H-2 and $-\underline{CH_2}OBn$, 3.38 (dd, 1H, $-\underline{CH_2}OBn$, J = 12,7), 2.45-1.19 (m, 8H).

1-Ethenyl-2-benzyloxymethylcyclohexanol (228):

To a stirred solution of vinylmagnesium bromide (prepared from 0.122 g of Mg and a solution of vinyl bromide in THF) in THF (5 ml) at 0^{o} was added a solution of the ketone **229** (0.545 g, 2.5 mmol) in THF (3 ml). The reaction mixture was stirred at room temperature

for 15h, then refluxed for 30 min and again cooled to room temperature. The reaction mixture was quenched by adding saturated NH_4Cl and the product extracted into ether (3 x 25 ml) and the combined organic layers dried, evaporated, and loaded onto a silica gel (20 g) column. Elution with 5% ethyl acetate in hexane afforded the required alcohol **228** (0.428 g, 70%) as a colourless oil.

IR (neat): 3450, 2950, 2890, 1460, 1110, 970, 920, 740, 700

PMR : δ 7.28 (s, 5H, Ph), 5.88 (dd, 1H, $-\underline{CH}=CH_2$, J = 10,18), 5.23 (ddd, 2H, $-CH=\underline{CH_2}$, J = 2,10,18), 4.44 (s, 2H, $-\underline{CH_2}Ph$), 3.80 (dd, 1H, $-\underline{CH_2}OBn$, J = 3,9), 3.41 (dd, 1H, $-\underline{CH_2}OBn$, J = 3,9), 2.00-1.16 (m, 8H).

Dehydration of the alcohol 228:

A mixture of the alcohol **228** (0.036 g, 0.146 mmol), anhydrous $CuSO_4$ (1.0 g) and xylene (2 ml) was heated at 150° for 1h. The reaction mixture was cooled to room temperature, filtered, and the solvent evaporated. Chromatographic purification over a silica gel (10 g) column by eluting with 1% ethyl acetate in hexane led to a mixture of two dienes (0.025 g, 75%). The PMR spectrum of this mixture showed 55% of 2-ethenyl-3-benzyloxymethylcyclohexene (**223a**) and 45% of 1-ethenyl-2-benzyloxymethylcyclohexene (**223b**). When p-TsOH/C_6H_6 or $POCl_3$/pyridine were used as dehydrating agents, similar mixtures were obtained. Since the two products were inseparable on tlc, no attempt was made to separate them.

IR (neat): 2950, 1610, 1460, 1100, 1000, 900, 740, 700

PMR : δ 7.28(br s), 6.05 (dd, J = 10,18), 5.74 (t, J = 4), 5.20-4.72 (m), 4.46 (two narrow singlets), 3.62-3.16

(m), 2.26-1.36 (m).

2-Methyl-2-cyclohexenone:[100]

2-Methylcyclohexanone (20.0 g) was chlorinated with sulfuryl chloride and dehydrochlorinated with sym-collidine to give 2-methyl-2-cyclohexenone (11.0 g, 56%).

b.p. : 83-85°/35 mm (Lit.[100] 83-85.5°/35 mm)
IR (neat): 2950, 2930, 1670, 1360, 1100, 900, 880.

2-Methyl-2-cyclohexen-1-ol (241):[99]

This compound was prepared by a slight modification of the literature procedure. To a stirred suspension of LAH (1.824 g, excess) in THF (25 ml) at 20° was added a solution of 2-methyl-2-cyclohexenone (4.40 g, 40 mmol) in THF (10 ml). The reaction mixture was stirred for 4h under nitrogen and cooled to 0° and quenched with saturated Na_2SO_4. After destroying the excess LAH, the mixture was filtered, and the inorganic salts washed with ethyl acetate. The combined organic layers were dried, evaporated and the crude product distilled to give the alcohol **241** (4.10 g, 92%).

b.p. : 75-80°/18 mm (Lit.[99] 76-78°/18 mm)
IR (neat): 3325, 2925, 1430, 1050, 980, 960, 800
PMR : δ 5.51 (br s, 1H, H-3), 3.96 (br s, 1H, -CHOH), 2.08-1.30 (m, 6H), 1.74 (br s, 3H, 2-CH_3).

General procedure for preparation of the ethers 242 and 243:

A mixture of the alcohol (n mmol), ethyl vinyl ether (80 ml, freshly distilled over sodium), and mercuric acetate (0.256 g/mmol, freshly recrystallized from absolute alcohol) was refluxed under

nitrogen for 18h. About 50-60 ml of ethyl vinyl ether was distilled out from the reaction mixture and the residue cooled to room temperature. A few drops of glacial acetic acid were added to the reaction mixture and the contents stirred for 2h. After dilution with 50 ml of pet. ether (40-60°), the mixture was poured into 30 ml of 5% KOH solution and the layers separated. The organic layer was once again washed with 20 ml of 5% KOH solution and then dried over anhydrous K_2CO_3, filtered, and evaporated. The crude compound was distilled under vacuum to give the required ether as volatile colourless liquid.

(2-Cyclohexen-1-yl) ethenyl ether (242):[91]

Yield : 46%

b.p. : 70° (bath temperature)/10 mm (Lit.[91] 48°/10 mm)

IR (neat): 2925, 1635, 1600, 1190, 1060, 1010, 900, 810.

(2-Methyl-2-cyclohexen-1-yl) ethenyl ether (243):

Yield : 85%

b.p. : 75° (bath temperature)/10 mm

IR (neat): 2925, 1635, 1190, 1060, 1000, 920, 800

PMR : δ 6.34 (dd, 1H, -CH=CH_2, J = 6,14), 5.64 (br s, 1H, H-3), 4.3 (dd, 1H, -CH=CH-H, J = 1,14), 4.07 (br s, 1H, -CHO-), 3.96 (dd, 1H, -CH=CH-H, J = 1,7), 2.08-1.30 (m, 9H).

General procedure for the Claisen rearrangement of vinyl ethers 242 and 243:

The neat vinyl ether was heated to 190° in a sealed tube under

nitrogen atmosphere for 1h. After cooling to room temperature, the crude compound was distilled under vacuum to give the pure rearranged product as colourless liquid.

(2-Cyclohexen-1-yl)acetaldehyde (239):[91]

Yield : 28%

b.p. : 95° (bath temperature)/10 mm (Lit.[91] 65°/11 mm)

IR (neat): 2925, 2700, 1720, 1440, 1380, 1240, 1120, 1040, 840

PMR : δ 9.78 (t, 1H, -CHO), 5.93-5.40 (m, 2H, -CH=CH-), 2.46 (d, 2H, $-\underline{CH_2}CHO$), 2.10-1.02 (m, 7H).

(2-Methyl-2-cyclohexen-1-yl)acetaldehyde (244):

Yield : 95%

b.p. : 80° (bath temperature)/8 mm

IR (neat): 2950, 2875, 2740, 1725, 1450

PMR : δ 9.77 (t, 1H, -CHO), 5.46 (br s, 1H, H-3), 2.49 (dd, 2H, $-\underline{CH_2}CHO$, J = 2,4), 1.66 (s, 3H, 2- CH_3), 2.10-1.15 (m, 7H)

CMR : 201.66, 134.18, 123.36, 46.70, 32.70, 28.06, 24.64, 21.23, 18.64.

General procedure for Wittig reaction of aldehydes 239 and 244:

In a 100 ml two necked RB flask methoxymethyltriphenylphosphonium chloride (2 equiv.) was placed under nitrogen atmosphere and 30 ml of ether was injected. To this stirred suspension of the salt at 0°, was added a solution of sodium t-amyloxide (1.5 equiv., freshly sublimed) in ether (10 ml). The orange red reaction mixture was stirred for 30 min and a solution of the aldehyde **239** or **244**

(1 equiv.) in ether (5 ml) was added. After stirring for another 30 min at 0^{o}, the reaction mixture was quenched by adding water. The product was extracted into ether (3 x 25 ml), the combined organic layers dried over anhydrous K_2CO_3 and evaporated. The crude residue was purified by chromatography on silica gel [25 g, eluant: 5% ether in pet. ether ($40-60^{o}$)] and then by distillation.

1-(3-Methoxy-2(E/Z)-propenyl)-2-cyclohexene (245):

Yield : 92%

b.p. : $95-100^{o}$ (bath temperature)/10 mm

IR (neat): 3010, 2925, 2850, 1625, 1605, 1185, 920.

1-(3-Methoxy-2(E/Z)-propenyl)-2-methyl-2-cyclohexene (246):

Yield : 94%

b.p. : 120^{o} (bath temperature)/10 mm

IR (neat): 2930, 2850, 1625, 1605, 1185, 940

PMR : δ 6.26 and 5.89 (d, together integrating for one proton, $=\underline{CH}OCH_3$), 5.38 (br s, 1H, -CH=C-), 4.84-4.16 (m, 1H, $-\underline{CH}=CHOCH_3$), 3.74 and 3.48 (s, together integrating for three protons, $-OCH_3$), 2.14 (dd, 2H, $-\underline{CH_2}CH=CH-$, J = 8,6), 1.66 (br s, 3H, $2-CH_3$), 2.00-1.28 (m, 7H)

CMR : 147.71, 146.71, 133.98, 133.16, 128.39, 128.14, 122.76, 122.58, 109.03, 100.36, 58.95, 55.31, 39.34, 38.75, 30.88, 27.65, 27.01, 25.54, 22.01, 19.84, 19.55.

General procedure for hydrolysis of enol ethers 245 and 246:

To a solution of the enol ether **245** or **246** in chloroform (5 ml/mmol) at 0^{o} was added 50% CF_3CO_2H (1 ml/mmol). The reaction

was monitored by tlc and was complete in 2h. Water (20 ml) was added to the reaction mixture and the compound was extracted into dichloromethane (2 x 20 ml). The combined organic layers were washed with saturated $NaHCO_3$, dried, and evaporated. The crude compound was distilled under reduced presure to give a colourless liquid.

3-(2-Cyclohexen-1-yl)propionaldehyde (247):

Yield : 94%

b.p. : 120° (bath temperature)/10 mm

IR (neat): 2925, 2700, 1720, 1445, 880, 800.

3-(2-Methyl-2-cyclohexen-1-yl)propionaldehyde (248):

Yield 93%

b.p. : 120° (bath temperature)/10 mm

IR (neat): 2950, 2875, 2740, 1725, 1460

PMR : δ 9.81 (dd, 1H, -CHO), 5.42 (br s, 1H, H-3), 2.44 (dt, 2H, $-\underline{CH_2}CHO$, J = 8,1), 1.94 (m, 4H), 1.68 (br s, 3H, $2-CH_3$), 1.72-1.20 (m, 5H)

CMR : 202.36, 135.83, 123.30, 41.35, 37.70, 27.06, 25.23, 24.35, 21.70, 19.47.

5-(2-Cyclohexen-1-yl)-1-pentyn-3-ol (249):

A suspension of lithium acetylide-ethylenediamine complex (0.508 g, 5.52 mmol) in THF (2 ml) at room temperature was treated with a solution of the aldehyde **247** (0.077 g, 0.56 mmol) in THF (2 ml). The reaction mixture was stirred at room temperature for 6h before quenching with ice (10 g). Workup as usual with ether as the

extracting solvent gave the crude product which was purified by column chromatography on silica gel, eluting with 3-4% ethyl acetate in hexane to afford the required product **249** (0.015 g, 16.4%) as a colourless liquid.

IR (neat): 3350, 3300, 2950, 1170, 1120

PMR : δ 5.88-5.40 (m, 2H, -CH=CH-), 4.40 (dt, 1H, -CHOH, J = 2,6), 2.50 (d, 1H, -C≡CH, J = 2), 2.30-1.00 (m, 12H).

5-(2-Cyclohexen-1-yl)-3-t-butyldimethylsilyloxy-1-pentyne (238):

A mixture of the alcohol **249** (0.015 g, 0.09 mmol), imidazole (0.012 g, 0.18 mmol), TBDMSCl (0.015 g, 0.1 mmol) in DMF (1 ml) was stirred under nitrogen for 15h at room temperature. The reaction was quenched by adding water and after usual workup with ether (3 x 20 ml), the crude product purified on a silica gel (15 g) column, eluting with 0.5% ethyl acetate in hexane to afford the required ether **238** (0.010 g, 74% based on recovered alcohol (0.007 g)).

IR (neat): 3300, 2925, 1250, 1100, 840, 780.

General procedure for intramolecular Pauson-Khand reaction:

Carbon monoxide gas was bubbled for 2h at room temperature into a 25 ml three necked RB flask containing a solution of dicobalt octacarbonyl (1 equiv.) in benzene (10 ml). A solution of the ene-yne (1 equiv.) in benzene (5 ml) was injected and carbon monoxide bubbling was continued for 1h. The reaction mixture was heated under reflux and carbon monoxide bubbling was discontinued. The refluxing was continued for 20h and the contents cooled to room temperature and filtered through a short column of fluorosil (5 g) and the column washed with ethyl acetate. Evaporation of the

solvent gave the crude product.

3-t-Butyldimethylsilyloxy-3,4,5,5a,6,7,8,8a-octahydro-1(8bH)-acenaphthylenone (237):

Intramolecular Pauson-Khand reaction on the ene-yne **238** (0.010 g) was carried out according to the above general procedure. The crude compound was loaded onto a silica gel (15 g) column. Elution with 1-2% ethyl acetate in hexane led to the separation of the cobalt impurities. Further elution of the column with 3-5% ethyl acetate in hexane afforded the required product **237** (0.005 g, 45.5%) as a colourless liquid.

IR (neat): 2925, 2875, 1700, 1260, 1140, 1110, 1060, 840, 780

PMR : δ 6.00 and 5.77 (br s, together integrating for one olefinic proton), 4.74 (br s) and 4.46 (t) [together integrating for one proton, -CHOSi-], 2.76-1.10 (m, 12H), 0.93 and 0.90 (singlets, together integrating for nine protons, t-Bu), 0.10 (br s, 6H, $-Si(CH_3)_2$).

3-t-Butyldimethylsilyloxy-2a,8b,3,4,5,5a,6,7,8,8a-decahydro-1(2H)-acenaphthylenone (250):

A solution of the enone **237** (0.005 g, 0.016 mmol) in ethyl acetate (2 ml) containing 5% palladium-on-carbon (0.005 g) was stirred in a hydrogen atmosphere (balloon) for 8h. The reaction mixture was filtered and evaporated to give the crude compound. Purification was effected by chromatography on silica gel using 3-4% ethyl acetate in hexane as eluant to give the saturated ketone **250** (0.004 g, 80%) as a low melting solid.

IR (neat): 1730, 1250, 1085, 840, 770

PMR : δ 4.04-3.88 (m, 1H, -CHOSi-), 2.50-1.92 (m, 6H), 1.72-1.08 (m, 10H), 0.92 and 0.88 (two singlets, together integrating for nine protons, t-Bu), 0.07 (s, 6H, $-Si(CH_3)_2$)

MS : 308 (M^+), 293, 251, 159, 135, 75, 73.

2-(2,2-Dimethoxyethyl)-2-(2-cyclohexen-1-yl)-1,3-dithiane (257):

In a 25 ml two necked RB flask, a solution of the dithiane **125** (0.208 g, 1 mmol) in THF (5 ml) was cooled to -20° (ice-salt) under nitrogen. A solution of n-butyllithium (0.69 ml, 1.45M in hexane) was slowly injected and the contents stirred at the same temperature for 4h. After cooling to -40° (acetonitrile/N_2), a solution of 3-bromocyclohexene (0.177 g, 1.1 mmol) in THF (2 ml) was added. The reaction mixture was allowed to reach room temperature (ca. 2h) and a catalytic amount of NaI was added. The contents were stirred overnight (10h) before quenching with water. Workup as usual with dichloromethane (2 x 25 ml) gave the crude product, which was adsorbed on a silica gel (15 g) column. Elution with 1% ethyl acetate in hexane afforded the alkylated product **257** (0.105 g, 36.5%) as a colourless liquid.

IR (neat): 2925, 2825, 1430, 1180, 1120(s), 1070(s), 900, 720

PMR : δ 6.08-5.84 (m, 2H, -CH=CH-), 4.08 (t, 1H, -OCHO-), 3.34 (s, 6H, $-OCH_3$), 2.96-2.68 (m, 4H, $-SCH_2-$), 2.16-1.28 (m, 11H).

2-(2-Oxoethyl)-2-(2-cyclohexen-1-yl)-1,3-dithiane (258):

To a stirred solution of the acetal **257** (0.105 g, 0.36 mmol) in $CHCl_3$ (15 ml) at 0° was added a solution of 50% CF_3CO_2H (10 ml) and

the contents allowed to reach room temperature. After stirring at room temperature for 4h, water (20 ml) was added to the reaction mixture and the compound was extracted into dichloromethane (2 x 25 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 ml), brine, and dried. The solvent was evaporated and the crude compound was charged on a silica gel (15 g) column. Elution of the column with 2-3% ethyl acetate in hexane afforded the required aldehyde **258** (0.086 g, 98%) as a colourless liquid.

IR (neat): 2925, 2725, 1710, 1420, 1270, 1060

PMR : δ 9.85 (t, 1H, -CHO), 5.94 (br s, 2H, -CH=CH-), 3.00-2.72 (m, 4H, $-SCH_2-$), 2.20-1.32 (m, 11H).

2-(2-Hydroxy-3-butynyl)-2-(2-cyclohexen-1-yl)-1,3-dithiane (259):

To a stirred suspension of lithium acetylide-ethylenediamine complex (0.213 g, 2.315 mmol) in THF (3 ml) at room temperature was added a solution of the aldehyde **258** (0.086 g, 0.355 mmol) in THF (2 ml). The reaction mixture was stirred under nitrogen for 16h and quenched by pouring onto crushed ice (10 g). The compound was extracted into ether (3 x 25 ml) and worked up as usual. The residue was purified by chromatography on silica gel. Eluting with 3-5% ethyl acetate in hexane afforded the required alcohol **259** (0.020 g, 21%) as a syrup.

IR (neat): 3400, 3300, 2940, 2120, 1425, 1075, 1050, 950, 810

PMR : δ 6.02-5.72 (m, 2H, -CH=CH-), 4.98-4.68 (m, 1H, -CHOH-), 2.98-2.62 (m, 4H, $-SCH_2-$), 2.56-2.32 (m, 2H), 2.40 (d, 1H, $-C\equiv CH$), 2.20-1.30 (m, 10H).

2-(2-t-Butyldimethylsilyloxy-3-butynyl)-2-(2-cyclohexen-1-yl)-1,3-dithiane (251):

A mixture of the alcohol **259** (0.020 g, 0.070 mmol), imidazole (0.009 g, 0.14 mmol), and TBDMSCl (0.013 g, 0.077 mmol) in dichloromethane (2 ml) was stirred at room temperature for 24h under nitrogen. The reaction mixture was diluted with water and after usual workup with ether (2 x 20 ml), the residue was loaded onto a silica gel (15 g) column. Elution of the column with 1-2% ethyl acetate in hexane afforded the required ether **251** (0.010 g, 48%, based on the recovered alcohol) as a colourless liquid. Further elution of the column with 5-7% ethyl acetate in hexane gave the starting alcohol (0.005 g).

IR (neat): 3295, 2925, 2100, 1440, 1240, 1080, 1040, 810, 750

PMR : δ 6.20-5.66 (m, 2H, -CH=CH-), 4.88-4.68 (m, 1H, -CHOSi-), 2.94-2.48 (m, 6H), 2.44 (d, 1H, -C≡CH), 2.20-1.40 (m, 9H), 0.90 (s, 9H, t-Bu), 0.18 (s, 3H, $-SiCH_3$), 0.14 (s, 3H, $-SiCH_3$).

Attempted IMPK reaction on the ene-yne 251:

IMPK reaction on the ene-yne **251** (0.011 g, 0.029 mmol) was attempted according to the above mentioned general procedure. After usual workup, the IR spectrum and tlc of the crude mixture did not show the presence of the required product. No pure compound could be obtained from the crude residue.

4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-butanone (261):[95]

To a stirred blue solution of lithium (0.420 g, 60.0 mg-atom) in ethylamine (about 200 ml) at -20^{o}, was added a solution of -

ionone (1.92 g, 10 mmol) in THF (10 ml) over a period of 15 min. The blue reaction mixture was stirred at the same temperature for 5h and then allowed to reach room temperature and the ethylamine allowed to evaporate overnight (ca. 12h). The reaction mixture was quenched with MeOH (2 ml), and then water (25 ml). The compound was extracted into ether (3 x 25 ml) and the combined organic layers were dried and evaporated to give the crude compound, which upon distillation afforded the dihydroionone **261** (1.716 g, 88%) as a colourless liquid.

b.p. : 150° (bath temperature)/12 mm (Lit.[95] 125°/12 mm)

IR (neat): 2925, 1720, 1440, 1350

PMR : δ 5.32 (br s, 1H, olefinic proton), 2.56-2.28 (distorted triplet, 2H, $-CH_2CO-$), 2.12 (s, 3H, $-COCH_3$), 1.86-1.08 (m, 7H), 1.68 (br s, 3H, allylic CH_3), 0.92 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$).

3-(2,6,6-Trimethyl-2-cyclohexen-1-yl)propanoic acid (263):[97]

To a stirred solution of the ketone **261** (0.582 g, 3 mmol) in MeOH (6 ml) at 0° was slowly added a solution of NaOCl [3 ml, 1.49M, prepared from NaOH (2.18 g), chlorine (1.61 g) and water (15.5 ml)]. The reaction mixture was allowed to reach room temperature and then stirred for 12h. Methanol was evaporated on a steam bath and the crude material was diluted with water. The aqueous layer was washed with ether (3 x 20 ml) and then acidified with dil. HCl and saturated with NaCl (solid). Extraction with ether (3 x 25) gave the crude acid **263** (0.432 g, 74%) as a syrup.

IR (neat): 3500-2600 (broad), 2925, 1710, 1440, 1260, 1200.

3-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-1-propanol (264):[98]

This compound was prepared according to the literature procedure by reducing the acid **263** (0.430 g, 2.2 mmol) with LAH (0.135 g, excess) in THF (10 ml). The crude compound was purified over a column of silica gel (15 g), eluting with 5-7% ethyl acetate in hexane to give the alcohol **264** (0.175 g, 44%).

IR (neat): 3300, 2925, 1440, 1040

PMR : δ 5.31 (br s, 1H, olefinic proton), 3.72-3.56 (m, 2H, $-\underline{CH_2}OH$), 2.08-1.04 (m, 9H), 1.68 (br s, 3H, allylic CH_3), 0.92 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$).

3-(2,6,6-Trimethyl-2-cyclohexen-1-yl)propionaldehyde (265):

A mixture of the alcohol **264** (0.091 g, 0.5 mmol) and PDC (0.282 g, 0.75 mmol) in dichloromethane (15 ml) was stirred at room temperature for 12h and then diluted by adding ether (20 ml). The chromium impurities were filtered and the filtrate was evaporated. The crude compound was loaded onto a silica gel (15 g) column and eluted with 3% ethyl acetate in hexane to give the required aldehyde **265** (0.055 g, 61%) as a colourless liquid.

IR (neat): 2925, 2700, 1720, 1440

PMR : δ 9.72 (t, 1H, -CHO), 5.38 (br s, 1H, olefinic proton), 2.60-2.32 (distorted triplet, 2H, $-\underline{CH_2}CHO$), 2.12-1.10 (m, 7H), 1.64 (br s, 3H, allylic CH_3), 0.92 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$).

General procedure for preparation of the alcohols 252 and 266:

To a stirred suspension of lithium acetylide-ethylenediamine complex (3 equiv.) in THF at 0^o was added a solution of the carbonyl

compound **261** or **265** (1 equiv.) in THF. The reaction mixture was allowed to reach room temperature and then stirred at this temperature for 10-12h. After quenching with ice (10 g), the compound was extracted into ether (3 x 20 mmol) and the combined organic layers dried, evaporated, and loaded onto a silica gel (15 g) column. Elution with 5-6% ethyl acetate in hexane afforded the acetylenic alcohols **252** or **266**.

1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-methyl-3-hydroxy-4-pentyne (252):

Yield : 50% (based on recovered ketone **261**)

IR (neat): 3400, 3300, 2960, 2920, 2860, 2105, 1450, 1115, 915, 740

PMR : δ 5.37-5.19 (m, 1H, -CH=C-), 2.42 (s, 1H, -C≡CH), 2.01-1.20 (m, 8H), 1.66 (br s, 3H, allylic CH_3), 1.48 (s, 3H, $-CH_3$), 0.93 (s, 3H, $-CH_3$), 0.87 (s, 3H, $-CH_3$).

1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-hydroxy-4-pentyne (265):

Yield : 31%

IR (neat): 3375, 3300, 2910, 1440, 1010

PMR : δ 5.30 (br s, 1H, -CH=C-), 4.42-4.04 (m, 1H, -CHOH), 2.45 (d, 1H, -C≡CH), 2.08-1.04 (m, 9H), 1.66 (br s, 3H, allylic CH_3), 0.92 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$).

Attempted preparation of 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-methyl-3-(t-butyldimethylsilyloxy)-4-pentyne:

A mixture of the alcohol **261** (0.041 g, 0.186 mmol), imidazole (0.028 g, 0.409 mmol), and TBDMSCl (0.056 g, 0.373 mmol) in DMF (2 ml) was stirred at room temperature for 15h. The reaction was

quenched with water. The compound was extracted into ether (2 x 20 ml) and worked up as usual. The IR spectrum and tlc of the crude material showed the presence of starting material only (recovery: 0.036 g). The same experiment was repeated using NaH (1.5 equiv.) as base and THF as solvent. After usual workup the crude material showed only starting material.

1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-(t-butyldimethylsilyloxy)-4-pentyne (253):

A mixture of the alcohol **266** (0.022g, 0.11 mmol), imidazole (0.016 g, 0.242 mmol), and TBDMSCl (0.032 g, 0.22 mmol) in DMF (2 ml) was stirred at room temperature for 18h. The reaction was quenched by adding water. Workup as usual with ether (2 x 25 ml), folllowed by chromatographic purification on silica gel (15 g) column eluting with 0.2% ethyl acetate in hexane afforded the required ether **259** (0.010 g, 54%, based on alcohol **26** (0.010 g)) as a colourless liquid.

IR (neat): 3300, 2925, 2850, 1460, 1260, 1100, 840, 780

PMR : δ 5.28 (br s, 1H, olefinic proton), 4.40-4.18 (m, 1H, -CHOSi-), 2.37 (d, 1H, -C≡CH), 2.04-1.05 (m, 9H), 1.68 (br s, 3H, allylic CH_3), 0.92 (s, 9H, t-Bu), 0.90 (s, 3H, $-CH_3$), 0.88 (s, 3H, $-CH_3$), 0.14 (s, 3H, $-SiCH_3$), 0.12 (s, 3H, $-SiCH_3$).

Attempted IMPK reaction on the ene-yne 252:

The ene-yne **252** (0.018 g, 0.082 mmol) was subjected to IMPK reaction according to previously mentioned general procedure. After usual workup, the IR spectrum of the crude reaction mixture showed

absence of acetylenic band and presence of a weak hydroxyl band (3400 cm^{-1}) and a broad carbonyl band (1720-1680 cm^{-1}). However, tlc showed a complex mixture, from which no single product could be isolated.

Attempted IMPK reaction on the ene-yne 253:

The IMPK reaction on the ene-yne **253** (0.010 g, 0.031 mmol) was attempted according to the previously mentioned general procedure. After usual workup, the crude reaction mixture showed no acetylenic band and also no carbonyl band in the IR spectrum. Similarly, tlc also showed a complex mixture.

(2-Methyl-2-cyclohexen-1-yl) 2-propynyl ether (270):

To a stirred suspension of mineral oil free NaH (0.360 g, 40% in mineral oil, 6 mmol) in THF (10 ml) was added a solution of 2-methyl-2-cyclohexen-1-ol (0.448 g, 4 mmol) in THF (4 ml) and the stirring was continued for 1h at room temperature. After stirring the reaction mixture at 60° for 2h, it was cooled to room temperature and 3-bromo-1-propyne (0.45 ml, 6 mmol) was injected. The contents were stirred at room temperature for 10h before quenching with water. After usual workup with ether (3 x 25 ml), the crude coloured product was distilled at 120° (bath temperature)/15 mm to give a mixture of the starting alcohol and the required ether as a colourless liquid. Chromatographic separation of this mixture over a silica gel (25 g) column (eluant: 2% and 5% ethyl acetate in hexane) afforded the required ether **270** (0.258 g, 67%, based on starting alcohol recovered) and the starting alcohol **241** (0.160 g).

IR (neat): 3300, 2950, 2120, 1440, 1040

PMR : δ 5.58 (br s, 1H, H-3), 4.20 (narrow doublet, 2H, $-OCH_2C\equiv C-$), 3.84 (br s, 1H, -CHO-), 3.40 (narrow triplet, 1H, $-C\equiv CH$), 2.08-1.40 (m, 6H), 1.76 (br s, 3H, $2-CH_3$)

CMR : 132.01, 124.48, 78.88, 72.88, 72.00, 54.06, 25,47, 23,59, 18.88, 16.41.

1-(2-Methyl-2-cyclohexen-1-yl)-2-propyn-1-ol (271):

To a stirred solution of the ether **270** (0.545 g, 3.63 mmol) in THF (10 ml) at 0^{o} under nitrogen was slowly added a solution of n-butyllithium (6.14 ml, 1.3M in hexane, 7.986 mmol) in hexane. The reaction mixture was stirred for 2h and quenched with water at 0^{o}. The compound was extracted into ether (3 x 30 ml) and the combined organic layers were dried and evaporated. Chromatographic purification on a silica gel (15 g) column with 4-5% ethyl acetate in hexane as eluant afforded the required rearranged product **271** (0.381 g, 70%) as a colourless liquid (diastereomeric mixture).

IR (neat): 3400, 3300, 2950, 2100(w), 1440, 1070, 1040, 1020

PMR : δ 5.64-5.38 (m, 1H, olefinic proton), 4.62 (br s, 1H, -CHOH), 2.22 and 1.98 (two narrow doublets, 1H, $-C\equiv CH$, J = 2), 2.12-1.20 (m, 7H), 1.76 (br s, 3H, allylic CH_3)

CMR : 130.72, 130.54, 125.59, 124.42, 82.59, 81.83, 72.42, 72.01, 62.71, 61.18, 42.95, 23.65, 23.53, 22.30, 21.83, 20.53, 20.06, 19.35, 18.88.

1-(2-Methyl-2-cyclohexen-1-yl)-1-benzyloxy-2-propyne (269):

To a stirred suspension of NaH (0.066 g, 40% in mineral oil,

1.1 mmol) in THF (5 ml) at room temperature was added a solution of the alcohol **271** (0.110 g, 0.73 mmol) in THF (3 ml) under a nitrogen atmosphere. The contents were refluxed for 5 min, cooled to room temperature and stirred for 4h. Benzyl bromide (0.17 ml, 0.146 mmol) was added followed by tetra-n-butylammonium iodide (0.010 g, 0.027 mmol). After stirring at room temperature for 12h, the reaction was quenched with water. After usual workup with dichloromethane (2 x 25 ml), the residue was purified on a silica gel (15 g) column. Elution with 2-3% ethyl acetate in hexane afforded the required benzyl ether **269** (0.128 g, 73%) as a colourless liquid.

IR (neat): 3275, 3075, 2950, 1600 (weak), 1460, 1075, 740, 700

PMR : δ 7.32 (s, 5H, Ph), 5.54 (br s, 1H, H-3), 4.96-4.26 (m, 3H, $Ph\underline{CH_2}O\underline{CH}$-), 2.28 (two narrow doublets appearing as a triplet, 1H, -C≡CH), 2.12-1.16 (m, 10H)

CMR : 131.45, 131.28, 126.99, 126.75, 126.40, 126.28, 125.99, 124.35, 74.03, 73.56, 70.75, 69.92, 69.57, 69.28, 68.88, 42.74, 42.21, 24.13, 23.95, 23.31, 21.14, 20.72, 19.90, 19.19.

Attempted hydroboration-oxidation of 269:

(i) With catecholborane:

Catecholborane (0.01 ml, 0.1 mmol) was added to a stirred solution of the acetylenic compound **269** (0.023 g, 0.1 mmol) in THF (1 ml) at room temperature under nitrogen. Initially, the reaction mixture was stirred at room temperature for 8h and then at reflux overnight. At this stage, tlc of the reaction mixture showed only starting material. The reaction was quenched by adding water and

the compound extracted into ether (2 x 25 ml). The combined organic extract was dried and evaporated to give back the starting material (0.020 g).

(ii) With dicyclohexylborane:

To a stirred solution of BH_3.THF (0.06 ml, 1.4M, 0.084 mmol) in THF at 0^o was added cyclohexene (0.03 ml, 0.197 mmol). After stirring for 15 min, solid dicyclohexylborane formed. To this suspension of dicyclohexylborane in THF, the acetylenic compound **269** (0.020 g, 0.08 mmol) in THF (1 ml) was injected. The homogeneous reaction mixture was allowed to reach room temperature and stirred for 12h before quenching with 3M NaOAc (0.03 ml) at 0^o. Hydrogen peroxide (0.06 ml, 30%) was added and the reaction mixture stirred for 15 min at room temperature. The compound was extracted into ether (2 x 20 ml) and the combined organic extract was dried and evaporated to give back the starting material (0.012 g).

1-(2-Methyl-2-cyclohexen-1-yl)-2-propen-1-ol (272):

To a stirred suspension of LAH (0.150 g, large excess) in THF (5 ml) at 0^o was added a solution of the alcohol **271** (0.112 g, 0.75 mmol) in THF (2 ml). The reaction mixture was refluxed for 1h and cooled to 0^o and then quenched with saturated Na_2SO_4. The inorganic salts were filtered and the residue washed with ethyl acetate. The combined filtrate was dried, evaporated, and purified by column chromatography (eluting solvent: 4-5% ethyl acetate in hexane) to give the desired product **272** (0.087 g, 77%) as a colourless liquid.

IR (neat): 3350, 2900, 1460, 1040, 980, 910

PMR : δ 6.08-5.76 (m, 1H, -CH=CH_2), 5.54 (br s, 1H, -CH=C-), 5.42-5.06 (m, 2H, -CH=CH_2), 4.58-4.36 (m, 1H, -CH(OH)-), 2.08-1.16 (m, 10H).

1-(2-Methyl-2-cyclohexen-1-yl)-1-benzyloxy-2-propene (273):

To a stirred suspension of mineral oil free NaH (0.052 g, 40% in mineral oil, 0.86 mmol) in THF (4 ml) at room temperature was added a solution of the alcohol **272** (0.087 g, 0.57 mmol) in THF (3 ml) under nitrogen. The reaction mixture was stirred for 4h and benzyl bromide (0.14 ml, 1.14 mmol) was injected. After stirring for 12h at room temperature, the reaction was quenched with water and worked up as usual with ether (2 x 20 ml). Purification by chromatography on silica gel (15 g) with 2-3% ethyl acetate in hexane as eluant afforded the benzyl ether **273** (0.120 g, 87%) as a colourless liquid.

IR (neat): 3010, 2925, 2850, 1450, 1080, 1060, 720, 690

PMR : δ 7.30 (br s, 5H, Ph), 6.00-5.62 (m, 1H, -CH=CH_2), 5.52 (br s, 1H, -CH=C-), 5.40-5.06 (m, 2H, -CH=CH_2), 4.70-3.86 (m, 3H, PhCH_2OCH-), 2.06-1.20 (m, 10H).

Attempted hydroboration-oxidation of 273:

(i) With 9-BBN:

A solution of 9-BBN (0.006 g, 0.045 mmol) in THF (1 ml) was added to a stired solution of the diene **273** (0.011 g, 0.045 mmol) in THF (1 ml) at 0^{o}. The reaction mixture was allowed to reach room temperature and stirred for 12h. Tlc of the reaction mixture showed only starting material. Workup as usual with dichloromethane (2 x 25 ml) returned the starting diene (0.009 g).

(ii) With dicyclohexylborane:

To a stirred suspension of dicyclohexylborane (prepared from 0.06 ml of 1.4M BH_3.THF and 0.03 ml of cyclohexene) in THF (1 ml) at 0° was added a solution of the diene **273** (0.020 g, 0.083 mmol) in THF (1 ml). The reaction mixture was allowed to reach room temperature and stirred for 15h. Workup as described for the previous experiment resulted in recovery of the starting material **273** (0.014 g).

5-(2-Methyl-2-cyclohexen-1-yl)-1-pentyn-3-ol (275):

Method 1:

To a stirred suspension of lithium acetylide-ethylenediamine complex in THF (2 ml) at room temperature was injected a solution of the aldehyde **248** (0.150 g, 1.00 mmol) in THF (2 ml). The reaction mixture was stirred for 18h and poured onto crushed ice (10 g). After usual workup with ether (2 x 20 ml), the crude compound was purified over a column of silica gel (eluant: 4-5% ethyl acetate in hexane) to give the required alcohol **275** (0.019 g, 11%) as a colourless liquid.

Method 2:

Acetylene gas was bubbled for 30 min into a 25 ml thre necked RB flask containing 5 ml of THF at -78°. A solution of n-butyllithium (1.0 ml of 1.3M in hexane) was slowly injected (reaction was very vigorous!) and the contents stirred for 30 min in a stream of acetylene. A solution of the aldehyde **248** (0.152 g, 1.0 mmol) in THF (2 ml) was injected into the reaction mixture and the stirring was continued for another 15 min. Acetylene gas bubbling was stopped and the reaction mixture was brought to -10° over a period

of 1h and quenched at this temperature with water. The compound was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried and evaporated. The crude compound was loaded onto a silica gel (15 g) column and eluted with 2-3% ethyl acetate in hexane to obtain the starting aldehyde **248** (0.030 g). Further elution with 10% ethyl acetate in hexane led to pure **275** (0.055 g, 39%, based on recovered aldehyde) as a colourless liquid .

IR (neat): 3350, 3300, 2925, 2850, 1440, 1020

PMR : δ 5.54-5.34 (m, 1H, olefinic proton), 4.46-4.24 (m, 1H, -CH(OH)-), 2.47 (d, 1H, -C≡CH, J = 3), 2.08-1.00 (m, 14H), 1.66 (br s, 3H, allylic CH_3).

5-(2-Methyl-2-cyclohexen-1-yl)-3-t-butyldimethylsilyloxy-1-pentyne (255):

Method 1:

To a stirred solution of the alcohol **275** (0.019 g, 0.106 mmol) in DMF (1 ml), imidazole (0.016 g, 0.33 mmol) was added and then TBDMSCl (0.032 g, 0.22 mmol). The reaction mixture was stirred at room temperature for 12h before quenching with water. Workup as usual with ether (2 x 20 ml), followed by chromatographic purification (eluant: 1-2% ethyl acetate in hexane) gave the ether **255** (0.011 g, 75% based on recovered alcohol (0.010 g)).

Method 2:

To a suspension of mineral oil free NaH (0.011 g, 40% in mineral oil, 0.18 mmol) in THF (2 ml) was added a solution of the alcohol **275** (0.021 g, 0.12 mmol) in THF (2 ml) and the contents stirred for 2h. TBDMSCl (0.036 g, 0.24 mmol) was added to the

reaction mixture and the stirring continued for 12h under nitrogen. The reaction was quenched by adding water and after usual workup with dichloromethane (2 x 20 ml), the crude compound was loaded onto a silica gel (15 g) column. Elution with 1-2% ethyl acetate in hexane afforded the required ether **255** (0.028 g, 82%) as a colourless liquid.

IR (neat): 3320, 2950, 2875, 1260, 1100, 840, 780

PMR : δ 5.56-5.28 (m, 1H, olefinic proton), 4.42-4.22 (m, 1H, -CHOSi-), 2.38 (d, 1H, -C≡CH, J = 3), 2.04-1.16 (m, 14H), 0.92 (s, 9H, t-Bu), 0.16 (s, 3H, $-SiCH_3$), 0.12 (s, 3H, $-SiCH_3$).

Attempted IMPK reaction of the ene-yne 255:

Method 1: General procedure:

The IMPK reaction on the ene-yne **255** (0.010 g, 0.034 mmol) was attempted according to the general procedure. The IR spectrum of the crude compound did not show any enone band and tlc indicated an intractable mixture.

Method 2: On silica gel:

The ene-yne **255** (0.010 g, 0.a034 mmol) was converted to its dicobalt hexacarbonyl complex according to the IMPK reaction general procedure at room temperature and silica gel (20 g, 100-200 mesh) was added. The solvent was evaported at room temperature and the adsorbed complex on silica gel was rotated in a Kugelrohr distillation set up at 50^{o} for 5h under a slow stream of oxygen and then at room temperature for 10h. The silica gel was extracted with ether. Evaporation of the solvent gave only the starting ene-yne **255** (0.010 g).

IV. 2 FIGURES

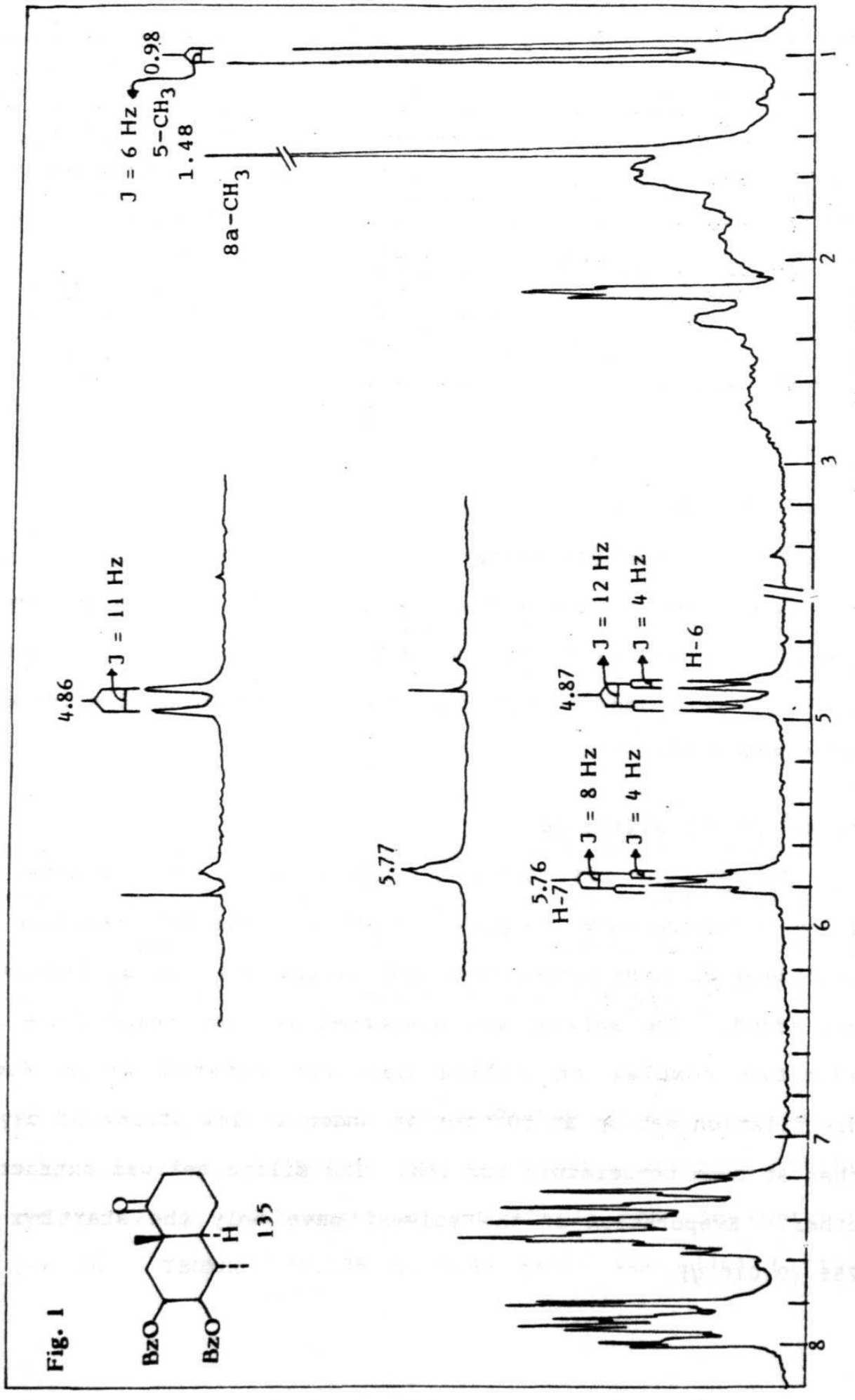


Fig. 1

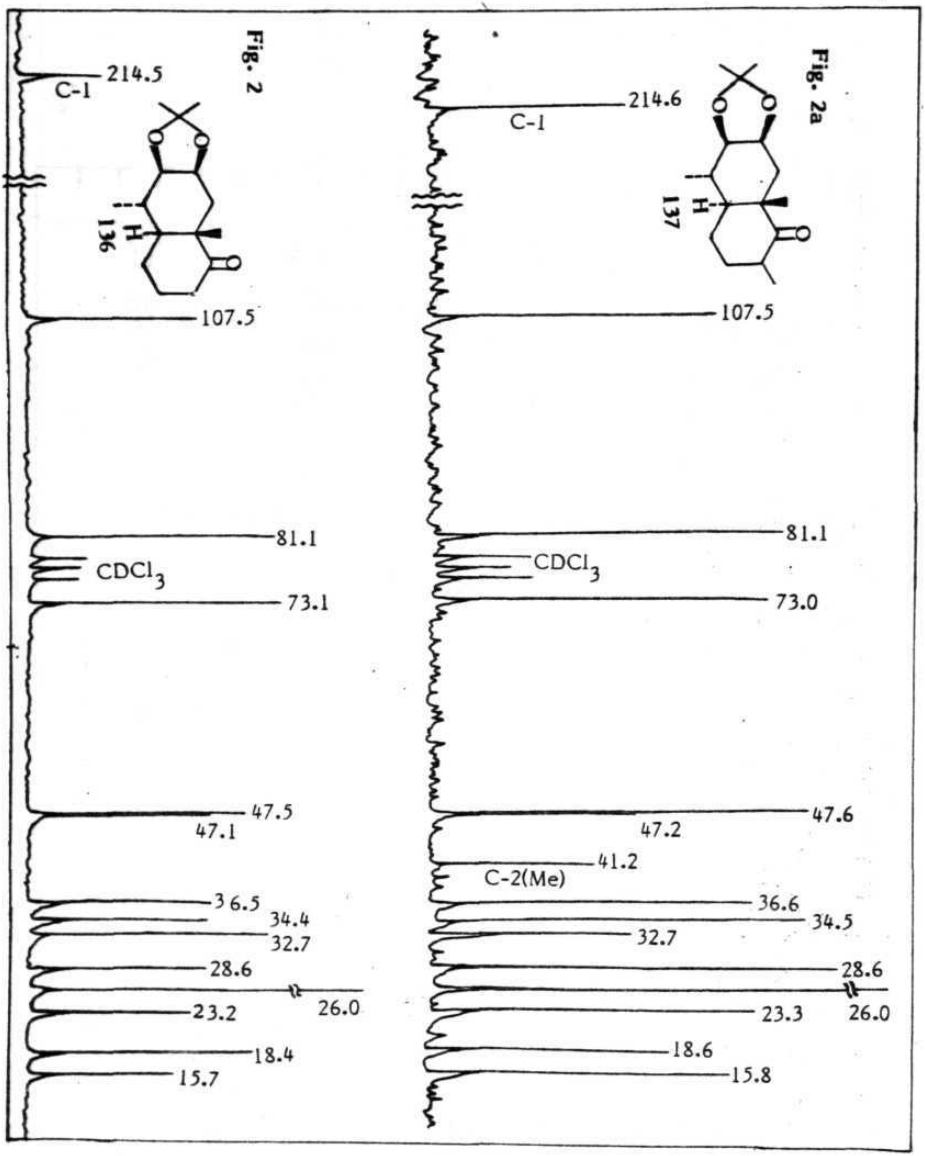
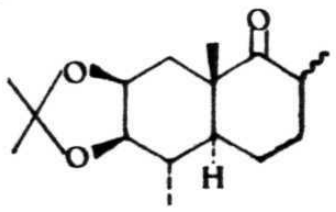


Fig. 2
214.5
C-1
136
107.5
81.1
CDCl3
73.1
47.5
47.1
36.5
34.4
32.7
28.6
26.0
23.2
18.4
15.7
Fig. 2a
214.6
C-1
137
107.5
81.1
CDCl3
73.0
47.6
47.2
41.2
C-2(Me)
36.6
34.5
32.7
28.6
26.0
23.3
18.6
15.8

Fig. 3



137

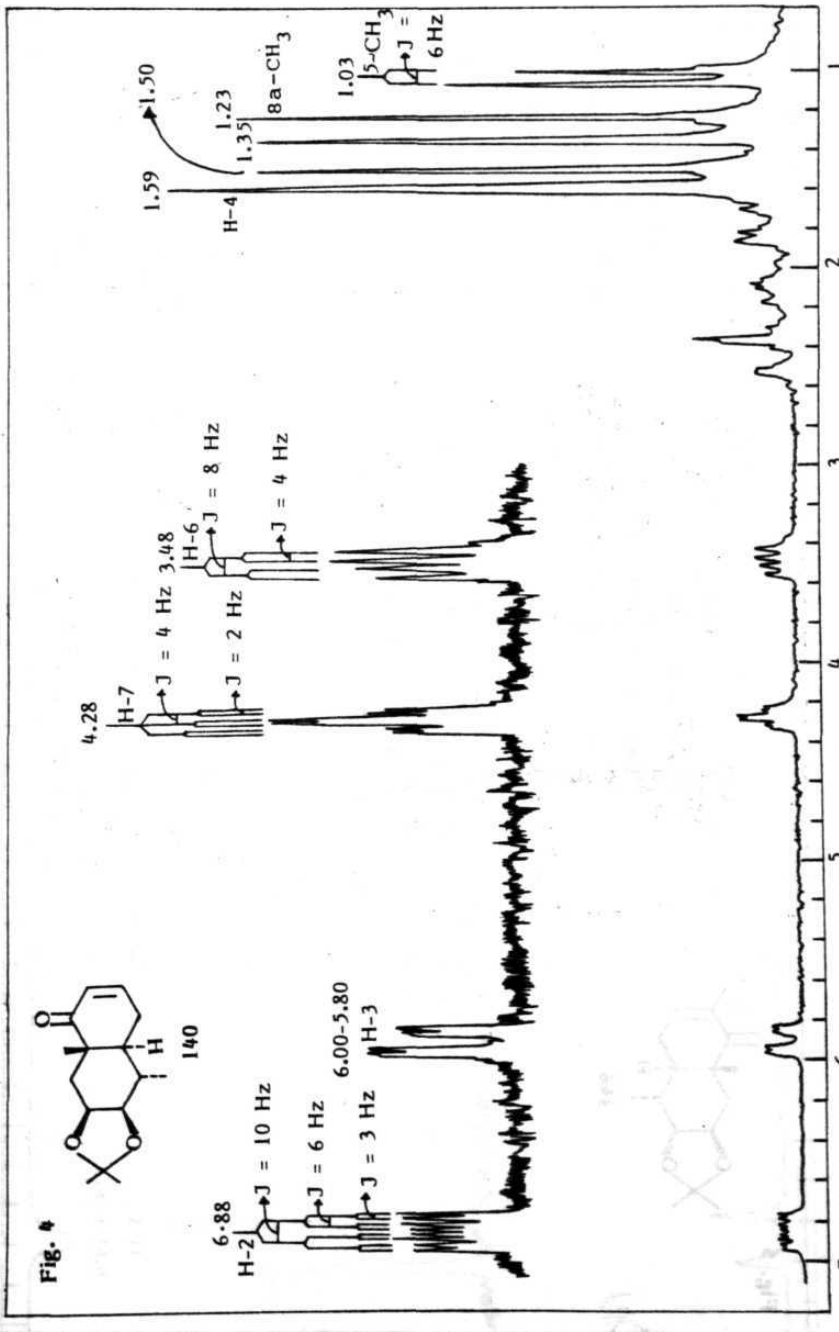


Fig. 4
140
6.88
H-2
J = 10 Hz
J = 6 Hz
J = 3 Hz
6.00-5.80
H-3
4.28
H-7
J = 4 Hz
J = 2 Hz
3.48
H-6
J = 8 Hz
J = 4 Hz
1.59
H-4
1.50
1.35
1.23
8a-CH3
1.03
5-CH3
J = 6 Hz
7
6
5
4
3
2
1

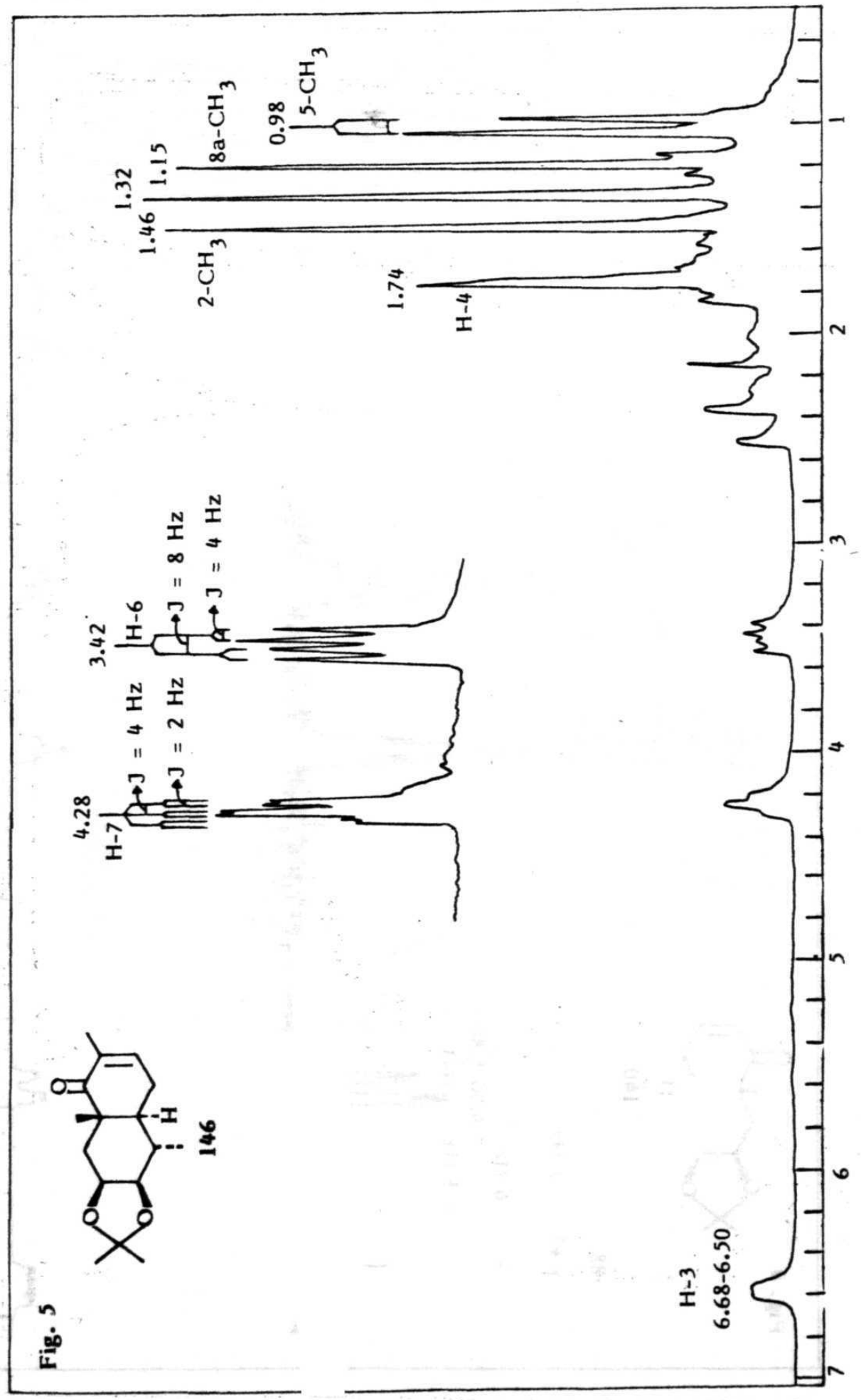

4.28
H-7
J = 4 Hz
J = 2 Hz
3.42
H-6
J = 8 Hz
J = 4 Hz
1.32
1.46
2-CH3
1.15
8a-CH3
0.98
5-CH3
1.74
H-4
H-3
6.68-6.50
1
2
3
4
5
6
7

Fig. 5

146

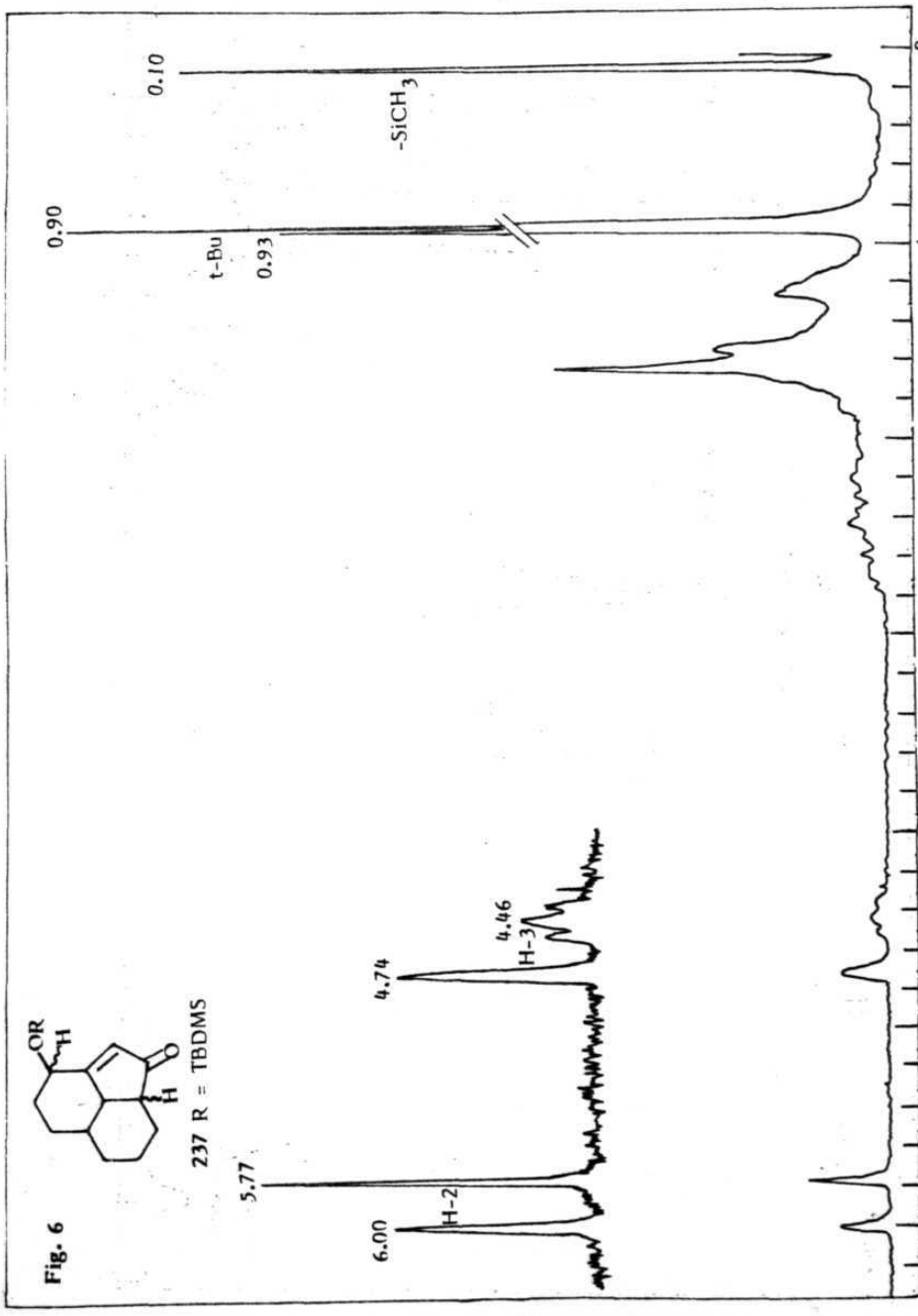


Fig. 6
237 R = TBDMS
OR
H
H
O
5.77
6.00
H-2
4.74
4.46
H-3
0.90
t-Bu
0.93
0.10
-SiCH3
6
5
4
3
2
1
0