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Recent Developments in General Methodologies for the Synthesis of Linear Triquinanes‡

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‡ *Dedicated to Prof. E. Osawa and Dr. V. V. Kane on the occasion of their 62nd and 65th birthday, respectively.*

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1. INTRODUCTION

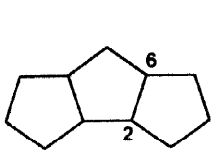
Polyquinane is a generic name given to carbocyclic frames composed of fused five membered rings and constitutes an important class of sesquiterpenoids. Since the discovery of polyquinane natural products they have generated a world wide interest among organic chemists due to their unique and fascinating molecular architecture and promising biological activity.[1] Among polyquinanes, the natural products having triquinane framework are more abundant. At present nearly eighty such natural products are known in the literature and they are frequently encountered among plants,[2] marine[3] and microbial sources.[4] Triquinane natural products containing all the three types of C-11 tricyclopentanoid skeleta, **1** (linearly fused five membered rings), **2** (angularly fused five membered rings) and **3** (five membered rings fused in propellane fashion), as the core ring systems are known (Fig.-1).[5,6]

The class of linearly fused tricyclopentanoids is further divided depending upon the mode of fusion of the third cyclopentane ring. The two isomers **4** and **5** are termed as *cis:anti:cis* and *cis:syn:cis*, respectively. Although, these two tricyclic hydrocarbons have not been characterized yet, their ΔH_f^O values have been calculated by Osawa and coworkers.[7] It has been shown that **4** is only marginally more stable than the hindered folded form **5**, which nevertheless forms the basic building block of aesthetically pleasing polyhedra such as peristylane **10**, dodecahedrane[8] **11** (Fig.-2) and a variety of molecular hosts.[9]

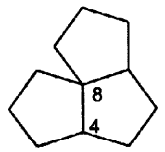
Of the two stereoisomeric C_{11} linear triquinanes, *cis:anti:cis* isomer **4** has received relatively greater attention because it constitutes the basic carbocyclic framework of a large number of naturally occurring triquinane sesquiterpenoids such as hirsutic acid **6**, coriolin **7**, capnellene **8** and hirsutene **9** (Fig.-1).

The intense interest in the chemistry of polycyclopentanoids is partly due to novel and intricate carbocyclic network of natural triquinanes and also because of diverse biological properties exhibited by some members. For example, hirsutic acid **6** has antibiotic properties while coriolin **7** shows antibacterial and antitumor activities.[6] Capnellene **8** and its congeners have been suggested to act as chemical defense agents to inhibit growth of micro organisms and to prevent larval settlement.[10] As a consequence, the last decade has witnessed a flurry of activity in the design and development of synthetic routes to cyclopentanoids.[11-13] The search for methods for the efficient and rapid synthesis of polyquinanes is continuing unabated.[14-16]

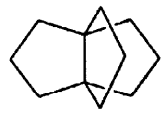
The literature on the synthesis of polyquinanes is vast and expanding and, comprehensive reviews[11a,b] on the subject are available covering the literature up to 1988.[11c] In this report, we concentrate on general methodologies leading to the linear *cis:anti:cis* triquinanes to reflect the recent proliferation of work in this area.



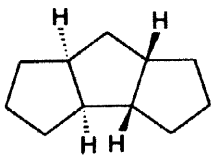
1
Linearly fused



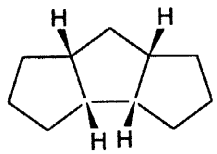
2
Angularly fused



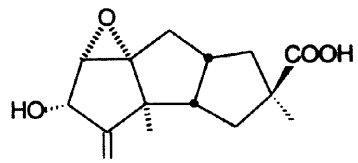
3
Propellane structure



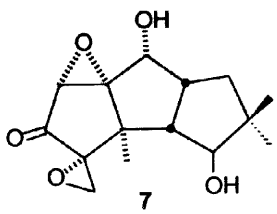
4
cis:anti:cis



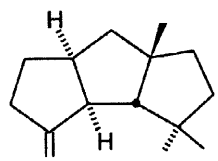
5
cis:syn:cis



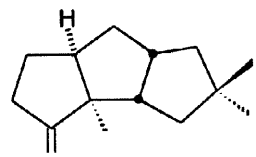
6
hirsutic acid



7
coriolin

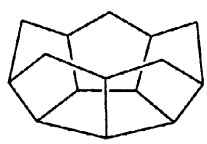


8
$\Delta^{9(12)}$-capnellene

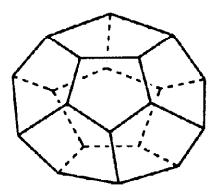


hirsutene
9

Fig.-1



10
peristylane



11
dodecahedrane

FIg.-2

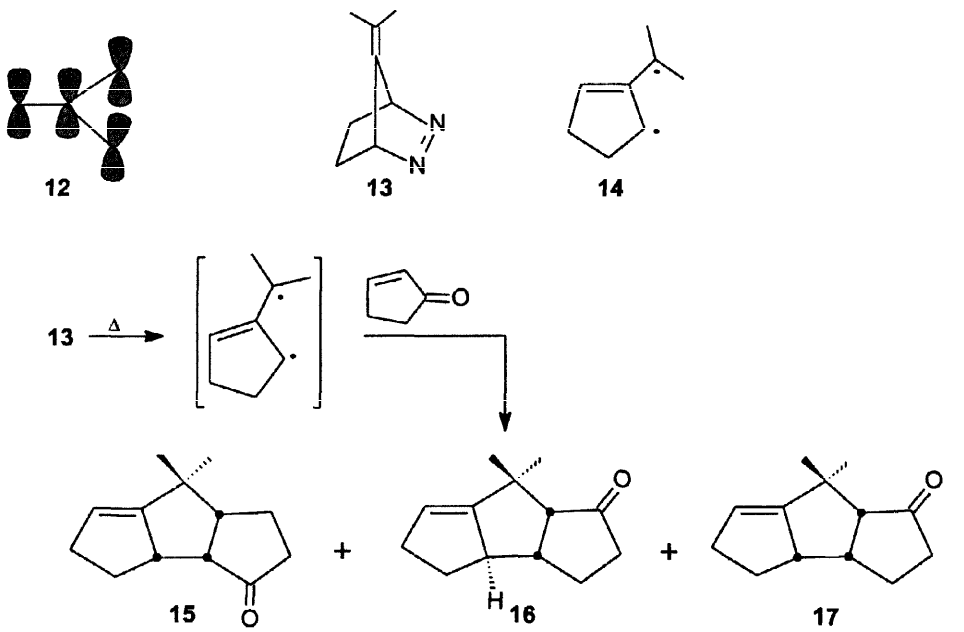
2. GENERAL METHODS LEADING TO TRIQUINANES IN A SINGLE STEP

In this section, those methods which generate the tricyclopentanoid framework directly in a single step from appropriate precursors have been presented.

2.1. 1,3-DIYL TRAPPING

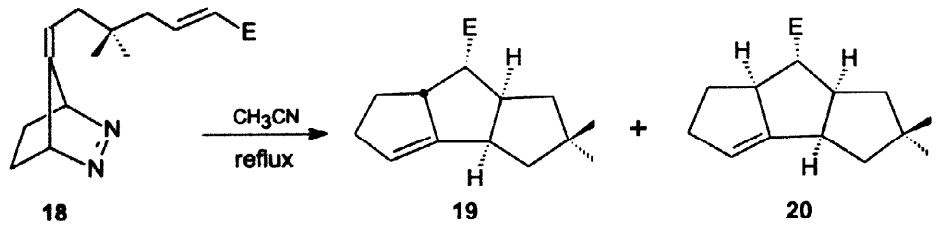
Little and coworkers[17-20] developed a new general method for synthesis of triquinane framework. The method involves *in situ* generation and trapping of a highly reactive diradical (diyl) of type **14**[21] which is

analogous to trimethylenemethane[22] (TMM) **12**. Their initial approach to tricyclopentanoids employed pyrolysis of the azo compound **13** to diyl **14** and its interception with cyclopentenone which led to various products (**15-17**) (Scheme-1). Analysis of the initial results, particularly the regio- and stereoselectivity of the intermolecular cycloaddition, led them to reason that an intramolecular version of the above reaction might prove to be more selective. Indeed, the pyrolysis of the azo compound **18** furnished two tricyclopentanoids **19** and **20** in a ratio of 9:1 and in very good yield (85%) (Scheme-2). The mechanistic details and the factors affecting the regio- and stereoselectivity of these reactions have been now discussed in detail.[20] After exploratory studies on the intramolecular diyl trapping, Little and his associates demonstrated the potential of the above method through synthesis of hirsutene,[18] coriolin[19] and capnellene.[20] The syntheses of coriolin and capnellene are briefly described here.

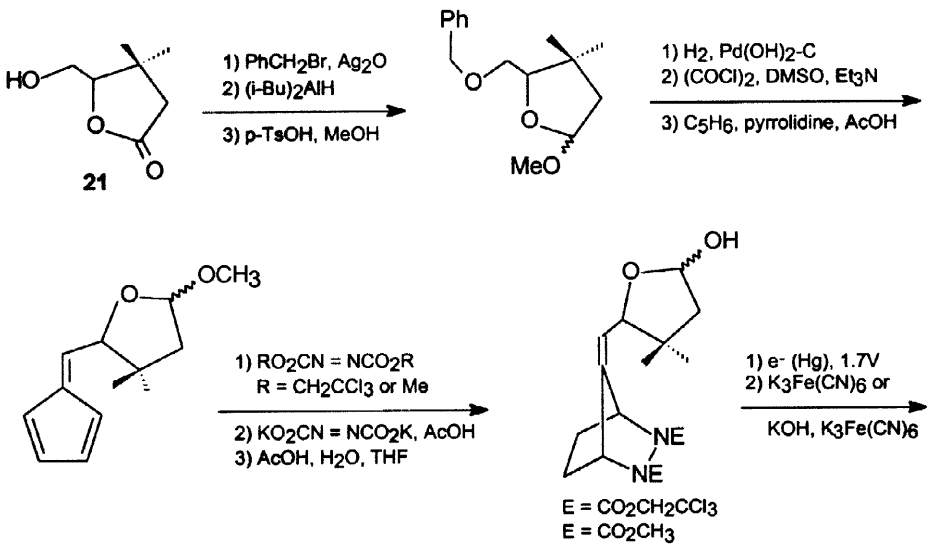


Scheme-1

In an application of the above methodology towards coriolin synthesis, the required azo compound **22** was prepared by a series of reactions from dihydro-5-(hydroxymethyl)-4,4-dimethyl-2(3*H*)-furanone **21** as shown in the Scheme-3. The facile conversion of **22** to the linear triquinane **23** was effected under photolytic conditions. The alcohol **23** was transformed into the enediol **24** by epoxidation with MCPBA, followed by Rickborn-Crandall[19c,d] ring opening initiated by LDA. Protection of the secondary alcoholic group and oxidation with PCC gave the enone **25**. Conjugate addition and generation of the double bond using LDA furnished **26**. The enone **26** has previously been converted into coriolin by Koreeda *et al.*[23]

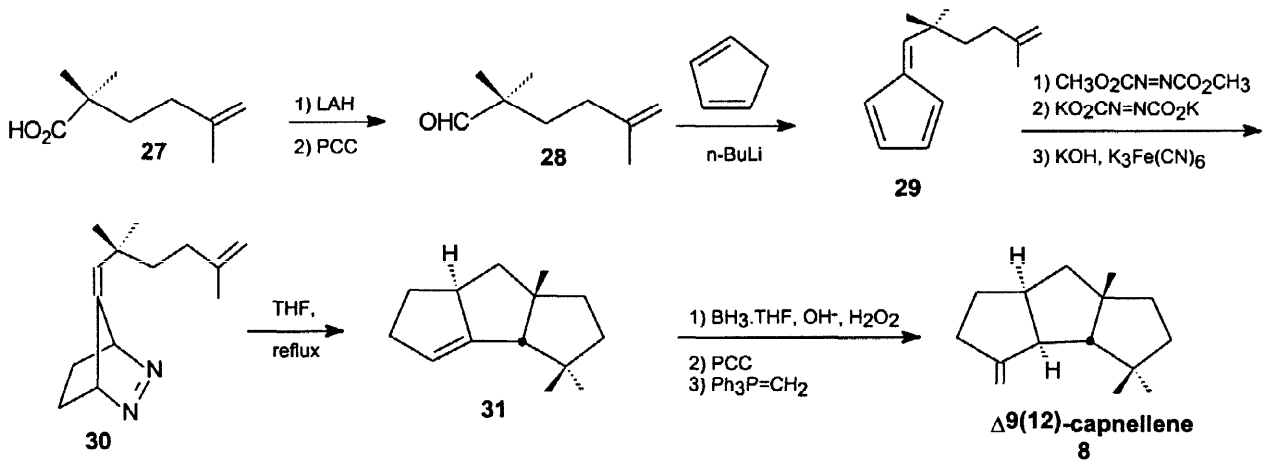


Scheme-2



Scheme-3

The synthesis of $\Delta^{9(12)}$-capnellene following the above methodology is delineated in the Scheme-4. The carboxylic acid **27** was first reduced to the corresponding alcohol, which was then oxidized with PCC to **28**. Subsequent fulvene formation using cyclopentadienyllithium, set the stage for a Diels-Alder reaction between fulvene **29** and dimethyl azodicarboxylate. The resulting dicarbamate was transformed efficiently into **30** which was converted to the triquinane **31** on heating under reflux in tetrahydrofuran. The hydrocarbon **31** on the hydroboration-oxidation sequence followed by PCC oxidation and Wittig olefination gave the desired natural product, $\Delta^{9(12)}$-capnellene **8**.



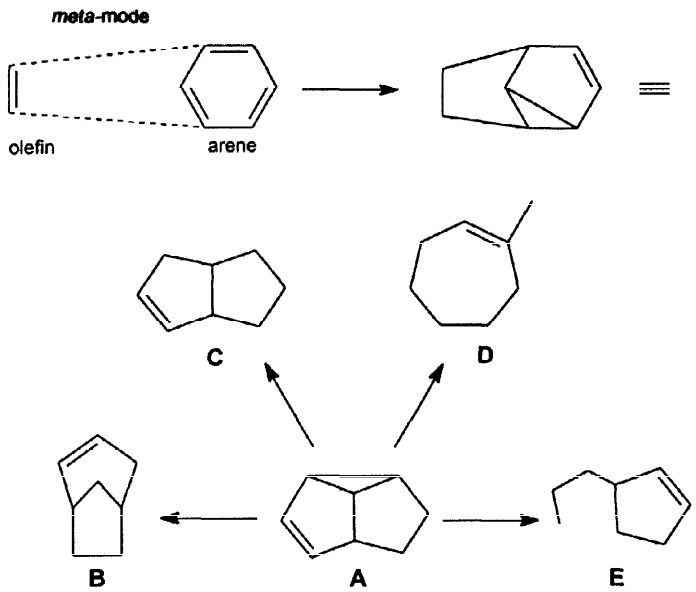
Scheme-4

The 1,3-diyl trapping method offers a simple and convenient route to triquinanes. The triquinane skeleton is built-up in one step having desired *cis:anti:cis* stereochemistry, though the preparation of the starting azo compound requires several steps. For example, the triquinane skeleton for the synthesis of hirsutene[18] and coriolin is generated after nine and twelve steps respectively. Moreover, in the case of synthesis of hirsutene, the key step resulted in the formation of isomers.

2.2. OLEFIN TO ARENE *META*-PHOTOCYCLOADDITION

The photocycloaddition of alkenes to arenes provides a potent tool for the synthesis of many novel and otherwise not accessible products. Among the three theoretically possible addition modes,[24] the *ortho*-, *meta*- and *para*-cycloadditions, the *meta*- type or 1,3-cycloaddition, especially in intramolecular fashion,[25] has proven to be of great value in natural product synthesis as demonstrated by Wender.[26] Three mechanisms have been suggested for the course of *meta*-cycloaddition: (a) interception of the isomerized biradicaloid aromatic by the olefin; (b) formation of an exciplex[25] of charge-transfer character;[27,28] or (c) a concerted process. The mechanistic data are in best accord with an exciplex mechanism for the singlet - state[27-29] which explains satisfactorily the regio- and stereoselective course of such reactions. The carbon

skeleton of the product, a tricyclo[3.3.0.$0^{2,8}$]octene [A], is a versatile synthetic intermediate, which allows entry into different structural units of high utility[26] (Scheme-5).

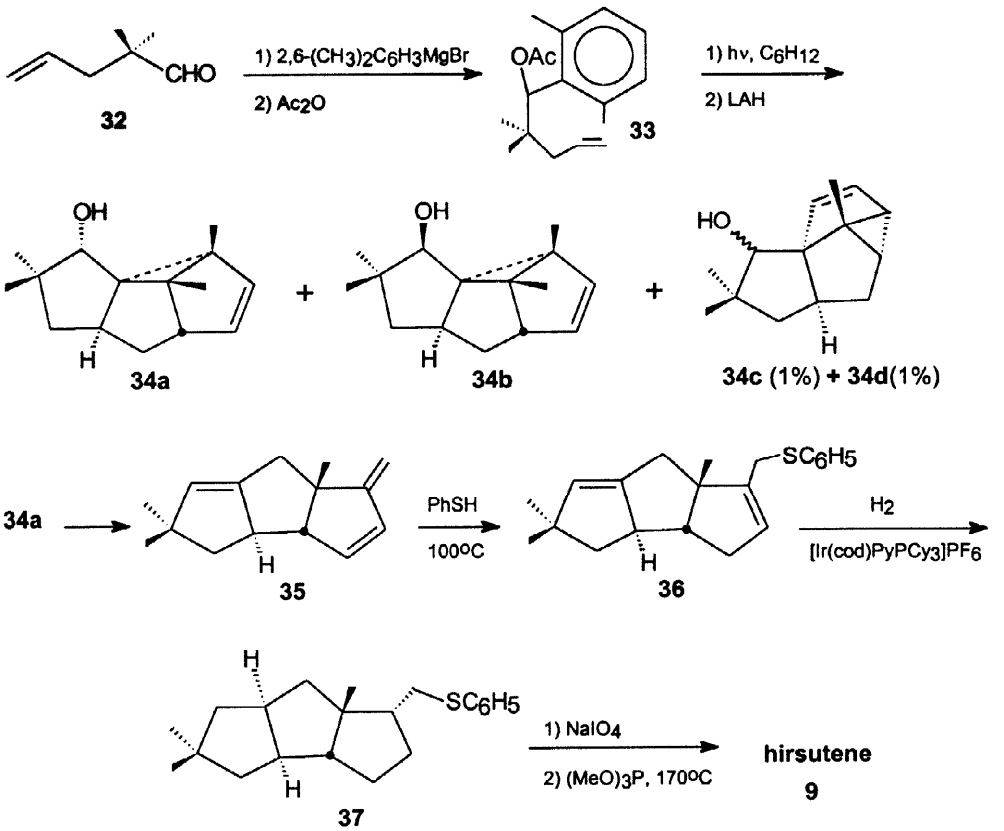


Scheme-5

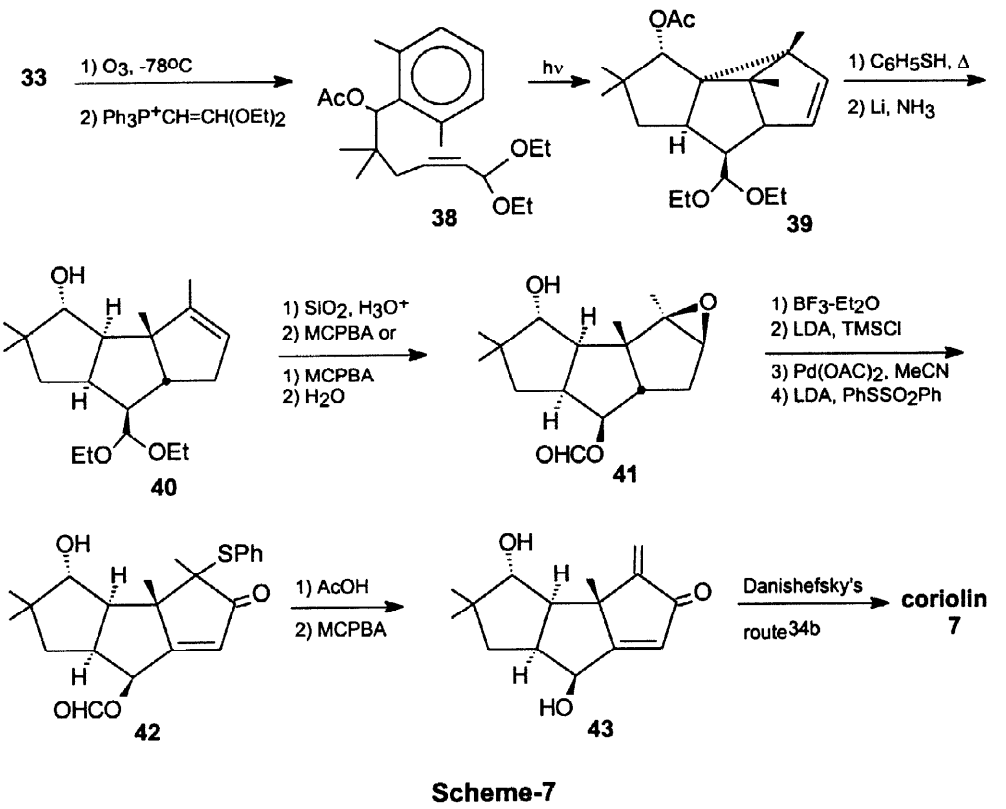
The method was first applied in the synthesis of (±)-cedrene,[30] a natural product with dicyclopentanoid moiety (A→B, transformation) and subsequently in the synthesis of angular triquinanes (±)-isocomene,[31] silphenene[32] and silphiperfol-6-ene[33] in order to prove its generality. Intramolecular *meta*-cycloaddition route was also exploited for the synthesis of linear tricyclopentanoids, hirsutene **9** and coriolin **7** as described below.

In the hirsutene synthesis, Wender and Howbert[34] started with 2,2-dimethyl-4-pentenal **32** as depicted in the Scheme-6. The requisite starting material **33** for the intramolecular *meta*-photoaddition was prepared by addition of the aryl-Grignard reagent of 2,6-dimethyl bromobenzene to **32** followed by protection of the secondary alcohol function. The photocycloaddition of **33** in intramolecular fashion offered **34a** in 23% yield along with other isomers (**34b-d**). Dehydrative acid-catalyzed rearrangement of **34a** led to **35**. Free radical 1,4-addition of thiophenol on **35** gave the compound **36** which was hydrogenated to give **37**. Oxidation of **37** to sulfoxide followed by elimination under standard conditions regenerated the exocyclic olefin to give hirsutene.

In the coriolin synthesis,[34a] **33** was transformed into **38** which upon photocycloaddition gave the tricyclic acetate **39**. The overall synthesis of coriolin from the triquinane **39** is shown in Scheme-7. Thus, the acetate **39** was hydrolysed to give the alcohol **40** which was converted into the enone **42** *via* the epoxyformate **41**. The intermediate **42** was transformed into the key precursor **43** as shown in the Scheme-7.



Scheme-6

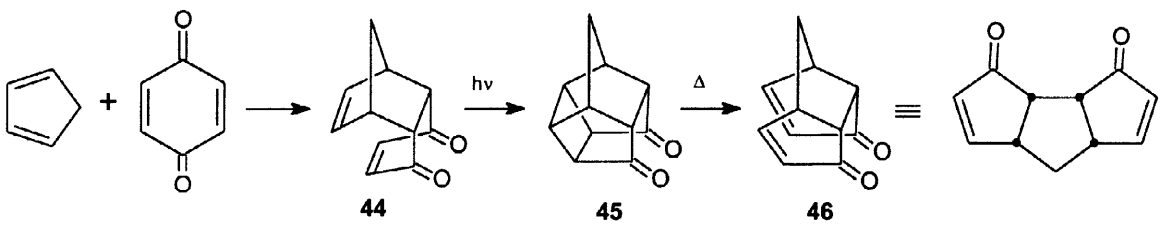


Scheme-7

Although the tricyclopentanoid framework is rapidly achieved by this method, the key photochemical step gives a mixture of the cycloaddition products depending upon the mode of cycloaddition and such products have to be separated. Moreover, a multi-step sequence is required to generate the desired starting material.

2.3. PHOTO-THERMAL METATHESIS REACTION

Mehta and coworkers[35] have developed a novel and versatile route for the synthesis of *cis:syn:cis* tricyclo[6.3.0.$0^{2,6}$]undecane (tricyclopentanoid) framework *via* a novel photo-thermal metathetic sequence. This method involves a photochemical $\pi^2s+\pi^2s$ cycloaddition in *endo* adducts of type **44** and a regiospecific thermal fragmentation of the cyclobutane ring of the resulting product **45** to give *cis:syn:cis* triquinane **46**. The strategy is depicted below (Scheme-8). The generality of this sequence is demonstrated by synthesis of a large number of *cis:syn:cis* triquinanes bearing a variety of substituents. It is interesting to note that *cis:syn:cis* triquinane framework thus generated was isomerized to *cis:anti:cis* framework and hence provided an opportunity to develop syntheses of many natural products. Application of this methodology to the synthesis of capnellene **8**, coriolin **7** and hirsutene **9** is described below.

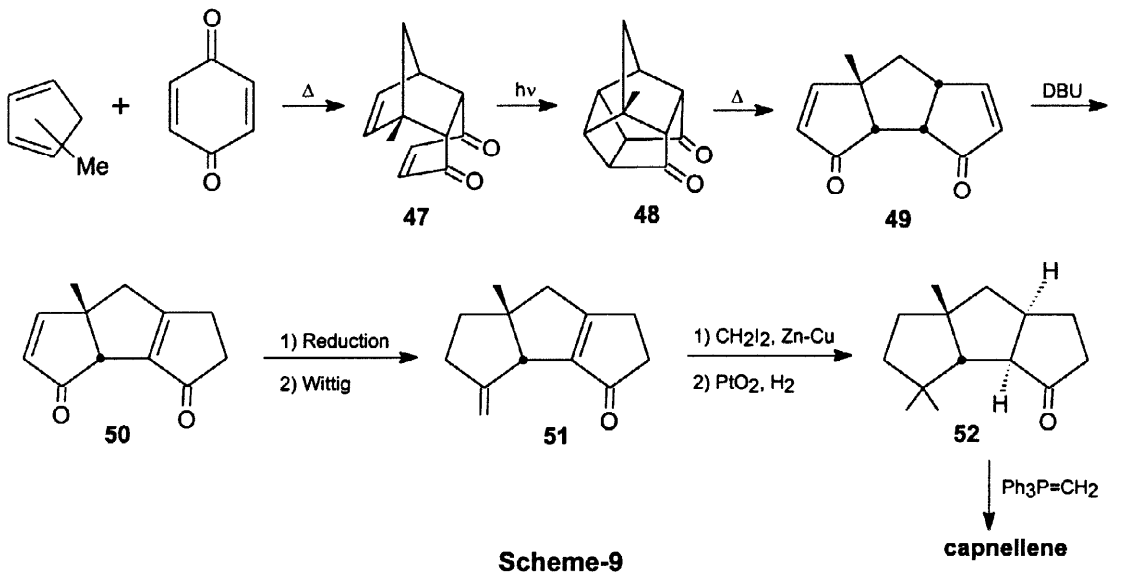


Scheme-8

The (±)-$\Delta^{9(12)}$-capnellene synthesis (Scheme-9) of Mehta and coworkers[36] employed Diels–Alder reaction of isomeric methylcyclopentadienes and *p*-benzoquinone from which the desired tricyclic *endo*-adduct **47** was obtained. Its intramolecular photocycloaddition to **48** followed by thermal fragmentation gave **49**. It was treated with base to obtain the diene-dione **50**. Selective catalytic hydrogenation of **50** followed by olefination gave **51**. The treatment of **51** with CH_2I_2 in the presence of Zn-Cu couple gave the spirocyclopropane derivative which was hydrogenated to give the intermediate **52**. Since the ketone **52** has already been transformed into capnellene,[37] the formal synthesis was complete.

Mehta's group have used a common intermediate for the synthesis of coriolin and hirsutene. In the coriolin synthesis[38] (Scheme-10), the tricyclic system **53** was obtained from thermal Diels–Alder reaction between cyclopentadiene and 2,5-dimethyl benzoquinone. The adduct **53** was subjected to intramolecular [2+2] photocycloaddition which furnished the cage dione **54**. Flash vacuum pyrolysis of **54** delivered the compound **55** which on thermal equilibration and hydrogenation afforded the *cis:anti:cis* dione **56**. The dione

56 was alkylated regioselectively to yield dimethyl dione 57. Chemoselective addition of MeMgI to the less hindered carbonyl group of 57 followed by dehydration gave 58 which was reduced stereoselectively with Li-NH_3 to obtain thermodynamically more stable alcohol 59. The alcohol 59 was elaborated to 61 *via* the ketoalcohol 60 as shown in Scheme-10. Phenyl selenylation-selenoxide elimination of 61 gave the precursor 62 which had previously been converted into (±)-coriolin 7.[39]



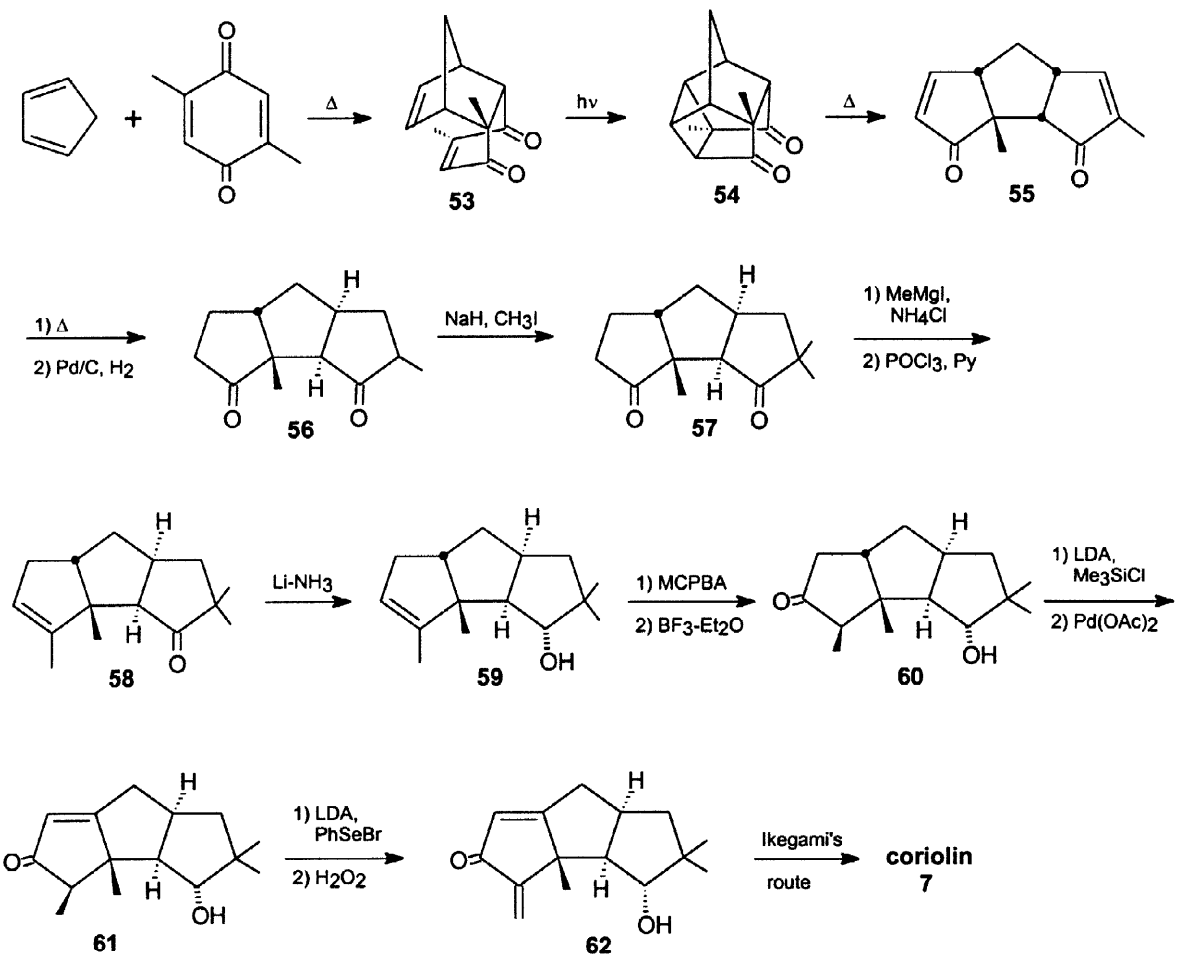
Scheme-9

Mehta's hirsutene synthesis (Scheme-11)[40] follows the same route upto compound 56. The compound 56 was selectively methylated with potassium *t*-butoxide to furnish 57. Regioselective Wittig reaction of 57 gave the enone 63, which was converted to 64. Transformation of 64 to 65 followed by reduction with tributyltin hydride furnished the hirsutene 9.

2.4. RADICAL INITIATED POLYOLEFINIC CYCLIZATIONS

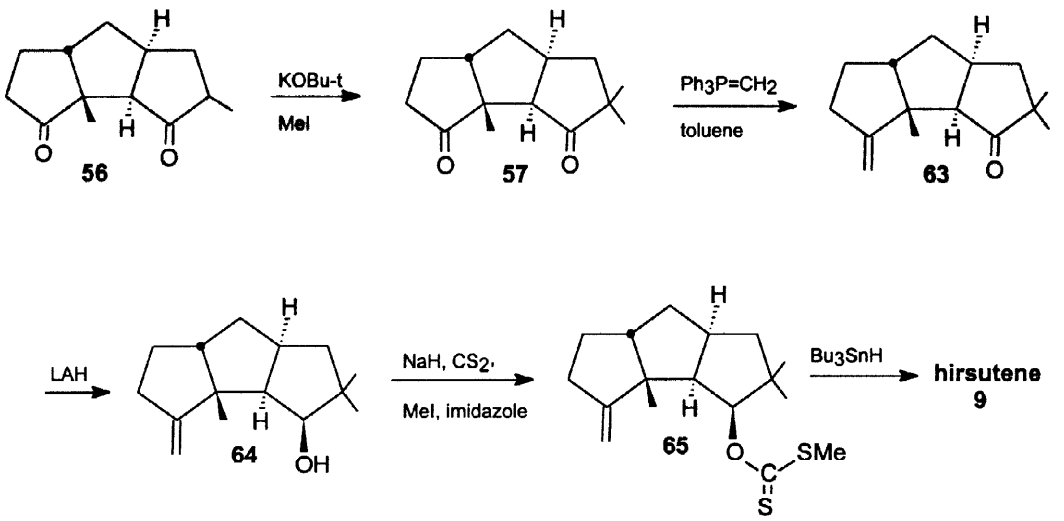
Curran and his associates have developed[41,42] a novel unified strategy for the synthesis of linear condensed cyclopentanoids employing a tandem hex-5-enyl radical cyclization as the key step.[43-45] The ability of radical cyclizations to construct multiple five membered rings in a controllable fashion has been featured in syntheses of the three major classes of triquinanes (linear, angular and propellane). The synthesis is executed in three steps: (1) S_N2-*anti* opening of a vinyl lactone 66 to provide a *trans*-disubstituted cyclopentene 67; (2) rapid elaboration to a cyclization precursor 68; and (3) tandem radical cyclization leading to 69. A tandem radical cyclization forms the two outer rings of a triquinane about a central pre-formed cyclopentene ring (Scheme-12). The generality and flexibility of this strategy are quite apparent in that variations in the nature and disposition of the side chains can lead to different triquinanes. The study of the mechanistic data indicates that in most cases these cyclizations are stereoelectronically

controlled, irreversible, proceed regardless of the degree of substitution of starting and product radicals and tolerate a wide variety of pendant functional groups.[42,43] The synthetic potential of the above method has been illustrated by efficient total syntheses of (±)-hirsutene,[41,42] capnellene[46], coriolin and hypnophilin.[47]

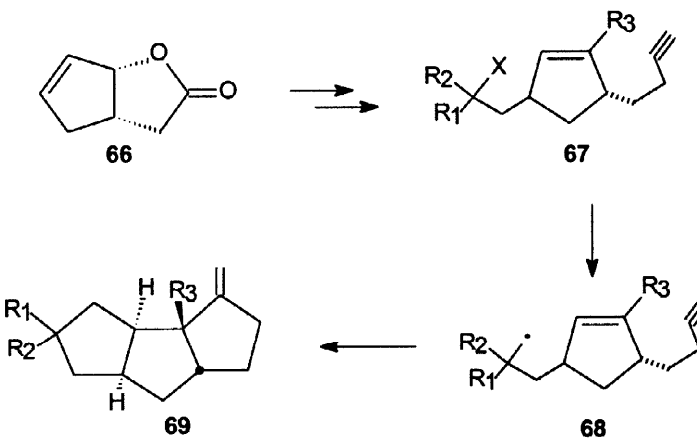


Scheme-10

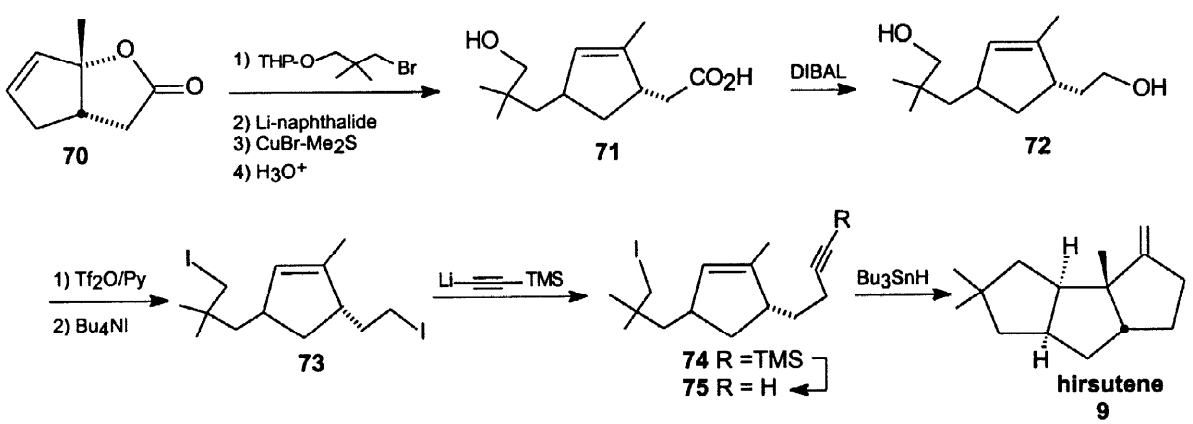
Towards application of this methodology for the synthesis of hirsutene, the vinyl lactone **70** was first converted into the *trans*-disubstituted hydroxy-acid **71** (Scheme-13). Reduction of **71** with DIBAL gave the diol **72** which was then transformed into the diiodide **73** as shown in the Scheme-13. Treatment of **73** with lithium trimethylsilyl acetylide furnished the silyl acetylene **74** which was desilylated with tetrabutylammonium fluoride to give **75**. Treatment of **75** with tributyltin hydride gave hirsutene in a single step (Scheme-13).



Scheme-11

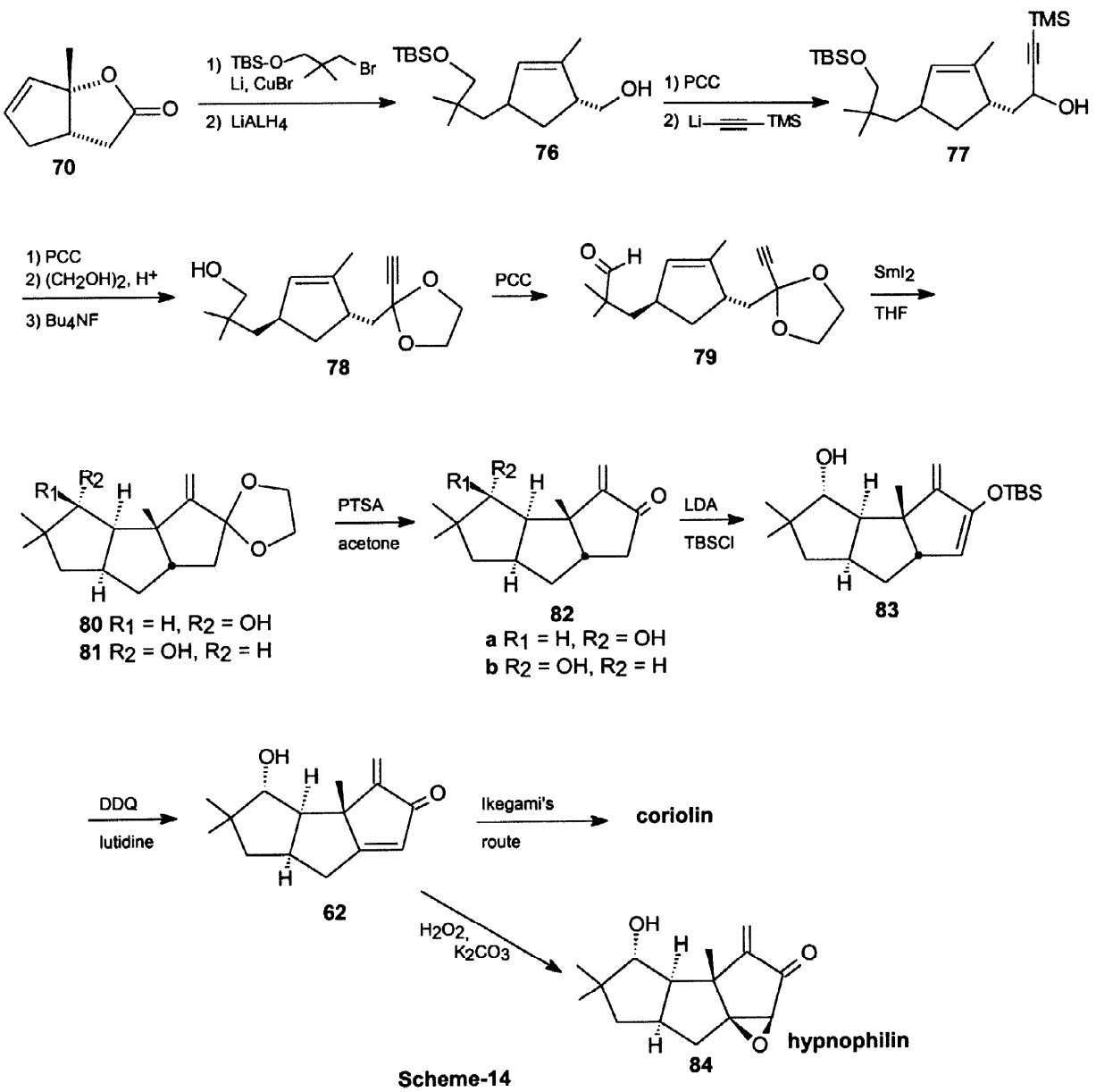


Scheme-12



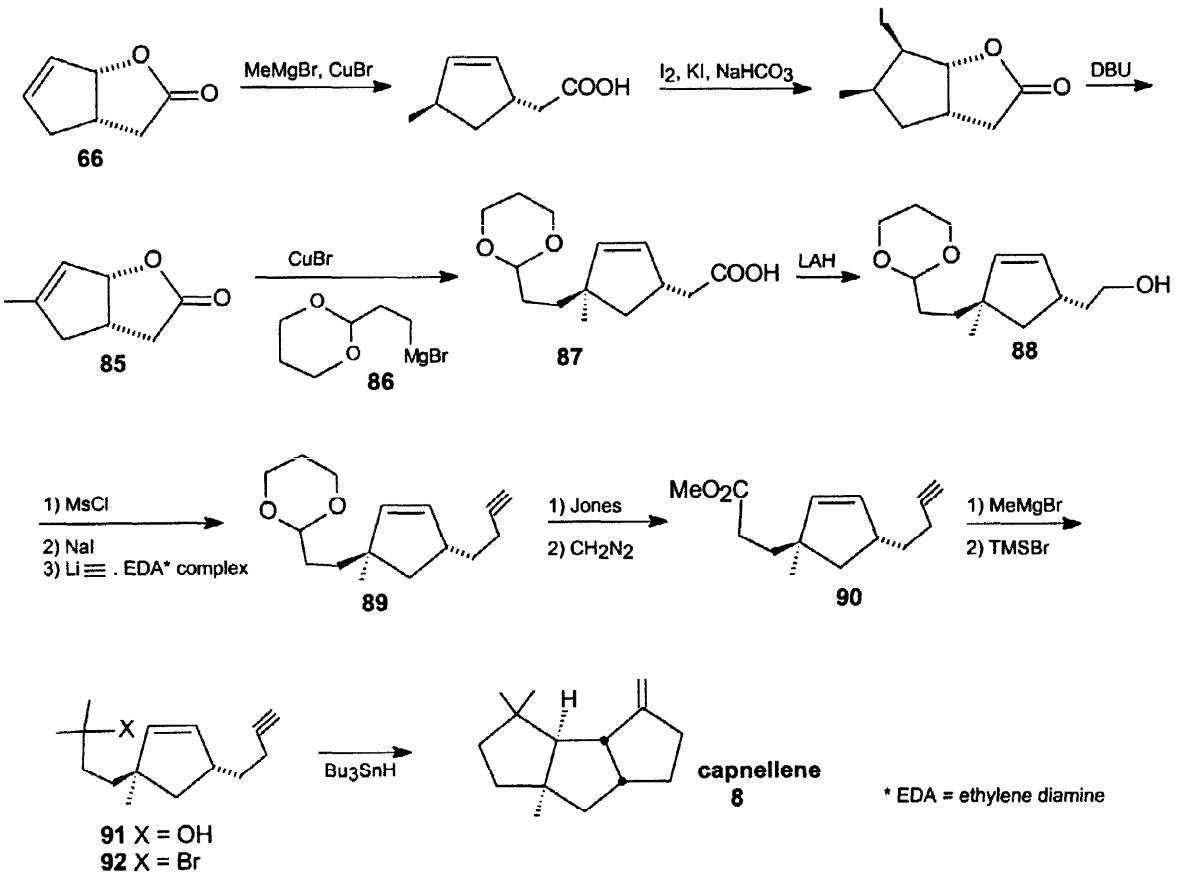
Scheme-13

The same lactone **70** was transformed into acetylenic ketone **79** for coriolin synthesis (Scheme-14). Herein, **70** was converted to the *trans*-substituted cyclopentene derivative **76**. Oxidation of **76** followed by a nucleophilic addition with the silyl acetylide gave **77**. The compound **77** was then transformed into the protected acetylide **78** which upon oxidation gave **79** as shown in Scheme-14. Samarium(II) catalyzed cyclization of **79** furnished stereisomeric alcohols **80** and **81** which contain most of the structural and stereochemical features of coriolin. Deprotection of **80** and **81** with pTSA gave the enones **82a, b**. **82a** was then converted to the silylenol ether **83**. Introduction of the double bond in **83** gave the intermediate **62**, a precursor to coriolin in an earlier synthesis.[39b] Epoxidation of **62** with H_2O_2 gave hypnophilin **84** (Scheme-14).[47]



Scheme-14

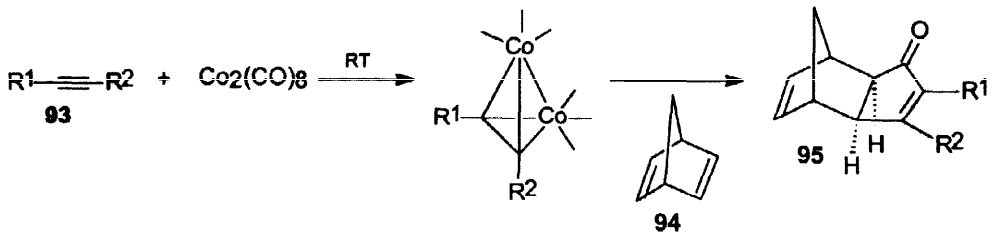
Synthesis of capnellene has also been completed along similar lines (Scheme-15).[46] The vinyl lactone **85** was synthesized from the unsubstituted vinyl lactone **66** *via* an S_N2-*anti* opening, iodolactonization followed by a base promoted elimination reaction sequence. The reaction of **85** with the species generated by addition of the Grignard reagent **86** to an equivalent of CuBr/DMS complex, produced the acid **87** which upon reduction with lithium aluminium hydride gave the alcohol **88**. The compound **88** was converted into the enyne **89**. Removal of the protective group and oxidation with Jones reagent followed by treatment of the resulting acid with diazomethane gave the ester **90**. The addition of excess methylmagnesium bromide produced the tertiary alcohol **91** which gave the cyclization precursor **92** on treatment with trimethylsilyl bromide. Cyclization of **92** with tributyltin hydride in presence of AIBN produced $\Delta^{9(12)}$-capnellene.



Scheme-15

2.5. PAUSON–KHAND REACTION

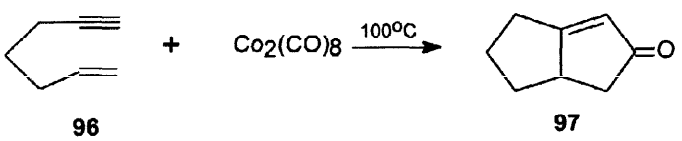
The [2+2+1] cycloaddition between an alkyne, alkene and CO (from $Co_2(CO)_8$) leading to cyclopentenone is called the Pauson–Khand reaction, for example, the formation of **95** by reaction of enyne **93** and norbornadiene (**94**) (Scheme-16).



Scheme-16

This reaction was first reported by Pauson and Khand in 1973[48] and now constitutes one of the popular approaches to cyclopentenone ring formation. The Pauson–Khand reaction has been well studied[49] and it has now been established[50] that: a) the yields of the cyclopentenones are improved if the alkene is strained; b) the reaction is regiospecific with the larger group of the alkyne being accomodated adjacent to the newly inserted CO group; c) the *cis-exo* ring fusion is achieved; d) with respect to the alkene regiochemistry the larger allylic substituent is placed *anti* to the new CO.

Schore reported the first intramolecular version of Pauson–Khand (IMPK) reaction to make the bicyclic system **97**[51] from the enyne **96** (Scheme-17). The first synthetic application of the intramolecular Pauson–Khand reaction was reported by Magnus and coworkers for the synthesis of coriolin[52] and hirsutic acid[53] as described below. The approach involved syntheses of the diquinane precursors which were transformed into triquinanes *via* annulation.

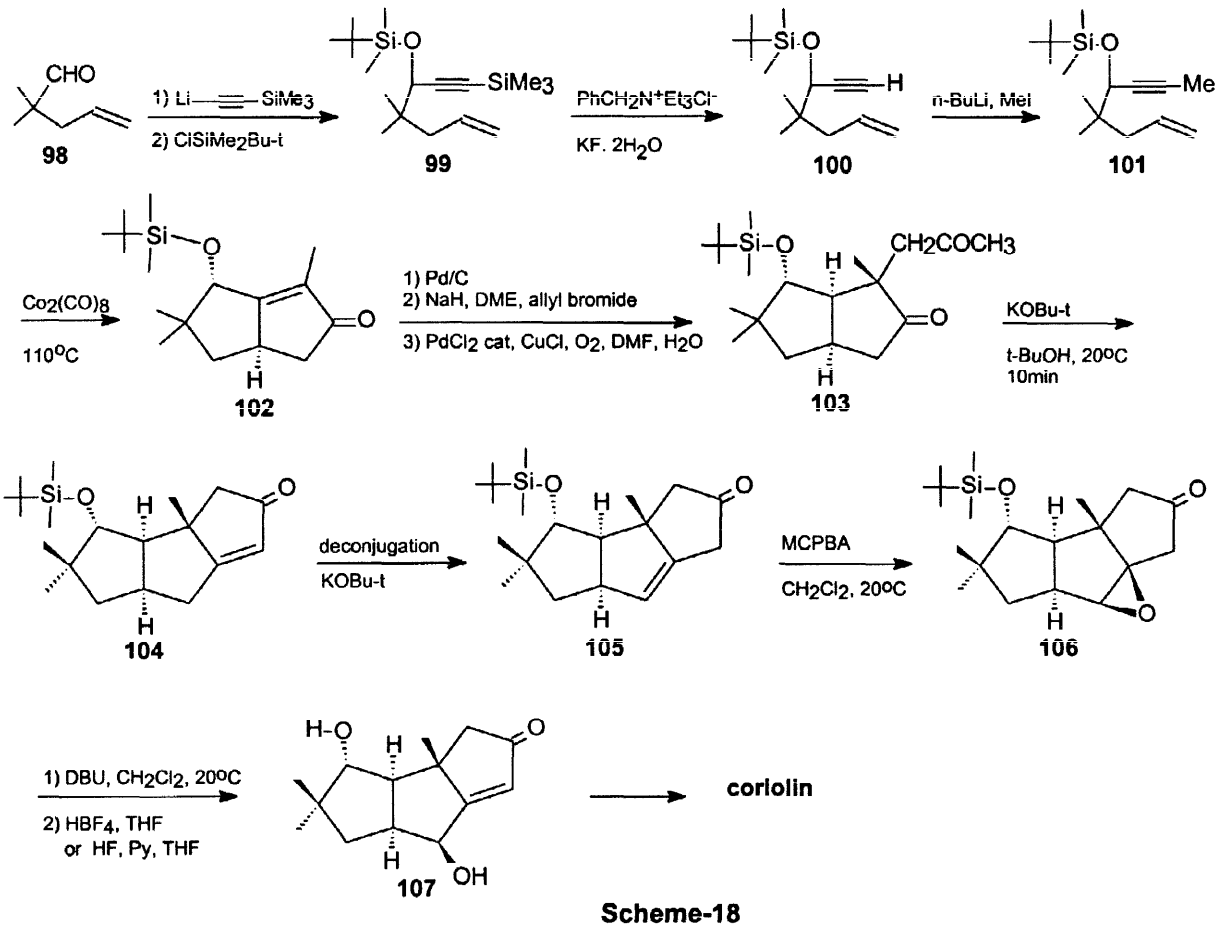


Scheme-17

In the coriolin synthesis, the acyclic aldehyde **98** was converted into **99**. Removal of trimethylsilyl group gave the enyne **100** which was alkylated to furnish the precursor **101**, as shown in Scheme-18. Intramolecular Pauson-Khand reaction of **101** gave the diquinane **102** which upon reduction, allylation and Wacker type oxidation gave the dione **103**. Aldol condensation of **103** furnished the triquinane **104** which was transformed into the enone **105**. Epoxidation of **105** gave the epoxy ketone **106** which was converted into the key precursor **107**. Since the compound **107** has already been converted by Danishefsky[34b] into coriolin, the formal synthesis was complete.

In a formal synthesis of hirsutic acid Magnus and coworkers prepared the diquinanes **112a** and **113a** which have already been taken to hirsutic acid. Thus, the malonic ester derivative **108** was transformed into the required alicyclic precursor **109** which through the Pauson–Khand reaction gave a mixture of the diquinane **110a**, with the correct stereochemistry and the undesired diquinane **110b**. Treatment of the

mixture of **110a, b** with $MsOH.2H_2O$ again gave a mixture of acids **111a, b**. The subsequent hydrogenation of this mixture gave **112** which upon esterification with CH_2N_2 yielded a mixture of esters **113a, b**. The epimer **111b** was re-equilibrated to **111a** with *p*-toluene sulphonic acid and therefore **111a** was synthesized from **110** in 90% yield (Scheme-19).



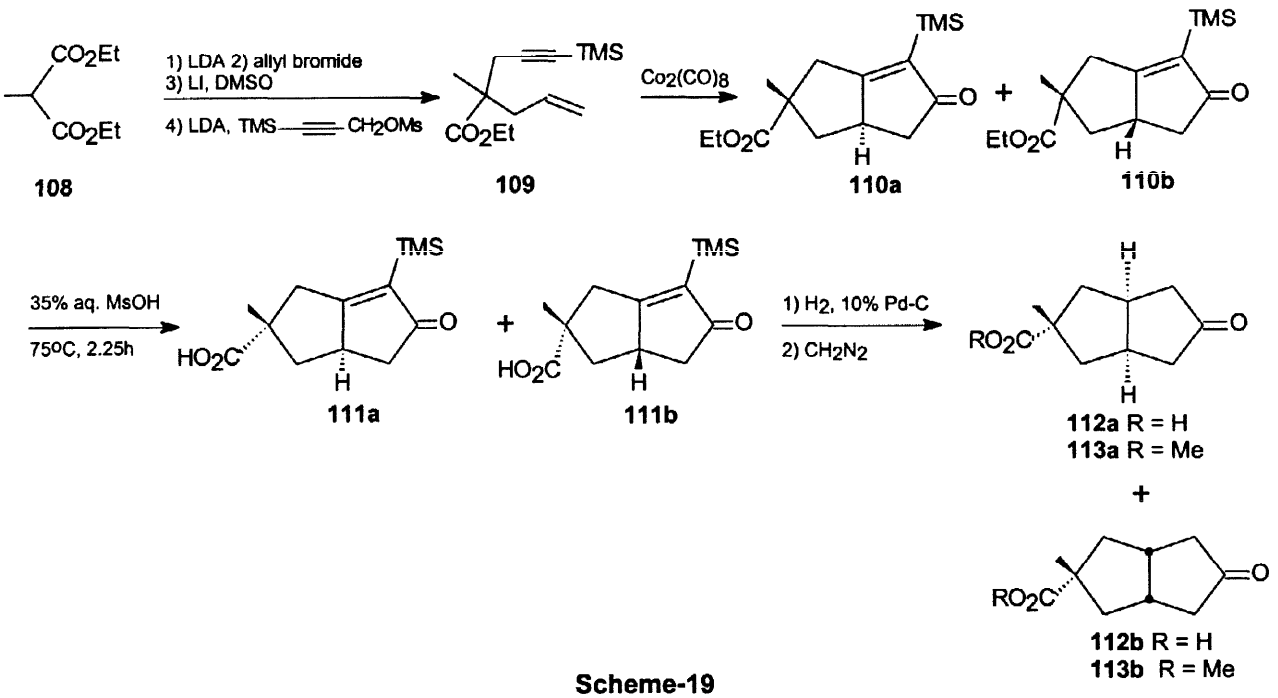
Scheme-18

Recently, Veretenov[54] and associates have been able to assemble the linear triquinane framework *via* a pathway described as "monocyclic precursor → triquinane ring formation" and this method has been employed for the synthesis of triquinanes **119-122** (Scheme-20).[55] The crucial step in the scheme is the generation of the correctly oriented enyne precursor **117** and its Pauson–Khand reaction. Thus, the *gem*-dimethylated carbomethoxy derivative of cyclopentanone **114** was allylated to **115** and subsequently demethoxycarboxylated to give **116**. The ethynylation of **116** proceeded with moderate efficiency to the required isomer **117** with *cis*-oriented allyl and ethynyl residues being formed with high stereoselectivity. The alcohol **117** and its acetate **118** were converted to dicobaltohexacarbonyl complexes upon treatment with $Co_2(CO)_8$. The IMPK reaction was carried out on **117** and **118** by thermolysis in solution or on surface of

silicagel or on oxidative initiation of the reaction with *N*-MMO to give **119**, **120** and **121**, **122**, respectively. The stereoselectivity of the reaction is still to be optimized for general applicability.

Hua[56] used the Pauson-Khand product, for the first time, to synthesize angularly fused triquinane skeletons of optically active pentalenene and racemic pentalenolactone-(*E*)-methyl ester. In another approach Billington and coworkers[57] carried out the IMPK reaction on an alicyclic enyne precursor, allyl propargyl ether, and applied it to the synthesis of an O-heterocyclic natural product aucubigenone.

The shortness and flexibility coupled with a high degree of stereocontrol are the highlights of the IMPK reaction.

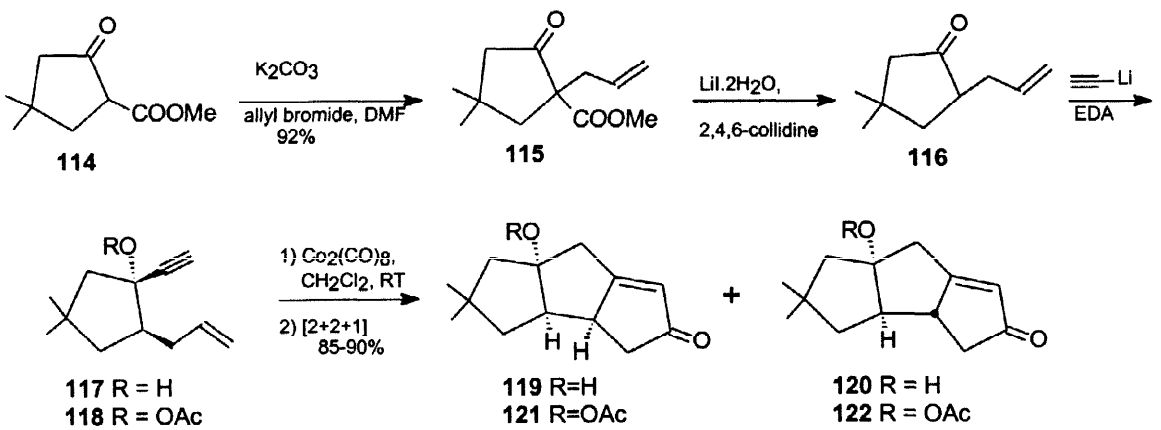


108 **109** **110a** **110b** **111a** **111b**

112a R = H
113a R = Me

112b R = H
113b R = Me

Scheme-19



114 **115** **116**

117 R = H
118 R = OAc

119 R=H
121 R=OAc

120 R = H
122 R = OAc

Scheme-20

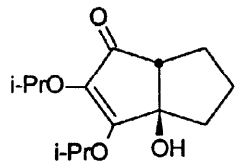
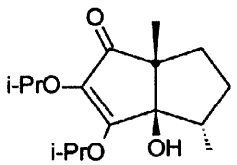
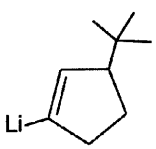
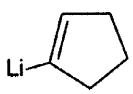
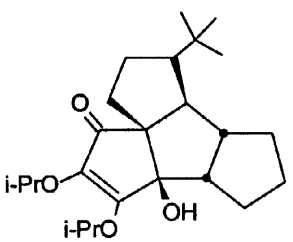
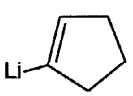
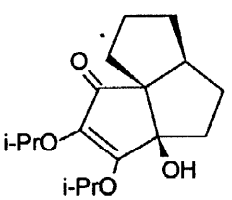
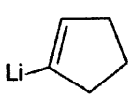
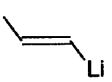
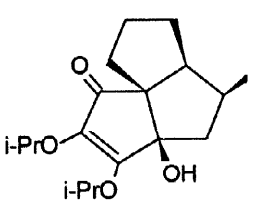
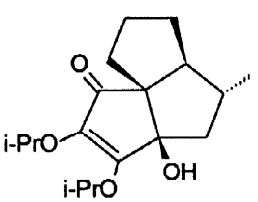
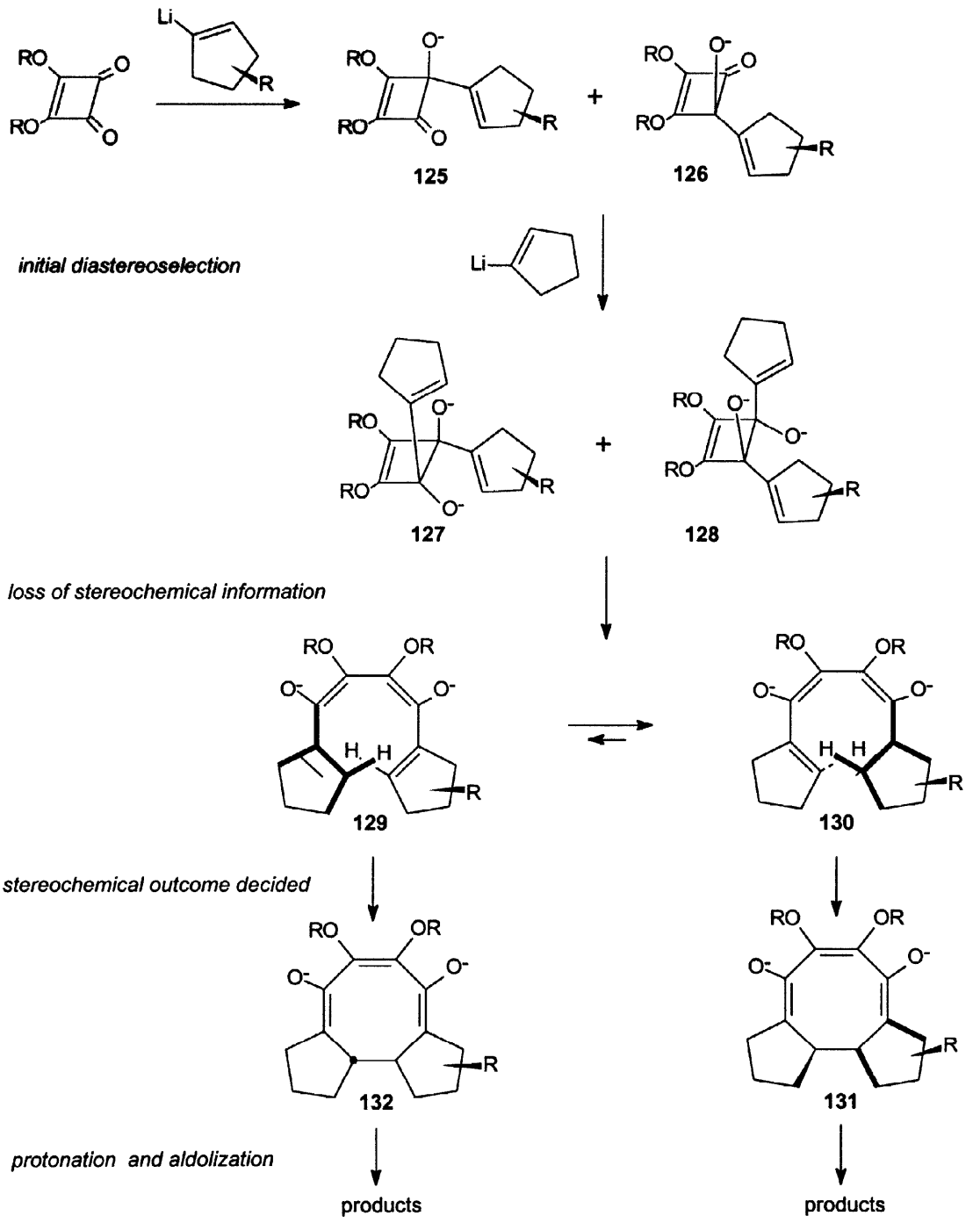
	First anion	Second anion	Products
1.	$LiCH{=}CH_2$ (3eq.)		
2.			
3.			
4.			
5.			 

Table-1


initial diastereoselection
loss of stereochemical information
stereochemical outcome decided
protonation and aldolization
products
products

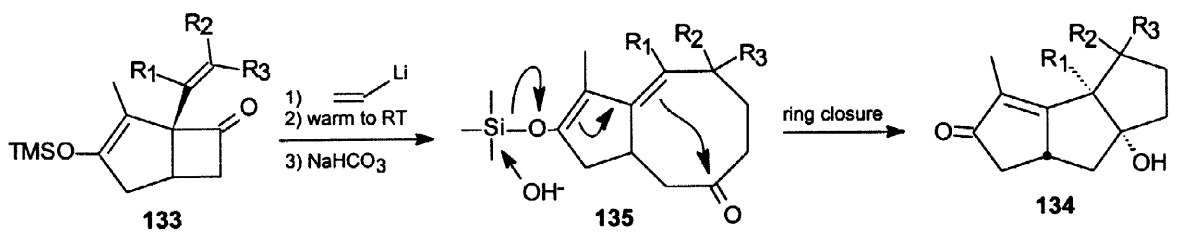
Scheme-22

2.7. TANDEM OXY-COPE-TRANSANNULAR RING CLOSURE ROUTE TO POLYQUINANES

Tandem reactions have become an important tool for construction of complex and functionalized carbocycles in as few steps as possible, and an example of this is the tandem oxy-Cope-transannular ring closure. Santora and Moore[63] have described preliminary results of the application of this sequence leading to the synthesis of highly functionalized polycyclopentanoids. The initial step is the addition of an appropriate vinyllithium reagent to bicyclo[3.2.0]heptenones **133**, and oxy-Cope rearrangement of the resulting species leading to the formation of the intermediate such as **135**, which upon transannular cyclization gives highly functionalized polyquinanes (Scheme-23). This approach like the previous one also utilizes the high reactivity of the cyclobutenone dimethyl squarate ester to generate the bicyloheptenone precursors **133**. The bicyclic precursors employed in this approach are synthesized from cyclobutadiendione.

The choice of the bicyclo[3.2.0]heptenones and substituted vinyllithium reagent determined the substitution pattern in the products as shown (Table-2, Equations 1-4). Thus, this tandem reaction provides a regiospecific route to highly substituted triquinanes. Substitution patterns are realized by stereoselective alkylation of the enolate intermediate prior to transannular ring closure, for example, addition of vinyllithium to bicycloheptenone followed by warming and quenching of the resulting enolate with methyl iodide afforded the triquinane **134a** (Table-2, Eq. 1). The addition of 2-lithiopropene to **133b** gave the diastereomer **134b**. Further, additional functionality may be introduced into the products by use of substituted vinyl anions.

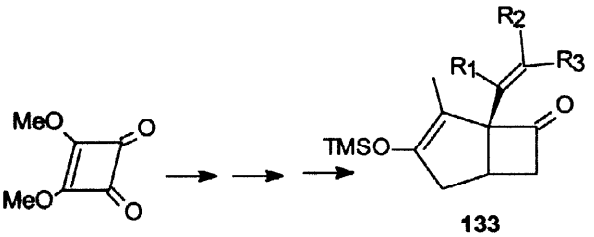
The synthesis of the linear tetraquinane (Eq. 3) and its angular analogue (Eq. 4) from **133b** and **133c** respectively, shows the generality of the sequence in construction of higher order polyquinanes.



133 **135** **134**

	R_1	R_2	R_3
a	H	CH_3	CH_3
b	H	H	H
c	$-(CH_2)_3-$		H

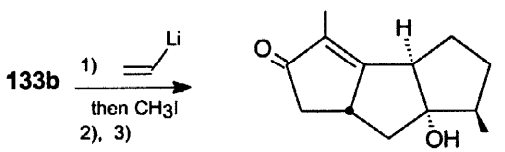
Scheme-23



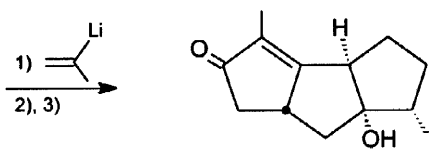
133

	R_1	R_2	R_3
a	H	CH_3	CH_3
b	H	H	H
c	$-(CH_2)_3-$		H

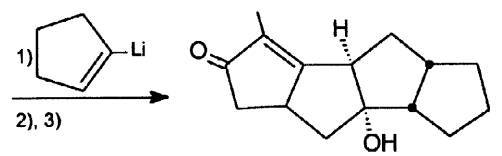
Scheme-24



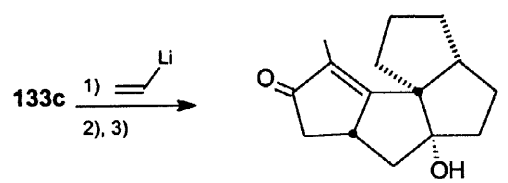
134a Eq. 1



134b Eq. 2



134c Eq. 3



134d Eq. 4

2) warm to RT, 3) $NaHCO_3$

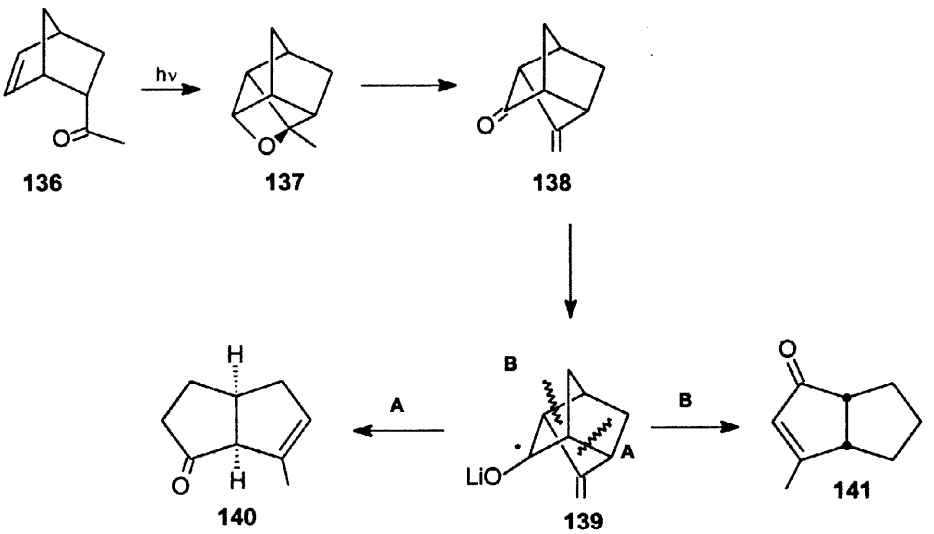
Table-2

2.8. PHOTOCYCLOADDITION-FRAGMENTATION APPROACH

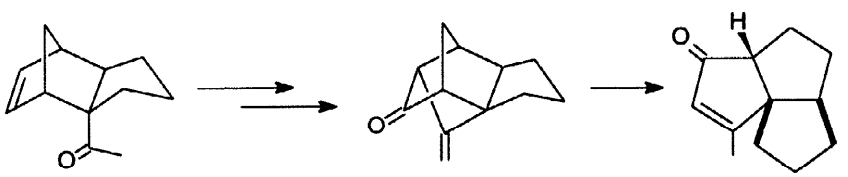
Rawal and coworkers developed an approach involving Diels–Alder reaction to construct first a norbornane skeleton followed by Paterno–Buchi[64] reaction for the construction of triquinane skeletons **140** and **141**, respectively (Scheme-25). The Paterno–Buchi reaction of the norbornane skeleton of type **136** generates an oxetane **137** which on cleavage and subsequent oxidation gives the ketoalkene **138**. The susceptibility of the ketoalkene to fragmentation due to the inherent strain energy gives the radical **139** which rearranges *via* either path A or B to yield the quinane **140** and **141**, respectively. Later studies showed that the reductive fragmentation of the cage compounds could be controlled by substituents on the norbornane

skeleton. The initial studies were directed towards diquinane and angular triquinane synthesis.[65] The angular triquinane was obtained *via* the sequence shown in Scheme-26. Subsequently, the linear triquinane *endo*-hirsutene was synthesized using this methodology (Scheme-27).[66]

Towards the synthesis of *endo*-hirsutene, the precursor **143** was generated from fulvene derivative **142** following Sternbach's procedure.[66b] Photolysis of **143** gave the oxetane derivative **144** which was cleaved with base and the resulting alcohol was oxidized with PDC to give the compound **145.** Base catalyzed fragmentation of **145** directly gave the triquinane **146** which was transformed into *endo*-hirsutene **147** (Scheme-27).



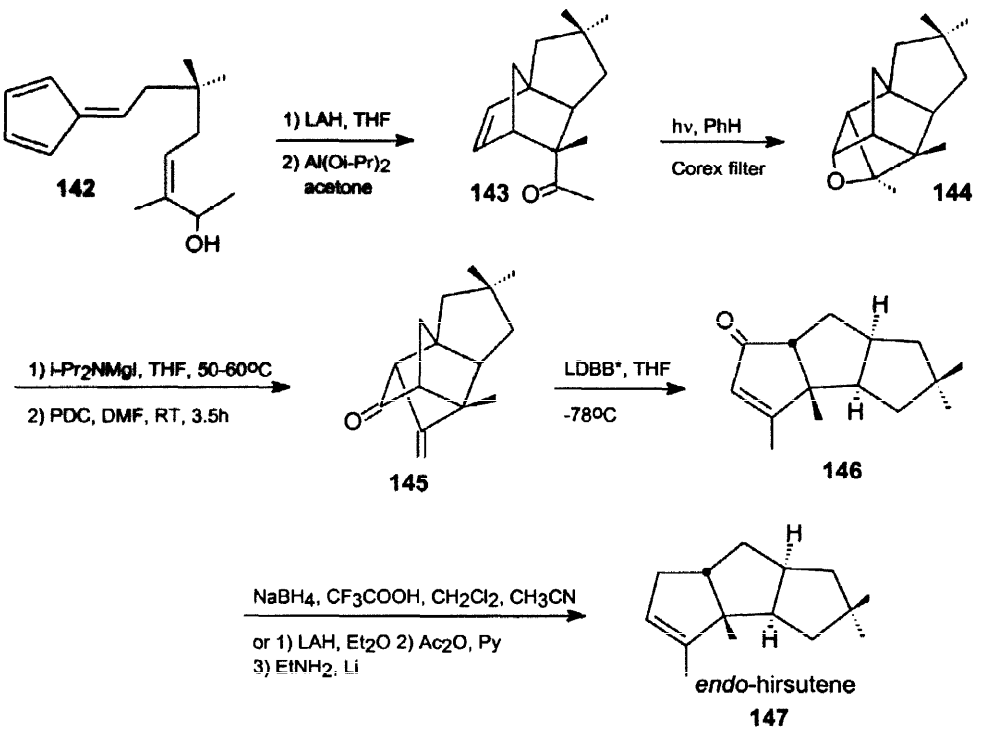
Scheme-25



Scheme-26

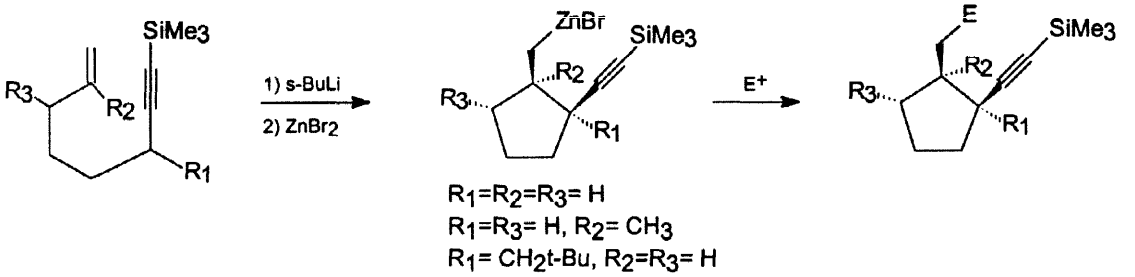
2.9. ZINCA-ENE-ALLENE REACTION

Meyer and associates[67] reported a methodology for carbocycle synthesis *via* an intramolecular zinc-ene-allene reaction as shown in Scheme-28. Extension of this methodology provided a route to linearly and angularly fused tricyclopentanoids starting from the same precursor.[68]



*Li di-t-butylbiphenelide

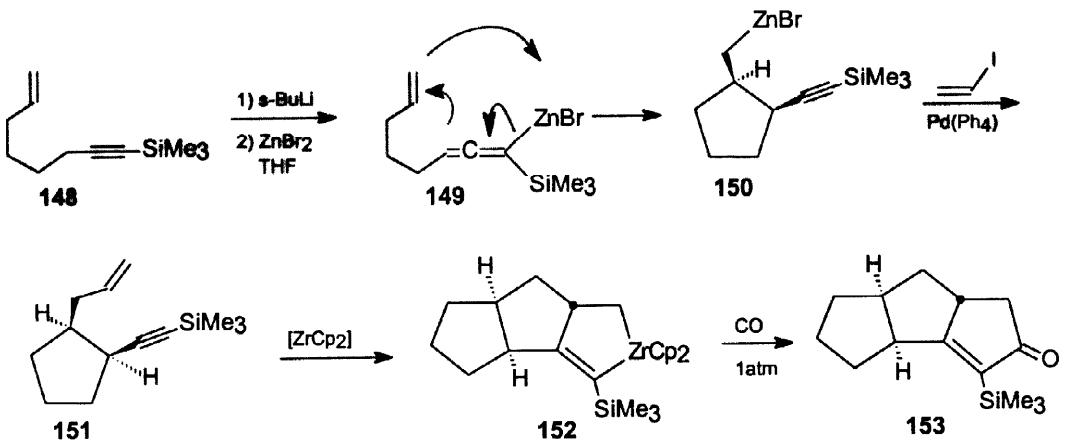
Scheme-27



$R_1=R_2=R_3=H$
$R_1=R_3=H$, $R_2=CH_3$
$R_1=CH_2t\text{-}Bu$, $R_2=R_3=H$

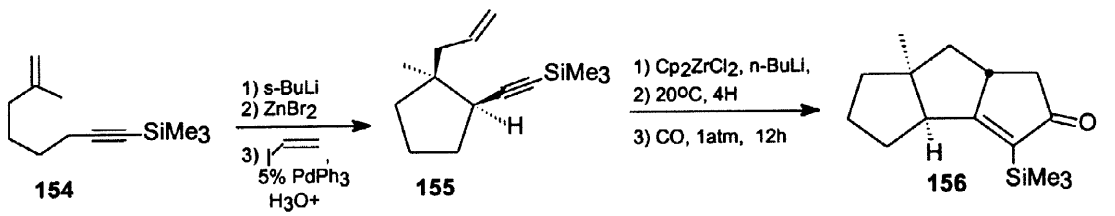
Scheme-28

The authors metallated 8-(trimethylsilyl)-1-octen-7-yne **148** at -45°C with butyllithium and added the Zn salt to the reaction mixture which led to the formation of **150** *via* the allenic intermediate **149**. The compound **150** was then coupled with 1-iodoethene in presence of tetrakistriphenylphosphine palladium to give **151** which on treatment with $ZrCp_2$, generated *in situ* from the reaction of $ZrCp_2Cl_2$ and n-butyllithium, gave the zirconatricylic product **152** which without isolation was subjected to carbonylation reaction to get the *cis*:*anti*:*cis* tricyclopentanoid ketone **153**.

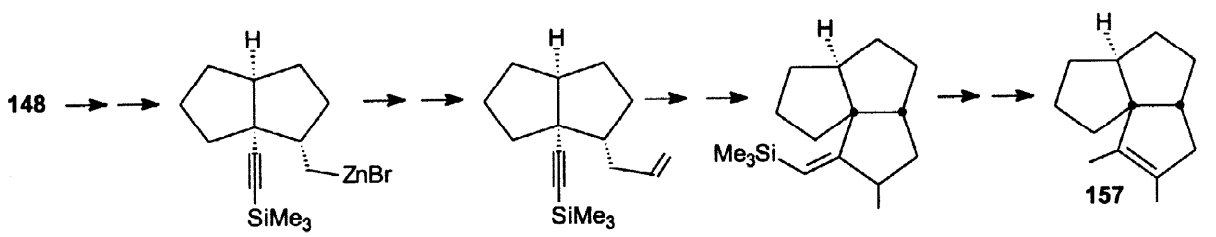


Scheme-29

Utilizing the same methodology α,α-disubstituted enyne **154** was converted to **155** and subsequently to the linear tricyclic enone **156** with an angular methyl group (Scheme-30). Further, this methodology was also used to synthesize an angular triquinane **157** starting from the enyne **148** (Scheme-31).[68]



Scheme-30

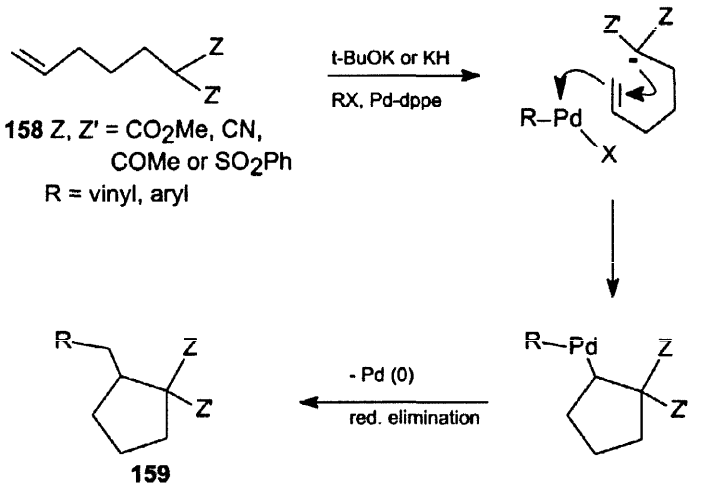


Scheme-31

2.10. PALLADIUM CATALYZED CYCLOPENTANATION OF ALKENES

Balme and his associates have also developed a unified method for rapid synthesis of linear triquinanes employing palladium mediated cyclopentanation of alkenes[69] bearing a nucleophilic substituent. The methodology is based on their observation that the treatment of n-alkene of type **158** with strong base,

palladium catalyst, and an electrophile gives cyclopentane derivatives such as **159** as shown in Scheme-32. Extension of this methodology led to synthesis of capnellene as shown in Scheme-33. The key precursor **163** was prepared from the cyclopentene derivative **160**. Thus, **160** was subjected to iodolactonization and dehydrohalogenation to **161** which was converted to the trisubstituted cyclopentene derivative **163** *via* **162**. **163** was then subjected to cyclization which gave a mixture of triquinanes **164** and **165** in a 93:7 ratio and good yield. The triquinane **164** was then readily taken to capnellene **8** *via* **166** as shown in Scheme-33.



Scheme-32

2.11. ONE POT SYNTHESIS *via* CONJUGATE ADDITION OF ENOLATE-CARBANIONS

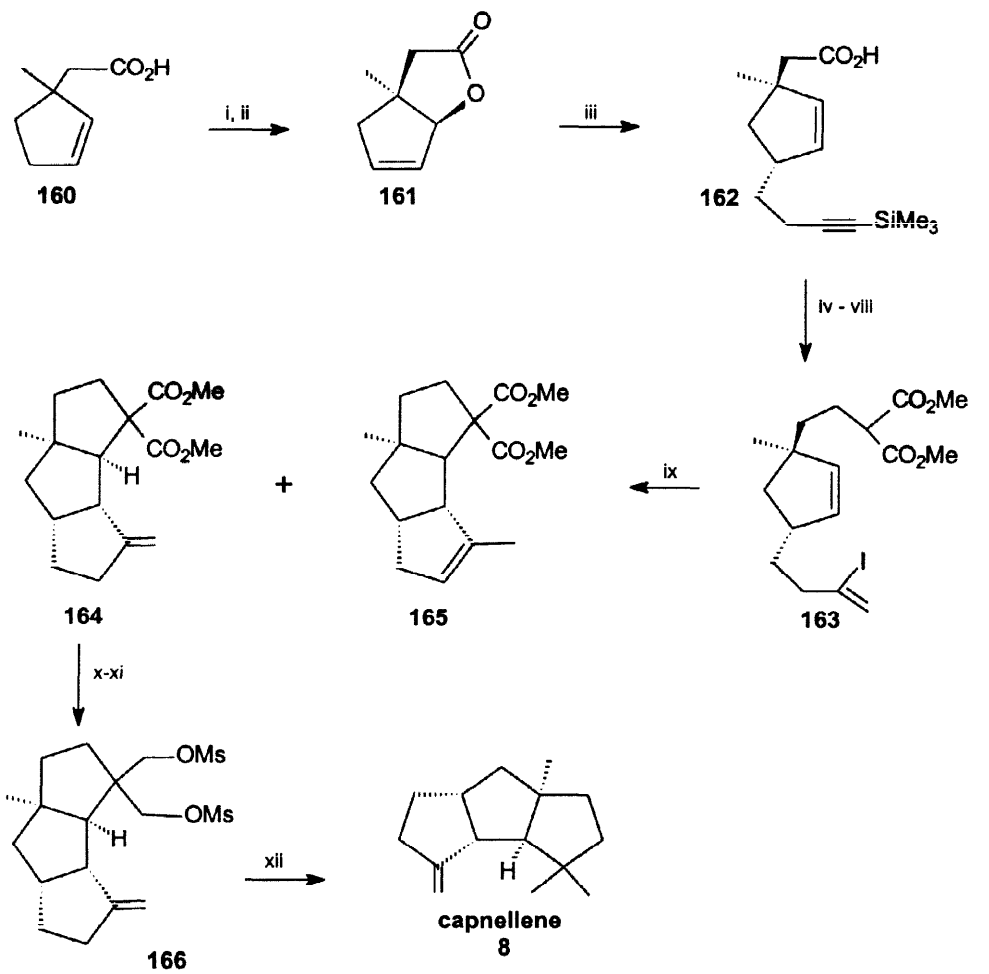
A highly novel and expedient method for a single step, one-pot synthesis of linearly fused triquinanes has been developed by Cohen and coworkers,[70] which is based on the observation that enolate-carbanions of the type **167** can be generated by the conjugate addition of tris(phenylthio)methyl lithium to an enone[71] and that the lithio thioacetal portion of the resulting species behaves as a nucleophile at -78°C and as an electrophilic carbenoid at slightly higher temperature.[72] Conjugate addition of **167** to cyclopentenone **168** followed by coupling led to linearly fused *cis:anti:cis* triquinane **169** as shown in the Scheme-34. The mechanism and origin of stereochemistry has been discussed.[70] The triquinane **169** was transformed into hirsutene as shown in the Scheme-35. Thus, reduction of **169** gave the dione **170** which upon selective ketalization furnished the ketoketal **171**. The carbonyl group was reduced with lithium-ammonia to give the alcohol **172** which was converted into the key intermediate **173**.

2.12 PALLADIUM CATALYZED CYCLIZATION OF ENYNES

Trost and Shi have also developed[73] an efficient method for synthesis of a variety of polyquinanes, based on palladium catalyzed cyclization of polyenynes. Thus, when a solution of dienyne **174** was heated in benzene in the presence of $(dba)_3Pd_2CHCl_3$, TPP and 10mol% acetic acid, it gave the fully symmetric

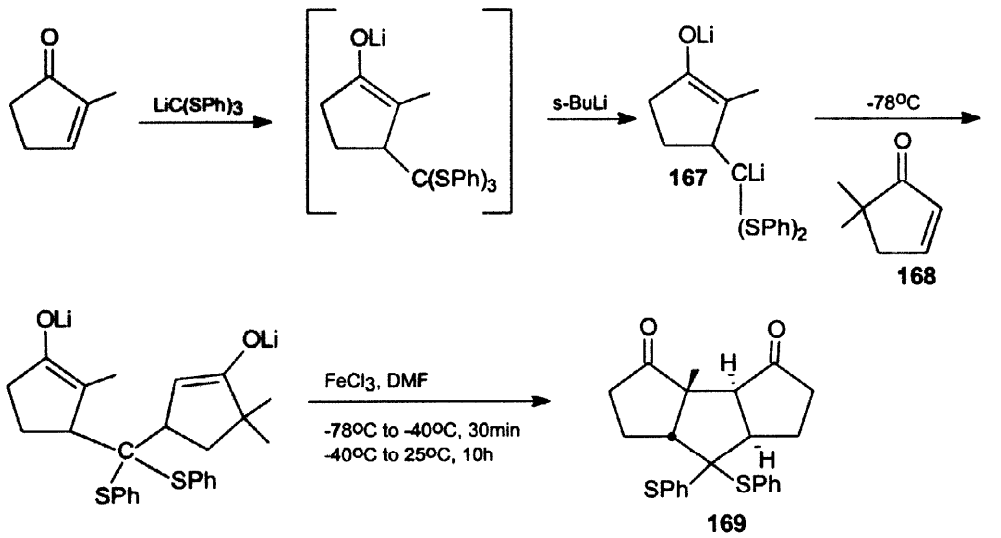
cis:syn:cis triquinane **177** (Scheme-36). The *cis:syn:cis* triquinane **177** is formed *via* cyclization of **174** to the diquinane-Pd complex **175** which further undergoes Pd initiated cyclization to give the intermediate **176.** The acid catalyzed removal of Pd led to formation of **177**. Similarly, the cyclization of the dienyne **178** in the presence of $(dba)_3Pd_2.CHCl_3$, PPh_3 in acetic acid gave the propellane type triquinanes **179** which was then converted into **180** (Scheme-37).

Several other interesting spiro polyquinanes **181-183** (Fig.-3) have also been prepared by cyclization of appropriate enynes. Various aspects of the cyclization mechanistic, regioisomeric and steric have been discussed.[73]

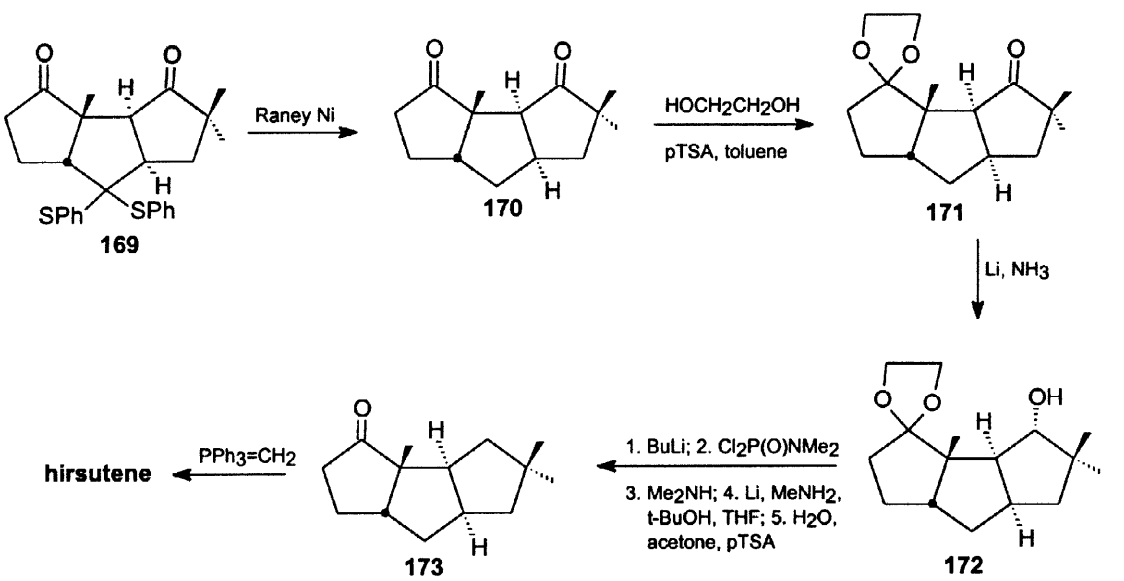


Reagents/Conditions: i) I_2, KI, $NaHCO_3$, H_2O, 20°C; ii) DBU, toluene, 110°C; iii) $Me_3SiC{\equiv}CCH_2CH_2MgBr$, CuBr-$Me_2S$, THF, Me_2S, -20°C; iv) LAH, ether, 0°C; v) KF, H_2O, DMF; vi) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; vii) NaH, $CH_2(CO_2Me)_2$, 10% KI, THF, DMF; viii) Me_3SiCl, NaI, H_2O, CH_3CN; ix) KH, THF, 25°C, 5% Pd(OAc) 10% tri(2-furyl)phosphine or 10% DPPE x) LAH, Et_2O; xi) $MeSO_2Cl$, Et_3N, CH_2Cl_2; xii) $LiEt_3BH$, THF, reflux.

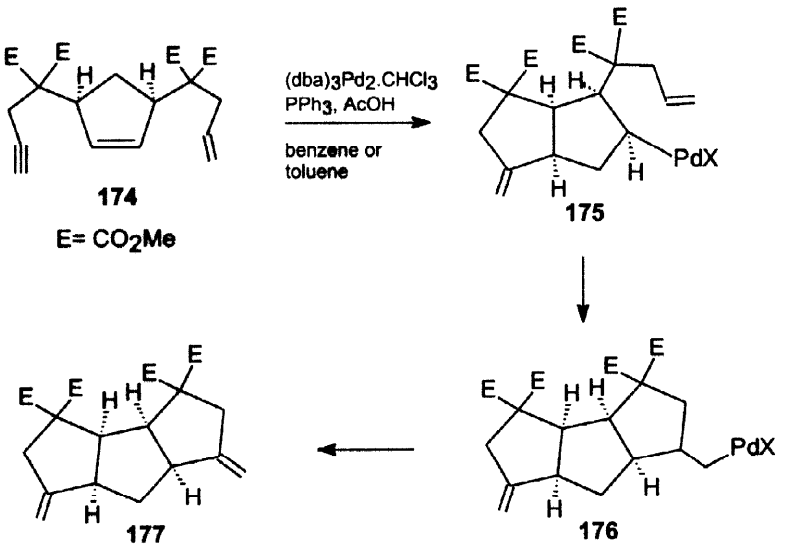
Scheme-33



Scheme-34

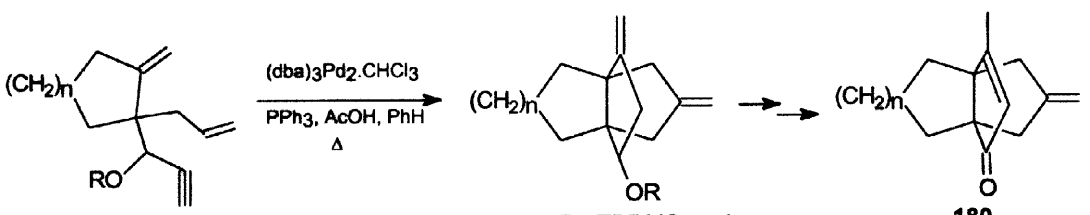


Scheme-35



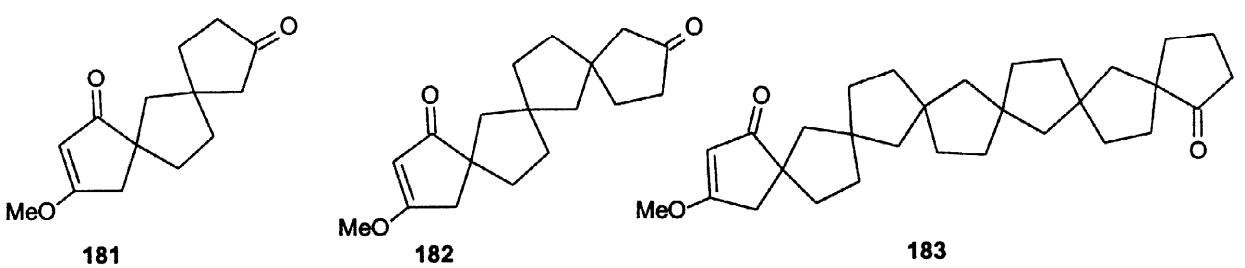
174
E= CO_2Me
175
176
177

Scheme-36



178a R =TBDMS, n=1
b R = Ac, n=2
179a R =TBDMS, n=1
b R = Ac, n=2
180

Scheme-37

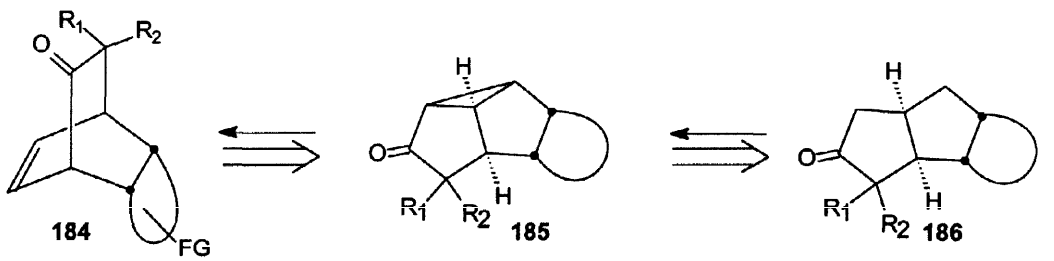


181
182
183

Fig.-3

2.13 DIELS–ALDER CYCLOADDITION-OXA-DI-π-METHANE REARRANGEMENT

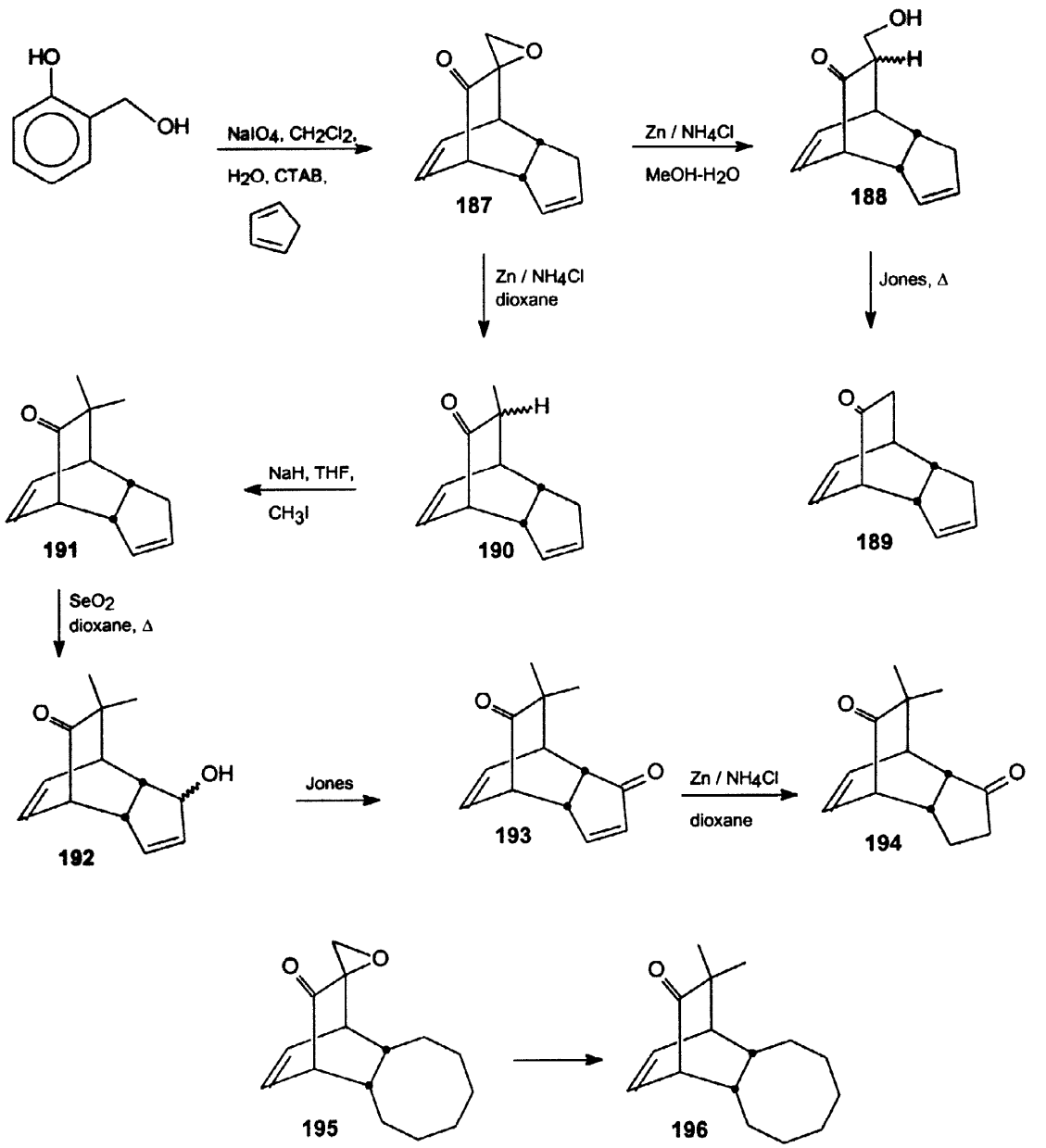
We have also been engaged[74] in the synthesis of polyquinanes and recently described an efficient and unified strategy for the linearly fused polyquinanes employing inverse demand $\pi^{4s}+\pi^{2s}$ cycloaddition of cyclohexa-2,4-dienones and photochemical oxa-di-π-methane rearrangement as key features of our strategy. Our methodology is based on the idea that linearly fused tricyclopentanoids such as **186** should be readily derived from the tetracyclic system **185**, which can be obtained from the *endo*-tricyclic system **184** *via* oxa-di-π-methane rearrangement (Scheme-38). However, there were no methods for the synthesis of the tricyclic systems of type **184** (Scheme-38). Hence, a general route to annulated bicyclo[2.2.2]octenones from phenols was developed. Thus, several *endo*-annulated tricyclic systems **187-194** were prepared from salicyl alcohol as shown in Scheme-39. The tricyclic system **196** was also obtained from **195** along similar lines. Triplet sensitized photoreaction of **189**, **191**, **192**, **194**, **196** in acetone (both sensitizer and solvent) gave the desired tetracyclic systems **197-201** containing the *cis:anti:cis* triquinane framework. The tetracyclic systems **198-201** (Fig.-4) were subjected to reductive cleavage with H_2/Pd-C to give the linearly fused polyquinanes **202-205** in good yield (Scheme-40).[74g]



Scheme-38

The methodology presented above was successfully applied to an efficient total synthesis[75] of capnellene, as shown in the Scheme-41. Thus, the *p*-cresol derivative **206** was converted into the annulated bicyclic compound **207** which was transformed into the dimethyl ketone **208**. Two fold oxidation of **208** gave the diene-dione **209** which was converted into the keto-ketal **210** following the methodology developed in our group. Triplet sensitized irradiation of the ketal **210** smoothly gave the rearranged product **211**. The reductive cleavage of the peripheral cyclopropyl sigma bond gave the triquinane-ketal **212**. Barton's deoxygenation of the carbonyl group followed by hydrolysis of the ketal gave the ketone **213** which upon Wittig reaction furnished the natural product capnellene (Scheme-41).

Alternatively, we also discovered a direct route to functionalized *cis:anti:cis* triquinanes of the type **215** *via* the photoreaction of annulated bicyclo[2.2.2] systems having an α-methoxy-β,γ-enone chromophore such as **214** as shown in the Scheme-42. A number of chromophoric systems have been prepared and rearranged to a variety of functionalized triquinanes **216-218** (Scheme-42).[76]



Scheme-39

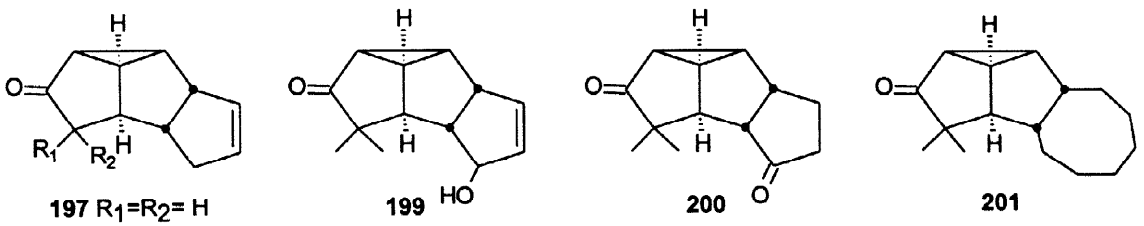
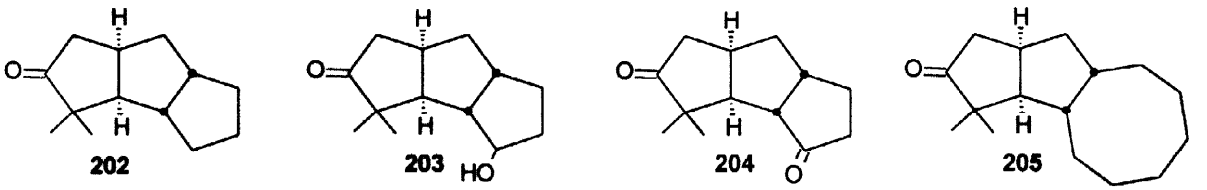
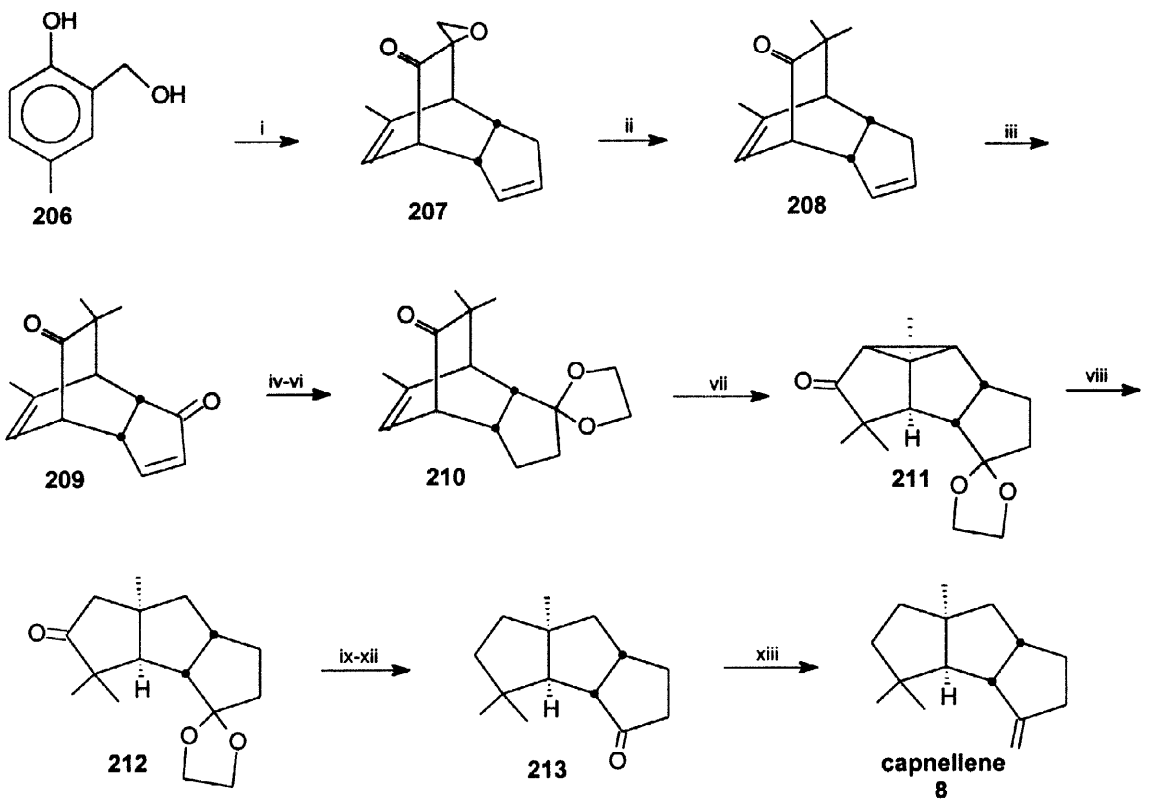


Fig.-4

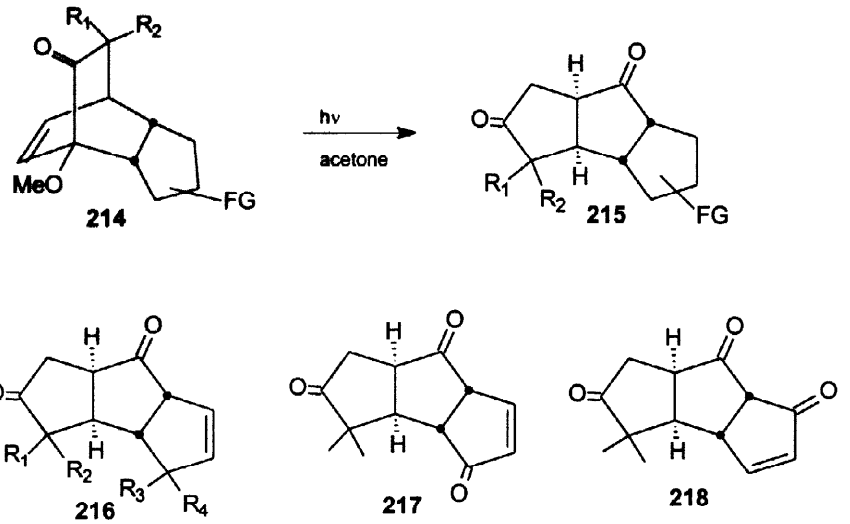


Scheme-40



Reagents/Conditions: i) $NaIO_4$, C_5H_6; ii) a) Zn, NH_4Cl, dioxane; b) NaH, THF, MeI; iii) a) SeO_2, dioxane; b) Jones iv) $NaBH_4$, MeOH; v) PCC; vi) ethylene glycol, pTSA; vii) hv, acetone; viii) H_2/Pd ix) $NaBH_4$, MeOH; x) CS_2, MeI, NaH; xi) Bu_3SnH; xii) H_2O/H^+; xiii) $CH_2=PPh_3$.

Scheme-41



R_1= CH_3, R_2=R_3=R_4= H
R_1= CH_3, R_2= $CH_2CH{=}CH_2$, R_3=R_4= H
R_1=R_2= CH_3, R_3=R_4= H
R_1=R_2= CH_3, R_3,R_4= $-CH_2CH_2-$
R_1=R_2= CH_3, R_3,R_4= $=CH(CH_3)_2$
R_1=R_2=R_3= H, R_4= OH

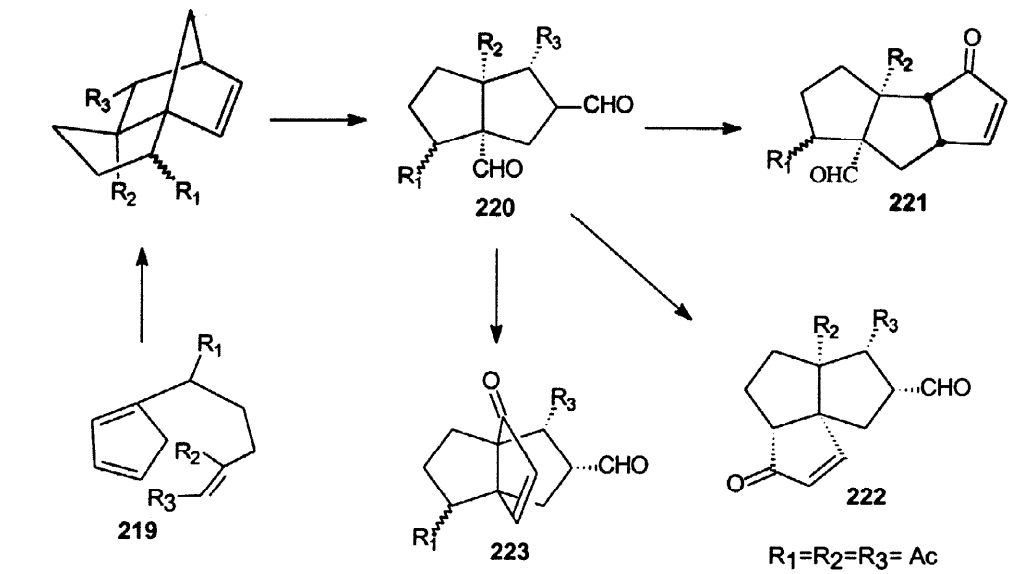
Scheme-42

3. GENERAL METHODS LEADING TO TRIQUINANES *via* DIQUINANES

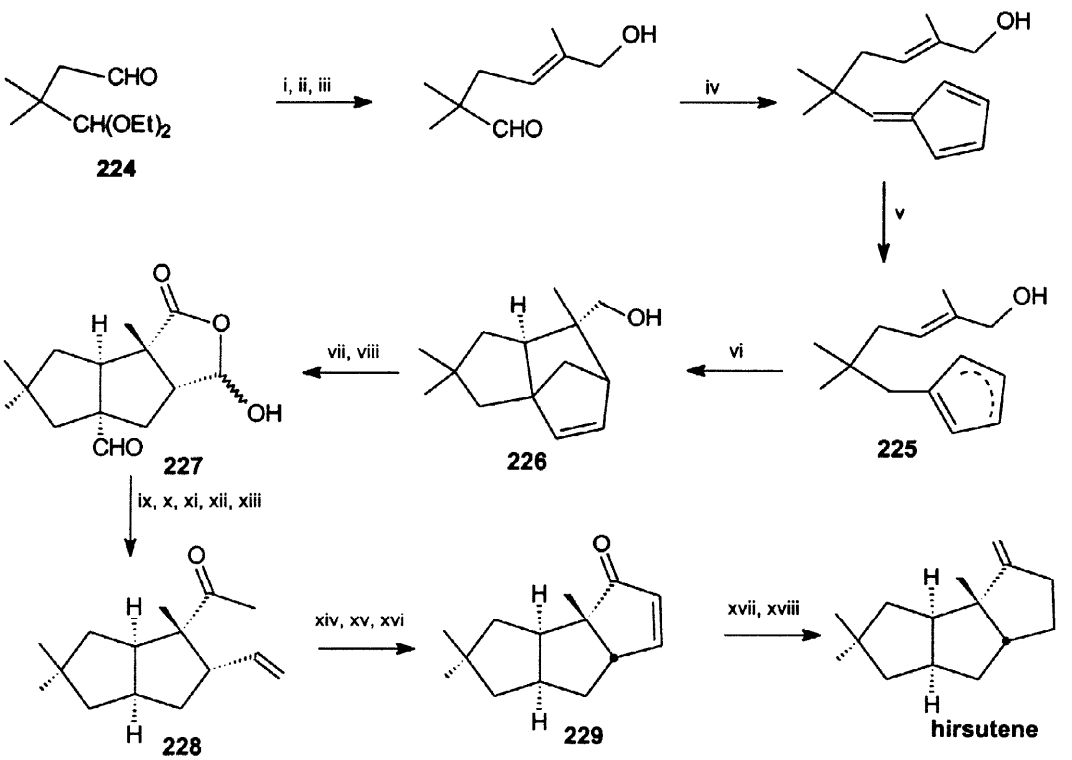
In the previous section we discussed those methods of triquinane syntheses which furnished the linearly fused triquinane frameworks in a single step from appropriate precursors. In this section we present some methods which produce diquinane intermediates which are further annulated to give triquinanes.

3.1. INTRAMOLECULAR DIELS–ALDER APPROACH

Sternbach[77] and his associates have developed a common strategy for the synthesis of linear (**221**), angular (**222**) and propellane type (**223**) triquinanes employing diquinane intermediates such as **220**, readily available through intramolecular Diels–Alder reaction of substituted cyclopentadienes of type **219** as shown in the Scheme-43. In a recent application of this method, Sternbach reported a synthesis of hirsutene[77a] wherein the desired cyclopentadiene derivative **225** was prepared from the aldehyde **224** as shown in the Scheme-44. The intramolecular Diels–Alder reaction of **225** gave the adduct **226** which was converted into the diquinane **227** by oxidation of the primary alcoholic group to carboxylic acid and cleavage of the double bond. Conversion of the aldehyde **227** to the olefinic ketone **228** and subsequent transformations led to the triquinane **229**, which was converted to hirsutene (Scheme-44). The present method thus required 16 steps for the triquinane intermediate (**229**).



Scheme-43

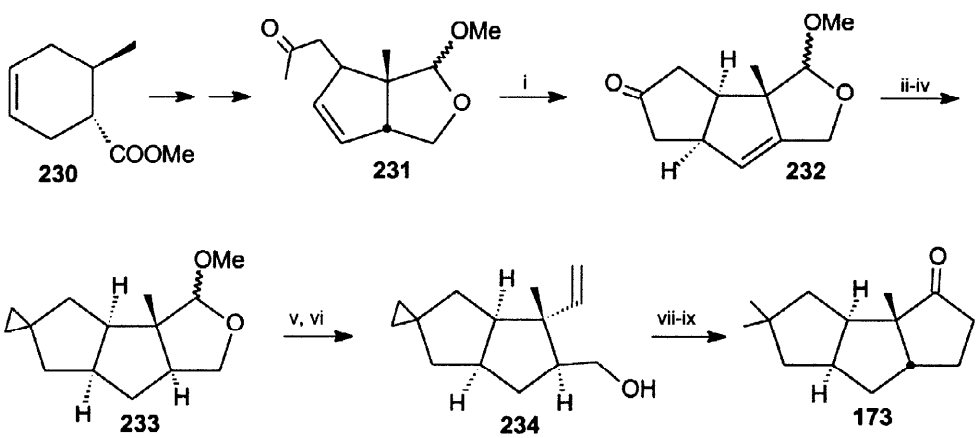


Reagents/Conditions: i) $Ph_3P{=}C(CH_3)CO_2Et$, PhH, reflux; ii) LAH, ether, 0°C; iii) 10% HCl, THF, r.t.; iv) cyclopentadien pyrrolidine, Na_2SO_4, MeOH; v) LAH, THF, r.t.; vi) mesitylene, Δ; vii) Jones reagent; viii) O_3, CH_2Cl_2, -78°C, DMS, -78°C to r.t.; ix) Ac_2O, Et_3N, DMAP; x) Jones reagent; xi) $(COCl)_2$, DMF, benzene, r.t., 2h, 2-mercaptopyridine-*N*-oxide sodium salt, t-BuSH, DMAP, PhMe, reflux; xii) MeOH, H_2O, Et_3N (5:4:1) r.t.; xiii) Ph_3PCH_3Br, KHDMS, THF, 0°C; xiv) NaH, benzene, r.t., 1h. $(COCl)_2$, r.t., 3h, Me_2CuLi, ether, -78°C to 0°C; xv) O_3, CH_2Cl_2, -78°C, DMS, -78°C, xvi) 5% KOH, ether, THF, n-Bu_4NOH, xvii) PtO_2, H_2, EtOAc, xviii) Ph_3PCH_2Br, KH, PhH, t-BuOH (5:1)

Scheme-44

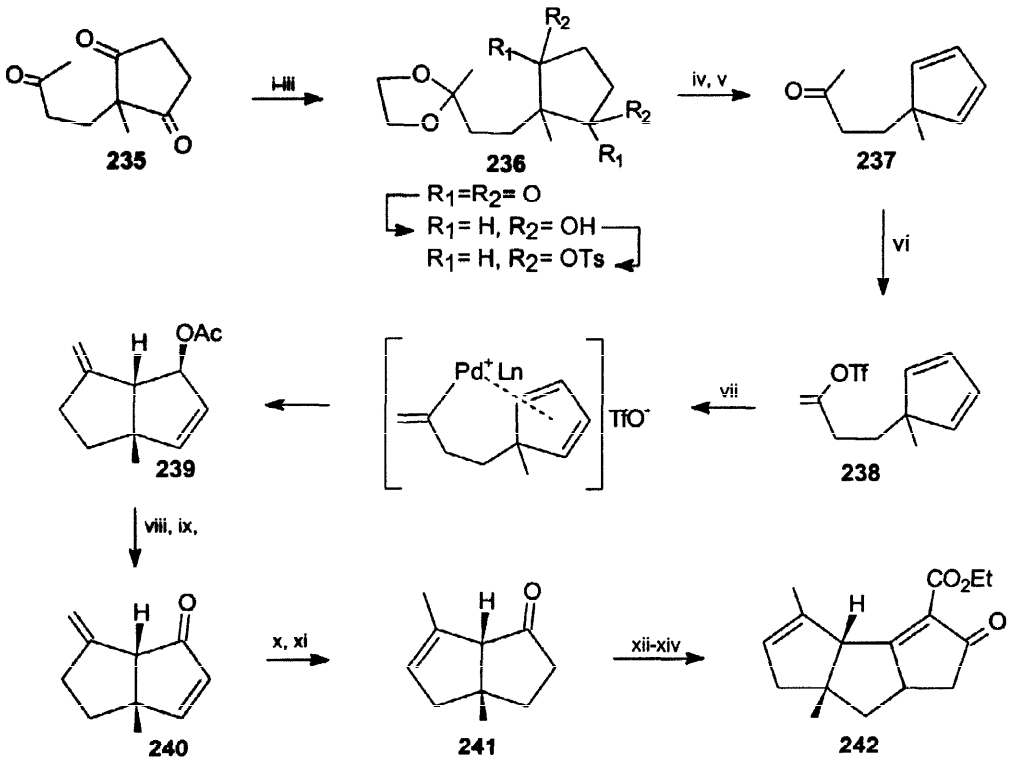
Fukumoto and coworkers[78] have developed a general route to triquinanes *via* palladium promoted cyclization to generate diquinane precursors which are further annulated to give linearly fused *cis:anti:cis* tricyclopentanoids and applied their method for total synthesis of hirsutene. The acetal **231** was prepared from cyclohexene derivative **230** in eleven steps and subjected to cyclization in the presence of lithium diisopropylamide, trimethylsilyl chloride and palladium acetate to give the diquinane **232**. The diquinane **232** was converted into the cyclopropyl homologue **233** as shown in the Scheme-45. Elaboration of the hemiacetal **233** to the olefinic alcohol **234** followed by annulation furnished the triquinane intermmediate **173** which has been taken to hirsutene.[70]

In context with their continuing interest in polyquinanes,[79] Shibasaki and coworkers[80] have reported a synthesis of a triquinane intermediate for capnellenols. Their methodology employed an asymmetric Heck reaction followed by anion capture to generate a diquinane which is annulated to give the tricyclopentanoid. The approach is shown in the Scheme-46. The precursor **238** for the Heck reaction was prepared from the trione **235**. The trione **235** was converted into ditosylate **236**, which upon treatment with DBU and hydrolysis of the ketal group gave the cyclopentadiene derivative **237**. Transformation of **237** to vinyltriflate **238** and Heck reaction in the presence of (*S*)-BINAP furnished the diquinane **239** in 80% ee. The diquinane **239** was transformed into **240** which after isomerization of the exocyclic double bond led to **241** subsequent annulation of which gave the optically active triquinane **242**, a precursor[79c,d] for the synthesis of oxygenated capnellenes. Recently synthesis of (–)-capnellene following the above methodology has appeared.[14g]



Reagents/Conditions: i) LDA, THF, -78°C, TMSCl; $Pd(OAc)_2$, CH_3CN-CH_2Cl_2; ii) H_2, 10% Pd-C, EtOAc; iii) $Ph_3P^+CH_3Br^-$, n-BuLi, DME, Δ; iv) CH_2I_2, Et_2Zn, C_6H_6; v) aq. $HClO_4$, acetone; vi) $Ph_3P^+CH_3Br$, nBuLi, DME, reflux; vii) PCC, NaOAc, CH_2Cl_2; viii) $PdCl_2$, CuCl, O_2, DMF-H_2O; ix) n-$Bu_4N^+OH^-$, THF-ether, 5% KOH, Δ; x) H_2, PtO_2, NaOAc, AcOH; xi) PCC, NaOAc, CH_2Cl_2.

Scheme-45



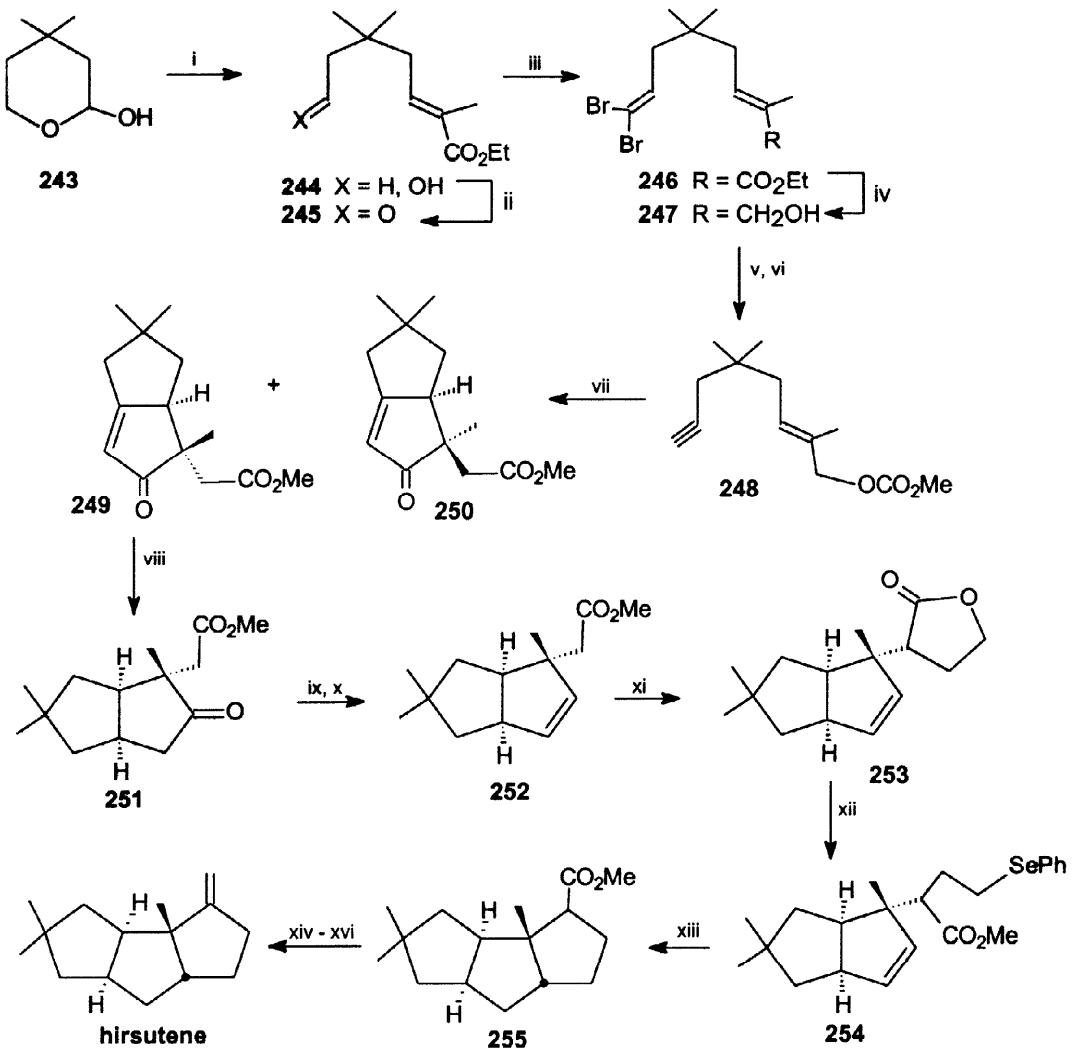
Reagents/Conditions: i) $(TMSOCH_2)_2TMSOTf$; ii) $NaBH_4$; iii) TsCl, DMAP; iv) DBU; v) TsOH, acetone; vi) LDA, Tf_2NPh; vii) $Pd(OAc)_2$(*S*)-BINAP, Bu_4NOAc, DMSO; viii) NaOMe; ix) PDC, MS-3A; x) CuBr, Red-Al, s-BuOH, THF; xi) DBU; xii) LDA, $ICH_2C(OMe)=CHCO_2Et$; xiii) 30% $HClO_4$, ether; xiv) NaOEt, EtOH.

Scheme-46

3.2. PALLADIUM PROMOTED SYNTHESES

Oppolzer's group developed a method for the synthesis of diquinane intermediates from acyclic enyne systems employing catalytic Pd^0, Pt^0 and Ni^0.[81] They recently reported the synthesis of hirsutene[81c] (Scheme-47) utilizing this allyl-palladium-alkyne cyclization/carbonylation cascade.

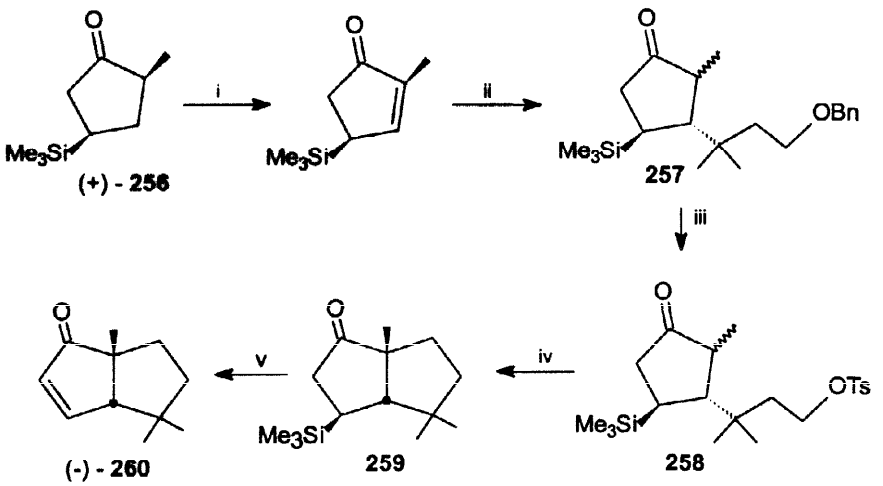
The requisite enyne substrate **248** was prepared from the hemiacetal **243** as follows. The hemiacetal **243** was transformed into the alicyclic alcohol **244** and oxidised to **245**. Wittig type condensation of **245** afforded the dihalo-diene ester **246** which was reduced with DIBAH to give the alcohol **247**. Transformation of **247** to the required substrate **248** followed by palladium catalyzed cyclization-carbonylation gave a mixture of diquinanes **249** and **250** (85:15). The major isomer **249** was then hydrogenated to **251** which upon reduction with $NaBH_4$ and dehydration gave **252**. Conversion of **252** into the lactone **253** and reaction of **253** with sodium phenylselenide followed by esterification with diazomethane gave the selenyl derivative **254** as shown in the Scheme-48. Treatment of **254** with tributyltin hydride gave the tricyclopentanoid **255** bearing all the requisite groups for the synthesis of hirsutene. Reduction of the ester group, transformation to selenocyanate and oxidative elimination of phenylselenyl group furnished the hirsutene.



Reagents/Conditions: i) $Ph_3P{=}C(Me)CO_2Et$; ii) PCC; iii) Zn, PPh_3, CBr_4; iv) DIBAH; v) BuLi, H_2O; vi) $ClCO_2Me$, Py; vii) (a) $Pd(dba)_2PPh_3$, CO, AcOH, 40°C, (b) CH_2N_2; viii) H_2, Pd/C; ix) $NaBH_4$; x) $POCl_3$, Py; xi) LDA, cyclic ethylene sulphate; xii) PhSeNa, CH_2N_2; xiii) Bu_3SnH, AIBN; xiv) LAH, xv) 2-$NO_2C_6H_4SeCN$, Bu_3P; xvi) H_2O_2, Δ.

Scheme-47

Asaoka developed[82] an enantioselective route to diquinane **260**, thus constituting a formal total synthesis of (–)-capnellene. The route to the diquinane is shown in the Scheme-48. Thus, (+)-2-methyl-4-trimethylsilylcyclopentanone **256** was transformed into the tosylated homologue **258** *via* benzyl derivative **257**. The intramolecular alkylation of **258** gave the optically active (–)-diquinane **259** which upon oxidative elimination of the silyl group gave **260**. The intermediate **260** has been converted into capnellene by Piers and coworkers.[83]

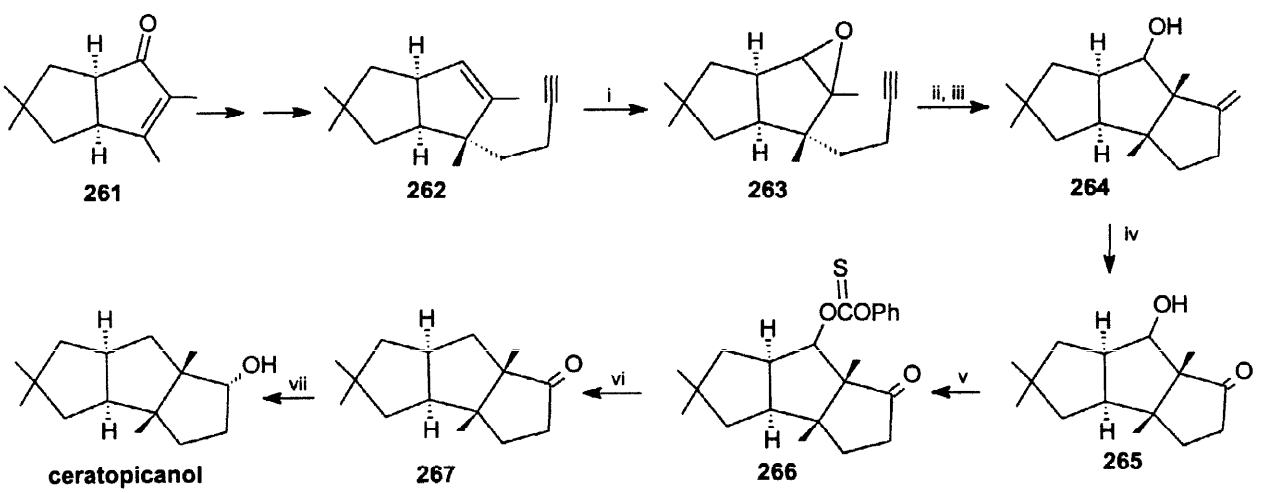


Reagents/Conditions: i) (a) Me_3SiOTf, Et_3N, toluene; (b) Pd $(OAC)_2$, CH_3CN, ii) (a) $BnOCH_2CH_2C(Me)_2MgCl$, CuBr.Me_2S, HMPA, Me_3SiCl, THF; (b) KF, MeOH; iii) (a) H_2, Pd-C, EtOH, (b) TsCl, Py; iv) t-BuOK, THF; v) (a) Me_3SiOTf, Et_3N, toluene, (b) NBS, THF, (c) TBAF, THF.

Scheme-48

3.3. RADICAL CYCLIZATION

Clive and Magnusson[84] developed a synthesis of ceratopicanol from a diquinane precursor employing radical cyclization of epoxyalkyne moiety to create a triquinane system (Scheme-49). The precursor **262** was obtained from the diquinane **261** in six steps. Epoxidation of **262** gave the epoxyalkyne **263** which was treated with Cp_2TiCl to give the triquinane alcohol **264** after an acidic workup. Protection of the hydroxyl group, cleavage of the exocyclic double bond and deprotection gave the keto alcohol **265**. Deoxygenation of the hydroxyl group *via* thiocarbonate **266** furnished the ketone **267**, a precursor which was taken to ceratopicanol.



Reagents/Conditions: i) mcpba, CH_2Cl_2, 0°C, 2h; ii) Cp_2TiCl, THF, rt, 7h; iii) 10% H_2SO_4 workup; iv) Ac_2O, AcCl, DMAP, Py, 25°C, 2-4h; OsO_4, 4-methylmorpholine-*N*-oxide, 10:1 acetone-H_2O, 12h; K_2CO_3, MeOH, 1h; $Pb(OAc)_4$, K_2CO_3, CH_2Cl_2, 0°C to 25°C; v) ClC(S)OPh, DMAP, CH_3CN, 8h; vi) Bu_3SnH, Et_3B, air, hexane, 0°C, 1h, workup and treatment with stannane/borane system; vii) $NaBH_4$, MeOH, -20°C, 20min.

Scheme-49

4. SUMMARY AND OUTLOOK

This review highlights that the realm of polyquinane chemistry continues to hold synthetic challenge to the organic chemists. In the previous decade most of the syntheses were multistep sequences directed towards linearly fused cyclopentanoids. The focus now appears to have shifted towards development of general protocols to achieve the syntheses of a large number of triquinanes *via* a short and stereoselective sequence. The goal being to synthesize the *cis:anti:cis* linear triquinane framework in a single step from a precursor embodying, as far as possible, all the requisite carbon atoms and functionalities such that the introduction of functional groups with the correct stereochemistry in the precursor determines the final outcome in the product. The methodologies described in this review are among the efforts made in this direction.

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Biographical sketch

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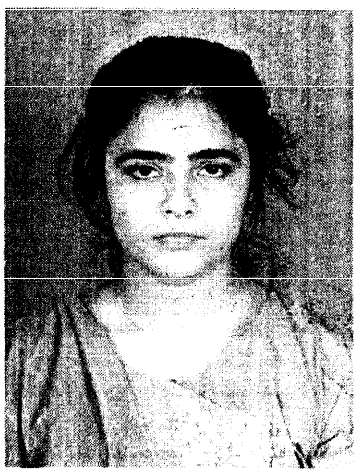

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Vishwakarma Singh received his Ph.D. degree in 1976 from University of Gorakhpur where he worked under the supervision of Prof. S. Giri. He continued his scientific education as a Senior Research Fellow (CSIR, New Delhi) under the direction of Prof. Goverdhan Mehta at Indian Institute of Technology, Kanpur and University of Hyderabad, where he worked in the area of strained polycyclics. He was awarded a Monbusho Fellowship from Ministry of Education, Govt. of Japan, to work with Prof. E. Osawa at Hokkaido University, Sapporo, Japan (1979-80). He then moved to United States and worked as a Research Associate with Prof. A. R. Martin and Dr. V. V. Kane at University of Arizona, Tucson, in the area of cannabinoids. Vishwakarma Singh also worked with Prof. J. B. Hendrickson at Brandeis University, Waltham, Mass, on synthesis of corticosteroids (1981-82).

Dr. Vishwakarma Singh returned to India and after working at Malti-Chem Research Center Nandesari, Baroda and M. S. University of Baroda, he joined Indian Institute of Technology, Bombay in October 1989 and currently he is an Associate Professor. His research interests are in the area of organic synthesis and photochemistry. He has completed total synthesis of triquinane natural products, $\Delta^{9(12)}$-capnellene and coriolin and, currently he is working on synthesis of Taxol and Phorbol esters, photochemical reactions and asymmetric synthesis.

Beena Thomas completed her M.Sc. degree at Indian Institute of Technology, Bombay in 1990. Beena Thomas was awarded a research fellowship (CSIR, New Delhi) to continue with Doctoral studies at I.I.T. Bombay. She worked for her Ph.D. with Prof. Vishwakarma Singh in the field of tricyclopentanoid chemistry and received her Ph. D. degree in 1997. Beena has accepted a post-doctoral position at Ohio State University to work with Professor Y. H. Chu from 1st December, 1997.